International PhD program in Cardiovascular Pathophysiology and Therapeutics - CardioPaTh

Personalized medicine in interventional cardiology: pharmacologic and mechanical strategies to balance ischemic and bleeding complications during and after percutaneous cardiovascular interventions

— *Searching for and fighting with a Chimera* —

Giuseppe Gargiulo

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TABLE OF CONTENTS

General Introduction

Part 1. Trade-off for ischemia and bleeding during and immediately after percutaneous coronary interventions:

Selecting the optimal antithrombotic strategy

Chapter 1.1 Bivalirudin versus heparin with or without glycoprotein IIb/IIIa inhibitors in patients with STEMI undergoing primary PCI: An updated meta-analysis of 10,350 patients from five randomized clinical trials.
Capodanno D*, **Gargiulo G***, Capranzano P, Mehran R, Tamburino C, Stone GW.
Eur Heart J Acute Cardiovasc Care. 2016 Jun;5(3):253-62. ***Equally contributed.**

Chapter 1.2 Developing drugs for use during percutaneous coronary intervention.
Gargiulo G, Moschovitis A, Windecker S, Valgimigli M.
Expert Opin Pharmacother. 2016;17(6):803-18. **IF: 3.475**

Chapter 1.3 Bivalirudin versus unfractionated heparin for acute coronary syndromes: do we have a winner?
Gargiulo G and Valgimigli M.
Rev Esp Cardiol (Engl Ed). 2016 Aug;69(8):721-4. **IF: 5.166**

Chapter 1.4 Bivalirudin in the current practice. Melius abundare quam deficiere?
Valgimigli M and **Gargiulo G.**
JACC Cardiovasc Interv. 2016 Jul 11;9(13):1321-3. **IF: 9.881**

Chapter 1.5 Bivalirudin or Heparin in Patients Undergoing Invasive Management of Acute Coronary Syndromes.
Gargiulo G, Carrara G, Frigoli E, Vranckx P, Leonardi S, Ciociano N, Campo G, Varbella F, Calabrò P, Garducci S, Iannone A, Briguori C, Andò G, Crimi G, Limbruno U, Garbo R, Sganzerla P, Russo F, Lupi A, Cortese B, Ausiello A, Ierna S, Esposito G, Zavalloni D, Santarelli A, Sardella G, Tresoldi S, de Cesare N, Sciahbasi A, Zingarelli A, Tosi P, van 't Hof A, Omerovic E, Brugaletta S, Windecker S, Valgimigli M.
J Am Coll Cardiol. 2018 Mar 20;71(11):1231-1242. **IF: 16.834**

Chapter 1.6 Activated Clotting Time During Unfractionated Heparin-Supported Coronary Intervention: Is Access Site the New Piece of the Puzzle?
Valgimigli M, **Gargiulo G**.
JACC Cardiovasc Interv. 2018 Jun 11;11(11):1046-1049. **IF: 9.881**

Chapter 1.7 Impact of Sex on Comparative Outcomes of Bivalirudin versus Unfractionated Heparin in Patients with Acute Coronary Syndromes Undergoing Invasive Management A pre-specified analysis of the MATRIX trial.
Gargiulo G, da Costa BR, Frigoli E, Palmieri C, Nazzaro MS, Falcone C, Liso A, Vigna C, Abate F, Comeglio M, Diletti R, Gabrielli G, Di Lorenzo E, Mazzarotto P, Zimarino M, Moretti C, Colombo A, Penzo C, Pasquetto G, Brugaletta S, Ferrari F, Casu G, Guiducci V, Dellavalle A, Liistro F, Mauro C, Van't Hof AWJ, Omerovic E, Curello S, de la Torre Hernandez JM, De Servi S, Belloni F, Windecker S, Valgimigli M.
EuroIntervention. 2018 May 15. pii: EIJ-D-18-00247. **IF: 4.417**

Chapter 1.8 Effect of Post-procedural Bivalirudin Infusion at Full or Low Regimen in Patients with Acute Coronary Syndrome with or without ST-segment Elevation: An Analysis of the MATRIX trial.
Gargiulo G, Carrara G, Frigoli E, Leonardi S, Vranckx P, Campo G, Varbella F, Calabrò P, Zaro T, Bartolini D, Briguori C, Andò G, Ferrario M, Limbruno U, Colangelo S, Sganzerla P,

Russo F, Nazzaro MS, Esposito G, Ferrante G, Santarelli A, Sardella G, Windecker S, Valgimigli M.
J Am Coll Cardiol. 2019. Accepted, in press. **IF: 16.834**

Implementing the Radial approach to improve clinical outcomes

Chapter 1.9 Radial versus femoral access for cardiac catheterisation - Authors' reply.
Valgimigli M, **Gargiulo G**, Juni P.
Lancet. 2015 Dec 12;386(10011):2394. **IF: 53.234**

Chapter 1.10 Impact of Sex on Comparative Outcomes of Radial Versus Femoral Access in Patients With Acute Coronary Syndromes Undergoing Invasive Management Data From the Randomized MATRIX-Access (Minimizing Adverse Haemorrhagic Events by TRansradial Access Site and Systemic Implementation of AngioX) Trial.
Gargiulo G, Ariotti S, Vranckx P, Leonardi S, Frigoli E, Ciociano N, Tumscitz C, Tomassini F, Calabrò P, Garducci S, Crimi G, Andò G, Ferrario M, Limbruno U, Cortese B, Sganzerla P, Lupi A, Russo F, Garbo R, Ausiello A, Zavalloni D, Sardella G, Esposito G, Santarelli A, Tresoldi S, Nazzaro MS, Zingarelli A, Petronio AS, Windecker S, da Costa BR, Valgimigli M.
JACC Cardiovasc Interv. 2018 Jan 8;11(1):36-50. **IF: 9.881**

Chapter 1.11 Association between Radial or Femoral Access and Acute Kidney Injury in Patients with Acute Coronary Syndromes Undergoing Invasive Management.
Andò G, Cortese B, Russo F, Rothenbuhler M, Frigoli E, **Gargiulo G**, Briguori C, Vranckx P, Leonardi S, Guiducci V, Belloni F, Ferrari F, de la Torre Hernandez JM, Curello S, Liistro F, Perkan A, De Servi S, Casu G, Dellavalle A, Fischetti D, Micari A, Loi B, Mangiacapra F, Russo N, Tarantino F, Saia F, Heg D, Windecker S, Juni P, Valgimigli M.
J Am Coll Cardiol. 2017 May 11. pii: S0735-1097(17)36897-3. **IF: 16.834**

Stenting strategies to optimize clinical outcomes

Chapter 1.12 Treatment strategies for coronary in-stent restenosis: a systematic review and hierarchical Bayesian network meta-analysis of 24 randomised trials and 4,880 patients.
Giacoppo D, **Gargiulo G**, Aruta P, Capranzano P, Tamburino C, Capodanno D.
BMJ. 2015 Nov 4;351:h5392. **IF: 23.259**

Chapter 1.13 One-year outcomes after Absorb bioresorbable vascular scaffold implantation in routine clinical practice.
Capranzano P, Longo G, Tamburino CI, **Gargiulo G**, Ohno Y, Francaviglia B, La Manna A, Di Salvo ME, Grasso C, Sgroi C, Capodanno D, Tamburino C.
EuroIntervention. 2016 Jun 12;12(2):e152-9. **IF: 4.417**

Chapter 1.14 Computing methods for composite clinical endpoints in unprotected left main coronary artery revascularization: a post-hoc analysis of the Drug Eluting stent for LefT main coronary Artery disease (DELTA) multicenter registry.
Capodanno D*****, **Gargiulo G***, Buccheri S, Chieffo A, Meliga E, Latib A, Park SJ, Onuma Y, Capranzano P, Valgimigli M, Narbute I, Makkar RR, Palacios IF, Kim YH, Buszman PE, Chakravarty T, Sheiban I, Mehran R, Naber C, Margey R, Agnihotri A, Marra S, Leon MB, Moses JW, Fajadet J, Lefèvre T, Morice MC, Erglis A, Alfieri O, Serruys PW, Colombo A, Tamburino C.
JACC Cardiovasc Interv. 2016 Nov 28;9(22):2280-2288. ***Equally contributed. IF: 9.881**

Chapter 1.15 Stent and DAPT Duration Comparisons in the Setting of a Multicenter Randomized Controlled Trial: Can the Operator Experience Affect the Study Results?
Gargiulo G, Heg D, Ferrari F, Percoco G, Campo G, Tumscitz C, Colombo F, Zuffi A, Castriota F, Cremonesi A, Windecker S, Valgimigli M.
Journal of American Heart Association 2017 Dec 23;6(12). pii: e007150. **IF: 4.450**

Chapter 1.16 Impact of angiographic coronary artery disease complexity on ischemic and bleeding risks and on the comparative effectiveness of Zotarolimus-eluting vs. Bare-Metal Stents in uncertain drug-eluting stent candidates.
Gargiulo G, Patialiakas A, Piccolo R, Thury A, Colangelo S, Campo G, Tebaldi M, Ungi I, Tondi S, Roffi M, Menozzi A, de Cesare N, Garbo R, Meliga E, Testa L, Gabriel HM Ferlini M Liistro F, Dellavalle A, Vranckx P, Briguori C, Windecker S, Valgimigli M.
Int J Cardiol. 2018 Oct 2. pii: S0167-5273(18)34840-X. **IF: 4.034**

Pharmacological strategies to prevent the risk of acute kidney injury (AKI)

Chapter 1.17 Preventive Strategies for Contrast-Induced Acute Kidney Injury in Patients Undergoing Percutaneous Coronary Procedures: Evidence from a Hierarchical Bayesian Network Meta-Analysis of 124 Trials and 28,240 Patients.
Giacoppo D*, **Gargiulo G***, Buccheri S, Aruta P, Byrne R, Cassese S, Dangas G, Kastrati A, Mehran R, Tamburino C, Capodanno D.
Circ Cardiovasc Interv. 2017 May;10(5). pii: e004383. ***Equally contributed. IF: 6.504**

Part 2. Trade-off for ischemia and bleeding after percutaneous coronary interventions: which is the optimal regimen of antiplatelet therapy?

Impact of residual platelet aggregation and concomitant therapies on ischemic and bleeding events in patients receiving dual antiplatelet therapy (DAPT)

Chapter 2.1 Impact of residual platelet reactivity on reperfusion in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention.
Capranzano P, Capodanno D, Bucciarelli-Ducci C, **Gargiulo G**, Tamburino CI, Francaviglia B, Ohno Y, La Manna A, Salemi A, Attizzani GF, Angiolillo DJ, Tamburino C.
Eur Heart J Acute Cardiovasc Care. 2016 Sep;5(5):475-86.

Chapter 2.2 Impact of proton pump inhibitors on clinical outcomes in patients treated with a 6-month or 24-month DAPT duration: insights from the PRODIGY trial.
Gargiulo G, Costa F, Ariotti S, Biscaglia S, Campo G, Esposito G, Leonardi S, P Vranckx, Windecker S, Valgimigli M.
Am Heart J. 2016 Apr;174:95-102. **IF: 4.171**

Chapter 2.3 Long-term dual antiplatelet therapy and concomitant optimal medical therapy following percutaneous coronary intervention.
Gargiulo G, Valgimigli M.
Cardiovasc Diagn Ther. 2017 Jun;7(Suppl 2):S102-S106.

Chapter 2.4 Effects of Carvedilol Versus Metoprolol on Platelet Aggregation in Patients With Acute Coronary Syndrome: The PLATE-BLOCK Study.
Ilardi F*, **Gargiulo G***, Schiattarella GG*, Giugliano G, Paolillo R, Menafra G, De Angelis E, Scudiero L, Franzone A, Stabile E, Perrino C, Cirillo P, Morisco C, Izzo R, Trimarco V, Esposito G.
Am J Cardiol. 2018 Jul 1;122(1):6-11. ***Equally contributed. IF: 3.172**

Personalizing type and duration of DAPT

Chapter 2.5 Duration of dual antiplatelet therapy after percutaneous coronary intervention and coronary stent implantation: past, present and future perspectives.
Gargiulo G, Valgimigli M, Capodanno D, Bittl J.
EuroIntervention. 2017;13(6):717-733. **IF: 4.417**

Chapter 2.6 Time for Science to Catch up with Clinical Practice?
Ariotti S, **Gargiulo G**, Windecker S, Valgimigli M.
J Thorac Dis. 2015 Dec;7(12):E603-6. **IF: 1.804**

Chapter 2.7 Impact of gender on 2-year clinical outcomes in patients treated with a 6-month or 24-month DAPT duration: a pre-specified analysis from the PRODIGY trial.
Gargiulo G, Ariotti S, Santucci A, Piccolo R, Baldo A, Franzone A, Magnani G, Marino M, Esposito G, Windecker S, Valgimigli M.
JACC Cardiovasc Interv. 2016 Sep 12;9(17):1780-9. **IF: 9.881**

Chapter 2.8 Prolonged versus Shortened Duration of Dual Antiplatelet Therapy after Percutaneous Coronary Intervention in Patients with or without Peripheral Arterial Disease. A Subgroup Analysis of the PRODIGY Randomized Trial.
Franzone A, Piccolo R, **Gargiulo G,** Ariotti S, Marino M, Santucci A, Baldo A, Magnani G, Moschovitis A, Windecker S, Valgimigli M.
JAMA Cardiol. 2016 Oct 1;1(7):795-803. **IF: 10.133**

Chapter 2.9 Long-Term Use of Ticagrelor in Patients with Coronary Artery Disease.
Ariotti S*, **Gargiulo G***, Valgimigli M.
Curr Cardiol Rep. 2017 Jan;19(1):2. ***Equally contributed. IF: 1.958**

Chapter 2.10 Short term versus long term dual antiplatelet therapy after implantation of drug eluting stent in patients with or without diabetes: Systematic review and meta-analysis of individual participant data from randomised trials.
Gargiulo G, Windecker S, da Costa BR, Feres F, Hong MK, Gilard M, Kim HS, Colombo A, Bhatt DL, Kim BK, Morice MC, Park KW, Chieffo A, Palmerini T, Stone GW, Valgimigli M.
BMJ. 2016 Nov 3;355:i5483. **IF: 23.259**

Chapter 2.11 A Critical Appraisal on Aspirin in Secondary Prevention: Is Less More?
Gargiulo G, Windecker S, Vranckx P, Gibson CM, Mehran R, Valgimigli M.
Circulation. 2016 Dec 6;134(23):1881-1906. **IF: 18.880**

Chapter 2.12 Ischemic and Bleeding Outcomes in Elderly Patients Undergoing a Prolonged versus Shortened Duration of Dual Antiplatelet Therapy after Percutaneous Coronary Intervention. Insights from the PRODIGY randomized trial.
Piccolo R, Magnani G, Ariotti S, **Gargiulo G**, Marino M, Santucci A, Franzone A, Tebaldi M, Heg D, Windecker S, Valgimigli M.
EuroIntervention. 2017 Jan 3;12(13). pii: EIJ-D-16-00497. **IF: 4.417**

Chapter 2.13 Impact of Chronic Kidney Disease on 2-Year Clinical Outcomes in Patients Treated with 6-Month or 24-Month DAPT Duration: An Analysis from the PRODIGY Trial.
Gargiulo G, Santucci A, Piccolo R, Franzone A, Ariotti S, Baldo A, Esposito G, Moschovitis A, Windecker S, Valgimigli M.
Catheter Cardiovasc Interv. 2017 Oct 1;90(4):E73-E84. **IF: 2.602**

Chapter 2.14 Deciding on the Duration of Dual Antiplatelet Therapy-When the Choice Between 2 Evils Is Still Evil.
Valgimigli M, **Gargiulo G**.
JAMA Cardiol. 2017 May 1;2(5):488-489. **10.133**

Chapter 2.15 Use of the Dual Antiplatelet Therapy (DAPT) Score to Guide Treatment Duration after Percutaneous Coronary Intervention.
Piccolo R, **Gargiulo G**, Franzone A, Santucci A, Ariotti S, Baldo A, Tumscitz C, Moschovitis A, Windecker S, Valgimigli M.
Ann Intern Med. 2017 Jul 4;167(1):17-25. **IF: 19.384**

Chapter 2.16 DAPT Duration after Drug-Eluting Stent Implantation: No News is Good News.
Valgimigli M, **Gargiulo G**.
JACC Cardiovasc Interv. 2017 Jun 26;10(12):1211-1214. **IF: 9.881**

Chapter 2.17 To EncourAGE Individualized DAPT Duration After DES Implantation: A New pAGE of an Intriguing Book.**Gargiulo G**.
JACC Cardiovasc Interv. 2018 Mar 12;11(5):444-447. **IF: 9.881**

Part 3. Trade-off for ischemia and bleeding and optimal clinical outcomes during and after transcatheter aortic valve implantation (TAVI)

Optimal antithrombotic therapy during and after TAVI

Chapter 3.1 Antithrombotic therapy in TAVI: changing concepts.
Gargiulo G, Collet JP, Valgimigli M.
EuroIntervention. 2015 Sep;11 Suppl W:W92-5. **IF: 4.417**

Chapter 3.2 Terapia antitrombotica nei pazienti sottoposti a impianto transcatetere di valvola aortica.
Gargiulo G, Valgimigli M.
Giornale Italiano di Cardiologia (Rome). 2016 Jun;17(6 Suppl 2):4S-10.

Chapter 3.3 Antithrombotic therapy after transcatheter aortic valve implantation: a new piece of the still unresolved puzzle.
Gargiulo G, Valgimigli M.
J Thorac Dis. 2017 Nov;9(11):4260-4265. **IF: 1.804**

Risk stratification and optimization of clinical outcomes in patients undergoing TAVI

Chapter 3.4 Transcatheter Aortic Valve Implantation Versus Surgical Aortic Valve Replacement. A Systematic Review and Meta-analysis.
Gargiulo G, Sannino A, Capodanno D, Barbanti M, Buccheri S, Perrino C, Capranzano P, Indolfi C, Trimarco B, Tamburino C, Esposito G.
Ann Intern Med. 2016 Sep 6;165(5):334-44. **IF: 19.384**

Chapter 3.5 A Meta-analysis on the Impact of Pre-existing and New-Onset Atrial Fibrillation on Clinical Outcomes in Patients Undergoing Transcatheter Aortic Valve Implantation.
Sannino A*****, **Gargiulo G***, Schiattarella GG, Perrino C, Stabile E, Losi MA, Galderisi M, Izzo R, De Simone G, Trimarco B, Esposito G.
EuroIntervention. 2016 Oct 10;12(8):e1047-e1056. ***Equally contributed. IF: 4.417**

Chapter 3.6 New-onset atrial fibrillation and increased mortality after transcatheter aortic valve implantation: a causal or spurious association?
Gargiulo G, Capodanno D, Sannino A, Barbanti M, Perrino C, Capranzano P, Stabile E, Indolfi C, Trimarco B, Tamburino C, Esposito G.
Int J Cardiol. 2016 Jan 15;203:264-6. **IF: 4.034**

Chapter 3.7 Meta-analysis of Effect of Body Mass Index on Outcomes after Transcatheter Aortic Valve Implantation.
Sannino A, Schiattarella GG, Toscano E, **Gargiulo G**, Giugliano G, Galderisi M, Losi MA, Stabile E, Cirillo P, Imbriaco M, Grayburn PA, Trimarco B, Esposito G.
Am J Cardiol. 2017 Jan 15;119(2):308-316. **IF: 3.172**

Chapter 3.8 Renal dysfunction and transcatheter aortic valve implantation.
Barbanti M*, **Gargiulo G***, Tamburino C
Expert Rev Cardiovasc Ther. 2016 Dec;14(12):1315-1323. ***Equally contributed.**

Chapter 3.9 Impact of Renal Dysfunction on Results of Transcatheter Aortic Valve Replacement Outcomes in a Large Multicenter Cohort.
Codner P, Levi A, **Gargiulo G**, Praz F, Hayashida K, Watanabe Y, Mylotte D, Debry N, Barbanti M, Lefèvre T, Modine T, Bosmans J, Windecker S, Barbash I, Sinning JM, Nickenig G, Barsheshet A, Kornowski R.
Am J Cardiol. 2016 Dec 15;118(12):1888-1896. **IF: 3.172**

Chapter 3.10 Predictors of 1-Year Mortality After Transcatheter Aortic Valve Implantation in Patients With and Without Advanced Chronic Kidney Disease.
Levi A, Codner P, Masalha A, **Gargiulo G**, Praz F, Hayashida K, Watanabe Y, Mylotte D, Debry N, Barbanti M, Lefèvre T, Modine T, Bosmans J, Windecker S, Barbash I, Sinning JM, Nickenig G, Barsheshet A, Kornowski R.
Am J Cardiol. 2017 Dec 1;120(11):2025-2030. **IF: 3.172**

Summary and conclusions

Curriculum vitae

List of publications

Acknowledgements

Introduction

Coronary artery disease (CAD) and Percutaneous coronary intervention (PCI)

CAD and relative morbidity are the leading cause of mortality in western countries. Since its birth in 1977, PCI has developed a central role to treat stable and unstable CAD and improve its prognosis. Today PCI is a milestone for CAD treatment and, accordingly, the number of procedures across Europe, both for stable and unstable CAD, increasingly growth in the last decade[1-3]. The implementation of refined treatment strategies, better devices and more efficacious pharmacological treatment to reduce the occurrence of ischemic complications early and late after PCI, reduced the burden of cardiovascular mortality. The inhibition of coagulation and platelet activity is essential to maintain the immediate results of PCI and prevent complications and recurrence of ischemic/thrombotic events; therefore, both anticoagulant and antiplatelet agents represent the mainstay of pharmacotherapy in patient undergoing PCI[1-3]. Even after PCI, it is crucial to prevent ischemic complications, and dual antiplatelet therapy (DAPT), constituted by the association of aspirin and an inhibitor of the platelet receptor P2Y12, became a pivotal pharmacological treatment after PCI, preventing both stent and non-stent related ischemic events[4]. On the other hand, the strengthening of antithrombotic therapy and the development of more potent drugs warranted special interest to the balance between the desirable antithrombotic effects and the increased risk of bleeding, a balance which has become a matter of great discussion and a topic of relevant scientific research[5,6]. Indeed, while these therapies prevent from ischemic events, they carry a risk of major and clinically relevant bleeding complications, which have been clearly found to affect morbidity and mortality at least as much as ischemic recurrences[5,6].

For years unfractionated heparin (UFH) has been the unique anticoagulant to be used before and during PCI, but some limitations, such as the need for ACT monitoring (related to its variable dose-response relationship with nonlinear pharmacokinetics and poor predictable effects), a narrow therapeutic window, platelet activation, and the potential for inducing thrombocytopenia (HIT) and HIT-thrombosis syndrome. For these reasons, during the last decades, studies have been conducted to test new anticoagulants with more pharmacologic and clinical advantages. Among them, the most studied is bivalirudin, a 20-amino acid synthetic polypeptide with a short half-life, which binds directly to circulating and fibrin-bound thrombin, blocking its enzymatic activity. Many studies have been conducted so far, and there is still great interest into such a comparison due to the potential to reduce bleeding events compared with UFH, despite some concerns have been raised in terms of stent thrombosis risks[7-12].

DAPT type and duration has been the focus of several trials in the last twenty years[4]. Evidence from multiple trials demonstrated that the beneficial anti-ischemic effect of P2Y12-inhibitors implemented on top of aspirin is linearly related to the pharmacological potency and the overall duration of treatment[13-16]. Nevertheless, the implementation of more potent or prolonged treatments raised the issue of a proportional increase of bleeding complications[13-17]. Bleedings are far from being innocent bystanders, and such complications both during and after PCI have been shown to significantly impact mortality in a similar or even greater magnitude than coronary ischemic events[5,6].

Important lines of research during last years have been focused to reduce ischemic and bleeding events. The use of the radial approach for coronary angiography and /or PCI, as compared to the more traumatic femoral

approach, has demonstrated a significant reduction of peri-procedural bleeding[1,18]. This holds particularly true in patients with ACS, when more potent antithrombotic drugs are used, increasing bleeding liability[1,18].

Stent type selection, and subsequent antiplatelet treatment, has also been considered an important factor for the ischemia/bleeding balance after PCI. Since the introduction of first-generation drug-eluting stents (DES), which were developed to reduce in-stent restenosis, concern was raised about their higher thrombogenicity, especially for late or very late events (>12 months after intervention)[19]. As a reaction to this preliminary data, the community and international guidelines took position for prolonging DAPT in patients treated with DES to at least 12 months. This practice, initially advocated for first generation DES, has been automatically translated also to second-generation DES despite their technical improvements (i.e. reduced strut-thickness, more biocompatible or resorbable drug carriers). Hence, since longer DAPT was recommended after DES implantation, it was common practice to use bare-metal stents (BMS) in patients deemed at high bleeding risk, despite no direct comparison between these two strategies was available. However, during last few years, important evidence has supported the use of DES over BMS even in patients at high bleeding risk[20-23], and stent type is not recommended to be a driver of the decision-making on the optimal DAPT duration[4].

Aortic stenosis (AS) and Transcatheter aortic valve implantation (TAVI)

AS has become the most frequent type of VHD in Europe and North America[24]. It primarily presents as calcific AS in adults of advanced age (2–7% of the population >65 years). The second most frequent aetiology, which dominates in the younger age group, is congenital, whereas rheumatic AS has become rare. Calcific AS is a chronic, progressive disease[24]. During a long latent period, patients remain asymptomatic. The duration of the asymptomatic phase varies widely between individuals. Sudden cardiac death is a frequent cause of death in symptomatic patients but appears to be rare in the truly asymptomatic (<1% per year), even in very severe AS[24]. As soon as symptoms occur, the prognosis of severe AS is dismal, with survival rates of only 15–50% at 5 years. Early therapy should be strongly recommended in all symptomatic patients with severe aortic stenosis because of their dismal spontaneous prognosis[24]. The only exceptions are patients with severe comorbidities indicating a survival of <1 year and patients in whom severe comorbidities or their general condition at an advanced age make it unlikely that the intervention will improve quality of life or survival. For more than 50 years, surgical aortic valve replacement (SAVR) has been the standard of care for patients with severe symptomatic AS, improving outcomes and prolonging the lives of these patients. The first human implantation of a percutaneous implantable prosthetic heart valve composed of 3 bovine pericardial leaflets mounted within a balloon-expandable stent was performed in Rouen on 16 April 2002 in a 57-year-old desperately ill man in cardiogenic shock, with critical aortic stenosis, subacute leg ischemia deemed inoperable due to multiple comorbidities (valve replacement had been declined for this patient, and balloon valvuloplasty had been performed with nonsustained results) [25]. Since then, TAVI has dramatically evolved, devices and procedural techniques have rapidly improved and results of randomized clinical trials have revolutionized the current treatment of severe aortic stenosis leading today to more than 300,000 procedures performed worldwide in more than 1,000 centres and 65 countries[25,26]. Fifteen years after the first-in-man case, we can consider TAVI, with its explosive potential, as one of the major medical breakthroughs of the past decade in cardiology[25,26]. A large

body of studies have addressed the issue of the optimization of risk stratification and clinical outcomes in patients undergoing TAVI, and explored the comparison of TAVI with SAVR[25,26]. Technological improvements and favourable clinical outcomes allowed to clearly establish the role of TAVI as the recommended strategy compared with medical therapy for inoperable patients, and alternative to surgery for high-risk patients, reaching more recently also the appropriate scientific evidence to recommend this procedure in patients at intermediate risk[24]. Furthermore, trials among low-risk patients are ongoing and evidence on feasibility and safety of TAVI in other clinical settings (treatment of patients with bicuspid aortic valve, pure native aortic regurgitation, degenerated surgical bioprosthetic valves or those with symptomatic moderate aortic stenosis or asymptomatic severe AS) is being accumulated[25,26]. However, ischemic and bleeding events soon after or at long-term after TAVI remain high, advocating dedicated investigations on optimal antithrombotic therapy even in this clinical setting [25-27]. For the post-procedural antithrombotic therapy, based on the increased thrombotic risks related to TAVI valve structure, DAPT with aspirin (indefinitely) and clopidogrel (1 to 6 months)—in the absence of a specific indication for anticoagulation—has been a widely accepted empirical treatment, which was incorporated into practice guidelines[24-28]. However, the limited evidence available has not clearly supported benefits of DAPT over aspirin alone, rather showed potential risks in terms of increased risk of bleeding complications[28]. Additionally, there are arguments supporting the preferential use of oral anticoagulation (OAC) instead of antiplatelet agents, including the uncertainties about the exact mechanisms causing thrombotic events after TAVI, the high rates of pre-existing and new-onset atrial fibrillation and the evidence that leaflet thrombosis, even subclinical, is not rare and might require OAC. However, while preventing such thrombotic complications, OAC therapy also increases the bleeding risks, so, again, as for patients undergoing PCI, clinicians have to face with the difficult decision-making to select the optimal approach to balance ischemia and bleeding in order to offer the most appropriate prevention of thrombotic events while minimizing bleeding complications.

Like Bellerophon searching for and fighting with the Chimera, clinicians should be aware of the trade-off of both bleeding and ischemia and their impact on patients' health, thus, should search for the optimal therapy which has not to face with a single animal (ischemia or bleeding), rather must account and balance for the effects on both these entities.

In light of the evidence produced by several observational and randomized clinical trials in patients undergoing PCI or TAVI, growing importance has been given to the selection of the right patient population for specific treatment strategies (including different types and duration of antithrombotic drugs, vascular approaches, stent types, type of revascularization or aortic valve replacement used, etc.). Hence, the individualization of the treatment type and duration based on the single-patient risk profile appears a promising approach in order to deliver the proper treatment to the right recipient, in line with the principles of precision medicine.

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Part 1

Trade-off for ischemia and bleeding during and immediately after percutaneous coronary interventions:

Selecting the optimal antithrombotic strategy

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Bivalirudin versus heparin with or without glycoprotein IIb/IIIa inhibitors in patients with STEMI undergoing primary PCI: An updated meta-analysis of 10,350 patients from five randomized clinical trials

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Abstract

Aims: To evaluate the impact of bivalirudin versus heparin on efficacy and safety outcomes of ST-segment elevation myocardial infarction (STEMI) patients undergoing primary percutaneous coronary intervention (PCI) and to explore the impact of differential use (bailout vs. routine) of glycoprotein IIb/IIIa inhibitors (GPI).

Methods and Results: Five randomized controlled trials encompassing 10,350 patients were included. Primary efficacy and safety endpoints were all-cause death and major bleeding, respectively. All-cause death at 30 days did not significantly differ with bivalirudin compared to heparin (odds ratio (OR) 0.97, 95% confidence interval (CI) 0.74–1.28; *P*=0.84). Major bleeding was significantly reduced by bivalirudin compared to heparin (OR 0.58, 95% CI 0.40–0.85; *P*=0.005). Bivalirudin use was associated with non-significantly different rates of 30-day definite stent thrombosis (ST) (OR 1.71, 95% CI 0.84–3.49; *P*=0.14), albeit with higher rates of acute ST (OR 3.55, 95% CI 1.67–7.56; *P*=0.001) and non-significantly different rates of subacute ST (OR 0.86, 95% CI 0.46–1.61; *P*=0.64). There were non-significant differences in the 30-day rates of reinfarction (OR 1.47, 95% CI 0.94–2.30; *P*=0.10) and cardiovascular death (OR 0.76, 95% CI 0.56–1.02; *P*=0.07). There were no significant interactions between bailout versus routine GPI use in the heparin arm for any of the safety or efficacy outcomes (all $P_{interaction}$>0.10).

Conclusions: Bivalirudin compared with heparin was associated with comparable 30-day rates of mortality with reduced major bleeding, at the price of an increased risk of acute ST, with non-significant differences in the overall 30-day rates of ST and reinfarction. Intended use of GPI in the heparin arm did not significantly modify the treatment effects of bivalirudin. Given the important differences between trials, as well as evolution in technique and adjunct pharmacotherapy, further randomized trials are warranted to discriminate whether there are substantial safety and efficacy differences between these agents during primary PCI in STEMI.

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Introduction

According to European and US guidelines, primary percutaneous coronary intervention (PCI) is the standard of care for patients with ST-segment elevation myocardial infarction (STEMI).[1,2] Among anticoagulation alternatives to support PCI, the direct antithrombin inhibitor bivalirudin was provided with a class I recommendation with level of evidence B based on data from the Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial.[3,4] In HORIZONS-AMI, bivalirudin reduced major bleeding at 30 days and cardiovascular mortality at 3 years compared with unfractionated heparin and routine use of a glycoprotein IIb/IIIa inhibitor (GPI), but increased the rates of acute stent thrombosis (ST).

PCI practice for STEMI has evolved in recent years, with more frequent pre-hospital initiation of antithrombotic treatment, widespread use of radial access, introduction of potent platelet $P2Y_{12}$ inhibitors (prasugrel, ticagrelor), and use of GPI restricted to bailout situations at selected centers. These changes were incorporated in the European Ambulance Acute Coronary Syndrome Angiography; (EUROMAX) trial, which demonstrated consistent results with HORIZONS-AMI.[5–8] Subsequently, conflicting results from three additional randomized controlled trials (RCTs) of bivalirudin versus heparin in STEMI have been published and/or presented at major cardiovascular congresses,[9–11] with one single-center trial[11] raising concerns regarding the risk–benefit profile of bivalirudin compared with heparin monotherapy, leading to a downgrade of the recommendation for bivalirudin in primary PCI (from I to IIa) in the recently published European guidelines for myocardial revascularization.[12] Following these events, contrary results were reported from a large multicenter trial reconfirming the safety benefit of bivalirudin compared to heparin monotherapy, with similar rates of adverse ischemic events at 30 days and 1 year.[9]

The manner in which GPI were used in the heparin arm (whether routine and/or for bailout only) may be an important modifying factor when interpreting the risk–benefit ratio of bivalirudin. Two meta-analyses of RCTs conducted across the broad spectrum of PCI (elective and acute coronary syndromes) concluded that bivalirudin, as compared to heparin without planned GPI use, reduces the risk of major bleeding at the expense of a higher risk of acute ST.[13,14] However, those meta-analyses did not have STEMI as a primary focus and did not include the full dataset from the recently presented large-scale Bivalirudin in Acute Myocardial Infarction vs. Glycoprotein IIb/IIIa and Heparin: a Randomised Controlled Trial (BRIGHT),[9] including ST and long-term outcomes. In addition, the potential modifying effect of different GPI use strategies in primary PCI RCTs of bivalirudin has not fully been examined. We therefore performed an updated meta-analysis of RCTs to evaluate the impact of bivalirudin on efficacy and safety outcomes of patients with STEMI undergoing primary PCI compared to heparin with or without routine GPI use.

Methods

The study was designed in compliance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) standards.[15] Full description of the study methodology is provided in the Online Supplement. Briefly, the analysis was restricted to studies published or presented at a major cardiovascular meeting through September 2014 that met all the following inclusion criteria: randomized trial of bivalirudin versus heparin; study population of patients with acute myocardial infarction (at least 85% STEMI) undergoing PCI; follow-up outcomes reported for at least 30 days. The primary efficacy and safety endpoints were the 30-day incidences of all-cause death and protocol-defined major bleeding, respectively.

Results

Search results and study details

The initial search strategy identified 300 citations, of which 12 were retrieved for full text review. Five trials encompassing a total of 10,350 patients met all inclusion criteria and had no exclusion criteria (Figure 1). Study details and related interventions are provided in the Online Supplement and in Supplementary Table S1. The mean age of patients was 61 years. Seventy-seven per cent were men, 16% presented with diabetes mellitus and 44% were treated with radial access (Supplementary Table S2).

Thirty-day results

All trials reported 30-day all-cause death, reinfarction, stroke, revascularization, definite ST and major bleeding rates. Four trials reported 30-day cardiovascular mortality and definite or probable ST (which was further classified as acute (<24 hours) and subacute (1–30 days)).

The pooled data showed no significant differences in all-cause mortality (primary efficacy outcome) with bivalirudin versus heparin (2.8% vs. 2.7%, odds ratio (OR) 0.97 (0.74–1.28); P=0.84; Supplementary Table S3, Figure 2), with low heterogeneity (I^2=18%), no asymmetry in the funnel plot, and no systematic bias apparent across studies (Begg's test P=0.62). Removal of individual studies did not significantly influence the point estimate (Supplementary Table S4). There was no significant difference in 30-day cardiovascular mortality with bivalirudin compared to heparin (2.0% vs. 2.5%, OR 0.76 (0.56–1.02); P=0.07; Supplementary Table S3, Figure 3), nor heterogeneity (I^2=0), evidence of asymmetry in the funnel plot, or systematic bias across studies (Begg's test P=0.17). The magnitude of the point estimate for cardiovascular mortality was influenced by the HORIZONS-AMI trial (Supplementary Table S4).

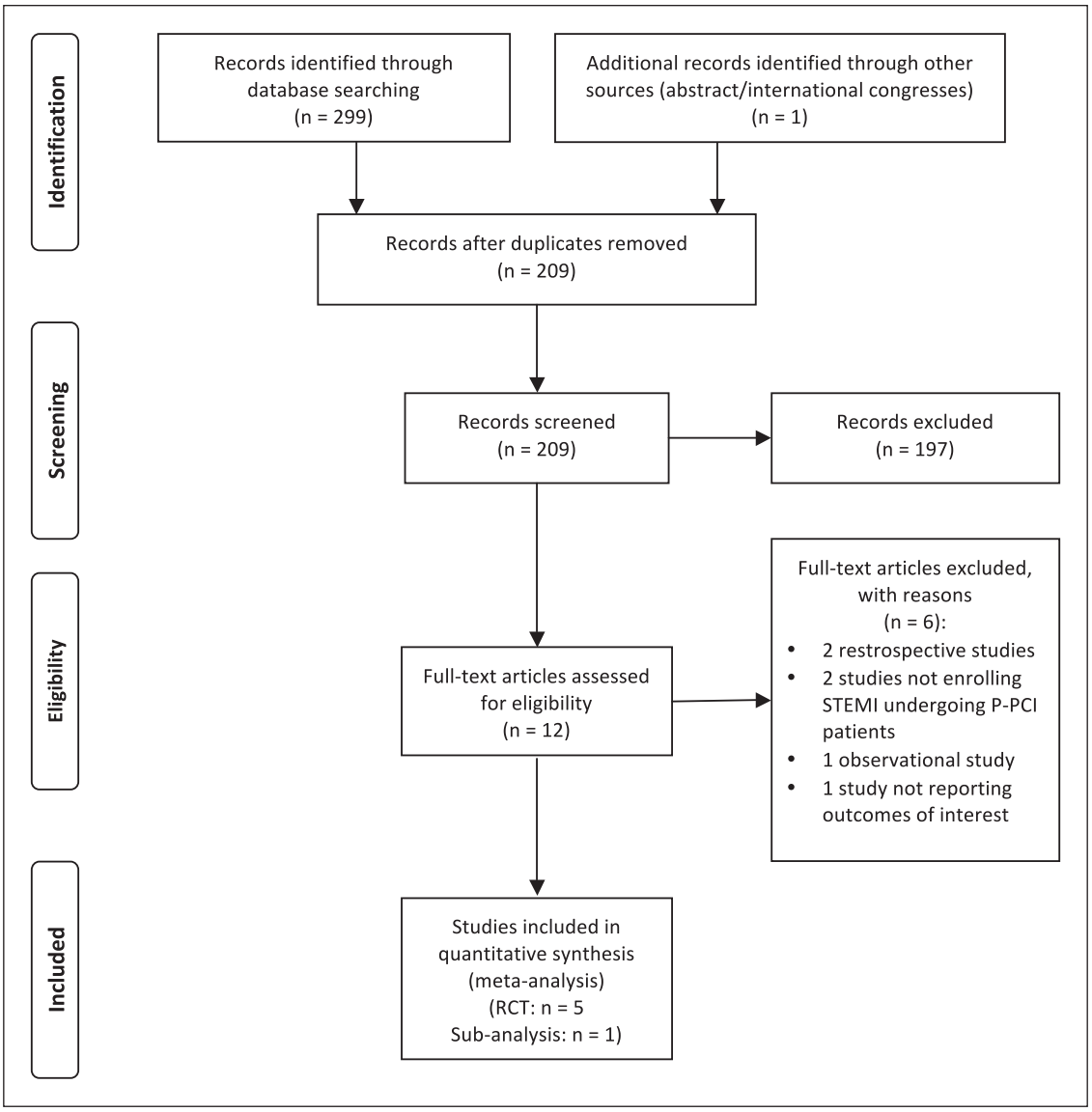

Figure 1. Flow diagram. Studies included in the meta-analysis. P-PCI: primary percutaneous coronary intervention; RCT: randomized controlled trial; STEMIL ST-elevation myocardial infarction.

Definitions of reinfarction used across studies are described in Supplementary Table S5. There was no significant difference in 30-day reinfarction with bivalirudin compared to heparin (1.9% vs. 1.2%, OR 1.47 (0.94–2.30); *P*=0.10; Supplementary Table S3, Figure 3), with mild heterogeneity (I^2=37%) and no evidence of asymmetry in the funnel plot or systematic bias across studies (Begg's test *P*=0.62). Removal of HEAT-PPCI or EUROMAX reduced the magnitude of the point estimate (Supplementary Table S4).

There was no significant difference in 30-day stroke with bivalirudin compared to heparin (0.8% vs. 0.9%, OR 0.87 (0.56–1.37); *P*=0.55; Supplementary Table S3, Figure 3), with no evidence of heterogeneity (I^2=0), asymmetry in the funnel plot, or systematic bias apparent across studies (Begg's test *P*=0.14). None of the studies unduly influenced the point estimate (Supplementary Table S4).

There was no significant difference in 30-day revascularization with bivalirudin compared to heparin (2.4% vs. 1.6%, OR 1.46 (0.95–2.25); *P*=0.09; Supplementary Table S3, Figure 2), with mild heterogeneity (I^2=45%) and no evidence of asymmetry in the funnel plot or systematic bias across studies (Begg's test *P*=0.62). Removal of HEAT-PPCI reduced the magnitude of the point estimate (Supplementary Table S4).

There was no significant difference in 30-day definite (1.9% vs. 1.0%, OR 1.71 (0.84–3.46); *P*=0.14; Supplementary Table S3, Figure 4) and definite or probable ST (2.1% vs. 1.2%, OR 1.77 (0.84–2.73); *P*=0.13; Supplementary Table S3, Figure 4) with bivalirudin compared to heparin. The risk of acute ST was significantly higher with bivalirudin (1.4% vs. 0.4%, OR 3.55 (1.67–7.56); *P*=0.001; Supplementary Table S3, Figure 4), with no significant differences in the risk

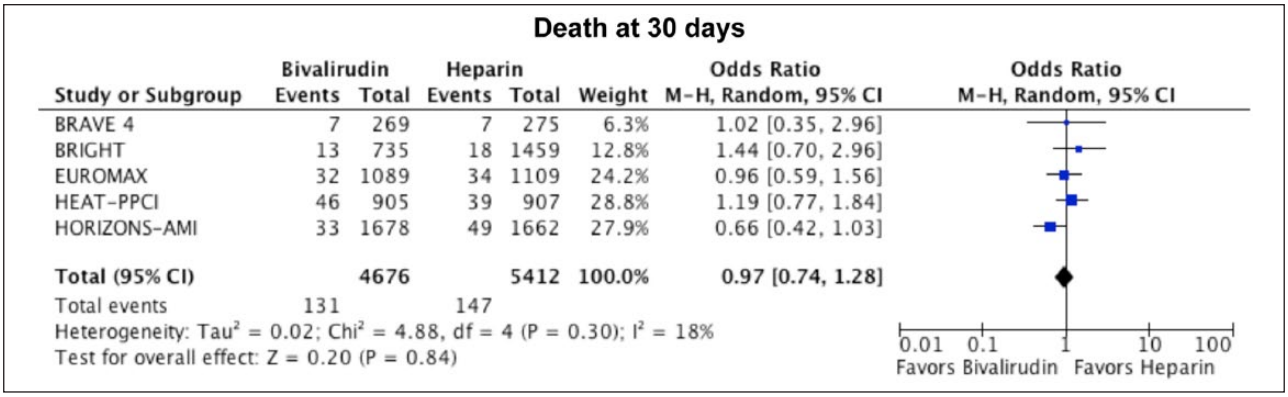

Figure 2. All-cause death. Thirty-day random-effects odds ratio and 95% confidence interval for all-cause death.

of subacute ST (0.8% vs. 0.8%, OR 0.86 (0.46–1.61); *P*=0.64; Supplementary Table S3, Figure 4). Moderate heterogeneity was observed for definite ST and definite or probable ST and mild heterogeneity for acute and subacute ST. There was no asymmetry in the funnel plot for any of the ST endpoints or systematic bias across studies (Begg's test *P*=NS for all endpoints). The point estimates of definite ST and definite or probable ST became significant after the exclusion of BRIGHT, whereas the point estimate of acute ST became non-significant after the exclusion of HORIZONS-AMI or HEAT-PPCI. None of the studies was found to influence the point estimate for subacute ST (Supplementary Table S4). The OR for acute ST was 1.98 (0.17–23.50; *P*=0.59) in analyses restricted to studies with routine post-PCI bivalirudin infusion and 4.04 (2.01–8.11; *P*<0.0001) in analyses restricted to studies with no routine post-PCI bivalirudin infusion ($P_{interaction}$=0.59; Table 1).

Definitions of protocol-defined major bleeding used across studies are described in Supplementary Table S6. The pooled data showed a significant reduction in major bleeding with bivalirudin (3.9% vs. 7.2%, OR 0.58 (0.40–0.85); *P*=0.005; Supplementary Table S3, Figure 5), with moderate heterogeneity (I^2=64%), and no evidence of asymmetry in the funnel plot or systematic bias across studies (Begg's test *P*=1.00). The reduction in major bleeding with bivalirudin persisted if BARC 1–5 bleeding in BRIGHT (the study definition) was replaced with BARC 2–5 bleeding (OR 0.57 (0.37–0.88); *P*=0.01) or BARC 3–5 bleeding (OR 0.61 (0.40–0.92); *P*=0.02). Although the risk of major bleeding remained numerically lower with bivalirudin, removal of HORIZONS-AMI, EUROMAX or BRIGHT one at a time resulted in loss of significance for the point estimate, and removal of HEAT-PPCI substantially strengthened the point estimate (Supplementary Table S4).

GPI interaction

There were no significant interactions between the pooled point estimate for any safety or efficacy endpoint of the meta-analysis and the modality of GPI use in the heparin arm (all $P_{interaction}$>0.10; Figure 6). The OR for major bleeding was 0.64 (0.33–1.23) in analyses restricted to studies with bailout GPI use and 0.49 (0.36–0.67) in analyses restricted to studies with routine GPI use ($P_{interaction}$=0.49; Figure 6).

Long-term results

BRIGHT reported 1-year event rates and HORIZONS-AMI reported 3-year event rates. The outcomes of the pooled analysis of the two trials at the longest available follow up are illustrated in Supplementary Table S7. Bivalirudin was associated with a reduced risk of all-cause mortality compared with heparin (OR 0.77 (0.61–0.99); *P*=0.04), with no heterogeneity (I^2=0). Conversely, there were no significant differences in reinfarction (OR 0.81 (0.62–1.06); *P*=0.12; I^2=5), stroke (OR 0.78 (0.51–1.22); *P*=0.28; I^2=0), revascularization (OR 1.21 (1.00–1.47); *P*=0.09; I^2=0), and definite or probable ST (OR 0.88 (0.65–1.20); *P*=0.43; I^2=0). There was a trend towards less bleeding with bivalirudin (OR 0.50 (0.24–1.03); *P*=0.06), with moderate heterogeneity (I^2=54).

Discussion

The major findings from this meta-analysis of five randomized trials are summarized as follows. First, in patients with STEMI undergoing primary PCI, bivalirudin reduced the 30-day risk of major bleeding with similar mortality compared with heparin. Second, bivalirudin was associated with a greater rate of ST within the first 24 hours of the procedure. Third, these results were consistent whether the control arm was heparin with the routine use of GPI or heparin alone with provisional GPI reserved for bailout. Fourth, mild-to-moderate heterogeneity was observed for many of the endpoints and the point estimates for several of the major outcomes were sensitive to the removal of single studies. The results of this meta-analysis should therefore

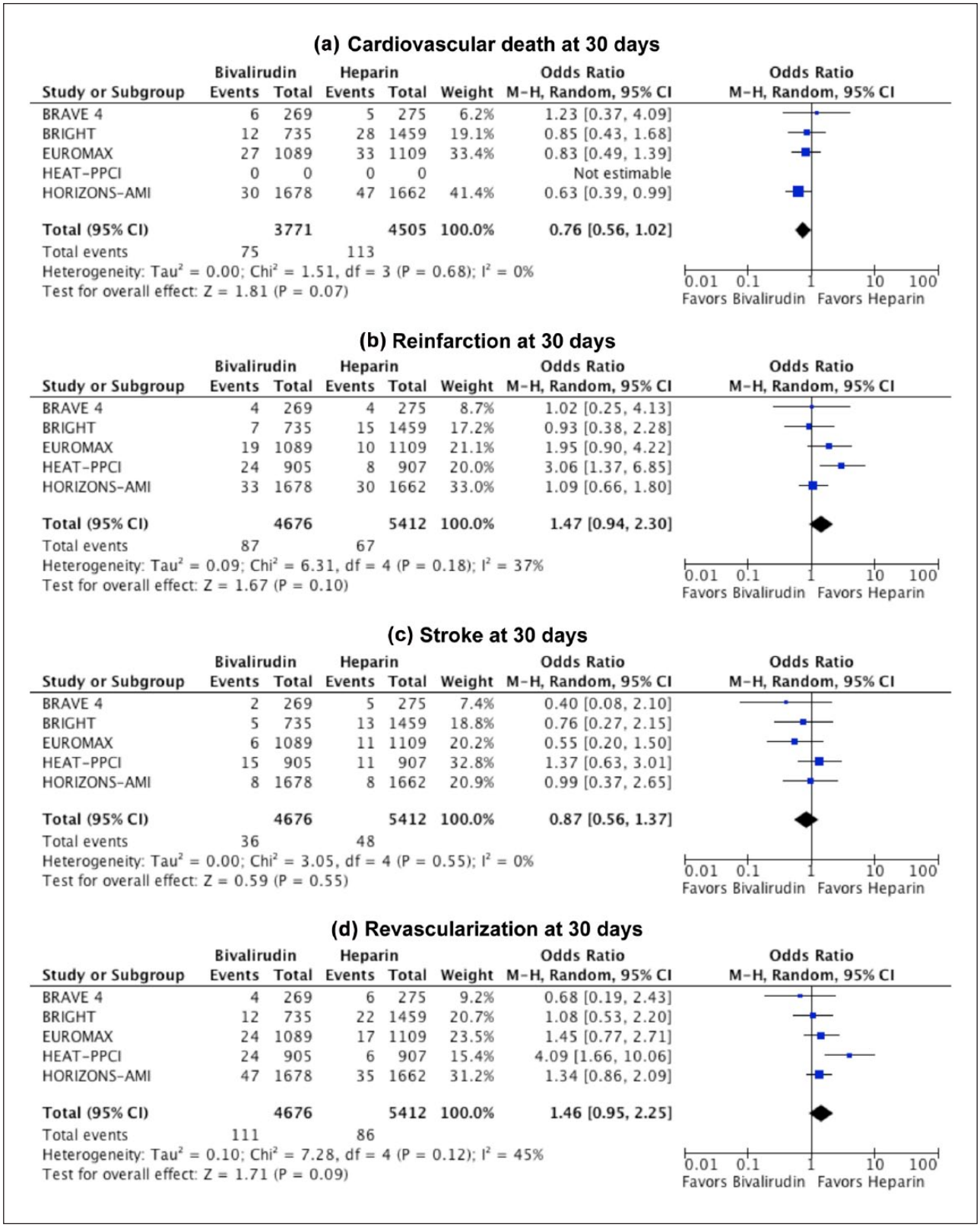

Figure 3. Cardiovascular death, reinfarction, stroke and revascularization. Thirty-day random-effects odds ratios and 95% confidence intervals for cardiovascular death (a), reinfarction (b), stroke (c) and revascularization (d).

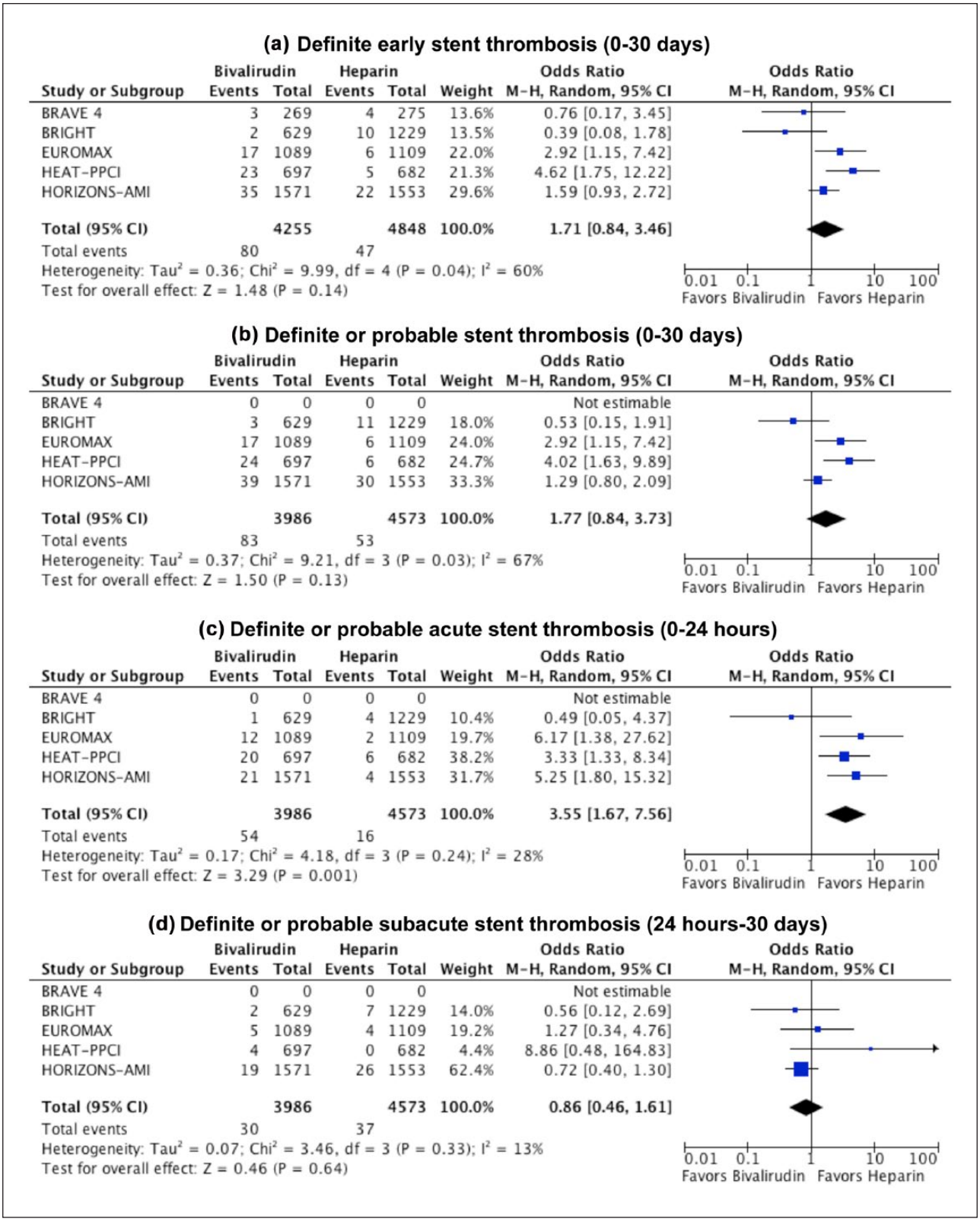

Figure 4. Stent thrombosis. Thirty-day random-effects odds ratios and 95% confidence intervals for 30-day definite (a), 30-day definite or probable (b), acute (c) and subacute (d) stent thrombosis.

Table 1. Stent thrombosis stratified by use of post-procedural bivalirudin infusion.

Outcome	Trials	Patients	OR (95% CI)	*P* level	Chi^2	I^2, %	$P_{interaction}$*
Definite ST							
Routine post-PCI infusion	2	4056	1.17 (0.16, 8.39)	0.88	4.92	80	0.65
No routine post-PCI infusion	3	5047	1.94 (0.81, 4.63)	0.14	5.09	61	
Definite or probable ST**							
Routine post-PCI infusion	2	4056	1.32 (0.25, 6.98)	0.74	4.44	77	0.64
No routine post-PCI infusion	2	4503	2.13 (0.70, 6.47)	0.18	4.79	79	
Acute (0–24 hours) ST**							
Routine post-PCI infusion	2	4056	1.98 (0.17, 23.50)	0.59	3.51	71	0.59
No routine post-PCI infusion	2	4503	4.04 (2.01, 8.11)	<0.0001	0.40	0	
Subacute (24 hours-30 days) ST**							
Routine post-PCI infusion	2	4056	0.91 (0.33, 2.49)	0.85	0.63	0	0.64
No routine post-PCI infusion	2	4503	1.68 (0.16, 17.93)	0.67	2.82	65	

*Test for subgroup differences between studies with routine post-procedural bivalirudin infusion and studies without.
CI: confidence interval; OR: odds ratio; PCI: percutaneous coronary intervention; ST: stent thrombosis.
**Not reported in BRAVE-4.

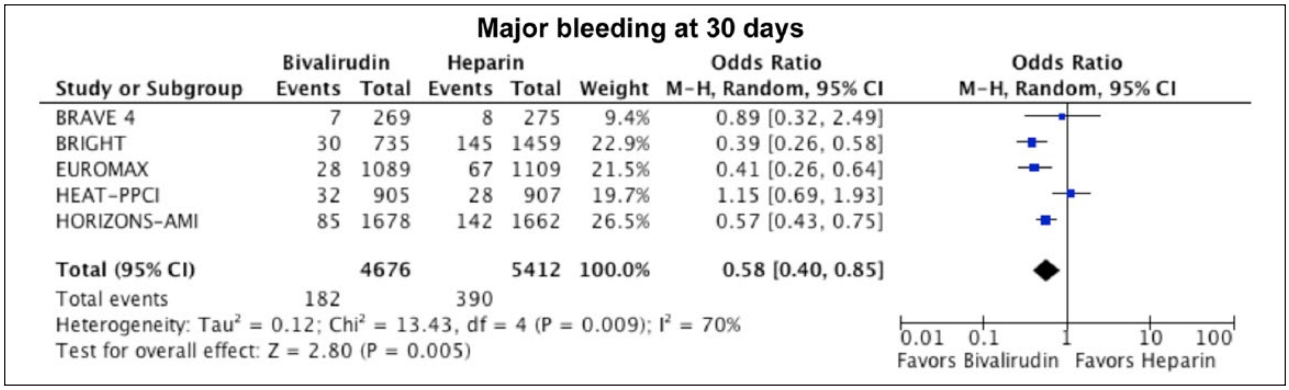

Figure 5. Major bleeding. Thirty-day random-effects odds ratio and 95% confidence interval for protocol-defined major bleeding.

be interpreted with caution given the differences between the included trials.

In the HORIZONS-AMI trial, bivalirudin resulted in reduced rates of major and minor bleeding compared to heparin plus routine GPI in STEMI, with reduced cardiovascular and all-cause mortality at 30 days and 3 years.[3,4] HORIZONS-AMI was also the first trial to report increased rates of acute ST with bivalirudin, a finding subsequently observed in EUROMAX and HEAT-PPCI, but not in BRIGHT or BRAVE-4. In no trial was ST increased with bivalirudin after 24 hours. Differences between trials may explain the inter-study variability in acute ST risk with bivalirudin. Bivalirudin has a short half-life, and the rapid door-to-balloon and procedure times achieved in contemporary trials may have offered minimal anti-thrombin exposure from bivalirudin if the drug was used during the procedure only. In this regard the use of a post-PCI bivalirudin infusion varied across studies, from being not routinely used in HORIZONS-AMI, HEAT-PPCI and BRAVE-4, to being used in most or all patients in EUROMAX (4:1 low-dose:high-dose at operator discretion) and BRIGHT (low-dose). In a post-hoc observation from EUROMAX, the use of a post-procedure bivalirudin infusion for median 4.5 hours at the PCI dose eliminated the acute ST risk after primary PCI.[16] In BRIGHT,[9] the use of a routine low-dose bivalirudin infusion for 4 hours was also associated with the absence of acute ST risk. In the present meta-analysis a significant interaction was not present between the use of a post-PCI bivalirudin infusion and the risk of acute ST, although the risk of acute ST with bivalirudin was significant in analyses restricted to studies in which routine infusion was used, and non-significant in analyses restricted to studies without routine infusion. The routine use of prasugrel may also have reduced the rate of acute ST in BRAVE-4, although given the delayed absorption of $P2Y_{12}$ inhibitors in STEMI[17,18] and the lack of a similar effect in EUROMAX and HEAT-PPCI, this finding may be due to chance. Pending further studies on the association with newer $P2Y_{12}$ inhibitors in STEMI, a 4-hour post-PCI infusion of bivalirudin seems prudent, and was not associated with increased bleeding in either BRIGHT or EUROMAX. Extending the bivalirudin infusion

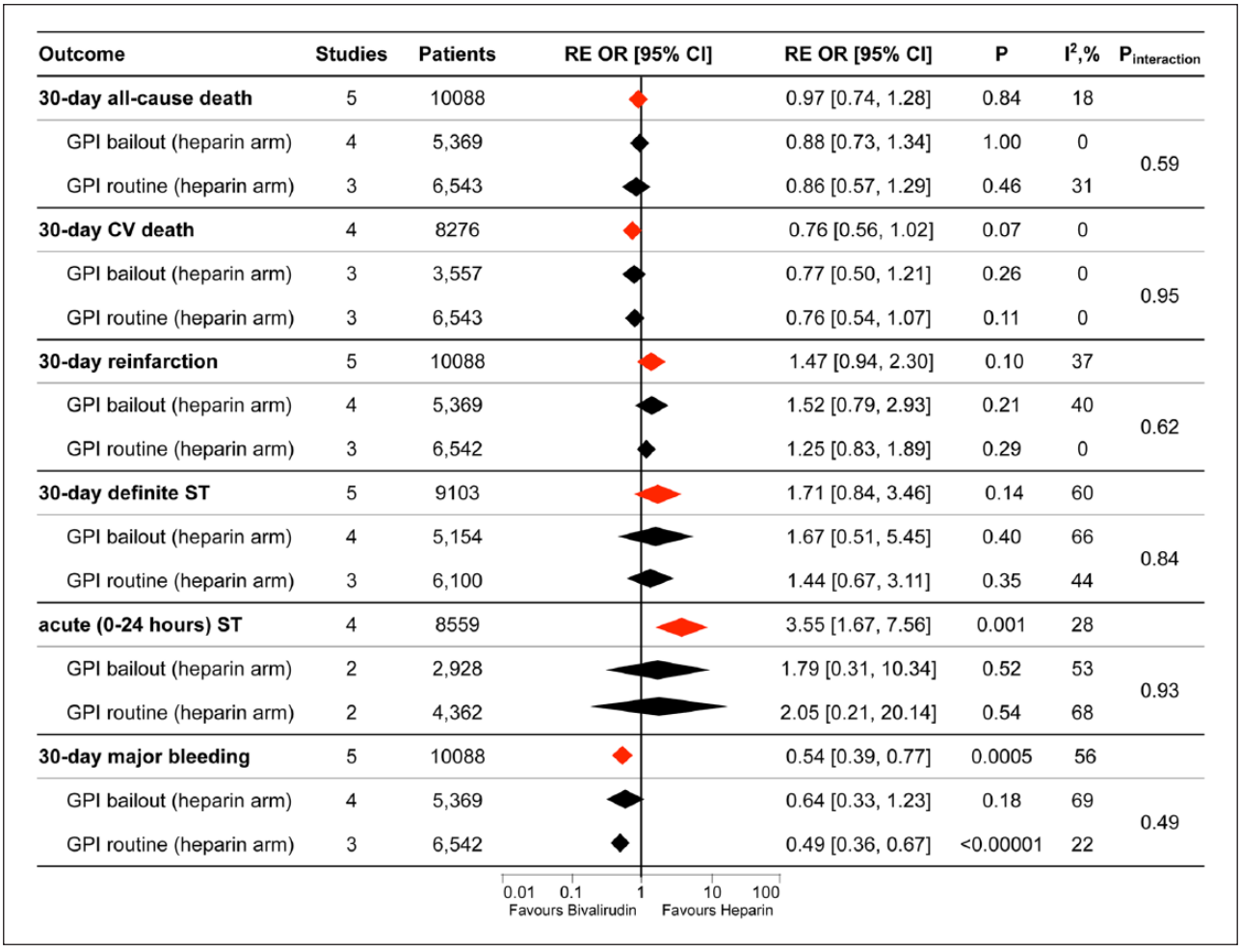

Figure 6. Outcomes of the meta-analysis stratified by GPI use in the heparin arm. Random-effects odds ratio and 95% confidence interval are reported according to GPI use (bailout vs. routine) in the heparin arm. Interaction values for subgroup differences between studies with routine GPI use in the heparin arm and studies with bailout GPI use in the heparin arm are reported. For the purpose of this analysis, the heparin arms of the BRIGHT trial were considered separately in the comparison versus the bivalirudin group.
CV: cardiovascular; GPI: glycoprotein IIb/IIIa inhibitors; OR: odds ratio; RE: random effects; ST: stent thrombosis.

post-procedure may overcome the theoretical treatment gap between the rapid offset of antithrombin therapy with bivalirudin and the slow onset of therapeutic efficacy of antiplatelet drugs in the setting of STEMI.[19] The impact of a prolonged low-dose bivalirudin infusion on the risk–benefit profile of bivalirudin is under further investigation in the Minimizing Adverse Haemorrhagic Events by TRansradial Access Site and Systemic Implementation of angioX (MATRIX) trial.[20]

Other important differences were present between the trials in the present (and previous) meta-analyses that may affect their interpretation. First, radial intervention, which may reduce major bleeding rates, was frequent in EUROMAX, BRIGHT and HEAT-PPCI, but uncommon in HORIZONS-AMI and BRAVE-4. Second, the potent $P2Y_{12}$ inhibitors prasugrel or ticagrelor were frequently used in EUROMAX, HEAT-PPCI and BRAVE-4, but not in HORIZONS-AMI or BRIGHT. Third, in EUROMAX, GPI use in the heparin arm was left to the operator's discretion, but no interaction was present between the treatment effect of bivalirudin and routine versus provisional GPI use.[5–7] Fourth, patients were randomly assigned early during transfer for primary PCI in EUROMAX, which avoided a possible confounding effect of pre-randomization heparin as noted in HORIZONS-AMI. Fifth, in the three-arm randomized BRIGHT trial, bivalirudin was found to reduce the risk of bleeding compared with heparin monotherapy or heparin plus routine GPI,[9] while in HEAT-PPCI, GPI was restricted to bailout use in both the bivalirudin and heparin groups, and an increased risk of acute ST was observed with bivalirudin without a reduction in bleeding.[11] In this regard it should be highlighted that the heparin dose used in heparin monotherapy-treated patients ranged from 70 U/kg in HEAT-PPCI to 100 U/kg in EUROMAX and BRIGHT. Bivalirudin was associated with reduced major bleeding in

EUROMAX and BRIGHT (the studies using a high dose in patients on heparin monotherapy), but not in HEAT-PPCI (which used a lower dose). Sixth, the BRAVE-4 trial was stopped prematurely and showed no differences in bleeding and ischemic endpoints between patients allocated to bivalirudin plus prasugrel compared to heparin plus clopidogrel.[10] The fact that both the antithrombin and $P2Y_{12}$ antagonist were randomized in this trial makes the findings difficult to interpret. Finally, all the trials were multicenter except HEAT-PPCI, which was unique in randomly assigning a near all-comers population, although lacking the external validity and generalizability of multicenter trials.[21]

In our analysis bivalirudin decreased major bleeding. Although this benefit was numerically greater in trials in which GPI use was routine rather than reserved for bailout, the interaction term for GPI use and treatment effect was not statistically significant, consistent with the BRIGHT results and the post-hoc analysis from EUROMAX.[7] These data thus suggest that bivalirudin reduces major bleeding in patients with STEMI undergoing primary PCI compared to heparin alone or heparin plus routine GPI. The significantly higher risk of acute ST with bivalirudin, with no difference in subacute ST, was also independent of GPI use (routine vs. provisional) in the heparin arm. The increased risk of acute ST likely drove trends toward increased 30-day rates of reinfarction and revascularization with bivalirudin treatment as well. No such trends were observed in BRIGHT or BRAVE-4, however, given the absence of an acute ST risk with bivalirudin. Mitigating the acute ST propensity with bivalirudin (e.g. with a 4-hour post-PCI infusion, if proved to be effective) would clearly improve its overall risk–benefit ratio.

Considering the net effects of ischemic and bleeding complications is important. In this regard, the use of bivalirudin rather than heparin (with or without GPI) was associated with a trend towards reduced 30-day cardiovascular mortality, with comparable all-cause mortality. A significant reduction in all-cause mortality was found at long term in the pooled analysis of HORIZONS-AMI and BRIGHT, the only studies reporting a 1-year or longer follow-up. Given the differences in study design and adjunctive therapies between trials it is clear that additional large-scale, adequately powered RCTs (with long-term follow-up) are required to resolve remaining uncertainties.

The definition of reinfarction varied substantially between trials, and the non-significant trend for greater reinfarction seen with bivalirudin was decreased after individually removing EUROMAX or HEAT-PPCI. In this regard these trials stand out in that the bailout rates of GPI were particularly high in the heparin-only arms (25.4% and 13.5%, respectively) compared to the others, a practice of uncertain clinical utility. In addition, door-to-balloon times in HEAT-PPCI were less than 30 minutes (leading to a very short bivalirudin infusion) and the activated clotting times were substantially lower than usually seen with bivalirudin, but not with heparin (a finding difficult to interpret, however, given the use of a non-standard assay). The definitions of protocol-defined major bleeding also varied substantially between trials, with BRIGHT pre-specifying all bleeding as the major safety endpoint. However, bivalirudin use was still associated with reduced rates of major bleeding when only BARC 2–5 or 3–5 bleeding rates from BRIGHT were considered in the meta-analysis.

Study limitations

The results of this meta-analysis are subject to the limitations and differences of the original included studies themselves. Variation in study design (Supplementary Tables S1 and S2), endpoint definitions (Supplementary Tables S5, S6 and S8) and publication bias are limitations of all meta-analyses. All included studies share the limitation of an open-label design. Randomization in EUROMAX was not stratified by intended routine versus bailout GPI use, introducing the possibility of imbalances between groups, although in a pre-specified multivariable analysis the relative effects of bivalirudin were not affected by GPI use pattern. The BRIGHT trial included 12% of patients with non-STEMI; outcomes of the STEMI cohort have not been separately presented, with the exception of ST. Moreover, data from BRIGHT are currently unpublished. The limitations inherent in the single-center HEAT-PPCI design have been discussed, as have the implications of the randomization scheme and early termination of BRAVE-4. In this regard several of the results were sensitive to the HEAT-PPCI results, whereas omitting BRAVE-4 did not significantly change any of the point estimates in our meta-analysis. In addition, the trials varied markedly in the use of pre-randomization heparin and study drug, radial artery access, potent $P2Y_{12}$ inhibitors, post-PCI bivalirudin and heparin infusions or low molecular-weight heparin use, and other factors that could not be completely accounted for in the present analysis (Online Supplement). Finally, follow-up beyond 30 days was available for only two of the studies. The 1–3 year data from HORIZONS-AMI and BRIGHT suggest a sustained or improving risk–benefit profile of bivalirudin over time, but more data are needed in this regard.

Conclusions

In this updated meta-analysis from five RCTs, bivalirudin was found to reduce the 30-day rates of major bleeding with similar survival compared to heparin monotherapy or heparin plus GPI in patients with STEMI undergoing primary PCI. Bivalirudin was associated with an increased risk of acute ST, but not subacute or total ST. Non-significant trends were present for an increased risk of reinfarction and repeat revascularization with bivalirudin, but also of reduced cardiovascular mortality, compared with heparin. Routine versus bailout GPI use in the heparin arm did not significantly modify the risk–benefit ratio of bivalirudin compared with heparin for any of these safety and efficacy endpoints. Bivalirudin was

associated with improved long-term survival based on the available data from two studies. Given differences between the included trials, however, and evolution in technique and adjunct pharmacotherapy, additional large-scale randomized trials (including embedded cost-effectiveness assessment) with long-term follow-up are warranted to determine whether there are clinically relevant differences between bivalirudin and heparin with or without routine GPI in patients with STEMI undergoing primary PCI.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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REVIEW

Developing drugs for use before, during and soon after percutaneous coronary intervention

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ABSTRACT

Introduction: Percutaneous coronary intervention (PCI) is a milestone for treating coronary artery disease (CAD). Antithrombotic therapy is essential to prevent ischemic complications, including the microvascular no-reflow, while minimizing bleeding events.

Areas covered: This overview discusses available and developing drugs for PCI including anticoagulants, antiplatelets and treatment of no-reflow.

Expert opinion: For years unfractionated heparin (UFH) has been the unique anticoagulant to be used before and during PCI. Enoxaparin showed similar efficacy and safety, yet, based on recent trials, bivalirudin has been shown to have some benefits, particularly for patients with ST-segment elevation myocardial infarction (STEMI). The evidence concerning new anticoagulants is still preliminary, except for new oral anticoagulants, particularly rivaroxaban that showed intriguing findings and is currently under investigation. Dual antiplatelet therapy (DAPT) is the standard of care after PCI, but new developments have recently emerged. Indeed, ticagrelor and prasugrel are currently recommended over clopidogrel due to their significant reduction of ischemic events in acute coronary syndrome (ACS) whereas clopidogrel remains the choice in stable CAD. Among new agents, vorapaxar and cangrelor showed positive but limited evidence and might be considered at least in selected patients. Conversely, evidence on effective treatments for no-reflow remains limited and would require future dedicated research.

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1. Introduction

Coronary artery disease (CAD) is the leading cause of morbidity and mortality in western countries and percutaneous coronary interventions (PCIs) have developed a central role in the management of patients with stable or unstable CAD. The inhibition of coagulation and platelet activity is essential to maintain the immediate results of PCI and prevent complications and recurrence of ischemic/thrombotic events; therefore, both anticoagulant and antiplatelet agents represent the mainstay of catheterization-laboratory pharmacotherapy. Conversely, the development of potent drugs warranted special interest to the balance between the desirable antithrombotic effects and the increased risk of bleeding.

Pharmacologic therapy also plays a crucial role in the management of no-reflow phenomenon, one of the most important complications during PCI (especially primary PCI).

Until the year 2000, few pharmacologic agents were available for the cath-lab use, but in the last decade, new antithrombotics have been developed for PCI and others are currently under evaluation. This has revolutionized the pharmacopeia for the treatment of patients undergoing PCI. When the dual antiplatelet therapy (DAPT) concept had been consolidated, clopidogrel became the most popular second antiplatelet to be added to low-dose aspirin, but in recent years, different new $P2Y_{12}$ inhibitors have emerged, changing the common clinical practice. At the same time, the role of glycoprotein IIb/IIIa inhibitors (GPIs) has been redefined and also anticoagulant alternatives to the commonly used unfractionated heparin (UFH) have emerged, such as enoxaparin, bivalirudin and fondaparinux, including other drugs. This study provides a comprehensive yet concise overview of multiple treatment options for patients undergoing PCI. Currently available and developing drugs for the cath-lab use during PCI will be discussed, including anticoagulants, antiplatelets, and therapies for the prevention and treatment of no-reflow.

The MEDLINE database was primarily explored via PubMed to analyze clinical trials, studies, meta-analyses, and reviews relevant to this topic. The registry ClinicalTrials.gov was also referred to evaluate the various recent ongoing clinical trials. All the relevant

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Article highlights

- A large body of evidence supports the recommendations on the currently used drugs during PCI.
- Several new pharmacologic options have recently emerged, but further studies are needed to support their benefits and to drive new recommendations.
- The evidence for new parenteral anticoagulants (i.e. argatroban, otamixaban, M118, pegnivacogin/anivamersen) is still preliminary, while new oral anticoagulants, particularly rivaroxaban, showed promising findings to be confirmed.
- Among the new antiplatelets, vorapaxar and cangrelor showed positive but limited evidence and might be considered at least in selected patients.
- No-reflow still remains a critical complication of PCI and further dedicated research is warranted.

This box summarizes key points contained in the article

studies were identified using the following keywords and their combination: 'percutaneous coronary intervention', 'drugs', 'antithrombotic', 'antiplatelet', 'anticoagulant', 'no-reflow', 'heparin', 'bivalirudin', 'fondaparinux', 'dabigatran', 'rivaroxaban', 'apixaban', 'edoxaban', 'otamixaban', 'argatroban', 'M118', 'aptamer', 'clopidogrel', 'prasugrel', 'ticagrelor', 'cangrelor', 'elinogrel', '$P2Y_{12}$ inhibitors or antagonists', 'vorapaxar', 'glycoprotein IIb/IIIa inhibitor', 'abciximab', 'tirofiban', and 'eptifibatide'.

2. Anticoagulant therapy

2.1. Unfractionated heparin

UFH is a sulfated glycosaminoglycan composed of alternating uronate and glucosamine units containing straight-chain mucopolysaccharides of highly variable length. This complex heterogeneous substance has a molecular weight ranging from 3000 to 30,000 Da (with a mean of 15,000 Da). UFH acts as an indirect thrombin inhibitor, exerting its effects through the endogenous serine protease antithrombin (AT) III. As AT complexes with heparin, it undergoes a conformational change, accelerating its enzymatic activity and rapidly inhibiting factor IIa (thrombin), factor Xa, and, to a lesser extent, factors IXa, XIa, and VIIa (Table 1). During PCI, UFH is administered intravenously, and the generally recommended dose is 70–100 U/kg as bolus, to achieve a target activated clotting time (ACT) of 250–350 s (50–70 U/kg bolus to achieve an ACT of 200–250 s is recommended if GPIs are used). ACT should be <180 s when the femoral sheath is removed to minimize bleeding complications. ACT monitoring is crucial to guide UFH dosing during PCI, because it is a predictor of thrombotic complications (ACT < 300 s), as recently demonstrated in the FUTURA/OASIS-8 (fondaparinux with unfractionated heparin during revascularization in ACS/optimal antiplatelet strategy for interventions) trial.[1]

Before cath-lab, UFH can be initiated with a bolus of 60–70 IU/kg (maximum of 5000 IU), followed by an initial infusion of 12–15 IU/kg/h (maximum 1000 IU/h), maintaining an activated partial thromboplastin time (aPTT) level of 50–75 s, corresponding to 1.5–2.5 times the upper limit of normal. This narrow therapeutic window is due to the increased risk of bleeding without further antithrombotic benefits at the higher aPTT values. In patients receiving prior UFH, at the time of

Table 1. Characteristics of the main anticoagulants.

	UFH	LMWH	Bivalirudin	Fondaparinux
Target of anticoagulation	IIa, Xa, IXa, XIa, VIIa	IIA and Xa	IIa	Xa
Administration	Intravenous	Subcutaneous	Intravenous	Subcutaneous
Half-life	30–60 min	3–6 h	25 min	17–21 h
Clearance	Cellular mechanisms and renal	Renal	Renal (20%)	Renal
Monitoring needed	Yes	Yes	No	No
Monitoring test	ACT	AntiXa level	ACT (not ideal)	AntiXa level
Reversibility	Yes	Yes (partial)	No	No
Antidote	Protamine 1 mg/100 IU of UFH	Protamine 1 mg/1 mg of LMWH	-	-
Dosage	*Prior to coronary angiography*: 60–70 IU/kg IV (max 5000 IU) and infusion (12–15 IU/kg/h) (max 1000 IU/h), target aPTT 1.5–2.5× control *During PCI*: 70–100 IU/kg IV with ACT target of 250–350 s (50–70 IU/kg with ACT target of 200–250 s if GPIs are used)	1 mg/kg s.c. twice a day	Bolus 0.75 mg/kg i.v., infusion 1.75 mg/kg/h	*Prior to coronary angiography*: 2.5 mg s.c. once a day *During PCI*: an additional bolus of UFH is needed
Dose adjustment in CKD	No adjustment	No adjustment[2] Not recommended for eGFR < 15 ml/min/1.73 m	No adjustment of bolus, reduce infusion rate to 1 mg/kg/h and to 0.25 for dialysis	No adjustment Not recommended for eGFR < 20 ml/min/1.73 m^2

Abbreviations: ACT = activated clotting time; aPTT = activated partial thromboplastin time; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; IU = international units; GPIs = glycoprotein IIb/IIIa inhibitors; LMWH = low-molecular weight heparin; PCI = percutaneous coronary intervention; UFH = unfractionated heparin.

PCI, an additional UFH bolus is administered as needed to achieve the ACT target level.

An important advantage of using UFH is that it can be antagonized with intravenous protamine sulfate (1 mg for each 100 UFH units). However, UFH has some limitations, such as the need for ACT monitoring that is related to its bound to cells and plasma proteins determining a variable dose-response relationship with nonlinear pharmacokinetics and poor predictable effects. Other limitations of UFH include a narrow therapeutic window, platelet activation, the potential for inducing thrombocytopenia (HIT) and HIT-thrombosis syndrome. For these reasons, during the last decades, studies have been conducted to test new anticoagulants with more pharmacologic and clinical advantages than UFH, despite the fact that it still remains the standard of care for thrombosis prevention during PCI. [2–4]

2.2. Low-molecular weight heparin (LMWH)

Low-molecular weight heparin (LMWH) is produced from enzymatic or chemical degradation of UFH, resulting in a lower molecular weight (5000 Da) with reduced binding capacity to proteins, yielding a predictable anticoagulant effect and less need for procedural monitoring. LMWH still acts through ATIII, but cannot form a ternary complex with AT and thrombin because of its smaller monosaccharide chains; therefore, LMWH has preferential anti-Xa as opposed to AT activity. LMWH incurs much less nonspecific binding, thus presenting a lower risk of HIT and less platelet activation compared with UFH. Among LMWHs, enoxaparin is the most studied in the setting of PCI. It is recommended as an alternative to UFH during elective PCI on the basis of the STEEPLE (safety and efficacy of enoxaparin in PCI patients, an international randomized evaluation) trial, in which 3528 patients were randomized to either intravenous enoxaparin 0.5 or 0.75 mg/kg or UFH.[5] The primary end point (noncoronary artery bypass graft (CABG)-related bleeding over 48 h) was significantly reduced with the lower but not the higher dose. Major bleeding was significantly reduced in both enoxaparin groups, with similar efficacy to UFH. Enoxaparin provided more predictable anticoagulation. However, the trial was not large enough to provide a definitive comparison of efficacy in the prevention of ischemic events.[5] The superior yield of the new strategy of enoxaparin, revascularization and glycoprotein IIb/IIIa inhibitors trial enrolled 10,027 high-risk patients with NSTE-acute coronary syndrome (ACS) to an early invasive strategy with either UFH or enoxaparin, showing that enoxaparin was non-inferior to UFH.[6] Enoxaparin was associated with increased risk of bleeding, but mainly in patients who switched from UFH to enoxaparin and vice versa.[6] Based on this trial, recommendations state that enoxaparin may be considered as an alternative to UFH in NSTE-ACS (with no additional drug given during PCI if the last enoxaparin dose was given <8 h prior to the procedure, while an additional enoxaparin bolus of 0.3 mg/kg administered prior to PCI if the last enoxaparin dose was given >8 h) and discourage the cross-overs between heparins. In the setting of ST-segment elevation myocardial infarction (STEMI), enoxaparin could be considered as an alternative to UFH based on the ATOLL (acute STEMI treated with primary PCI and intravenous enoxaparin or UFH to lower ischaemic and bleeding events at short- and long-term follow-up) trial, which randomized 910 patients.[7] The 30-day primary composite end point of death, myocardial infarction (MI), procedural failure, or major bleeding was reduced nonsignificantly in the enoxaparin arm (0.5 mg/kg IV) compared with UFH in the absence of bleeding difference.[7] However, LMWHs have little activity against thrombin, are not completely reversible (protamine may reverse only the anti-IIa effect but does not completely reverse the anti-Xa activity), cannot be monitored by point-of-care assays, need dose adjustment (not clearly defined) in case of obese patients or those with renal insufficiency.

2.3. Bivalirudin

Bivalirudin is a 20-amino acid synthetic polypeptide with a short half-life, which binds directly to circulating and fibrin-bound thrombin, blocking its enzymatic activity (Table 1). In contrast to UFH, bivalirudin does not have any natural inhibitors such as platelet factor 4 and does not require ACT monitoring of anticoagulation in the cath-lab, but assessing the ACT 5 min after dosing is a safety reminder to verify its effect. Moreover, not interacting with plasma proteins or cells, it does not activate platelets and does not cause HIT. Also, bivalirudin exerts some degree of antiplatelet effect by blocking platelet protease-activated 1 and 4 receptors (protease-activated receptor [PAR]-1 and -4), which are typically activated by thrombin.[8,9]

In stable CAD, bivalirudin was compared with UFH in the ISAR-REACT (intracoronary stenting and antithrombotic regimenrapid early action for coronary treatment) 3 trial, which showed a trend of increased risk of MI but significantly lower major bleeding with bivalirudin. [10,11]

Bivalirudin has emerged as a viable option for anticoagulation in ACS too. The efficacy and safety of bivalirudin in NSTE-ACS were demonstrated by ACUITY

(acute catheterization and urgent intervention triage strategy) and ISAR-REACT4 trials,[12–14] which both observed a consistently reduced bleeding rate in patients treated with bivalirudin and a comparable efficacy profile.

However, arguments on its safety and efficacy profile have been marked by intense controversy and debate in STEMI patients.[15] In the first trial, HORIZONS-AMI (harmonizing outcomes with revascularization and stents-acute myocardial infarction), bivalirudin reduced major bleeding at 30 days and cardiovascular mortality at 3 years compared with UFH and routine use of a GPI, but increased the rates of acute stent thrombosis (ST).[16] However, from that study, primary PCI practice has evolved, with more frequent prehospital initiation of antithrombotic treatment, widespread use of radial access, introduction of potent antiplatelet agents (prasugrel and ticagrelor), and use of GPI restricted to bail-out situations. The EUROMAX (european ambulance acute coronary syndrome angiography) trial incorporated these changes and demonstrated results consistent with those of HORIZONS-AMI.[17] However, contrasting evidence from three additional randomized trials of bivalirudin versus UFH in STEMI (bavarian reperfusion alternatives evaluation [BRAVE] 4, bivalirudin in acute myocardial infarction vs. glycoprotein IIb/IIIa and heparin: a randomized controlled trial, how effective are antithrombotic therapies in primary-PCI) has subsequently emerged.[18–20] In particular, the HEAT-PPCI trial raised concerns on the risk–benefit profile of bivalirudin compared with heparin monotherapy, leading to a downgrade in the recent European guidelines of the recommendation for bivalirudin in primary PCI (from I to IIa).[2] A pooled analysis from these five trials showed that compared to UFH, bivalirudin was associated with similar 30-day mortality with reduced major bleeding, at the price of increased acute ST, with non-significant differences in the overall 30-day rates of ST and reinfarction. Interestingly, the use of GPIs in the heparin arm did not significantly modify the treatment effects of bivalirudin.[15]

Importantly, the results of the MATRIX (minimizing adverse haemorrhagic events by transradial access site and systemic implementation of angiox) trial have been recently published (Figure 1). This trial randomly assigned either bivalirudin or UFH to 7213 ACS patients for whom PCI was anticipated.[21,22] Patients in the bivalirudin group were subsequently randomly assigned to receive or not a post-PCI bivalirudin infusion. Primary outcomes were the occurrence of major adverse cardiovascular events (MACE) (a composite of death, MI, or stroke) and net adverse clinical events (NACE) (a composite of major bleeding or a major adverse cardiovascular event). The primary outcome for the comparison of a post-PCI bivalirudin infusion with no post-PCI infusion was a composite of urgent target-vessel revascularization, definite ST, or NACE. The rates of MACE and NACE were not significantly different between bivalirudin and UFH, but bivalirudin was associated with reduced bleeding and also lower all-cause death, lower cardiovascular death at the price of higher definite ST (borderline *p*-values). Post-PCI bivalirudin infusion, as compared with no infusion, did not significantly decrease the rates of urgent target-vessel revascularization, definite ST, or NACE.[21,22] However, at explorative analysis,

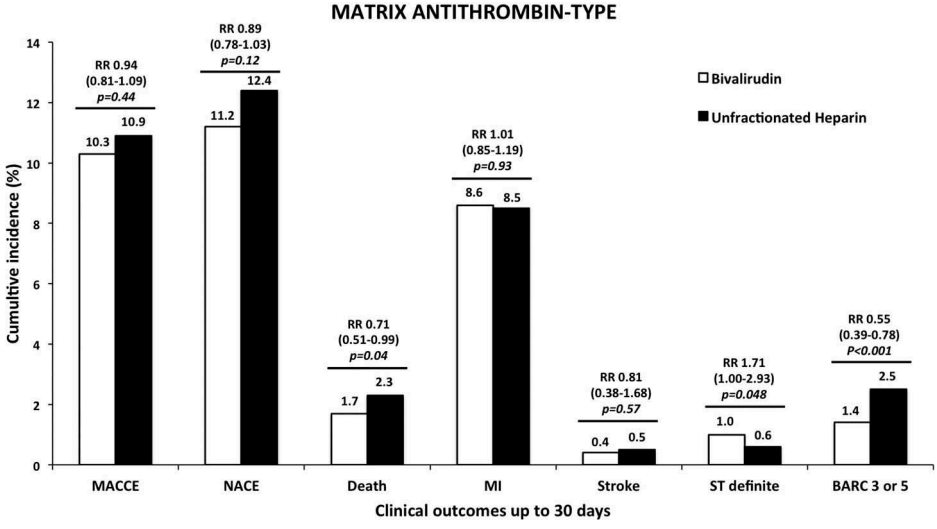

Figure 1. Clinical outcomes in the MATRIX Antithrombin-type trial. Cumulative incidence, risk ratios (RR) and confidence intervals (95% CI) are reported for ischemic and bleeding events in the bivalirudin and unfractionated heparin groups.

prolongation of PCI bivalirudin dose was associated with low ischemic and bleeding risk when compared to both low post-PCI regimen and UFH. The consistency of these results across the types of ACS remains to be seen.

2.4. Fondaparinux

This drug indirectly inhibits factor Xa. Currently, this is not a drug to be used in the cath-lab during PCI but in the pre-PCI period, being the recommended drug for patients with NSTE-ACS due to the most favorable efficacy/safety profile. In this case, an additional bolus of anticoagulant with anti-IIa activity (UFH, enoxaparin, or bivalirudin) at the time of PCI will be necessary due to the increased risk of catheter-related thrombosis. For this reason, in the setting of STEMI, fondaparinux is not recommended; indeed, the OASIS 6 trial enrolling STEMI patients showed a significantly higher rate of guiding catheter-related thrombosis.[23]

2.5. New developments in anticoagulation therapy

2.5.1. Non-vitamin-K oral anticoagulants

Rivaroxaban and dabigatran have been investigated for anticoagulation during PCI. Dabigatran was studied in the D-fine clinical trial, a phase IIa prospective, randomized, exploratory study conducted in four hospitals in The Netherlands.[24] This study included 50 stable patients undergoing elective PCI. Patients on standard DAPT were randomized (2:2:1) to either pre-procedural dabigatran 110 mg b.i.d. (n = 19) or 150 mg b.i.d. (n = 21), as compared to standard intraprocedural UFH (n = 10). Following PCI, a significant increase in the levels of the prothrombin fragment 1 + 2 (F1 + 2) in the combined dabigatran group was observed compared to the level just before PCI. Also, thrombin-AT (TAT) complexes were increased significantly in the combined dabigatran group compared to pre-PCI levels. Conversely, in the UFH control group, no increase was observed in F1 + 2 and TAT complexes during PCI. Five out of 40 patients required bailout anticoagulation in the dabigatran group, of whom four experienced a procedural MI. One minor access-site bleeding occurred in the dabigatran group. Therefore, this exploratory study showed that dabigatran did not provide a sufficient anticoagulation during PCI.[24] Contrarily, the X-PLORER (evaluating optimal concomitant anticoagulation in rivaroxaban treated patients, an oral direct factor Xa inhibitor, during percutaneous coronary revascularization) trial showed that rivaroxaban effectively suppressed coagulation activation for elective PCI and stenting.[25] Stable patients (n = 108) undergoing elective PCI and on DAPT were randomized (2:2:2:1) to a short treatment course of rivaroxaban 10 mg (n = 30), rivaroxaban 20 mg (n = 32), rivaroxaban 10 mg plus UFH (n = 30), or standard periprocedural UFH (n = 16). Blood samples for markers of thrombin generation and coagulation activation were drawn prior to and after start of PCI, confirming the efficacy of rivaroxaban.[25]

Some studies have also investigated on the long-term role for rivaroxaban, apixaban, and dabigatran in addition to DAPT in patients with recent ACS, but none of them is currently recommended because the results have been poorly encouraging, except for the 2.5 mg twice-daily dose of rivaroxaban. In the apixaban for prevention of acute ischemic and safety events-2, apixaban (5 mg twice daily) was compared with placebo, in addition to standard antiplatelet therapy, in patients with a recent ACS and at least two additional risk factors for recurrent ischemic events.[26] It was prematurely terminated after recruitment of 7392 patients due to an increase in major bleeding events with apixaban in the absence of a counterbalancing reduction in recurrent ischemic events.[26]

The RE-DEEM (dabigatran vs. placebo in patients with acute coronary syndromes on dual antiplatelet therapy: a randomized, double-blind, phase II trial) trial enrolled patients with recent ACS and randomized them to receive various doses of dabigatran (50, 75, 110, and 150 mg) or placebo; however, a dose-dependent increase in major or minor bleeding was observed with dabigatran, while no significant decrease of ischemic events with dabigatran was observed.[27]

In the recent ATLAS-ACS-2 TIMI 51 trial (anti-Xa therapy to lower cardiovascular events in addition to standard therapy in subjects with ACS 2-TIMI 51 trial), 15,526 patients with a recent ACS were randomized to receive rivaroxaban 2.5 or 5 mg twice daily or placebo.[28] Only the dose of 2.5 mg provided promising results; indeed, the twice-daily 2.5 mg, but not the 5 mg, dose of rivaroxaban reduced the rates of death from cardiovascular causes and from any cause. As compared with placebo, rivaroxaban increased the rates of major bleeding not related to CABG and intracranial hemorrhage, without a significant increase in fatal bleeding or other adverse events, but the twice-daily 2.5 mg dose resulted in fewer fatal bleeding events than the twice-daily 5 mg dose.[28] Based on these study results, rivaroxaban 2.5 mg b.i.d. is approved in Europe for the secondary prevention of ACS patients on top of aspirin and clopidogrel or aspirin only. However, it remains unclear how this triple

therapy treatment strategy compares with aspirin and ticagrelor or aspirin and prasugrel, which are the first-line, recommended P2Y12 inhibitors in ACS patients by European and American guidelines.

2.5.2. Argatroban

Argatroban is a synthetic arginine-derived direct thrombin inhibitor and is an attractive anticoagulant for PCI due to its rapid onset and offset and its hepatic elimination. It was approved for PCI in patients with HIT. The argatroban-E04 open-label, multiple-dose, controlled study examined the safety and efficacy of argatroban in non-HIT patients undergoing elective PCI.[29] A total of 140 patients were randomized to three argatroban doses (ARG250, ARG300, and ARG350 with 250, 300, or 350 μg/kg bolus, followed by 15, 20, or 25 μg/kg/min infusion) or UFH (70–100 IU/kg bolus). Argatroban prolonged ACT in a dose-dependent manner, with more patients reaching the minimum target ACT after the initial bolus injection (ARG250: 86.1%, ARG300: 89.5%, and ARG350: 96.8%) compared to 45.5% in UFH ($p < 0.001$). A significantly higher proportion of patients did not require additional bolus injections to start PCI in the argatroban arm when compared to the UFH arm ($p \leq 0.002$). Consequently, the time to start of PCI was shortened in the argatroban groups. Composite incidences of death, MI, and urgent revascularization until day 30 were not significantly different between the groups. Major bleeding was observed only in UFH (3.0%), while minor bleeding occurred in ARG350 (3.2%) and UFH (6.1%, n.s.).[29] Argatroban is currently recommended for HIT patients and does not appear to be an attractive treatment option beyond this niche patient population, in which, however, bivalirudin is also a recommended option.

2.5.3. Otamixaban

Otamixaban is a novel intravenous direct factor Xa inhibitor. In the SEPIA (study to evaluate the pharmacodynamics, the safety and tolerability, and the pharmacokinetics of several intravenous regimens of the Factor Xa inhibitor otamixaban in comparison to intravenous unfractionated heparin in subjects undergoing non-urgent percutaneous coronary intervention)-PCI double-blind, double-dummy, parallel-group, dose-ranging trial, 947 patients were randomly assigned to either one of five weight-adjusted otamixaban regimens or weight-adjusted UFH before PCI.[30] Otamixaban reduced F1 + 2 significantly more than UFH at the highest dose regimen, while no significant difference in the incidence of thrombolysis in MI (TIMI) bleeding was observed between the otamixaban and UFH groups. These results were the basis for further adequately powered clinical outcome trials in patients with ACS. Then, otamixaban was tested in 3241 patients with NSTE-ACS in a double-blind phase 2 trial (SEPIA-ACS1 TIMI42), which demonstrated that infusions of 0.100–0.140 mg/kg/h might reduce ischemic events and have a safety profile similar to UFH plus eptifibatide, supporting the need for a phase 3 trial.[31] Finally, in the phase 3 TAO (treatment of acute coronary syndromes with otamixaban trial, the clinical efficacy and safety of otamixaban) were compared with those of UFH plus downstream eptifibatide in patients with NSTE-ACS undergoing a planned early invasive strategy.[32] A total of 13,229 patients with NSTE-ACS were enrolled, and the otamixaban dose selected at interim-analysis was an intravenous bolus of 0.080 mg/kg followed by an infusion of 0.140 mg/kg/h. However, otamixaban did not reduce the rate of ischemic events but increased bleeding, thereby not supporting its use for patients with NSTE-ACS undergoing planned early PCI.[32]

2.5.4. M118

M118 is a novel LMWH that combines the beneficial properties of UFH and enoxaparin while addressing their respective limitations. It is produced by depolymerization of UFH that is derived from porcine intestinal mucosa, significantly reducing molecular weight (range from 5500 to 9000 Da). It is characterized by a broad anticoagulant activity, including potent activity against factor Xa and thrombin, low polydispersity, subcutaneous bioavailability (around 70% in humans), and predictable subcutaneous and intravenous pharmacokinetics. The anti-Xa to anti-IIa ratio of approximately 1.4:1 remains constant over time in vivo. The plasma half-life of M118 is approximately 1 h after intravenous bolus injection and 2–3 h after subcutaneous injection. Importantly, M118 does not activate platelets, and its anticoagulant activity can be monitored by standard coagulation assays such as ACT and aPTT. Additionally, owing to its charge, it is reversible to subtherapeutic levels with protamine sulfate (1 mg per 100-IU dose). In the Phase II EMINENCE (evaluation of M118 in percutaneous coronary intervention) multicenter trial (43 centers in the United States and Canada), 503 patients undergoing elective PCI were randomized in an open-label fashion to one of four arms: UFH 70 U/kg, M118 50 IU/kg IV, M118 75 IU/kg IV, or M118 100 IU/kg IV.[33] The rates of the primary end point between the pooled M118 groups versus UFH demonstrated that M118 was non-inferior to UFH at preventing PCI-related complications (28.4% pooled M118 arms versus 31.1% UFH), and the adverse event profiles of M118 and UFH were comparable.

2.5.5. RNA aptamers

RNA aptamers are single-stranded oligonucleotide sequences that bind with high specificity to some protein sequences. An important advantage of this strategy is related to the fact that they are nucleotides; therefore, it is possible to engineer complementary sequences to be used as very effective antidotes. The REG1 system (pegnivacogin/anivamersen) is an example of this anticoagulation system. Pegnivacogin represents an extremely potent, chemically unique anticoagulant that inhibits factor IXa and can be reversed by anivamersen. This system is being investigated for use in PCI. A recent Phase II trial, REVERSAL (feasibility and safety study comparing REG1 anticoagulation system with unfractionated heparin in elective)-PCI, compared the REG1 system (n = 20) with UFH (n = 4).[34] Anticoagulation was partially reversed after PCI (n = 10) and fully reversed 4 h later (n = 10). This study preliminarily demonstrated the adequate intraprocedural anticoagulation, with rapid and effective reversal after PCI using the REG1 system.

Subsequently, the RADAR (randomized, partially-blinded, multicenter, active-controlled, dose-ranging study assessing the safety, efficacy, and pharmacodynamics of the REG1 anticoagulation system compared to unfractionated heparin or low molecular heparin in subjects with ACS)-PCI phase II trial was conducted by randomizing ACS patients to pegnivacogin 1 mg/kg with 25%, 50%, 75%, or 100% anivamersen reversal or UFH. Of the 640 patients randomized, 388 (61%) underwent PCI.[35] The inhibition with at least 50% reversal had a favorable bleeding profile and appeared effective at suppressing ischemic events and thrombotic complications, supporting the need for larger phase trials in PCI.

The phase III trial REGULATE (a study to determine the efficacy and safety of REG1 compared to bivalirudin in patients undergoing)-PCI (NCT01848106) was started in 2013 to test the hypothesis of whether pegnivacogin could result in fewer ischemic events than bivalirudin while active control with anivamersen could preserve the benefit of reduced bleeding.[36] This trial compared REG1 with bivalirudin in preventing periprocedural ischemic complications and major bleeding in patients undergoing PCI (in stable and ACS [non ST-elevation myocardial infarction, NSTEMI and unstable angina, UA] patients). The study was terminated after enrollment of 3232 patients due to severe allergic reactions in 10 of 1605 (0.6%) patients receiving pegnivacogen, including one fatal event and nine anaphylactic reactions.[36] There were no differences in rates of the primary end point between REG1 and bivalirudin groups (6.7% vs. 6.4%; OR: 1.05; 95% CI: 0.80–1.39; p = 0.72). REG1 was associated with a numerically higher rate of major bleeding (0.4% vs. 0.1%; OR: 3.49; 95% CI: 0.73–16.82; p = 0.09) and a significantly higher rate of major or minor bleeding (6.5% vs. 4.1%; OR: 1.65; 95% CI: 1.19–2.25; p = 0.002). However, the incidence of ST trended lower in the REG-arm (<0.1 vs. 0.4%: OR: 0.17; 95% CI: 0.12–1.38; p = 0.06). We can speculate that these allergic reactions may have arisen from preexisting antibodies to polyethylene glycol, although the mechanism remains undefined at this time; future analyses using demographic information and stored immunologic blood samples are planned. While the concept of high-level anticoagulation with active reversal is promising, its clinical role requires additional studies.

3. Oral antiplatelet therapy

3.1. Standard of care

For several years, oral antiplatelet therapy with clopidogrel and low-dose aspirin has been the standard of care after PCI. During the last decade, important trials have demonstrated that new oral $P2Y_{12}$ inhibitors, prasugrel and ticagrelor (Table 2), are more potent and effective in preventing ischemic events than clopidogrel in the setting of DAPT in patients with ACS, despite an increased risk of bleeding being observed with both agents. Indeed, current guidelines support the use of these two agents over clopidogrel. An ongoing trial is comparing prasugrel and ticagrelor in ACS patients undergoing planned PCI (ISAR-REACT5).[37] However, the optimal duration of DAPT after PCI, with the aim of balancing ischemic and bleeding complications, still remains a great matter of debate.[38–43] Recently, the PEGASUS (prevention of cardiovascular events in patients with prior heart attack using ticagrelor compared to placebo on a background of aspirin) trial demonstrated that adding ticagrelor to aspirin in patients with prior MI (1–3 years earlier) was associated with significant benefits compared with aspirin alone.[44] Both dosages tested (60 mg or 90 mg twice daily) reduced the primary end point and rates of MI, with the 60 mg ticagrelor regimen also associated with lower stroke and cardiovascular mortality.

3.2. Vorapaxar

Vorapaxar acts by inhibiting PAR-1 and leading to prevention of thrombin-mediated platelet activation. It was approved in May 2014 on the basis of TRA2P-TIMI50 trial.[45] This study tested the hypothesis that adding a platelet-activated receptor 1 inhibitor to the current standard of DAPT may provide benefits by a

Table 2. Principal characteristics of $P2Y_{12}$ inhibitors.

	Clopidogrel	Prasugrel	Ticagrelor	Cangrelor
Chemical class	Thienopyridine	Thienopyridine	Cyclopentyl-triazolopyrimidine	Stabilized ATP analogue
Administration	Oral	Oral	Oral	Intravenous
Dose	300–600 mg then 75 mg a day	60 mg then 10 mg a day	180 mg then 90 mg twice a day	30 μg/kg bolus then 4 μg/kg/min infusion
Dose in CKD				
eGFR 15–60 ml/min/1.73 m^2	No adjustment	No adjustment	No adjustment	No adjustment
eGFR < 15 ml/min/1.73 m^2	Use only for selected indications (e.g. ST prevention)	Not recommended	Not recommended	No adjustment
Binding to $P2Y_{12}$	Irreversible	Irreversible	Reversible	Reversible
Activation	Prodrug, with variable liver metabolism	Prodrug, with predictable liver metabolism	Active drug, with additional active metabolite	Active drug
Onset of loading dose effect[a]	2–6 h[b]	30 min[b]	30 min[b]	2 min[b]
Duration effect	3–10 days	7–10 days	3–5 days	1–2 h
Withdrawal before surgery	5 days	7 days	5 days	1 h
Plasma half-life of active $P2Y_{12}$ inhibitor	30–60 min	30–60 min[c]	6–12 h	5–10 min
Inhibition of adenosine reuptake	No	No	Yes	Yes (the inactive metabolite only)

Abbreviations: ATP = adenosine triphosphate; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; ST = stent thrombosis.
[a]50% inhibition of ADP-induced platelet aggregation.
[b]Onset of effect may be delayed if intestinal absorption is delayed (e.g. by opiate).
[c]The distribution phase half-life is reported since it most likely reflects duration of clinically relevant plasma levels, while the corresponding elimination phase half-life is approximately 7 h.

more comprehensive platelet inhibition. Patients with prior MI on maintenance antiplatelet therapy were randomized 1:1 to vorapaxar (8898) or placebo (8881) and maintenance therapy with vorapaxar (2.5 mg daily) at a median follow-up of 2.5 years. A reduction of cardiovascular death, MI, or stroke at the expense of increased risk of moderate to severe bleeding was observed with vorapaxar.[45] However, the thrombin receptor antagonist for clinical event reduction trial in acute coronary syndrome, which randomized 12,944 patients with ACS (NSTEMI and UA but not STEMI) to vorapaxar or placebo, highlighted safety risks related to this treatment strategy.[46] Indeed, follow-up of the trial was prematurely interrupted due to safety concerns; in particular, the addition of vorapaxar to standard therapy did not significantly reduce the primary composite end point (death from cardiovascular causes, MI, stroke, recurrent ischemia with rehospitalization, or urgent coronary revascularization) but significantly increased the risk of major bleeding, including intracranial hemorrhage.[46]

4. Parenteral antiplatelet therapy

4.1. GPI

Currently three different GPIs are commercially available. These drugs are able to abrogate the effects of the IIb/IIIa receptor on platelet aggregation and adhesion through reversible or irreversible inhibition (Table 3).

Today, GPIs are not routinely recommended during PCI.[2] In elective PCI, some benefits have been demonstrated. The 3T/2R trial (3T/2R = tailoring treatment with tirofiban in patients showing resistance to aspirin and/or resistance to clopidogrel) showed reduction of MACE without increase of bleeding using high-bolus tirofiban in poor responders to aspirin or clopidogrel or both [47], while the additive value of tirofiban administered with the high-dose bolus in the prevention of ischemic complications during high-risk coronary angioplasty trial demonstrated a reduction of thrombotic complications, mainly MI, during high-risk PCI in patients pretreated with thienopyridines.[48] However, in elective PCI, GPIs are currently restricted to bailout situations (intra-procedural thrombus formation, slow-flow, threatened vessel closure), although suggested benefits emerged from anecdotal experiences.[2] Similarly, in patients with NSTE-ACS undergoing PCI, most recent trials (ISAR-REACT4, early glycoprotein IIb/IIIa inhibition in non-ST-segment elevation-ACS) did not support an important role for GPIs, particularly if administered before PCI (upstream); hence, European guidelines state that GPIs should not be used routinely in this setting, while they should be considered in bailout or thrombotic complications (class IIa, level C).[2] Conversely, American guidelines support GPI use in the case of NSTE-ACS with high-risk features (e.g. elevated troponin) but without adequate pretreatment with clopidogrel or ticagrelor (Class I, level A), as upstream therapy in case of patients treated with an early invasive strategy and DAPT with intermediate/

Table 3. Principal characteristics of GPI.

	Abciximab	Eptifibatide	Tirofiban
Type	Fab fragment of chimeric human-murine monoclonal antibody	Synthetic cyclic heptapeptide	Synthetic nonpeptide
Molecular weight	Large molecule (47,515 Da)	Small molecule (832 Da)	Small molecule (496 Da)
Antigenicity	Present	Absent	Absent
Inhibition	Noncompetitive	Competitive	Competitive
Binding	Irreversible	Competitive	Competitive
Plasma half-life	10–30 min	2.5–2.8 h	1.2–2 h
Receptor binding	Minutes	Seconds	Seconds
Recovery of platelet function	24–48 h	≈4 h	≈4 h
Elimination route	Spleen	Renal 60–75%	Renal 65–75%
Dosage recommended	Bolus of 0.25 mg/kg IV followed by 0.125 μg/kg/min infusion (maximum 10 μg/min) and can be continued for 12 h after PCI.	Bolus of 180 μg/kg IV over 1–2 min, a second bolus of 180 μg/kg 10 min later, and an infusion of 2 μg/kg/min.	High-bolus dose 25 μg/kg IV, then 0.15 μg/kg/min
Dose adjustment in CKD	No dose adjustment is needed	Infusion should be reduced by half if eGFR < 50 ml/min/1.73 m^2. Not recommended if <30 or on hemodialysis	Bolus and infusion should be reduced by 50% with eGFR 15–30 ml/min/1.73 m^2. Not recommended if <15 ml/min/1.73 m^2.

Abbreviations: CKD = chronic kidney disease; Da = dalton; eGFR = estimated glomerular filtration rate; IU = international units; GPI = glycoprotein IIb/IIIa inhibitor; PCI = percutaneous coronary intervention.

high-risk features (e.g. positive troponin) (Class IIb, level B) and at the time of PCI in patients with NSTE-ACS and high-risk features treated with UFH and adequately pretreated with clopidogrel (class IIa, level B), but this latter recommendation should be reserved to patients without high risk of bleeding complications and does not include prasugrel or ticagrelor because the data are still insufficient to make specific recommendations.[3]

The most relevant clinical setting for the use of GPIs remains that of STEMI.[49] In the era before preloading with thienopyridines, several studies have shown that GPI, mainly abciximab, added to UFH in STEMI patients treated with primary PCI was associated with improved outcomes, but also high-dose tirofiban showed to be non-inferior to abciximab in this setting (multicentre evaluation of single high-dose bolus tirofiban vs abciximab with sirolimus-eluting stent or bare metal stent in acute myocardial infarction study trial).[50] Also, in the era of routine use of thienopyridines, GPIs could be useful, indeed the FABOLUS-PRO (facilitation through aggrastat by dropping or shortening infusion line in patients with ST-segment elevation myocardial infarction compared to or on top of prasugrel given at loading dose) showed that better platelet inhibition in STEMI patients was reached by adding tirofiban bolus to pretreatment with prasugrel and that a bolus followed by 2 h infusion was necessary in patients pretreated with clopidogrel.[51]

However, subsequent trials (FINESSE [facilitated intervention with enhanced reperfusion speed to stop events], On-TIME2 [continuing tirofiban in myocardial infarction evaluation], BRAVE 3, intracoronary abciximab and aspiration thrombectomy in patients with large anterior-myocardial infarction) provided contrasting results on clinical benefits; thus, there is no definitive answer regarding routine use of GPIs in primary PCI, particularly when prasugrel or ticagrelor is used, and the value of starting upstream of PCI remains uncertain.[2]

Several studies have assessed the administration of abciximab as intracoronary instead of an intravenous bolus. Small studies suggested potential benefits of the intracoronary route, but they were not confirmed in large randomized trials and in a recent meta-analysis of five randomized trials.[49,52,53]

The main concern related to GPI use is the increase of bleeding complications, but to reduce this risk and provide similar efficacy, abciximab could be administered as only bolus without post-PCI infusion, as shown in the facilitation through abciximab by dropping infusion line in patients undergoing coronary stenting-synergy with clopidogrel at high loading dose regimen.[54]

Currently, European STEMI guidelines [2] state that: (1) the upstream use of GPIs (versus in-lab use) may be considered only in high-risk patients undergoing transfer for primary PCI (class IIb, level B); (2) in-lab use is reasonable for angiographic evidence of large thrombus, slow- or no-reflow, and other thrombotic complications as bailout therapy (class IIa, level C), although this has not been tested in randomized trials. American guidelines [4] recommend that: (1) it is reasonable to begin treatment with an intravenous GPI such as abciximab (level of evidence A), high-bolus-dose tirofiban (level of evidence B), or double-bolus eptifibatide (level of evidence B) at the time of primary PCI (with

or without stenting or clopidogrel pretreatment) in selected patients with STEMI who are receiving UFH (class IIa); (2) it may be reasonable to administer an intravenous GPI in the pre-catheterization laboratory setting (e.g. ambulance, emergency department) to patients with STEMI for whom primary PCI is intended (class IIb, level B of recommendation); (3) it may be reasonable to administer intracoronary abciximab to patients with STEMI undergoing primary PCI (class IIb, level B of recommendation).

4.2. Cangrelor

Cangrelor is an intravenous reversible $P2Y_{12}$ inhibitor. It is chemically known as *N*-2-methylthio-ethyl-2-(3,3,3-trilflouroprpylthiol)-5′-adenyl acid, being this an analogue of adenosine triphosphate (ATP), the natural antagonist of the $P2Y_{12}$ receptor (Table 2). It is dephosphorylated to the nucleoside and its primary metabolite is essentially inactive. It is characterized by a potent, predictable inhibition of ADP-induced inhibition of platelet aggregation that is virtually immediate (when administered as a bolus) and rapidly reversible. Cangrelor achieves almost complete and immediate inhibition of ADP-induced platelet aggregation when administered as a bolus of 30 μg/kg, and continuous infusion sustains the high degree of inhibition. The plasma half-life is approximately 3–5 min, and platelet function is restored within 1 h after cessation of infusion. In contrast to other $P2Y_{12}$ inhibitors, cangrelor is not characterized by a significant renal or hepatic metabolism. Pivotal trials showed a satisfactory rate of major bleeding events, but no significant decrease of adverse cardiac events. Based on phase II studies, the cangrelor phase III program CHAMPION (cangrelor versus standard therapy to achieve optimal management of platelet inhibition) was designed. This program originally consisted of two randomized 1:1, double-blind, double-dummy trials, CHAMPION PCI and CHAMPION PLATFORM (Table 4).[55,56] The hypothesis tested in these trials was that cangrelor, given during PCI, could reduce thrombotic events compared with clopidogrel administered at the beginning or at the end of PCI, respectively, with an acceptable safety profile. The phase III

Table 4. Cangrelor phase III trials.

	CHAMPION PLATFORM	CHAMPION PCI	CHAMPION PHOENIX	BRIDGE
Number of patients	5295 (modified ITT)	8877 (ITT)	10,942 (modified ITT)	210
Patients included	Requiring PCI (with or without stent) in elective or ACS excluding STEMI and $P2Y_{12}$-naive	Requiring PCI (with or without stent) in patients with ACS. Previous daily use of clopidogrel 75 mg allowed	Requiring either urgent or elective PCI and $P2Y_{12}$-naive	ACS or treated with a coronary stent and receiving a thienopyridine Awaiting CABG
Cangrelor protocol	30 μg/kg IV bolus and 4 μg/kg/min IV infusion	30 μg/kg IV bolus and 4 μg/kg/min IV infusion	30 μg/kg IV bolus and 4 μg/kg/min IV infusion	Infusion of 0.75 μg/kg/min IV on the basis of a stage I dose-finding study in 10 patients
Duration of treatment	Minimum infusion of 2 h and a maximum of 4 h, followed by clopidogrel 600 mg	Infusion for at least 2 h or for the duration of PCI, and a maximum of 4 h followed by clopidogrel 600 mg	Infusion for at least 2 h or for the duration of PCI, and a maximum of 4 h followed by clopidogrel 600 mg	Thienopyridines were stopped (clopidogrel 5 days before CABG, prasugrel 7 days) and cangrelor or placebo was administered for at least 48 h, which was discontinued 1–6 h before CABG.
Comparator	Clopidogrel 600 mg loading dose (end of PCI)	Clopidogrel 600 mg loading dose (before PCI)	Clopidogrel 300 or 600 mg loading dose (before PCI)	Placebo
Primary end point	Composite of death, MI, or IDR at 48 h	Composite of death from any cause, MI, or IDR at 48 h	Composite of death, MI, IDR, or ST at 48 h	Platelet reactivity (PRU) assessed daily
Safety endpoint	Bleeding events at 48 h (single events and categorized events [ACUITY, GUSTO, TIMI criteria]	Bleeding events at 48 h (single events and categorized events [ACUITY, GUSTO, TIMI criteria]	Major/minor non-CABG-related hemorrhage by clinically relevant criteria at 48 h (TIMI, GUSTO, others); Incidence of blood product transfusion until 48 h, categorized according to relationship with CABG	Excessive CABG surgery-related bleeding
Notes	Enrollment was stopped when a 70% interim analysis concluded that the trial would be unlikely to show superiority for the primary end point	Enrollment was stopped when a 70% interim analysis concluded that the trial would be unlikely to show superiority for the primary end point		

Abbreviations: ACS = acute coronary syndrome; ACUITY = acute catheterization and urgent intervention triage strategy; CABG = coronary artery bypass graft; GUSTO = global use of strategies to open occluded coronary arteries; IDR = ischemia-driven revascularization; ITT = intention-to-treat; MI = myocardial infarction; PCI = percutaneous coronary interventions; PRU = $P2Y_{12}$ reaction unit; ST = stent thrombosis; STEMI = ST-segment elevation myocardial infarction; TIMI = thrombolysis in myocardial infarction.

CHAMPION-PCI and CHAMPION-PLATFORM trials compared cangrelor with clopidogrel 600 mg in ACS patients scheduled for PCI, but they were different with regard to the timing of the clopidogrel dose administration. Unfortunately, due to insufficient evidence of the cangrelor clinical effectiveness, both trials were prematurely discontinued. However, a further trial was subsequently planned (CHAMPION-PHOENIX) [57] on the basis of important considerations: (1) the reduction of ST and death from any cause was observed in CHAMPION-PCI and CHAMPION-PLATFORM trials; (2) the absence of expected overall benefit of cangrelor may be related to the definition of MI used, which was considered inappropriate. Therefore, in the new CHAMPION-PHOENIX trial, different from the two previous studies, the following characteristics were included: (1) the definition of MI as end point; (2) the comparator arm was clopidogrel 300 or 600 mg, at the investigator discretion; (3) the primary end point was the composite of death, MI, ischemia-driven revascularization, or ST (including intraprocedural) at 48 h; (4) the population of interest was restricted to clopidogrel-naïve patients. The definition of MI used in PHOENIX was based on the Second Universal definition of MI for all types of MI but PCI-related (type 4a) MI, where this definition was expanded to include some elements (like angiographic complications) that were later included in the Third Universal MI definition.[57] In PHOENIX, PCI-related MI could be assessed using cardiac biomarkers only if troponin pre-PCI was normal or elevated but stable or falling according to at least two samples over 6 h. A great relevance was placed on the accurate assessment of baseline status, in fact 98% of the enrolled patients had at least two troponin values before PCI. Patients with NSTE-ACS, with one or no biomarker assessment available, or increasing biomarkers before PCI, required additional evidence of MI, while in STEMI patients PCI-related MI was not adjudicated by definition.

CHAMPION-PHOENIX (Table 4) randomized to cangrelor or clopidogrel 11,145 patients who had not previously received a $P2Y_{12}$ antagonist and required PCI, including patients with stable angina and ACS (with or without ST-segment elevation).[57] The primary efficacy end point (composite of death, MI, ischemia-driven revascularization or ST at 48 h after randomization) was lower with cangrelor compared to clopidogrel (4.7% vs. 5.9%, respectively, $p = 0.005$), driven by decrease of acute periprocedural MI and ST. The benefit from cangrelor was consistent across several prespecified subgroups, except for diabetic patients, who represented 27.8% of the global population ($p = 0.26$). No differences were observed in the primary safety end point (0.16% vs. 0.11%; $p = 0.44$). Overall, the data suggest a promising role for cangrelor, particularly for patients with ACS who could benefit from its pharmacologic rapidity in the onset/offset of action. Future studies are needed, however, to determine the optimal way to transition ACS-PCI patients from cangrelor to prasugrel or ticagrelor; such patients represented only 43% of patients recruited in the CHAMPION-PHOENIX trial. The prespecified pooled analysis of patient-level data from the three cangrelor trials confirmed the lower rates of PCI periprocedural thrombotic complications (3.8% vs. 4.7%; $p = 0.0007$) and ST (0.5% vs. 0.8%, $p = 0.0008$), with no difference in major bleeding.[58]

Due to its rapid on/off effect, cangrelor also has potential as a bridging agent in patients requiring surgery, by adequately preventing ischemic events while allowing rapid restoration of platelet function on therapy discontinuation in the event of bleeding. The BRIDGE (bridging anticoagulation in patients who require temporary interruption of warfarin therapy for an elective invasive procedure or surgery) study evaluated the efficacy of this strategy for patients taking clopidogrel who are scheduled for surgery (Table 4).[59] A total of 210 patients taking thienopyridines for ACS or after stent placement, who were awaiting CABG, had their thienopyridine stopped and were then randomized to either cangrelor (0.75 μg/kg/min) or placebo for at least 48 h. The study drug was discontinued 1–6 h before CABG surgery. Patients randomized to cangrelor had lower levels of platelet reactivity throughout the treatment period compared with placebo. There was no significant difference in major bleeding prior to CABG surgery, although minor bleeding episodes were numerically higher with cangrelor.[59] These findings demonstrate the potential role of cangrelor in this common clinical setting; however, due to the use of a surrogate end point (platelet reactivity as the primary end point), this trial must be interpreted with caution.

Cangrelor has been approved in Europe and United States for the reduction of thrombotic cardiovascular events in adult patients with CAD undergoing PCI who have not received an oral $P2Y_{12}$ inhibitor prior to the PCI procedure and in whom oral therapy with $P2Y_{12}$ inhibitors is not feasible or desirable. Current European guidelines on NSTE-ACS state that its use may be considered in $P2Y_{12}$ inhibitor-naive patients undergoing PCI (Class IIb level of evidence A).[60]

4.3. Elinogrel

Elinogrel has the unique advantage of being the only $P2Y_{12}$ inhibitor to be administered both orally and intravenously. This could provide a rapid effect like cangrelor, but without the need of shifting after PCI to another oral $P2Y_{12}$ inhibitor. However, elinogrel is not

currently approved due to absence of phase 3 trials supporting its safety and effectiveness. The phase 2A trial ERASE-MI (early rapid reversal of platelet thrombosis with intravenous elinogrel before PCI to optimize reperfusion in acute myocardial infarction) was designed to investigate the safety and tolerability of escalating doses (10, 20, 40, and 60 mg) as a single intravenous bolus before diagnostic coronary angiography (except primary PCI).[61] Seventy patients were randomized in the dose-escalation study, but the dose confirmation phase was not started because the trial was prematurely terminated for administrative reasons. No differences in serious adverse events, bleeding, laboratory values, corrected TIMI frame count, or ST-resolution were demonstrated between elinogrel and placebo.[61] The phase 2B trial INNOVATE (intravenous and oral administration of elinogrel to evaluate tolerability and efficacy)-PCI randomized 652 patients to receive clopidogrel (300 or 600 mg loading dose before PCI followed by 75 mg daily) or elinogrel (80 or 120 mg IV followed by 50 or 100 or 150 mg twice daily).[62] Elinogrel was found to be associated with increased TIMI combined bleeding (largely related to increased bleeding requiring medical attention), nonsignificant increase of periprocedural MI, significant increase of dyspnea and transaminase elevation, but there were no cases of heart block, bradycardia, hypotension, or liver failure.[62]

5. No-reflow treatment

During the last decades, the use of new pharmacological and mechanical therapies allowing recanalization of the infarct-related epicardial coronary artery (IRA) has determined a significant improvement of the acute MI prognosis. Many efforts have been made in order to achieve a more rapid and effective IRA recanalization and myocardial reperfusion, particularly through primary PCI in the setting of STEMI. However, mortality still remains considerable and 'no-reflow' phenomenon is responsible, at least in part, for worse outcomes.[63,64] It is described as the inability to effectively restore myocardial reperfusion in a previously ischemic region in the IRA territory despite its successful recanalization.[63,64] The rate of no-reflow widely ranges (5–50%) on the basis of the method used for its assessment. Its pathogenesis is mainly related to ischemia damage (particularly when >45 min), distal embolization, and reperfusion injury.[63,64] Therefore, the reduction of time from ischemia onset and the use of strategies reducing ischemia and micro-thromboemboli could be able to reduce no-reflow. A chronic therapy with statins also seems to reduce no-reflow by reducing the susceptibility of microcirculation to injury.[65,66]

Among the pharmacologic approaches to treat no-reflow, the most studied include:

GPIs, particularly abciximab, have shown to provide benefits in case of no-reflow.[67,68] Their use seems to reduce thrombus burden, improving microvascular perfusion. Intracoronary administration of abciximab could be considered for this indication.[52,67]

Adenosine induces coronary vasodilation and activates intracellular cardioprotective signaling pathways and can be administered either intracoronarily or intravenously. It has demonstrated benefits on reduction of no-reflow and improvement of outcomes.[69–72] Generally, an intracoronary dose of 30–60 µg or more is recommended during primary PCI in case of no-reflow, particularly if a microvascular spasm is supposed. Also, an investigational product (GP-531), able to increase adenosine levels during ischemia, was shown to reduce the 'no-reflow' and the infarct size in an animal model.[73]

Other vasodilators such as verapamil, nitroprusside, and nicardipine have also been investigated to improve microvascular perfusion through counterbalancing coronary spasm and regulating endothelial function.[74–77] Although initial benefits were observed with nitroprusside, the intracoronary injection of 60 µg compared with placebo in a randomized trial failed to improve coronary flow and myocardial reperfusion.[74] The intracoronary administration of verapamil has been studied in several studies and a meta-analysis of 539 patients has shown benefits in reducing no-reflow/slow-reflow, corrected TIMI frame count, wall motion index, and also the 2-month rate of MACE.[77]

Nicorandil has been supposed to be useful for no-reflow due to its anti-ischemia and antianginal benefits.[78,79] Although some benefits have been described, no firm data support its use and it is not widely used for no-reflow during primary PCI.

6. Conclusions

The pharmacologic strategies to be used in the periprocedural period in order to prevent and treat PCI complications have increased in the last few years. New interesting options have been recently developed, but they need to be further studied in the near future to demonstrate their beneficial efficacy and safety profiles compared with the currently available drugs.

7. Expert opinion

In the last decade, several efforts have been made in the research regarding drugs to be used before, during, and after PCI, with several important new developments currently available as compared with 10–20 years ago.

Further new drugs are hoped to be available in the next years in order to minimize ischemic and bleeding events and to improve patients' prognosis during and after PCI.

The anticoagulation therapy has achieved a satisfying balance between benefits and risks, because bivalirudin has demonstrated to have similar ischemic complications compared to heparin, but a lower rate of bleeding events.

The evidence concerning other anticoagulants (i.e. argatroban, otamixaban, M118, pegnivacogin/anivamersen) is still preliminary and none of them could be currently considered as a potential alternative to UFH, LMWH, or bivalirudin.

Also, the pharmacopeia of antiplatelet agents has been greatly expanded in the last few years. The addition of clopidogrel to aspirin was clearly demonstrated to be beneficial for all patients undergoing PCI, particularly those with ACS in whom the duration of the DAPT should be longer that those patients undergoing PCI for stable CAD. Indeed, DAPT has become the cornerstone of all patients treated with PCI. Prasugrel and ticagrelor have clearly demonstrated to be associated with better outcomes compared with clopidogrel in the setting of ACS patients. Moreover, ticagrelor has recently demonstrated to improve prognosis when given well beyond 1 year in post-MI patients with stable CAD, in addition to aspirin therapy.[44] All these findings have open the door for a present and a future changing approach to patients with CAD compared to the previous standard of clopidogrel plus aspirin. Moreover, other new drugs have been developed with other potential implications for the future management of these patients. Whereas elinogrel did not provide encouraging results, vorapaxar and cangrelor seem to be a reasonable treatment option in selected patient subsets. In particular, cangrelor has the unique characteristic of being immediately active/inactive through its venous administration and might become a precious support for therapy before and during PCI, particularly for those with ACS in whom a more rapid antiplatelet effect is desired. As concerned GPIs, although their role has been downsized in the last years, they are still important for interventional cardiologists during the PCI and probably will continue to be precious in the future particularly in the setting of STEMI patients and in the case of PCI complications (thrombosis, no-reflow).

Finally, the no-reflow still remains a crucial complication during PCI because it negatively affects the patient's prognosis despite the vessel patency being properly achieved by stenting. In this field, the research has been focused mainly on the complex pathophysiological mechanisms and on the use of old drugs rather than designing or studying new drugs. The future perspective on the no-reflow phenomenon would be that of reducing its incidence (by improving antithrombotic therapy, reducing timing to PCI in ACS patients, and implementing PCI procedures) and trying to find more effective strategies to reverse it when occurs.

Declaration of interest

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Editorial

Bivalirudin Versus Unfractionated Heparin for Acute Coronary Syndromes: Do We Have a Winner?

Bivalirudina frente a heparina no fraccionada en síndromes coronarios agudos: ¿hay un vencedor?

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The most effective antithrombotic therapy for preventing ischemic complications while limiting bleeding risk in patients with an acute coronary syndrome (ACS) who are undergoing a percutaneous coronary intervention (PCI) is strongly debated.[1,2]

Bivalirudin and unfractionated heparin (UFH) are 2 of the most commonly used treatment regimens and have been compared in different trials.[1] Unfractionated heparin used to be the only anticoagulant drug used before and during PCI in ACS patients. The main advantage of using UFH is that it can be antagonized with intravenous protamine sulfate. However, UFH has some limitations including: *a)* the need for activated clotting time monitoring due to its variable dose-response relationship with poor predictable effects, *b)* platelet activation, and *c)* risk of heparin-induced thrombocytopenia (HIT) and HIT-thrombosis syndrome. Consequently, in the last few years, new anticoagulants with more pharmacologic and clinical advantages than UFH have been tested, although UFH still remains the standard of care for thrombosis prevention during PCI.[1]

Bivalirudin is a 20 amino-acid synthetic polypeptide that binds directly to thrombin thus inhibiting its enzymatic activity. Bivalirudin cannot be antagonized, but due to its short half-life, its effects are limited by stopping its infusion, and activated clotting time monitoring is not mandatory to verify the effects. Furthermore, bivalirudin does not activate platelets and does not cause HIT given that it does not interact with plasma proteins or cells.[1] In recent years, bivalirudin has emerged as an intriguing alternative to UFH, with the main advantage being the lower rates of major bleeding in patients with ACS, particularly in those with ST-segment elevation myocardial infarction (STEMI).[3–6] However, some concerns about bivalirudin use have been raised in terms of stent thrombosis (ST).[3,5,7,8]

Recently, interest in comparing these 2 drugs has been further increased due to the publication of the MATRIX trial.[9] This is the latest and largest study comparing bivalirudin and UFH in the setting of ACS. In a contemporary clinical practice (high percentage of revascularization, patients equally balanced to radial and femoral approach, UFH arm without routine use of glycoprotein IIb/IIIa inhibitors (GPI), prehospital antithrombotic treatment, inclusion of new platelet P2Y12 antagonists), this trial showed that the rates of major adverse cardiovascular events and net adverse clinical events were not significantly lower in ACS patients treated with bivalirudin compared with those treated with UFH at 30-days. Notably, bivalirudin was associated with lower rates of major bleeding and mortality but higher rates of ST as previously shown in some of the other trials, although these observations are limited by statistical considerations since the trial was not powered to explore these single endpoints. However, given the previous results of HORIZONS-AMI[3] and BRIGHT[4] trials, it will be interesting to see if the results of MATRIX will be confirmed or not during a longer follow-up.

In the article published in *Revista Española de Cardiología*, Verdoia et al[10] report the results of a systematic review and meta-analysis of randomized clinical trials comparing bivalirudin and UFH in patients with ACS. The study included 12 randomized clinical trials and 32 746 patients. The 12 trials were categorized as subgroups for clinical presentation (5 for STEMI and 6 for non—ST-segment elevation acute coronary syndrome [NSTEACS] and 1, MATRIX, divided the subgroups into both). Outcomes were analyzed at 30 days, although 1 trial provided in-hospital (SWITCH III) data and 1 at 48 hours after discharge (PROTECT-TIMI30). At 30 days, there were no significant differences in all-cause mortality (odds ratio [OR] = 0.91; 95% confidence interval [95%CI], 0.77-1.08; P = .28) without significant overall heterogeneity (I^2 = 4%). This result was consistent between subgroups of STEMI and NSTEACS (interaction P = .12), although a significant heterogeneity was observed (I^2 = 58%) with an opposite trend: NSTEACS OR 1.13 (95% CI, 0.82-1.55); STEMI OR 0.84 (95% CI 0.69-1.02). Stent thrombosis was higher in the bivalirudin treated patients (OR = 1.42; 95% CI 1.09-1.83; P = .008), although this result was calculated from only 8 of 12 trials and it is not clear if it referred to definite or to definite/probable ST. Interestingly, some heterogeneity emerged between subgroups (I^2 = 45%) with ST being significantly increased only in the 5 STEMI trials analyzed (MATRIX data are missing) but not in the 3 NSTEACS trials. Bivalirudin was found to be associated with lower rates of major bleeding (OR = 0.60; 95% CI, 0.54-0.67; $P < .0001$), consistently in STEMI and NSTEACS trials. However, a

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high heterogeneity emerged in the latter analysis (I^2 = 71%) and the meta-regression analysis demonstrated that this finding was significantly driven by the differential use of GPI with bivalirudin benefits observed in trials with higher use of GPI (P = .02). The study did not explore whether the use of GPI might have influenced mortality or ST. Similarly, there was no exploration of other outcomes (ie, cardiac mortality, myocardial infarction or composite endpoints) as well as the impact of other relevant differential factors (ie, access site or use on new P2Y12 inhibitors).

Systematic reviews and meta-analyses identify, appraise and synthesize all evidence on a specific research question. They allow an increase in the statistical power of treatment comparisons beyond that of individual studies. Thus, meta-analyses are considered the highest level of evidence and could contribute to help physicians stay up to date and to guide healthcare decisions in daily clinical practice.

However, the increasing popularity of these studies has led to duplicate meta-analyses on the same topic, sometimes with different results, which make their interpretation difficult for readers.[11] Notably, a recent study showed that more than half of meta-analyses have at least 1 overlapping meta-analysis, and some topics had up to 13 overlapping meta-analyses.[12] This is exactly what has happened in the comparison between bivalirudin and UFH. When making a search in PubMed, in which we restricted the search to publications from 2014 onward, we found that 24 meta-analyses have been published on this topic (Table).[7,8,10,13–33] Although there were some differences among these 24 studies, this is probably one of the more appropriate examples of overlapping meta-analysis on the same clinical question, which significantly contributes to confusion among readers.

A further relevant consideration on the performance of a meta-analysis concerns its methodology. The main principle to pool different studies in a single analysis is that the data/studies included should be similar (study design, eligibility criteria, type of patients and procedures, type of outcomes and their definitions, etc). Are we seeing an analysis of apples and oranges in the comparison of bivalirudin and UFH in ACS or PCI?[34] When considering the studies included, one could argue that clinical characteristics and clinical practice differ strongly among them. Trials including different clinical presentations (STEMI, NSTEMI, unstable angina) are pooled together and this is *per se* a relevant confounding factor. Nevertheless, the TENACITY trial was included in the meta-analysis, even though a quarter of patients underwent elective PCI. If we focus on the 5 trials on STEMI patients and the MATRIX subgroup of STEMI patients, important differences should be considered when pooling these studies together and interpreting the overall results: *a)* the bivalirudin regimen of post-PCI infusion significantly varied across trials, from being not routinely adopted in the HORIZONS-AMI, BRAVE-4 (Bavarian Reperfusion Alternatives Evaluation-4)[35] and HEAT-PPCI,[36] to being used in most of the patients in the EUROMAX trial[5] (low-dose or high-dose left at the operator's discretion, being finally used in 77.5% and

Table
Meta-analyses on Bivalirudin vs UFH Appearing in PubMed From 2014 to 1st April 2016

First author	Journal	Year	Setting	Studies included
Verdoia et al[10]	Rev Esp Cardiol	2016	ACS	12
Barria Perez et al[13]	Am J Cardiol	2016	PCI	30 (12 RCTs)
Zhang et al[14]	Int J Cardiol	2016	PCI	17
Shah et al[15]	Am Heart J	2016	STEMI	6
Farag et al[16]	Open Heart	2015	ACS	19
Li et al[17]	Medicine	2015	PCI	17
Navarese et al[18,a]	Thromb Haemost	2015	ACS	16
Kianoush et al[19,b]	Thromb Res	2015	PCI	25
Bavry et al[20]	PloS One	2015	PCI	15
Nairooz et al[21,c]	Catheter Cardiovasc Interv	2015	PCI	4
Ferrante et al[22]	Catheter Cardiovasc Interv	2015	STEMI	3
Ibebuogu er al[23,c]	Am J Cardiovasc Drugs	2015	PCI	6
Verdoia et al[24]	Thromb Res	2015	PCI	22
Capodanno et al[7]	Eur Heart J Acute Cardiovasc Care	2015	STEMI	5
Piccolo et al[25,d]	Thromb Haemost	2015	PCI	11
Huang et al[26]	Angiology	2015	PCI	20
Navarese et al[8]	J Am Coll Cardiol Intv	2015	ACS	13
Stone GW et al[27,e]	J Am Coll Cardiol	2015	STEMI	2 (patient-level)
Cassese et al[28]	Eurointervention	2015	PCI	10
Lipinski et al[29]	Cardiovasc Revasc Med	2014	PCI	14
Bangalore et al[30,f]	BMJ	2014	STEMI	5
Cavender et al[31]	Lancet	2014	PCI	16
Nairooz et al[32]	Am J Cardiol	2014	PCI/STEMI	7/2
Tarantini et al[33]	Am Heart J	2014	PCI	12

ACS, acute coronary syndrome; PCI, percutaneous coronary intervention; RCTs, randomized clinical trials; STEMI; ST-segment elevation myocardial infarction; UFH, unfractionated heparin.

[a] This is a network meta-analysis including various antithrombotic regimens for a total of 42 trials, but 16 were those comparing bivalirudin vs UFH with or without GPI.

[b] This meta-analysis includes RCTs comparing bivalirudin and an active control.

[c] This meta-analysis is focused on diabetic patients.

[d] This meta-analysis is focused on stent thrombosis as outcome.

[e] This is a patient-level meta-analysis of HORIZONS-AMI and EUROMAX trials.

[f] This is a network meta-analysis including various antithrombotic regimens for a total of 22 trials, but 5 were those comparing bivalirudin vs UFH with or without GPI.

22.5%, respectively) and BRIGHT (only high-dose allowed) or randomized in the MATRIX to post-PCI infusion or no infusion (low-dose or high-dose left at the operator's discretion, being used in approximately 63% and 37% respectively); *b)* GPI use differed markedly across trials (HORIZONS-AMI: 7.5% and 97.7% in the bivalirudin and UFH groups; EUROMAX: 11.5% and 69.1%; BRIGHT: 4.4% and 52.9%; HEAT-PPCI: 13.5% and 15.5%; BRAVE-4: 3.0% and 6.1%; MATRIX: 4.6% and 25.9%); *c)* access site for PCI (almost all femoral access in HORIZONS-AMI and BRAVE-4; three-quarters radial access in BRIGHT and HEAT-PPCI; well balanced in EUROMAX and MATRIX); *d)* new potent P2Y12 inhibitors (prasugrel or ticagrelor) were frequently used in EUROMAX, HEAT-PPCI, BRAVE-4 (all patients received prasugrel in the bivalirudin arm while all UFH patients received clopidogrel) and MATRIX, but not in HORIZONS-AMI or BRIGHT; *e)* the UFH dose adopted in heparin monotherapy-treated patients ranged from 70 U/kg in HEAT-PPCI to 100 U/kg in EUROMAX and BRIGHT with the first trial not showing that bivalirudin reduced major bleeding compared with the other trials; *f)* the HEAT-PPCI, which was the only trial to support UFH advantages over bivalirudin, enrolled all-comer patients but was the only single-center trial; and *g)* EUROMAX also included 8.5% of patients treated with enoxaparin in the control group. Similarly, substantial differences also can be found in the 6 trials classified as NSTEACS, such as clinical practice and definitions (for example the BAS [Bivalirudin Angioplasty Study] trial was published in 1995[37] and was reanalyzed in 2001[38] and enrolled patients in 1993-1994).

In addition to the obvious limitations related to the different designs and patient characteristics of the primary trials included, it should also be considered that pooled data from publications do not offer the opportunity to adjust, and—most of all—published data are sometimes managed or pooled differently from the original design of the trial. In the present analysis, for example, the BRIGHT trial, which randomized patients to 3 arms, was considered as 2-arm by pooling the UFH and UFH+GPI arms. Moreover, the MATRIX trial enrolled all ACS patients and for the present analysis its results were divided for STEMI and NSTEACS. Although sensitivity and meta-regression analyses often help to explore sources of heterogeneity in standard meta-analyses, only patient-level data overcome common limitations by improving internal validity and allowing time-to-event, subgroup, and covariable adjusted analyses.

The results of the present meta-analysis by Verdoia et al seem to be in line with previous literature regarding the benefits of bivalirudin on major bleeding and its risks in terms of ST. However, it is also important to stress that the main increase in ST related to bivalirudin use has been commonly described in acute rather than subacute ST[5–8] and that the post-PCI infusion of bivalirudin appears to reduce ST risks.[4,5] Future detailed subanalyses from the MATRIX trial could help to clarify this issue because this trial randomized patients to receive the bivalirudin post-PCI infusion or not and also included a large number of patients treated with the 2 different infusion regimens.[9] Verdoia et al, however, found no significant differences between bivalirudin and UFH in terms of mortality. The major doubt that remains unresolved is exactly the impact of the drug on mortality: is bivalirudin able to reduce all-cause and cardiovascular death? Major bleeding is an important prognostic determinant of mortality, but all-cause death seems nonsignificantly decreased despite the reduction of major bleeding events.[8,10] Interestingly, bivalirudin seems to offer benefits in mortality only in patients with STEMI undergoing primary-PCI, as shown in this and other meta-analyses.[7,10,15] However, this apparent differential impact on STEMI and NSTEACS could also be related to the characteristics and differences among the trials included in the analysis. Indeed, the most contemporary MATRIX trial demonstrated consistent results between ACS subgroups.[9] Overall, the absence of mortality benefits here described reinforces the concept that reducing bleeding, even the most severe bleeding events, does not necessarily translate into a reduction of major adverse cardiovascular events. It is possible that the increase of ST, as well as a trend toward an increase of myocardial infarction and target vessel revascularization, could mitigate the advantages in bleeding events, which would help to explain the absence of differences in composite events and the uncertainties on mortality benefits.[7,9,15]

Finally, the cost-effectiveness of choosing bivalirudin rather than UFH should be considered. Are the overall results sufficient to justify the use of bivalirudin despite its much more higher cost?

Some important suggestions for readers have been previously published to aid understanding and to contrast uncertainties when overlapping meta-analyses obtain discordant conclusions.[11]

In conclusion, do we finally have a winner between bivalirudin and UFH? Although well conducted, this meta-analysis does not provide a definitive conclusion and practitioners still need to use clinical judgment in deciding between a costly bleeding-saving treatment strategy and the costless standard of care, consisting of UFH and limited use of GPI. It remains to be understood whether the use of bivalirudin translates into a real mortality advantage and whether prolongation of infusion after PCI in a full PCI regimen mitigates the risks of ST without trade-offs. While research is still on-going to tease out these outstanding questions, the market penetration of bivalirudin will be probably more affected by the affordability of generic bivalirudin formulations than by its scientific merits.

CONFLICTS OF INTEREST

None declared.

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EDITORIAL COMMENT

Bivalirudin in Current Practice

Melius Abundare Quam Deficere?*

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The optimal antithrombotic therapy for preventing ischemic complications while limiting bleeding risk in patients with acute coronary syndrome (ACS) who are undergoing primary percutaneous coronary intervention (pPCI) remains an area of great controversy (1). The quest for an ideal parenteral anticoagulant agent able to replace unfractionated heparin (UFH) has remained an ongoing topic for investigation since the 1990s. Bivalirudin was compared with UFH first in experimental models and then in patients with coronary artery disease (CAD). During this long-lasting journey, contrasting evidence has been accumulated on bivalirudin efficacy and safety profile compared with UFH. After initial promising findings in the early 1990s, HAS/BAS (Hirulog/Bivalirudin Angioplasty Study) published in 1995 (conducted in 1993 to 1994) showed that bivalirudin (bolus of 1.0 mg/kg followed by infusion of 2.5 mg/kg/h for 4 h, then 0.2 mg/kg/h for 14 to 20 h) had similar efficacy but lower bleeding risk than high and prolonged regimen of UFH (bolus of 175 U/kg followed by infusion of 15 U/kg/h for 18 to 24 h). However, the sponsor interpreted these findings as insufficient to warrant further investment, which led to terminate further clinical studies with bivalirudin, including the ongoing TIMI-8 (Thrombolysis In Myocardial Infarction-8) trial. Bivalirudin was then acquired by The Medicines Company, which profoundly invested in a new era of clinical studies. A meta-analysis of randomized trials by Kong et al. (2) in 1999 suggested that bivalirudin was as effective as UFH but safer in patients with CAD. The results of HAS/BAS study were also reanalyzed updating the primary endpoint definition and modifying its time point, which generated new evidence suggesting that bivalirudin was superior for both efficacy and safety at 7 and 90 days (3). Multiple trials were then conducted with bivalirudin at a revised bolus and post-bolus infusion regimen in patients with Non-ST-segment elevation-acute coronary syndrome (NSTE-ACS), ST-segment elevation myocardial infarction (STEMI), or both (Online Table 1) against various comparator arms (UFH with or without glycoprotein IIb/IIIa inhibitors [GPI] and on top of various oral $P2Y_{12}$ inhibitors), which resulted in a large body of evidence for bivalirudin in PCI patients.

Across studies and regimens, bivalirudin has consistently shown to mitigate the bleeding risk (4). This benefit has been observed against all possible comparator arms, including UFH plus routine use of GPI, UFH plus liberal or restricted use of GPI and UFH alone. Importantly, not only access site bleeding was attenuated by bivalirudin but also those not access site-related, which are at least as frequent in ACS patients and most likely more detrimental on prognosis.

Yet, in STEMI patients undergoing pPCI, all major studies so far conducted have identified a sizable risk of acute stent thrombosis (ST) across all compactors, including UFH+GPI, UFH±GPI, or UFH alone (4). This observation fueled an ongoing debate on the value of this anticoagulant option in current practice, where, despite growing awareness on the importance of bleeding on patient outcomes, the avoidance of ST remains the number 1 *obsession* by all interventionists.

To mitigate that risk, 2 studies have protocol mandated and 1 study randomly allocated bivalirudin patients to continue the treatment well after PCI.

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Results were mixed as in only 1 of the 3 trials no excess of ST risk was observed in patients receiving post-intervention bivalirudin infusion. Yet, focusing on the post-PCI bivalirudin regimen, results are apparently concordant in suggesting that only a full PCI regimen after intervention can mitigate that risk excess to null.

SEE PAGE 1313

In this issue of *JACC: Cardiovascular Interventions*, Shah et al. (5) should be commended for the completion of a traditional and network meta-analysis, apparently restricted to patients with STEMI undergoing pPCI, with a specific focus to acute ST. This analysis is timely and provides additional evidence that the effects of anti-thrombotic drugs are largely regimen-dependent. Bivalirudin was unsurprisingly associated to a significantly higher risk of acute ST (4). Yet, the new finding is that a post-pPCI infusion at full dose (Biv-Full) (1.75 mg/kg/h) abolished that risk as compared with the low-dose (Biv-Low) (0.25 mg/kg/h) or no infusion as well as with UFH. Notably, the significant benefit of bivalirudin over UFH in terms of reduction of major bleeding persisted in studies using the post-pPCI Biv-Full treatment strategy.

These results are potentially practice changing and largely consistent with the updated recommendations for use of bivalirudin in the United States.

However, there are numerous limitations to this analysis, which should raise caution.

Shah et al. (5) aimed at restricting the analysis to pPCI patients. Yet, they included a sizable proportion of NSTE-ACS patients. Although the inclusion of all MATRIX (Minimizing Adverse Hemorrhagic Events by Transradial Access Site and Systemic Implementation of Angiox) study patients (i.e., including 3,203 [44%] NSTE-ACS) was acknowledged, Shah et al. (5) did not clarify to the readers that 269 NSTE-ACS patients also included in BRIGHT (Bivalirudin in Acute Myocardial Infarction vs Heparin and GPI Plus Heparin Trial) were pooled due to unavailability of individual patient data. This may have diluted the relative and absolute risks of ST in bivalirudin-treated patients.

The main limitation to this analysis however is its largely nonrandomized and unadjusted nature.

Network meta-analyses are very powerful and increasingly accepted tools to enhance study power and artificially create comparator arm(s) levering on the relative risk reductions observed within randomized arms. Yet, its use for observational findings may amplify the biases known to occur when treatment is not randomly allocated.

The MATRIX trial remains today the only study where patients treated with bivalirudin were randomized to receive post-PCI infusion or no infusion of bivalirudin (6). Hence, the data comparing post-PCI versus no post-PCI bivalirudin infusion (Biv-No) are largely indirect since HORIZONS-AMI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction) and HEAT-PPCI (How Effective Are Antithrombotic Therapies in Primary Percutaneous Coronary Intervention) studies provided only data on Biv-No strategy, whereas BRIGHT and EUROMAX (European Ambulance Acute Coronary Syndrome Angiography Trial) provided only data on Biv-Full. Even more worrisome is the comparison between low versus full post-PCI regimen.

No study so far has randomized the post-PCI bivalirudin regimen. A full bivalirudin regimen was protocol mandated in BRIGHT, whereas both the EUROMAX and MATRIX studies left post-PCI regimens to the discretion of the treating physicians, which was consistent with current and previous European or North American bivalirudin label, respectively.

Consequently, the Biv-Full population is a mixture of patients derived from BRIGHT, EUROMAX, and MATRIX studies, whereas Biv-Low is a smaller population that was derived exclusively from the EUROMAX and MATRIX trials. In both trials, the 2 populations were imbalanced in number with a majority of patients receiving Biv-Low rather than Biv-Full (63% vs. 37% in MATRIX and 77.5% vs. 22.5% in EUROMAX, respectively). Operators have probably applied a clinical selection in using a regimen over the other, administering Biv-Low to patients with higher bleeding risk whereas Biv-Full to those at increased risk of acute ST.

Additionally, the heterogeneity in the duration of post-PCI infusion should be considered as further potential source of bias. In EUROMAX, bivalirudin had to be prolonged per protocol for at least 4 h after PCI and overall the median duration was 268 min (interquartile range [IQR]: 250 to 292 min). In BRIGHT, the protocol stated that Biv-Full was at least 30 min, but maximum 4 h and that a supplementary infusion at low dose (0.2 mg/kg/h) was allowed up to 20 h at operator's discretion. All patients received a post-PCI infusion of Biv-Full for a median duration of 180 min (IQR: 148 to 240) but 115 patients (15.6%) thereafter also received the optional 0.2 mg/kg/h dose for a median duration of 400 min (IQR: 375 to 410 min). Finally, MATRIX patients assigned to post-PCI infusion were to receive Biv-Full for up to 4 h or Biv-Low for at least 6 h and, overall the average durations were 264 ± 209.8 min and 433 ± 248 min, respectively.

Hence, these results would need prospective validation. Currently, the SWEDEHEART (Bivalirudin vs Heparin in NSTEMI and STEMI in Patients on Modern Antiplatelet Therapy in SWEDEHEART A Multicenter, Prospective, Randomized Controlled Clinical Trial Based on the SWEDEHEART Platform; NCT02311231) trial is ongoing. Although it will contribute to the evidence in the long-lasting journey of bivalirudin versus UFH comparison, the protocol mandates the use of post-PCI bivalirudin at full regimen only.

Should bivalirudin be used from now on in STEMI patients with post-PCI full dose infusion? An individual patient meta-analysis is planned which shall at least try to adjust for measurable and measured confounders given the largely non-randomized nature of this comparison. Whether prolonging bivalirudin at full PCI regimen after PCI mitigates ST while not increasing bleeding risks remains to be ascertained.

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KEY WORDS anticoagulation, bivalirudin, heparin, percutaneous coronary intervention, post-procedural dosage

APPENDIX For a supplemental table, please see the online version of the article.

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Bivalirudin or Heparin in Patients Undergoing Invasive Management of Acute Coronary Syndromes

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ABSTRACT

BACKGROUND Contrasting evidence exists on the comparative efficacy and safety of bivalirudin and unfractionated heparin (UFH) in relation to the planned use of glycoprotein IIb/IIIa inhibitors (GPIs).

OBJECTIVES This study assessed the efficacy and safety of bivalirudin compared with UFH with or without GPIs in patients with acute coronary syndrome (ACS) who underwent invasive management.

METHODS In the MATRIX (Minimizing Adverse Haemorrhagic Events by Transradial Access Site and Systemic Implementation of AngioX) program, 7,213 patients were randomly assigned to receive either bivalirudin or UFH with or without GPIs at discretion of the operator. The 30-day coprimary outcomes were major adverse cardiovascular events (MACEs) (a composite of death, myocardial infarction, or stroke), and net adverse clinical events (NACEs) (a composite of MACEs or major bleeding).

RESULTS Among 3,603 patients assigned to receive UFH, 781 (21.7%) underwent planned treatment with GPI before coronary intervention. Bailout use of GPIs was similar between the bivalirudin and UFH groups (4.5% and 5.4%) ($p = 0.11$). At 30 days, the 2 coprimary endpoints of MACEs and NACEs, as well as individual endpoints of mortality, myocardial infarction, stent thrombosis or stroke did not differ among the 3 groups after adjustment. Compared with the UFH and UFH+GPI groups, bivalirudin reduced bleeding, mainly the most severe bleeds, including fatal and nonaccess site–related events, as well as transfusion rates and the need for surgical access site repair. These findings were not influenced by the administered intraprocedural dose of UFH and were confirmed at multiple sensitivity analyses, including the randomly allocated access site.

CONCLUSIONS In patients with ACS, the rates of MACEs and NACEs were not significantly lower with bivalirudin than with UFH, irrespective of planned GPI use. However, bivalirudin significantly reduced bleeding complications, mainly those not related to access site, irrespective of planned use of GPIs. (Minimizing Adverse Haemorrhagic Events by Transradial Access Site and Systemic Implementation of AngioX [MATRIX]; NCT01433627) (J Am Coll Cardiol 2018;71:1231–42) © 2018 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome(s)

CABG = coronary artery bypass grafting

GPI = glycoprotein IIb/IIIa inhibitor

MACE = major adverse cardiovascular event

NACE = net adverse clinical event

NSTE-ACS = non–ST-segment elevation acute coronary syndrome(s)

PCI = percutaneous coronary intervention

ST = stent thrombosis

TIMI = Thrombolysis In Myocardial Infarction

UFH = unfractionated heparin

The most effective antithrombotic therapy in patients with an acute coronary syndrome (ACS) who are undergoing a percutaneous coronary intervention (PCI) remains strongly debated (1–3). Unfractionated heparin (UFH) (with or without planned glycoprotein IIb/IIIa inhibitors [GPIs]) and bivalirudin are 2 of the most commonly used antithrombotic strategies and have been compared in different trials since the 1990s (4). Conflicting data have accumulated since then, so that the comparative safety and effectiveness profile of bivalirudin compared with UFH alone in current practice remains unclear.

Although some trials, including EUROMAX (European Ambulance Acute Coronary Syndrome Angiography Trial) (5,6) and BRIGHT (Bivalirudin in Acute Myocardial Infarction vs Heparin and GPI Plus Heparin Trial) (7), have shown benefits in terms of major bleeding reduction related to bivalirudin use, irrespective of GPI use in the UFH arm, the HEAT-PPCI (How Effective are Antithrombotic Therapies in Primary Percutaneous Coronary Intervention) and the most recent VALIDATE-SWEDEHEART (Bivalirudin versus Heparin in ST-Segment and Non-ST-Segment Elevation Myocardial Infarction in Patients on Modern Antiplatelet Therapy in the Swedish Web System for Enhancement and Development of Evidence-based Care in Heart Disease Evaluated according to Recommended Therapies Registry Trial) studies showed that heparin alone did not increase bleeding events compared with bivalirudin (8,9). Because planned use of GPIs in patients who receive UFH has been reduced, this discrepancy is notable.

SEE PAGE 1243

Therefore, we pre-specified to examine the comparative efficacy and safety profile of bivalirudin compared with UFH alone or with UFH+GPI in the context of the largest contemporary trial to assess the value of bivalirudin in an all-comer ACS population and the only study that allocated access site by random selection.

METHODS

STUDY DESIGN. The MATRIX (Minimizing Adverse Haemorrhagic Events by Transradial Access Site and Systemic Implementation of AngioX) antithrombin study is a randomized, multicenter trial that compared bivalirudin (the use of GPIs was restricted

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to bailout conditions) with UFH (use of GPI was left to the discretion of the investigator) in 7,213 patients with ACS with or without ST-segment elevation, in whom PCI was planned. This was 1 of 3 trials of the MATRIX program (NCT01433627), as previously described (1,10).

STUDY PATIENTS. Patients with non–ST-segment elevation acute coronary syndrome (NSTE-ACS) were eligible if they had a history consistent with new or worsening cardiac ischemia that occurred while they were at rest or with minimal activity within 7 days before randomization, and met at least 2 high-risk criteria among the following: 1) age of 60 years or older, elevation of cardiac biomarkers, or electrocardiographic changes compatible with ischemia; and 2) if they were considered to be candidates for PCI after completion of coronary angiography. Patients with ST-segment elevation myocardial infarction (STEMI) were eligible if they presented within 12 h of the onset of symptoms or between 12 and 24 h after symptom onset if there was evidence of continued ischemia or previous fibrinolytic treatment. The main inclusion and exclusion criteria were previously reported (1,10). All patients provided written informed consent.

STUDY PROTOCOL AND RANDOMIZATION. Using a computer-generated random sequence, we randomized patients in a 1:1 ratio to receive bivalirudin or UFH, with a random block size stratified by the type of ACS (i.e., with ST-segment elevation vs. without ST-segment elevation) intended for or ongoing use of a $P2Y_{12}$ inhibitor (clopidogrel vs. ticagrelor or prasugrel), and study site. Patients with STEMI underwent randomization before coronary angiography; patients with NSTE-ACS underwent randomization immediately after completion of angiography but before the start of PCI.

All interventions were administered in an open-label fashion. Bivalirudin was given according to the product labeling, with a bolus of 0.75 mg/kg of body weight, followed immediately by an infusion of 1.75 mg/kg/h until completion of PCI. Receiving a post-PCI bivalirudin infusion or no post-PCI infusion was randomly determined (MATRIX treatment duration). In those assigned to bivalirudin prolongation, the choice between 2 regimens (full dose for up to 4 h or reduced dose of 0.25 mg/kg/h for at least 6 h) was made at the discretion of the treating physicians. UFH was administered at a dose of 70 to 100 U or 50 to 70 U/kg in patients who did not receive or received GPI, respectively. Subsequent UFH dose adjustment based on the activated clotting time was left to the discretion of the treating physicians. A GPI could be administered before PCI in all patients in the UFH group based on judgment of the treating physician, but the drug was to be administered in the bivalirudin group only to patients who had periprocedural ischemic complications (i.e., no-reflow or giant thrombus) after PCI. The use of other medications was allowed according to professional guidelines.

FOLLOW-UP AND STUDY OUTCOMES. Clinical follow-up was performed at 30 days. Two coprimary 30-day composite outcomes were pre-specified: major adverse cardiovascular events (MACEs), defined as the composite of all-cause mortality, myocardial infarction (MI), or stroke; and net adverse clinical events (NACEs), defined as the composite of MACEs or major bleeding not related to coronary artery bypass graft (CABG) (Bleeding Academic Research Consortium type 3 or 5). Secondary outcomes included each component of the composite outcomes, cardiovascular mortality, and stent thrombosis (ST). Bleeding was also assessed and adjudicated on the basis of the TIMI (Thrombolysis In Myocardial Infarction) and GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator) scales. Stent thrombosis was defined as the definite or probable occurrence of a stent-related thrombotic event according to the Academic Research Consortium classification. All outcomes were pre-specified. An independent clinical events committee blinded to treatment allocation adjudicated all suspected events.

STATISTICAL ANALYSIS. The trial was powered for superiority on the 2 coprimary composite outcomes at 30 days, expecting a rate reduction of 30% that corresponded to a rate ratio of 0.70.

All analyses were performed per intention-to-treat principle, including all patients in the analysis based on the allocated access. Events up to 30 days post-randomization were considered. We analyzed primary and secondary outcomes as time to first event using the Mantel-Cox method, accompanied by log-rank tests to calculate corresponding 2-sided p values. We did not perform any adjustments for multiple comparisons but set the alpha error at 2.5% to correct for the 2 coprimary outcomes. We analyzed secondary outcomes with a 2-sided alpha set at 5% to allow conventional interpretation of results. Survival curves were constructed using Kaplan-Meier estimates. We performed stratified analyses according to the dosage of heparin used or to access site (radial or femoral) and we estimated possible interaction terms across comparisons.

Whether the attribution to bivalirudin and UFH arms was randomized, the planned use of GPI was only allowed in the UFH arm and was left to the discretion of the physician. Because of the

nonrandomized nature of the planned GPI use in the UFH arm, clinical outcomes were adjusted for confounders. A multivariable logistic model was used to obtain adjusted analyses, and the variables included were age, sex, body mass index, type of ACS, center, diabetes, smoking, hypertension, previous MI, previous CABG, previous stroke and/or transient ischemic attack (TIA), peripheral vascular disease, Killip class, previous lytic therapy, creatinine, intra-aortic balloon pump, heparin use before arrival at the catheterization laboratory, full procedural success, duration of the procedure, treated vessel, SYNTAX (Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) score, proximal location of lesion, large vessel caliber (defined by using a stent ≥3 mm or post-dilatation balloon ≥3.5 mm), ≥1 complex lesion, thrombus in the treated lesion, TIMI flow 0 to 1 before PCI, and clopidogrel at discharge.

As a sensitivity analysis, a propensity score was calculated to minimize any selection bias due to the differences in clinical characteristics between the 2 treatment groups (i.e., UFH alone and UFH + GPI). For each patient in the UFH arm, a propensity score that indicated the likelihood of receiving GPI was calculated by the use of a nonparsimonious multivariable logistic regression. A propensity score that indicated the predicted probability of receiving a specific treatment conditional on the observed covariates was then calculated from the logistic equation for each patient. Then, the formula was also applied for patients in the bivalirudin arm (in which per-protocol planned GPI was not allowed). The following variables were included: age, sex, body mass index, type of ACS, center, diabetes, smoking, family history of coronary artery disease, hypertension, hypercholesterolemia, previous MI, previous PCI, previous stroke and/or TIA, peripheral vascular disease, chronic obstructive pulmonary disease, Killip class, cardiac arrest, left ventricular ejection fraction, creatinine, treated vessel, SYNTAX score, proximal location of the lesion, large and/or small vessel caliber, ≥1 complex lesion, thrombus in the treated lesion, TIMI flow 0 to 1 before PCI, medication in the catheterization laboratory (fondaparinux, enoxaparin, beta-blockers, ticagrelor, clopidogrel), and lesions treated and stented per patients. The individual propensity score was incorporated into the adjustment model to compare outcomes. In addition, to reduce the effect of treatment selection bias and potential confounding related to these observational comparisons, we performed rigorous adjustment for significant differences in the baseline characteristics of patients with propensity score matching using the following algorithm: 1:1 optimal match with a 0.1 SD caliper and no replacement. All analyses were performed using the STATA version 14.1 (StataCorp, College Station, Texas) and R (R Foundation, Vienna, Austria) statistical packages.

RESULTS

PATIENTS. The MATRIX-antithrombin trial enrolled 7,213 patients with ACS from 78 centers in Italy, the Netherlands, Spain, and Sweden between October 2011 and November 2014. Of these patients, 3,610 patients were assigned to receive bivalirudin and 3,603 were assigned to receive UFH, of whom 2,822 received UFH without planned GPI infusion (UFH alone group) and 781 patients underwent planned treatment with GPI before coronary intervention (UFH+GPI group). In the bivalirudin and UFH groups, a similar proportion of patients received bailout use of GPIs during treatment (4.5% and 5.4%, respectively; $p = 0.11$).

Clinical and procedural characteristics as well as choice of concomitant medications during hospitalization or at discharge were imbalanced among the 3 groups (Online Tables 1 to 3).

Compared with UFH alone, patients with planned GPI were younger, more frequently male, smokers, and had STEMI or cardiac arrest at presentation, but less frequently had a history of diabetes, hypertension, MI, PCI, CABG, stroke/TIA, chronic obstructive pulmonary disease, peripheral vascular disease, or renal dysfunction (Online Table 1). Patients who received planned GPI infusion experienced a longer procedural time, despite more frequently receiving single-vessel intervention. They more frequently required intra-aortic balloon pumps; recanalization of occluded, proximally located, and thrombus-containing lesion(s); and required larger stent diameters and longer overall stent length (Online Table 2).

CLINICAL OUTCOMES. Unadjusted and adjusted comparisons for the 30-day outcomes across the groups are shown in **Tables 1 to 3**. After multivariable or propensity-score adjustment, the 2 coprimary endpoints of MACEs and NACEs did not differ among the 3 groups (**Figure 1, Central Illustration, Tables 1 to 3**).

Similarly, there were no within-groups differences with respect to the individual endpoints of mortality, MI, ST, or stroke (**Tables 1 to 3**). However, bivalirudin remained associated with reduced risks of bleeding due to lower rates of the most severe occurrences, including fatal and nonaccess site–related, mainly gastrointestinal events compared with UFH alone and to lower risks of both gastrointestinal and

TABLE 1 Clinical Outcomes up to 30 Days in Bivalirudin Versus UFH Alone

	All (N = 7,213)	Bivalirudin (n = 3,610)	UFH Alone (n = 2,822)	Unadjusted Rate Ratio (95% CI)	p Value	Multivariable Adjusted Rate Ratio (95% CI)	p Value	Propensity Score Adjusted Rate Ratio (95% CI)	p Value
Death, MI, stroke	762 (10.6)	371 (10.3)	327 (11.6)	0.89 (0.76–1.03)	0.113	1.02 (0.85–1.22)	0.843	0.96 (0.81–1.13)	0.618
Death, MI, stroke, BARC 3 or 5	845 (11.7)	401 (11.1)	362 (12.8)	0.87 (0.75–1.00)	0.047	0.96 (0.81–1.14)	0.664	0.92 (0.78–1.07)	0.282
Death, MI, stroke, BARC 3 or 5, TVR, ST	860 (11.9)	410 (11.4)	367 (13.0)	0.87 (0.76–1.01)	0.059	0.97 (0.82–1.15)	0.739	0.92 (0.79–1.08)	0.309
Death	142 (2.0)	59 (1.6)	65 (2.3)	0.71 (0.5–1.01)	0.055	0.91 (0.43–1.94)	0.805	0.71 (0.48–1.04)	0.08
Cardiovascular death	136 (1.9)	56 (1.6)	63 (2.2)	0.69 (0.48–1.00)	0.046	1.01 (0.45–2.28)	0.976	0.69 (0.47–1.03)	0.072
MI	610 (8.5)	307 (8.5)	258 (9.1)	0.93 (0.79–1.1)	0.391	1.03 (0.85–1.24)	0.771	1.03 (0.86–1.23)	0.778
Stroke	29 (0.4)	13 (0.4)	15 (0.5)	0.68 (0.32–1.42)	0.301	0.56 (0.24–1.28)	0.17	0.58 (0.27–1.28)	0.178
TIA	14 (0.2)	5 (0.1)	7 (0.2)	0.56 (0.18–1.76)	0.313	0.91 (0.21–4.02)	0.905	0.73 (0.22–2.42)	0.611
TVR	87 (1.2)	52 (1.4)	25 (0.9)	1.63 (1.01–2.62)	0.044	1.50 (0.90–2.51)	0.118	1.40 (0.85–2.29)	0.186
ST definite	57 (0.8)	36 (1.0)	15 (0.5)	1.88 (1.03–3.43)	0.037	1.77 (0.91–3.41)	0.091	1.56 (0.84–2.91)	0.163
Acute	33 (0.5)	20 (0.6)	9 (0.3)	1.74 (0.79–3.82)	0.164	1.85 (0.76–4.50)	0.178	1.45 (0.64–3.27)	0.369
Subacute	24 (0.3)	16 (0.4)	6 (0.2)	2.08 (0.82–5.33)	0.117	1.56 (0.57–4.25)	0.386	1.72 (0.65–4.54)	0.275
ST definite/probable	80 (1.1)	45 (1.2)	26 (0.9)	1.35 (0.83–2.19)	0.218	1.57 (0.88–2.83)	0.129	1.32 (0.79–2.23)	0.291
Acute	38 (0.5)	22 (0.6)	12 (0.4)	1.43 (0.71–2.90)	0.313	1.93 (0.80–4.68)	0.144	1.25 (0.59–2.66)	0.562
Subacute	42 (0.6)	23 (0.6)	14 (0.5)	1.28 (0.66–2.50)	0.459	1.18 (0.52–2.64)	0.692	1.39 (0.68–2.85)	0.371
Bleeding	873 (12.1)	391 (10.8)	345 (12.2)	0.89 (0.77–1.02)	0.101	0.84 (0.71–1.00)	0.044	0.85 (0.72–1.00)	0.043
BARC 1	427 (5.9)	190 (5.3)	170 (6.0)	0.87 (0.71–1.07)	0.201	0.83 (0.66–1.04)	0.10	0.84 (0.68–1.05)	0.126
BARC 2	304 (4.2)	151 (4.2)	107 (3.8)	1.10 (0.86–1.41)	0.437	1.03 (0.79–1.34)	0.827	1.09 (0.84–1.42)	0.505
BARC 3	116 (1.6)	44 (1.2)	50 (1.8)	0.69 (0.46–1.03)	0.069	0.69 (0.45–1.07)	0.096	0.65 (0.42–0.99)	0.045
BARC 3a	62 (0.9)	24 (0.7)	24 (0.9)	0.78 (0.44–1.38)	0.392	1.03 (0.55–1.90)	0.935	0.76 (0.42–1.37)	0.361
BARC 3b	49 (0.7)	16 (0.4)	25 (0.9)	0.50 (0.27–0.94)	0.027	0.42 (0.22–0.81)	0.01	0.47 (0.24–0.90)	0.024
BARC 3c	5 (0.1)	4 (0.1)	1 (0)	3.13 (0.35–27.98)	0.282	–	–	2.17 (0.23-20.59)	0.499
BARC 4	5 (0.1)	1 (0)	4 (0.1)	0.20 (0.02–1.75)	0.104	–	–	0.31 (0.03–2.98)	0.31
BARC 5	21 (0.3)	5 (0.1)	14 (0.5)	0.28 (0.10–0.78)	0.009	–	–	0.20 (0.06–0.62)	0.006
BARC 5a	15 (0.2)	4 (0.1)	9 (0.3)	0.35 (0.11–1.13)	0.065	0.26 (0.03–2.08)	0.206	0.24 (0.06–0.96)	0.043
BARC 5b	6 (0.1)	1 (0)	5 (0.2)	0.16 (0.02–1.34)	0.051	–	–	0.12 (0.01–1.12)	0.063
BARC 3 or 5	137 (1.9)	49 (1.4)	64 (2.3)	0.60 (0.41–0.87)	0.006	0.65 (0.43–0.99)	0.043	0.55 (0.37–0.81)	0.003
BARC 3 or 5 access site	51 (0.7)	19 (0.5)	23 (0.8)	0.65 (0.35–1.19)	0.155	0.65 (0.34–1.24)	0.19	0.66 (0.35–1.26)	0.209
BARC 3 or 5 nonaccess site	86 (1.2)	30 (0.8)	41 (1.5)	0.57 (0.36–0.92)	0.018	0.64 (0.37–1.12)	0.117	0.49 (0.30–0.81)	0.005
BARC 2, 3 or 5	441 (6.1)	200 (5.5)	171 (6.1)	0.91 (0.75–1.12)	0.389	0.90 (0.72–1.13)	0.361	0.88 (0.71–1.10)	0.257
BARC 2, 3 or 5 access site	237 (3.3)	105 (2.9)	98 (3.5)	0.84 (0.64–1.10)	0.206	0.81 (0.61–1.09)	0.165	0.86 (0.65–1.14)	0.298
BARC 2, 3 or 5 nonaccess site	204 (2.8)	95 (2.6)	73 (2.6)	1.02 (0.75–1.38)	0.912	1.04 (0.74–1.46)	0.83	0.92 (0.66–1.27)	0.599
TIMI major	49 (0.7)	16 (0.4)	26 (0.9)	0.48 (0.26–0.9)	0.019	0.39 (0.18–0.83)	0.015	0.38 (0.20–0.74)	0.005
TIMI minor	50 (0.7)	17 (0.5)	20 (0.7)	0.66 (0.35–1.27)	0.212	0.79 (0.40–1.56)	0.492	0.65 (0.33–1.29)	0.216
TIMI major/minor	99 (1.4)	33 (0.9)	46 (1.6)	0.56 (0.36–0.88)	0.010	0.57 (0.34–0.95)	0.03	0.49 (0.30–0.79)	0.004
GUSTO severe	42 (0.6)	16 (0.4)	20 (0.7)	0.63 (0.32–1.21)	0.158	0.67 (0.29–1.54)	0.35	0.47 (0.23–0.95)	0.037
GUSTO moderate	42 (0.6)	16 (0.4)	17 (0.6)	0.74 (0.37–1.46)	0.376	0.92 (0.43–1.96)	0.823	0.79 (0.39–1.62)	0.526
GUSTO mild	784 (10.9)	358 (9.9)	304 (10.8)	0.92 (0.79–1.07)	0.289	0.86 (0.72–1.02)	0.081	0.89 (0.75–1.05)	0.173
GUSTO moderate/severe	84 (1.2)	32 (0.9)	37 (1.3)	0.68 (0.42–1.09)	0.103	0.79 (0.45–1.37)	0.398	0.61 (0.37–1.01)	0.053
Composite of surgical access site repair and blood transfusion	103 (1.4)	36 (1.0)	51 (1.8)	0.55 (0.36–0.85)	0.006	0.52 (0.32–0.84)	0.008	0.58 (0.37–0.91)	0.018
Surgical access site repair	17 (0.2)	5 (0.1)	8 (0.3)	0.49 (0.16–1.49)	0.199	0.52 (0.15–1.74)	0.289	0.58 (0.18–1.84)	0.354
Blood transfusion	94 (1.3)	31 (0.9)	47 (1.7)	0.52 (0.33–0.81)	0.004	0.47 (0.28–0.79)	0.004	0.54 (0.33–0.87)	0.011
Distribution of BARC 3 or 5									
Intracranial bleeding	7 (0.1)	4 (0.1)	3 (0.1)	1.04 (0.23–4.66)	0.957	0.48 (0.06–3.92)	0.496	0.83 (0.18–3.91)	0.815
Pericardial bleeding	28 (0.4)	11 (0.3)	14 (0.5)	0.61 (0.28–1.35)	0.222	0.76 (0.24–2.40)	0.637	0.49 (0.21–1.13)	0.094
Gastrointestinal bleeding	27 (0.4)	6 (0.2)	16 (0.6)	0.29 (0.11–0.75)	0.006	0.31 (0.12–0.85)	0.023	0.26 (0.09–0.71)	0.008
Genito-urinary bleeding	12 (0.2)	5 (0.1)	2 (0.1)	1.95 (0.38–10.07)	0.415	2.80 (0.40–19.41)	0.298	2.04 (0.39–10.64)	0.399
Access site bleeding	49 (0.7)	19 (0.5)	22 (0.8)	0.68 (0.37–1.25)	0.207	0.70 (0.36–1.33)	0.27	0.69 (0.36–1.33)	0.267
Other bleeding	10 (0.1)	3 (0.1)	5 (0.2)	0.47 (0.11–1.96)	0.288	1.17 (0.12–11.52)	0.891	0.37 (0.07–1.90)	0.232

Values are n (%) unless otherwise indicated.

BARC = Bleeding Academic Research Consortium; CI = confidence interval; GUSTO = Global Utilization of Streptokinase and Tissue Plasminogen Activator; MI = myocardial infarction; ST = stent thrombosis; TIA = transient ischemic attack; TIMI = Thrombolysis In Myocardial Infarction; TVR = target vessel revascularization; UFH = unfractionated heparin.

TABLE 2 Clinical Outcomes up to 30 Days in Bivalirudin Versus UFH Plus Planned GPI

	All (N = 7,213)	Bivalirudin (n = 3,610)	UFH + GPI (n = 781)	Unadjusted Rate Ratio (95% CI)	p Value	Multivariable Adjusted Rate Ratio (95% CI)	p Value	Propensity Score Adjusted Rate Ratio (95% CI)	p Value
Death, MI, stroke	762 (10.6)	371 (10.3)	64 (8.2)	1.25 (0.96–1.64)	0.094	0.99 (0.70–1.39)	0.947	0.95 (0.70–1.29)	0.731
Death, MI, stroke, BARC 3 or 5	845 (11.7)	401 (11.1)	82 (10.5)	1.06 (0.83–1.34)	0.642	0.80 (0.59–1.09)	0.153	0.79 (0.60–1.05)	0.108
Death, MI, stroke, BARC 3 or 5, TVR, ST	860 (11.9)	410 (11.4)	83 (10.6)	1.07 (0.84–1.35)	0.581	0.81 (0.60–1.10)	0.170	0.81 (0.62–1.07)	0.146
Death	142 (2.0)	59 (1.6)	18 (2.3)	0.71 (0.42–1.2)	0.2	0.60 (0.29–1.27)	0.184	0.75 (0.40–1.41)	0.377
Cardiovascular death	136 (1.9)	56 (1.6)	17 (2.2)	0.71 (0.41–1.23)	0.219	0.60 (0.28–1.29)	0.190	0.76 (0.40–1.45)	0.406
MI	610 (8.5)	307 (8.5)	45 (5.8)	1.48 (1.08–2.02)	0.014	1.05 (0.73–1.50)	0.800	0.97 (0.68–1.38)	0.856
Stroke	29 (0.4)	13 (0.4)	1 (0.1)	2.81 (0.37–21.5)	0.298	2.40 (0.27–21.18)	0.43	4.50 (0.56–35.99)	0.156
TIA	14 (0.2)	5 (0.1)	2 (0.3)	0.54 (0.1–2.79)	0.456	0.57 (0.06–5.46)	0.624	0.45 (0.07–2.77)	0.391
TVR	87 (1.2)	52 (1.4)	10 (1.3)	1.12 (0.57–2.21)	0.733	1.16 (0.57–2.39)	0.678	1.20 (0.58–2.49)	0.619
ST definite	57 (0.8)	36 (1)	6 (0.8)	1.30 (0.55–3.08)	0.553	1.55 (0.63–3.85)	0.341	1.68 (0.67–4.21)	0.265
Acute	33 (0.5)	20 (0.6)	4 (0.5)	1.08 (0.37–3.16)	0.886	1.53 (0.50–4.68)	0.459	1.65 (0.53–5.12)	0.385
Subacute	24 (0.3)	16 (0.4)	2 (0.3)	1.73 (0.4–7.53)	0.459	1.36 (0.28–6.59)	0.699	1.73 (0.36–8.19)	0.492
ST definite/probable	80 (1.1)	45 (1.2)	9 (1.2)	1.08 (0.53–2.21)	0.83	1.28 (0.57–2.86)	0.554	1.33 (0.62–2.87)	0.467
Acute	38 (0.5)	22 (0.6)	4 (0.5)	1.19 (0.41–3.45)	0.749	1.62 (0.53–4.94)	0.394	1.80 (0.58–5.53)	0.306
Subacute	42 (0.6)	23 (0.6)	5 (0.6)	1.00 (0.38–2.62)	0.992	0.78 (0.23–2.65)	0.686	0.97 (0.34–2.77)	0.953
Bleeding	873 (12.1)	391 (10.8)	137 (17.5)	0.62 (0.51–0.75)	<0.001	0.64 (0.5–0.83)	0.001	0.64 (0.50–0.80)	<0.001
BARC 1	427 (5.9)	190 (5.3)	67 (8.6)	0.61 (0.46–0.81)	0.001	0.72 (0.52–1.00)	0.052	0.70 (0.51–0.96)	0.029
BARC 2	304 (4.2)	151 (4.2)	46 (5.9)	0.71 (0.51–0.99)	0.041	0.75 (0.51–1.10)	0.139	0.72 (0.49–1.04)	0.080
BARC 3	116 (1.6)	44 (1.2)	22 (2.8)	0.43 (0.26–0.72)	0.001	0.46 (0.25–0.85)	0.013	0.43 (0.24–0.77)	0.005
BARC 3a	62 (0.9)	24 (0.7)	14 (1.8)	0.37 (0.19–0.72)	0.002	0.30 (0.13–0.68)	0.004	0.32 (0.15–0.70)	0.004
BARC 3b	49 (0.7)	16 (0.4)	8 (1.0)	0.43 (0.19–1.01)	0.046	0.60 (0.24–1.50)	0.275	0.43 (0.16–1.10)	0.078
BARC 3c	5 (0.1)	4 (0.1)	0 (0)	–	–	–	–	–	–
BARC 4	5 (0.1)	1 (0)	0 (0)	–	–	–	–	–	–
BARC 5	21 (0.3)	5 (0.1)	2 (0.3)	0.54 (0.10–2.79)	0.456	–	–	0.57 (0.09–3.63)	0.553
BARC 5a	15 (0.2)	4 (0.1)	2 (0.3)	0.43 (0.08–2.36)	0.319	–	–	0.38 (0.05–2.73)	0.336
BARC 5b	6 (0.1)	1 (0)	0 (0)	–	–	–	–	–	–
BARC 3 or 5	137 (1.9)	49 (1.4)	24 (3.1)	0.44 (0.27–0.72)	0.001	0.47 (0.26–0.85)	0.013	0.44 (0.25–0.77)	0.004
BARC 3 or 5 access site	51 (0.7)	19 (0.5)	9 (1.2)	0.46 (0.21–1.01)	0.047	0.57 (0.23–1.37)	0.209	0.44 (0.18–1.07)	0.070
BARC 3 or 5 nonaccess site	86 (1.2)	30 (0.8)	15 (1.9)	0.43 (0.23–0.8)	0.006	0.42 (0.19–0.95)	0.036	0.45 (0.22–0.91)	0.027
BARC 2, 3 or 5	441 (6.1)	200 (5.5)	70 (9.0)	0.62 (0.47–0.81)	<0.001	0.64 (0.46–0.89)	0.009	0.61 (0.45–0.84)	0.002
BARC 2, 3 or 5 access site	237 (3.3)	105 (2.9)	34 (4.4)	0.67 (0.45–0.98)	0.04	0.66 (0.42–1.03)	0.067	0.60 (0.39–0.93)	0.021
BARC 2, 3 or 5 nonaccess site	204 (2.8)	95 (2.6)	36 (4.6)	0.57 (0.39–0.84)	0.004	0.65 (0.40–1.03)	0.069	0.65 (0.42–1.00)	0.049
TIMI major	49 (0.7)	16 (0.4)	7 (0.9)	0.49 (0.20–1.20)	0.113	0.47 (0.15–1.43)	0.183	0.68 (0.26–1.79)	0.430
TIMI minor	50 (0.7)	17 (0.5)	13 (1.7)	0.28 (0.14–0.58)	<0.001	0.29 (0.11–0.76)	0.012	0.30 (0.13–0.70)	0.006
TIMI major/minor	99 (1.4)	33 (0.9)	20 (2.6)	0.36 (0.20–0.62)	<0.001	0.37 (0.18–0.76)	0.007	0.43 (0.23–0.81)	0.009
GUSTO severe	42 (0.6)	16 (0.4)	6 (0.8)	0.58 (0.23–1.47)	0.245	0.67 (0.20–2.20)	0.505	0.75 (0.27–2.11)	0.590
GUSTO moderate	42 (0.6)	16 (0.4)	9 (1.2)	0.38 (0.17–0.87)	0.017	0.29 (0.11–0.80)	0.017	0.29 (0.12–0.74)	0.010
GUSTO mild	784 (10.9)	358 (9.9)	122 (15.6)	0.63 (0.52–0.78)	<0.001	0.68 (0.53–0.88)	0.004	0.67 (0.52–0.85)	0.001
GUSTO moderate/severe	84 (1.2)	32 (0.9)	15 (1.9)	0.46 (0.25–0.85)	0.011	0.42 (0.20–0.88)	0.022	0.46 (0.23–0.92)	0.027
Composite of surgical access site repair and blood transfusion	103 (1.4)	36 (1)	16 (2.0)	0.49 (0.27–0.88)	0.014	0.42 (0.20–0.88)	0.022	0.39 (0.20–0.76)	0.006
Surgical access site repair	17 (0.2)	5 (0.1)	4 (0.5)	0.27 (0.07–1.01)	0.036	0.25 (0.06–1.15)	0.075	0.18 (0.04–0.79)	0.023
Blood transfusion	94 (1.3)	31 (0.9)	16 (2.0)	0.42 (0.23–0.77)	0.004	0.33 (0.15–0.72)	0.005	0.34 (0.17–0.67)	0.002
Distribution of BARC 3 or 5									
Intracranial bleeding	7 (0.1)	4 (0.1)	0 (0)	–	–	–	–	–	–
Pericardial bleeding	28 (0.4)	11 (0.3)	3 (0.4)	0.79 (0.22–2.84)	0.722	0.81 (0.16–4.23)	0.807	1.02 (0.26–4.05)	0.976
Gastrointestinal bleeding	27 (0.4)	6 (0.2)	5 (0.6)	0.26 (0.08–0.85)	0.016	0.18 (0.03–0.93)	0.041	0.16 (0.04–0.64)	0.009
Genito-urinary bleeding	12 (0.2)	5 (0.1)	5 (0.6)	0.22 (0.06–0.75)	0.008	0.07 (0.01–0.67)	0.021	0.22 (0.06–0.88)	0.032
Access site bleeding	49 (0.7)	19 (0.5)	8 (1.0)	0.51 (0.22–1.17)	0.108	0.65 (0.26–1.64)	0.36	0.51 (0.20–1.28)	0.150
Other bleeding	10 (0.1)	3 (0.1)	2 (0.3)	0.32 (0.05–1.94)	0.194	–	–	0.11 (0.01–1.51)	0.098

Values are n (%) unless otherwise indicated.

GPI = glycoprotein IIb/IIIa inhibitor; other abbreviations as in Table 1.

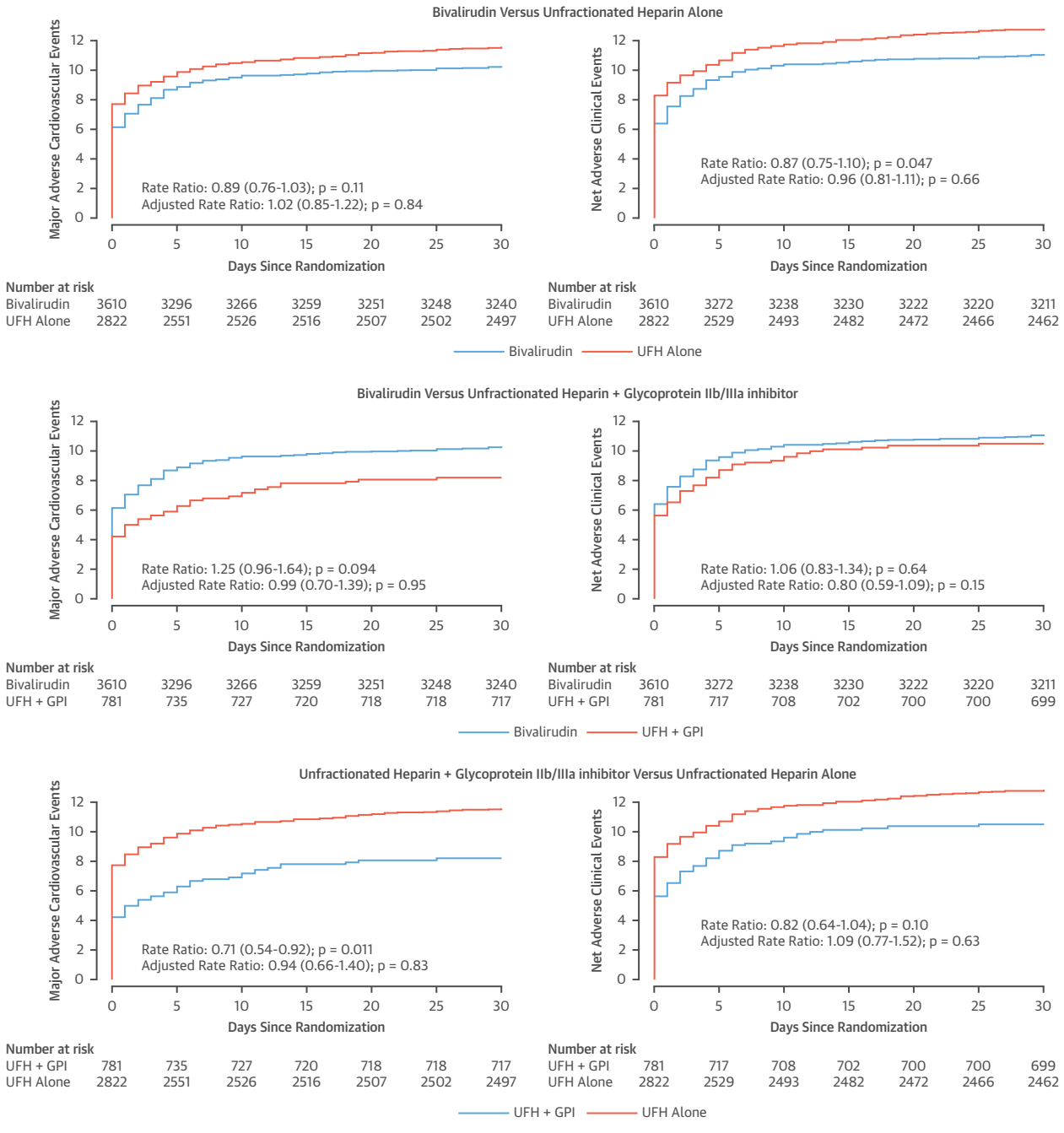
TABLE 3 Clinical Outcomes up to 30 Days in UFH Plus Planned GPI Versus UFH Alone

	All (N = 7,213)	UFH+GPI (n = 781)	UFH Alone (n = 2822)	Unadjusted Rate Ratio (95% CI)	p Value	Multivariable Adjusted Rate Ratio (95% CI)	p Value	Propensity Score Adjusted Rate Ratio (95% CI)	p Value
Death, MI, stroke	762 (10.6)	64 (8.2)	327 (11.6)	0.71 (0.54–0.92)	0.011	0.96 (0.66–1.4)	0.827	1.02 (0.73–1.44)	0.888
Death, MI, stroke, BARC 3 or 5	845 (11.7)	82 (10.5)	362 (12.8)	0.82 (0.64–1.04)	0.101	1.09 (0.77–1.52)	0.633	1.15 (0.84–1.57)	0.377
Death, MI, stroke, BARC 3 or 5, TVR, ST	860 (11.9)	83 (10.6)	367 (13.0)	0.82 (0.64–1.04)	0.096	1.05 (0.75–1.47)	0.785	1.10 (0.81–1.50)	0.526
Death	142 (2.0)	18 (2.3)	65 (2.3)	1.00 (0.59–1.69)	0.998	0.84 (0.22–3.18)	0.799	0.82 (0.41–1.63)	0.565
Cardiovascular death	136 (1.9)	17 (2.2)	63 (2.2)	0.98 (0.57–1.67)	0.926	0.59 (0.12–2.89)	0.515	0.74 (0.36–1.51)	0.401
MI	610 (8.5)	45 (5.8)	258 (9.1)	0.63 (0.46–0.86)	0.004	0.99 (0.66–1.47)	0.959	1.11 (0.76–1.64)	0.581
Stroke	29 (0.4)	1 (0.1)	15 (0.5)	0.24 (0.03–1.82)	0.134	0.11 (0.01–1.50)	0.098	0.15 (0.02–1.37)	0.093
TIA	14 (0.2)	2 (0.3)	7 (0.2)	1.03 (0.21–4.97)	0.968	2.60 (0.32–21.17)	0.372	1.42 (0.20–9.84)	0.725
TVR	87 (1.2)	10 (1.3)	25 (0.9)	1.45 (0.69–3.01)	0.322	1.08 (0.47–2.45)	0.859	0.86 (0.35–2.14)	0.747
ST definite	57 (0.8)	6 (0.8)	15 (0.5)	1.45 (0.56–3.73)	0.443	1.09 (0.38–3.17)	0.871	0.78 (0.24–2.52)	0.683
Acute	33 (0.5)	4 (0.5)	9 (0.3)	1.61 (0.49–5.21)	0.426	1.22 (0.30–5.00)	0.780	0.81 (0.19–3.47)	0.775
Subacute	24 (0.3)	2 (0.3)	6 (0.2)	1.20 (0.24–5.97)	0.820	1.22 (0.20–7.68)	0.829	0.74 (0.11–5.24)	0.766
ST definite/probable	80 (1.1)	9 (1.2)	26 (0.9)	1.25 (0.59–2.67)	0.562	1.13 (0.43–2.93)	0.805	1.02 (0.39–2.65)	0.969
Acute	38 (0.5)	4 (0.5)	12 (0.4)	1.20 (0.39–3.73)	0.747	1.22 (0.30–5.00)	0.780	0.80 (0.2–3.27)	0.757
Subacute	42 (0.6)	5 (0.6)	14 (0.5)	1.29 (0.46–3.58)	0.624	1.22 (0.30–4.95)	0.782	1.26 (0.35–4.59)	0.724
Bleeding	873 (12.1)	137 (17.5)	345 (12.2)	1.43 (1.18–1.75)	<0.001	1.27 (0.97–1.68)	0.084	1.27 (0.97–1.66)	0.082
BARC 1	427 (5.9)	67 (8.6)	170 (6.0)	1.42 (1.07–1.89)	0.014	1.14 (0.79–1.65)	0.471	1.08 (0.75–1.55)	0.687
BARC 2	304 (4.2)	46 (5.9)	107 (3.8)	1.55 (1.10–2.19)	0.012	1.45 (0.95–2.20)	0.084	1.48 (0.95–2.30)	0.084
BARC 3	116 (1.6)	22 (2.8)	50 (1.8)	1.59 (0.96–2.63)	0.067	1.66 (0.86–3.18)	0.129	1.84 (0.98–3.46)	0.059
BARC 3a	62 (0.9)	14 (1.8)	24 (0.9)	2.11 (1.09–4.07)	0.023	3.07 (1.20–7.86)	0.019	2.82 (1.24–6.44)	0.014
BARC 3b	49 (0.7)	8 (1.0)	25 (0.9)	1.16 (0.52–2.56)	0.721	0.94 (0.35–2.47)	0.892	1.10 (0.41–2.93)	0.851
BARC 3c	5 (0.1)	0 (0)	1 (0)	–	–	–	–	–	–
BARC 4	5 (0.1)	0 (0)	4 (0.1)	–	–	–	–	–	–
BARC 5	21 (0.3)	2 (0.3)	14 (0.5)	0.52 (0.12–2.27)	0.373	–	–	0.25 (0.05–1.34)	0.105
BARC 5a	15 (0.2)	2 (0.3)	9 (0.3)	0.80 (0.17–3.72)	0.778	–	–	0.37 (0.06–2.28)	0.284
BARC 5b	6 (0.1)	0 (0)	5 (0.2)	–	–	–	–	–	–
BARC 3 or 5	137 (1.9)	24 (3.1)	64 (2.3)	1.35 (0.85–2.17)	0.203	1.41 (0.74–2.68)	0.293	1.33 (0.74–2.41)	0.342
BARC 3 or 5 access site	51 (0.7)	9 (1.2)	23 (0.8)	1.41 (0.65–3.06)	0.376	1.49 (0.57–3.91)	0.417	1.86 (0.71–4.84)	0.205
BARC 3 or 5 nonaccess site	86 (1.2)	15 (1.9)	41 (1.5)	1.32 (0.73–2.39)	0.353	1.35 (0.58–3.13)	0.482	1.10 (0.52–2.32)	0.805
BARC 2, 3 or 5	441 (6.1)	70 (9.0)	171 (6.1)	1.48 (1.12–1.95)	0.005	1.43 (1.00–2.05)	0.051	1.44 (1.01–2.07)	0.047
BARC 2, 3 or 5 access site	237 (3.3)	34 (4.4)	98 (3.5)	1.25 (0.85–1.85)	0.255	1.31 (0.82–2.12)	0.262	1.53 (0.94–2.49)	0.089
BARC 2, 3 or 5 nonaccess site	204 (2.8)	36 (4.6)	73 (2.6)	1.78 (1.20–2.66)	0.004	1.65 (0.98–2.79)	0.062	1.32 (0.79–2.21)	0.285
TIMI major	49 (0.7)	7 (0.9)	26 (0.9)	0.97 (0.42–2.24)	0.948	0.66 (0.23–1.93)	0.447	0.66 (0.24–1.83)	0.424
TIMI minor	50 (0.7)	13 (1.7)	20 (0.7)	2.35 (1.17–4.72)	0.014	2.61 (0.92–7.43)	0.072	2.66 (1.09–6.51)	0.032
TIMI major/minor	99 (1.4)	20 (2.6)	46 (1.6)	1.57 (0.93–2.66)	0.089	1.37 (0.66–2.84)	0.404	1.38 (0.70–2.70)	0.351
GUSTO severe	42 (0.6)	6 (0.8)	20 (0.7)	1.08 (0.44–2.7)	0.862	0.86 (0.25–2.99)	0.816	0.83 (0.27–2.53)	0.746
GUSTO moderate	42 (0.6)	9 (1.2)	17 (0.6)	1.91 (0.85–4.29)	0.109	3.11 (1.03–9.43)	0.044	3.04 (1.13–8.21)	0.028
GUSTO mild	784 (10.9)	122 (15.6)	304 (10.8)	1.45 (1.18–1.79)	<0.001	1.22 (0.92–1.62)	0.167	1.23 (0.92–1.62)	0.158
GUSTO moderate/severe	84 (1.2)	15 (1.9)	37 (1.3)	1.46 (0.80–2.67)	0.21	1.73 (0.76–3.94)	0.192	1.63 (0.77–3.43)	0.199
Composite of surgical access site repair and blood transfusion	103 (1.4)	16 (2.0)	51 (1.8)	1.13 (0.65–1.99)	0.661	1.29 (0.61–2.72)	0.51	1.52 (0.76–3.05)	0.233
Surgical access site repair	17 (0.2)	4 (0.5)	8 (0.3)	1.81 (0.54–6.00)	0.327	2.54 (0.49–13.23)	0.267	2.91 (0.65–12.95)	0.161
Blood transfusion	94 (1.3)	16 (2.0)	47 (1.7)	1.23 (0.7–2.17)	0.474	1.39 (0.65–2.97)	0.400	1.65 (0.82–3.33)	0.163
Distribution of BARC 3 or 5									
Intracranial bleeding	7 (0.1)	0 (0)	3 (0.1)	–	–	–	–	–	–
Pericardial bleeding	28 (0.4)	3 (0.4)	14 (0.5)	0.77 (0.22–2.69)	0.687	0.92 (0.15–5.78)	0.928	0.52 (0.12–2.27)	0.384
Gastrointestinal bleeding	27 (0.4)	5 (0.6)	16 (0.6)	1.13 (0.41–3.08)	0.812	1.30 (0.34–5.05)	0.703	0.99 (0.29–3.36)	0.985
Genito-urinary bleeding	12 (0.2)	5 (0.6)	2 (0.1)	9.03 (1.75–46.56)	0.001	–	–	11.14 (1.69–73.65)	0.012
Access site bleeding	49 (0.7)	8 (1.0)	22 (0.8)	1.31 (0.58–2.95)	0.507	1.41 (0.51–3.90)	0.505	1.62 (0.59–4.44)	0.345
Other bleeding	10 (0.1)	2 (0.3)	5 (0.2)	1.45 (0.28–7.45)	0.658	0.87 (0.03–27.51)	0.936	1.88 (0.17–21.24)	0.610

Values are n (%) unless otherwise indicated.

Abbreviations as in Tables 1 and 2.

FIGURE 1 Coprimary Composite Study Outcomes at 30 Days

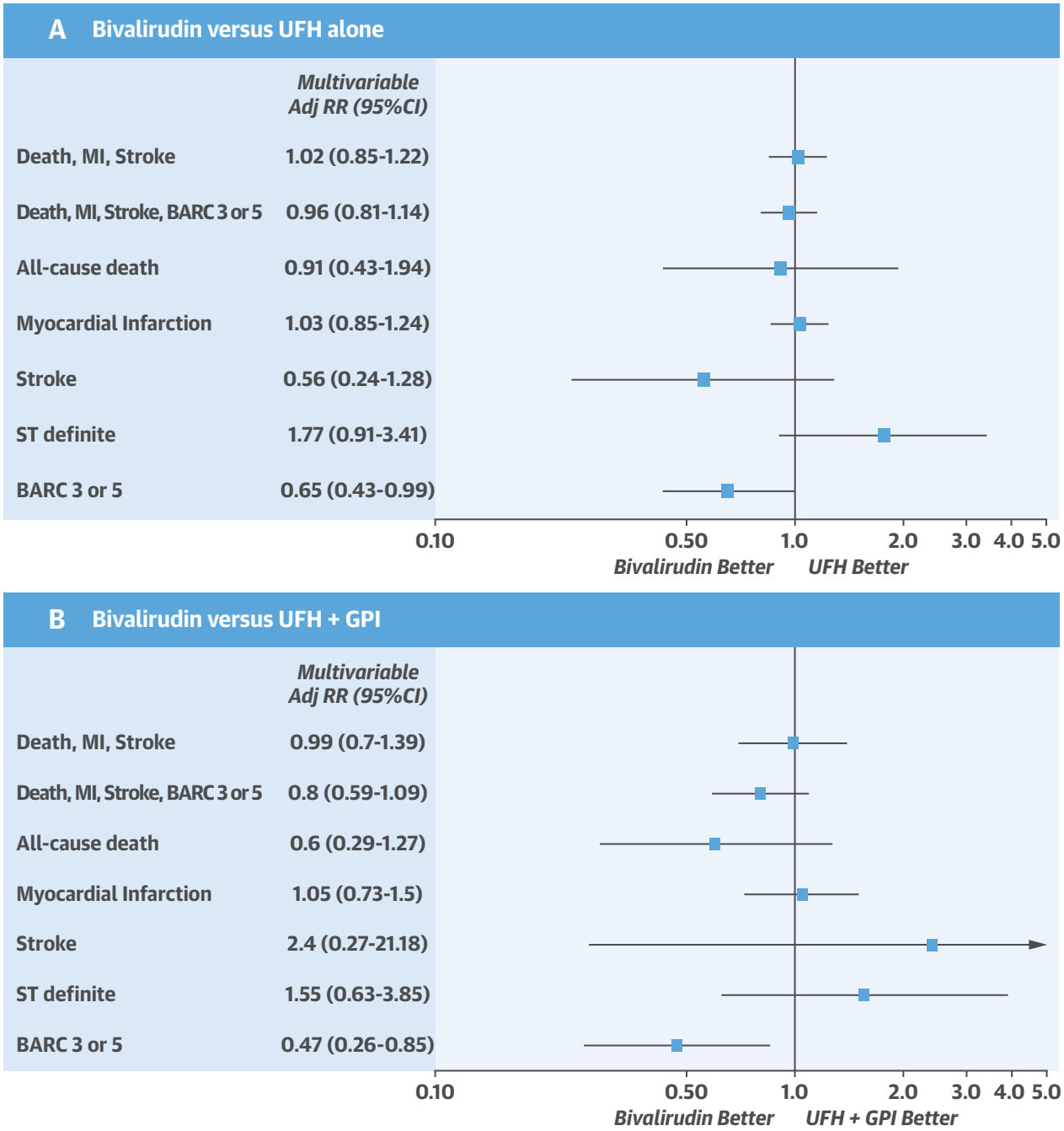


(Left) The cumulative incidence of the coprimary outcome of major adverse cardiovascular events and **(right)** net adverse clinical events up to 30 days, **(top)** among patients who received bivalirudin versus unfractionated heparin (UFH) alone, **(middle)** bivalirudin versus UFH plus glycoprotein IIb/IIIa inhibitors (GPI), and **(bottom)** UFH plus planned GPI versus UFH alone.

genito-urinary hemorrhages compared with UFH+GPI (Tables 1 and 2).

Transfusion rates and need for surgical access site repair were also reduced in the bivalirudin group (Tables 1 and 2). Conversely, bleeding complications, mainly genito-urinary hemorrhages that fulfilled Bleeding Academic Research Consortium grade 3A, TIMI minor, or GUSTO moderate criteria were

CENTRAL ILLUSTRATION **Bivalirudin or Heparin in ACS: Forest Plots of Main Outcomes**



Gargiulo, G. et al. J Am Coll Cardiol. 2018;71(11):1231-42.

Multivariable adjusted rate ratios (RR) of main outcomes at 30 days for **(A)** bivalirudin versus unfractionated heparin (UFH) alone or **(B)** bivalirudin versus UFH plus planned glycoprotein IIb/IIIa inhibitors (GPIs) comparisons. BARC = Bleeding Academic Research Consortium; CI = confidence interval; MI = myocardial infarction; ST = stent thrombosis.

increased in the UFH+GPI group compared with UFH alone (**Table 3**).

STRATIFIED AND PROPENSITY-MATCHING ANALYSES. We performed stratified analyses of the main clinical outcomes in the 3 comparisons, and we observed that, after adjustment, results remained consistent across UFH dose subgroups (Online Table 4). We also stratified major bleeding events by access site and observed that bivalirudin consistently reduced access site and nonaccess site bleeding compared with UFH groups, irrespective of the randomly allocated arterial access (Online Table 5).

After propensity-score matching was applied to the MATRIX population, 2,698 matched pairs of patients were identified for the comparison of bivalirudin versus UFH alone; there were 747 pairs of patients for the comparison bivalirudin versus UFH+GPI group and 578 pairs of patients for the comparison of UFH alone versus UFH+GPI. This model, developed to account for the nonrandomized use of GPI in the UFH arm, showed good discrimination and calibration (area under the curve: 0.85; 95% confidence interval: 0.83 to 0.87; Hosmer-Lemeshow: $p = 0.352$) (Online Figure 1). Post-match standardized differences for almost all measured covariates were <10%, which suggested substantial balance across the groups (Online Figures 2 to 4, Online Tables 6 to 11). Results of clinical outcomes at 30 days remained consistent with primary adjusted analyses (Online Tables 12 to 14), which confirmed a beneficial effect of bivalirudin versus UFH alone with respect to fatal and major bleeding across all adopted bleeding classifications.

DISCUSSION

The salient findings of this pre-specified analysis of the MATRIX trial can be summarized as follows:

1. The rates of MACEs and NACEs were not significantly lower among those who received bivalirudin compared with among those who received unfractionated heparin alone or with planned GPI at the time of PCI.
2. Compared with UFH and UFH+GPI groups, bivalirudin consistently reduced major bleeding, including fatal and nonaccess site–related events, as well as transfusion rates and need for surgical access site repair. This observation was consistent with the multivariable, propensity score–adjusted and propensity score–matched analyses. Although ST trended higher and mortality lower with bivalirudin compared with UFH alone or UFH+GPI, none of the single components of the primary composite endpoints, apart from bleeding, differed at a statistically significant level.

After initial studies, bivalirudin was approved and used during PCI due to the reduction of bleeding complications and similar ischemic risks compared with UFH+GPI. Although an excess of acute ST has been consistently noted in STEMI patients treated with bivalirudin compared with UFH+GPI (11), an early mortality benefit in the bivalirudin arm of the pivotal HORIZONS-AMI (Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction) trial has reinforced the notion in the community that bleeding prevention has the potential to affect mortality endpoints at least as much as ischemic events (12). However, the routine use of GPI on top of UFH has been regarded as unwarranted, and it may have further increased the bleeding risk in the comparator arms of approval bivalirudin studies.

In the last decade, the introduction of potent oral $P2Y_{12}$ inhibitors and the diffusion of the radial access have reduced the rates of PCI-related ischemic and bleeding events, respectively, thus, further questioning the need for routine or even selective use of GPI in most ACS cases. Most recent trials, including EUROMAX (6) and BRIGHT (7), have shown benefits in terms of major bleeding reduction related to bivalirudin use, irrespective of GPI use in the UFH arm. In opposite, the HEAT-PPCI trial showed that heparin compared with bivalirudin reduced the incidence of MACEs and ST, with no increase in bleeding complications (8). The most recent VALIDATE-SWEDEHEART study aimed at addressing these uncertainties by comparing bivalirudin versus UFH alone in ACS patients (matched STEMI and NSTEMI) who underwent PCI by radial access site and treatment with new $P2Y_{12}$ inhibitors (9). The trial enrolled 6,006 patients and showed a null effect of bivalirudin versus UFH with respect to the composite primary endpoint, including ischemic and bleeding events, as well as for each individual endpoint at 6 months. The absence of clear bleeding benefits with bivalirudin was attributed to the high rate of radial access (≈90%) and negligible use of GPI, which were restricted to bailout situations (≈3%) (9). However, there were additional factors beyond radial access and no planned use of GPI that might have contributed to explaining the lack of bleeding benefit in this study. A trend in favor of bivalirudin for bleeding endpoints was noted at 30 days, a time frame that seems more suitable to capturing the true value of a purely periprocedural antithrombotic compound. In addition, the allowance of UFH administration both before (up to 5,000 U) and in the catheterization

laboratory (up to 3,000 U) in the bivalirudin arm might have contributed to bias the results towards the null. In the MATRIX trial, planned GPI was allowed in the UFH arm and actually used in less than one-quarter of patients. Moreover, by study design, an equal and random proportion of patients were intervened upon by either radial or femoral access.

We found a consistent effect of bivalirudin in mitigating the bleeding risk across groups, largely from nonaccess site–related complications. This observation suggested that differences in study design and/or study populations might explain the apparently inconsistent effect of bivalirudin on bleeding endpoints beyond the selected access site or planned GPI use.

However, similar to VALIDATE-SWEDEHEART and other previous studies, no clear effect of bivalirudin on the primary composite endpoints was noted, irrespective of concomitant use of GPI in the UFH arm. Moreover, no clear effect of bivalirudin on ST or mortality rates was identified compared with UFH alone. This might reflect the limited study power to assess a treatment effect for relatively rare endpoints, which was further amplified by the need to apply multivariable analytical tools to account for the nonrandomized nature of GPI or the lack of a true treatment effect.

The dose of UFH in the control arms of available studies is also worth discussing. In the HEAT-PPCI study, UFH was dosed at 70 U/kg, which might have contributed to the absence of bleeding advantages with bivalirudin (8). In contrast, the use of 100 U/kg UFH might have inflated the risks of bleeding in the UFH arms of the EUROMAX and BRIGHT studies (5-7). However, in the MATRIX trial, UFH was administered at a mean dose of 78 U/kg in the control group, and our results remained entirely consistent at stratified analyses by low and high UFH doses. Thus, our present results did not support the interpretation that differences across studies might be reconciled by simply taking the different recommended UFH doses into account.

The present study added to previous evidence and supported the concept that bivalirudin does not provide benefits in terms of composite endpoints, including ischemic or ischemic and bleeding events. However, our results suggested benefits for bivalirudin in terms of bleeding risk mitigation, in either femoral or radial access. Thus, in addition to the well-established recommendation for patients with heparin-induced thrombocytopenia, bivalirudin should be considered as an alternative to UFH, particularly in high risk of bleeding patients. Ultimately, an individual patient data meta-analysis of all major bivalirudin studies could shed new light on the merits and limits of bivalirudin versus UFH with or without GPI in current practice (3).

STUDY LIMITATIONS. Although this was a prespecified analysis, use of planned GPI was left to the discretion of the physician, thus, generating 3 groups that were imbalanced in number and characteristics. The use of multivariable adjustment and propensity score matching successfully eliminated measured confounders. However, residual unmeasured confounding could not be excluded. The value of post-PCI bivalirudin infusion was not analyzed due to the need to account for 2 different nonrandomly allocated post-PCI bivalirudin regimens, which were seemingly associated with different study results at univariate analysis (1) and required further dedicated multivariable investigations.

CONCLUSIONS

Among patients with ACS who underwent invasive treatment, the planned use of GPIs in the control group did not affect the comparative effectiveness and safety profile of bivalirudin versus UFH. Consistent with the main study results, bivalirudin did not decrease the rates of the coprimary endpoints compared with UFH alone, but it did remain associated with consistent bleeding benefits, largely coming from major episodes, which were unrelated to the access site. The effect of bivalirudin versus UFH alone on more infrequent endpoints, such as ST or fatal events requires further investigation.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: In patients with ACSs who underwent percutaneous revascularization, bivalirudin was associated with comparable efficacy and less bleeding compared with UFH, regardless of access site or concurrent therapy with GPIs.

TRANSLATIONAL OUTLOOK: Additional investigation is needed to compare bivalirudin against UFH on other endpoints, such as stent thrombosis and mortality, and to assess the cost-effectiveness of these strategies.

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KEY WORDS acute coronary syndrome, bivalirudin, GP IIb/IIIa inhibitor, heparin, MATRIX

APPENDIX For supplemental tables and figures, please see the online version of this paper.

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EDITORIAL COMMENT

Activated Clotting Time During Unfractionated Heparin-Supported Coronary Intervention

Is Access Site the New Piece of the Puzzle?*

Marco Valgimigli, MD, PhD, Giuseppe Gargiulo, MD

Percutaneous coronary intervention (PCI) has developed a pivotal role in the management of patients with stable or unstable coronary artery disease (CAD). The inhibition of the coagulation cascade, and platelet activation, adhesion, and aggregation are key steps to optimize the results of PCI and prevent periprocedural ischemic complications; however, the degree of antithrombotic effect should minimize bleeding risks. Unfractionated heparin (UFH) has the main advantages of being cheap and antagonizable by means of intravenous protamine sulfate, thus it remains the most widely used anticoagulant agent during PCI. However, UFH has a poorly predictable effect on the coagulation cascade and a relatively narrow therapeutic window (1,2). Consequently, the measurement of activated clotting time (ACT) at the time of PCI has been advocated to mitigate both ischemic and bleeding events during or soon after intervention. The use of ACT was initially recommended in the mid-1970s to guide administration and reversal of UFH during cardiopulmonary bypass, then the diffusion of these interventions led to the development of automated ACT measurements (3). In 1990s, with the advances in the field of interventional cardiology, more and more cardiologists proposed to use in-laboratory bedside coagulation monitoring to assess heparin requirements during interventional procedures (3). Throughout the years, ACT monitoring to adjust UFH dosing during PCI has been promoted as the standard practice, although many centers, especially in Europe, do not assess it routinely. An intravenous UFH bolus of 70 to 100 U/kg is recommended to achieve a target ACT of 250 to 300 s (Hemotech device) or 300 to 350 (Hemochron device) without planned use of glycoprotein IIb/IIIa inhibitors (GPI) or 50 to 70 U/kg bolus to achieve an ACT of 200 to 250 s when the concomitant use of GPI is anticipated. Interestingly, no study has prospectively assessed the value of ACT-guided UFH administration as compared with standard UFH dosing, and all recommendations concerning optimal ACT values are based on retrospective and relatively underpowered registry data. What further complicates the interpretation of available data is that conflicting data have been reported on the association of ACT with ischemic or bleeding complications (**Table 1**) (4–14).

To date, a large body of evidence supports the use of transradial (TR) approach over transfemoral (TF) for PCI, particularly in acute coronary syndrome (ACS) patients, due to the lower risk of access-site-related bleeding complications and decreased mortality risk (15). However, there is limited evidence on whether the ACT target to avoid ischemic and bleeding complications should vary based on the selected access site. Interestingly, the lack of association between high ACT values and bleeding outcomes in some recent studies may be justified by the frequent use of

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TABLE 1 Main Studies Exploring the Impact of ACT on Ischemic and Bleeding Outcomes

First Author, Year, Trial	Design	Type of Patients	N	Antithrombotic Treatment	Main Findings
Ferguson et al., 1994	Observational retrospective	Stable or unstable	1,469	UFH alone	A diminished ACT response (<250 s) to an initial UFH bolus was associated with major in-hospital ischemic complications
Chew et al., 2001, EPIC, EPILOG, EPISTENT, IMPACT II, RAPPORT, HAS	Pool of 6 RCTs	Stable or unstable	5,216	UFH alone (control group of each RCT)	An ACT in the range of 350–375 s provided the lowest composite ischemic event rate in 7-day ischemic events compared with rates observed between 171–295 s by quartile analysis (p = 0.001). The maximum ACT was correlated with the incidence of major and minor bleeding (lowest rate for 325–350 s, which progressively increased with higher ACT values).
Ashby et al., 2003	Observational retrospective	Stable or unstable	1,020	UFH alone	High ACT levels were found to increase hemorrhagic complications without improving clinical or angiographic outcomes (these were paradoxically higher with increasing ACT)
Tolleson et al., 2003, ESPRIT	RCT analysis	Stable or unstable	2,064	UFH alone and UFH + eptifibatide groups	Ischemic events did not increase by decreasing ACT levels, at least to a level of 200s. Bleeding events did increase with increasing ACT levels and were enhanced with eptifibatide treatment. An ACT of 200–250 s seemed reasonable in terms of efficacy and safety.
Pinto et al., 2003, TACTICTS-TIMI 18	RCT analysis	NSTE-ACS	378	UFH + tirofiban	A peak ACT of ≤250 s was associated with higher ischemic events. A target ACT >250 was not associated with an increased risk of major or minor bleeds.
Brener et al., 2004, TARGET, CREDO, REPLACE 1 and 2	Pool of 4 RCTs	Stable or unstable	9,974	UFH + GPI (used in roughly 90%)	ACT did not correlate with ischemic complications and had a modest association with bleeding complications, driven mainly by minor bleeding. Lower values did not appear to compromise efficacy while increasing safety.
Montalescot et al., 2008, STEEPLE	RCT analysis	Stable	1,230	UFH ± GPI (roughly 40%)	Major bleeding increased significantly with an ACT >325 s. A significant relationship with increasing ischemic events was observed when ACT was <325 s indicating a narrow therapeutic window.
Bertrand et al., 2009, EASY	RCT analysis	NSTE-ACS, transradial PCI	1,234	UFH + abciximab	ACT value of >330 s were protective against peri-PCI myonecrosis, and this benefit was maintained up to 3 yrs. Greater ACT values did not correlate with an increased risk of bleeding.
Rozenman et al., 2012, HORIZONS-AMI	RCT analysis	STEMI	1,624	UFH + GPI	The peak procedural ACT achieved did not have a substantial effect on major bleeding, mortality, or MACE, although lower peak ACT was associated with less minor bleeding.
Ducrocq et al., 2015, FUTURA/OASIS-8	RCT analysis	NSTE-ACS	1,882	Fondaparinux followed by UFH (low or standard dose) ± GPI (roughly 27%)	An ACT≤300 s increased the risk of thrombotic complications in patients not receiving GPI. ACT, however, did not predict bleeding complications.
Rajpurohit et al., 2016	Observational retrospective	Stable or unstable	12,055	UFH ± GPI (roughly 55%)	After multivariable adjustment for baseline and procedural characteristics, ACT was not independently associated with in-hospital or 1-year ischemic, thrombotic, or bleeding outcomes.

ACS = acute coronary syndrome(s); ACT = activated clotting time; CREDO = Clopidogrel for the Reduction of Events During Observation; EASY = EArly Discharge after Transradial Stenting of CoronarY Arteries; EPIC = Evaluation of c7E3 for the Prevention of Ischemic Complications; EPILOG = Evaluation in PTCA to Improve Long-Term Outcome with abciximab Glycoprotein IIb/IIIa blockade; EPISTENT = Evaluation of IIb/IIIa Platelet Inhibitor for Stenting; ESPRIT = Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy trial; FUTURA/OASIS-8 = Fondaparinux With Unfractionated Heparin During Revascularization in Acute Coronary Syndromes; GPI = glycoprotein IIb/IIIa inhibitor; HAS = Hirudin Angioplasty Study; HORIZONS-AMI = Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction; IMPACT II = Integrilin to Minimize Platelet Aggregation and Coronary Thrombosis II; MACE = major adverse cardiovascular event(s); NSTE = non-ST-segment elevation; PCI = percutaneous coronary intervention; RAPPORT = Reopro and Primary PTCA Organization and Randomized Trial; RCT = randomized controlled trial; REPLACE 1-2 = Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events; STEEPLE = SafeTy and Efficacy of Enoxaparin in PCI patients, an internationaL randomized Evaluation; STEMI = ST-segment elevation myocardial infarction; UFH = unfractionated heparin; TARGET = Tirofiban And Reopro Give similar Efficacy outcomes Trial.

radial access site for coronary angiography and intervention (7,9).

SEE PAGE 1036

In this issue of *JACC: Cardiovascular Interventions*, Louis et al. (16) present the results of a large, 2-center, retrospective observational study exploring the role of ACT in patients undergoing PCI and receiving UFH alone. Overall, unadjusted and adjusted analyses showed that maximal ACT was associated with higher rates of major bleeding after TF (ACT value >290 s), but not TR PCI, whereas there was no clear association with the in-hospital ischemic risk, irrespective of the vascular access site. This finding may suggest that during TR-PCI, a more intense anticoagulation might be tolerated compared with TF-PCI as a result of a much lower access site bleeding risk in the former over the latter group of patients. This study comes from data collected in 2 American centers on 9,169 patients (mean age 66 years) who underwent PCI

without GPI. Two-thirds of the patients were male, roughly 85% presented with ACS, and the majority of them received a single-vessel PCI. Only 13% of patients received new $P2Y_{12}$ inhibitors, however.

Some important points of this study should be considered.

1. ACT values were missing in 10.5% of patients initially screened (1,532 of 14,634).
2. The ACT value at peak is analyzed as a standalone parameter, irrespective of relevant factors relating to UFH management (use of pre-PCI bolus and infusion of UFH, dose and number of intraprocedural UFH boluses, additional use of UFH doses guided by prior ACT values, patient body weight, and duration of the procedure).
3. The definition of bleeding occurrences is not standardized (i.e., BARC [Bleeding Academic Research Consortium], TIMI [Thrombolysis In Myocardial Infarction], or GUSTO [Global Use of Strategies to Open Occluded Arteries]), and bleeding events were not independently adjudicated. Moreover, the definition of periprocedural or non-procedural-related myocardial infarction is missing.
4. TR and TF cohorts were imbalanced (the TR group comprised roughly one-third of the overall population), and the TR cohort experienced a lower rate of overall bleeding complications, which were entirely driven by a lower rate of access site events. As a result, the lower statistical power to assess an association between ACT and bleeding in the TR group might explain the null finding in this group of patients. Moreover, in the TF group, the majority of bleeding events were access-related. The bottom line is that this analysis is largely underpowered to assess a possible association between non-access site bleeding and peak ACT values.
5. Hemochron device was used in all patients, thus, although this is the most widely used device, these findings should not be extended to other devices.

These findings, therefore, should be interpreted with caution and should not support the misleading conclusion that radialist operators can dose or overdose UFH liberally.

Non-access site bleeding, especially in the context of prospective randomized studies comparing TR versus TF intervention in ACS patients (7,15), is not so rare, is not influenced by the selection of the access site, and more closely correlates with mortality outcomes (17,18). On the other hand, this observation does reinforce the role of radial artery in current practice and adds to the growing body of evidence that both technical and pharmacological aspects should be regarded as highly interconnected: It is only then when the puzzle comes together!

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KEY WORDS activated clotted time (ACT), clinical outcomes, heparin, percutaneous coronary intervention (PCI), radial access

Impact of Sex on Comparative Outcomes of Bivalirudin versus Unfractionated Heparin in Patients with Acute Coronary Syndromes Undergoing Invasive Management: A pre-specified analysis of the MATRIX trial

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Running title: Sex in MATRIX-Antithrombin and Treatment-Duration trial

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ABSTRACT

Aims: To assess whether bivalirudin compared with unfractionated heparin (UFH) is associated with consistent outcomes in males and females with acute coronary syndrome (ACS) undergoing invasive management.

Methods and Results: In the MATRIX program, 7213 patients were randomized to bivalirudin or UFH. Patients in the bivalirudin group were subsequently randomly assigned to receive or not a post-PCI bivalirudin infusion. The 30-day coprimary outcomes were major adverse cardiovascular and cerebrovascular events (MACE), defined as death, myocardial infarction, or stroke, and net adverse clinical events (NACE), defined as MACE or major bleeding. The primary outcome for the comparison of a post-PCI bivalirudin infusion with no post-PCI infusion was a composite of urgent target-vessel revascularization (TVR), definite stent thrombosis (ST), or NACE. The rate of MACE was not significantly lower with bivalirudin than with heparin in male (rate ratio, 0.90; 95% confidence interval [CI], 0.75-1.07; P=0.22) and female patients (rate ratio, 1.06; 95% CI, 0.80-1.40; P=0.67) without significant interaction (Pint=0.31), nor was the rate of NACE (males: rate ratio, 0.85; 95% CI, 0.72-1.01; P=0.07; females: rate ratio, 0.98; 95% CI, 0.76-1.28; P=0.91; Pint=0.38). Post-PCI bivalirudin infusion, as compared with no infusion, did not significantly decrease the rate of urgent TVR, definite ST, or NACE (males: rate ratio, 0.84; 95% CI, 0.66-1.07; P=0.15; females: rate ratio, 1.06; 95% CI, 0.74-1.53; P=0.74; Pint=0.28).

Conclusion: In ACS patients, the rates of MACE and NACE were not significantly lower with bivalirudin than with UFH in both sexes. The rate of the composite of urgent TVR, definite ST, or NACE was not significantly lower with a post-PCI bivalirudin infusion than with no post-PCI infusion in both sexes.

Keywords: ACS/NSTE-ACS; STEMI; Adjunctive pharmacotherapy

INTRODUCTION

Over the past decade, antithrombotic therapies after acute coronary syndrome (ACS) have improved outcomes more in men than in women[1, 2], raising the question of whether there are sex-specific differences in treatment patterns and response to such therapy. However, there is contrasting evidence on the impact of sex on clinical outcomes, particularly on overall and cardiovascular mortality, in patients treated for coronary artery disease and differences in presenting clinical characteristics, pathophysiologic profile, as well as disparities in treatment may considerably contribute to this outcome discrepancy[3]. A large body of evidence suggests that female patients have increased peri-procedural bleeding risk as compared to males[4, 5], and recently the radial access showed to be effective in reducing such risk compared to femoral access in ACS patients invasively managed[6].

We sought to investigate whether the use of bivalirudin, either continued or discontinued after percutaneous coronary intervention (PCI), instead of unfractionated heparin (UFH), might be associated with consistent or differential efficacy and safety effects in male and female patients with ACS undergoing invasive management as part of a pre-specified analysis in the Minimizing Adverse Haemorrhagic Events by Transradial Access Site and Systemic Implementation of Angiox (MATRIX) programme.

METHODS

Study design, outcomes and statistical analysis

Design and main results of the MATRIX trial have been previously reported[7-9]. Details are reported in the supplement.

RESULTS

Patients

From October 11, 2011, to November 7, 2014, at 78 centres in Italy, the Netherlands, Spain, and Sweden, 3610 patients were assigned to receive bivalirudin (males: 2731, 75.7%; females: 879, 24.3%), either with a post-PCI infusion (1799 patients of whom males: 1351, 75.1% and females: 448, 24.9%) or without a post-PCI infusion (1811 patients of whom males: 1380, 76.2% and females: 431, 23.8%), and 3603 were assigned to receive UFH (males: 2764, 76.7%; females: 839, 23.3%).

Female and male subgroups allocated to bivalirudin versus UFH and to post-PCI bivalirudin infusion versus no post-PCI infusion were generally well matched in terms of demographics, medical history, clinical presentation, procedural aspects and therapy at discharge (**Supplementary Tables 1-3**).

Clinical outcomes according to antithrombin type

MACE occurred in 256 patients (9.4%) in the bivalirudin group and in 287 patients (10.5%) in the UFH group (rate ratio, 0.90; 95% confidence interval [CI], 0.75 to 1.07; P=0.22) in males and in 115 (13.1%) and 104 (12.4%) females (rate ratio, 1.06; 95% CI, 0.80 to 1.40; P=0.67) without significant interaction (Pint=0.31) (**Table 1, Figures 1 and 2**). A total of 276 patients (10.2%) in the bivalirudin group, as compared with 323 patients (11.8%) in the UFH group, had a NACE (rate ratio, 0.85; 95% CI, 0.72 to 1.01; P=0.07) in males and 125 (14.2%) as compared with 121 (14.4%) female patients had a NACE (rate ratio, 0.98; 95% CI, 0.76 to 1.28; P=0.91) without significant interaction (Pint=0.38) (**Table 1, Figures 1 and 2**).

Compared with UFH, bivalirudin was apparently associated with a lower rate of all-cause death in male (1.2% vs. 1.9%; rate ratio, 0.63; 95% CI, 0.41 to 0.98; P=0.041) but not in female patients (3.1% vs. 3.8%; rate ratio, 0.80; 95% CI, 0.48 to 1.34; P=0.40), however there was no detectable signal of heterogeneity across gender (Pint=0.49) (**Table 1, Figures 1 and 3**). This was similarly observed for cardiovascular death (males: 1.1% vs. 1.8%; rate ratio, 0.60; 95% CI, 0.38 to 0.95; P=0.028; females: 3.0% vs. 3.6%; rate ratio, 0.82; 95% CI, 0.49 to 1.40; P=0.47; Pint=0.38; **Table 1**). There were no significant differences between bivalirudin and UFH in both male and female patients for the rates of individual endpoints of MI, stroke, TVR, and ST (**Table 1, Figures 1 and 3**). Bivalirudin consistently reduced rates of major bleeding (BARC 3 or 5) compared with UFH across gender (males: 1.2% vs. 2.0%; rate ratio, 0.59; 95% CI, 0.38 to 0.92; P=0.019; females: 2.0% vs. 4.1%; rate ratio, 0.47; 95% CI, 0.26 to 0.85; P=0.01; Pint=0.53) (**Table 1, Figures 1 and 3**). This difference was mainly driven by access-related events in males and by non–access-related bleeding in females, with fatal, TIMI major and GUSTO severe bleeding being lower in female patients only (**Table 1**).

Clinical outcomes according to bivalirudin treatment duration

The primary composite outcome was observed in 128 patients (9.6%) who received post-PCI bivalirudin and in 154 patients (11.2%) who did not receive post-PCI bivalirudin (rate ratio, 0.84;
95% CI, 0.66 to 1.07; P=0.15) in males and respectively in 67 (15.0%) versus 61 patients (14.2%) (rate ratio, 1.06; 95% CI, 0.74 to 1.53; P=0.74) in females (Pint=0.28) (**Supplementary Table 4, Figures 4 and 5**). No significant differences or interactions were observed in terms of MACE, NACE, or individual endpoints of death, MI, stroke, TVR or ST (**Supplementary Table 4 and Figure 6**).

There was no significant between-group heterogeneity in the rate of bleeding, with BARC 2 events being significantly higher male and numerically higher in female patients in the post-PCI bivalirudin arm while BARC 3 or 5 events which were not related to the access site being lower in both sexes (**Supplementary Table 4**).

Additional analyses

Supplementary Figures 1-4 list the effect of randomized antithrombin type on MACE and NACE, in male and female patients according to pre-specified subgroups. In male patients, the randomized treatment effect appeared consistent across most subgroups, with the exception of patients with an increased BMI or those with prior exposure to UFH, in

whom bivalirudin, as compared to UFH, lowered MACE and NACE. Treatment effect was also largely consistent in female patients.
Supplementary Figures 5-8 show the effect of randomized bivalirudin treatment duration on MACE and NACE, in male and female patients according to pre-specified subgroups.

DISCUSSION
MATRIX is the largest randomized study on bivalirudin in STEMI, one of the largest in NSTE-ACS patients, and the only randomized comparison of post-PCI versus no post-PCI bivalirudin infusion. The study failed to show that bivalirudin as compared to UFH±GPI reduces MACE or NACE and post-PCI bivalirudin infusion did not reduce the rate of the primary endpoint compared with no post-PCI infusion. At secondary endpoint analyses, bivalirudin compared to UFH±GPI decreased the rate of fatalities and the risk of major, mainly non-access-site related, bleeding in both randomly allocated access sites.
The results of the sex-based pre-specified analysis can be summarized as follows:
1) There was no signal of heterogeneity across sexes for any of the primary endpoints, including MACE and NACE for the bivalirudin versus UFH±GPI comparison and the composite of NACE definite ST and urgent TVR for the assessment of post-PCI bivalirudin infusion.
2) In secondary stratified analyses, bivalirudin remained associated to lower risks of mortality and bleeding in both sexes, with no signal of a sex-based treatment effect at interaction testing. Mortality was numerically lower with bivalirudin in both female and male patients, albeit it reached statistical significance in the latter group only, likely reflecting a power issue. BARC 3 or 5 bleeding were significantly reduced in both sexes, interestingly owing to a reduction of access site events in males and non-access site related occurrences in females.
Sex differences in cardiovascular outcomes is a topic of great interest and debate in the cardiology community, with data supporting such discrepancy in opposite to others suggesting that women treated for coronary artery disease have different clinical, procedural and treatment profiles compared with men which may largely explain the observed dissimilarities in prognosis. Indeed, after correcting for sex-based confounders such disparities, particularly in mortality and major composite endpoints seem to be no longer demonstrated[3, 6]. However, female patients have been associated with higher rates of peri-procedural bleeding[4, 5], and this was also confirmed in a previous pre-specified analysis of MATRIX where we observed a greater risk of access-site bleeding and transfusion rates in female as compared with male patients after adjusting for confounders[6]. Additional interest to this topic is related to the fact that women represent a limited amount of patients included in the majority of cardiovascular trials. On this background, it seems particularly relevant to explore whether there are sex-specific differences in treatment patterns and response to antithrombotic therapy.
In a patient-level pooled analysis of 3 randomized controlled trials (the Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events, REPLACE-2; Acute Catheterization and Urgent Intervention Triage strategY, ACUITY; and Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction, HORIZONS-AMI) including 14,784 patients (25.6% were women) bivalirudin was compared with UFH plus GPI in ACS patients undergoing PCI. Compared with males, females were associated with higher 30-day bleeding events that in turn emerged to be the strongest independent predictor of 1-year mortality rather than gender per se. Additionally, both sexes experienced similar safety benefits of bivalirudin in reducing bleeding complications, but women experienced a more pronounced benefit of bivalirudin in reducing 1-year mortality than men[10]. Importantly, these results come from trials in which UFH was administered with routine use of GPI, there were no use of newer antiplatelet agents and PCI procedures were almost exclusively performed by femoral access. In the sex-based analysis of BRIGHT, a trial comparing bivalirudin versus heparin versus heparin plus tirofiban in acute MI patients undergoing PCI, female patients receiving bivalirudin were associated with significantly lower rates of 30-day bleeding and NACE, but no differences in terms of mortality, ST or MACE[11]. In the sex-based analysis of the ISAR-REACT 4, where patients with NSTEMI (n=1,721; 399 women, 23.2%) were randomly allocated to receive bivalirudin or heparin plus abciximab, there were no between-groups differences of the main outcome (30-day composite of death, large recurrent MI, urgent TVR or major bleeding), but bivalirudin reduced major bleeding in both male and female patients[12].
Our current results are entirely consistent with previous evidence, indicating that bivalirudin provides consistent effect in both sexes, resulting in lower risks of bleeding complications across many of the available RCTs. Additionally, in the MATRIX we found that reduction of bleeding, mainly most severe episodes, was irrespective of GPI use[12].
Interestingly, however, in the context of the recently reported VALIDATE-SWEDEHAERT trial, where bivaluridin did not reduce the primary composite endpoint of NACE or clinically relevant bleeding at 6 months after intervention as compared to UFH alone, there was a signal of heterogeneity across sexes (Pint=0.05), with female patients deriving apparently a greater benefit from treatment as compared to males[2]. Therefore, in summary, current evidence shows either a consistent or perhaps a slightly greater treatment effect in female patients treated with bivalirudin as compared to UFH; a finding which seems to be justifiable by prior observations that females are at increased risk for peri-procedural bleeding occurrences.
The inconsistent effect of bivalirudin on the NACE endpoint likely reflects difference in study design, choice of the comparator arm, patients' selection and endpoints definitions across available studies. Similarly, the effect of bivalirudin on mortality has been inconsistently observed across trials and some registry data[13], which may reflect the

fact that this effect, if real, may be small, and likely confounded by the baseline risk status of patients and concomitant treatment and medications.
Prior observations that the use of bivalirudin increases the risks of acute ST have prompted investigations to mitigate that risk by prolonging bivalirudin infusion after PCI[14, 15]. Overall, MATRIX-Treatment-Duration found that post-PCI infusion of bivalirudin did not result in lower rates of the primary endpoint or definite ST at 30 days than the rates with no post-PCI infusion. This latter finding was also confirmed in the present analysis in both male and female patients. In the current practice, when deciding on the anticoagulation strategy to adopt in ACS patients undergoing PCI, it should be also considered that bivalirudin remains much more expensive than UFH, however, updated cost-effectiveness analyses are warranted.

Limitations
Although this is a pre-specified subgroup analysis, the MATRIX-Antithrombin and Treatment-Duration trials were not powered to explore differences between sexes, and randomization was not stratified by sex. We did not adjust for multiple comparisons, increasing the risk of type I error. Protocol allowed for discretionary use of GPI in the heparin group and two different infusion regimens in the post-PCI bivalirudin infusion group. Although this is consistent with clinical practice, it makes the study results more difficult to interpret.

CONCLUSIONS
Among male and female patients with ACS undergoing invasive treatment, neither the rate of MACE nor the rate of NACE was significantly lower with bivalirudin than with unfractionated heparin and discretionary use of glycoprotein IIb/IIIa inhibitors. In both sexes, the post-PCI infusion of bivalirudin for at least 4 hours after the intervention did not result in a lower rate of the composite outcome of ischemic and bleeding events, including stent thrombosis, than the rate with no post-PCI infusion. Our observations of lower risks of bleeding and especially of fatality rates both in male and female patients undergoing an invasive management should be interpreted in the context of available evidence, which suggests a rather consistent and inconsistent treatment effect of bivalirudin on bleeding and fatal endpoints, respectively, both in males and females.

IMPACT ON DAILY PRACTICE
Current data shows that neither male nor female patients gained significant benefit in terms of composite endpoints by receiving bivalirudin compared with heparin with discretionary use of GPI, although a lower rate of bleeding was observed. Also the post-PCI infusion of bivalirudin was not superior to no infusion in both sexes.

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Figure Legend.

Figure 1. Main Outcomes of Bivalirudin Versus Unfractionated Heparin in Male and Female Patients. Bivalirudin and UFH were compared on the basis of sex subgroups, with rate ratios and 95% confidence intervals (CIs), for the coprimary endpoints and their components (death, myocardial infarction, stroke, BARC 3 or 5).

Figure 2. Coprimary Composite Outcomes of Bivalirudin Versus Unfractionated Heparin at 30 Days in Male and Female Patients. Panels A and B show the cumulative incidence of the coprimary outcome of MACE and NACE respectively. Blue indicates bivalirudin, red indicates UFH, continuous line indicates male, dashed line indicates female.

Figure 3. Components of Coprimary Composite Outcomes of Bivalirudin Versus Unfractionated Heparin at 30 Days in Male and Female Patients. Panels show the cumulative incidence of the coprimary outcome components of all-cause death (A), myocardial infarction (B), stroke (C), and BARC 3 or 5 bleeding (D). Blue indicates bivalirudin, red indicates UFH, continuous line indicates male, dashed line indicates female.

Figure 4. Main Outcomes of Post-PCI Bivalirudin Infusion Versus No Post-PCI Bivalirudin Infusion in Male and Female Patients. Bivalirudin infusion and no infusion post-PCI were compared on the basis of sex subgroups, with rate ratios and 95% confidence intervals (CIs), for the primary endpoint and its components (death, myocardial infarction, stroke, BARC 3 or 5, urgent TVR and definite ST).

Figure 5. Primary Composite Outcome of Post-PCI Bivalirudin Infusion Versus No Post-PCI Bivalirudin Infusion at 30 Days in Male and Female Patients. Figure shows the cumulative incidence of the primary composite outcome of urgent target-vessel revascularization (TVR), definite ST, or NACE. Blue indicates prolonged bivalirudin infusion, red indicates no post-PCI infusion, continuous line indicates male, dashed line indicates female.

Figure 6. Components of Primary Composite Outcome of Post-PCI Bivalirudin Infusion Versus No Post-PCI Bivalirudin Infusion at 30 Days in Male and Female Patients. Panels show the cumulative incidence of the primary outcome components of all-cause death (A), myocardial infarction (B), stroke (C), BARC 3 or 5 bleeding (D), urgent TVR (E) and definite ST (F). Blue indicates prolonged bivalirudin infusion, red indicates no post-PCI infusion, continuous line indicates male, dashed line indicates female.

Figure 1

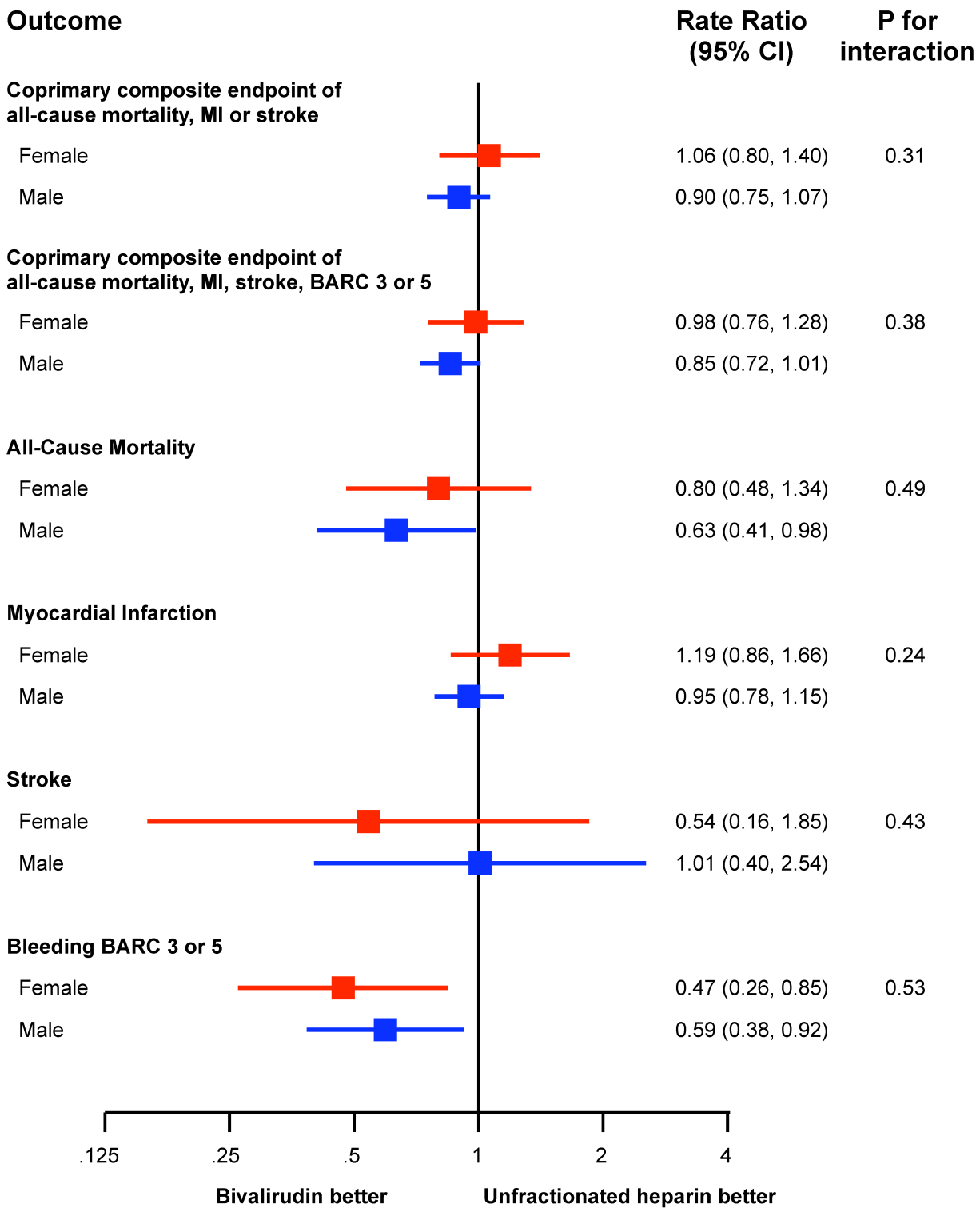

Outcome
Rate Ratio (95% CI)
P for interaction
Coprimary composite endpoint of all-cause mortality, MI or stroke
Female
1.06 (0.80, 1.40)
0.31
Male
0.90 (0.75, 1.07)
Coprimary composite endpoint of all-cause mortality, MI, stroke, BARC 3 or 5
Female
0.98 (0.76, 1.28)
0.38
Male
0.85 (0.72, 1.01)
All-Cause Mortality
Female
0.80 (0.48, 1.34)
0.49
Male
0.63 (0.41, 0.98)
Myocardial Infarction
Female
1.19 (0.86, 1.66)
0.24
Male
0.95 (0.78, 1.15)
Stroke
Female
0.54 (0.16, 1.85)
0.43
Male
1.01 (0.40, 2.54)
Bleeding BARC 3 or 5
Female
0.47 (0.26, 0.85)
0.53
Male
0.59 (0.38, 0.92)
.125
.25
.5
1
2
4
Bivalirudin better
Unfractionated heparin better

Figure 2.

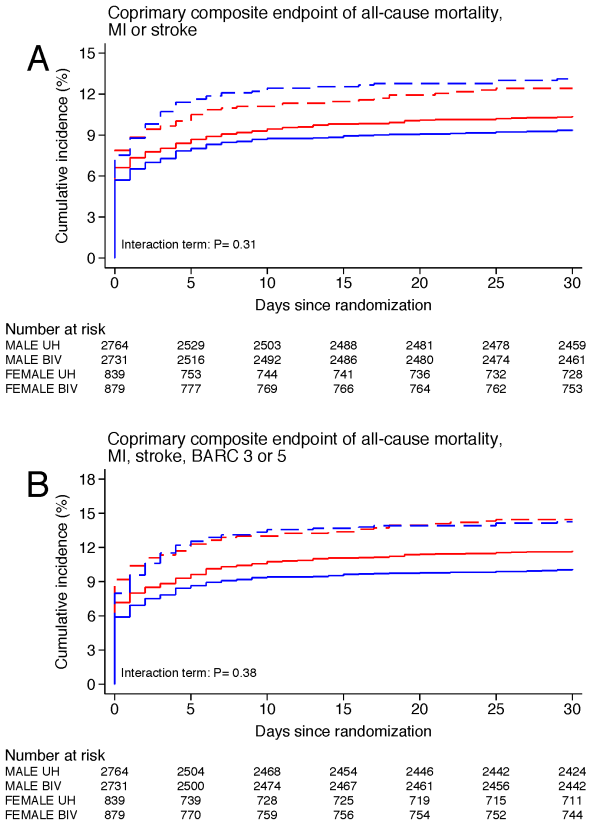


Figure 3.

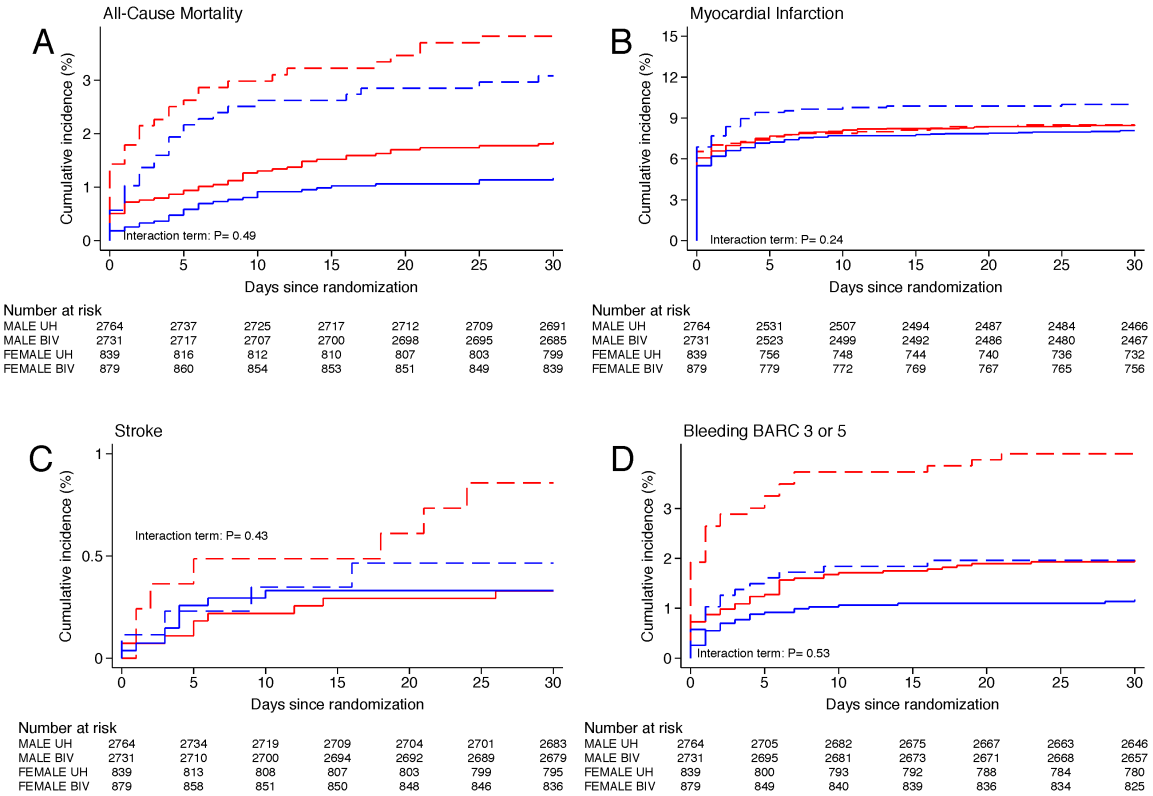


Figure 4.

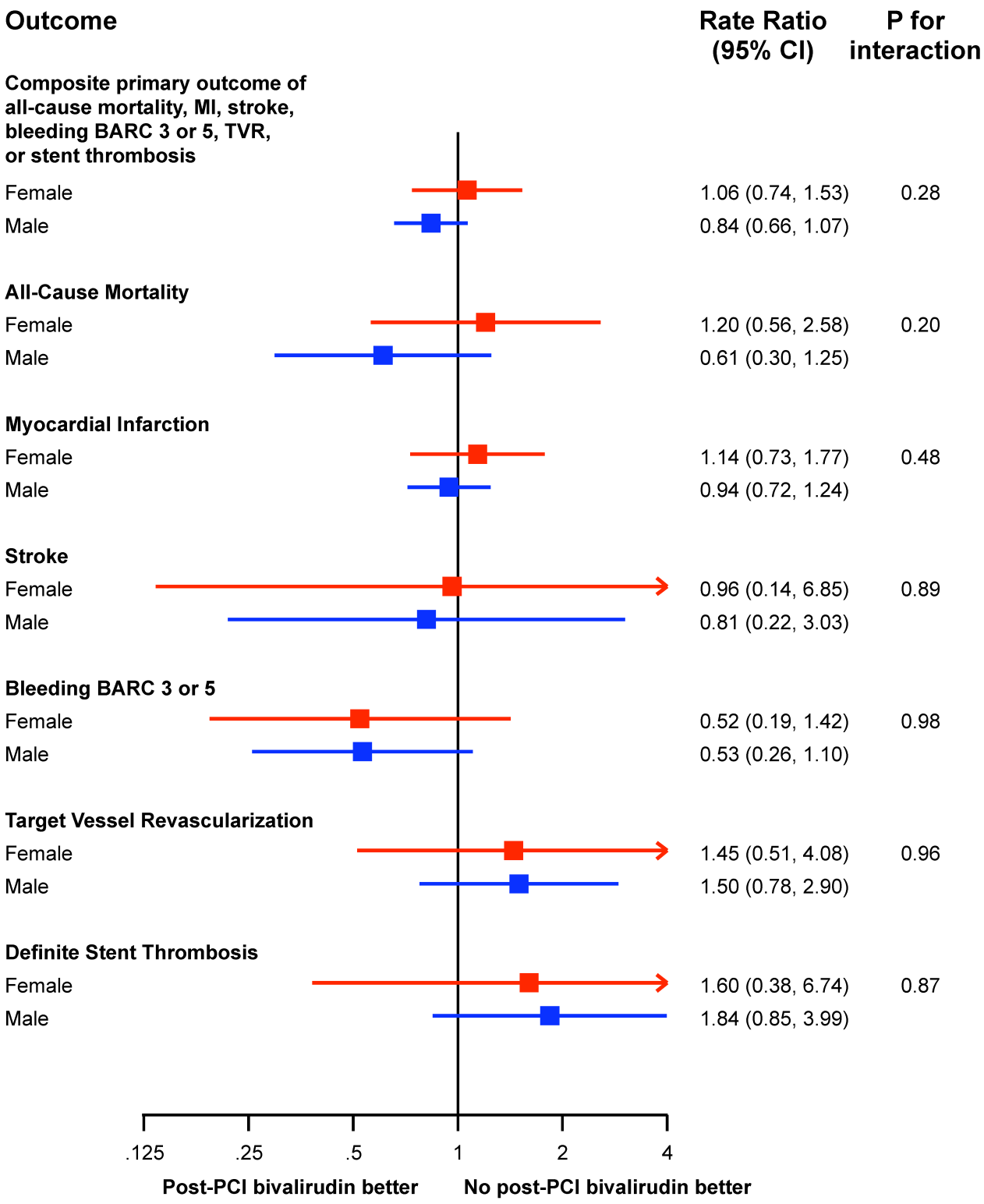
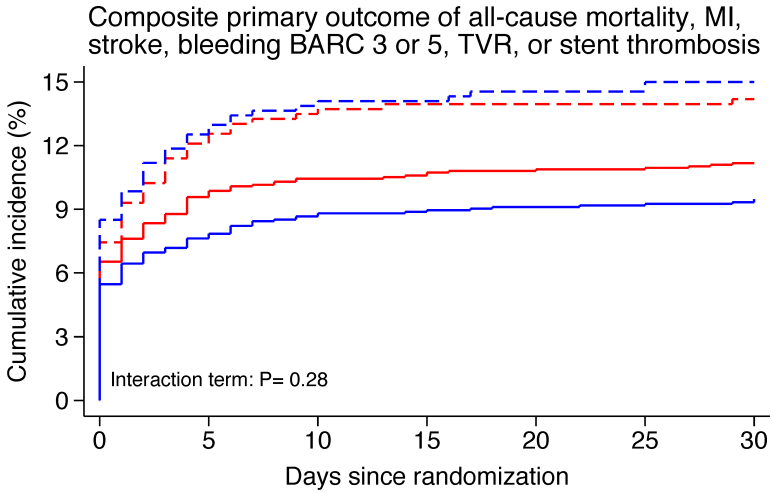

Outcome
Rate Ratio (95% CI)
P for interaction
Composite primary outcome of all-cause mortality, MI, stroke, bleeding BARC 3 or 5, TVR, or stent thrombosis
Female
1.06 (0.74, 1.53)
0.28
Male
0.84 (0.66, 1.07)
All-Cause Mortality
Female
1.20 (0.56, 2.58)
0.20
Male
0.61 (0.30, 1.25)
Myocardial Infarction
Female
1.14 (0.73, 1.77)
0.48
Male
0.94 (0.72, 1.24)
Stroke
Female
0.96 (0.14, 6.85)
0.89
Male
0.81 (0.22, 3.03)
Bleeding BARC 3 or 5
Female
0.52 (0.19, 1.42)
0.98
Male
0.53 (0.26, 1.10)
Target Vessel Revascularization
Female
1.45 (0.51, 4.08)
0.96
Male
1.50 (0.78, 2.90)
Definite Stent Thrombosis
Female
1.60 (0.38, 6.74)
0.87
Male
1.84 (0.85, 3.99)
.125
.25
.5
1
2
4
Post-PCI bivalirudin better
No post-PCI bivalirudin better

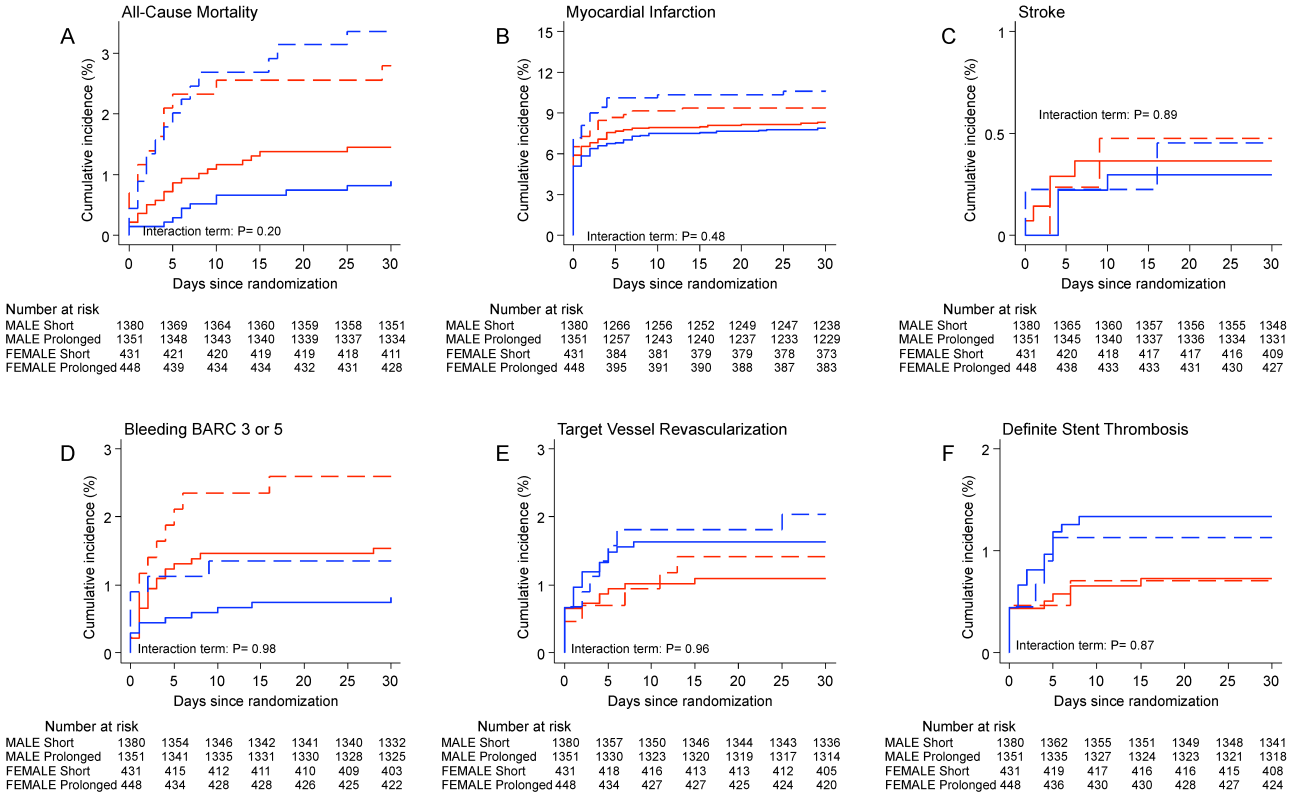
Figure 5.



Number at risk

MALE Short	1380	1247	1235	1232	1229	1227	1217
MALE Prolonged	1351	1248	1233	1229	1226	1223	1219
FEMALE Short	431	378	372	370	370	369	365
FEMALE Prolonged	448	391	384	383	381	380	376

Figure 6.



Number at risk

MALE Short	1380	1369	1364	1360	1359	1358	1351
MALE Prolonged	1351	1348	1343	1340	1339	1337	1334
FEMALE Short	431	421	420	419	419	418	411
FEMALE Prolonged	448	439	434	434	432	431	428

Number at risk

MALE Short	1380	1266	1256	1252	1249	1247	1238
MALE Prolonged	1351	1257	1243	1240	1237	1233	1229
FEMALE Short	431	384	381	379	379	378	373
FEMALE Prolonged	448	395	391	390	388	387	383

Number at risk

MALE Short	1380	1365	1360	1357	1356	1355	1348
MALE Prolonged	1351	1345	1340	1337	1336	1334	1331
FEMALE Short	431	420	418	417	417	416	409
FEMALE Prolonged	448	438	433	433	431	430	427

Number at risk

MALE Short	1380	1354	1346	1342	1341	1340	1332
MALE Prolonged	1351	1341	1335	1331	1330	1328	1325
FEMALE Short	431	415	412	411	410	409	403
FEMALE Prolonged	448	434	428	428	426	425	422

Number at risk

MALE Short	1380	1357	1350	1346	1344	1343	1336
MALE Prolonged	1351	1330	1323	1320	1319	1317	1314
FEMALE Short	431	418	416	413	413	412	405
FEMALE Prolonged	448	434	427	427	425	424	420

Number at risk

MALE Short	1380	1362	1355	1351	1349	1348	1341
MALE Prolonged	1351	1335	1327	1324	1323	1321	1318
FEMALE Short	431	419	417	416	416	415	408
FEMALE Prolonged	448	436	430	430	428	427	424

Table 1. Clinical outcomes at 30 days for the antithrombin type study

	ANTITHROMBIN-TYPE STUDY								
	MALE				FEMALE				
Number of patients	Bivalirudin (N=2731)	UFH (N=2764)	Rate Ratio (95% CI)	p Value	Bivalirudin (N=879)	UFH (N=839)	Rate Ratio (95% CI)	p Value	p V int
At 30 Days									
Co-primary composite endpoint of all-cause mortality, MI or stroke	256 (9.4)	287 (10.5)	0.90 (0.75-1.07)	0.22	115 (13.1)	104 (12.4)	1.06 (0.80-1.40)	0.67	
Co-primary composite endpoint of all-cause mortality, MI, stroke, or BARC 3 or 5	276 (10.2)	323 (11.8)	0.85 (0.72-1.01)	0.066	125 (14.2)	121 (14.4)	0.98 (0.76-1.28)	0.91	
Composite of all-cause mortality, MI, stroke, BARC 3 or 5, urgent TVR, or definite stent thrombosis	282 (10.4)	329 (12.0)	0.86 (0.73-1.01)	0.069	128 (14.6)	121 (14.4)	1.01 (0.78-1.31)	0.94	
All-cause mortality	32 (1.2)	51 (1.9)	0.63 (0.41-0.98)	0.041	27 (3.1)	32 (3.8)	0.80 (0.48-1.34)	0.40	
Cardiovascular death	30 (1.1)	50 (1.8)	0.60 (0.38-0.95)	0.028	26 (3.0)	30 (3.6)	0.82 (0.49-1.40)	0.47	
Myocardial infarction	220 (8.1)	233 (8.5)	0.95 (0.78-1.15)	0.59	87 (10.0)	70 (8.4)	1.19 (0.86-1.66)	0.30	
Stroke	9 (0.3)	9 (0.3)	1.01 (0.40-2.54)	0.99	4 (0.5)	7 (0.9)	0.54 (0.16-1.85)	0.32	
Transient ischemic attack	1 (0.0)	2 (0.1)	0.50 (0.05-5.56)	0.57	4 (0.5)	7 (0.8)	0.54 (0.16-1.85)	0.32	
Urgent target vessel revascularisation	37 (1.4)	26 (0.9)	1.44 (0.87-2.38)	0.15	15 (1.7)	9 (1.1)	1.59 (0.69-3.63)	0.27	
Definite stent thrombosis	28 (1.0)	17 (0.6)	1.66 (0.91-3.05)	0.094	8 (0.9)	4 (0.5)	1.90 (0.57-6.33)	0.29	
Acute definite stent thrombosis	15 (0.6)	11 (0.4)	1.38 (0.63-3.00)	0.42	5 (0.6)	2 (0.2)	2.37 (0.46-12.27)	0.29	
Subacute definite stent thrombosis	13 (0.5)	6 (0.2)	2.19 (0.83-5.76)	0.10	3 (0.3)	2 (0.2)	1.42 (0.24-8.54)	0.70	
Definite or probable stent thrombosis	33 (1.2)	30 (1.1)	1.11 (0.68-1.82)	0.68	12 (1.4)	5 (0.6)	2.28 (0.80-6.49)	0.11	
Acute definite or probable stent thrombosis	17 (0.6)	13 (0.5)	1.32 (0.64-2.73)	0.45	5 (0.6)	3 (0.4)	1.58 (0.38-6.64)	0.53	
Subacute definite or probable stent thrombosis	16 (0.6)	17 (0.7)	0.95 (0.48-1.88)	0.88	7 (0.8)	2 (0.2)	3.33 (0.69-16.07)	0.11	
Bleeding	274 (10.1)	337 (12.3)	0.81 (0.69-0.95)	0.012	117 (13.6)	145 (17.6)	0.74 (0.58-0.95)	0.019	
Type 1	135 (5.0)	169 (6.2)	0.80 (0.64-1.01)	0.056	55 (6.5)	68 (8.4)	0.76 (0.53-1.08)	0.13	
Type 2	106 (3.9)	110 (4.0)	0.97 (0.74-1.27)	0.84	45 (5.2)	43 (5.2)	0.98 (0.64-1.50)	0.94	
Type 3abc	29 (1.1)	51 (1.9)	0.57 (0.36-0.90)	0.015	15 (1.7)	21 (2.5)	0.67 (0.35-1.31)	0.24	
Type 3a	14 (0.6)	25 (0.9)	0.56 (0.29-1.08)	0.081	10 (1.2)	13 (1.6)	0.73 (0.32-1.66)	0.45	
Type 3b	12 (0.4)	25 (0.9)	0.48 (0.24-0.96)	0.034	4 (0.5)	8 (1.0)	0.47 (0.14-1.57)	0.21	
Type 3c	3 (0.1)	1 (0.0)	3.02 (0.31-29.10)	0.31	1 (0.1)	0 (0.0)	2.86 (0.12-70.11)	1.00	
Type 4	1 (0.0)	4 (0.1)	0.25 (0.03-2.25)	0.18	0 (0.0)	0 (0.0)	-	-	
Type 5ab	3 (0.1)	3 (0.1)	1.01 (0.20-4.99)	0.99	2 (0.2)	13 (1.6)	0.15 (0.03-0.65)	0.0033	
Type 5a	2 (0.1)	1 (0.0)	2.01 (0.18-22.21)	0.56	2 (0.2)	10 (1.2)	0.19 (0.04-0.87)	0.016	

Type 5b	1 (0.0)	2 (0.1)	0.50 (0.05-5.56)	0.57	0 (0.0)	3 (0.4)	0.14 (0.01-2.71)	0.12
Type 3 or 5	32 (1.2)	54 (2.0)	0.59 (0.38-0.92)	0.019	17 (2.0)	34 (4.1)	0.47 (0.26-0.85)	0.010
Type 3 or 5 related to access site	9 (0.4)	20 (0.7)	0.45 (0.21-0.99)	0.043	10 (1.2)	12 (1.4)	0.79 (0.34-1.83)	0.58
Type 3 or 5 not related to access site	23 (0.8)	34 (1.3)	0.68 (0.40-1.16)	0.15	7 (0.8)	22 (2.7)	0.30 (0.13-0.70)	0.0033
Type 2, 3 or 5	138 (5.1)	164 (6.0)	0.85 (0.67-1.06)	0.15	62 (7.1)	77 (9.3)	0.75 (0.53-1.06)	0.10
Type 2, 3 or 5 related to access site	65 (2.4)	84 (3.1)	0.78 (0.56-1.08)	0.13	40 (4.6)	48 (5.8)	0.78 (0.51-1.19)	0.25
Type 2, 3 or 5 not related to access site	73 (2.7)	80 (3.0)	0.92 (0.67-1.27)	0.61	22 (2.5)	29 (3.5)	0.72 (0.41-1.26)	0.24
Major bleeding	12 (0.4)	18 (0.7)	0.67 (0.32-1.39)	0.28	4 (0.5)	15 (1.8)	0.25 (0.08-0.76)	0.0082
Minor bleeding	9 (0.4)	20 (0.8)	0.45 (0.21-0.99)	0.043	8 (0.9)	13 (1.6)	0.58 (0.24-1.41)	0.22
Major or minor bleeding	21 (0.8)	38 (1.4)	0.55 (0.33-0.95)	0.028	12 (1.4)	28 (3.4)	0.40 (0.20-0.80)	0.0067
Severe bleeding	13 (0.5)	14 (0.5)	0.94 (0.44-1.99)	0.86	3 (0.3)	12 (1.4)	0.24 (0.07-0.84)	0.015
Moderate bleeding	8 (0.3)	13 (0.5)	0.62 (0.26-1.50)	0.28	8 (0.9)	13 (1.6)	0.58 (0.24-1.41)	0.22
Mild bleeding	252 (9.3)	307 (11.2)	0.82 (0.69-0.97)	0.023	106 (12.3)	119 (14.6)	0.82 (0.63-1.08)	0.16
Severe or moderate bleeding	21 (0.8)	27 (1.0)	0.78 (0.44-1.39)	0.40	11 (1.3)	25 (3.0)	0.41 (0.20-0.85)	0.012
Composite of surgical access site repair or blood products transfusion	18 (0.7)	38 (1.4)	0.48 (0.27-0.83)	0.0079	18 (2.1)	29 (3.5)	0.58 (0.32-1.05)	0.070
Surgical access site repair	1 (0.0)	9 (0.3)	0.11 (0.01-0.88)	0.012	4 (0.5)	3 (0.4)	1.26 (0.28-5.64)	0.76
Blood products transfusion	17 (0.7)	34 (1.3)	0.50 (0.28-0.90)	0.018	14 (1.6)	29 (3.5)	0.45 (0.24-0.86)	0.013

Effect of Post-procedural Bivalirudin Infusion at Full or Low Regimen in Patients with Acute Coronary Syndrome with or without ST-segment Elevation: An Analysis of the MATRIX trial.

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Running title: Optimal regimen of bivalirudin in ACS

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ABSTRACT
Background: The value of prolonged bivalirudin infusion after percutaneous coronary intervention (PCI) in acute coronary syndrome (ACS) patients with or without ST-segment elevation remains unclear.
Objectives: To assess efficacy and safety of a full or low post-PCI bivalirudin regimen in ACS patients with or without ST-segment elevation.
Methods: The MATRIX program assigned bivalirudin to patients without or with a post-PCI infusion at either a full (1.75 mg/kg/h) for up to 4 hours, or reduced (0.25 mg/kg/h) for up to 6 hours, regimen at the operator's discretion. The primary endpoint was the 30-day composite of urgent target-vessel revascularization, definite stent thrombosis, or net adverse clinical events (composite of all-cause death, myocardial infarction, or stroke [MACE] or major bleeding).
Results: Among 3610 patients assigned to bivalirudin, 1799 were randomized to receive and 1811 not to receive a post-PCI bivalirudin infusion. Post-PCI full bivalirudin was administered in 612 (STEMI=399; NSTE-ACS=213) whereas 1068 (STEMI=519; NSTE-ACS=549) patients received the low regimen. The primary outcome did not differ in STEMI or NSTE-ACS patients who received or did not receive post-PCI bivalirudin. However, full as compared to low bivalirudin regimen remained associated with a significant reduction of the primary endpoint after multivariable (rate ratio 0.21, 95% CI 0.12-0.35; $p<0.001$) or propensity-score (rate ratio 0.16, 95% CI 0.09-0.26; $p<0.001$) adjustment. Full post-PCI bivalrudin was associated with improved outcomes consistently across ACS types and in comparison with the no post-PCI infusion or heparin groups.
Conclusion: In ACS patients with or without ST-segment elevation, the primary endpoint did not differ with or without post-PCI bivalirudin infusion but a post-PCI full dose was associated with improved outcomes when compared with no or low-dose post-PCI infusion or heparin (Minimizing Adverse Haemorrhagic Events by TRansradial Access Site and Systemic Implementation of angioX [MATRIX]; NCT01433627).

Keywords: MATRIX, bivalirudin duration, bivalirudin dose, acute coronary syndrome, STEMI, NSTE-ACS.

CONDENSED ABSTRACT
The optimal regimen of bivalirudin after percutaneous coronary intervention (PCI) and whether this differs across acute coronary syndrome (ACS) with or without ST-segment elevation is unknown. This analysis found no differences between post-PCI bivalirudin infusion vs no infusion for the primary endpoint or other outcomes in STEMI and NSTE-ACS. Yet after adjustment, the full post-PCI bivalirudin dose was associated to improved efficacy and safety outcomes when compared to the low post-PCI bivalirudin regimen, no post-PCI infusion or unfractionated heparin groups.

ABBREVIATIONS
ACS=acute coronary syndrome
BARC=Bleeding Academic Research Consortium
CABG=coronary artery bypass grafting
GPI=glycoprotein IIb/IIIa inhibitor
GUSTO=Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries
MACE=major adverse cardiovascular events
MI=myocardial infarction
NACE=net adverse clinical events
NSTE-ACS=non-ST-segment elevation ACS
PCI=percutaneous coronary intervention
ST=stent thrombosis
STEMI=ST-segment elevation myocardial infarction
TIMI=thrombolysis in myocardial infarction
UFH=unfractionated heparin

INTRODUCTION

Percutaneous coronary intervention (PCI) in conjunction with periprocedural anticoagulant and antiplatelet therapy improves clinical outcomes in patients suffering from either ST-segment elevation myocardial infarction (STEMI) or non–ST-segment elevation acute coronary syndromes (NSTE-ACS). Yet, invasively managed ACS patients have an increased risk of bleeding, which in turn could be associated with higher mortality (1). Bivalirudin administration at the time of PCI has been repeatedly shown to mitigate bleeding complications compared to unfractionated heparin (UFH) with or without glycoprotein IIb/IIIa inhibitors (GPI) (2-8). Moreover, while major adverse cardiovascular events (MACE) did not differ at 30 days, bivalirudin administration was associated to higher acute stent thrombosis (ST) in STEMI (but not NSTE-ACS) and trends towards higher peri-procedural MI in NSTE-ACS patients, especially in those in whom administration of oral P2Y12 inhibitors was delayed (5,8-10).

The prolongation of bivalirudin infusion after PCI has been empirically employed as a potentially safe measure to mitigate the ischemic hazards associated to the use of bivalirudin. However, evidence remains limited.

Data comparing post-PCI versus no post-PCI bivalirudin infusion is largely indirect considering that HORIZONS-AMI (2) and HEAT-PPCI (11) studies investigated only a no-post-PCI infusion strategy, BRIGHT (4) and EUROMAX (3) mandated the use of a full and a full or low post-PCI bivalirudin dose, respectively, and no other large study prior to MATRIX had so far investigated the value of a post-PCI bivalirudin regimen in NSTE-ACS patients.

Therefore, the aim of this analysis was to assess the role of post-PCI bivalirudin in patients with STEMI and NSTE-ACS enrolled in the MATRIX Treatment Duration trial, with a focus on the comparative effectiveness of the full versus the low post-PCI regimen.

METHODS

Study Design

The main results of the MATRIX program including three randomized, multicenter, open-label superiority trials in patients with an ACS had been reported previously (6,12,13).

Here, we report the outcomes stratified by the type of ACS (STEMI and NSTE-ACS) from the MATRIX Treatment Duration, whereby 3610 patients were assigned to receive bivalirudin with or without a prolonged post-PCI bivalirudin infusion.

Patients

Detailed inclusion and exclusion criteria were previously reported (6,12,14). Briefly, patients with NSTE-ACS were eligible if they had a history consistent with new or worsening cardiac ischemia, occurring while they were at rest or with minimal activity within 7 days before randomization, and met at least two high-risk criteria among the following: aged 60 years or older, elevated cardiac biomarkers, or electrocardiographic changes compatible with ischemia and if they were considered to be candidates for PCI after completion of coronary angiography. Patients with STEMI were eligible if presenting within 12 hours after the onset of symptoms or between 12 and 24 hours after symptom onset if there was evidence of continuing ischemia or previous fibrinolytic treatment. All patients provided written informed consent.

Study Protocol and Randomization

Patients were randomly assigned, in a 1:1 ratio, to receive bivalirudin or UFH. Patients who were assigned to the bivalirudin group were subsequently randomly assigned, in a 1:1 ratio, to receive a post-PCI bivalirudin infusion or no post-PCI infusion. Central randomization was concealed with the use of a Web-based system. Randomization sequences were computer generated, blocked, and stratified according to type of ACS (STEMI vs troponin positive vs troponin-negative NSTE-ACS) and intended new or ongoing use of a $P2Y_{12}$ inhibitor (clopidogrel vs ticagrelor or prasugrel). Randomization was performed before coronary angiography for STEMI patients and immediately after completion of angiography but before the start of PCI for patients with NSTE-ACS.

All interventions were administered in an open label fashion. Bivalirudin was given according to the product labeling, with a bolus of 0.75 mg per kilogram of body weight, immediately followed by an infusion of 1.75 mg per kilogram per hour until completion of the PCI. Bivalirudin was then stopped at the end of PCI or prolonged in accordance with the subsequent random assignment.

Among patients assigned to receive prolonged treatment, bivalirudin could be administered either at the full dose for up to 4 hours or at a reduced dose of 0.25 mg per kilogram per hour for at least 6 hours. The choice between the two regimens was at the the treating physician’s discretion . A GPI was allowed in the bivalirudin group only in patients who had periprocedural ischemic complications (i.e., no reflow or giant thrombus) after PCI (bailout therapy). Other medications were allowed according to professional guidelines. The protocol mandated a consistent use of the randomly allocated antithrombin regimen in cases of staged procedures.

Follow-up and Outcomes

Clinical follow-up was performed at 30-day. The primary outcome for MATRIX Treatment Duration was a composite of urgent target-vessel revascularization, definite ST, or net adverse clinical events (NACE) up to 30 days. Coprimary outcomes for MATRIX Antithrombin and Access site were MACE, defined as a composite of death from any cause, myocardial infarction, or stroke, and NACE, defined as a composite of major bleeding that was not related to coronary-

artery bypass grafting (CABG) (Bleeding Academic Research Consortium [BARC] type 3 or 5) or MACE. Secondary outcomes included each component of the composite outcomes, death from cardiovascular causes, and ST. Bleeding was also assessed and adjudicated on the basis of the Thrombolysis in Myocardial Infarction (TIMI) and Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) scales. All outcomes were prespecified.
An independent clinical-events committee whose members were unaware of the study-group assignments adjudicated all suspected events. Detailed definitions of outcomes and procedures of the clinical-events committee were previously provided (6,12,14).

Statistical analysis
Details regarding the statistical analysis have been reported previously (6,12,14). Briefly, MATRIX Treatment Duration was powered assuming that the incidence of the primary endpoint at 30 days would be 10.0% with short-term bivalirudin and 7.0% with prolonged bivalirudin (rate ratio of 0.70), therefore, the enrollment of 1700 patients in each study group provided a power of 86% to detect this difference at a two-sided alpha level of 0.05. Analyses were performed according to the intention-to-treat principle, including all patients in the analysis according to the allocated post-PCI regimen of bivalirudin. Primary and secondary outcomes were analyzed as time-to-first event using the Mantel–Cox method, accompanied by log–rank tests to calculate corresponding two-sided p-values. Survival curves were constructed using Kaplan–Meier estimates and percentages reported for outcomes are Kaplan–Meier estimates of cumulative incidence.
To compare the two different bivalirudin dosages (full vs low, irrespective of the final treatment duration) in the group receiving post-PCI infusion, multivariable and propensity score adjustment models were performed. The multivariable model included the following variables: year of randomization, center, access site randomized, diabetes, type of ACS, hypertension, previous PCI, previous stroke or TIA, peripheral vascular disease, eGFR, hemoglobin at baseline, TIMI flow 0-1 before PCI, P2Y12 inhibitor at discharge, and procedure duration. A propensity score that indicated the likelihood of receiving a full or low post-PCI bivalirudin infusion was calculated by using a nonparsimonious multivariable logistic regression including the following variables: year of randomization, center, access-site randomized, age, sex, body mass index, diabetes, type of ACS, smoking, hypertension, hypercholesterolemia, previous MI, previous PCI, previous CABG, previous stroke or TIA, peripheral vascular disease, eGFR, left ventricular ejection fraction, hemoglobin at baseline, medications pre-PCI (clopidogrel, fondaparinux, ACE-inhibitors, statins, beta blockers, proton pump inhibitors, unfractionated heparin), PCI completed, GPI intraprocedural, ticagrelor intraprocedural, ≥2 vessels treated, ≥3 lesions treated, total SYNTAX score, ≥1 BMS, TIMI flow 0-1 before PCI, procedural success in all lesions, large and/or small vessel caliber, proximal location of the lesion, presence of thrombus in the treated lesion. This score had a very good predictive ability (ROC 0.92; **Supplementary Figure 1**). The individual propensity score was incorporated into the adjustment model to compare outcomes.
All analyses in the overall study population were stratified by type of ACS and accompanied by $\chi 2$ tests for interaction. Secondary analyses were also performed separately in STEMI and NSTE-ACS subgroups and were stratified according to age, sex, body mass index, type of P2Y12 inhibitor, overall or transradial PCI volume by center, renal function, diabetes mellitus, peripheral vascular disease and access site randomization, and accompanied by $\chi 2$ tests for interaction or tests for trend across ordered groups".
Secondary outcomes were analyzed with a two-sided alpha set at 5% to allow conventional interpretation of results. All analyses were performed using the STATA version 14.1 (StataCorp, College Station, Texas) and R (R Foundation, Vienna, Austria) statistical packages.

RESULTS

Patients
From October 11, 2011, to November 7, 2014, at 78 centers in Italy, the Netherlands, Spain, and Sweden, 3610 patients were assigned to receive bivalirudin as part of the MATRIX program. Of these, 1799 (STEMI=1006; NSTE-ACS=793) patients were randomized to receive and 1811 (STEMI=1006; NSTE-ACS=805) to not receive a post-PCI bivalirudin infusion. Post-PCI bivalirudin infusion was administered at full or low dose in 612 (STEMI=399; NSTE-ACS=213) and 1068 (STEMI=519; NSTE-ACS=549) patients respectively, whereas 119 patients did not receive post-PCI infusion. The distribution of patients receiving a full or low dose during time is shown in **Figure 1**.
Baseline and procedural characteristics, stratified by ACS type, of patients randomized to receive or not to receive post-PCI bivalirudin infusion were generally well-balanced (**Supplementary Tables 1-3**). Baseline and procedural characteristics stratified by actual post-PCI bivalirudin regimen in those assigned to post-PCI bivalirudin are shown in **Supplementary Tables 4-6**. Compared with patients receiving a low bivalirudin regimen, those treated with a full post-PCI bivalirudin dose were slightly younger, less frequently affected by cardiovascular risk factors, had a history of MI or coronary revascularization or were treated with anti-hypertensive/lipid-lowering agents. Yet, they were more frequently smokers or exposed to ticagrelor (as opposed to clopidogrel) or UFH before angiography, more frequently presenting TIMI flow 0-1 before PCI, and more frequently treated with ticagrelor or DES implantation (**Supplementary Tables 4-6**).

Clinical outcomes of post-PCI prolonged vs no infusion of bivalirudin
The primary composite outcome was similar in patients who either did or did not receive post-PCI bivalirudin in the entire population (rate ratio, 0.91, 95% CI 0.74-1.11; p=0.34). When separately appraised in STEMI and NSTEACS patients, the results remained consistent in indicating no benefit from post-PCI bivalirudin (**Supplementary Results**).
Clinical outcomes of Full vs Low dose of post-PCI prolonged bivalirudin infusion
At univariate analysis, post-PCI full dose bivalirudin was associated with a significant reduction of the primary endpoint consisting of urgent target-vessel revascularization, definite ST, or NACE as compared to low dose bivalirudin infusion (rate ratio 0.29, 95% CI 0.19-0.44; p<0.001). After multivariable adjustment, this composite endpoint remained lower in the full versus low post-PCI bivalirudin arm (rate ratio 0.21, 95% CI 0.12-0.35; p<0.001). The propensity-score adjustment provided consistent results (rate ratio 0.16, 95% CI 0.09-0.26; p<0.001) (**Table 1; Central illustration and Figure 2**).
Similar findings were observed for the MACE (unadjusted rate ratio 0.31, 95% CI 0.2-0.47; p<0.001; multivariable adjusted rate ratio 0.23, 95% CI 0.13-0.39; p<0.001; propensity-score adjusted rate ratio 0.17, 95% CI 0.1-0.29; p<0.001) or NACE (unadjusted rate ratio 0.30, 95% CI 0.2-0.45; p<0.001; multivariable adjusted rate ratio 0.22, 95% CI 0.13-0.36; p<0.001; propensity-score adjusted rate ratio 0.16, 95% CI 0.09-0.27; p<0.001) endpoints favoring the full as compared to the low post-PCI bivalirudin regimens (**Table 1**). The benefit of post-PCI full bivalirudin dose was driven by a reduction of MI, ST, TVR and BARC 3 or 5, whereas the rates of all-cause death, cardiovascular mortality or stroke did not differ (**Table 1; Central illustration and Figures 3-4**). Overall, these findings remained consistent across the ACS subtypes (**Supplementary Tables 8 and 9**).

Clinical outcomes of post-PCI Full dose bivalirudin vs no post-PCI infusion or vs heparin
Compared with the no post-PCI bivalirudin infusion group, full dose post-PCI bivalirudin was associated with a significantly lower rate of the primary endpoint, as well as MACE or NACE, and this effect was mainly driven by lower rates of MI and BARC 3 or 5 bleeding events (**Table 2, Supplementary Tables 10 and 11**). When compared with the heparin plus provisional GPI group, full dose post-PCI bivalirudin regimen was associated with a significantly lower rate of the primary endpoint, as well as MACE or NACE, and this effect was driven by lower rates of all-cause and cardiovascular death as well as of MI or BARC 3 or 5 bleeding events (**Table 3, Supplementary Tables 12 and 13**).

DISCUSSION
MATRIX was the first trial to explore, in a randomized manner, the differences among post-PCI bivalirudin infusion versus no bivalirudin infusion in invasively managed ACS patients. The present analysis sought to further investigate the stratified outcomes of post-PCI bivalirudin infusion versus no infusion in STEMI versus NSTE-ACS patients across the full spectrum of all pre-defined endpoints as well as the impact of post-PCI bivalirudin dose on outcomes. The main findings of this analysis can be summarized as follows: a) there were no differences between post-PCI bivalirudin infusion vs no infusion for the primary or other secondary efficacy and safety endpoints in patients either presenting STEMI or NSTE-ACS. This observation further reinforces the notion that the type of ACS was not a treatment modifier in our study; b) the post-PCI full dose of bivalirudin remained associated after both multivariable or propensity score adjusted analyses to beneficial effects in terms of ischemic non-fatal endpoints, including ST and MI as well as bleeding events when compared to the low post-PCI bivalirudin dose; c) after multivariable or propensity-score adjustment, patients receiving full dose bivalirudin after PCI showed improved outcomes as compared to patients receiving only intra-procedural bivalirudin or UFH with provisional GPI. The improved outcome with full dose post-PCI bivalirudin was driven by lower MI and bleeding rates when the group was compared with bivalirudin without post-PCI bivalirudin infusion, whereas all-cause and cardiovascular mortality endpoints also favored the full dose post-PCI bivalirudin group when it was compared with UFH±GPI.

STEMI and NSTE-ACS patients differ with respect to multiple baseline and procedural characteristics as well as with post-procedural risks. Yet, they share the same underlying coronary artery disease characterized by plaque rupture and show similar independent association with adverse outcome (15).
STEMI patients, who are intervened upon as early as possible after symptoms onset, are characterized by having an evolving MI with rising cardiac biomarkers, which prevents in many instances the ascertainment of periprocedural necrotic injury after coronary intervention. This is at variance with NSTE-ACS patients in whom an invasive management is typically performed hours or days after symptoms onset when cardiac biomarkers are declining; a setting which allows peri-procedural MI ascertainment. On the other hand, the risk of acute and subacute ST is higher in STEMI as compared to NSTE-ACS patients, which is at least in part explained by a slow onset of action from oral P2Y12 inhibitors (16). Prolonging bivalirudin infusion after primary PCI completion has therefore been proposed as a therapeutic measure to mitigate that risk. At variance with STEMI patients undergoing coronary intervention, no study has so far observed a higher risk of acute or subacute ST in patients receiving bivalirduin as compared to UFH with or without GPI. This observation may speak against the need to prolong bivalirudin infusion to further optimize outcomes. Yet, a small randomized study in 178 patients with stable (58%) or unstable (42%) angina and complex coronary anatomy, found that prolonged post-PCI infusion significantly reduced the incidence of periprocedural myocardial damage (defined as creatine kinase-MB increase ≥3 times upper limit of normal) compared with no infusion without differences in death and other clinical outcomes at 1- and 6-month follow-up (17).

In the HORIZONS-AMI, bivalirudin administration was limited, as per protocol, to the procedural period with interruption of the infusion at the end of PCI (2). The study showed a significant increase in the acute ST (absolute 1% excess that was not extended in ST rates at 30 days) in the bivaluridin arm compared with UFH plus GPI. Subsequently, the EUROMAX trial was designed to test whether bivalirudin, initiated during transport for primary PCI in STEMI, was superior to UFH in a more contemporary practice of the STEMI patients' management (3). As opposed to HORIZONS-AMI, bivalirudin in the EUROMAX trial was prolonged as per protocol for at least 4 hours after PCI. Moreover, the protocol specified that the dosage after PCI had to be 0.25 mg/kg/h, but the full dose (1.75 mg/kg/h) was also permitted. In accordance with the HORIZONS-AMI, the EUROMAX confirmed the same 1% absolute increase in acute ST as compared with UFH with optional GPI, despite extending bivalirudin infusion for up to 4 hours after PCI, but major bleeding was reduced. A specific subanalysis of this trial showed that a high-dose of post-PCI bivalirudin was associated to similar rates of acute ST compared with UFH+GPI, while low-dose was independently associated to higher rates of acute ST (18). In the BRIGHT trial, bivalirudin was administered during and after the procedure at 1.75 mg/kg/h (4). The post-procedure infusion was at least 30 minutes and up to 4 hours. At the operator's discretion, a supplementary infusion at low dose (0.2 mg/kg/h) was allowed for up to 20 hours. All patients received a postprocedure infusion of the 1.75mg/kg/h bivalirudin PCI dose for a median duration of 180 minutes, and 115 patients (15.6%) thereafter received the optional 0.2mg/kg/h dose for a median duration of 400 minutes. Any ST and acute ST were not increased, while bleeding and NACE were reduced in the bivalirudin-treated patients. In the HEAT-PPCI, bivalirudin was administered without post-PCI prolonged infusion (a re-bolus of 0.3 mg/kg was provided in case of activated clotting time <225s at the end of PCI), and was associated with increased ST and MACE rates whereas bleeding did not differ (11). ST was observed at a high rate of incidence, at approximately 3.4% at variance with the 1.0% rate in the MATRIX Trial (6).

Most of the evidence in NSTE-ACS patients is outdated and almost exclusively based on bivalirudin administration during PCI only (19). Thus, before MATRIX, limited data existed on the value of bivalirudin used at the currently suggested regimen versus UFH alone in contemporary practice. Our study explored the benefit of bivalirudin compared with UFH across the whole spectrum of ACS patients receiving a concomitant bleeding-avoidance strategy, such as trans-radial access and/or UFH alone. An aggregate data network meta-analysis suggested that post-PCI bivalirudin given at full regimen decreases the rate of ST and ischemic events (19,20). This analysis was largely based on MATRIX study results, but the existence of bias in the analysis was not assessed. The recent VALIDATE-SWEEDHEART trial contributed to new evidence on bivalirudin versus UFH alone, showing no differences between groups (including ST) across ACS types (21). In this study, the protocol mandated the use of post-PCI bivalirudin at full regimen. So the MATRIX trial remains today the only study in which STEMI and NSTE-ACS patients treated with bivalirudin were randomized to either receive or not to receive post-PCI bivalirudin infusion.

Our findings altogether lend support to the use of a post-PCI full bivalirudin infusion regimen to further optimize outcomes in bivalirudin-treated ACS patients (which is in keeping with the updated FDA label of the product), owing to the reduction of ischemic risk without compromising safety, and extend the previous evidence that came from the EUROMAX substudy, which focused on ST only (18). Full post-PCI bivalirudin infusion provided consistent protection in both STEMI and NSTE-ACS towards ST and periprocedural MI risks. While as expected, the risk of ST was in absolute terms greater in STEMI as compared to NSTE-ACS patients, full post-PCI bivalirudin infusion decreased that risk consistently across both types of ACS. In addition, full post-PCI bivalirudin decreased the risks of MI, mainly periprocedural MI. Interestingly, benefits largely came from a mitigation of the risk during index intervention in NSTE-ACS, whereas full post-PCI bivalirudin was associated to lower periprocedural MI risk which was mainly during planned staged interventions in STEMI patients. This observation is explained by the difficulties in ascertaining additional necrotic injury in patients already suffering from an evolving MI.

The rates of BARC 3 or 5 bleeding also remained lower after adjustment in the group that received post-PCI full bivalirudin regimen as compared to who received a low post-PCI bivalirudin regimen or those who did not receive a post-PCI drug infusion. The bleeding risk remained lower in patients treated with the full post-PCI bivalirudin infusion also as compared to those assigned to UFH±GPI, owing to lower risks of access-site and non-access site related bleeding.

Study limitations

This study is affected by the protocol limitation which allowed for two different regimens of post-PCI bivalirudin infusion. Therefore, even if we had conducted multiple adjustments to account for differences between the groups, all these secondary findings should be considered explorative and interpreted with caution.

This analysis provides important knowledge regarding the role of the bivalirudin regimens during the periprocedural period. However, as in previous studies, it is not powered for ST as a primary outcome, and therefore these findings should be considered as hypothesis-generating.

The higher risk of bleeding in patients who received the low post-PCI bivalirudin regimen might have arisen by the protocol mandated longer duration of post-PCI bivalirudin infusion in such patients. Conversely, the lower risk of bleeding in patients receiving the full post-PCI bivalirudin regimen, when compared to those who did not receive infusion -largely attributable to an excess of pericardial bleeding- is counterintuitive. This may reflect a spurious finding or be explained by residual confounding not totally corrected by adjustment. Only a large randomized trial of bivalirudin with a prolonged post-PCI infusion at full dose versus UFH alone would provide conclusive evidence.

CONCLUSION

In patients with ACS, with or without ST-segment elevation undergoing invasive management, the composite of urgent target-vessel revascularization, definite stent thrombosis, or net adverse clinical events, as well as other explored endpoints, were not significantly lower with a post-PCI bivalirudin infusion compared with no post-PCI infusion. However, a post-PCI bivalirudin infusion at full dose was associated with improved outcomes and was safe when compared with other investigated anti-thrombin strategies, including low post-PCI bivalirudin infusion, no infusion or unfractionated heparin±GPI. Further studies are needed to confirm these observations.

CLINICAL PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE. Multiple data shows that bivalirudin was associated to higher risk of acute stent thrombosis (ST) in STEMI (but not NSTE-ACS) patients, suggesting that a prolonged post-PCI infusion might reduce such risk. However, the optimal regimen of bivalirudin after percutaneous coronary intervention (PCI), and whether this differs across acute coronary syndrome (ACS) with or without ST-segment elevation, is unknown.
COMPETENCY IN PATIENT CARE. In the MATRIX trial, there were no differences between post-PCI bivalirudin infusion vs no infusion for the primary endpoint or other outcomes in STEMI and NSTE-ACS. Additionally, the full post-PCI bivalirudin dose was associated to improved efficacy and safety outcomes after an adjustment was made/applied, when compared to the low post-PCI bivalirudin regimen, no post-PCI infusion or unfractionated heparin groups.
TRANSLATIONAL OUTLOOK. Additional investigation is needed to assess the effects of bivalirudin at full dose post-PCI versus UFH alone in contemporary practice and to assess the cost-effectiveness of these strategies.

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FIGURE LEGENDS

Central Illustration. Full or Low post-PCI bivalirudin regimen: Forest Plot of Main Clinical Outcomes. Propensity score adjusted rate ratios (RR) of main outcomes at 30 days for Full versus Low post-PCI bivalirudin regimen in the overall population and stratified by STEMI and NSTE-ACS.
BARC=Bleeding Academic Research Consortium; CI=confidence interval; MI=myocardial infarction; ST=stent thrombosis; TVR=Target Vessel Revascularization.

Figure 1. Distribution of patients receiving a Full or a Low post-PCI bivalirudin infusion during time. Bars report the proportion per week of Full and Low dose of post-PCI bivalirudin infusion during each month of trial enrollment. Vertical dashed lines indicate the publication time of relevant scientific evidence that might have influenced operators' decision. Circles indicate the proportion per week of myocardial infarction (red) and definite stent thrombosis (orange) and continuous lines (red and orange) indicate the corresponding regressions.

Figure 2. Kaplan-Meier curve for the primary endpoint according to the dose (full vs low) of post-PCI bivalirudin infusion and ACS type. The cumulative incidence of the primary outcome (composite of all-cause death, myocardial infarction, stroke, bleeding BARC 3 or 5, target vessel revascularization or definite stent thrombosis) up to 30 days, among patients with STEMI or NSTE-ACS who received full or low post-PCI bivalirudin dose.

Figure 3. Kaplan-Meier curve for individual components of the primary endpoint according to the dose (full vs low) of post-PCI bivalirudin infusion and ACS type. The cumulative incidence of the primary outcome components including all-cause death (A), myocardial infarction (B), stroke (C), bleeding BARC 3 or 5 (D), target vessel revascularization (E) and definite stent thrombosis (F) up to 30 days, among patients with STEMI or NSTE-ACS who received full or low post-PCI bivalirudin dose.

Figure 4. Kaplan-Meier curve for myocardial infarction according to the dose (full vs low) of post-PCI bivalirudin infusion and ACS type. The cumulative incidence of myocardial infarction up to 30 days and stratified by time (<24h, 2-7 days and 8-30 days) among patients with STEMI or NSTE-ACS who received full or low post-PCI bivalirudin dose.

Central Illustration. Full or Low post-PCI bivalirudin regimen: Forest Plot of Main Clinical Outcomes.

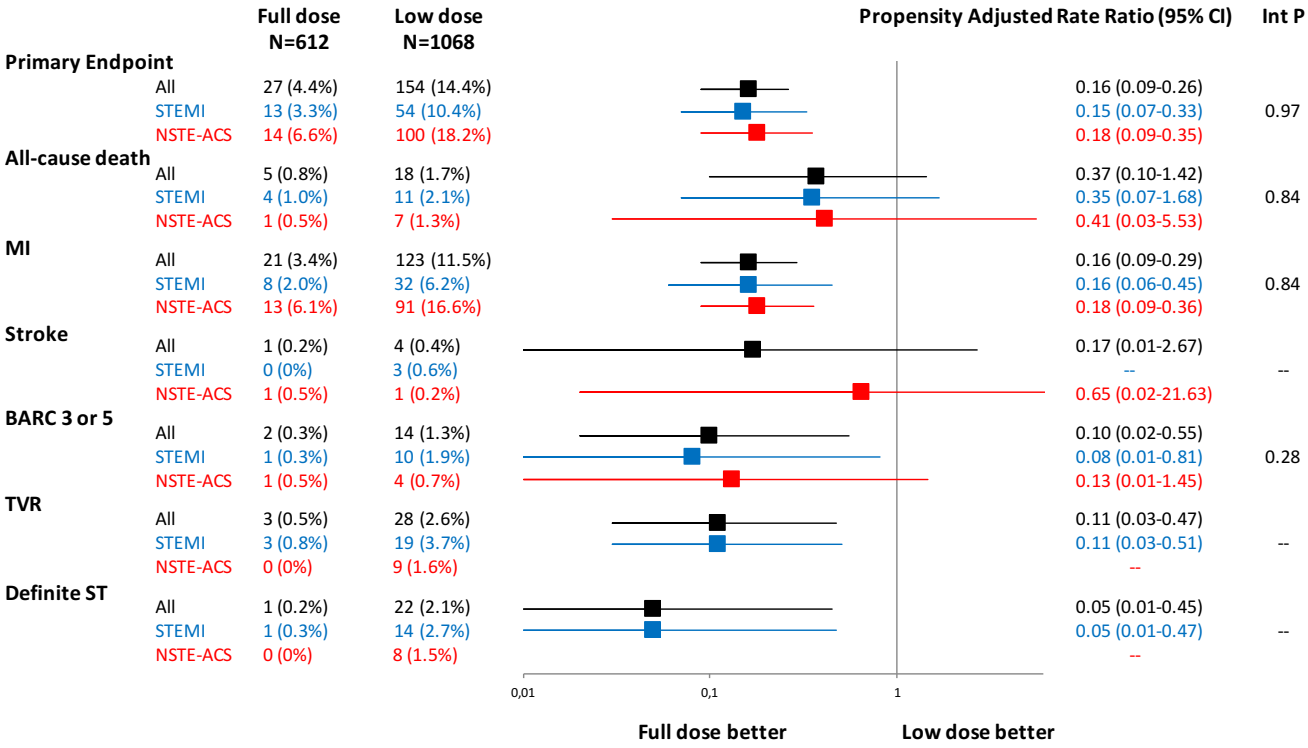

Figure 1. Distribution of patients receiving a Full or a Low post-PCI bivalirudin infusion during time.

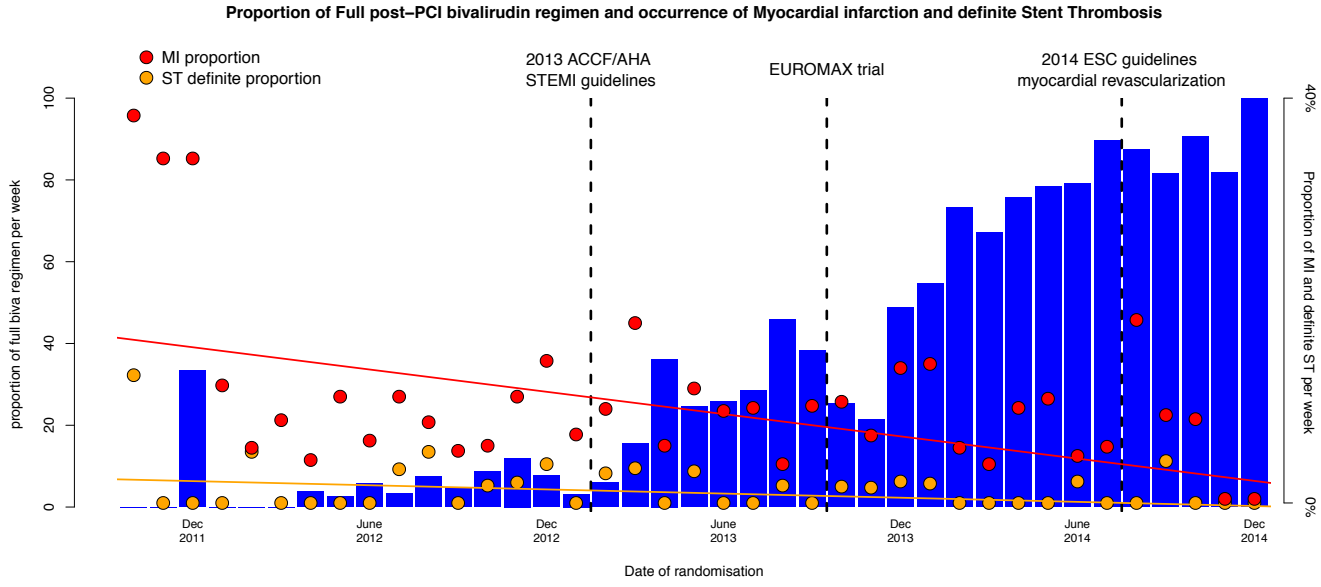

Figure 2. Kaplan-Meier curve for the primary endpoint according to the dose (full vs low) of post-PCI bivalirudin infusion and ACS type.

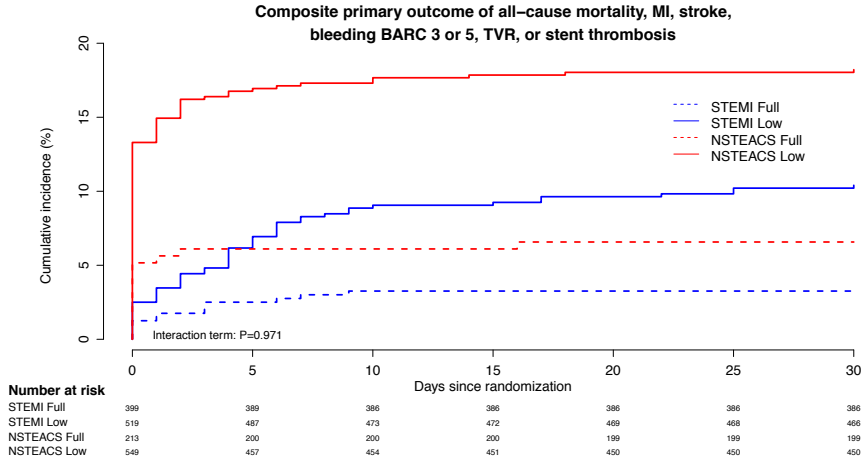

Figure 3. Kaplan-Meier curve for individual components of the primary endpoint according to the dose (full vs low) of post-PCI bivalirudin infusion and ACS type.

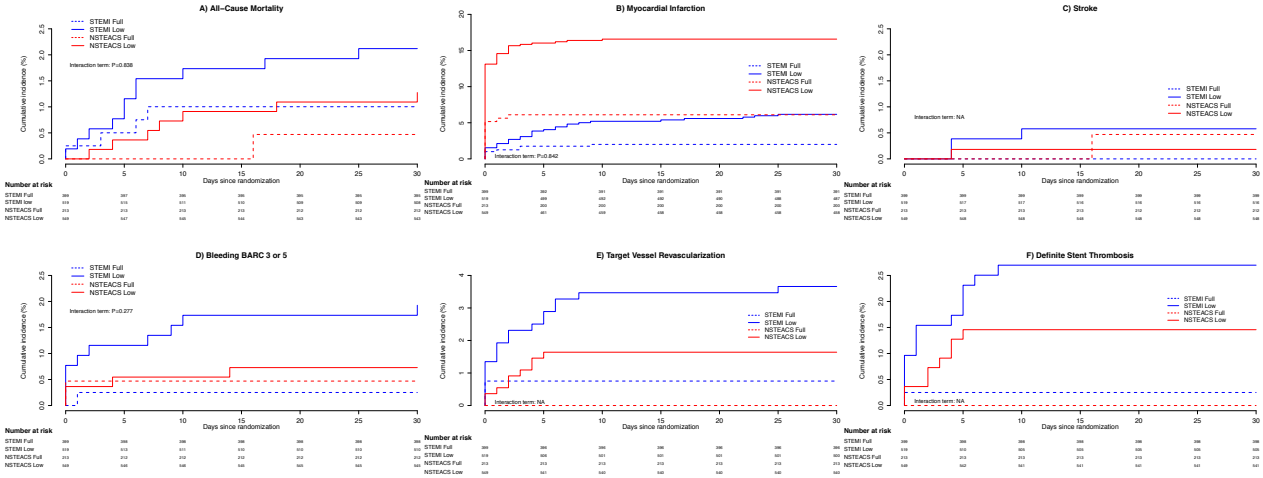

Figure 4. Kaplan-Meier curve for myocardial infarction according to the dose (full vs low) of post-PCI bivalirudin infusion and ACS type.

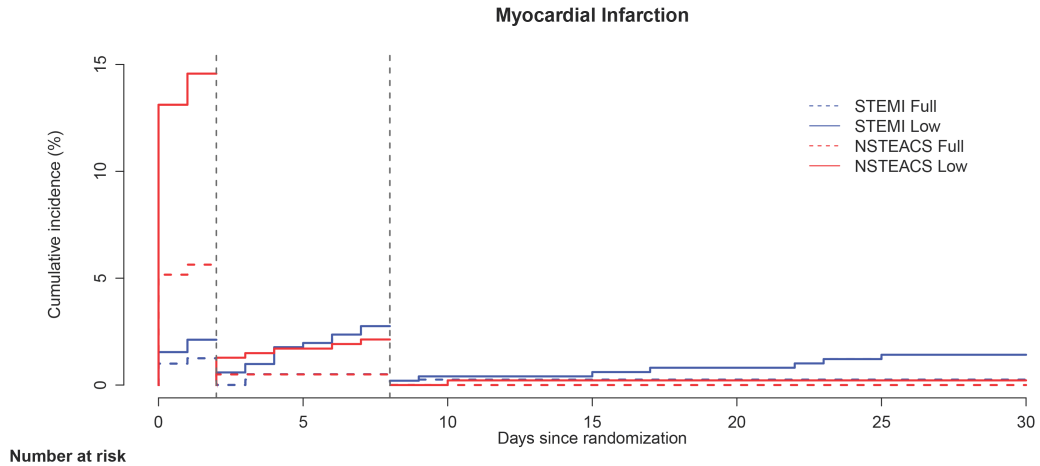

Table 1. Clinical outcomes at 30 days in post-PCI bivalirudin prolonged infusion at full versus low dose.

OUTCOME	Post-PCI prolonged bivalirudin Full dose (n=612)	Post-PCI prolonged bivalirudin Low dose (n=1068)	Unadjusted Rate Ratio (95% CI)	P-value*	Multivariable Adjusted Rate Ratio (95% CI)	P-value	Propensity Score Adjusted Rate Ratio (95% CI)	P-value
Death, MI, Stroke, BARC 3 or 5, TVR, ST	27 (4.4%)	154 (14.4%)	0.29 (0.19-0.44)	<0.001	0.21 (0.12-0.35)	<0.001	0.16 (0.09-0.26)	<0.001
Death, MI, Stroke	26 (4.2%)	141 (13.2%)	0.31 (0.2-0.47)	<0.001	0.23 (0.13-0.39)	<0.001	0.17 (0.1-0.29)	<0.001
Death, MI, Stroke, BARC 3 or 5	27 (4.4%)	149 (14%)	0.3 (0.2-0.45)	<0.001	0.22 (0.13-0.36)	<0.001	0.16 (0.09-0.27)	<0.001
Death	5 (0.8%)	18 (1.7%)	0.48 (0.18-1.3)	0.141	---	---	0.37 (0.1-1.42)	0.15
Cardiovascular death	5 (0.8%)	16 (1.5%)	0.54 (0.2-1.48)	0.227	---	---	0.46 (0.11-1.82)	0.27
MI	21 (3.4%)	123 (11.5%)	0.29 (0.18-0.45)	<0.001	0.24 (0.14-0.41)	<0.001	0.16 (0.09-0.29)	<0.001
MI <24h	17 (2.8%)	91 (8.5%)	0.32 (0.19-0.53)	<0.001	0.31 (0.17-0.56)	<0.001	0.18 (0.04-0.36)	<0.001
MI 2-7days	3 (0.5%)	24 (2.2%)	0.2 (0.06-0.68)	0.004	0.22 (0.05-0.90)	0.035	0.16 (0.04-0.72)	0.017
MI 8-30 days	1 (0.2%)	8 (0.7%)	0.2 (0.03-1.61)	0.093	0.02 (0.0-0.24)	0.002	0.04 (0.0-0.39)	0.005
Stroke	1 (0.2%)	4 (0.4%)	0.44 (0.05-3.9)	0.444	---	---	0.17 (0.01-2.67)	0.21
TIA	1 (0.2%)	2 (0.2%)	0.87 (0.08-9.63)	0.911	---	---	1.07 (0.03-35.82)	0.97
TVR	3 (0.5%)	28 (2.6%)	0.19 (0.06-0.61)	0.002	0.15 (0.04-0.6)	0.007	0.11 (0.03-0.47)	0.003
ST definite	1 (0.2%)	22 (2.1%)	0.08 (0.01-0.58)	0.001	0.05 (0.01-0.47)	0.008	0.05 (0.01-0.45)	0.008
Acute	1 (0.2%)	9 (0.8%)	0.19 (0.02-1.53)	0.082	0.11 (0.01-1.09)	0.059	0.08 (0.01-0.88)	0.038
Subacute	0 (0%)	13 (1.2%)	---	---	---	---	---	---
ST definite <24h	1 (0.2%)	10 (0.9%)	0.17 (0.02-1.36)	0.059	0.10 (0.01-1.00)	0.05	0.09 (0.01-0.93)	0.044
ST definite 2-7days	0 (0%)	11 (1.1%)	---	---	---	---	---	---
ST definite 8-30 days	0 (0%)	1 (0.1%)	---	---	---	---	---	---
ST definite/probable	1 (0.2%)	25 (2.3%)	0.07 (0.01-0.51)	0.001	0.04 (0.01-0.36)	0.004	0.04 (0-0.34)	0.003
Acute	1 (0.2%)	10 (0.9%)	0.17 (0.02-1.36)	0.059	0.06 (0.01-0.63)	0.018	0.05 (0.01-0.52)	0.012
Subacute	0 (0%)	15 (1.4%)	---	---	---	---	---	---
Bleeding	30 (4.9%)	147 (13.8%)	0.34 (0.23-0.5)	<0.001	0.17 (0.11-0.28)	<0.001	0.16 (0.1-0.27)	<0.001
BARC 1	16 (2.6%)	71 (6.6%)	0.39 (0.22-0.66)	<0.001	0.23 (0.12-0.45)	<0.001	0.22 (0.11-0.45)	<0.001
BARC 2	12 (2%)	62 (5.8%)	0.33 (0.18-0.61)	<0.001	0.18 (0.09-0.39)	<0.001	0.15 (0.07-0.34)	<0.001
BARC 3	2 (0.3%)	13 (1.2%)	0.27 (0.06-1.19)	0.062	0.11 (0.02-0.59)	0.011	0.1 (0.02-0.59)	0.011
BARC 3a	0 (0%)	8 (0.7%)	---	---	---	---	---	---
BARC 3b	2 (0.3%)	3 (0.3%)	1.16 (0.19-6.96)	0.868	0.49 (0.06-4.09)	0.51	0.31 (0.03-3.15)	0.32
BARC 3c	0 (0%)	2 (0.2%)	---	---	---	---	---	---
BARC 4	0 (0%)	0 (0%)	---	---	---	---	---	---
BARC 5	0 (0%)	1 (0.1%)	---	---	---	---	---	---
BARC 5a	0 (0%)	1 (0.1%)	---	---	---	---	---	---
BARC 5b	0 (0%)	0 (0%)	---	---	---	---	---	---

BARC 3 or 5	2 (0.3%)	14 (1.3%)	0.25 (0.06-1.09)	0.046	0.12 (0.02-0.64)	0.013	0.1 (0.02-0.55)	0.008
BARC 3 or 5 access site	2 (0.3%)	8 (0.7%)	0.44 (0.09-2.05)	0.279	0.21 (0.03-1.34)	0.1	0.18 (0.03-1.26)	0.084
BARC 3 or 5 non-access site	0 (0%)	6 (0.6%)	---	---	---	---	---	---
BARC 2, 3 or 5	14 (2.3%)	76 (7.1%)	0.31 (0.18-0.55)	<0.001	0.16 (0.08-0.32)	<0.001	0.13 (0.06-0.28)	<0.001
BARC 2, 3 or 5 access site	10 (1.6%)	41 (3.8%)	0.42 (0.21-0.84)	0.011	0.29 (0.12-0.69)	0.006	0.29 (0.11-0.76)	0.011
BARC 2, 3 or 5 non-access site	4 (0.7%)	35 (3.3%)	0.2 (0.07-0.55)	0.001	0.08 (0.03-0.26)	<0.001	0.05 (0.01-0.18)	<0.001
TIMI major	0 (0%)	5 (0.5%)	---	---	---	---	---	---
TIMI minor	0 (0%)	7 (0.7%)	---	---	---	---	---	---
TIMI major/minor	0 (0%)	12 (1.1%)	---	---	---	---	---	---
GUSTO severe	0 (0%)	4 (0.4%)	---	---	---	---	---	---
GUSTO moderate	1 (0.2%)	4 (0.4%)	0.44 (0.05-3.9)	0.445	0.5 (0.03-8.27)	0.63	0.57 (0.03-11.61)	0.71
GUSTO mild	29 (4.7%)	139 (13%)	0.35 (0.23-0.52)	<0.001	0.18 (0.11-0.3)	<0.001	0.17 (0.1-0.28)	<0.001
GUSTO moderate/severe	1 (0.2%)	8 (0.7%)	0.22 (0.03-1.74)	0.114	0.2 (0.02-2.2)	0.19	0.11 (0.01-1.32)	0.083
Composite of surgical access site repair and blood transfusion	3 (0.5%)	15 (1.4%)	0.35 (0.1-1.2)	0.079	0.29 (0.05-1.68)	0.17	0.37 (0.07-1.91)	0.23
Surgical access site repair	1 (0.2%)	1 (0.1%)	1.75 (0.11-27.92)	0.69	---	---	0.84 (0.02-45.33)	0.93
Blood transfusion	2 (0.3%)	14 (1.3%)	0.25 (0.06-1.09)	0.046	0.17 (0.02-1.68)	0.13	0.3 (0.04-1.98)	0.21
Distribution of BARC 3 or 5								
Intracranial bleeding	0 (0%)	3 (0.3%)	---	---	---	---	---	---
Pericardial bleeding	0 (0%)	1 (0.1%)	---	---	---	---	---	---
Gastrointestinal bleeding	0 (0%)	1 (0.1%)	---	---	---	---	---	---
Genito-urinary bleeding	0 (0%)	1 (0.1%)	---	---	---	---	---	---
Access site bleeding	2 (0.3%)	8 (0.7%)	0.43 (0.09-2.05)	0.278	0.21 (0.03-1.33)	0.097	0.18 (0.03-1.25)	0.083
Other bleeding	0 (0%)	0 (0%)	---	---	---	---	---	---

* Log-rank test

Table 2. Clinical outcomes at 30 days in post-PCI bivalirudin prolonged infusion at full dose versus no post-PCI infusion.

OUTCOME	Post-PCI prolonged bivalirudin Full dose (n=612)	No infusion (n=1811)	Unadjusted Rate Ratio (95% CI)	P-value*	Multivariable Adjusted Rate Ratio (95% CI)	P-value	Propensity Score Adjusted Rate Ratio (95% CI)	P-value
Death, MI, Stroke, BARC 3 or 5, TVR, ST	27 (4.4%)	215 (11.9%)	0.36 (0.24-0.53)	<0.001	0.36 (0.22-0.56)	<0.001	0.4 (0.26-0.62)	<0.001
Death, MI, Stroke	26 (4.2%)	190 (10.5%)	0.39 (0.26-0.59)	<0.001	0.4 (0.25-0.65)	<0.001	0.45 (0.29-0.7)	<0.001
Death, MI, Stroke, BARC 3 or 5	27 (4.4%)	211 (11.7%)	0.36 (0.24-0.54)	<0.001	0.37 (0.23-0.58)	<0.001	0.42 (0.27-0.64)	<0.001
Death	5 (0.8%)	32 (1.8%)	0.46 (0.18-1.18)	0.098	---	---	0.5 (0.18-1.36)	0.17
Cardiovascular death	5 (0.8%)	31 (1.7%)	0.47 (0.18-1.22)	0.114	---	---	0.54 (0.2-1.49)	0.23
MI	21 (3.4%)	154 (8.5%)	0.39 (0.25-0.62)	<0.001	0.43 (0.27-0.7)	0.001	0.46 (0.28-0.76)	0.002
MI <24h	17 (2.8%)	121 (6.7%)	0.41 (0.25-0.68)	<0.001	0.51 (0.30-0.88)	0.015	0.50 (0.29-0.88)	0.016
MI 2-7days	3 (0.5%)	26 (1.4%)	0.33 (0.1-1.08)	0.053	0.22 (0.06-0.76)	0.017	0.32 (0.09-1.10)	0.070
MI 8-30 days	1 (0.2%)	7 (0.4%)	0.4 (0.05-3.26)	0.377	0.36 (0.04-3.10)	0.36	0.45 (0.05-4.07)	0.48
Stroke	1 (0.2%)	7 (0.4%)	0.42 (0.05-3.43)	0.405	---	---	0.39 (0.04-3.41)	0.39
TIA	1 (0.2%)	2 (0.1%)	1.48 (0.13-16.33)	0.747	0.44 (0.01-14.5)	0.64	0.73 (0.07-8.29)	0.8
TVR	3 (0.5%)	21 (1.2%)	0.42 (0.13-1.41)	0.149	0.44 (0.12-1.53)	0.2	0.45 (0.13-1.62)	0.22
ST definite	1 (0.2%)	13 (0.7%)	0.23 (0.03-1.74)	0.118	0.25 (0.03-2.02)	0.19	0.34 (0.04-2.88)	0.32
Acute	1 (0.2%)	10 (0.6%)	0.3 (0.04-2.31)	0.216	0.35 (0.04-2.96)	0.33	0.52 (0.06-4.76)	0.57
Subacute	0 (0%)	3 (0.2%)	---	---	---	---	---	---
ST definite <24h	1 (0.2%)	8 (0.4%)	0.37 (0.05-2.95)	0.328	0.50 (0.06-4.36)	0.53	0.57 (0.06-5.24)	0.62
ST definite 2-7days	0 (0%)	4 (0.2%)	---	---	---	---	---	---
ST definite 8-30 days	0 (0%)	1 (0.1%)	---	---	---	---	---	---
ST definite/probable	1 (0.2%)	19 (1%)	0.16 (0.02-1.16)	0.037	0.24 (0.03-1.88)	0.17	0.23 (0.03-1.81)	0.16
Acute	1 (0.2%)	11 (0.6%)	0.27 (0.03-2.08)	0.176	0.35 (0.04-2.96)	0.33	0.52 (0.06-4.76)	0.57
Subacute	0 (0%)	8 (0.4%)	---	---	---	---	---	---
Bleeding	30 (4.9%)	192 (10.6%)	0.45 (0.31-0.66)	<0.001	0.46 (0.3-0.7)	<0.001	0.5 (0.33-0.77)	0.002
BARC 1	16 (2.6%)	97 (5.4%)	0.48 (0.28-0.82)	0.006	0.5 (0.27-0.92)	0.025	0.66 (0.37-1.19)	0.17
BARC 2	12 (2%)	62 (3.4%)	0.57 (0.31-1.06)	0.07	0.56 (0.28-1.11)	0.095	0.5 (0.25-1.02)	0.058
BARC 3	2 (0.3%)	28 (1.5%)	0.21 (0.05-0.88)	0.019	0.21 (0.05-0.92)	0.038	0.23 (0.05-1)	0.05
BARC 3a	0 (0%)	15 (0.8%)	---	---	---	---	---	---
BARC 3b	2 (0.3%)	11 (0.6%)	0.54 (0.12-2.43)	0.412	0.67 (0.13-3.34)	0.62	0.69 (0.14-3.54)	0.66
BARC 3c	0 (0%)	2 (0.1%)	---	---	---	---	---	---
BARC 4	0 (0%)	1 (0.1%)	---	---	---	---	---	---
BARC 5	0 (0%)	4 (0.2%)	---	---	---	---	---	---
BARC 5a	0 (0%)	3 (0.2%)	---	---	---	---	---	---
BARC 5b	0 (0%)	1 (0.1%)	---	---	---	---	---	---

BARC 3 or 5	2 (0.3%)	32 (1.8%)	0.18 (0.04-0.77)	0.009	0.21 (0.05-0.92)	0.038	0.19 (0.04-0.81)	0.025
BARC 3 or 5 access site	2 (0.3%)	8 (0.4%)	0.74 (0.16-3.49)	0.702	1.13 (0.21-6.14)	0.88	0.91 (0.16-4.99)	0.91
BARC 3 or 5 non-access site	0 (0%)	24 (1.3%)	---	---	---	---	---	---
BARC 2, 3 or 5	14 (2.3%)	94 (5.2%)	0.44 (0.25-0.76)	0.003	0.44 (0.24-0.8)	0.008	0.39 (0.21-0.74)	0.004
BARC 2, 3 or 5 access site	10 (1.6%)	45 (2.5%)	0.66 (0.33-1.3)	0.224	0.69 (0.32-1.48)	0.34	0.69 (0.32-1.5)	0.35
BARC 2, 3 or 5 non-access site	4 (0.7%)	49 (2.7%)	0.24 (0.09-0.66)	0.003	0.25 (0.09-0.72)	0.01	0.17 (0.05-0.56)	0.004
TIMI major	0 (0%)	11 (0.6%)	---	---	---	---	---	---
TIMI minor	0 (0%)	9 (0.5%)	---	---	---	---	---	---
TIMI major/minor	0 (0%)	20 (1.1%)	---	---	---	---	---	---
GUSTO severe	0 (0%)	12 (0.7%)	---	---	---	---	---	---
GUSTO moderate	1 (0.2%)	11 (0.6%)	0.27 (0.03-2.08)	0.177	0.33 (0.04-2.7)	0.3	0.24 (0.03-1.93)	0.18
GUSTO mild	29 (4.7%)	168 (9.3%)	0.5 (0.34-0.74)	<0.001	0.49 (0.32-0.77)	0.002	0.58 (0.37-0.9)	0.015
GUSTO moderate/severe	1 (0.2%)	23 (1.3%)	0.13 (0.02-0.95)	0.017	0.18 (0.02-1.36)	0.096	0.12 (0.02-0.92)	0.041
Composite of surgical access site repair and blood transfusion	3 (0.5%)	16 (0.9%)	0.55 (0.16-1.9)	0.339	0.36 (0.08-1.76)	0.21	0.48 (0.13-1.75)	0.27
Surgical access site repair	1 (0.2%)	3 (0.2%)	0.99 (0.1-9.48)	0.99	---	---	2.28 (0.16-31.8)	0.54
Blood transfusion	2 (0.3%)	13 (0.7%)	0.45 (0.1-2.01)	0.286	0.11 (0.01-1.4)	0.088	0.34 (0.07-1.57)	0.17
Distribution of BARC 3 or 5								
Intracranial bleeding	0 (0%)	1 (0.1%)	---	---	---	---	---	---
Pericardial bleeding	0 (0%)	10 (0.6%)	---	---	---	---	---	---
Gastrointestinal bleeding	0 (0%)	5 (0.3%)	---	---	---	---	---	---
Genito-urinary bleeding	0 (0%)	4 (0.2%)	---	---	---	---	---	---
Access site bleeding	2 (0.3%)	8 (0.4%)	0.74 (0.16-3.47)	0.698	1.13 (0.21-6.12)	0.89	0.9 (0.16-4.97)	0.91
Other bleeding	0 (0%)	3 (0.2%)	---	---	---	---	---	---

* Log-rank test

Table 3. Clinical outcomes at 30 days in post-PCI bivalirudin prolonged infusion at full dose versus unfractionated heparin.

OUTCOME	Post-PCI prolonged bivalirudin Full dose (n=612)	Unfractionated heparin (n=3603)	Unadjusted Rate Ratio (95% CI)	P-value*	Multivariable Adjusted Rate Ratio (95% CI)	P-value	Propensity Score Adjusted Rate Ratio (95% CI)	P-v
Death, MI, Stroke, BARC 3 or 5, TVR, ST	27 (4.4%)	450 (12.5%)	0.34 (0.23-0.5)	<0.001	0.38 (0.24-0.59)	<0.001	0.41 (0.27-0.61)	<0.
Death, MI, Stroke	26 (4.2%)	391 (10.9%)	0.38 (0.25-0.56)	<0.001	0.44 (0.28-0.69)	<0.001	0.47 (0.31-0.72)	<0.
Death, MI, Stroke, BARC 3 or 5	27 (4.4%)	444 (12.3%)	0.34 (0.23-0.51)	<0.001	0.38 (0.25-0.6)	<0.001	0.41 (0.27-0.62)	<0.
Death	5 (0.8%)	83 (2.3%)	0.35 (0.14-0.87)	0.018	---	---	0.39 (0.15-0.98)	0.
Cardiovascular death	5 (0.8%)	80 (2.2%)	0.37 (0.15-0.9)	0.023	---	---	0.41 (0.16-1.03)	0.
MI	21 (3.4%)	303 (8.4%)	0.4 (0.26-0.62)	<0.001	0.47 (0.3-0.75)	0.001	0.51 (0.32-0.81)	0.
MI <24h	17 (2.8%)	239 (6.6%)	0.41 (0.25-0.67)	<0.001	0.49 (0.29-0.83)	0.007	0.54 (0.32-0.92)	0..
MI 2-7days	3 (0.5%)	44 (1.2%)	0.38 (0.12-1.24)	0.096	0.41 (0.12-1.32)	0.13	0.37 (0.11-1.25)	0.
MI 8-30 days	1 (0.2%)	20 (0.6%)	0.28 (0.04-2.09)	0.184	0.39 (0.05-3.04)	0.37	0.52 (0.06-4.19)	0.
Stroke	1 (0.2%)	16 (0.4%)	0.37 (0.05-2.77)	0.311	---	---	0.53 (0.06-4.35)	0.
TIA	1 (0.2%)	9 (0.2%)	0.65 (0.08-5.16)	0.685	0.99 (0.1-9.51)	0.99	0.86 (0.09-7.84)	0.
TVR	3 (0.5%)	35 (1%)	0.5 (0.16-1.64)	0.246	0.79 (0.23-2.66)	0.7	0.84 (0.24-2.95)	0.
ST definite	1 (0.2%)	21 (0.6%)	0.28 (0.04-2.08)	0.183	0.51 (0.07-3.96)	0.52	0.41 (0.05-3.27)	0
Acute	1 (0.2%)	13 (0.4%)	0.45 (0.06-3.46)	0.433	0.88 (0.11-7.25)	0.91	0.66 (0.08-5.57)	0
Subacute	0 (0%)	8 (0.2%)	---	---	---	---	---	-
ST definite <24h	1 (0.2%)	11 (0.3%)	0.53 (0.07-4.14)	0.543	1.03 (0.12-8.61)	0.98	0.67 (0.08-5.78)	0.
ST definite 2-7days	0 (0%)	7 (0.2%)	---	---	---	---	---	-
ST definite 8-30 days	0 (0%)	3 (0.1%)	---	---	---	---	---	-
ST definite/probable	1 (0.2%)	35 (1%)	0.17 (0.02-1.22)	0.045	0.33 (0.04-2.54)	0.29	0.27 (0.03-2.06)	0.
Acute	1 (0.2%)	16 (0.4%)	0.37 (0.05-2.77)	0.311	0.88 (0.11-7.25)	0.91	0.63 (0.08-5.29)	0.
Subacute	0 (0%)	19 (0.5%)	---	---	---	---	---	-
Bleeding	30 (4.9%)	482 (13.4%)	0.35 (0.24-0.51)	<0.001	0.35 (0.23-0.52)	<0.001	0.35 (0.24-0.52)	<0.
BARC 1	16 (2.6%)	237 (6.6%)	0.39 (0.23-0.65)	<0.001	0.38 (0.22-0.66)	0.001	0.43 (0.25-0.74)	0.
BARC 2	12 (2%)	153 (4.2%)	0.46 (0.25-0.82)	0.007	0.44 (0.24-0.83)	0.011	0.42 (0.22-0.81)	0.
BARC 3	2 (0.3%)	72 (2%)	0.16 (0.04-0.66)	0.004	0.18 (0.04-0.74)	0.018	0.16 (0.04-0.67)	0.
BARC 3a	0 (0%)	38 (1.1%)	---	---	---	---	---	-
BARC 3b	2 (0.3%)	33 (0.9%)	0.36 (0.09-1.48)	0.138	0.36 (0.08-1.57)	0.17	0.35 (0.08-1.51)	0.
BARC 3c	0 (0%)	1 (0%)	---	---	---	---	---	-
BARC 4	0 (0%)	4 (0.1%)	---	---	---	---	---	-
BARC 5	0 (0%)	16 (0.4%)	---	---	---	---	---	-
BARC 5a	0 (0%)	11 (0.3%)	---	---	---	---	---	-
BARC 5b	0 (0%)	5 (0.1%)	---	---	---	---	---	-

BARC 3 or 5	2 (0.3%)	88 (2.4%)	0.13 (0.03-0.54)	0.001	0.17 (0.04-0.72)	0.015	0.13 (0.03-0.52)	0.(
BARC 3 or 5 access site	2 (0.3%)	32 (0.9%)	0.37 (0.09-1.53)	0.152	0.38 (0.09-1.65)	0.2	0.34 (0.08-1.47)	0.
BARC 3 or 5 non-access site	0 (0%)	56 (1.6%)	---	---	---	---	---	-
BARC 2, 3 or 5	14 (2.3%)	241 (6.7%)	0.33 (0.2-0.57)	<0.001	0.35 (0.2-0.62)	<0.001	0.3 (0.16-0.54)	<0.
BARC 2, 3 or 5 access site	10 (1.6%)	132 (3.7%)	0.44 (0.23-0.84)	0.01	0.4 (0.2-0.8)	0.01	0.39 (0.2-0.79)	0.(
BARC 2, 3 or 5 non-access site	4 (0.7%)	109 (3%)	0.21 (0.08-0.58)	0.001	0.29 (0.1-0.81)	0.017	0.18 (0.06-0.57)	0.(
TIMI major	0 (0%)	33 (0.9%)	---	---	---	---	---	-
TIMI minor	0 (0%)	33 (0.9%)	---	---	---	---	---	-
TIMI major/minor	0 (0%)	66 (1.8%)	---	---	---	---	---	-
GUSTO severe	0 (0%)	26 (0.7%)	---	---	---	---	---	-
GUSTO moderate	1 (0.2%)	26 (0.7%)	0.23 (0.03-1.67)	0.11	0.26 (0.03-1.97)	0.19	0.18 (0.02-1.34)	0.(
GUSTO mild	29 (4.7%)	426 (11.8%)	0.39 (0.27-0.56)	<0.001	0.38 (0.25-0.57)	<0.001	0.4 (0.27-0.6)	<0.
GUSTO moderate/severe	1 (0.2%)	52 (1.4%)	0.11 (0.02-0.81)	0.009	0.15 (0.02-1.14)	0.067	0.09 (0.01-0.69)	0.
Composite of surgical access site repair and blood transfusion	3 (0.5%)	67 (1.9%)	0.26 (0.08-0.83)	0.014	0.25 (0.06-1.07)	0.061	0.26 (0.08-0.85)	0.(
Surgical access site repair	1 (0.2%)	12 (0.3%)	0.49 (0.06-3.77)	0.484	0.56 (0.07-4.65)	0.59	0.47 (0.06-3.85)	0.
Blood transfusion	2 (0.3%)	63 (1.7%)	0.19 (0.05-0.76)	0.008	0.13 (0.02-0.99)	0.048	0.18 (0.04-0.76)	0.
Distribution of BARC 3 or 5								
Intracranial bleeding	0 (0%)	3 (0.1%)	---	---	---	---	---	-
Pericardial bleeding	0 (0%)	17 (0.5%)	---	---	---	---	---	-
Gastrointestinal bleeding	0 (0%)	21 (0.6%)	---	---	---	---	---	-
Genito-urinary bleeding	0 (0%)	7 (0.2%)	---	---	---	---	---	-
Access site bleeding	2 (0.3%)	30 (0.8%)	0.39 (0.09-1.63)	0.181	0.4 (0.09-1.73)	0.22	0.35 (0.08-1.54)	0.
Other bleeding	0 (0%)	7 (0.2%)	---	---	---	---	---	-

* Log-rank test

Part 1

Trade-off for ischemia and bleeding during and immediately after percutaneous coronary interventions:

Implementing the Radial approach to improve clinical outcomes

pay the penalty. Rather than concluding that radial access should be the default for acute coronary syndromes, we believe that clinicians and institutions should be careful to retain expertise in both procedures.

We declare no competing interests.

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Authors' reply

We thank Cameron Dowling and colleagues, David Brieger and Andy Yong, and Rahman Shah and Jonathan D Gardner for their interest in our study.[1] We agree that MATRIX requested a fairly robust radial expertise for operators to qualify, with at least 75 radial interventions in the year before the start of the study and at least 50% of these interventions in patients with acute coronary syndrome. By contrast, the RIVAL trial[2] requested operators to have done a minimum of 50 radial catheterisations overall to participate. However, although interpretation of subgroups as if they were properly powered trials is well known, it should be resisted to avoid over interpretation.[3] Our conclusion that radial access should be the default for patients with acute coronary syndrome undergoing percutaneous coronary intervention was not expressed on the basis of a subgroup analysis, nor on the basis of our study alone, but on a meta-analysis of all available clinical trials so far, including MATRIX.[1]

We identified no heterogeneity for any of the outcomes addressed in this meta-analysis, and results from RIVAL and MATRIX are fully compatible, with 95% CIs of the two trials overlapping widely. Rather than focusing on subgroup results of an individual trial, we advise Dowling and colleagues, Brieger and Yong, and Shah and Gardner to take the overall body of evidence into consideration. If their hypotheses were true, some extent of between-trial heterogeneity would be expected, caused by variation in expertise with radial or femoral access across included trials.

We are not sure that their hypothesis is clinically plausible: most interventional cardiologists treating patients in MATRIX were originally trained to do percutaneous coronary intervention through femoral access. Most cardiologists who have successfully undergone transition from femoral to radial access will agree that gaining proficiency with radial access will not result in loss of the skills needed to access the femoral artery for diagnostic or interventional purposes.

We therefore stand by our conclusion that radial access emerges as the gold standard for coronary intervention, providing improved safety and effectiveness, resulting in lower direct and indirect costs,[4] and being mostly preferred to conventional femoral intervention by patients.[5]

We declare no competing interests.

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Department of Error

Owens, B. Profile: The Scripps Research Institute under new leadership. Lancet *2015;* **386:** *2045*—In this World Report (Nov 21), Peter Schultz's name was misspelt. This correction was made to the online version as of Dec 10, 2015.

Lenze EJ, Mulsant BH, Blumberger DM, et al. Efficacy, safety, and tolerability of augmentation pharmacotherapy with aripiprazole for treatment-resistant depression in late life: a randomised, double-blind, placebo-controlled trial. Lancet *2015;* **386:** *2404–12*—In the abstract of this Article, the findings for akathisia in placebo group participants has been corrected to "*vs* 11 [12%] of 90 on placebo". Dr Benoit H Mulsant's affiliation has been corrected. The trial profile in figure 1 should have read "90 randomly assigned to placebo". The fourth sentence in the figure 2 legend should have read "Based on the Bayesian information criterion, a longitudinal mixed model with linear, quadratic, and cubic terms fit best". The final sentence of the figure 2 legend has been corrected to "Based on the modelled data, the aripiprazole group decreases 7·6 points over 12 weeks whereas the placebo group decreases roughly 5·0 points over the same time period". These corrections have been made to the online version as of Dec 10, 2015, and the printed Article is correct.

Sutter RW, Bahl S, Deshpande JM, et al. Immunogenicity of a new routine vaccination schedule for global poliomyelitis prevention: an open-label, randomised controlled trial. Lancet *2015;* **385:** *2413–21*—The findings section of abstract should have read "152 (99·3%, 96·4–100) of 153 in the tOPV plus IPV group" for seroconversion against poliovirus type 3. Numbers in the "children in household" section of table 1 have been corrected. These corrections have been made to the online version as of Dec 10, 2015, and the printed Article is correct.

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Impact of Sex on Comparative Outcomes of Radial Versus Femoral Access in Patients With Acute Coronary Syndromes Undergoing Invasive Management

Data From the Randomized MATRIX-Access Trial

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ABSTRACT

OBJECTIVES This study sought to assess whether transradial access (TRA) compared with transfemoral access (TFA) is associated with consistent outcomes in male and female patients with acute coronary syndrome undergoing invasive management.

BACKGROUND There are limited and contrasting data about sex disparities for the safety and efficacy of TRA versus TFA for coronary intervention.

METHODS In the MATRIX (Minimizing Adverse Haemorrhagic Events by TRansradial Access Site and Systemic Implementation of angioX) program, 8,404 patients were randomized to TRA or TFA. The 30-day coprimary outcomes were major adverse cardiovascular and cerebrovascular events (MACCE), defined as death, myocardial infarction, or stroke, and net adverse clinical events (NACE), defined as MACCE or major bleeding.

RESULTS Among 8,404 patients, 2,232 (26.6%) were women and 6,172 (73.4%) were men. MACCE and NACE were not significantly different between men and women after adjustment, but women had higher risk of access site bleeding (male vs. female rate ratio [RR]: 0.64; $p = 0.0016$), severe bleeding (RR: 0.17; $p = 0.0012$), and transfusion (RR: 0.56; $p = 0.0089$). When comparing radial versus femoral, there was no significant interaction for MACCE and NACE stratified by sex ($p_{int} = 0.15$ and 0.18, respectively), although for both coprimary endpoints the benefit with TRA was relatively greater in women (RR: 0.73; $p = 0.019$; and RR: 0.73; $p = 0.012$, respectively). Similarly, there was no significant interaction between male and female patients for the individual endpoints of all-cause death ($p_{int} = 0.79$), myocardial infarction ($p_{int} = 0.25$), stroke ($p_{int} = 0.18$), and Bleeding Academic Research Consortium type 3 or 5 ($p_{int} = 0.45$).

CONCLUSIONS Women showed a higher risk of severe bleeding and access site complications, and radial access was an effective method to reduce these complications as well as composite ischemic and ischemic or bleeding endpoints. (J Am Coll Cardiol Intv 2018;11:36–50) © 2018 by the American College of Cardiology Foundation.

The advent of combined antithrombotic therapies and early invasive management has reduced the ischemic burden but increased bleeding risk in patients with acute coronary syndrome (ACS) (1–3). The use of radial instead of femoral access mitigates bleeding while preserving ischemic risks, thereby providing consistent mortality benefit across trials (4).

Female patients have increased periprocedural bleeding risk as compared with men (1,5). However, female patients have smaller radial arteries that are more prone to spasm as well as shorter aortic roots than men, which adds to the operative difficulty and may undermine the efficacy of radial access in this population. Previous studies have shown contrasting evidence about potential sex disparities for the safety and efficacy of transradial access (TRA) versus transfemoral access (TFA) (6,7).

SEE PAGE 51

We sought to investigate the comparative efficacy and safety outcomes across sex of radial versus femoral access in ACS patients participating in the MATRIX-Access (Minimizing Adverse Haemorrhagic Events by TRansradial Access Site and Systemic Implementation of angioX) trial.

METHODS

STUDY DESIGN. The MATRIX-Access was a randomized, multicenter, superiority trial comparing radial with femoral access in patients with ACS with or without ST-segment elevation undergoing coronary angiography and percutaneous coronary intervention (PCI), if indicated (4,8). This was the first of 3 trials of the MATRIX program (ClinicalTrials.gov; NCT01433627) and was performed in all patients with an ACS consenting to participate in the program. The institutional review board at each participating center approved the trial, and all patients gave written informed consent to participate.

STUDY PATIENTS. Patients were eligible if they had an ACS with or without ST-segment elevation, were scheduled to undergo an invasive approach, and the interventional cardiologist was willing to proceed with either radial or femoral access with expertise for both, including at least 75 coronary interventions performed and at least 50% of interventions in ACS via the radial route during the previous year. Patients

ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome(s)

BARC = Bleeding Academic Research Consortium

CABG = coronary artery bypass grafting

MACCE = major adverse cardiovascular and cerebrovascular event(s)

MI = myocardial infarction

NACE = net adverse clinical event(s)

NSTE-ACS = non-ST-segment elevation acute coronary syndrome(s)

PCI = percutaneous coronary intervention

RR = rate ratio

TFA = transfemoral access

TRA = transradial access

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TABLE 1 Baseline Characteristics According to Access Site and Sex

	Male Patients			Female Patients					
	Radial (n = 3,126)	Femoral (n = 3,046)	p Value	Radial (n = 1,071)	Femoral (n = 1,161)	p Value	Male Patients (n = 6,172)	Female Patients (n = 2,232)	p Value
Age, yrs	63.8 ± 11.6	64.2 ± 11.6	0.18	70.7 ± 11.2	70.2 ± 11.1	0.36	64.0 ± 11.6	70.4 ± 11.1	<0.0001
Age ≥75 yrs	623 (19.9)	636 (20.9)	0.35	445 (41.5)	466 (40.1)	0.50	1,259 (20.4)	911 (40.8)	<0.0001
STEMI	1,552 (49.6)	1,541 (50.6)	0.46	449 (41.9)	468 (40.3)	0.44	3,093 (50.1)	917 (41.1)	<0.0001
NSTE-ACS	1,574 (50.4)	1,505 (49.4)	0.46	622 (58.1)	693 (59.7)	0.44	3,079 (49.9)	1,315 (58.9)	<0.0001
Weight, kg	80.7 ± 13.1	80.0 ± 12.3	0.020	67.8 ± 12.7	69.4 ± 13.7	0.0042	80.3 ± 12.8	68.6 ± 13.2	<0.0001
Body mass index, kg/m^2	27.3 ± 3.9	27.1 ± 3.8	0.0083	26.4 ± 4.7	27.0 ± 5.1	0.0083	27.2 ± 3.8	26.7 ± 4.9	<0.0001
Diabetes mellitus	687 (22.0)	656 (21.5)	0.018	272 (25.4)	288 (24.8)	0.75	1,343 (21.8)	560 (25.1)	0.0001
Insulin dependent	135 (4.3)	171 (5.6)	0.75	74 (6.9)	86 (7.4)	0.75	306 (5.0)	160 (7.2)	0.0001
Current smoker	1,218 (39.0)	1,141 (37.5)	0.36	241 (22.5)	287 (24.7)	0.42	2,359 (38.2)	528 (23.7)	<0.0001
Hypercholesterolemia	1,292 (41.3)	1,340 (44.0)	0.035	507 (47.3)	552 (47.5)	0.92	2,632 (42.6)	1,059 (47.4)	0.0001
Hypertension	1,839 (58.8)	1,830 (60.1)	0.86	786 (73.4)	856 (73.7)	0.86	3,669 (59.4)	1,642 (73.6)	<0.0001
Family history of CAD	861 (27.5)	861 (28.3)	0.53	285 (26.6)	286 (24.6)	0.28	1,722 (27.9)	571 (25.6)	0.035
Previous MI	473 (15.1)	486 (16.0)	0.37	112 (10.5)	132 (11.4)	0.49	959 (15.5)	244 (10.9)	<0.0001
Previous PCI	501 (16.0)	474 (15.6)	0.62	109 (10.2)	111 (9.6)	0.63	975 (15.8)	220 (9.9)	<0.0001
Radial access	94 (3.0)	63 (2.1)	0.019	25 (2.3)	21 (1.8)	0.38	157 (2.5)	46 (2.1)	0.20
Femoral access	225 (7.2)	234 (7.7)	0.47	51 (4.8)	52 (4.5)	0.75	459 (7.4)	103 (4.6)	<0.0001
Both radial and femoral access	29 (0.9)	32 (1.1)	0.63	7 (0.7)	3 (0.3)	0.16	61 (1.0)	10 (0.4)	0.017
Access site unknown	153 (4.9)	145 (4.8)	0.81	26 (2.4)	35 (3.0)	0.40	298 (4.8)	61 (2.7)	<0.0001
Previous CABG	92 (2.9)	124 (4.1)	0.016	19 (1.8)	22 (1.9)	0.83	216 (3.5)	41 (1.8)	0.0001
Previous TIA or stroke	135 (4.3)	147 (4.8)	0.34	60 (5.6)	83 (7.1)	0.14	282 (4.6)	143 (6.4)	0.0007
Peripheral vascular disease	249 (8.0)	272 (8.9)	0.17	92 (8.6)	100 (8.6)	0.98	521 (8.4)	192 (8.6)	0.82
COPD	182 (5.8)	201 (6.6)	0.21	68 (6.3)	82 (7.1)	0.50	383 (6.2)	150 (6.7)	0.39
History of renal failure	36 (1.2)	36 (1.2)	0.91	10 (0.9)	23 (2.0)	0.041	72 (1.2)	33 (1.5)	0.26
Dialysis	3 (0.1)	3 (0.1)	1.00	1 (0.1)	1 (0.1)	1.00	6 (0.1)	2 (0.1)	0.92

Continued on the next page

presenting with non-ST-segment elevation ACS (NSTE-ACS) were eligible if they had a history consistent with new or worsening ischemia, occurring at rest or with minimal activity within 7 days before randomization, and fulfilled at least 2 high-risk criteria (4,8). Patients with ST-segment elevation myocardial infarction were eligible if they presented within 12 h of the onset of symptoms or between 12 and 24 h after symptom onset if there was evidence of continued ischemia or previous fibrinolytic treatment and if they had ST-segment elevation of at least 1 mm in 2 or more contiguous leads, new left bundle branch block, or true posterior MI. The main inclusion and exclusion criteria were previously reported (4,8).

STUDY PROTOCOL AND RANDOMIZATION. Before the start of angiography, patients were randomly assigned 1:1 to radial or femoral access for diagnostic angiography and PCI, if indicated, using a web-based system to ensure adequate concealment of allocation. The randomization sequence was computer generated, blocked, and stratified by site, intended new or ongoing use of ticagrelor or prasugrel, type of ACS (ST-segment elevation myocardial infarction or troponin-positive or troponin-negative NSTE-ACS), and anticipated use of immediate PCI. Access site management during and after the diagnostic or therapeutic procedure was left to the discretion of the treating physician, and closure devices were allowed as per local practice. The use of anticoagulant agents outside the protocol of the MATRIX program was not allowed. Bivalirudin administration was consistent with the approved product labeling, whereas unfractionated heparin was dosed at 70 to 100 U/kg in patients not receiving glycoprotein IIb or IIIa inhibitors and at 50 to 70 U/kg in patients receiving glycoprotein IIb or IIIa inhibitors. Use of all other antithrombotic medications, including oral antiplatelet agents and nonantithrombotic medications, such as beta-blockers, angiotensin-converting enzyme inhibitors,

TABLE 1 Continued

	Male Patients			Female Patients					
	Radial (n = 3,126)	Femoral (n = 3,046)	p Value	Radial (n = 1,071)	Femoral (n = 1,161)	p Value	Male Patients (n = 6,172)	Female Patients (n = 2,232)	p Value
Clinical presentation									
Cardiac arrest	59 (1.9)	66 (2.2)	0.44	26 (2.4)	17 (1.5)	0.098	125 (2.0)	43 (1.9)	0.78
Killip class									
I	2,845 (91.0)	2,781 (91.3)	0.69	951 (88.8)	1,019 (87.8)	0.45	5,626 (91.2)	1,970 (88.3)	0.0001
II	193 (6.2)	197 (6.5)	0.64	75 (7.0)	104 (9.0)	0.089	390 (6.3)	179 (8.0)	0.0061
III	56 (1.8)	49 (1.6)	0.58	32 (3.0)	30 (2.6)	0.56	105 (1.7)	62 (2.8)	0.0018
IV	32 (1.0)	19 (0.6)	0.083	13 (1.2)	8 (0.7)	0.27	51 (0.8)	21 (0.9)	0.61
Previous lytic therapy	73 (2.3)	83 (2.7)	0.33	21 (2.0)	21 (1.8)	0.88	156 (2.5)	42 (1.9)	0.085
Systolic arterial pressure, mm Hg	138.3 ± 25.1	138.1 ± 25.4	0.80	139.1 ± 26.8	140.7 ± 26.3	0.16	138.2 ± 25.2	139.9 ± 26.6	0.0081
Heart rate, beats/min	75.8 ± 16.3	75.3 ± 16.4	0.27	77.9 ± 17.1	77.9 ± 17.7	0.97	75.5 ± 16.4	77.9 ± 17.4	<0.0001
Left ventricular ejection fraction, %	51.1 ± 9.5	51.0 ± 9.6	0.48	51.7 ± 9.8	50.6 ± 10.2	0.0093	51.0 ± 9.5	51.1 ± 10.0	0.81
eGFR	86.2 ± 24.9	85.8 ± 24.5	0.54	78.4 ± 26.2	76.9 ± 27.0	0.19	86.0 ± 24.7	77.6 ± 26.6	<0.0001
<60 ml/min/1.73 m^2	433 (13.9)	399 (13.2)	0.39	267 (25.2)	316 (27.5)	0.23	832 (13.6)	583 (26.4)	<0.0001
<30 ml/min/1.73 m^2	20 (0.6)	19 (0.6)	0.94	15 (1.4)	30 (2.6)	0.047	39 (0.6)	45 (2.0)	<0.0001
Medications before the cath lab									
Aspirin	2,960 (94.7)	2,884 (94.7)	0.99	996 (93.0)	1,070 (92.2)	0.45	5,844 (94.7)	2,066 (92.6)	0.0003
Clopidogrel	1,445 (46.2)	1,386 (45.5)	0.57	570 (53.2)	611 (52.6)	0.78	2,831 (45.9)	1,181 (52.9)	<0.0001
Prasugrel	411 (13.1)	402 (13.2)	0.95	74 (6.9)	66 (5.7)	0.23	813 (13.2)	140 (6.3)	<0.0001
Ticagrelor	754 (24.1)	758 (24.9)	0.48	224 (20.9)	271 (23.3)	0.17	1,512 (24.5)	495 (22.2)	0.028
Enoxaparin	476 (15.2)	488 (16.0)	0.39	211 (19.7)	254 (21.9)	0.21	964 (15.6)	465 (20.8)	<0.0001
Fondaparinux	309 (9.9)	332 (10.9)	0.19	119 (11.1)	136 (11.7)	0.65	641 (10.4)	255 (11.4)	0.17
ACE inhibitor	915 (29.3)	899 (29.5)	0.83	338 (31.6)	402 (34.6)	0.12	1,814 (29.4)	740 (33.2)	0.0009
Angiotensin II receptor blocker	290 (9.3)	290 (9.5)	0.74	160 (14.9)	172 (14.8)	0.93	580 (9.4)	332 (14.9)	<0.0001
Statins	1,356 (43.4)	1,303 (42.8)	0.63	456 (42.6)	560 (48.2)	0.0073	2,659 (43.1)	1,016 (45.5)	0.047
Beta-blocker	1,216 (38.9)	1,206 (39.6)	0.58	478 (44.6)	569 (49.0)	0.038	2,422 (39.2)	1,047 (46.9)	<0.0001
Warfarin	44 (1.4)	39 (1.3)	0.66	28 (2.6)	25 (2.2)	0.47	83 (1.3)	53 (2.4)	0.0010
PPI	1,552 (49.6)	1,546 (50.8)	0.38	606 (56.6)	646 (55.6)	0.65	3,098 (50.2)	1,252 (56.1)	<0.0001
Previous unfractionated heparin	991 (31.7)	961 (31.5)	0.90	248 (23.2)	276 (23.8)	0.73	1,952 (31.6)	524 (23.5)	<0.0001
Bivalirudin	4 (0.1)	2 (0.1)	0.69	0 (0.0)	0 (0.0)	1.00	6 (0.1)	0 (0.0)	0.35

Values are mean ± SD or n (%).

ACE = angiotensin-converting enzyme; CABG = coronary artery bypass graft; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; MI = myocardial infarction; NSTE-ACS = non-ST-segment elevation acute coronary syndrome; PCI = percutaneous coronary intervention; PPI = proton pump inhibitor; STEMI = ST-segment elevation myocardial infarction; TIA = transient ischemic attack.

and other antihypertensive agents, were allowed as per guidelines (9).

STUDY OUTCOMES. Two coprimary 30-day composite outcomes were pre-specified: major adverse cardiovascular and cerebrovascular events (MACCE), defined as the composite of all-cause mortality, MI, or stroke; and net adverse clinical events (NACE), defined as the composite of MACCE or noncoronary artery bypass grafting-related major bleeding (Bleeding Academic Research Consortium [BARC] type 3 or 5) (10). Secondary outcomes included each component of the composite outcomes, cardiovascular mortality, and stent thrombosis. Bleeding was also assessed and adjudicated on the basis of the Thrombolysis In Myocardial Infarction and GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries) scales (11,12). Stent thrombosis was defined as the definite or probable occurrence of a stent-related thrombotic event according to the Academic Research Consortium classification (13). All outcomes were pre-specified (4,8). An independent clinical events committee blinded to treatment allocation adjudicated all suspected outcome events by reviewing relevant medical records after site

TABLE 2 Procedural Characteristics According to Access Site and Sex

	Male Patients			Female Patients					
	Radial (n = 3,126)	Femoral (n = 3,046)	p Value	Radial (n = 1,071)	Femoral (n = 1,161)	p Value	Male Patients (n = 6,172)	Female Patients (n = 2,232)	p Value
No PCI attempted after coronary angiography	490 (15.7)	501 (16.4)	0.41	337 (31.5)	342 (29.5)	0.30	991 (16.1)	679 (30.4)	<0.0001
CABG	130 (4.2)	122 (4.0)	0.76	25 (2.3)	33 (2.8)	0.45	252 (4.1)	58 (2.6)	0.0016
Patient with significant lesion and medical treatment	246 (7.9)	243 (8.0)	0.87	244 (22.8)	256 (22.0)	0.68	489 (7.9)	500 (22.4)	<0.0001
Patient without significant lesion	114 (3.6)	136 (4.5)	0.10	68 (6.3)	53 (4.6)	0.063	250 (4.1)	121 (5.4)	0.0073
PCI attempted	2,634 (84.3)	2,542 (83.5)	0.39	734 (68.5)	816 (70.3)	0.37	5,176 (83.9)	1,550 (69.4)	<0.0001
PCI completed	2,634 (84.3)	2,542 (83.5)	0.39	733 (68.4)	815 (70.2)	0.37	5,176 (83.9)	1,548 (69.4)	<0.0001
Crossover	162 (5.2)	72 (2.4)	<0.0001	81 (7.6)	24 (2.1)	<0.0001	234 (3.8)	105 (4.7)	0.037
Medications in the cath lab									
Aspirin	161 (5.2)	193 (6.3)	0.045	61 (5.7)	66 (5.7)	0.99	354 (5.7)	127 (5.7)	0.90
Clopidogrel	200 (6.4)	180 (5.9)	0.42	69 (6.4)	74 (6.4)	0.95	380 (6.2)	143 (6.4)	0.66
Prasugrel	281 (9.0)	246 (8.1)	0.20	54 (5.0)	45 (3.9)	0.18	527 (8.5)	99 (4.4)	<0.0001
Ticagrelor	283 (9.1)	297 (9.8)	0.35	98 (9.2)	98 (8.4)	0.55	580 (9.4)	196 (8.8)	0.38
Glycoprotein IIb/IIIa inhibitor	473 (15.1)	423 (13.9)	0.17	100 (9.3)	99 (8.5)	0.50	896 (14.5)	199 (8.9)	<0.0001
Planned GPI	354 (11.3)	307 (10.1)	0.11	65 (6.1)	65 (5.6)	0.64	661 (10.7)	130 (5.8)	<0.0001
Bailout GPI	119 (3.8)	116 (3.8)	1.00	35 (3.3)	34 (2.9)	0.64	235 (3.8)	69 (3.1)	0.12
Unfractionated heparin	1,568 (50.2)	1,415 (46.5)	0.0036	464 (43.3)	449 (38.7)	0.026	2983 (48.3)	913 (40.9)	<0.0001
Unfractionated heparin, U/kg	73.6 ± 30.1	73.7 ± 28.8	0.92	81.9 ± 31.8	79.2 ± 27.3	0.20	73.7 ± 29.5	80.5 ± 29.6	<0.0001
Subtherapeutic regimen (<50 U/kg)	356 (11.4)	258 (8.5)	0.00013	106 (9.9)	75 (6.5)	0.0030	614 (9.9)	181 (8.1)	0.015
Therapeutic regimen (≥50 U/kg)	1,212 (38.8)	1,157 (38.0)	0.52	358 (33.4)	374 (32.2)	0.54	2,369 (38.4)	732 (32.8)	<0.0001
Bivalirudin	1,332 (42.6)	1,300 (42.7)	0.96	387 (36.1)	437 (37.6)	0.46	2,632 (42.6)	824 (36.9)	<0.0001
Prolonged infusion post-PCI	672 (21.5)	647 (21.2)	0.81	197 (18.4)	224 (19.3)	0.59	1,319 (21.4)	421 (18.9)	0.012
Average duration of post-PCI bivalirudin infusion	360.0 ± 204.5	372.2 ± 269.9	0.35	370.5 ± 293.9	403.7 ± 286.3	0.24	366.0 ± 238.8	388.2 ± 290.0	0.13
Full bivalirudin regimen post-PCI	241 (7.7)	225 (7.4)	0.63	82 (7.7)	78 (6.7)	0.39	466 (7.6)	160 (7.2)	0.57
Average duration of full bivalirudin regimen	249.3 ± 64.8	272.3 ± 292.1	0.23	288.1 ± 267.7	270.7 ± 153.7	0.62	260.4 ± 208.3	279.6 ± 219.1	0.32
Low bivalirudin regimen post-PCI	431 (13.8)	422 (13.9)	0.94	115 (10.7)	146 (12.6)	0.18	853 (13.8)	261 (11.7)	0.011
Average duration of low bivalirudin regimen	421.9 ± 228.5	425.5 ± 241.3	0.82	429.2 ± 298.8	474.8 ± 314.5	0.24	423.7 ± 234.8	454.7 ± 307.9	0.094
Intra-aortic balloon pump	51 (1.6)	68 (2.2)	0.086	33 (3.1)	34 (2.9)	0.83	119 (1.9)	67 (3.0)	0.0037
PCI completed	(n = 2,634)	(n = 2,542)		(n = 733)	(n = 815)		(n = 5,176)	(n = 1,548)	
TIMI flow grade 3 in all treated lesions	2,501 (95.0)	2,421 (95.2)	0.63	695 (94.8)	773 (94.8)	0.98	4,922 (95.1)	1,468 (94.8)	0.67
Coronary stenosis <30% in all treated lesions	2,524 (95.8)	2,423 (95.3)	0.38	695 (94.8)	780 (95.7)	0.41	4,947 (95.6)	1,475 (95.3)	0.64
Procedural success in all treated lesions	2,446 (92.9)	2,361 (92.9)	0.98	677 (92.4)	756 (92.8)	0.76	4,807 (92.9)	1,433 (92.6)	0.69
Duration of procedure, min	51.8 ± 29.1	50.0 ± 28.3	0.017	45.6 ± 26.9	45.6 ± 27.7	1.00	50.9 ± 28.7	45.6 ± 27.3	<0.0001

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monitoring by Trial Form Support (Lund, Sweden) in Italy and the Netherlands, FLS-Research Support (Barcelona, Spain) in Spain, and Gothia Forum (Västra Götaland) in Sweden.

STATISTICAL ANALYSIS. Statistical analyses were performed by an academic statistical group led by 1 of the authors (B.R.d.C.), who had access to the full deidentified data set.

The trial was powered for superiority on the 2 coprimary composite outcomes at 30 days expecting a rate reduction of 30%, corresponding to rate ratio (RR) of 0.70.

All analyses were performed per intention-to-treat principle, including all patients in the analysis based on the allocated access. Events up to 30 days post-randomization were considered. We analyzed primary and secondary outcomes separately for male and female patients as time to first event using the Mantel-Cox method, accompanied by log-rank tests to calculate corresponding 2-sided p values. We did not perform any adjustments for multiple

TABLE 2 Continued

	Male Patients			Female Patients					
	Radial (n = 3,126)	Femoral (n = 3,046)	p Value	Radial (n = 1,071)	Femoral (n = 1,161)	p Value	Male Patients (n = 6,172)	Female Patients (n = 2,232)	p Value
Fluoroscopic time, min	11.0 (6.7–17.1)	9.7 (5.5–15.2)	0.88	9.2 (5.0–15.0)	8.1 (4.2–14.4)	0.43	10.2 (6.0–16.2)	9.0 (4.5–14.6)	0.27
Treated vessel(s) per patient									
Left main coronary artery	107 (4.1)	88 (3.5)	0.26	45 (6.1)	31 (3.8)	0.033	195 (3.8)	76 (4.9)	0.039
Left anterior descending artery	1,318 (50.1)	1,248 (49.2)	0.51	367 (50.1)	402 (49.3)	0.75	2,566 (49.6)	769 (49.7)	0.93
Left circumflex artery	707 (26.9)	709 (27.9)	0.39	197 (26.9)	200 (24.5)	0.29	1,416 (27.4)	397 (25.7)	0.18
Right coronary artery	872 (33.1)	833 (32.8)	0.81	244 (33.3)	289 (35.5)	0.38	1,705 (33.0)	533 (34.5)	0.28
Bypass graft	18 (0.7)	33 (1.3)	0.025	2 (0.3)	3 (0.4)	0.74	51 (1.0)	5 (0.3)	0.015
At least 2 vessels treated	344 (13.1)	339 (13.4)	0.76	107 (14.6)	101 (12.4)	0.20	683 (13.2)	208 (13.4)	0.80
Lesions treated per patient	1.0 (1.0–1.0)	1.0 (1.0–1.0)	0.92	1.0 (1.0–1.0)	1.0 (1.0–1.0)	0.71	1.0 (1.0–1.0)	1.0 (1.0–1.0)	0.52
1	2,068 (78.5)	1,993 (78.5)		576 (78.7)	657 (80.6)		4,061 (78.5)	1,233 (79.7)	
2	454 (17.2)	448 (17.6)		132 (18.0)	133 (16.3)		902 (17.4)	265 (17.1)	
3 or more	111 (4.2)	98 (3.9)		24 (3.3)	25 (3.1)		209 (4.0)	49 (3.2)	
At least 1 complex lesion	1,393 (52.9)	1,306 (51.4)	0.29	375 (51.2)	398 (48.8)	0.35	2,699 (52.2)	773 (49.9)	0.13
Median number of stents per patient	1.0 (1.0–2.0)	1.0 (1.0–2.0)	0.13	1.0 (1.0–2.0)	1.0 (1.0–2.0)	0.62	1.0 (1.0–2.0)	1.0 (1.0–2.0)	0.49
Overall stent length per patient, mm	71.3 ± 44.9	70.5 ± 44.5	0.54	66.6 ± 39.7	66.9 ± 42.7	0.88	70.9 ± 44.7	66.8 ± 41.3	0.0018
Lesions									
Number of lesions with PCI	(n = 3,332)	(n = 3,205)		(n = 919)	(n = 1,000)		(n = 6,537)	(n = 1,919)	
Lesions stented	3,052 (91.6)	2,892 (90.2)	0.070	826 (89.9)	909 (90.9)	0.57	5,944 (90.9)	1,735 (90.4)	0.51
At least 1 drug-eluting stent	2,251 (67.6)	2,150 (67.1)	0.51	565 (61.5)	647 (64.7)	0.068	4,401 (67.3)	1,212 (63.2)	0.0011
At least 1 bare-metal stent	801 (24.0)	742 (23.2)	0.77	261 (28.4)	262 (26.2)	0.093	1,543 (23.6)	523 (27.3)	0.0016
Lesions not stented	280 (8.4)	313 (9.8)	0.070	93 (10.1)	91 (9.1)	0.57	593 (9.1)	184 (9.6)	0.51
TIMI flow grade pre-procedure									
0 or 1	1,289 (38.7)	1,254 (39.2)	0.80	342 (37.2)	371 (37.1)	0.79	2,543 (38.9)	713 (37.2)	0.070
2	428 (12.9)	417 (13.0)	0.86	103 (11.2)	113 (11.3)	0.95	845 (12.9)	216 (11.3)	0.070
3	1,613 (48.4)	1,532 (47.8)	0.90	474 (51.6)	516 (51.6)	0.81	3,145 (48.1)	990 (51.6)	0.0042
TIMI flow grade post-procedure									
0 or 1	58 (1.7)	53 (1.7)	0.81	19 (2.1)	20 (2.0)	0.94	111 (1.7)	39 (2.0)	0.66
2	82 (2.5)	74 (2.3)	0.75	23 (2.5)	27 (2.7)	0.80	156 (2.4)	50 (2.6)	0.53
3	3,190 (95.8)	3,076 (96.0)	0.65	877 (95.4)	953 (95.3)	0.31	6,266 (95.9)	1,830 (95.4)	0.50
Coronary stenosis <30%	3,215 (96.5)	3,080 (96.2)	0.41	870 (94.7)	959 (95.9)	0.36	6,295 (96.4)	1,829 (95.3)	0.21
Procedural success	3,129 (93.9)	3,012 (94.0)	0.91	852 (92.7)	935 (93.5)	0.55	6,141 (93.9)	1,787 (93.1)	0.24
Number of lesions stented	(n = 3,052)	(n = 2,892)		(n = 826)	(n = 909)		(n = 5,944)	(n = 1,735)	
Total stent length per lesion, mm	26.2 ± 14.5	26.0 ± 14.0	0.49	25.1 ± 14.5	25.9 ± 14.6	0.34	26.1 ± 14.3	25.5 ± 14.5	0.16
Average stent diameter per lesion, mm	3.1 ± 0.5	3.1 ± 0.5	0.74	3.0 ± 0.4	2.9 ± 0.4	0.33	3.1 ± 0.5	3.0 ± 0.4	<0.0001
At least 1 direct stenting	697 (22.8)	641 (22.2)	0.68	166 (20.1)	195 (21.5)	0.30	1,338 (22.5)	361 (20.8)	0.14
Post-dilatation	1,382 (45.3)	1,304 (45.1)	0.92	344 (41.6)	418 (46.0)	0.13	2,686 (45.2)	762 (43.9)	0.28

Values are mean ± SD, n (%), or median (range).

GPI = glycoprotein IIb/IIIa inhibitor; PCI = percutaneous coronary intervention; TIMI = Thrombolysis In Myocardial Infarction.

comparisons but set the alpha error at 2.5% to correct for the 2 coprimary outcomes. We analyzed secondary outcomes with a 2-sided alpha value set at 5% to allow conventional interpretation of results. Survival curves were constructed using Kaplan-Meier estimates. We performed stratified analyses according to the pre-specified subgroup of randomization to heparin or bivalirudin, and estimated possible interaction terms across ordered groups separately for the male and female study populations. We also analyzed clinical outcomes in the overall population irrespective of randomized access to compare male and female patients, but due to the significant differences in baseline and procedural characteristics, multivariable adjustment was performed including the following variables: age, type

TABLE 3 Clinical Outcomes at 30 Days in Male and Female Patients

	Male Patients (n = 6,172)	Female Patients (n = 2,232)	Rate Ratio (95% CI) (Unadjusted)	Unadjusted p Value	Rate Ratio (95% CI) (Adjusted)	Adjusted p Value
Death, MI, stroke	560 (9.1)	238 (10.7)	0.84 (0.72-0.98)	0.030	1.04 (0.88-1.22)	0.67
Death, MI, stroke, BARC type 3 or 5	624 (10.2)	272 (12.2)	0.82 (0.70-0.95)	0.0071	1.02 (0.88-1.20)	0.76
Death, MI, stroke, BARC type 3 or 5, TVR, ST	636 (10.4)	274 (12.3)	0.83 (0.71-0.96)	0.011	1.03 (0.88-1.20)	0.74
Death	91 (1.5)	66 (3.0)	0.49 (0.36-0.68)	<0.0001	0.80 (0.56-1.16)	0.24
Death cardiovascular	88 (1.4)	61 (2.7)	0.52 (0.37-0.72)	0.0001	0.82 (0.56-1.19)	0.30
MI	460 (7.5)	169 (7.6)	0.98 (0.81-1.17)	0.80	1.11 (0.92-1.34)	0.29
Stroke	20 (0.3)	12 (0.5)	0.60 (0.29-1.22)	0.15	0.75 (0.33-1.71)	0.49
TIA	6 (0.1)	12 (0.5)	0.18 (0.07-0.48)	0.0001	0.31 (0.10-0.91)	0.033
TVR	65 (1.1)	24 (1.1)	0.97 (0.61-1.55)	0.90	0.88 (0.53-1.47)	0.63
ST definite	45 (0.7)	12 (0.5)	1.35 (0.71-2.55)	0.36	1.32 (0.67-2.59)	0.43
Acute	26 (0.4)	7 (0.3)	1.34 (0.58-3.08)	0.50	1.15 (0.48-2.78)	0.75
Subacute	20 (0.3)	5 (0.2)	1.43 (0.54-3.81)	0.47	1.65 (0.58-4.71)	0.35
ST definite/probable	63 (1.0)	17 (0.8)	1.33 (0.78-2.27)	0.30	1.45 (0.81-2.57)	0.21
Acute	30 (0.5)	8 (0.4)	1.35 (0.62-2.95)	0.45	1.24 (0.54-2.85)	0.61
Subacute	35 (0.6)	9 (0.4)	1.39 (0.67-2.89)	0.38	1.82 (0.83-4.02)	0.14
Bleeding	654 (10.7)	302 (13.7)	0.76 (0.66-0.88)	0.0002	0.87 (0.75-1.01)	0.067
BARC type 1	327 (5.3)	147 (6.8)	0.79 (0.65-0.96)	0.020	0.84 (0.68-1.04)	0.11
BARC type 2	238 (3.9)	104 (4.7)	0.82 (0.65-1.03)	0.090	0.92 (0.71-1.18)	0.51
BARC type 3	93 (1.6)	45 (2.0)	0.74 (0.52-1.05)	0.094	1.06 (0.72-1.56)	0.77
BARC type 3a	47 (0.8)	26 (1.2)	0.65 (0.40-1.04)	0.072	1.03 (0.61-1.75)	0.91
BARC type 3b	42 (0.7)	18 (0.8)	0.84 (0.48-1.45)	0.52	1.11 (0.61-2.03)	0.73
BARC type 3c	5 (0.1)	1 (0.0)	1.79 (0.21-15.36)	0.59	1.55 (0.14-16.68)	0.72
BARC type 4	10 (0.2)	2 (0.1)	1.79 (0.39-8.17)	0.45	2.12 (0.43-10.48)	0.36
BARC type 5	6 (0.1)	15 (0.7)	0.14 (0.06-0.37)	<0.0001	0.17 (0.06-0.50)	0.0012
BARC type 5a	3 (0.0)	12 (0.5)	0.09 (0.03-0.32)	<0.0001	0.13 (0.03-0.51)	0.0036
BARC type 5b	3 (0.0)	3 (0.1)	0.36 (0.07-1.78)	0.19	0.25 (0.04-1.63)	0.15
BARC type 3 or 5	99 (1.6)	60 (2.7)	0.59 (0.43-0.81)	0.0011	0.84 (0.59-1.19)	0.32
BARC type 3 or 5 access site	33 (0.6)	26 (1.2)	0.45 (0.27-0.76)	0.0020	0.65 (0.37-1.16)	0.14
BARC type 3 or 5 non-access site	66 (1.1)	34 (1.5)	0.70 (0.46-1.05)	0.084	0.97 (0.62-1.53)	0.90
BARC type 2, 3, or 5	335 (5.5)	161 (7.3)	0.74 (0.61-0.90)	0.0019	0.90 (0.73-1.10)	0.29
BARC type 2, 3, or 5 access site	165 (2.7)	101 (4.6)	0.58 (0.45-0.74)	<0.0001	0.64 (0.49-0.85)	0.0016
BARC type 2, 3, or 5 non-access site	176 (2.9)	60 (2.7)	1.06 (0.79-1.42)	0.71	1.39 (1.01-1.90)	0.042
TIMI major	38 (0.6)	25 (1.1)	0.54 (0.33-0.90)	0.017	0.68 (0.39-1.20)	0.18
TIMI minor	32 (0.6)	24 (1.1)	0.48 (0.28-0.81)	0.0050	0.75 (0.42-1.36)	0.35
TIMI major/minor	70 (1.2)	49 (2.2)	0.51 (0.35-0.74)	0.0002	0.71 (0.47-1.07)	0.10
GUSTO severe	32 (0.5)	18 (0.8)	0.64 (0.36-1.14)	0.12	0.91 (0.48-1.72)	0.77
GUSTO moderate	31 (0.5)	24 (1.1)	0.46 (0.27-0.79)	0.0036	0.65 (0.36-1.17)	0.15
GUSTO mild	591 (9.7)	264 (12.1)	0.79 (0.68-0.92)	0.0020	0.88 (0.75-1.03)	0.11
GUSTO moderate/severe	63 (1.0)	42 (1.9)	0.54 (0.36-0.79)	0.0015	0.74 (0.48-1.14)	0.18
Composite of surgical access site repair and blood transfusion	61 (1.0)	53 (2.4)	0.41 (0.28-0.59)	<0.0001	0.56 (0.37-0.84)	0.0056
Surgical access site repair	11 (0.2)	8 (0.4)	0.49 (0.20-1.22)	0.12	0.49 (0.18-1.32)	0.16
Blood transfusion	55 (0.9)	49 (2.2)	0.40 (0.27-0.59)	<0.0001	0.56 (0.37-0.87)	0.0089

Values are n (%), unless otherwise indicated.

BARC = Bleeding Academic Research Consortium; CI = confidence interval; GUSTO = Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries; ST = stent thrombosis; TVR = other abbreviations as in Tables 1 and 2.

of ACS, body mass index, diabetes, smoking, hypercholesterolemia, hypertension, previous MI, previous CABG, previous stroke or transient ischemic attack, Killip class, renal function, crossover, glycoprotein IIb or IIIa, and intra-aortic balloon pump. All analyses were performed using the statistical package Stata 13.1 (StataCorp, College Station, Texas).

RESULTS

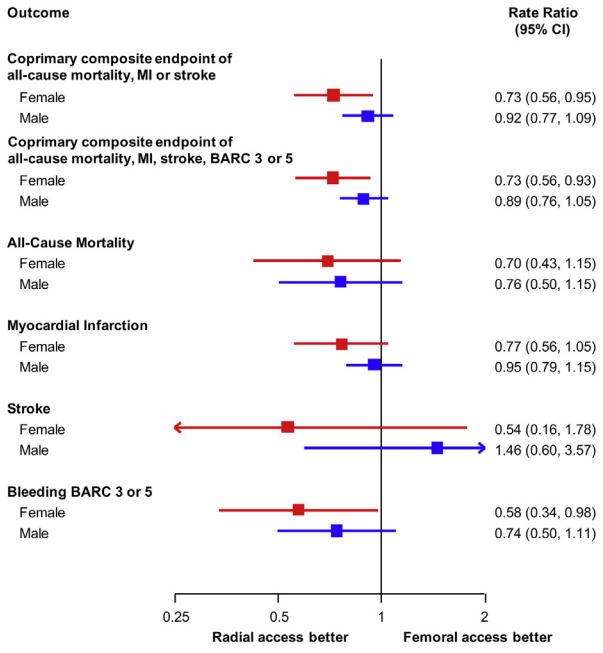
PATIENTS. The MATRIX-Access trial enrolled 8,404 patients with ACS from 78 centers in Italy, the Netherlands, Spain, and Sweden between October 2011 and November 2014. Of these patients, 6,172 (73.4%) were men, of whom 3,126 (37.2%) were allocated to radial and 3,046 (36.2%) to femoral access; and 2,232 (26.6%) were women, of whom 1,071 (12.8%) were assigned to radial and 1,161 (13.8%) to femoral access.

Baseline and procedural characteristics were largely imbalanced between sexes (Tables 1 and 2). Compared with men, women were older; had lower body weight and body mass index; presented more frequently with NSTE-ACS and advanced Killip class; and had a higher prevalence of diabetes, hypercholesterolemia, hypertension, renal dysfunction, and prior cerebrovascular events. However, women less frequently were smokers or had prior MI, PCI, or CABG. Crossover rates, use of intra-aortic balloon pump, left main treatment, and bare-metal stent implantation occurred more often in women, while attempted PCI, use of glycoprotein IIb/IIIa inhibitors, and bypass graft treatment were less frequent in women and stent diameter and length were lower (Table 1). Before arrival in the catheterization laboratory, female patients received aspirin and new $P2Y_{12}$ inhibitors less frequently as compared with men (Table 1).

On the contrary, female and male subgroups allocated to radial versus femoral access were generally well matched in terms of demographics, medical history, clinical presentation, and procedural aspects (Tables 1 and 2). Medications at discharge are shown in Online Table 1. Crossover rate from radial to femoral was numerically higher in women as compared with men (Table 2), however interaction testing did not confirm heterogeneity across sexes (interaction p = 0.051).

CLINICAL OUTCOMES OF MALE VERSUS FEMALE PATIENTS. MACCE and NACE were significantly lower in men compared with women at unadjusted analysis but they no longer differed after adjustment for the multiple imbalances identified across patients' characteristics (Table 3). Similarly, after adjustment, neither of the single components of both coprimary endpoints differed significantly in male compared with female patients (Table 3). There was however a trend toward higher risk of BARC type 3 or 5 access site bleeding and a 36% increase of BARC type 2, 3, or 5 access site bleeding rates in women compared with men after adjustment (Table 3). The need for transfusion and the composite of surgical access site repair and blood transfusion were also increased after adjustment in female compared with male patients (Table 3).

FIGURE 1 Main Outcomes of Radial Versus Femoral Access in Male and Female Patients

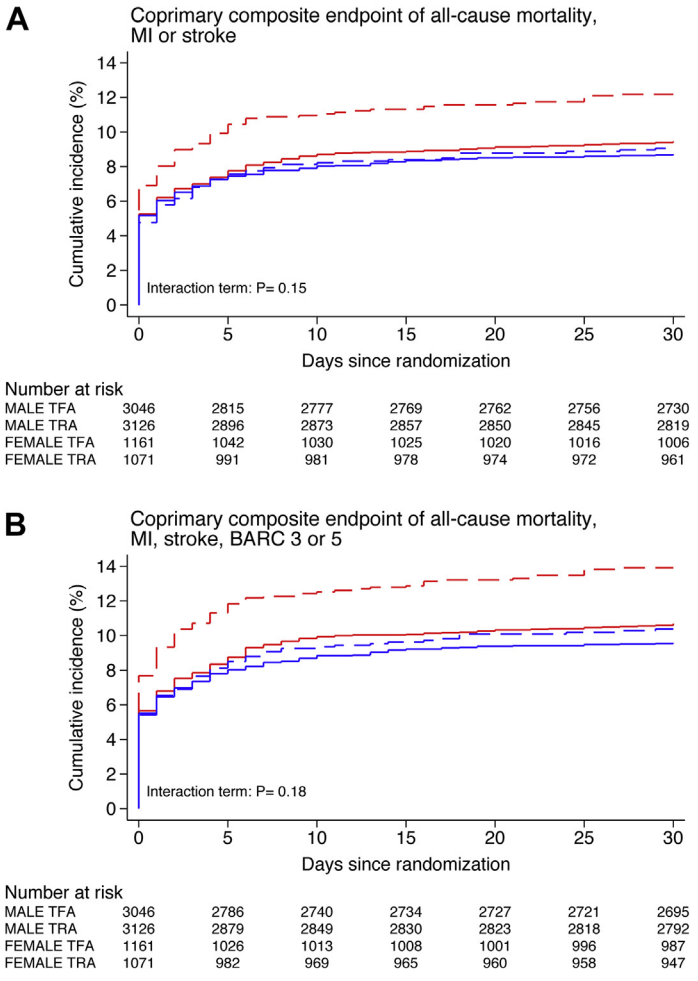


Radial and femoral access were compared on the basis of sex subgroups, with rate ratios and 95% confidence intervals (CIs), for the coprimary endpoints and their components (death, myocardial infarction [MI], stroke, Bleeding Academic Research Consortium [BARC] type 3 or 5).

CLINICAL OUTCOMES OF RADIAL VERSUS FEMORAL ACCESS ACCORDING TO SEX. Overall crossover rates were higher in women as compared with men (4.7% vs. 3.8%; p = 0.037), however this difference disappeared after adjustment (p = 0.42).

No significant interaction was noted between access site and sex with respect to both coprimary endpoints of 30-day MACCE and NACE (interaction p = 0.15 and 0.18, respectively) (Figures 1 and 2, Table 4). MACCE and NACE were significantly reduced with radial as compared with femoral in female patients (MACCE: 9.1% vs. 12.2%; RR: 0.73; 95% confidence interval [CI]: 0.56 to 0.95; p = 0.019; NACE: 10.4% vs. 13.9%; RR: 0.73; 95% CI: 0.56 to 0.93;

FIGURE 2 Coprimary Composite Outcomes at 30 Days in Male and Female Patients



(A, B) Cumulative incidence of the coprimary outcome of major adverse cardiac or cerebrovascular events and net adverse clinical events, respectively. **Blue** indicates radial access (transradial access [TRA]), **red** indicates femoral access (transfemoral access [TFA]), **continuous line** indicates male patient, **dashed line** indicates female patient. Abbreviations as in Figure 1.

p = 0.012) (Figure 1, Table 4) and trended in favor of radial, albeit nonsignificantly in men (MACCE: 8.7% vs. 9.5%; RR: 0.92; 95% CI: 0.77 to 1.09; p = 0.31; NACE: 9.6% vs. 10.8%; RR: 0.89; 95% CI: 0.76 to 1.05; p = 0.16) (Figure 1, Table 4). Radial access was consistently (interaction p = 0.79) associated to lower all-cause fatalities in both sex groups (women: 2.4% vs. 3.5%; RR: 0.70; 95% CI: 0.43 to 1.15; men: 1.3% vs. 1.7%; RR: 0.76; 95% CI: 0.50 to 1.15) (Figure 3, Table 4). At further analysis, no signal of interaction was noted between access site and sex for stroke (interaction p = 0.18), myocardial infarction (interaction p = 0.25) and for other secondary endpoints including cardiovascular mortality (interaction p = 0.92), stent thrombosis (interaction p = 0.18), target vessel revascularization (interaction p = 0.18), or the composite of access site surgery or blood transfusion (interaction p = 0.18) (Figure 3, Table 4).

The key safety endpoint of BARC type 3 or 5 bleeding was similarly reduced (interaction p = 0.45) in the radial groups across sex, even if formal statistical significance was achieved in female (2.0% vs. 3.4%; RR: 0.58; 95% CI: 0.34 to 0.98; p = 0.040) but not in male patients (1.4% vs. 1.9%; RR: 0.74; 95% CI: 0.50 to 1.11; p = 0.14) (Table 4). Access site BARC type 3 or 5 bleeding was consistently (interaction p = 0.45) reduced in both female and male patients whereas non-access site BARC type 3 or 5 bleeding did not differ with radial in both sexes (Table 4). Results remained consistent across any BARC, TIMI, or GUSTO bleeding scales.

ADDITIONAL ANALYSES. Figures 4 and 5 show the consistency of randomized treatment effect (radial vs. femoral) on MACCE, NACE, all-cause death and BARC bleeds in female and male patients stratified by randomly allocated antithrombin type (bivalirudin or unfractionated heparin).

DISCUSSION

We assessed the role of sex disparities on clinical outcomes in largely unselected ACS patients recruited in the MATRIX-Access trial and undergoing invasive management via either radial or femoral access. The main findings are the following.

First, male and female patients differed considerably for multiple baseline characteristics, procedural features, and choice of medications. Although unadjusted analyses apparently yielded greater risk of main efficacy and safety endpoints in female patients as compared with men, they no longer differed after adjustment. Only access site bleeding, but not overall bleeding, along with transfusion rates alone or in combination with surgical repair for the instrumented access site, remained higher in female as compared with male patients.

Second, there was no clear signal of heterogeneity across sex with respect to any of the investigated

TABLE 4 Clinical Outcomes at 30 Days in Radial Versus Femoral Access According to Sex

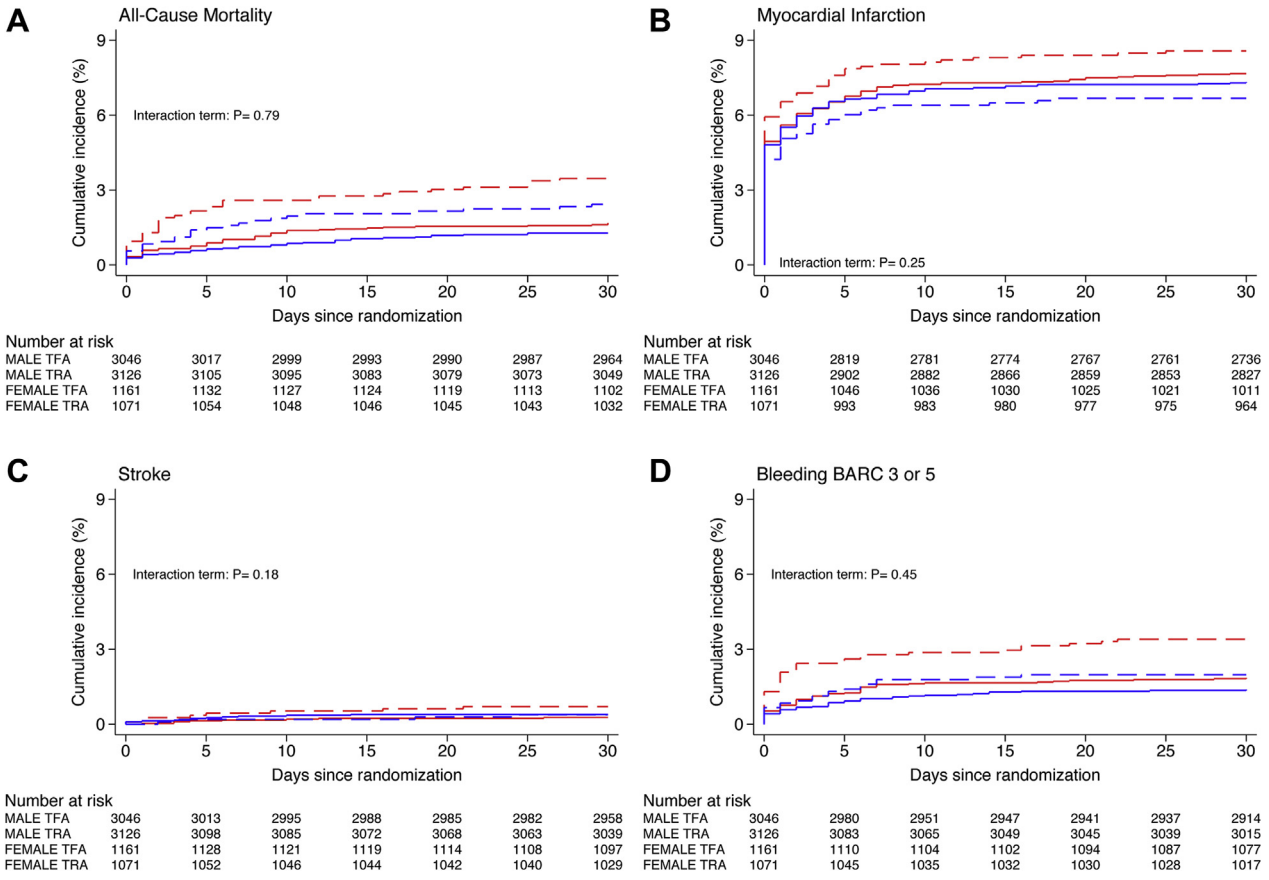
	Male Patients				Female Patients				
	Radial (n = 3,126)	Femoral (n = 3,046)	Rate Ratio (95% CI)	p Value	Radial (n = 1,071)	Femoral (n = 1,161)	Rate Ratio (95%CI)	p Value	p For Interaction
Death, MI, stroke	272 (8.7)	288 (9.5)	0.92 (0.77–1.09)	0.31	97 (9.1)	141 (12.2)	0.73 (0.56–0.95)	0.019	0.15
Death, MI, stroke, BARC type 3 or 5	299 (9.6)	325 (10.8)	0.89 (0.76–1.05)	0.16	111 (10.4)	161 (13.9)	0.73 (0.56–0.93)	0.012	0.18
Death, MI, stroke, BARC type 3 or 5, TVR, ST	307 (9.9)	329 (10.9)	0.90 (0.77–1.06)	0.21	112 (10.5)	162 (14.0)	0.73 (0.57–0.93)	0.012	0.15
Death	40 (1.3)	51 (1.7)	0.76 (0.50–1.15)	0.20	26 (2.4)	40 (3.5)	0.70 (0.43–1.15)	0.15	0.79
Death cardiovascular	39 (1.2)	49 (1.6)	0.77 (0.51–1.18)	0.23	25 (2.3)	36 (3.1)	0.75 (0.45–1.25)	0.26	0.92
MI	228 (7.4)	232 (7.7)	0.95 (0.79–1.15)	0.62	71 (6.7)	98 (8.5)	0.77 (0.56–1.05)	0.10	0.25
Stroke	12 (0.4)	8 (0.3)	1.46 (0.60–3.57)	0.41	4 (0.4)	8 (0.7)	0.54 (0.16–1.78)	0.30	0.18
TIA	2 (0.1)	4 (0.1)	0.49 (0.09–2.65)	0.39	3 (0.3)	9 (0.8)	0.36 (0.10–1.32)	0.11	0.78
TVR	39 (1.3)	26 (0.9)	1.46 (0.89–2.40)	0.13	10 (0.9)	14 (1.2)	0.77 (0.34–1.73)	0.52	0.18
ST definite	26 (0.8)	19 (0.6)	1.33 (0.74–2.41)	0.34	4 (0.4)	8 (0.7)	0.54 (0.16–1.78)	0.30	0.18
Acute	18 (0.6)	8 (0.3)	2.19 (0.95–5.06)	0.058	3 (0.3)	4 (0.3)	0.81 (0.18–3.61)	0.78	0.24
Subacute	9 (0.3)	11 (0.4)	0.79 (0.33–1.92)	0.61	1 (0.1)	4 (0.4)	0.27 (0.03–2.40)	0.21	0.35
ST definite/probable	35 (1.1)	28 (1.0)	1.22 (0.74–2.00)	0.44	7 (0.7)	10 (0.9)	0.75 (0.29–1.98)	0.56	0.38
Acute	20 (0.6)	10 (0.3)	1.95 (0.91–4.17)	0.080	4 (0.4)	4 (0.3)	1.08 (0.27–4.31)	0.92	0.46
Subacute	17 (0.5)	18 (0.6)	0.92 (0.47–1.78)	0.80	3 (0.3)	6 (0.5)	0.54 (0.13–2.15)	0.37	0.49
Bleeding	236 (7.6)	418 (13.9)	0.53 (0.45–0.62)	<0.0001	114 (10.7)	188 (16.5)	0.63 (0.50–0.80)	0.0001	0.23
BARC type 1	113 (3.6)	214 (7.1)	0.50 (0.40–0.63)	<0.0001	55 (5.2)	92 (8.2)	0.63 (0.45–0.89)	0.0073	0.27
BARC type 2	85 (2.7)	153 (5.1)	0.53 (0.41–0.70)	<0.0001	42 (4.0)	62 (5.4)	0.72 (0.49–1.08)	0.11	0.21
BARC type 3	37 (1.2)	56 (1.9)	0.64 (0.42–0.97)	0.034	17 (1.6)	28 (2.5)	0.65 (0.35–1.19)	0.16	0.97
BARC type 3a	18 (0.6)	29 (1.0)	0.60 (0.33–1.08)	0.087	11 (1.0)	15 (1.3)	0.79 (0.36–1.72)	0.55	0.59
BARC type 3b	17 (0.5)	25 (0.8)	0.66 (0.36–1.22)	0.18	6 (0.6)	12 (1.1)	0.54 (0.20–1.43)	0.21	0.72
BARC type 3c	2 (0.1)	3 (0.1)	0.65 (0.11–3.88)	0.63	0 (0.0)	1 (0.1)	0.36 (0.01–8.83)	1.00	0.46
BARC type 4	5 (0.2)	5 (0.2)	0.97 (0.28–3.36)	0.96	1 (0.1)	1 (0.1)	1.08 (0.07–17.16)	0.96	0.95
BARC type 5	6 (0.2)	0 (0.0)	12.67 (0.71–224.81)	0.031	4 (0.4)	11 (1.0)	0.39 (0.12–1.23)	0.095	0.0033
BARC type 5a	3 (0.1)	0 (0.0)	6.82 (0.35–131.98)	0.25	3 (0.3)	9 (0.8)	0.36 (0.10–1.32)	0.11	0.022
BARC type 5b	3 (0.1)	0 (0.0)	6.82 (0.35–131.98)	0.25	1 (0.1)	2 (0.2)	0.54 (0.05–5.95)	0.61	0.094
BARC type 3 or 5	43 (1.4)	56 (1.9)	0.74 (0.50–1.11)	0.14	21 (2.0)	39 (3.4)	0.58 (0.34–0.98)	0.040	0.45
BARC type 3 or 5 access site	8 (0.3)	25 (0.9)	0.31 (0.14–0.69)	0.0023	8 (0.8)	18 (1.6)	0.48 (0.21–1.10)	0.075	0.47
BARC type 3 or 5 non-access site	35 (1.2)	31 (1.0)	1.10 (0.68–1.78)	0.71	13 (1.2)	21 (1.8)	0.66 (0.33–1.33)	0.24	0.24
BARC type 2, 3, or 5	127 (4.1)	208 (6.9)	0.58 (0.47–0.73)	<0.0001	62 (5.8)	99 (8.6)	0.66 (0.48–0.92)	0.012	0.51
BARC type 2, 3, or 5 access site	36 (1.2)	129 (4.3)	0.27 (0.18–0.39)	<0.0001	33 (3.1)	68 (5.9)	0.51 (0.34–0.78)	0.0016	0.021
BARC type 2, 3, or 5 non-access site	92 (3.0)	84 (2.8)	1.06 (0.79–1.43)	0.68	29 (2.7)	31 (2.7)	1.01 (0.61–1.67)	0.98	0.85
TIMI major	19 (0.6)	19 (0.6)	0.97 (0.51–1.84)	0.93	7 (0.7)	18 (1.6)	0.42 (0.17–1.00)	0.043	0.12
TIMI minor	15 (0.5)	17 (0.6)	0.86 (0.43–1.72)	0.66	9 (0.8)	15 (1.3)	0.64 (0.28–1.48)	0.29	0.61
TIMI major/minor	34 (1.1)	36 (1.2)	0.92 (0.57–1.47)	0.72	16 (1.5)	33 (2.9)	0.52 (0.28–0.94)	0.029	0.14
GUSTO severe	17 (0.5)	15 (0.5)	1.10 (0.55–2.21)	0.79	6 (0.6)	12 (1.0)	0.54 (0.20–1.43)	0.21	0.24
GUSTO moderate	14 (0.5)	17 (0.6)	0.80 (0.39–1.62)	0.53	9 (0.9)	15 (1.3)	0.64 (0.28–1.47)	0.29	0.69
GUSTO mild	206 (6.6)	385 (12.8)	0.50 (0.42–0.60)	<0.0001	100 (9.4)	164 (14.5)	0.64 (0.49–0.82)	0.0005	0.13
GUSTO moderate/severe	31 (1.0)	32 (1.1)	0.94 (0.57–1.54)	0.81	15 (1.4)	27 (2.4)	0.59 (0.32–1.12)	0.10	0.26
Composite of surgical access site repair and blood transfusion	26 (0.9)	35 (1.2)	0.72 (0.43–1.20)	0.20	15 (1.4)	38 (3.3)	0.42 (0.23–0.77)	0.0035	0.18
Surgical access site repair	2 (0.1)	9 (0.3)	0.22 (0.05–1.00)	0.031	2 (0.2)	6 (0.5)	0.36 (0.07–1.78)	0.19	0.65
Blood transfusion	25 (0.9)	30 (1.0)	0.81 (0.48–1.38)	0.43	15 (1.4)	34 (3.0)	0.47 (0.26–0.87)	0.013	0.19

Values are n (%), unless otherwise indicated.

Abbreviations as in Tables 1 to 3.

outcome measures, including the 2 coprimary composite endpoints or each of the individual components. Women but not men showed a significant reduction of both coprimary endpoints (fulfilling the pre-specified level of significance at an alpha error of 2.5%) with radial access, indicating that the well-known sex-specific procedural challenges of transradial coronary catheterization and intervention do not mitigate the expected benefits in female patients.

FIGURE 3 Components of Coprimary Composite Outcomes at 30 Days in Male and Female Patients

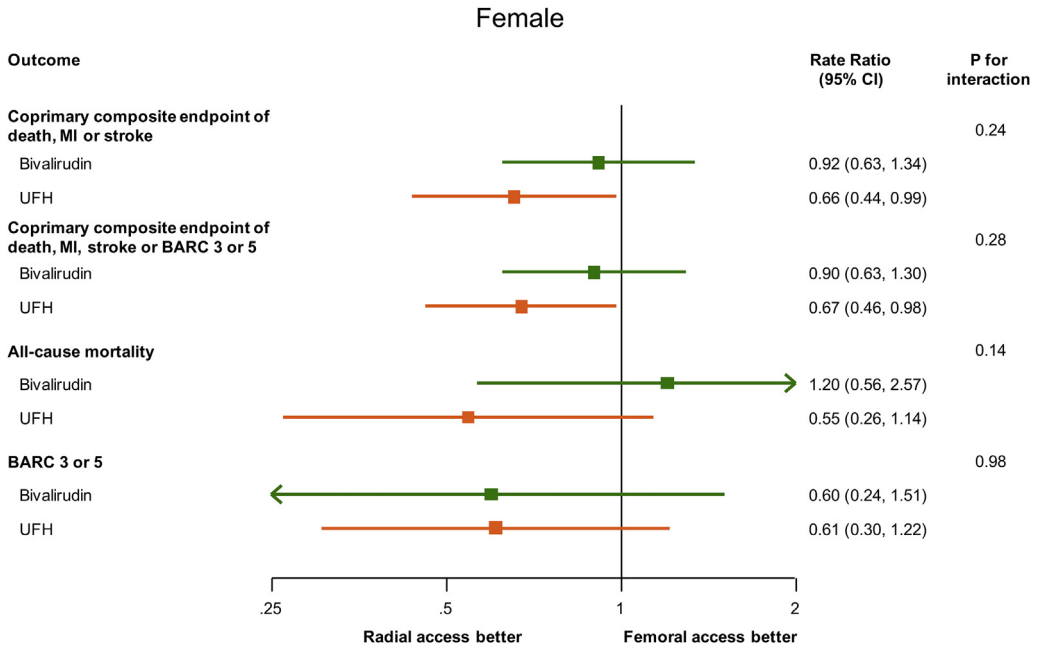


Panels show the cumulative incidence of the coprimary outcome of **(A)** all-cause death, **(B)** myocardial infarction, **(C)** stroke, and **(D)** BARC type 3 or 5 bleeding. **Blue** indicates radial access (TRA), **red** indicates femoral access (TFA), **continuous line** indicates male patient, **dashed line** indicates female patient. Abbreviations as in Figures 1 and 2.

Advances in PCI procedures and optimization of concomitant antithrombotic agents have improved outcomes of patients with ACS by reducing ischemic events, but at the cost of greater bleeding risk. The latter remains a matter of concerns especially for patients at increased procedural hemorrhagic risk such as female patients. Although the spontaneous (i.e., out of hospital) bleeding risk appears not to differ among sexes (14–17), female patients have been consistently shown to suffer the greatest from access site hemorrhagic complications as compared with male counterparts (1,5) Access site bleeds represent a large part of periprocedural bleeding and TRA has emerged as the most appealing and cost-saving treatment strategy to mitigate those complications. However, sex-specific procedural challenges of transradial coronary catheterization and intervention, possibly leading to a delayed or less effective percutaneous treatment especially in ACS female patients, remain a matter of concern. Previous studies have reported that female sex is an independent predictor of failure of transradial PCI (18) and an independent predictor of radial spasm (19), limiting the success of the transradial procedure.

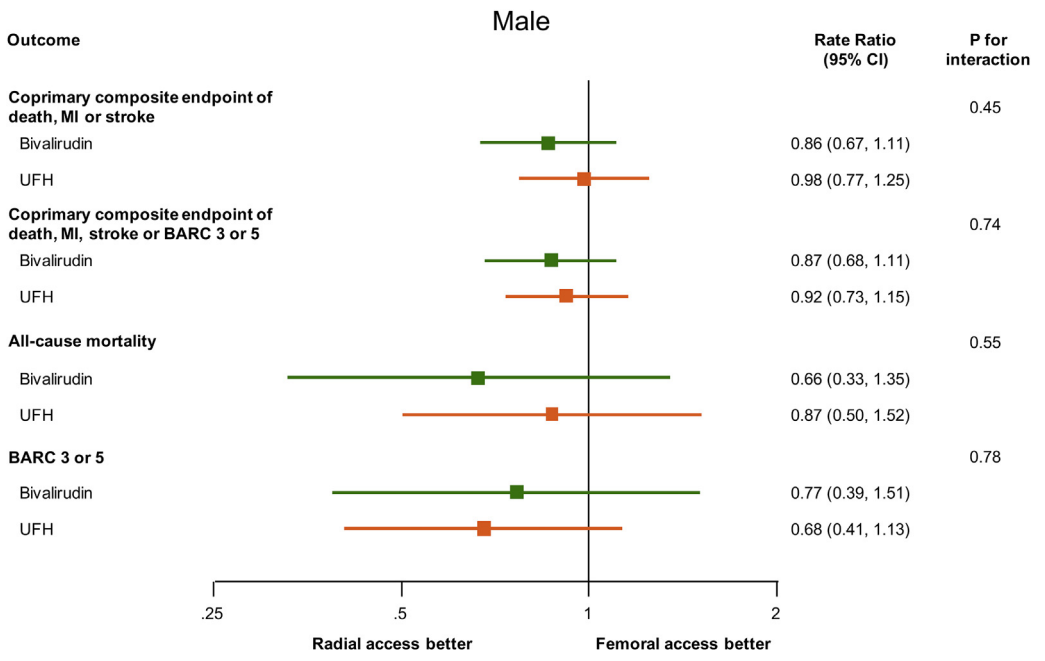
The MATRIX-Access trial is the largest (n = 8,404) randomized trial to compare radial and femoral access, including unselected patients at high baseline and procedural risk. Our current findings are in agreement with those of previous observational

FIGURE 4 Main Outcomes of Radial Versus Femoral Access Stratified by Antithrombin Type in Female Patients



Radial and femoral access were compared on the basis of the randomly assigned antithrombin type (bivalirudin or unfractionated heparin [UFH]), with rate ratios and 95% CIs, for the coprimary endpoints, death, and BARC type 3 or 5. Abbreviations as in Figure 1.

FIGURE 5 Main Outcomes of Radial Versus Femoral Access Stratified by Antithrombin Type in Male Patients



Radial and femoral access were compared on the basis of the randomly assigned antithrombin type (bivalirudin or unfractionated heparin), with rate ratios and 95% CIs, for the coprimary endpoints, death, and BARC type 3 or 5. Abbreviations as in Figure 1.

studies (20,21), and those reported in the RIVAL (Radial Vs femorAL access for coronary intervention) trial. A pre-specified subgroup analysis of RIVAL compared outcomes in women (n = 1,861) and men (n = 5,160) who were randomized to radial versus femoral access and showed that women undergoing coronary angiography and PCI had a higher risk of vascular access site complications compared with men, but radial access was an effective method to reduce these complications (7). In the RIVAL trial the type of antithrombotic medications during coronary intervention was not protocol-mandated. As a result, the majority of patients were treated with heparin rather than bivalirudin (approximately 2.6%). Therefore, it was not possible to exclude that using bivalirudin would have reduced the benefits of radial access especially in female patients (22). In the MATRIX-Access trial, heparin and bivalirudin were randomly and evenly assigned to patients at the time of coronary intervention. No signal of heterogeneity was noted for type of anticoagulant agent and access site for both men and women across the coprimary endpoints, mortality, or the key safety bleeding endpoint. This novel and unique observation that the benefits of radial access remain consistent in both sexes irrespective of the choice of parenteral anticoagulation during PCI has notable implications for current practice. Against the widespread belief that radial access and use of bivalirudin represent competing treatment strategies to minimize bleeding risks, our findings support their complementary role to mitigate both access site and non-access site bleeding risks, both in male and female patients.

The SAFE-PCI for Women (Study of Access Site for Enhancement of PCI for Women) trial was unique for selecting exquisitely women to undergo radial or femoral access (6). The trial was stopped prematurely due to lower than expected event rate and no significant difference was found in the primary efficacy endpoint (BARC 2, 3, or 5 bleeding or vascular complications requiring intervention) between TRA and TFA in patients undergoing PCI (n = 691; primary endpoint cohort). However, in a secondary analysis also including female patients who underwent cardiac catheterization (n = 1,787), radial access significantly reduced bleeding and vascular complications (6). Hence, the apparent lack of benefit of radial over femoral access in this study likely reflects limited study power more than lack of treatment effect in women.

We observed that women randomized to TRA more frequently needed crossovers to TFA compared with men (7.6% vs. 5.2%). This likely reflects greater challenges in women to obtain vascular access when attempting TRA, likely because of smaller and more prone to spasm radial arteries. Yet, the duration of the procedure was overall shorter in women as compared with men, and in the former group TRA did not require longer procedural or fluoroscopic time as compared with TFA. This observation suggests that female patients who are intervened upon via the radial access do not pose specific further technical challenges once vascular access has been established.

Overall, present findings contribute to support the concept that radial access should be preferred over the femoral access, adding to the current knowledge firm evidence that this approach is applicable to both male and female patients, and that probably it is even more beneficial in women who are characterized by increased risk of bleeding and access site related complications. Therefore, efforts should be done to increase the adoption of radial access, but at the same time improving the operators' training, which is fundamental to reach the most appropriate skills, particularly in women where radial access might be more challenging due to anatomical reasons.

STUDY LIMITATIONS. Although a sex subgroup analysis was pre-specified, the MATRIX-Access trial was not powered to explore differences between sexes, and randomization was not stratified by sex. As such, the current analyses may be subject to type II error. As expected in an exploratory analysis of effect modification, an ad hoc power analysis indicates a 30% power for the analysis of our primary outcome. Female study population was smaller compared with the male group, as observed in most trials investigating patients with CAD. Yet, the benefits of TRA over TFA were consistent across sexes and if anything seemed to be slightly more pronounced among women. We did not adjust for multiple comparisons, increasing the risk of type I error. Radial artery occlusion was not systematically looked for in the context of the MATRIX study. Results apply to the context of this trial in which most centers participating were highly experienced in the radial

technique; therefore, similar outcomes may not apply in centers performing lower volumes of radial access.

CONCLUSIONS

This sex-specific analysis of the largest trial comparing radial versus femoral access in ACS patients invasively managed suggests that women experienced a higher risk of severe bleeding and access site complications, and radial access was an effective method to reduce these complications, as well as composite ischemic and ischemic or bleeding endpoints.

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PERSPECTIVES

WHAT IS KNOWN? There are limited and contrasting data about sex disparities for the safety and efficacy of TRA versus TFA for coronary intervention.

WHAT IS NEW? The MATRIX-Access trial results showing superiority of TRA versus TFA were consistent across sexes. Women experienced a higher risk of severe bleeding and access site complications, and radial access was an effective method to reduce these complications, as well as composite ischemic and ischemic or bleeding endpoints.

WHAT IS NEXT? Radial access should become the default access for patients with ACS undergoing invasive management, irrespective of sex.

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KEY WORDS acute coronary syndrome(s), female, femoral access, male, MATRIX, radial access

APPENDIX For a supplemental table, please see the online version of this paper.

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Acute Kidney Injury After Radial or Femoral Access for Invasive Acute Coronary Syndrome Management

AKI-MATRIX

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for the MATRIX Investigators

ABSTRACT

BACKGROUND It remains unclear whether radial access (RA), compared with femoral access (FA), mitigates the risk of acute kidney injury (AKI).

OBJECTIVES The authors assessed the incidence of AKI in patients with acute coronary syndrome (ACS) enrolled in the MATRIX-Access (Minimizing Adverse Haemorrhagic Events by Transradial Access Site and Systemic Implementation of Angiox) trial.

METHODS Among 8,404 patients, 194 (2.3%) were excluded due to missing creatinine values, no or an incomplete coronary angiogram, or previous dialysis. The primary AKI-MATRIX endpoint was AKI, defined as an absolute (>0.5 mg/dl) or a relative (>25%) increase in serum creatinine (sCr).

RESULTS AKI occurred in 634 patients (15.4%) with RA and 712 patients (17.4%) with FA (odds ratio [OR]: 0.87; 95% confidence interval [CI]: 0.77 to 0.98; p = 0.0181). A >25% sCr increase was noted in 633 patients (15.4%) with RA and 710 patients (17.3%) with FA (OR: 0.87; 95% CI: 0.77 to 0.98; p = 0.0195), whereas a >0.5 mg/dl absolute sCr increase occurred in 175 patients (4.3%) with RA versus 223 patients (5.4%) with FA (OR: 0.77; 95% CI: 0.63 to 0.95; p = 0.0131). By implementing the Kidney Disease Improving Global Outcomes criteria, AKI was 3-fold less prevalent and trended lower with RA (OR: 0.85; 95% CI: 0.70 to 1.03; p = 0.090), with stage 3 AKI occurring in 28 patients (0.68%) with RA versus 46 patients (1.12%) with FA (p = 0.0367). Post-intervention dialysis was needed in 6 patients (0.15%) with RA and 14 patients (0.34%) with FA (p = 0.0814). Stratified analyses suggested greater benefit with RA than FA in patients at greater risk for AKI.

CONCLUSIONS In ACS patients who underwent invasive management, RA was associated with a reduced risk of AKI compared with FA. (Minimizing Adverse Haemorrhagic Events by TRansradial Access Site and Systemic Implementation of angioX [MATRIX]; NCT01433627) (J Am Coll Cardiol 2017;69:2592-603) © 2017 by the American College of Cardiology Foundation.

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Acute kidney injury (AKI) occurs in 10% to 27% of patients with acute coronary syndrome (ACS) who undergo percutaneous coronary intervention (PCI) and is associated with greater morbidity and mortality (1,2). Pathophysiology of AKI in these patients is multifactorial, involving contrast volume, impaired systemic and renal hemodynamic conditions, imbalance of endogenous vasodilating and vasoconstrictive factors, and direct cholesterol embolization (1). Although the risk of AKI can be predicted (3), and contrast media volume plays a central role in its pathogenesis (4), the possibility of implementing prophylactic interventions is limited (5). This is especially relevant for patients who require urgent PCI, such as those undergoing intervention for ACS. Observational data with propensity matching (6,7) and a meta-analysis (8) have suggested an association between the use of radial access (RA) and a lower incidence of AKI. Putative explanations for this effect are a reduction of bleeding events (7) and/or a lower risk of cholesterol embolization in the renal circulation (9,10) offered by RA (11). However, no prospective assessment of the incidence of AKI has been carried out in randomized studies of patients receiving RA compared with femoral access (FA). In the largest randomized comparison between RA and FA to date, the MATRIX (Minimizing Adverse Haemorrhagic Events by Transradial Access Site and Systemic Implementation of Angiox) trial, RA was associated with a reduced incidence of net adverse clinical events because of a reduction of bleeding and fatalities compared with FA (12).

SEE PAGE 2604

We pre-specified (11) a prospective assessment of whether RA compared with FA reduced the incidence of AKI in patients with ACS, including analysis of patients with ST-segment elevation myocardial infarction (STEMI) or non–ST-segment elevation myocardial infarction (NSTEMI) who underwent invasive management.

METHODS

MATRIX-Access was designed as a randomized, multicenter, superiority trial comparing RA with FA in patients with myocardial infarction with or without ST-segment elevation who underwent coronary angiography, and, if clinically indicated, PCI (12,13). This was the first of 3 randomized comparisons of the MATRIX program and was performed in all consenting patients. The trial was approved by the institutional review board at each center, and all patients gave written

ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome

AKI = acute kidney injury

BARC = Bleeding Academic Research Consortium

CES = cholesterol embolization syndrome

CI = confidence interval

CIN = contrast-induced nephropathy

eGFR = estimated glomerular filtration rate

FA = femoral access

KDIGO = Kidney Disease Improving Global Outcomes

NSTEMI = non–ST-segment elevation myocardial infarction

OR = odds ratio

PCI = percutaneous coronary intervention

RA = radial access

RRR = relative risk ratio

sCR = serum creatinine

STEMI = ST-segment elevation myocardial infarction

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TABLE 1 Baseline Clinical and Procedural Characteristics

	Radial Access (n = 4,109)	Femoral Access (n = 4,101)	p Value
Clinical characteristics			
Age, yrs	65.5 ± 11.8	65.9 ± 11.8	0.17
≥75 yrs	1,040 (25.3)	1,076 (26.2)	0.34
Male	3,063 (74.5)	2,977 (72.6)	0.045
Hypotension*	26 (0.6)	33 (0.8)	0.36
Anemia†	796 (19.4)	810 (19.8)	0.66
Diabetes	936 (22.8)	917 (22.4)	0.65
Creatinine >1.5 mg/dl	4,003 (97.4)	4,003 (97.6)	0.58
Killip class III or IV	129 (3.1)	101 (2.5)	0.063
STEMI	1,977 (48.1)	1,975 (48.2)	0.97
NSTEMI	2,132 (51.9)	2,126 (51.8)	0.97
Troponin negative	233 (5.7)	255 (6.2)	0.29
Troponin positive	1,899 (46.2)	1,871 (45.6)	0.59
With ST-segment deviation	983 (23.9)	956 (23.3)	0.51
With T-wave inversion	637 (15.5)	656 (16.0)	0.54
Ejection fraction ≤35%	339 (8.6)	362 (9.2)	0.33
Systolic arterial pressure, mm Hg	138.6 ± 25.5	139.0 ± 25.7	0.50
Hemoglobin at baseline, g/dl	13.9 ± 1.9	13.9 ± 1.9	0.26
Glucose at baseline, mg/dl	138.3 ± 66.8	138.9 ± 63.9	0.67
Medications administered before catheterization laboratory			
Statins	1,766 (43.0)	1,815 (44.3)	0.24
ACE inhibitors	1,227 (29.9)	1,266 (30.9)	0.32
Angiotensin II receptor antagonist	441 (10.7)	456 (11.1)	0.57
Loop diuretics	463 (11.3)	471 (11.5)	0.76
Potassium-sparing diuretics	85 (2.1)	95 (2.3)	0.44
Other diuretics	114 (2.8)	94 (2.3)	0.16
Procedural characteristics			
Any crossover during index hospitalization	329 (8.0)	231 (5.6)	0.00012
Total amount of contrast used during index hospitalization	183.3 ± 104.5	183.9 ± 110.1	0.83
No PCI attempted after coronary angiography during index hospitalization	742 (18.1)	747 (18.2)	0.85
CABG	144 (3.5)	146 (3.6)	0.89
Patients with significant lesion and medical treatment	472 (11.5)	474 (11.6)	0.92
Patients without significant lesion	129 (3.1)	128 (3.1)	0.96
≥1 PCI attempted	3,367 (81.9)	3,354 (81.8)	0.85
Died during PCI	1 (0.0)	0 (0.0)	1.00
≥1 PCI completed during index hospitalization	3,366 (81.9)	3,354 (81.8)	0.88
Medications administered in and after the catheterization laboratory			
Aspirin	228 (5.5)	274 (6.7)	0.032
Clopidogrel	270 (6.6)	257 (6.3)	0.57
Prasugrel	331 (8.1)	291 (7.1)	0.10
Ticagrelor	376 (9.2)	391 (9.5)	0.55
GPIs	582 (14.2)	522 (12.7)	0.057
Planned GPI	420 (10.2)	369 (9.0)	0.060
Bailout GPI	165 (4.0)	154 (3.8)	0.54
Unfractionated heparin	2,071 (50.4)	1,908 (46.5)	0.00044
Total unfractionated heparin, U/kg	41.0 ± 51.3	37.9 ± 48.8	0.0066
At least 1 subtherapeutic regimen, <50 U/kg	465 (11.3)	337 (8.2)	<0.0001
At least 1 therapeutic regimen, ≥50 U/kg	1,643 (40.0)	1,597 (38.9)	0.33
Bivalirudin	1,697 (41.3)	1,719 (41.9)	0.57
Prolonged infusion post-PCI	863 (21.0)	868 (21.2)	0.86
Average of total duration of post-PCI bivalirudin infusion, min	82.2 ± 201.8	87.5 ± 223.8	0.26
Patients receiving full bivalirudin regimen post-PCI	320 (7.8)	301 (7.3)	0.44
Average of total duration of full bivalirudin regimen, min	21.7 ± 86.9	21.1 ± 104.6	0.78
Patients receiving low bivalirudin regimen post-PCI	552 (13.4)	580 (14.1)	0.35
Average of total duration of low bivalirudin regimen, min	60.4 ± 187.8	66.4 ± 203.8	0.17
≥1 intra-aortic balloon pump	80 (1.9)	96 (2.3)	0.22

Continued on the next page

TABLE 1 Continued

	Radial Access (n = 4,109)	Femoral Access (n = 4,101)	p Value
≥1 PCI completed	3,366	3,354	
TIMI flow grade 3 in all treated lesions during whole index hospitalization	3,193 (94.9)	3,189 (95.1)	0.68
Coronary stenosis <30% in all treated lesions	3,206 (95.2)	3,185 (95.0)	0.59
Procedural success in all treated lesions	3,109 (92.4)	3,098 (92.4)	1.00
Duration of procedure	61.2 ± 36.6	60.1 ± 37.4	0.22
Amount of contrast used	202.8 ± 103.1	204.2 ± 109.6	0.61
Treated vessel(s) per patient			
Left main coronary artery	175 (5.2)	156 (4.7)	0.30
Left anterior descending artery	1,846 (54.9)	1,813 (54.1)	0.51
Left circumflex artery	1,055 (31.4)	1,044 (31.1)	0.84
Right coronary artery	1,241 (36.9)	1,232 (36.7)	0.90
Bypass graft	21 (0.6)	37 (1.1)	0.034
At least 2 vessels treated	806 (24.0)	793 (23.7)	0.77
Lesions treated per patient, n	1.0 (1.0–2.0)	1.0 (1.0–2.0)	0.74
1	2,314 (68.8)	2,313 (69.0)	
2	738 (21.9)	754 (22.5)	
≥3	312 (9.3)	286 (8.5)	
≥1 complex lesion	1,856 (55.2)	1,789 (53.4)	0.13
Stents per patient, n	1.0 (1.0–2.0)	1.0 (1.0–2.0)	0.26
Overall stent length per patient, mm	58.1 ± 54.6	57.3 ± 55.0	0.50
Lesions			
Number of lesions with PCI	4,843	4,768	
Lesions stented	4,437 (91.6)	4,324 (90.7)	0.13
≥1 drug-eluting stent	3,281 (67.7)	3,240 (68.0)	0.79
≥1 bare-metal stent	1,156 (23.9)	1,084 (22.7)	0.26
Lesions not stented	406 (8.4)	444 (9.3)	0.13
TIMI flow grade pre-procedure			0.88
0 or 1	1,657 (34.2)	1,645 (34.5)	0.87
2	565 (11.7)	562 (11.8)	0.87
3	2,619 (54.1)	2,559 (53.7)	0.99
TIMI flow grade post-procedure			0.76
0 or 1	79 (1.6)	73 (1.5)	0.73
2	106 (2.2)	103 (2.2)	0.98
3	4,656 (96.2)	4,590 (96.3)	0.78
Coronary stenosis <30%	4,661 (96.3)	4,582 (96.1)	0.67
Procedural success	4,554 (94.0)	4,489 (94.1)	0.82
Number of lesions stented	4,437	4,324	
Total stent length per lesion, mm	26.2 ± 14.7	26.5 ± 14.9	0.61
Average stent diameter per lesion, mm	3.0 ± 0.5	3.0 ± 0.5	0.25
≥1 direct stenting	978 (22.0)	922 (21.3)	0.77
Post-dilation	2,034 (45.8)	2,016 (46.6)	0.48

Values are mean ± SD, n (%), n, or median (interquartile range). *Systolic blood pressure <80 mm Hg. †<12 g/dl for women, <13 g/dl for men.

ACE = angiotensin-converting enzyme; CABG = coronary artery bypass graft surgery; GPI = glycoprotein IIb/IIIa inhibitor; NSTEMI = non–ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction; TIMI = Thrombolysis In Myocardial Infarction.

informed consent. Patients were eligible if they had ACS and planned coronary angiography, and the interventional cardiologist was willing to proceed with either RA or FA. That meant cardiologists were required to have expertise in both, including at least 75 coronary interventions performed and at least 50% of interventions in ACS via the radial route during the previous year. The main inclusion and exclusion criteria of the MATRIX-Access trial were previously reported (Online Appendix) (12,14). All patients enrolled in MATRIX-Access were eligible for the AKI-MATRIX substudy, except those with incomplete creatinine data who did not receive a complete angiogram or those who had end-stage renal disease that required dialysis.

STUDY PROTOCOL AND RANDOMIZATION. Before angiography, patients were centrally allocated 1:1 to

RA or FA for diagnostic angiography and PCI, if indicated, using a web-based system to ensure adequate concealment of allocation. The randomization sequence was computer-generated, blocked, and stratified by site, intended new or ongoing use of ticagrelor or prasugrel, type of ACS (STEMI or NSTEMI, and in the latter case, whether troponin-positive or not), and anticipated use of immediate PCI. Patients proceeding to PCI were further randomized to bivalirudin, administered according to product labeling, or to unfractionated heparin, dosed at 70 to 100 U/kg in patients who did not receive glycoprotein IIb/IIIa inhibitors or at 50 to 70 U/kg in patients who received planned glycoprotein IIb/IIIa inhibitors. Use of other anticoagulants was not allowed, whereas other antithrombotic medications, including oral antiplatelet agents and non-antithrombotic medications, were allowed as per guidelines (15).

STUDY OUTCOMES. The endpoints of the MATRIX-Access study have been previously reported (12,13). The primary endpoint of the AKI-MATRIX substudy was the incidence of AKI, defined as either an absolute (>0.5 mg/dl) or a relative (>25%) increase from baseline in serum creatinine (sCr) levels during hospitalization in the intention-to-treat population (16). The incidence of AKI was also assessed using either defining criterion, as well as the Kidney Disease Improving Global Outcomes (KDIGO) criteria and staged for severity (17). Sensitivity analyses were also performed in patients who had the randomly allocated access site (i.e., excluding patients with access site crossover) or in those proceeding to PCI after diagnostic coronary angiography (i.e., excluding patients who received only an angiogram and no further PCI). Bleeding complications were defined per the Bleeding Academic Research Consortium (BARC) scale (Online Appendix).

STATISTICAL ANALYSIS. Details related to the sample size calculation and the statistical analyses have been described previously (12). No a priori sample size considerations were performed to assess AKI-MATRIX study power (11). However, for explorative purposes, power analyses were previously computed assuming a 5% absolute increase in sCr of >0.5 mg/dl in the FA group and 50%, 35%, and 25% relative risk reductions (RRRs) in the RA group. We conservatively assumed a 5% incidence of AKI in the FA group, although the incidence of AKI in contemporary studies of PCI in ACS could be 3-fold higher. Available data suggested a possible 25% RRR in AKI incidence with the RA approach across unselected populations who underwent PCI. Hypothesizing a 33% RRR of AKI with RA in the MATRIX study, with 3,400 patients per group who underwent PCI, we would have >93% power of detecting a reduction in the incidence of AKI to 3.3% in the RA group at the 5% alpha level.

All analyses were performed according to the intention-to-treat principle. Differences across groups were assessed using the Student *t* test in case of continuous variables and the chi-square or Fisher exact test in case of categorical data. The differences at lesion level considered the nested structure of lesions within individuals, and then were analyzed using multilevel general or generalized mixed models, as appropriate. We applied both univariate and multivariable logistic regression models to evaluate the association of AKI during index hospitalization with Mehran's score, bleeding, and measures of bleeding severity. Furthermore, we performed stratified logistic regressions by subgroups, including the center's proportion of radial PCI, diabetes at baseline, estimated glomerular filtration rate (eGFR), age, clinical presentation, Killip class, left ventricular ejection fraction, and Mehran's score. The analyses were done using Stata release 14.1 (StataCorp LLC, College Station, Texas) and R 3.3.0 (R Foundation, Vienna, Austria).

RESULTS

Among 8,404 patients enrolled in the MATRIX-Access trial from 78 centers in Italy, the Netherlands, Spain, and Sweden between October 2011 and July 2014, 194 patients (2.3%) were excluded due to an incomplete sCr dataset (96 FA and 82 RA patients), no or an incomplete coronary angiogram (6 FA and 2 RA patients), or previous dialysis at randomization (4 patients in each group) (Online Figure 1). Among the 8,210 patients included in the analysis, one-half (n = 4,109) were allocated to RA and the other 4,101 participating patients were allocated to FA. Baseline demographics and procedural characteristics were similar for the 2 groups (**Table 1**).

AKI occurred in 1,345 patients (16.4%), per the primary endpoint as defined by a relative (>25%) increase in sCr and in 387 patients (4.7%) according to an absolute increase in sCr of >0.5 mg/dl. Patients with AKI were older and more frequently women, and had a higher prevalence of diabetes and anemia (Online Table 1). Study participants who developed AKI were more likely to have presented with STEMI and advanced Killip class; plus, their access site crossover rate was twice as frequent. Patients with AKI more commonly underwent PCI or received treatment for complex or multiple lesions, including

left main or left anterior coronary arteries (Online Table 1). Patients who had AKI had lower rates of statin therapy but higher rates of angiotensin II receptor blocker and diuretic use before presentation to the catheterization laboratory. The amount of contrast used and procedural failure rate were higher in patients with AKI compared with those without AKI (Online Table 1).

ENDPOINTS ACCORDING TO ACCESS SITE. Before randomization, sCr and eGFR were similar between the RA and FA groups (Table 2). Peak sCr after intervention or at discharge did not differ in the RA group versus the FA group, whereas nadir eGFR was lower in the FA group during hospitalization (79.6 ± 25.9 ml/min/1.73 m^2 vs. 78.2 ± 25.7 ml/min/1.73 m^2; p = 0.0099) and at discharge (84.6 ± 26.5 ml/min/1.73 m^2 vs. 83.4 ± 26.1 ml/min/1.73 m^2; p = 0.030) (Table 2).

The primary outcome of AKI occurred in significantly fewer patients with RA than in those with FA (15.4% vs. 17.4%; p = 0.0181) (Central Illustration, Table 3). Both components of the AKI primary endpoint definition were significantly lower in patients with RA. Specifically, a >25% increase in sCr was observed in 633 patients (15.4%) with RA and 710 patients (17.3%) with FA (odds ratio [OR]: 0.87; 95% confidence interval [CI]: 0.77 to 0.98; p = 0.0195), and a >0.5 mg/dl absolute increase in sCr occurred in 175 patients (4.3%) with RA and 223 patients (5.4%) with FA (relative risk: 0.77; 95% CI: 0.63 to 0.95; p = 0.0131). Post-intervention dialysis occurred in fewer patients with RA than in those with FA (0.15% vs. 0.34%; p = 0.0814) (Table 3).

After excluding patients who did not receive the randomly allocated access site (n = 605), either because it failed or it was not attempted, AKI occurred in significantly fewer patients with RA compared with FA (14.3% vs. 16.7%; p = 0.0038) because of significant reductions of both components of the primary endpoint. The need for dialysis was also lower with RA access compared with FA (OR: 0.16; 95% CI: 0.04 to 0.69; p = 0.0146) (Table 3).

Among patients who received PCI after coronary angiography during the index hospitalization (n = 6,616; 80.5% of the AKI-MATRIX population), RA was associated with a 14% risk reduction of AKI compared with FA (OR: 0.86; 95% CI: 0.76 to 0.98; p = 0.0202). Three (0.09%) patients in the RA group and 10 (0.3%) patients in the FA group underwent dialysis therapy (p = 0.0659) (Table 3).

By implementing the KDIGO criteria, AKI occurred in 213 patients (5.2%) with RA and 248 patients (6.1%) with FA (p = 0.090). Stage 1 or 2 AKI were not reduced in the RA group (Table 2), but stage 3 was lower with RA (0.7% vs. 1.1%; p = 0.037) (Central Illustration, Table 3).

TABLE 2 Renal Function

	Randomized to Radial Access (n = 4,109)	Randomized to Femoral Access (n = 4,101)	p Value
Creatinine, mg/dl			
Pre-PCI	0.97 ± 0.36	0.98 ± 0.32	0.7434
Post-PCI	1.06 ± 0.55	1.08 ± 0.54	0.1271
At hospital discharge	0.99 ± 0.44	1.00 ± 0.43	0.2361
eGFR, ml/min/1.73 m^2 (MDRD formula)			
Pre-PCI	84.22 ± 25.36	83.46 ± 25.51	0.1786
Post-PCI	79.63 ± 25.87	78.16 ± 25.65	0.0099
At hospital discharge	84.62 ± 26.50	83.35 ± 26.10	0.0300

Values are mean ± SD.

eGFR = estimated glomerular filtration rate; MDRD = Modification of Diet in Renal Disease; PCI = percutaneous coronary intervention.

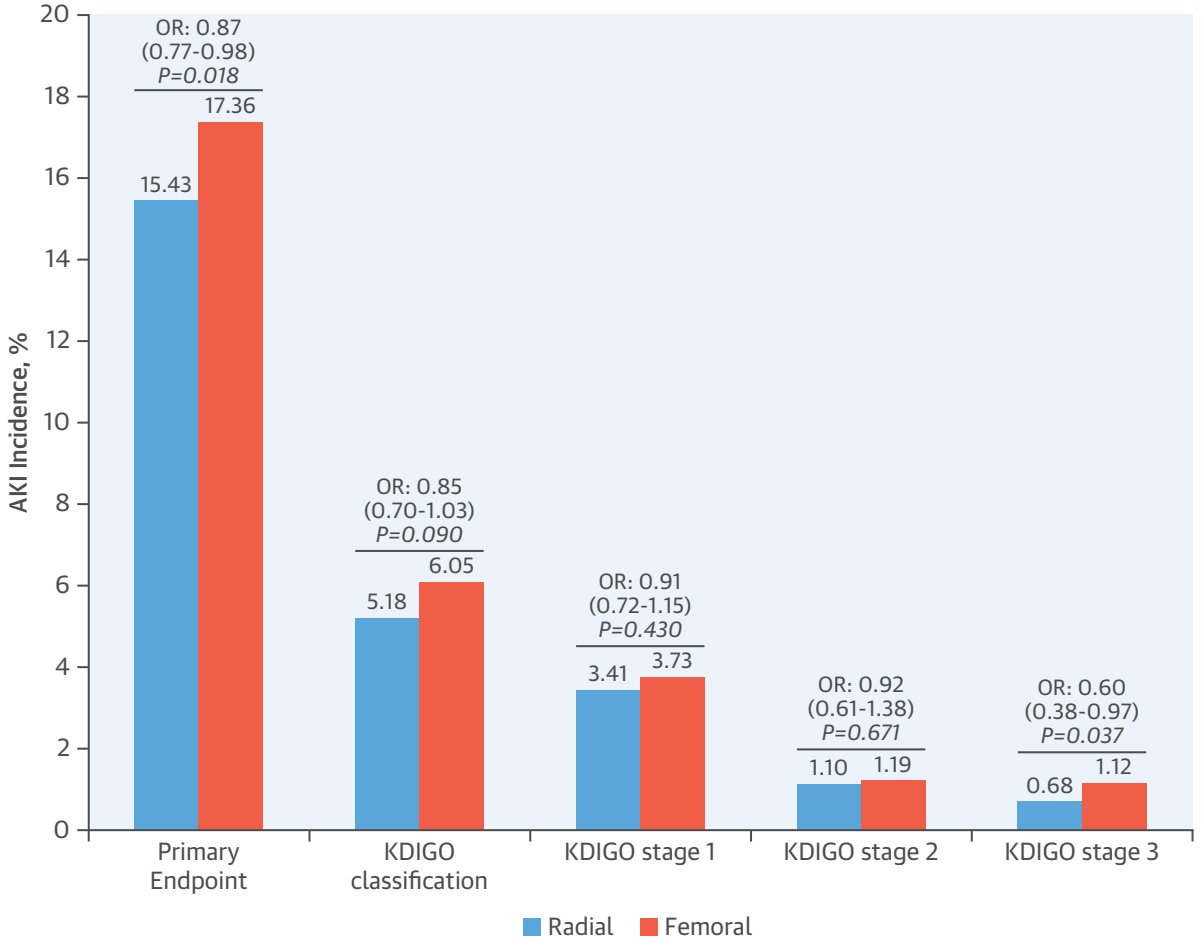
SUBGROUP ANALYSIS AND MULTIVARIATE MODELING. The effects of RA versus the effects of FA in reducing the incidence of AKI was largely consistent across subgroups, including the participating center's proportion of radial PCI, diabetes, age, and clinical presentation (Figure 1). Positive quantitative interaction testing was noted between the randomized access site and the pre-procedural renal function, Killip class, and Mehran score, which suggested relatively greater benefit with RA compared with FA in patients at higher baseline risk for AKI. There was significant interaction also between the access site and antithrombotic therapy, with RA showing benefit in patients who received unfractionated heparin, but apparently no benefit was seen in those allocated to bivalirudin. Online Figure 2 shows subgroup analysis according to the components of the Mehran risk score.

At multivariable modeling, random allocation to RA remained associated with a significantly lower risk of AKI (OR: 0.87; 95% CI: 0.77 to 0.98; p = 0.0217) when the covariates included in the Mehran score were entered (Table 4). When access site bleeding was entered into the logistic model (model 2), random allocation to RA was associated with a nonsignificant 11% RRR (p = 0.0647), whereas an access-related BARC score of ≥2 complications showed a 2-fold significantly increased risk (OR: 2.19; 95% CI: 1.66 to 2.89; p < 0.0001) (Table 4). Hemoglobin drop after randomization (model 3) and blood red transfusion (model 4) were also associated with AKI (Table 4).

DISCUSSION

Among patients with ACS (with or without ST-segment elevation) who were managed invasively,

CENTRAL ILLUSTRATION **Radial Versus Femoral Approach in AKI Patients Undergoing Invasive Management**



Andò, G. et al. J Am Coll Cardiol. 2017;69(21):2592–603.

We assessed whether use of radial versus femoral access mitigated incidence of acute kidney injury (AKI) in patients with acute coronary syndrome who underwent invasive management. Radial access significantly reduced AKI incidence in terms of the primary endpoint (defined as either a 25% relative increase or a 0.5 mg/dl absolute increase of serum creatinine). Reductions also were seen by Kidney Disease Improving Global Outcomes (KDIGO) classification, but only significantly so in stage 3. OR = odds ratio.

the use of RA was significantly associated with a reduced occurrence of AKI compared with FA. Both components of the primary endpoint (i.e., an absolute >0.5 mg/dl or a relative >25% increase in sCR) were reduced with RA, and fewer patients in the RA group underwent dialysis, even if this difference did not reach statistical significance. These findings were consistent across pre-defined patient subgroups. However, there was quantitative positive interaction testing in patients at the highest risk for AKI, such as those with reduced eGFR, advanced Killip class, or high Mehran score, in whom a greater benefit of RA versus FA was observed. In the subpopulation of patients who entered the antithrombin portion of the study, we also noted a significant interaction with the type of allocated anticoagulant at the time of PCI. A greater than average treatment effect was observed in patients who received unfractionated heparin, but no apparent effect was seen in those allocated to bivalirudin.

Sensitivity analyses showed consistent results among patients in whom access was made as randomly allocated and in patients who underwent PCI during their index hospitalization. The

TABLE 3 Acute Kidney Injury

	Randomized to Radial Access	Randomized to Femoral Access	Odds Ratio (95% CI)	p Value
All patients receiving an angiography and/or PCI	4,109	4,101		
AKI according to primary endpoint definition	634 (15.43)	712 (17.36)	0.87 (0.77–0.98)	0.0181
AKI 25% relative increase	633 (15.41)	710 (17.31)	0.87 (0.77–0.98)	0.0195
AKI 0.5 absolute increase	175 (4.26)	223 (5.44)	0.77 (0.63–0.95)	0.0131
After index procedure only	605 (14.72)	670 (16.34)	0.88 (0.78–1.00)	0.0436
AKI 25% relative increase	603 (14.68)	668 (16.29)	0.88 (0.78–1.00)	0.0434
AKI 0.5 absolute increase	170 (4.14)	217 (5.29)	0.77 (0.63–0.95)	0.0138
After staged procedure only	75 (1.83)	95 (2.32)	0.78 (0.58–1.06)	0.1189
AKI 25% relative increase	72 (1.75)	95 (2.32)	0.75 (0.55–1.02)	0.0711
AKI 0.5 absolute increase	19 (0.46)	25 (0.61)	0.76 (0.42–1.38)	0.3625
AKI according to the KDIGO classification	213 (5.18)	248 (6.05)	0.85 (0.70–1.03)	0.0900
Stage 1	140 (3.41)	153 (3.73)	0.91 (0.72–1.15)	0.4295
Stage 2	45 (1.10)	49 (1.19)	0.92 (0.61–1.38)	0.6713
Stage 3	28 (0.68)	46 (1.12)	0.60 (0.38–0.97)	0.0367
Dialysis during hospitalization	6 (0.15)	14 (0.34)	0.43 (0.16–1.11)	0.0814
Patients without crossover during PCI	3,765	3,840		
AKI according to primary endpoint definition	538 (14.29)	641 (16.69)	0.83 (0.73–0.94)	0.0038
AKI 25% relative increase	538 (14.29)	639 (16.64)	0.84 (0.74–0.95)	0.0046
AKI 0.5 absolute increase	140 (3.72)	198 (5.16)	0.71 (0.57–0.89)	0.0025
Dialysis during hospitalization	2 (0.05)	13 (0.34)	0.16 (0.04–0.69)	0.0146
Only patients who underwent index PCI*	3,317	3,299		
AKI according to primary endpoint definition	530 (15.98)	598 (18.13)	0.86 (0.76–0.98)	0.0202
AKI 25% relative increase	529 (15.95)	596 (18.07)	0.86 (0.76–0.98)	0.0219
AKI 0.5 absolute increase	145 (4.37)	184 (5.58)	0.77 (0.62–0.97)	0.0244
Dialysis during hospitalization	3 (0.09)	10 (0.30)	0.30 (0.08–1.08)	0.0659

Values are n or n (%) unless otherwise indicated. *Excluding patients who underwent angiography only.

AKI = acute kidney injury; CI = confidence interval; KDIGO = Kidney Disease Improving Global Outcomes; PCI = percutaneous coronary intervention.

occurrence of AKI was further assessed according to KDIGO criteria (17), which revealed a much lower prevalence of AKI and a consistent 15% risk reduction in favor of RA, even if the treatment effect did not reach statistical significance. Notably, when analyzed by AKI severity, rates of stage 1 or 2 AKI were similar regardless of access site, but stage 3 AKI was reduced by 40% with RA compared with FA.

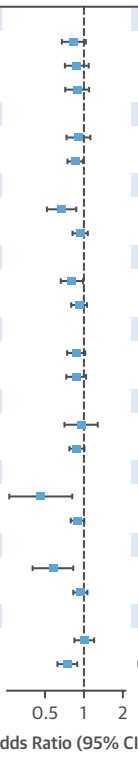
No randomized controlled trial of RA versus FA has assessed whether the access site might affect the risk of AKI. Therefore, AKI-MATRIX was the first prespecified analysis of a large randomized controlled trial that prospectively analyzed the occurrence of AKI in relation to RA or FA.

The British Columbia Cardiac and Renal Registries reported a reduced risk for chronic kidney disease within 6 months after catheterization among patients who underwent RA (18). However, the occurrence of AKI during hospitalization was not collected. A propensity-matched analysis of 17,714 patients who received urgent or elective PCI from the Blue Cross Blue Shield of Michigan Cardiovascular Consortium database showed a 24% reduction in the risk of AKI, defined as an absolute increase in sCr of >0.5 mg/dl in patients who underwent RA (7). A single-center registry also showed a reduced risk of AKI (defined as sCr >0.5 mg/dl or a 50% increase of sCr) with RA compared with FA, but the access site was no longer associated with increased risk of AKI after propensity matching (OR: 1.48; 95% CI: 0.72 to 3.04; p = 0.286) (19). Finally, in a STEMI population that underwent primary PCI at high-volume urban centers, FA compared with RA was associated with a 56% greater adjusted risk of AKI, which occurred in 12.7% of the patients based on an increase in sCr >0.5 mg/dl or >25% (6).

The prevalence of AKI varies largely across studies based on the definition and the population investigated (1,2). However, there is accumulating evidence indicating that small increments in sCR are associated, in a variety of settings, with adverse outcomes that manifest in short-term morbidity and mortality as well as in longer term outcomes, including 1-year mortality (1,2,20). Because no effective therapeutic

FIGURE 1 Primary Endpoint: Subgroup Analysis

AKI during index hospitalization	Randomized to Radial Access	Randomized to Femoral Access	Odds Ratio (95% CI)	p Value	p Value for interaction	Numbers needed to treat to prevent 1 AKI
Center's proportion of radial PCI					0.70*	
Low (14.9-64.4%)	181/1391	225/1473	0.83 (0.67-1.02)	0.083		45 (21 to ∞)
Intermediate (65.4-79.0%)	230/1433	251/1400	0.88 (0.72-1.07)	0.18		54 (22 to ∞)
High (80.0-98.0%)	223/1285	236/1228	0.88 (0.72-1.08)	0.23		54 (21 to ∞)
Diabetes					0.68	
Yes	191/936	203/917	0.90 (0.72-1.13)	0.36		58 (19 to ∞)
No	443/3173	509/3184	0.85 (0.74-0.98)	0.024		50 (27 to 369)
Estimated glomerular filtration rate (eGFR)					0.027	
<60 ml/min/1.73 m^2	126/688	174/695	0.67 (0.52-0.87)	0.0025		15 (10 to 42)
≥60 ml/min/1.73 m^2	508/3406	538/3396	0.93 (0.82-1.06)	0.29		108 (38 to ∞)
Age					0.31	
≥75 years	239/1040	291/1076	0.80 (0.66-0.98)	0.031		25 (13 to 265)
<75 years	395/3069	421/3025	0.91 (0.79-1.06)	0.23		96 (37 to ∞)
Clinical presentation					0.98	
STEMI	354/1977	397/1975	0.87 (0.74-1.02)	0.079		46 (22 to ∞)
NSTEACS	280/2132	315/2126	0.87 (0.73-1.03)	0.11		60 (27 to ∞)
LVEF under 40%					0.65	
<40%	122/397	135/423	0.95 (0.70-1.27)	0.71		85 (14 to ∞)
≥40%	500/3566	552/3522	0.88 (0.77-1.00)	0.051		61 (31 to ∞)
Killip class					0.026	
Killip class III or IV	34/129	44/101	0.46 (0.27-0.81)	0.0066		6 (4 to 21)
Killip class I or II	600/3980	668/4000	0.89 (0.79-1.00)	0.047		62 (31 to 4767)
Mehran score					0.013	
>10 points	79/274	111/269	0.58 (0.40-0.82)	0.0025		9 (5 to 23)
≤10 points	550/3754	587/3774	0.93 (0.82-1.06)	0.27		111 (40 to ∞)
Randomization to bivalirudin					0.018	
Bivalirudin	300/1770	301/1780	1.00 (0.84-1.20)	0.98		-2561 (42 to ∞)
UFH	271/1771	345/1764	0.74 (0.62-0.89)	0.00087		24 (15 to 57)



*P value for trend across ordered groups

Radial access reduced incidence of acute kidney injury (AKI) across analyzed subgroups. CI = confidence interval; LVEF = left ventricular ejection fraction; NSTEACS = non–ST-segment elevation acute coronary syndrome; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction; UFH = unfractionated heparin.

measure, apart from renal replacement therapy, exists in patients with AKI, there is a growing awareness in the medical community of the need to implement preventive measures in patients at greater risk.

Hydration with isotonic saline remains the only Class I recommended intervention in patients at medium to high risk who are undergoing invasive management (15). Yet, many patients with ACS, especially those with ongoing myocardial ischemia, are not eligible for this preventive treatment due to the need to expedite catheterization. Therefore, contrast minimization during intervention remains the most important preventive intervention in these patients. Importantly, we also confirmed that some drug categories might help prevent (statins) or increase the risk of AKI (renin-angiotensin inhibitors and diuretics) (Online Table 1), as previously shown (21,22).

In a seminal paper, Nikolsky et al. (23) were the first to investigate the association between baseline hematocrit and AKI, which occurred in 13.9% of 6,773 consecutive patients treated with PCI, based on an increase of ≥25% or ≥0.5 mg/dl in pre-procedure sCr. By multivariate analysis, lower baseline hematocrit was associated with contrast-induced nephropathy (CIN); each 3% decrease in baseline hematocrit resulted in a significant increase in the odds of CIN in patients with and without chronic kidney disease (11% and 23%, respectively) (23). When introduced into the multivariate model, change in hematocrit also showed a significant association with CIN after coronary intervention. Interestingly, a procedure-related drop in hematocrit was an independent prognostic determinant of CIN, regardless of baseline hematocrit (23). More recently, Ohno et al. (24) confirmed that patients who experienced

peri-procedural bleeding had a higher incidence of AKI, the severity of which, in turn, correlated closely with the severity of bleeding. The mechanism by which the drop in hemoglobin causes AKI is likely the impairment in renal perfusion due to significant blood loss, regardless of changes in systemic blood pressure (23,24). Blood transfusion was also identified as a risk factor for AKI in cardiac surgery (25) and in transcatheter aortic valve replacement. Moreover, in patients with ACS who underwent PCI within the CathPCI Registry (n = 1,756,864), blood transfusion was strongly associated with AKI, which was defined as an increase in sCr post-PCI of ≥0.5 mg/dl or ≥25% during hospitalization compared with baseline values (26).

Our present findings expanded on previous observations by showing that a bleeding minimization strategy, such as RA as opposed to FA, reduced the risk of AKI, with a greater effect observed in patients at higher risk for AKI. The mechanisms by which RA reduced the incidence of AKI might be due to a reduction of bleeding events (7), by a reduction in embolization in the renal circulation (9,10), or by a combination of both (11). When access site bleeding, hemoglobin drop, need for transfusion, and/or randomly allocated access site were simultaneously entered into the model, bleeding complications per se and their possible consequences (i.e., hemoglobin drop and blood transfusion) remained strongly associated with AKI. However, only a trend remained for the association between RA and AKI. Hence, our results confirmed previous observations that access site bleeding is associated with AKI, and suggested that RA, by minimizing those, mitigated the risk of AKI.

Unlike in the parent trial (12), the proportion of PCI undertaken with RA among participating centers did not emerge as an effect modifier for the study endpoint. This finding suggested that kidney protection was conferred by RA at any stage of the learning curve for transradial procedures. This observation indirectly confirmed the importance of bleeding prevention as a possible mechanism through which RA reduces the risk of AKI; operator proficiency significantly affected the occurrence of major adverse cardiovascular events, but failed to affect bleeding endpoints in our study (12). Conversely, RA provided greater benefits for AKI prevention in patients at higher risk of AKI and in those randomly assigned to unfractionated heparin compared with bivalirudin. This latter finding should be interpreted with caution because it was based on the subpopulation randomized to receive the 2 tested parenteral anticoagulants, and no interaction was observed between access site and type of antithrombin in the MATRIX-Access or antithrombin type programs with respect to both co-primary endpoints or bleeding events.

It remains unclear as to whether RA, by avoiding direct passage of catheters in proximity to renal arteries, might also contribute to lower risk of AKI through a reduction and/or avoidance of direct embolization into the renal circulation. Coronary angiography is the most common procedure to cause embolisms (27). Estimates of the incidence of cholesterol embolization syndrome (CES) after vascular procedures ranged from 0.15% in clinical studies to 25% to 30% in pathological series (27). Clinical studies probably underestimated the incidence because only a minority of patients could be clinically recognized. Therefore, despite the importance of CES as a complication of percutaneous diagnostic and interventional procedures, its relative contribution remains uncertain to the overall occurrence of AKI in patients who have undergone vascular cardiac catheterization and who received contrast media.

In light of our findings, future studies should evaluate whether the use of RA in patients with

TABLE 4 Associations of AKI During Index Hospitalization*

	Odds Ratio (95% CI)	p Value
Model 1		
Randomized to radial access	0.87 (0.77–0.98)	0.0217
Components of the Mehran score†		
Hypotension‡	0.87 (0.44–1.72)	0.6957
Use of intra-aortic balloon pump	2.96 (2.13–4.11)	<0.0001
Killip class III or IV	1.83 (1.35–2.50)	0.0001
Age >75 yrs	1.99 (1.75–2.27)	<0.0001
Anemia§	1.20 (1.04–1.39)	0.0135
Diabetes	1.33 (1.16–1.52)	<0.0001
Contrast media volume, per 100 ml	1.34 (1.26–1.43)	<0.0001
Creatinine >1.5 mg/dl	1.15 (0.76–1.72)	0.5108
Model 2		
Randomized to radial access	0.89 (0.80–1.01)	0.0647
Bleeding BARC 2, 3, or 5 related to access site	2.19 (1.66–2.89)	<0.0001
Model 3		
Randomized to radial access	0.90 (0.80–1.01)	0.0758
Bleeding BARC 2, 3, or 5 related to access site	1.81 (1.36–2.40)	<0.0001
Hemoglobin nadir <9 g/dl	3.35 (2.71–4.13)	<0.0001
Model 4		
Randomized to radial access	0.90 (0.80–1.02)	0.0868
Bleeding BARC 2, 3, or 5 related to access site	1.68 (1.25–2.25)	0.0005
Hemoglobin nadir <9 g/dl	2.81 (2.23–3.53)	<0.0001
Blood transfusion	2.57 (1.63–4.03)	<0.0001

Number of included patients = 8,210. *With Mehran score, bleeding, and measures of bleeding severity. †Range 0 to 30. ‡Systolic blood pressure <80 mm Hg. §<12 g/dl for women and <13 g/dl for men.
BARC = Bleeding Academic Research Consortium; CI = confidence interval.

advanced chronic kidney disease affects or prevents a conduit for fistula for dialysis.

STUDY LIMITATIONS. Most centers participating in the MATRIX program were highly experienced in RA; similar outcomes might not be applicable in centers that perform lower volumes of RA. Although reported subgroups were pre-specified in the statistical analysis plan, we did not adjust for multiple comparisons, increasing the risk of a type I error. We were not able to adjust the results for the intensity of either periprocedural hydration or type of contrast media used, because these 2 variables were not collected in the data set. However, the unrestricted use of hydration to expand intravascular fluid in clinical practice is the simplest and cheapest intervention aimed at preventing AKI and is unlikely to have influenced the effect of RA (28). Patients with STEMI, who are routinely referred to emergent intervention without hydration, derived consistent benefit in terms of lower AKI from RA. Time and date of sCr peak during hospitalization and sCr values after discharge were not collected. Although blood loss minimization, also based on our multivariable model, appeared to be the most likely explanation for our findings, it remains possible that use of RA as opposed to FA decreased the occurrence of CES. Although with low sensitivity, presence of eosinophilia could raise the level of suspicion for CES or occurrence of extrarenal emboli, this was not systematically collected in the study case report form. Hence, the mechanisms through which RA mitigated the risk of AKI remain unclear.

CONCLUSIONS

Our results showed that in a broad population of patients with ACS who underwent invasive management, the use of RA versus FA was associated with a reduced incidence of post-procedural AKI. This analysis lent further support to the concept that RA should be prioritized over FA in ACS patients undergoing invasive management.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: In patients with acute coronary syndromes undergoing invasive management, radial arterial access is associated with a lower risk of acute kidney injury than femoral access.

TRANSLATIONAL OUTLOOK: Additional research is needed to assess whether this advantage of radial over femoral access applies across specific subsets of patients, such as the elderly or those with cardiogenic shock, coronary bypass grafts, or chronic kidney disease, and whether concurrent medication therapies modify the difference in renal outcomes.

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KEY WORDS bleeding, coronary intervention, creatinine, estimated glomerular filtration rate, ST-segment elevation

APPENDIX For supplemental information regarding the MATRIX trial as well as supplemental figures and table, please see the online version of this article.

Part 1

Trade-off for ischemia and bleeding during and immediately after percutaneous coronary interventions:

Stenting strategies to optimize clinical outcomes

Treatment strategies for coronary in-stent restenosis: systematic review and hierarchical Bayesian network meta-analysis of 24 randomised trials and 4880 patients

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ABSTRACT

STUDY QUESTION

What is the most safe and effective interventional treatment for coronary in-stent restenosis?

METHODS

In a hierarchical Bayesian network meta-analysis, PubMed, Embase, Scopus, Cochrane Library, Web of Science, ScienceDirect, and major scientific websites were screened up to 10 August 2015. Randomised controlled trials of patients with any type of coronary in-stent restenosis (either of bare metal stents or drug eluting stents; and either first or recurrent instances) were included. Trials including multiple treatments at the same time in the same group or comparing variants of the same intervention were excluded. Primary endpoints were target lesion revascularisation and late lumen loss, both at six to 12 months. The main analysis was complemented by network subanalyses, standard pairwise comparisons, and subgroup and sensitivity analyses.

STUDY ANSWER AND LIMITATIONS

Twenty four trials (4880 patients), including seven interventional treatments, were identified. Compared with plain balloons, bare metal stents, brachytherapy, rotational atherectomy, and cutting balloons, drug coated balloons and drug eluting stents were associated with a reduced risk of target lesion revascularisation and major adverse cardiac events, and with reduced late lumen loss. Treatment ranking indicated that drug eluting stents had the highest probability (61.4%) of being the most effective for target lesion vascularisation; drug coated balloons were similarly indicated as the most effective treatment for late lumen loss (probability 70.3%). The comparative efficacy of drug coated balloons and drug eluting stents was similar for target lesion revascularisation (summary odds ratio 1.10, 95% credible interval 0.59 to 2.01) and late lumen loss reduction (mean difference in minimum lumen diameter 0.04 mm, 95% credible interval −0.20 to 0.10). Risks of death, myocardial infarction, and stent thrombosis were comparable across all treatments, but these analyses were limited by a low number of events. Trials had heterogeneity regarding investigation periods, baseline characteristics, and endpoint reporting, with a lack of information at long term follow-up. Direct and indirect evidence was also inconsistent for the comparison between drug eluting stents and drug coated balloons.

WHAT THIS STUDY ADDS

Compared with other currently available interventional treatments for coronary in-stent restenosis, drug coated balloons and drug eluting stents are associated with superior clinical and angiographic outcomes, with a similar comparative efficacy.

FUNDING, COMPETING INTERESTS, DATA SHARING

This study received no external funding. The authors declare no competing interests. No additional data available.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Management of patients with coronary in-stent restenosis is difficult, owing to many factors such as varying causes (aggressive neointimal proliferation, neoatherosclerosis) and the high tendency to recur

In the past 20 years, several strategies have been proposed to counteract in-stent restenosis, but randomised trials comparing different treatments have given mixed and inconclusive results

WHAT THIS STUDY ADDS

In a network meta-analysis, contemporary treatment strategies for coronary in-stent restenosis (drug coated balloons and drug eluting stents) were compared with other treatments investigated over the years

Pooled evidence suggested comparable clinical and angiographic antirestenotic efficacy for drug coated balloons and drug eluting stents; plain balloons, bare metal stents, brachytherapy, rotational atherectomy, and cutting balloons were associated with an increased risk of target lesion revascularisation and inferior angiographic results

No differences in death, myocardial infarction, and stent thrombosis were noted across all the treatments investigated

Introduction

Drug eluting stents have substantially reduced the risk of coronary in-stent restenosis and the need for target lesion revascularisation compared with bare metal stents by counteracting the exuberant neointimal proliferation that follows stent implantation.[1] However, current rates of in-stent restenosis in clinical practice remain higher than 10%.[2 3]

Management of patients with in-stent restenosis is challenging and the best therapeutic strategy remains unclear.[4] Treatment with plain balloons is technically simple and generally associated with acceptable procedural success, due to axial and longitudinal tissue extrusion and incremental stent expansion.[5] However, observational studies and randomised trials have consistently shown inferior clinical and angiographic results compared with implantation of a second drug eluting stent.[6-8] Nevertheless, plain balloon angioplasty is still used for in-stent restenosis treatment in a consistent proportion of patients.[9 10] Furthermore, in-stent implantation of drug eluting stents tends to be

restricted to a limited proportion of patients, owing to concerns related to positioning a permanent additional stent layer. Additional layers promote further endothelial growth as well as potential mechanical complications, either acutely or later on (such as fracture, malapposition, thrombosis).[4 11]

Recently, drug coated balloons have emerged as promising alternatives to drug eluting stents for in-stent restenosis, but large randomised trials comparing drug coated balloons with other therapeutic options are limited.[12-14] Other treatment options for in-stent restenosis have been used over time with heterogeneous results, including implantation of bare metal stents, vascular brachytherapy, rotational atherectomy, and cutting balloons.[4 15]

Network meta-analyses are an extension of traditional pairwise meta-analyses that enable the simultaneous pooling of data from clinical trials comparing at least two treatments and strengthen the inference on the relative efficacy of each treatment by including both direct and indirect information.[16 17] The objective of this systematic review and hierarchical Bayesian network meta-analysis was to pool data from randomised trials comparing at least two interventional treatments for coronary in-stent restenosis and to identify which strategy is eventually the most effective and safe.

Methods

Data sources and study strategy

This meta-analysis was performed in agreement with the PRISMA (preferred reporting items for systematic reviews and meta-analyses) statement, the PRISMA network meta-analysis extension statement, and the Cochrane Collaboration recommendations (web appendix, PRISMA checklist).[18-20] Randomised trials comparing at least two different treatments were searched in PubMed, Embase, Scopus, Cochrane Library, Web of Science, and ScienceDirect electronic databases, as well as major scientific websites (www.tctmd.com, www.pcronline.com, www.clinicaltrials.gov, www.clinicaltrialresults.org, www.acc.org, www.heart.org, www.medscape.com). Abstracts and presentations from major cardiovascular meetings were considered. The electronic search process was integrated by tangential exploration of bibliography of relevant reviews on in-stent restenosis and major interventional cardiology books.

The web appendix reports the combination of subject headings used for studies identification. No language restriction or filters were imposed. The search was performed from the date of databases' inception to 10 August 2015.

Selection criteria and study design

Inclusion criteria were the following: randomised controlled trials of patients with coronary in-stent restenosis; patients of any age, sex, ischaemic risk profile, and clinical presentation; either in-stent restenosis of a previously implanted bare metal stent (BMS-ISR) or in-stent restenosis of a previously implanted drug eluting stent (DES-ISR); and either first or recurrent instances of in-stent restenosis. Exclusion criteria were: non-interventional treatment for in-stent restenosis; comparison between variants of the same type of device (same treatment group); and investigations including combinations of multiple treatments in the same group at the same time, except for the use of plain balloons or cutting balloons for lesion preparation before other treatments (that is, brachytherapy or stent implantation).

Coronary in-stent restenosis is classically defined as the angiographic detection of a recurrent stenosis with diameter greater than 50% at the stent segment or its 5 mm adjacent segments (in-segment restenosis). However, some trials have considered only the segment of the implanted stent, without inclusion of proximal and distal edges (in-lesion restenosis).[21] In this meta-analysis, we prioritised events related to in-segment restenosis; if they were not available, we included events related to in-lesion restenosis-related events.

The primary clinical endpoint was target lesion revascularisation at six to 12 months, defined as any repeated revascularisation involving the target lesion, both percutaneous and surgical; if target lesion revascularisation was not available, target vessel revascularisation was pooled.[22] The primary angiographic endpoint was late lumen loss at six to 12 months, defined as the difference between the minimum lumen diameter after the procedure and at follow-up, as evaluated by quantitative coronary angiography.[23] Late lumen loss was designated as a coprimary endpoint, because this angiographic measure is known to be consistent and reliable in discriminating the propensity for restenosis.[24]

Secondary clinical endpoints were death, myocardial infarction, stent thrombosis, and combined major adverse cardiac events including death, myocardial infarction, target lesion revascularisation, and stent thrombosis.[22] The definition of major adverse cardiac events was modified retrospectively because of the observed heterogeneity across the trials, allowing for the inclusion of target vessel revascularisation instead of target lesion revascularisation. Very dissimilar definitions, however, were not allowed, leading to the exclusion of the corresponding trial from the meta-analysis for major adverse cardiac events. Secondary angiographic endpoints were minimum lumen diameter and binary restenosis at six to 12 months.[23]

Search and screening of retrieved records at the title and abstract level were independently performed by three reviewers (DG, PA, GG). The same three reviewers assessed full text eligibility of the identified trials and discrepancies were resolved by consensus under the supervision of other two investigators (PC, DC). The validity of the meta-analysis was assessed by qualitative appraisal of study designs and methods before statistical analyses were performed, with the use of the risk of bias tool recommended by the Cochrane Collaboration.[20] Data from original reports were collected into specific electronic spreadsheets.

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Patient involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in the design and implementation of the study. There are no plans to involve patients in dissemination.

Statistical analyses

Data used in this meta-analysis were intention to treat. Most of the included trials did not report as treated results. A hierarchical Bayesian network meta-analysis was carried out for each endpoint using random effects consistency models.[25-27] Briefly, in a network meta-analysis, each study provides an estimate of the study specific treatment effects, which are assumed to be similar and exchangeable (that is, transitivity), deriving from a normal common distribution.[28] Each relative treatment effect estimate results from the combination of the direct evidence between the two treatments and the indirect evidence deriving from the network meta-analysis, which are assumed to be coherent.[26 29] When a direct connection between two treatments is not available, the effect estimates derives only from indirect evidence.[26 29]

We used random effects models because they are probably the most appropriate and conservative methodology to account for between-trial heterogeneity within each comparison.[29 30] Models were computed with Markov chain Monte Carlo simulations, using three chains with over-dispersed initial values, with Gibbs sampling based on 100 000 iterations after a burn-in phase of 50 000 iterations. Non-informative or vague priors for the overall mean effect ($\theta \sim N(0, 100^2)$) and the between-study standard deviation ($\tau \sim$ uniform (0, 2)) were given.[27 29 31] We evaluated convergence according to Brooks-Gelman-Rubin.[32]

The information was imputed according to the arm based approach, and modelled by use of binomial data (binomial likelihood, logit link) or sample means (normal likelihood, identity link) with normal distribution, according to the specific type of outcome explored.[17 27] We computed posterior mean effect, odds ratio or mean difference, where appropriate, and 95% credible intervals for each comparison. The included treatments were ranked to define the probability associated to each one being the best interventional strategy when significant variations in treatment effect were observed.[30 33]

We assessed inconsistency by comparing statistics for the deviance information criterion in fitted consistency and inconsistency models, and by contrasting direct evidence with indirect evidence from the entire network on each node (node-split).[25-27] A Bayesian P value was calculated to estimate the measure of the conflict between direct and indirect evidence by counting the proportion of times the direct treatment effect exceeded the indirect treatment effect.[26] The estimates of Bayesian pairwise comparisons were also calculated with results complemented by standard frequentist DerSimonian-Laird meta-analyses with inverse variance weighting.[34] In the frequentist framework, the pooled estimates were quantified as summary odds ratios or mean differences, where appropriate, and corresponding 95% confidence intervals.

The amount of the observed variance reflecting real differences in the effect size across the included trials was graded with the Q test and I^2 statistic with values representing mild, moderate, and severe heterogeneity (<25%, 25-75%, and >75%, respectively).[35] The variance of the true effect size across the included trials (τ^2) was calculated.[36] We assessed publication bias and small study effect by visual inspection of comparison adjusted and contours enhanced funnel plots complemented by Peters' and Egger's tests, where appropriate.[36-40]

We did subgroup analyses according to the type of restenotic stent (BMS-ISR or DES-ISR), and the generation of drug eluting stent implanted for in-stent restenosis treatment (first or second generation). As another sensitivity analysis, we removed each trial from the others when results suggested the mean effect to be potentially driven by individual studies.[36] All analyses were performed using R (version 3.1.1), Stata (version 12.1), and RevMan (version 5.3).

Results

Systematic review and qualitative assessment

A total of 24 trials (n=4880) and seven interventional treatments (plain balloon, drug coated balloon, drug eluting stent, bare metal stent, brachytherapy, rotational atherectomy, and cutting balloon) were included. Fig 1 shows each phase of the screening process, and fig 2 shows the weighted network. The web appendix includes the list of acronyms and identification numbers (www.clinicaltrials.gov) of the trials included in the analysis. Potential sources of bias in trial design and investigational methods graded according to the

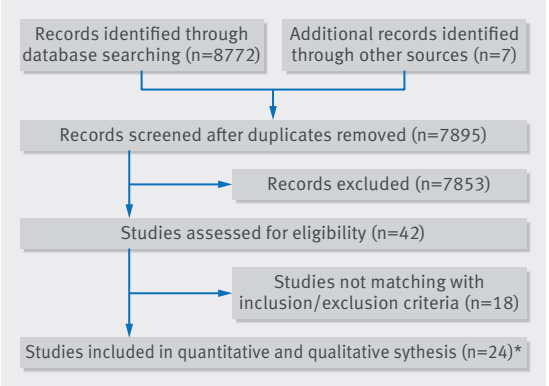

Fig 1 | Systematic search and screening process of trials. *The study by Ragosta and colleagues had two cohorts with independent randomisation processes that were separately included in the meta-analysis. Similarly, the study by Song and colleagues had two cohorts with independent randomisation processes, but only the first (cutting balloon *v* sirolimus eluting stent) was included in this meta-analysis because the second (sirolimus eluting stent *v* everolimus eluting stent) compared two variants of the same treatment. Finally, we considered the PACCOCATH ISR I and II trials together because the second study is the cohorts' extension of the first one

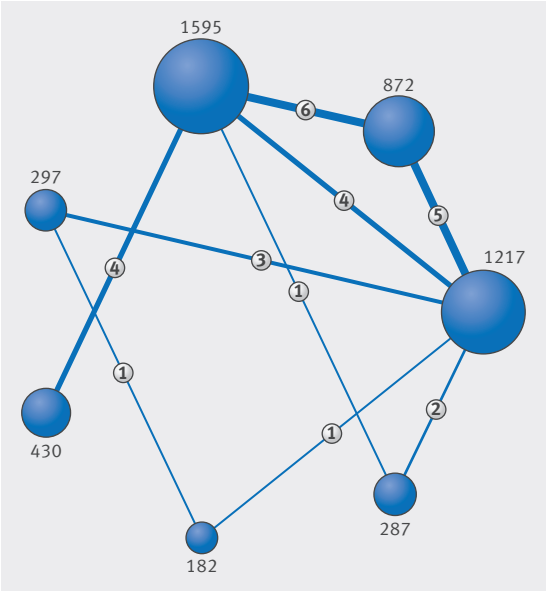

Fig 2 | Network of interventional treatments included in meta-analysis. A=plain balloon; B=drug coated balloon; C=drug eluting stent; D=bare metal stent; E=brachytherapy; F=rotational atherectomy; G=cutting balloon. Numbers on connecting lines between each intervention=head to head comparisons; numbers next to specific interventions=patients receiving a treatment

Cochrane's Collaboration risk of bias tool (web fig 1) suggested most of the trials to be open label and therefore potentially affected by performance bias.[20]

Table 1 describes key characteristics of the included studies (design, samples size, treatments, in-stent restenosis definition, follow-up length, and original endpoints). Almost all trials were powered for angiographic endpoints, mainly late lumen loss, and scheduled for angiographic surveillance. Two trials did not plan mid-term angiographic follow-up, and were excluded from all meta-analyses of angiographic endpoints. In about 70% of trials, angiographic follow-up was performed starting from six months after procedure, while 62.5% of trials had planned clinical follow-up at 12 months. Almost 60% of trials included only patients with BMS-ISR, nearly 30% included only patients with DES-ISR, while two trials included both stent types of in-stent restenosis.

Table 2 summarises the clinical and angiographic characteristics of patients enrolled in each trial. The included participants had a mean age of 64 years, were prevalently male (76%), and underwent repeated percutaneous coronary intervention mainly for silent ischaemia/stable angina or unstable angina. Prevalence of diabetes was highly variable across trials (14-62%). Web table 1 reports all the inclusion and exclusion criteria of each trial.

Bayesian network meta-analyses

With respect to the primary clinical endpoint (fig 3), use of drug coated balloons or drug eluting stents markedly reduced the risk of target lesion revascularisation compared with all the other treatments. When compared directly, drug coated balloons and drug eluting stents had similar antirestenotic efficacy (summary odds ratio 1.10, 95% credible interval 0.59 to 2.01). Treatment ranking reflected the consistent reduction in the risk of target lesion revascularisation associated with drug coated balloons or drug eluting stents over the other strategies, but also indicated that drug eluting stents had a higher probability (61.4%) of being the best therapy. Rotational atherectomy was associated with the highest risk of target lesion revascularisation compared with the other treatments.

With respect to the primary angiographic endpoint (fig 4), use of a drug coated balloon or drug eluting stent were the most effective treatments, while use of a bare metal stent showed the highest mean difference in late lumen loss, followed by rotational atherectomy. Drug coated balloons emerged as the best therapy in treatment ranking (probability of 70.3%), but the extent of the late lumen loss reduction compared with drug eluting stents was marginal (mean difference −0.04 mm, 95% credible interval −0.20 to 0.10).

Risk of major adverse cardiac events was consistently reduced with use of drug coated balloons or drug eluting stents, compared with all the other treatments (fig 5). Rotational atherectomy therapy led to an increased risk also when compared with poorly effective treatments such as brachytherapy and bare metal stent. The endpoint of major adverse cardiac events was mainly driven by target lesion revascularisation, since no remarkable differences across treatment strategies were noted in terms of death and myocardial infarction (fig 6). However, the incidences of death and myocardial infarction were overall extremely low and conclusions about these endpoints remain limited, especially for treatment comparisons supported by single or few trials. The angiographic superiority of drug coated balloons or drug eluting stents over the other treatments was also confirmed by evaluation of the angiographic secondary endpoints of minimum lumen diameter and binary restenosis (web fig 2). In particular, patients treated with a drug coated balloon or drug eluting stent achieved a higher minimum lumen diameter at follow-up than did the other treatment strategies, and the risk of binary restenosis generally followed the distribution observed for target lesion revascularisation.

All models converged adequately. Heterogeneity (global I^2) was moderate for target lesion revascularisation (43.5%), high for late lumen loss (95.3%), and low to moderate for secondary endpoints (major adverse cardiac events=8.5%, death=0%, myocardial infarction=11.8%, minimum lumen diameter=45.4%, binary restenosis=59.4%). Model fitting was compared by use of the deviance information criterion and shown to be similar. The node-split in the analyses for target lesion revascularisation and late lumen loss showed a significant inconsistency in the comparison of drug coated balloons versus drug eluting stents. However, the node-split for the secondary endpoint analyses showed significant inconsistency between drug coated balloons and drug eluting stents only for myocardial infarction.

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Table 1 | Main characteristics of included trials

Study*	Design and location	Treatments (sample size)	In-stent restenosis		Follow-up	Primary endpoint
			Definition	Stent type		
ARTIST	1:1 randomisation, open label, multicentre (n=24), Europe	PB *v* ROTA (148 *v* 152)	>70%	BMS	Angiographic, IVUS (n=86), and clinical: 6 months	MLD
RESCUT	1:1 randomisation, open label, multicentre (n=23), Europe	PB *v* CUT (214 *v* 214)	>50%	BMS	Angiographic and clinical: 7 months	BR
RIBS	1:1 Randomisation, open label, multicentre (n=24), Spain/Portugal	PB *v* BMS (226 *v* 224)	>50%	BMS	Angiographic: 6 months; clinical: 12 months	BR
Ragosta et al	1:1 Randomisation, open label, single centre, United States	Cohort 1: PB *v* BMS (29 *v* 29); cohort 2: BMS *v* ROTA (25 *v* 30)	n/a	BMS	Clinical: 9 months	MACE (CD, MI, or TVR), cohort 1 *v* 2
Montorsi et al	1:1 randomisation, open label, single centre, Italy	PB *v* CUT (25 *v* 25)	>50%	BMS	Angiographic and IVUS: 24 h; clinical: 6 months	n/a
ISAR DESIRE	1:1:1 randomisation, open label, two centres, Germany	PB *v* SES *v* PES (100 *v* 100 *v* 100)	≥50%	BMS	Angiographic: 6/8 months; clinical: 12 months	BR
Alfonso et al	1:1 randomisation, open label, single centre, Spain	PB *v* BMS (20 *v* 20)	>50%	BMS	Angiographic: 6 months; clinical: 12 months	Early lumen loss
RIBS II	1:1 randomisation, open label, multicentre (n=8), Spain	PB *v* SES (74 *v* 76)	>50%	BMS	Angiographic and IVUS (n=82): 9 months; clinical: 12 months	BR
SISR	2:1 randomisation, open label, multicentre (n=26), United States	SES *v* BT (259 *v* 125)	>50%	BMS	Angiographic and IVUS (n=100): 6 months; clinical: 9 months	TVF (CD, MI, or TVR)
TAXUS V ISR	1:1 randomisation, open label, multicentre (n=37), United States	PES *v* BT (195 *v* 201)	n/a	BMS	Angiographic and clinical: 9 months	Ischaemia drivenTVR
INDEED	1:1 randomisation, open label, single centre, South Korea	SES *v* BT (65 *v* 64)	>50%	BMS	Angiographic and IVUS (n=79): 6 months; clinical: 12 months	LLL
PEPCAD II	1:1 randomisation, open label, multicentre (n=10), Germany	DCB *v* DES (66 *v* 65)	≥70%	BMS	Angiographic: 6 months; clinical: 12 months	LLL
Habara et al (2011)	1:1 randomisation, single blind, single centre, Japan	PB *v* DCB (25 *v* 25)	≥50%	DES	Angiographic and clinical: 6 months	LLL
Wiemer et al	1:1 randomisation, open label, two centres, Germany	SES *v* ROTA (44 *v* 47)	≥50%	n/a	Angiographic and IVUS (n=86): 6 months; clinical: 12 months	Neointima hyperplasia (%)
PACCOCATH ISR I/II	1:1 randomisation, double blind, multicentre (n=5), Germany	PB *v* DCB (54 *v* 54)	≥70%	BMS (96%) DES (4%)	Angiographic: 6/9 months; clinical: 12 months	LLL
PEPCAD DES	1:2 randomisation, single blind, multicentre (n=6), Germany	PB *v* DCB (38 *v* 72)	≥70% or ≥50% and ischaemia	DES	Angiographic and clinical: 6 months	LLL
Song et al (cohort 1)	1:1 randomisation, open label, multicentre (n=7), South Korea	SES *v* DCB (48 *v* 48)	≥50%	DES	Angiographic: 9 months; clinical: 12 months	LLL
CRISTAL	1:2 randomisation, open label, multicentre (n=34), France	PB *v* SES (61 *v* 136)	≥50%	DES	Angiographic: 9/12 months; clinical: 12 months	LLL
ISAR DESIRE 3	1:1:1 randomisation, open label, three centres, Germany	PB *v* DCB *v* PES (134 *v* 137 *v* 131)	≥50%	DES	Angiographic: 6/8 months; clinical: 12 months	Stenosis diameter (%)
Habara et al (2013)	1:2 randomisation, open label, multicentre (n=13), Japan	PB *v* DCB (71 *v* 137)	≥50%	BMS (58%); DES (42%)	Angiographic: 6 months; clinical: 6 months	TVF (CD, MI, or TVR)
PEPCAD China ISR	1:1 randomisation, single blind, multicentre (n=17), China	DCB *v* PES (108 *v* 106)	≥70% or ≥50% and ischaemia	DES	Angiographic: 9 months; clinical: 12 months	LLL
RIBS V	1:1 randomisation, open label, multicentre (n=25), Spain	DCB *v* EES (95 *v* 94)	≥50%	BMS	Angiographic: 6/9 months; clinical: 12 months	MLD
SEDUCE	1:1 randomisation, open label, two centres, Belgium	DCB *v* EES (24 *v* 25)	>70%	BMS	Angiographic and OCT: 9 months; clinical: 12 months	Uncovered struts (%)
RIBS IV	1:1 randomisation, open label, multicentre (n=23), Spain	DCB *v* EES (154 *v* 155)	>50%	DES	Angiographic: 6/9 months; clinical: 12 months	MLD

BMS=bare metal stent; BR=binary restenosis; BT=brachytherapy; CD=cardiac death; CUT=cutting balloon; DCB=drug coated balloon; DES=drug eluting stent; EES=everolimus eluting stent; IVUS=intravascular ultrasound; LLL=late lumen loss; MACE=major adverse cardiac events; MI=myocardial infarction; MLD=minimum lumen diameter; n/a=not applicable; OCT=optical coherence tomography; PB=plain balloon; PES=paclitaxel eluting stent; ROTA=rotational atherectomy; SES=sirolimus eluting stent; TVF=target vessel failure; TVR=target vessel revascularisation.
*Web appendix includes list of acronyms and identification numbers of the included trials.

Table 2 | Clinical and angiographic characteristics

Study*	Age (years)	Male (%, n)	Diabetes (%, n)	Clinical presentation (%, n)	Pattern of in-stent restenosis (%, n)†	Length of in-stent restenosis (mm)	Baseline MLD (mm)	RVD (mm)
ARTIST	61	80.2 (239)	25.2 (75)	No MI 100 (298)	n/a	13.6	0.53	2.64
RESCUT	62	73.0 (340)	23.4 (109)	UA: 21.5 (100)	Focal: 44.6 (174); multifocal/diffuse/proliferative: 55.4 (216)	<20: 85.5 (333); >20: 14.5 (57)	0.84	2.56
RIBS	61	77.6 (349)	26.2 (118)	Silent: 7.1 (32); SA: 49.8; (224); UA: 43.1 (194)	n/a	12.9	0.68	2.85
Ragosta et al								
Cohort 1	62	67.2 (39)	15.5 (9)	n/a	Focal: 100 (58)	<10: 100 (58)‡	0.82	3.07
Cohort 2	59	61.8 (34)	40.0 (22)	n/a	Diffuse: 100 (55)	>10: 100 (55)‡	0.74	2.90
Montorsi et al	64	72.0 (36)	n/a	Silent: 26.0 (13); SA: 74.0 (37)	Focal: 80.0 (40); diffuse: 20.0 (10)	n/a	1.07	3.19
ISAR DESIRE	64	78.3 (235)	27.7 (83)	Silent/SA: 100 (300)	Focal: 56.3 (169); diffuse: 38.7 (116); proliferative: 1.7 (5); occlusive: 3.3 (10)	12.1	0.94	2.59
Alfonso et al	66	80.0 (32)	35.0 (14)	Silent: 17.5 (7); SA: 55.0 (22); UA: 27.5 (11)	Focal: 30.0 (12); diffuse: 70.0 (28)	12.4	0.96	2.55
RIBS II	64	75.3 (113)	45.3 (52)	Silent: 15.3 (23); SA: 39.3 (59); UA: 45.3 (68)	Focal: 26.7 (40); diffuse: 61.3 (92); proliferative: 12.0 (18)	16.3	0.72	2.67
SISR	63	67.4 (258)	32.0 (123)	UA: 48.3 (154)	n/a	17.0	0.82	2.63
TAXUS V ISR	63	66.2 (262)	35.1 (139)	UA: 28.0 (111)	Focal: 23.9 (94); diffuse: 53.9 (212); proliferative: 21.4 (84); occlusive: 0.8 (3)	15.3	n/a	2.65
INDEED	60	79.1 (102)	31.0 (40)	SA: 53.5 (69); UA: 46.5 (60)	Diffuse: 100 (129)	27.6	0.79	2.72
PEPCAD II	65	74.8 (98)	29.8 (39)	Silent/SA: 74.8 (98)UA: 25.2 (33)	Focal: 42.7 (56); diffuse: 35.1 (46); proliferative: 19.9 (26); occlusive: 2.3 (3)	15.6	0.76	2.84
Habara et al (2011)	69	86.0 (43)	62.0 (31)	SA: 100 (50)	Focal: 58.0 (29); diffuse: 34.0 (17); proliferative: 8.0 (4)	13.0	0.96	2.80
Wiemer et al	64	82.4 (75)	48.4 (44)	UA: 27.5 (25)	Diffuse: 86.8 (79); occlusive: 13.2 (12)	21.2	0.78	2.83
PACCOCATH ISR I/II	66	67.6 (73)	26.9 (29)	Silent/SA: 61.1 (66); UA: 38.9 (42)	Focal: 65.5 (72); diffuse: 34.5 (38)	18.5	0.67	2.94
PEPCAD DES	68	70.9 (78)	35.5 (39)	SA: 96.4 (106); UA: 3.6 (4)	Focal: 52.1 (111); diffuse: 43.7 (93); proliferative: 4.2 (9)	11.5	0.65	2.29
Song et al (cohort 1)	63	73.9 (71)	34.4 (33)	SA: 71.9 (69); ACS: 28.1 (27)	Focal: 100 (96)	8.1	0.74	3.55
CRISTAL	68	71.1 (140)	38.6 (76)	n/a	n/a	14.2	1.12	2.55
ISAR DESIRE 3	68	71.6 (288)	41.5 (167)	Silent/SA: 80.3 (323); ACS: 19.7 (79)	Focal: 66.8 (334); diffuse: 27.6 (138); proliferative: 1.4 (7); occlusive: 4.2 (21)	n/a	0.93	2.76
Habara et al (2013)	69	82.7 (171)	44.7 (93)	SA: 93.3 (194); ACS: 6.7 (14)	Focal: 52.1 (111); diffuse: 43.7 (93); proliferative: 4.2 (9)	13.1	0.85	2.51
PEPCAD China ISR	62	80.9 (174)	36.7 (79)	Silent: 14.9 (32); SA: 24.2 (52); UA: 60.9 (131)	Focal: 63.3 (140); diffuse: 19.5 (43); proliferative: 15.4 (34); occlusive: 1.8 (4)	12.8	0.86	2.69
RIBS V	66	86.8 (164)	25.9 (49)	Silent: 12.2 (25); SA: 44.5 (84); UA: 42.3 (80)	Focal: 38.1 (72); diffuse: 46.0 (87); proliferative/ occlusive: 15.9 (30)	13.7	0.98	2.64
SEDUCE	66	86.0 (43)	14.0 (7)	Silent: 16.0 (8); SA: 60.0 (30); UA: 20.0 (10); NSTEMI: 4.0 (2)	Focal: 34.0 (17); diffuse: 46.0 (23); proliferative: 18.0 (9); occlusive: 2.0 (1)	n/a	0.78	2.93
RIBS IV	66	83.2 (157)	45.6 (141)	Silent/SA: 48.5 (150); UA: 51.5 (159)	Focal: 63.4 (196); diffuse: 31.4 (97); proliferative: 5.2 (16)	10.6	0.77	2.63

Data are proportion (%) and number of participants for sex, diabetes, clinical presentation, and pattern of in-stent restenosis; data are pooled mean or median for age, length on in-stent restenosis, minimum lumen diameter (MLD), and reference vessel diameter (RVD).
ACS=acute coronary syndrome; MI=myocardial infarction; MLD=minimum lumen diameter; n/a=not applicable; NSTEMI=non-ST elevation myocardial infarction; RVD=reference vessel diameter; SA=stable angina; UA=unstable angina.
*Web appendix includes list of acronyms and identification numbers of included trials.
†Mehran classification.[21]

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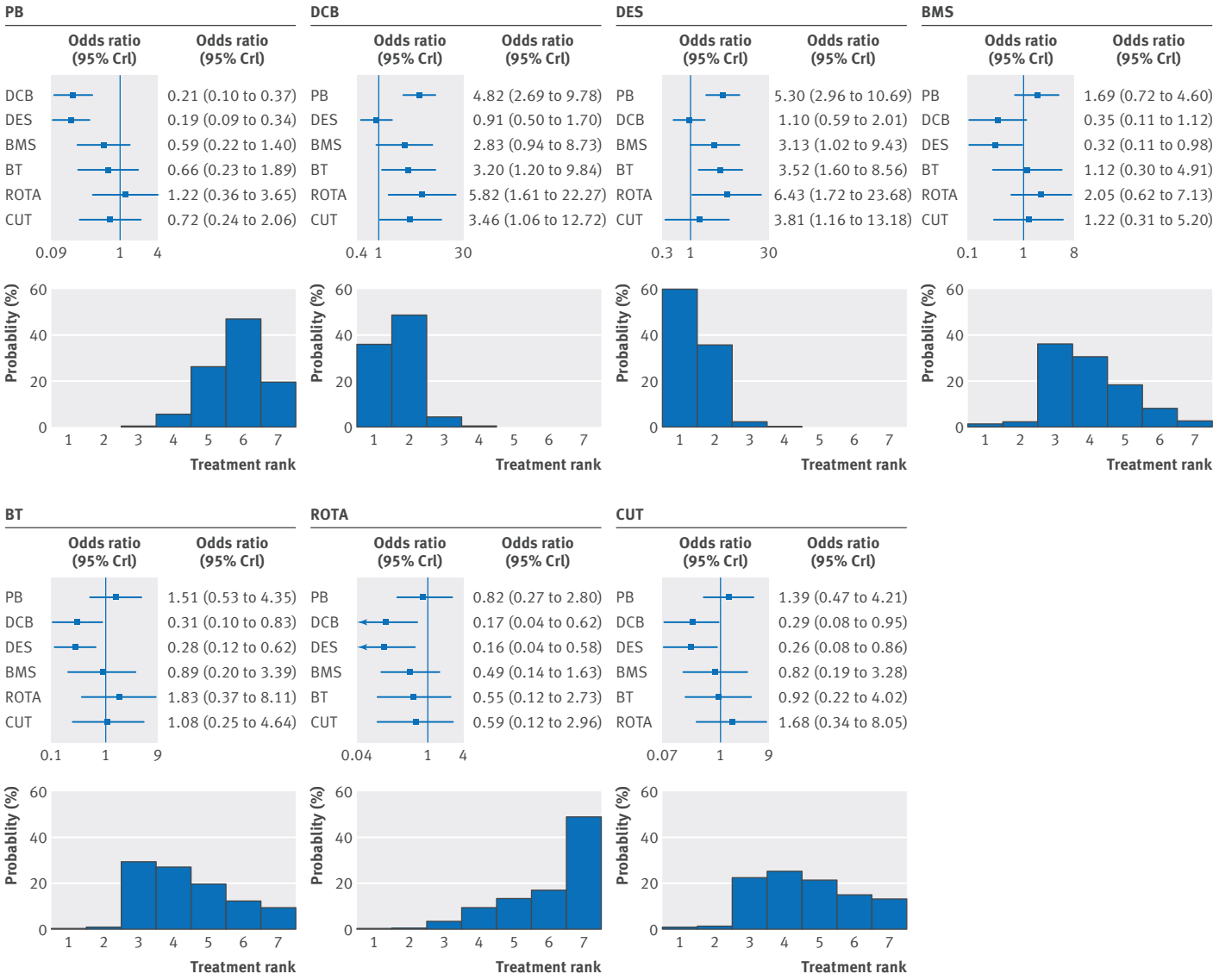

Fig 3 | Effect of interventional treatments on risk of target lesion revascularisation. Forest plots show relative effect of each treatment on target lesion revascularisation as compared with a common reference treatment. Histograms are shown for each treatment reflecting corresponding probabilities for each position in the ranking of the seven strategies (rankograms). I^2 value=43.5%. PB=plain balloon; DCB=drug coated balloon; DES=drug eluting stent; BMS=bare metal stent; BT=brachytherapy; ROTA=rotational atherectomy; CUT=cutting balloon; OR=odds ratio; CrI=credible interval

We detected a significant inconsistency between comparisons involving cutting balloons for each endpoint.

Bayesian network subanalyses and frequentist head to head comparisons

The main network meta-analysis indicated that drug coated balloons and drug eluting stents were the most effective treatments; thus, we further investigated variations in mean effect, heterogeneity, and consistency in subanalyses. We did a network meta-analysis of closed loop plain balloons, drug coated balloons, and drug eluting stents (13 trials; 2417 patients) to reduce the inconsistency arising from indirect evidence. Web tables 2 and 3 show additional information on the trials included in this network meta-analysis. We also did standard, frequentist, pairwise meta-analyses to complement the results of the network meta-analysis.

Compared with plain balloons, use of drug coated balloons and drug eluting stents continued to be associated with a strong reduction in the risk of target lesion revascularisation (drug coated balloons *v* plain balloons: summary odds ratio 0.21, 95% credible interval 0.09 to 0.43; drug eluting stents *v* plain balloons: 0.19, 0.08 to 0.42; fig 7). Similar results were observed for the mean difference in late lumen loss (–0.44 mm, –0.63 to –0.27; –0.39 mm, –0.60 to –0.18; fig 8). After comparison of drug coated balloons with and drug eluting stents, the risk estimates of target lesion revascularisation and late lumen loss did not show a significant benefit favouring one treatment over the other. The node-split analysis showed that the pooled risk of target lesion revascularisation and late lumen loss between the two treatments in the network meta-analysis was differentially driven by indirect (plain balloon *v* drug coated

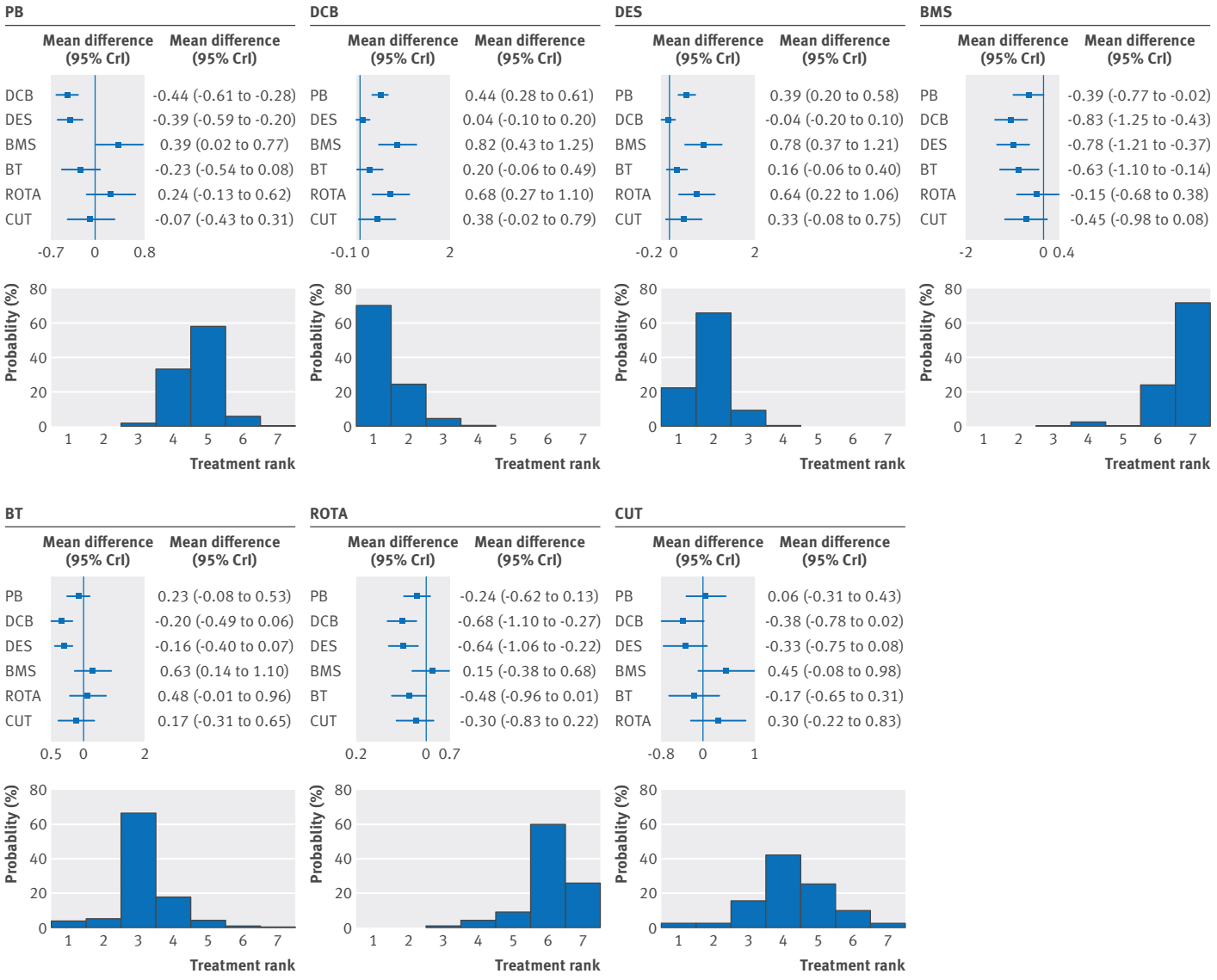

Fig 4 | Effect of interventional treatments on late lumen loss. Forest plots show relative effect of each treatment on late lumen loss as compared with a common reference treatment. Histograms are shown for each treatment reflecting corresponding probabilities for each position in the ranking of the seven strategies (rankograms). I^2 value=95.3%. PB=plain balloon; DCB=drug coated balloon; DES=drug eluting stent; BMS=bare metal stent; BT=brachytherapy; ROTA=rotational atherectomy; CUT=cutting balloon; MD=mean difference; CrI=credible interval

balloon; and plain balloon *v* drug eluting stent) and direct evidence (Bayesian values P=0.043 for target lesion revascularisation and P=0.036 for late lumen loss). Results of corresponding standard pairwise meta-analyses were concordant with those of the network meta-analysis.

At treatment ranking, use of plain balloons was associated with a 99.9% probability of being the least effective treatment both in terms of target lesion revascularisation and late lumen loss. The risk of major adverse cardiac events was reduced in patients treated with drug coated balloons and drug eluting stents compared with those treated with plain balloons, but similar effects were noted between the two strategies (web fig 3). The risk of death and myocardial infarction in both the network meta-analysis and standard pairwise meta-analyses tended to be lower with drug coated balloons than with drug eluting stents (web figs 4 and 5). But owing to the low number of events, this distribution could reflect the effect of chance.

Subgroup and sensitivity analyses

To explore whether earlier devices are affected by a differential response when treated for in-stent restenosis, we stratified patients by categories of BMS-ISR or DES-ISR, and re-evaluated the antirestenotic efficacy of plain balloons, drug coated balloons, and drug eluting stents (figs 9 and 10). Drug coated balloons and drug eluting stents were consistently associated with a significant reduction in the risk of target lesion revascularisation compared with plain balloons both in BMS-ISR and DES-ISR. Both the network and standard pairwise meta-analyses suggested that the magnitude of the benefit of drug coated balloons compared with plain

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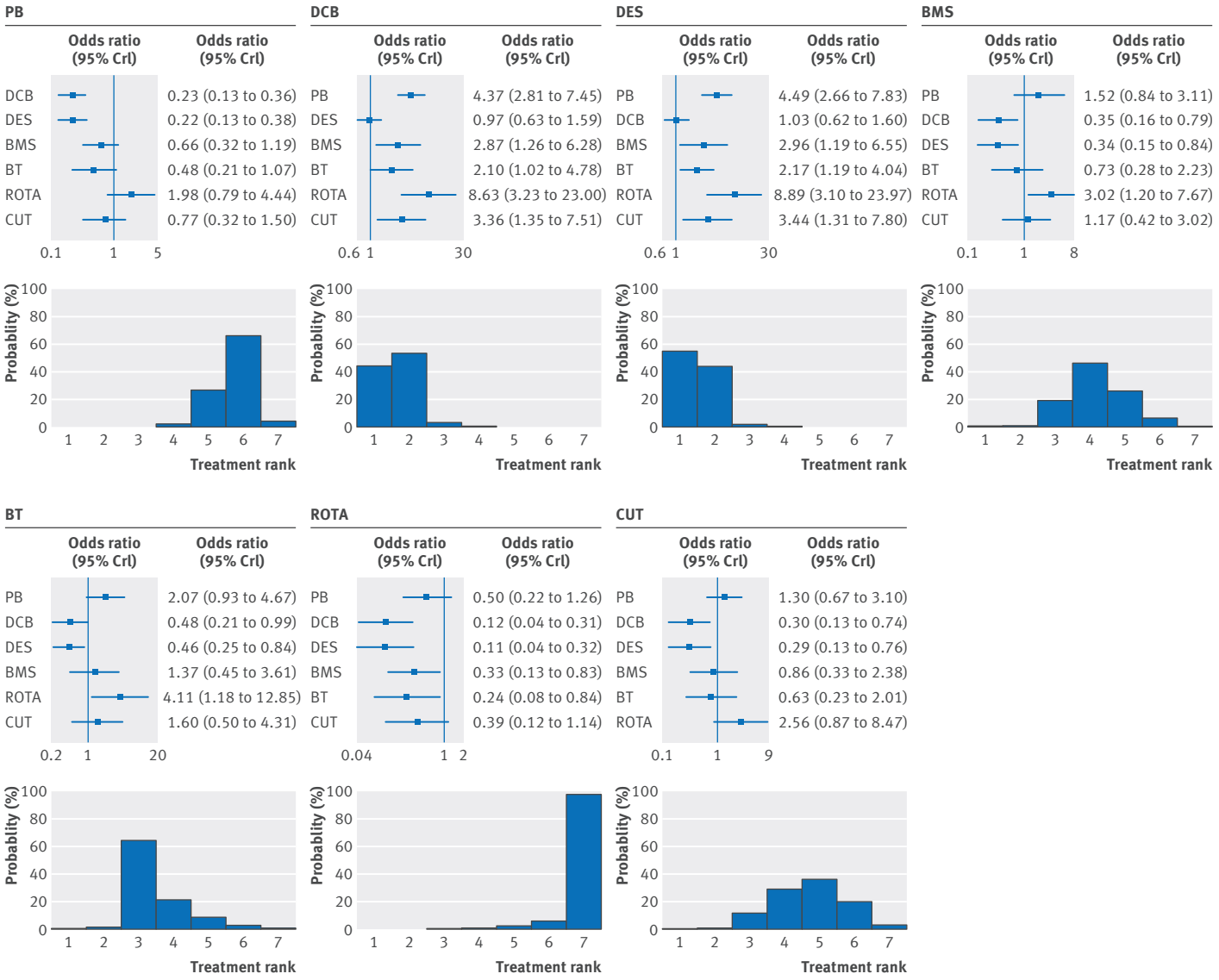

Fig 5 | Effect of interventional treatments on major adverse cardiac events. Forest plots show relative effect of each treatment on major adverse cardiac events as compared with a common reference treatment. Histograms are shown for each treatment reflecting corresponding probabilities for each position in the ranking of the seven strategies (rankograms). I^2 value=8.5%. PB=plain balloon; DCB=drug coated balloon; DES=drug eluting stent; BMS=bare metal stent; BT=brachytherapy; ROTA=rotational atherectomy; CUT=cutting balloon; OR=odds ratio; CrI=credible interval

balloons may be larger in BMS-ISR than in DES-ISR, whereas the effect of drug eluting stents compared with plain balloons was less influenced by restenotic stent type. After comparing drug coated balloons with drug eluting stents in BMS-ISR and DES-ISR, we saw no differences in their respective network meta-analyses. However, the corresponding frequentist, pairwise meta-analysis showed a significant reduction in the risk of target lesion revascularisation associated with the reimplantation of drug eluting stents for DES-ISR.

Figure 11 shows the stratification of trials comparing drug coated balloons with drug eluting stents in standard pairwise meta-analyses according to the generation of drug eluting stent implanted for in-stent restenosis. Risk of target lesion revascularisation was similar between first generation drug eluting stents and drug coated balloons. However, the risk decreased consistently in the analysis of second generation drug eluting stents versus drug coated balloons, where repeated stenting with everolimus eluting stents was associated with a trend towards a 65% risk reduction (P=0.052).

In the study removal analysis, the PEPCAD II trial appeared to unduly influence the pooled estimate of target lesion revascularisation for the comparison of drug eluting stents versus drug coated balloons. After exclusion of PEPCAD II from the main analysis, use of drug eluting stents for in-stent restenosis was associated with a larger reduction in target lesion revascularisation compared with drug coated balloons. This finding was seen in both the network meta-analysis (summary odds ratio 0.49, 95% credible interval 0.22 to 1.08) and corresponding standard pairwise meta-analysis (0.51, 95% confidence interval 0.31 to 0.84; fig 12).

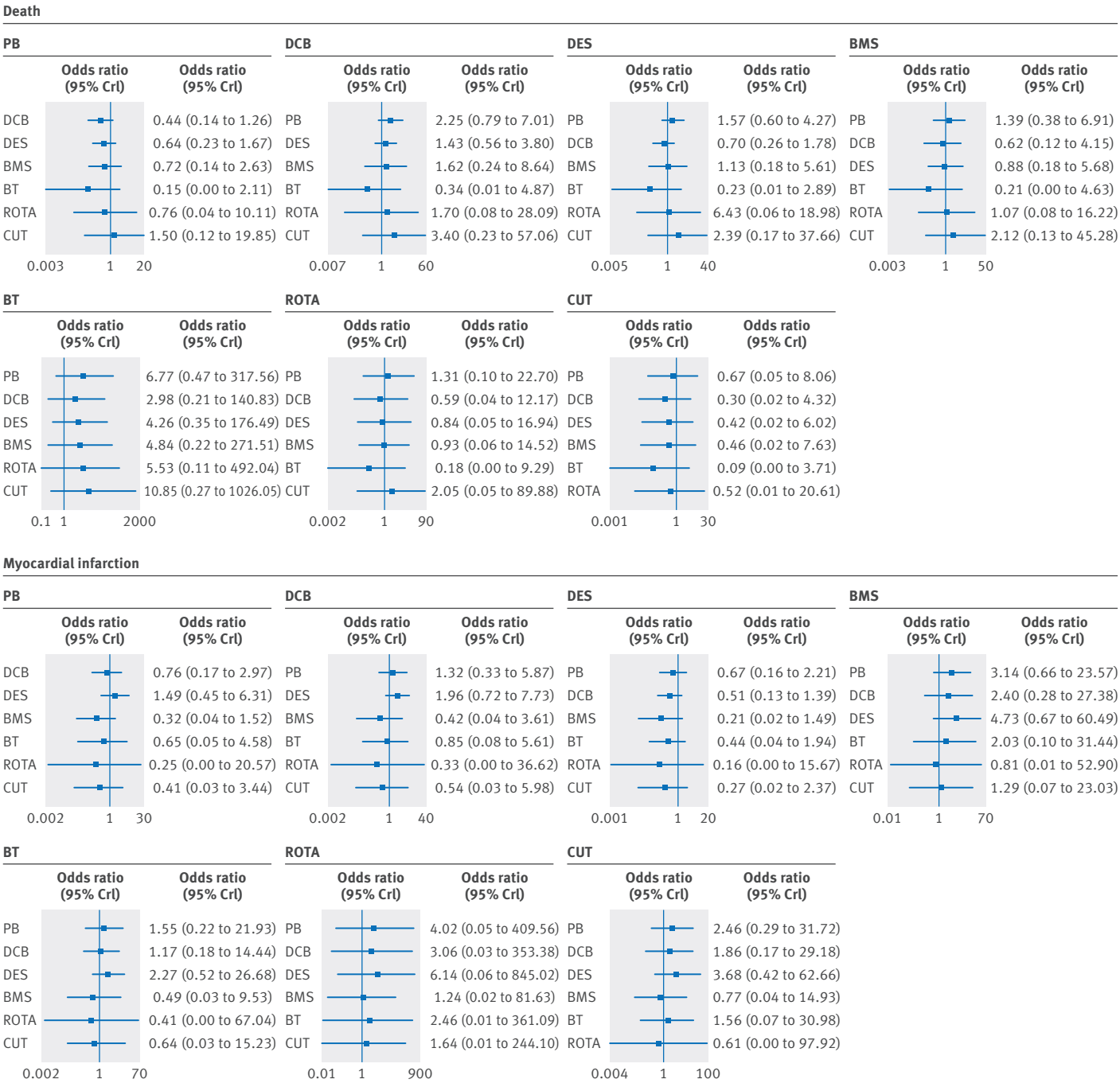

Fig 6 | Effect of interventional treatments on secondary clinical endpoints. Forest plots show relative effect of each treatment on secondary clinical endpoints as compared with a common reference treatment. I^2 values: death=0%; myocardial infarction=11.8%. PB=plain balloon; DCB=drug coated balloon; DES=drug eluting stent; BMS=bare metal stent; BT=brachytherapy; ROTA=rotational atherectomy; CUT=cutting balloon; OR=odds ratio; CrI=credible interval

A stent thrombosis network meta-analysis was not feasible due to the low number of events and trials reporting on such endpoint. However, we did standard pairwise meta-analyses for the loop plain balloons, drug coated balloons, and drug eluting stents. No significant differences among treatments were observed (web fig 6).

We also excluded rotational atherectomy and brachytherapy from the main network and applied a study size filter of at least 50 patients per arm in the attempt to minimise possible influences of outdated treatments and smaller trials. The results of this network subanalysis for target lesion revascularisation and late lumen loss did not show substantial variations compared with the conclusions of the main analysis (web fig 7).

Publication bias

Overall, visual estimation of comparison adjusted funnel plots did not suggest significant asymmetry for all

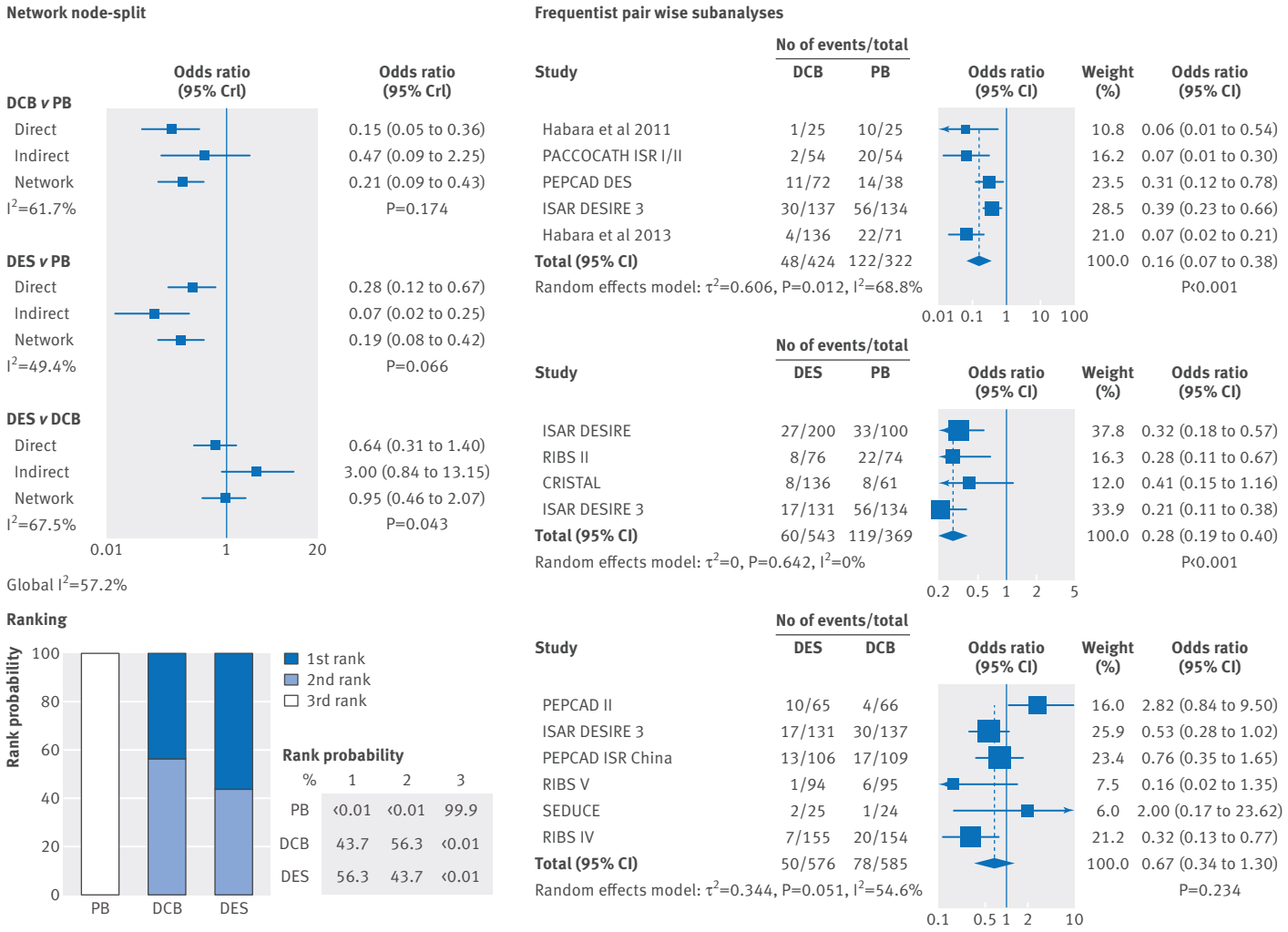

Fig 7 | Bayesian network subanalysis of closed loop plain balloons (PB), drug coated balloons (DCB), and drug eluting stents (DES), with additional frequentist pairwise comparisons for the endpoint of target lesion revascularisation. Network of trials investigating the effects of each treatment was considered. Left section of figure shows network node-split (network subanalysis) and corresponding rank probabilities for target lesion revascularisation; direct evidence estimates represent results of the Bayesian pairwise meta-analyses, and I^2 values for each comparison grade the heterogeneity between trials from a Bayesian estimate of τ^2. Right section of figure shows standard, frequentist pairwise comparisons from the DerSimonian-Laird random effect model. OR=odds ratio; CrI=credible interval; CI=confidence interval

endpoints. However, a consistent number of trials (almost all involving drug coated balloons) fell outside the significance boundaries in the late lumen loss analysis (web figs 8 and 9). Contour enhanced funnel plots for the comparison of drug eluting stents versus drug coated balloon were implemented by Peters' test (target lesion revascularisation) and Egger's test (late lumen loss). These plots did not outline significant publication bias (web figs 10 and 11). However, for late lumen loss, this non-significance could be due to the limited number of trials, because visual inspection suggested an asymmetric distribution and the Egger's test P value of 0.127 was close to the formal significance threshold of 0.10.

Discussion

This updated network meta-analysis comparing all available treatments for in-stent restenosis had four main findings. Firstly, drug coated balloons and drug eluting stents are the most effective interventional treatments for in-stent restenosis compared with other currently available strategies, leading to superior and long term efficacy in terms of clinical, angiographic and antirestenotic outcomes. Secondly, use of a plain balloon alone is significantly less effective than a drug coated balloon or a drug eluting stent. Thirdly, drug coated balloons might exert a larger efficacy in BMS-ISR than in DES-ISR. Finally, second generation everolimus eluting stents have shown a tendency to reduce the risk of target lesion revascularisation compared with drug coated balloons.

Recently, a meta-analysis by Lee and colleagues evaluated plain balloons, drug coated balloons, and drug eluting stents in the treatment of in-stent restenosis, suggesting drug coated balloons to be the best therapy.[41] Our meta-analysis differs from that earlier study in several ways.

Firstly, the main objective of our study was the evaluation of all existing interventional strategies for in-stent restenosis using data from randomised trials, whereas Lee and colleagues' study included only three

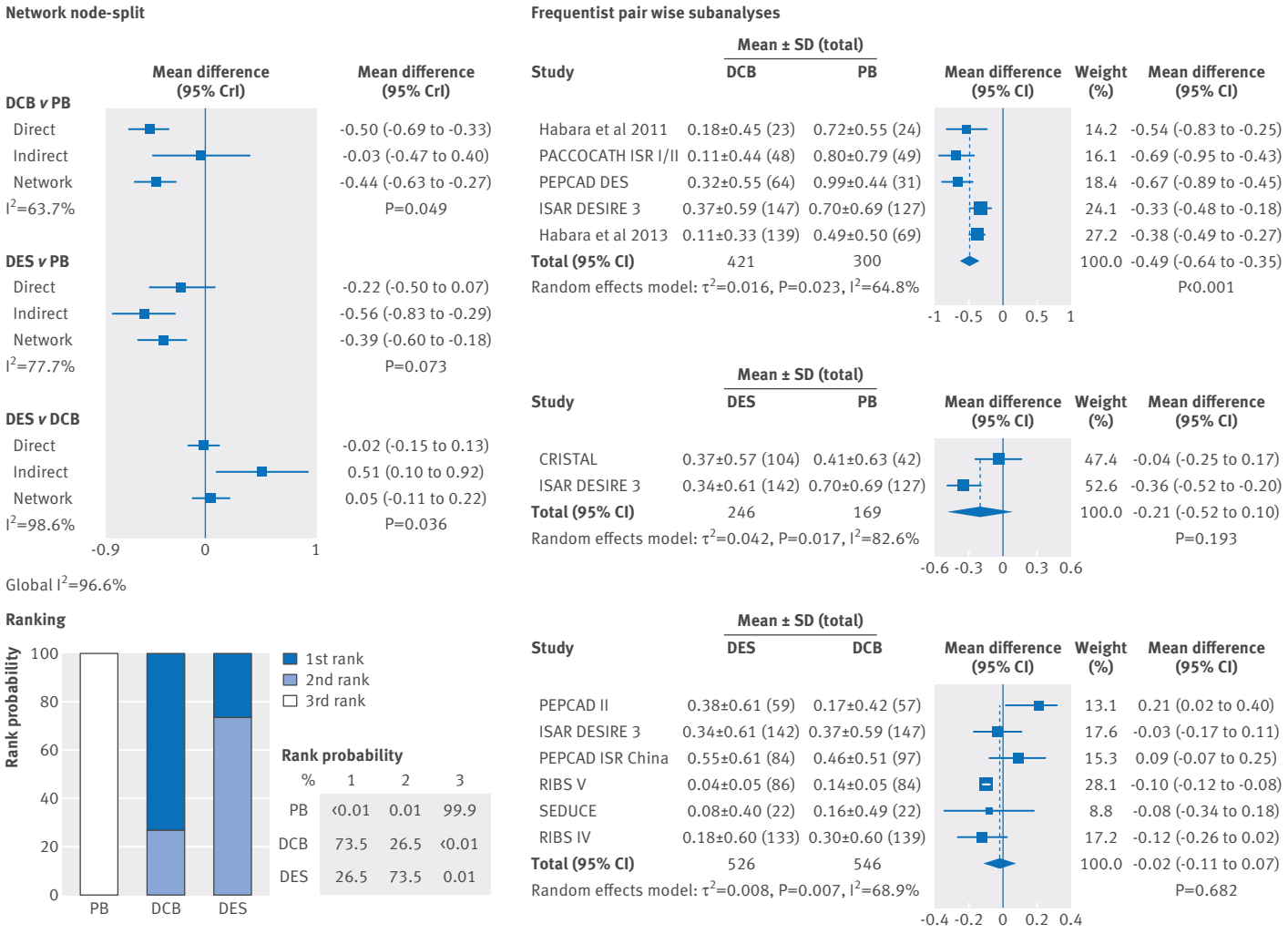

Fig 8 | Bayesian network subanalysis of closed loop plain balloons (PB), drug coated balloons (DCB), and drug eluting stents (DES), with additional frequentist pairwise comparisons for the endpoint of late lumen loss. Network of trials investigating the effects of each treatment was considered. Left section of figure shows network node-split (network subanalysis) and corresponding rank probabilities for target lesion revascularisation; direct evidence estimates represent results of the Bayesian pairwise meta-analyses, and I^2 values for each comparison grade the heterogeneity between trials from a Bayesian estimate of τ^2. Right section of figure shows standard, frequentist pairwise comparisons from the DerSimonian-Laird random effect model. MD=mean difference; CrI=credible interval; CI=confidence interval; SD=standard deviation

treatments. Secondly, the previous meta-analysis did not include two of the six available randomised trials comparing drug coated balloons with drug eluting stents (SEDUCE, RIBS IV), which could explain the disparity between our results and their conclusions. Thirdly, we also performed standard pairwise comparisons between treatment arms and multiple subanalyses to critically complement the results of the network meta-analysis. Finally, we also considered angiographic endpoints whereas the study by Lee and colleagues focused essentially on clinical outcomes.

Use of drug coated balloons versus drug eluting stents for coronary in-stent restenosis

Intracoronary imaging indicates a leading role of exuberant neointimal proliferation among the potential mechanisms of in-stent restenosis.[42] Use of drug coated balloons is an emerging treatment for in-stent restenosis, with the putative advantage of delivering an antiproliferative treatment without adding a second layer of metal.[4] Our study showed that compared with plain balloons, drug coated balloons resulted in reductions of 79% relative risk of target lesion revascularisation and 0.44 mm mean difference in late lumen loss. However, in-stent restenosis has been also associated with stent underexpansion (that is, insufficient stent expansion at implantation or chronic recoil), uneven stent struts disposition in complex lesions, and neoatherosclerosis.[43 44] These factors could theoretically disfavour drug coated balloons, a treatment that cannot guarantee a constant radial strength.[11 43]

In-stent implantation of drug eluting stents, providing additional permanent scaffolding inside the restenotic stent,[45] could overcome the mechanical limitations of drug coated balloons. Although the trials in our systematic review showed no significant differences in periprocedural complications and treatment crossover between drug coated balloons and drug eluting stents, repeated

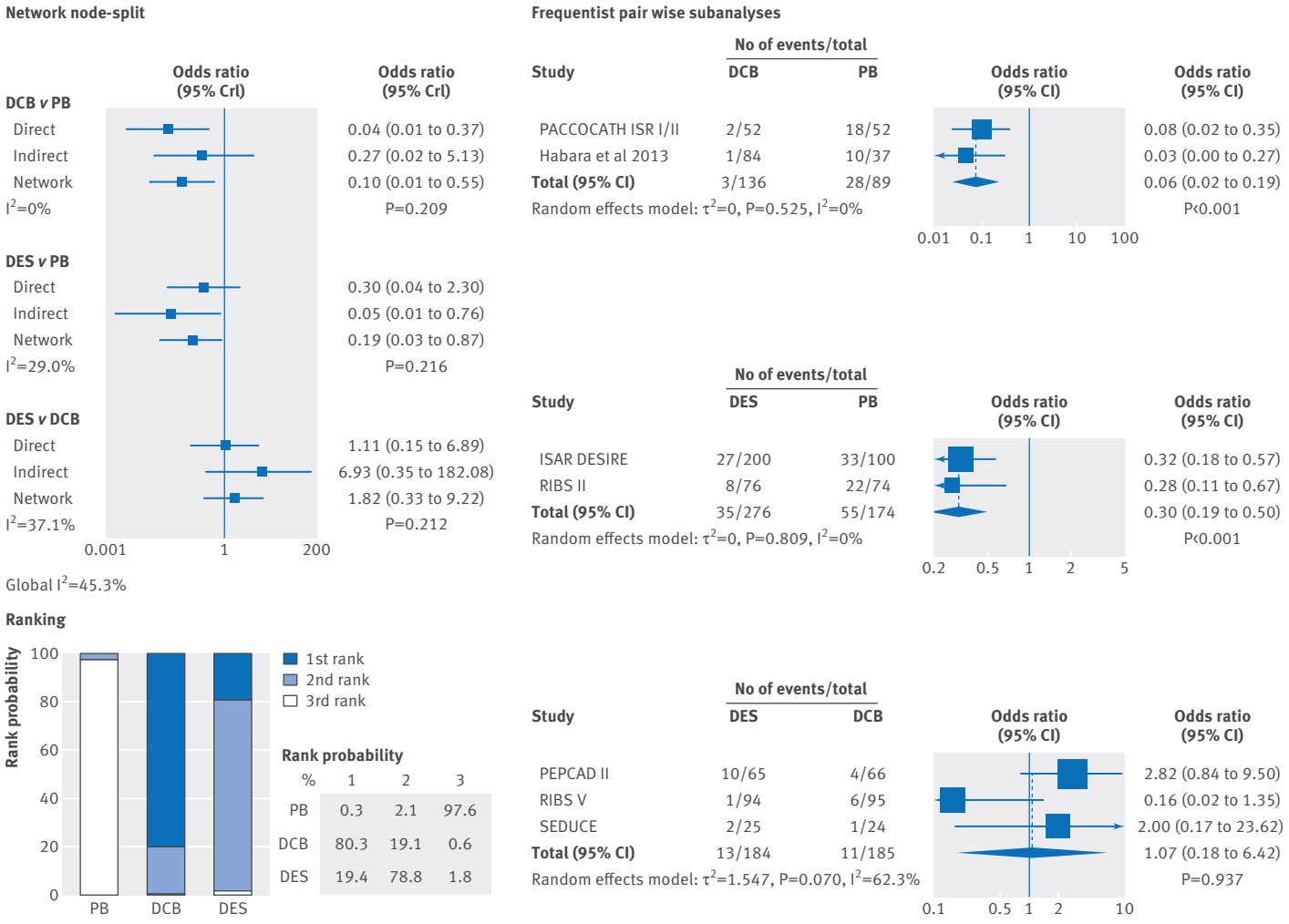

Fig 9 | Subgroup analysis of antirestenotic efficacy of plain balloons, drug coated balloons, and drug eluting stents, according to BMS-ISR. Network node-split and treatment rank probabilities are displayed; direct evidence estimates represent the results of the Bayesian pairwise meta-analyses, and I^2 values for each comparison grade the heterogeneity between trials from a Bayesian estimate of τ^2. Results of Bayesian analyses were implemented by frequentist, random effect, pairwise comparisons. OR=odds ratio; CrI=credible interval; CI=confidence interval

stenting with drug eluting stents might be a more reasonable indication for relevant periprocedural tissue protrusion and in-stent or stent edge dissection. However, small vessel size and diabetes trigger further neointimal proliferation, and an additional metallic layer could critically amplify the risk of recurrent in-stent restenosis.[46 47] Selection of the best revascularisation strategy between drug coated balloons and drug eluting stents should be therefore tailored on a case by case basis according to lesion and patient characteristics.

The similar antirestenotic efficacy of drug coated balloons and drug eluting stents observed in our meta-analysis could result from the trade-off between advantages and shortcoming of the two devices. Drug coated balloons are associated with worse acute angiographic results, but are more respectful of the original coronary anatomy, induce lower vascular inflammatory response, and exert a lower stimulus to endothelial growth in the long term. Drug eluting stents guarantee a larger, immediate minimum lumen diameter and more predictable acute effects at the risk of reiterating the process of neointimal growth.[45 48] The most relevant concern about drug coated balloons is the durability of the antirestenotic effect, because local drug use in the short term may not result in a longlasting inhibition of restenosis. However, the putative angiographic and clinical superiority of drug eluting stents in the long term for in-stent restenosis is presently not supported by a solid evidence basis.

Our meta-analysis suggests that second generation everolimus eluting stents might be the best strategy for in-stent restenosis. In agreement with large and unselected observational studies,[49 50] our stratified analysis showed that these second generation stents produced an almost significant 65% reduction in the risk of target lesion revascularisation compared with drug coated balloons. The efficacy of drug coated balloons and first generation stents was comparable. However, it is still unknown whether this possible benefit is generalisable to diffuse and neoatherosclerotic in-stent restenosis, especially if recurrent.

The available data do not allow for comparison between drug coated balloons and drug eluting stents according to first or recurrent in-stent restenosis, and

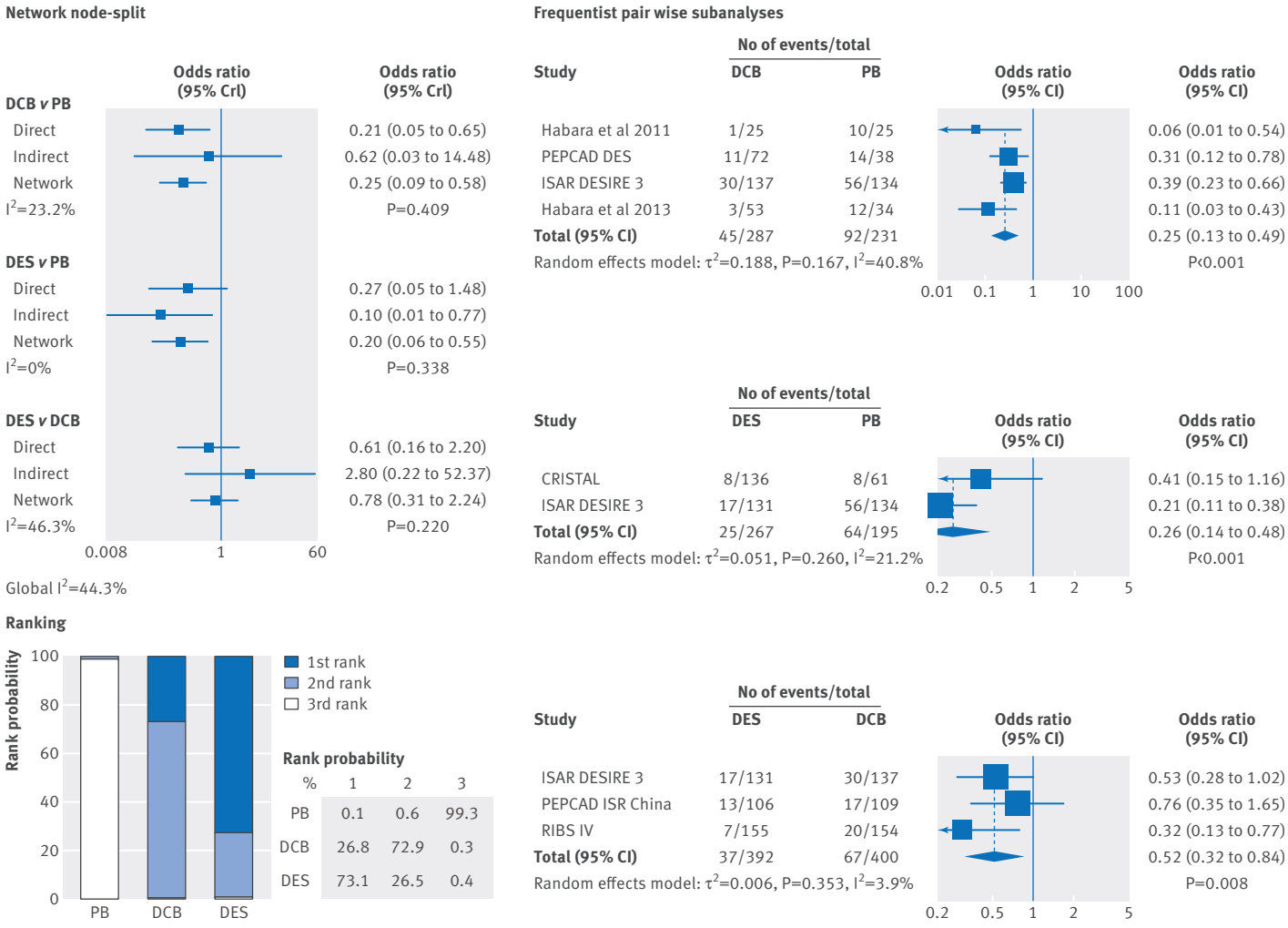

Fig 10 | **Subgroup analysis of antirestenotic efficacy of plain balloons, drug coated balloons, and drug eluting stents, according to DES-ISR. Network node-split and treatment rank probabilities are displayed; direct evidence estimates represent the results of the Bayesian pairwise meta-analyses, and I^2 values for each comparison grade the heterogeneity between trials from a Bayesian estimate of τ^2. Results of Bayesian analyses were implemented by frequentist, random effect, pairwise comparisons. OR=odds ratio; CrI=credible interval; CI=confidence interval**

selection of the best strategy for patients with resistant in-stent restenosis (that is, at least three instances) remains uncertain. Owing to a lack of evidence, we could not establish whether implantation of drug eluting stents for recurrent in-stent restenosis is better than repeat use of drug coated balloons after a failed drug coated balloon strategy. However, the first option seems to be a rational second line treatment.[50] Overall, an initial approach to in-stent restenosis with drug coated balloons might be reasonable, especially in BMS-ISR and in patients with small vessels or diabetes. Second generation drug eluting stents should then be prioritised for DES-ISR and complex in-stent restenosis. Because patients with resistant in-stent restenosis tend to have multiple recurrent events, coronary artery bypass grafting should be also considered after multiple failures of percutaneous coronary intervention.[21]

In view of the anatomical variables potentially influencing early and late procedural antirestenotic efficacy depending on the selection of drug coated balloons or drug eluting stents, both treatments should be considered quick, safe, and effective for non-complex instances of coronary in-stent restenosis. However, in angiographic and unstable lesions and clinical patterns, implantation of drug eluting stents could be preferable owing to the superior mechanical guarantees of metallic scaffolding. In addition, the decision between these two treatments could be affected by varying post-procedural pharmacological management.[48] Second generation drug eluting stents have shown to be more biocompatible and less thrombogenic, hence allowing for only six months of dual antiplatelet therapy in de novo lesions.[51] However, drug coated balloons deliver locally the antiproliferative medication and avoid permanent structures inside the vessel that need prolonged antithrombotic coverage. Although planned duration of dual antiplatelet therapy varies widely in randomised trials with drug coated balloons (including de novo lesions, in-stent restenosis, or peripheral artery disease), manufacturers advise three months of therapy following use of drug coated balloons. In some trials investigating the efficacy of drug coated balloons for in-stent restenosis or small vessel lesions, one month of dual antiplatelet therapy did not show any safety

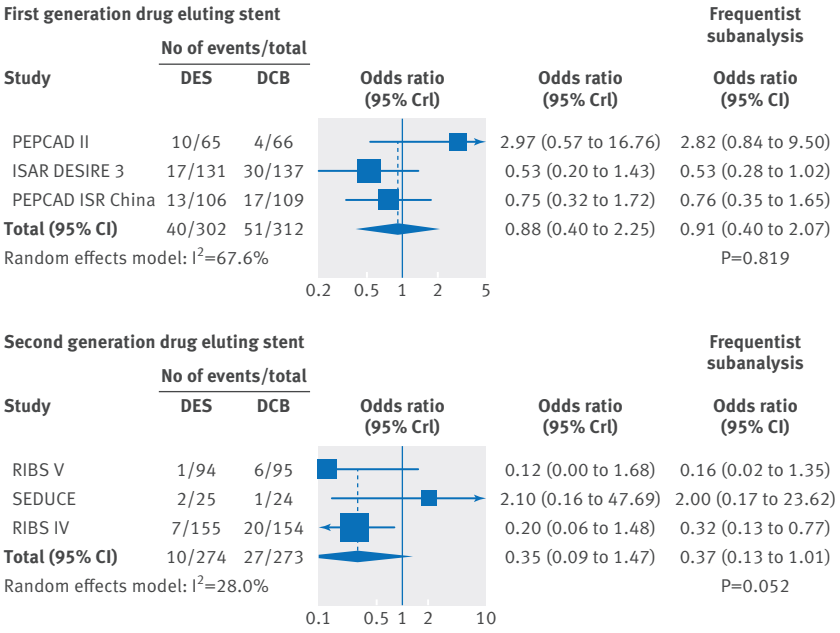

Fig 11 | Risk of target lesion revascularisation between use of first generation or second generation drug eluting stents and drug coated balloons for in-stent restenosis. Bayesian results were implemented by frequentist analyses. DCB=drug coated balloon; DES=drug eluting stent; OR=odds ratio; CrI=credible interval; CI=confidence interval

issue.[48] Therefore, drug coated balloons might be indicated in patients with urgent surgical indications or at high haemorrhagic risk.

Potential sources of inconsistency and heterogeneity

The need for a meta-analysis comparing drug eluting stents versus drug coated balloons is supported by the absence of robust antirestenotic differences between treatments across trials of in-stent restenosis. An objective of the meta-analysis is to combine non-conclusive evidence from individual trials to strengthen evidence from the comparison of two or more treatments. Importantly, characteristics of original trials (including design, eligibility criteria, clinical and procedural features) can make the results of indirect comparisons quite different from those of direct comparison. The significant incoherence between direct and indirect effects is known as inconsistency.

We attempted to reduce potential sources of inconsistency affecting the indirect evidence (that is, obsolete treatments, cutting balloon node) by restricting our analysis to the smallest network of plain balloons, drug coated balloons, and drug eluting stents. A network meta-analysis can identify external influences on the mean effect of a specific comparison that otherwise would have remained unreported with standard pairwise meta-analytical methods. However, even in the smallest network subanalysis, the inconsistency remained unchanged and significant Bayesian P values were observed.

Therefore, the conflict between direct and indirect evidence in the comparison of drug coated balloons versus drug eluting stents could have two explanations that are not mutually exclusive. Firstly, if we assume the direct evidence (which numerically favoured drug eluting stents) to be true, one possible explanation to the indirect evidence trending in the opposite direction is that trials comparing drug coated balloons with plain balloons overstate the efficacy of drug coated balloons, or trials comparing drug eluting stents with plain balloons understate the efficacy of drug eluting stents. In our analysis, we detected a high heterogeneity in the comparison of drug coated balloons versus plain balloons, with two smaller trials showing larger treatment effects.

Secondly, if we assume the indirect evidence (which numerically disfavoured drug eluting stent) to be true, a possible explanation is a significant intrinsic inconsistency in the comparison of drug coated balloons with drug eluting stents. In the individual removal analysis, results were in line with this hypothesis, showing that the risk of target lesion revascularisation tended to be influenced by the oldest trial (PEPCAD II). Conversely, the inconsistency for late lumen loss could have been driven by very different, trial specific, mean estimates ranging from 0.04 to 0.55 mm for drug eluting stents and from 0.14 to 0.46 mm for drug coated balloons (same device).

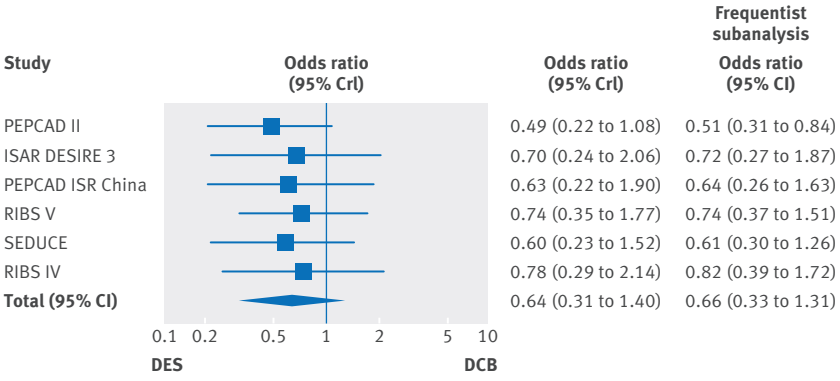

Fig 12 | Risk of target lesion revascularisation after sequential removal of each trial comparing use of drug eluting stents with drug coated balloons for treatment for in-stent restenosis. One trial was removed at a time from the overall analysis to define its individual impact on the pooled risk of target lesion revascularisation. Bayesian results were implemented by frequentist analyses. DCB=drug coated balloon; DES=drug eluting stent; OR=odds ratio; CrI=credible interval; CI=confidence interval

Other treatments for coronary in-stent restenosis

Our results support the notion that bare metal stents and brachytherapy should be no longer considered in the contemporary management of in-stent restenosis. Indeed, although in-stent implantation of bare metal stents for in-stent restenosis provides higher acute lumen gain and better procedural results than plain balloons, it leads to a comparable minimum lumen diameter and percent diameter stenosis after only six months, largely due to significantly higher levels of late lumen loss.[52 53] In addition, at six to 12 months, bare metal stents were associated with the highest mean difference in late lumen loss. Several trials in this network meta-analysis concluded that vascular brachytherapy is less effective in treating in-stent restenosis than drug eluting stents. We included brachytherapy in our

network meta-analysis to provide an additional reference for more effective strategies in the network, and to quantify a pooled estimate of the antirestenotic effect of this treatment compared with drug coated balloons and drug eluting stents.

This meta-analysis also underlines that rotational atherectomy cannot be considered a standalone treatment for in-stent restenosis, because its outcomes are significantly inferior than those observed with the other treatments. Still, this strategy could be considered as complementary and preliminary to the implantation of drug eluting stents in old, hard, and calcified lesions caused by in-stent restenosis.[54 55] Importantly, although rotational atherectomy for in-stent restenosis could be associated with a higher incidence of mechanical complications (that is, stent fracture, coronary perforation, and plaque embolisation), we did not observe a significant increase in death and myocardial infarction at follow-up.

Cutting balloon use was associated with a higher risk of target lesion revascularisation and higher mean difference in late lumen loss than use of a drug coated balloon or drug eluting stent. We did not evaluate the effects of the newer scoring balloon in this meta-analysis because data from randomised trials were not available. However, results from the ISAR-DESIRE 4 trial (NCT01632371) and other reports exploring the use of scoring balloons to prepare in-stent restenosis lesions for drug coated balloons are pending.

Future perspectives

Future direction of in-stent restenosis treatment will depend from the results of additional and larger randomised trials currently comparing drug coated balloons with second generation drug eluting stents. The ongoing DARE (NCT01127958) and TIS (NCT01735825) trials are investigating the superiority of second generation everolimus eluting stents over drug coated balloons. In the MAGIC-TOUCH trial (NCT02400632), researchers are investigating a new sirolimus coated balloon; these results will provide an additional reference for current types of drug coated balloons that elute paclitaxel.

Isolated initial reports have suggested that bioresorbable scaffolds may offer sufficient mechanical support as well as reduced neointimal proliferative stimuli in in-stent restenosis.[56 57] However, unfavourable properties of current bioresorbable scaffolds (that is, thick struts, lower radial force than drug eluting stents, and narrower margins for overexpansion after deployment[58]) could frustrate this approach, which warrants validation in targeted investigations in a sufficient number of patients.

Limitations

The results of our meta-analysis should be interpreted taking the following limitations into account. Firstly, a meta-analysis shares the limitations of the studies included. To minimise this unavoidable shortcoming, only randomised trials were included. The qualitative bias assessment did not suggest significant causes of concern, and differences in follow-up completeness were trivial as the consequence of the strict angiographic surveillance scheduled in all studies. However, we noticed that studies had different proportions of diabetes mellitus, focal or diffuse angiographic patterns in in-stent restenosis, and different minimum lumen diameters at baseline, which cannot be fully appreciated at the study level.

Furthermore, the trials covered a period of about 15 years, which could have introduced unmeasured differences among treatments. Almost all studies were of open label design; this was an unavoidable consequence of the different constitutive characteristics of the devices under investigation, which do not consent complete masking to the operator, with few exceptions (plain balloons and drug coated balloons in PACCOCATH ISR I/II).

The absence of long term follow-up and the varying periods of investigation across trials were also limitations. There are insufficient data on clinical and angiographic outcomes several years after in-stent restenosis treatment, and almost all the studies included in our meta-analysis did not provide information beyond 12 months.

We were forced to select summary odds ratios as an outcome measure owing to the trials not providing enough information to indirectly calculate hazard ratios. However, we compared estimated summary odds ratios with hazard ratios from individual patient data from trials reporting those values, and found that the difference between the two outcome measures was trivial. This lack of difference could have been a result of the favourable follow-up length (≤12 months) and the fact that very few patients were lost at follow-up.

Although this meta-analysis included nearly 5000 patients, some trials were small, of which a large number were powered only for a specific angiographic endpoint, mainly late lumen loss. However, sensitivity analyses on target lesion revascularisation and late lumen loss that were restricted to newer and larger studies did not show relevant deviations from the main results. Additionally, although we observed a numerical distribution for myocardial infarction favouring some treatments over the others, the event rate was low and did not allow us to draw robust conclusions for this endpoint. For similar reasons, the network meta-analysis for stent thrombosis was not feasible because most of the included trials did not report the number of stent thrombosis events, and the remaining reported a low incidence.

Some trials were not included in all analyses because they did not have the specific endpoint of interest or report angiographic values as median and interquartile range. In addition, although few older trials reported only target vessel revascularisation, we pooled these events with target lesion revascularisation, and events of the drug eluting stent group of the ISAR DESIRE trial were derived from collapsing the original groups using sirolimus eluting stents and paclitaxel eluting stents.

Subgroup analyses according to the type of restenotic stent—either bare metal or drug eluting—could not benefit from randomisation in all instances. The trial by Habara and colleagues (2013) included both devices, and in the PACCOCATH ISR I/II trial (which was included in the subgroup analysis for BMS-ISR), 4% of patients actually had DES-ISR. We did not stratify groups by first or recurrent in-stent restenosis because the original data did not allow a clear identification of such variants.

Unrelated mean effect models are not well suited to handle trials with more than two arms. Node-split, the most powerful tool to detect inconsistency, is limited to closed loops. However, our meta-analysis included only one three arm trial (ISAR DESIRE 3), and the most effective treatments were all part of closed loops. Finally, our meta-analysis investigated the efficacy of first generation and second generation everolimus eluting stents, but questions regarding the efficacy of newer stents (that is, second and third generations) remain.

Conclusions

In this network meta-analysis, drug coated balloons and drug eluting stents were shown to be the most effective treatments for in-stent restenosis. Plain balloons, bare metal stents, brachytherapy, rotational atherectomy, and cutting balloons were associated with a higher risk of target lesion revascularisation and inferior angiographic results. We saw no differences in death, myocardial infarction, and stent thrombosis among all included treatments, but such comparisons remain limited by the low number of events. The risk of major adverse cardiac events was consistently reduced with drug coated balloons and drug eluting stents, driven by target lesion revascularisation. Although the main analysis suggested a similar efficacy of drug coated balloons and drug eluting stents, an exploratory subgroup analysis indicated a trend towards a risk reduction in target lesion revascularisation with second generation everolimus eluting stents.

Contributors: DG conceived and designed the study; DG, GG, and PA collected and abstracted the data; DG undertook the statistical analysis; DG, GG, and DC drafted the manuscript; all authors had full access to all the data, including statistical reports and tables; all authors analysed and interpreted the data; all authors critically revised the manuscript for important intellectual content; DC is the guarantor.

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Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: None was required.

Data sharing: No additional data available.

The manuscript's guarantor affirms that the manuscript is an honest, accurate, and transparent account of the study being reported, that no important aspects of the study have been omitted and that any discrepancies from the study as planned have been explained.

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Web appendix: Supplementary material

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One-year outcomes after Absorb bioresorbable vascular scaffold implantation in routine clinical practice

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KEYWORDS

- Absorb
- all-comers registry
- bioresorbable scaffolds
- one-year outcomes

Abstract

Aims: Our aim was to report one-year outcomes of Absorb bioresorbable scaffold implantation under real-world conditions in an all-comers population of patients with high proportions of complex lesions.

Methods and results: Patients undergoing Absorb 1.1 implantation were included in a single-centre, prospective, all-comers registry. The primary outcome was target lesion failure (TLF), defined as the combination of cardiac death, target vessel myocardial infarction (MI), or clinically driven target lesion revascularisation (TLR). A total of 319 patients received 604 Absorb BVS in 406 lesions. Of note, 24.8% of patients had diabetes and 49.5% presented with an acute coronary syndrome. A total of 51% of lesions were type B2/C. The reference vessel diameter and lesion length were 2.9±0.5 and 21.2±16.8 mm, respectively. The one-year cumulative rate of TLF was 4.9%. Rates of cardiac death, target vessel MI and TLR were 0.9%, 1.3% and 4.2%, respectively. The cumulative one-year rate of definite/probable scaffold thrombosis was 1.3%, with all events occurring within 30 days.

Conclusions: These data suggest that twelve-month clinical outcomes of Absorb use in "real-world" unselected patients with high proportions of complex lesions are reasonably good.

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Introduction

Bioresorbable scaffolds (BRS) have recently been introduced for coronary interventions. These novel devices degrade completely over 12-36 months after implantation, enabling transient luminal support, while preventing long-term metallic "caging" of coronaries, promising to overcome the limitations of permanent drug-eluting stents (DES)[1]. Indeed, BRS implantation has been associated with vessel lumen enlargement, plaque/media reduction, vasomotion restoration, expansive remodelling (which may reduce angina), and new media formation, potentially reducing mechanisms underlying late events, such as inflammation and neoatherosclerosis[2]. In addition to these biological effects, the complete bioresorption eliminates malapposed, fractured or non-endothelialised struts, and late polymer/metal reactions, with the potential of reducing late thrombotic events triggered by these latter mechanisms. Additional effects of BRS may be important in high-risk settings, in which mechanisms underlying late thrombotic events are more pronounced. However, BRS have specific features, including larger crossing profile, thicker struts and expansion capability limitations, which may impact on their clinical performance, in complex lesions.

Among BRS, the everolimus-eluting scaffold (Absorb; Abbott Vascular, Santa Clara, CA, USA) has been the most extensively investigated in clinical studies. The use of the Absorb appears to provide a similar degree of safety and efficacy compared with metallic DES in the treatment of relatively simple lesions treated under trial conditions[3,4]. Clinical reports on the use of these novel devices in the more complex settings commonly encountered in routine practice have shown promising results overall[5-9], although non-negligible rates of early scaffold thrombosis (ST) were observed in some registries[5-8]. Nevertheless, real-world data on BRS in unselected populations at more advanced stages of follow-up and with the use of a standardised implantation technique are still limited[10].

The aim of this single-centre study was to report one-year clinical outcomes of Absorb implantation under real-world conditions in an unselected population with high proportions of complex coronary lesions.

Methods

PATIENT POPULATION

The GHOST (Gauging coronary Healing with biOresorbable Scaffolding plaTforms) is an ongoing prospective non-randomised, single-centre registry conducted at Ferrarotto Hospital, University of Catania, Italy, from March 2013. The registry includes patients undergoing single-vessel or multivessel percutaneous coronary intervention (PCI) with the Absorb (revision 1.1). Concurrent implantation of DES or bare metal stents was allowed at the operator's discretion.

Lesions suitable for stenting with a reference vessel diameter of ≥2.0 mm and ≤3.8 mm were eligible for treatment with the Absorb. If these criteria were present and the correct scaffold size was in stock, all angiographic lesions were considered eligible, with the choice between Absorb and permanent metallic stents left to the discretion of the operator. Exclusion criteria for Absorb treatment included: contraindication to prolonged dual antiplatelet therapy (DAPT); high likelihood of poor DAPT compliance; indication for oral anticoagulation; high bleeding risk; planned surgery within 12 months; cardiogenic shock; Killip class III or IV; unstable arrhythmias; cancer or comorbidities with limited expected survival.

The registry population also encompassed patients with clinical and angiographic characteristics that were among the exclusion criteria of the ABSORB II trial[11], reflecting a broader "real-world" use. Outcomes were compared between two subgroups stratified according to the entry and exit ABSORB II trial criteria.

Only patients with at least one-year follow-up eligibility were evaluated in the present analysis. The first 209 patients of our registry were part of the larger multicentre GHOST-EU registry, including patients from 10 European centres and reporting six-month outcomes[6].

The local ethics committee approved the use of aggregated clinical data for this analysis, and written informed consent was obtained from all patients.

INTERVENTIONAL PROCEDURE

All procedures were performed according to current PCI standards. Lesion preparation by predilatation with non-compliant balloons 0.5 mm smaller than or equal to the scaffold device diameter was mandatory. The recommended pressure for scaffold implantation was at least 10 atm. Post-dilatation at high pressure with non-compliant balloons 0.5 mm larger than or equal to the scaffold device diameter was strongly recommended regardless of the angiographic results. The use of on-line quantitative coronary angiography (QCA) to assess appropriate device size and the use of intravascular imaging techniques were left to the discretion of the operator.

During the procedure, patients received appropriate anticoagulation according to standard hospital practice. Glycoprotein IIb/IIIa inhibitors were used at the physician's discretion. A loading dose of aspirin 250-500 mg was given before PCI, followed by 75-100 mg oral daily indefinitely thereafter. A loading dose of a $P2Y_{12}$ inhibitor was administered before or immediately after PCI. Dual antiplatelet therapy (DAPT) was recommended for at least 12 months (with a strict minimum of six months) after Absorb implantation.

ANGIOGRAPHIC ANALYSIS

The QCA was performed with a dedicated software (Cardiovascular Angiographic Analysis System II; Pie Medical Imaging, Maastricht, The Netherlands) using an automated detection algorithm. The interpolated and proximal reference vessel diameters (RVD) in the treated segment were assessed. The acute gain was calculated as minimal lumen diameter (MLD) post scaffold implantation minus MLD pre scaffold implantation.

Technical failure was defined as residual in-scaffold diameter stenosis >30% by QCA.

Scaffold undersizing, correct sizing and oversizing were defined as the ratios between the nominal scaffold size and the proximal RVD ≤0.9, >0.9 and <1.1, and ≥1.1, respectively.

FOLLOW-UP DATA

Clinical follow-up information on medical therapy and the clinical status of patients was prospectively collected through scheduled outpatient clinic evaluations and/or phone contact. Additional information, if necessary, was obtained from referring cardiologists and general practitioners. In case of inability to reach the patient and the referring doctor, the vital status was verified at the registry office. Clinical follow-up was scheduled at one, six and 12 months. There was no independent or external monitoring of data entry.

OUTCOMES AND DEFINITIONS

The primary outcome of interest was a device-oriented composite endpoint (target lesion failure [TLF]), defined as the combination of cardiac death, target vessel myocardial infarction (MI), or clinically driven target lesion revascularisation (TLR), either percutaneous or surgical[12]. Secondary outcomes of interest included the components of TLF, target vessel failure (TVF), defined as the composite of cardiac death, target vessel MI, or clinically driven target vessel revascularisation (TVR), and ST. Deaths that could not be attributed to another cause were regarded as cardiac deaths. Recurrent MI was defined according to the universal definition[13]. ST was classified according to the Academic Research Consortium criteria[12].

STATISTICAL ANALYSIS

Continuous variables are presented as mean±standard deviations and were compared using a Student's unpaired t-test for comparisons. Categorical variables are presented as counts and percentages, and were compared using chi-square or Fisher's exact tests, as appropriate. Kaplan-Meier methods were used to derive the event rates at follow-up. Time-to-event curves were compared between groups using the log-rank test. All reported probability values are two-sided, and a probability value <0.05 was considered significant. All data were processed using the Statistical Package for Social Sciences, Version 20 (IBM Corp., Armonk, NY, USA).

Results

PATIENT POPULATION

Between March 2013 and June 2014, 319 patients underwent PCI with one or more Absorb in a total of 406 lesions. These Absorb-treated patients represent 19.8% of the overall number of patients (n=1,610) undergoing PCI in the same period. Baseline clinical and angiographic characteristics of the overall population and in subgroups stratified by entry and exit criteria of ABSORB II are reported in **Table 1** and **Table 2**. The mean age was 60.7±9.6 years and 85% were male. Of note, 24.8% of patients had diabetes and 49.5% presented with an acute coronary syndrome (ACS).

Table 1. Baseline demographic and clinical characteristics of overall population and subgroups stratified according to ABSORB II trial inclusion and exclusion criteria.

Variable	All patients N=319	ABSORB II inclusion N=89	ABSORB II exclusion N=230	*p*-value
Age, years	60.7±9.6	61.1±8.7	60.6±9.9	0.70
Male	272 (85.3)	77 (86.5)	195 (84.8)	0.83
Hypertension	221 (69.3)	65 (73.0)	156 (67.8)	0.44
Diabetes	79 (24.8)	27 (30.3)	52 (22.6)	0.20
Current smoking	117 (36.7)	30 (33.7)	87 (37.8)	0.58
Family history of CAD	145 (45.5)	47 (52.8)	98 (42.6)	0.13
Hyperlipidaemia	187 (58.6)	58 (65.2)	129 (56.1)	0.18
Prior CABG	10 (3.1)	2 (2.2)	8 (3.5)	0.73
Prior PCI	102 (32.0)	24 (27.0)	78 (33.9)	0.29
Prior stroke/TIA	13 (4.1)	4 (4.5)	9 (3.9)	0.76
eGFR <60 ml/min	31 (9.7)	na	31 (14.2)	
Silent or stable angina	161 (50.5)	58 (65.2)	103 (44.8)	0.002
Unstable angina	54 (16.9)	31 (34.8)	23 (10.0)	<0.001
NSTEMI	46 (14.4)	na	46 (20.0)	
STEMI	58 (18.2)	na	58 (25.2)	
LVEF (%)	51.1±8.7	51.6±8.9	50.8±8.7	0.48
LVEF <30%	6 (1.9)	na	6 (2.8)	
Multivessel disease	124 (38.9)	25 (28.1)	99 (43.0)	0.02

Data are presented as mean±SD or n (%). na: not applicable, because the variable was an exclusion criterion in the ABSORB II trial. CABG: coronary artery bypass graft; CAD: coronary artery disease; eGFR: estimated glomerular filtration rate; LVEF: left ventricular ejection fraction; NSTEMI: non-ST-elevation myocardial infarction; PCI: percutaneous coronary intervention; STEMI: ST-elevation myocardial infarction; TIA: transient ischaemic attack

Table 2. Angiographic and procedural characteristics of overall population and subgroups stratified according to ABSORB II trial inclusion and exclusion criteria.

Variable	Patients N=319 Lesions N=406	ABSORB II inclusion Patients n=89 Lesions n=110	ABSORB II exclusion Patients n=230 Lesions n=296	*p*-value
Scaffolds implanted, n	1.9±1.2*	1.5±0.7*	2.0±1.3*	<0.001
Target vessel	0.07			
LMCA	9 (2.2)	na	9 (3.0)	
LAD	202 (49.8)	59 (53.6)	143 (48.3)	
CX	86 (21.2)	28 (25.5)	58 (19.6)	
RCA	108 (26.6)	23 (20.9)	85 (28.7)	
SVG	1 (0.2)	na	1 (0.3)	
Scaffolds and stents	69 (21.6)*	12 (13.5)*	57 (24.8)*	0.04
Lesion type	0.01			
A	57 (14.0)	22 (20.0)	35 (11.8)	
B1	141 (34.7)	46 (41.8)	95 (32.1)	
B2	86 (21.2)	19 (17.3)	67 (22.6)	
C	122 (30.0)	23 (20.9)	99 (33.4)	
De novo lesions	381 (93.8)	110 (100)	271 (91.6)	0.004
In-stent restenosis	25 (6.2)	na	25 (8.4)	
Chronic total occlusion	34 (8.4)	na	34 (11.5)	
Ostial lesion	16 (3.9)	na	16 (5.4)	
Bifurcation	68 (16.7)	12 (10.9)#	56 (18.9)	0.07
Lesion length (mm)	21.2±16.8	16.4±7.9	22.9±18.7	<0.0001
Lesion length >34 mm	55 (13.5)	6 (5.5)	49 (16.6)	0.006
Interpolated RVD (mm)	2.9±0.5	2.9±0.5	2.9±0.5	0.32
Lesion %diameter stenosis	83.4±12.0	81.1±10.0	84.2±12.5	0.03
Total scaffold length (mm)	32.8±21.6	25.8±11.5	35.3±23.8	<0.0001
Mean scaffold diameter (mm)	3.1±0.4	3.1±0.4	3.2±0.4	0.11
Scaffold implantation pressure, atm	13.5±3.4	13.3±3.3	13.5±3.5	0.43
Predilatation	391 (96.3)	104 (94.5)	287 (97.0)	0.39
Post-dilatation	289 (71.2)	65 (59.1)	224 (75.7)	0.002
Post-dilation balloon pressure, atm	16.6±4.3	16.3±4.2	16.7±4.4	0.49
Overlapping	132 (32.5)	24 (21.5)	108 (36.5)	0.005
Intravascular ultrasound use	37 (11.6)*	10 (11.2)*	27 (11.7)*	1.00
Optical coherence tomography use	80 (25.1)*	8 (9.0)*	72 (31.3)*	<0.0001

Data are presented as mean±SD or n (%). *Patient-based variable. # Side branch <2 mm. na: not applicable, because the variable was an ABSORB II exclusion criterion. LAD: left anterior descending; LCX: left circumflex; LMCA: left main coronary artery; RCA: right coronary artery; RVD: reference vessel diameter; SVG: saphenous vein graft

A total of 51% of lesions were type B2/C. The means of RVD and lesion length were 2.9±0.5 and 21.2±16.8 mm, respectively. The two subgroups did not differ for most demographic and clinical characteristics, except for acute MI (ABSORB II exclusion criteria) and for multivessel disease, which were significantly more common among patients with ABSORB II exclusion criteria. Compared with those fitting the trial entry criteria, these latter patients had higher proportions of type B2/C and longer lesions. Among patients with ABSORB exclusion criteria there were considerable proportions of complex lesions (i.e., bifurcation 18.9%, chronic total occlusion [CTO] 11.5%).

PROCEDURAL DETAILS AND MEDICATIONS

A total of 604 Absorb of 3.1±0.4 mm mean scaffold diameter were implanted at a mean of 13.5±3.4 atm, with a mean number of scaffolds implanted per patient of 1.9±1.2 **(Table 2)**. Predilation was performed in 96.3% of lesions. Mean scaffold length per lesion was 32.8±21 mm and placement of overlapping scaffolds was required in 32.5% of lesions. Post-dilation, at a mean pressure of 16.6±4.3 atm, was performed in 71.2% of lesions. Manual thrombectomy was performed in 59% of STEMI patients. Compared with those fitting the trial entry criteria, patients with ABSORB II exclusion criteria had received higher means of number of scaffolds

per patient and of scaffold length per lesion, and underwent post-dilatation, overlapping and intravascular imaging more frequently.

QCA data are shown in **Table 3**: the acute gain was 2.2±0.5 mm and 2.1±0.5 mm in the overall population and in patients without baseline total occlusions, respectively. Technical failure was observed in seven patients (2.2%), six of whom had a CTO treated.

At discharge, DAPT was prescribed for 12 months in 97.2% of patients. Clopidogrel, prasugrel and ticagrelor were prescribed in 50.8%, 23.2% and 26.0% of patients, respectively.

Table 3. Quantitative angiographic results.

Angiographic data	Lesion-based
Overall population	
Baseline reference vessel diameter, mm	2.94±0.45
Final reference vessel diameter, mm	3.00±0.43
Baseline in-scaffold diameter stenosis, %	83.4±12.0
Final in-scaffold diameter stenosis, %	10.3±7.6
Baseline minimal lumen diameter, mm	0.49±0.39
Final minimal lumen diameter, mm	2.69±0.41
Acute gain, mm	2.19±0.53
Non-total occlusions	
Baseline reference vessel diameter, mm	2.93±0.46
Final reference vessel diameter, mm	2.99±0.44
Baseline in-scaffold diameter stenosis, %	80.6±10.6
Final in-scaffold diameter stenosis, %	9.76±7.2
Baseline minimal lumen diameter, mm	0.58±0.36
Final minimal lumen diameter, mm	2.69±0.42
Acute gain, mm	2.10±0.51

CLINICAL OUTCOME

Complete clinical twelve-month follow-up information was available in 310 patients (97.2%). The vital status at one year was known in all patients, except one who had moved from Italy.

Over one year after Absorb implantation, TLF was recorded in 15 patients, occurring between 0-30 days in four (26.7%) patients, 30-180 days in four (26.7%) patients, and after 180 days in seven (46.6%) patients. The Kaplan-Meier cumulative incidences of TLF were 2.6% at six months and 4.9% at one year **(Table 4)**. Cumulative one-year TLF rates were 2.4% and 5.8% (p=0.19) in the subgroups with ABSORB II trial inclusion and exclusion criteria, respectively **(Table 5, Figure 1)**. Patients with one-year TLF had significantly lower (1.91±0.38 mm) acute gain than patients without TLF (2.16±0.52 mm). In addition, one-year TLF occurred at rates of 9%, 5% and 3% among patients with scaffold undersizing (n=22), correct sizing (n=201) and oversizing (n=96), respectively.

At one year, in the overall population the rate of cardiac death was 0.9%, target vessel MI was 1.3%, TLR was 4.2%, TVR was 4.5% and TVF was 5.2% **(Table 4)**. All cases of cardiac death, MI and ST occurred among patients with ABSORB II trial exclusion criteria **(Table 5)**.

Table 4. Kaplan-Meier estimates of cardiac events in the overall population.

Endpoint	6-month	1-year
Target lesion failure	2.6%	4.9%
Target vessel failure	2.6%	5.2%
All deaths	1.6%	1.9%
Non-cardiac death	0.6%	0.9%
Cardiac death	0.9%	0.9%
Any myocardial infarction*	1.3%	1.3%
TVR	2.2%	4.5%
TLR	2.2%	4.2%
Definite/probable ST	1.3%	1.3%

*All MIs were target vessel-related. TLR: target lesion revascularisation; TVR: target vessel revascularisation; ST: scaffold thrombosis

Four ST were observed: two acute definite, and two subacute, of which one was definite (at 25 days) and one was probable (at 26 days). No cases of ST were observed after 30 days. The

Table 5. One-year Kaplan-Meier estimates of cardiac events in subgroups stratified according to ABSORB II trial inclusion and exclusion criteria.

Endpoint	ABSORB II inclusion (N=89)	ABSORB II exclusion (N=230)	*p*-value
Target lesion failure	2.4%	5.8%	0.19
Target vessel failure	2.4%	6.3%	0.13
All deaths	2.2%	1.7%	0.40
Non-cardiac death	2.2%	0.4%	0.13
Cardiac death	0	1.3%	0.86
Any myocardial infarction*	0	1.8%	0.22
TVR	2.4%	5.3%	0.15
TLR	2.4%	4.9%	0.23
Definite/probable ST	0	1.7%	0.22

*All MIs were target vessel-related. TLR: target lesion revascularisation; TVR: target vessel revascularisation; ST: scaffold thrombosis

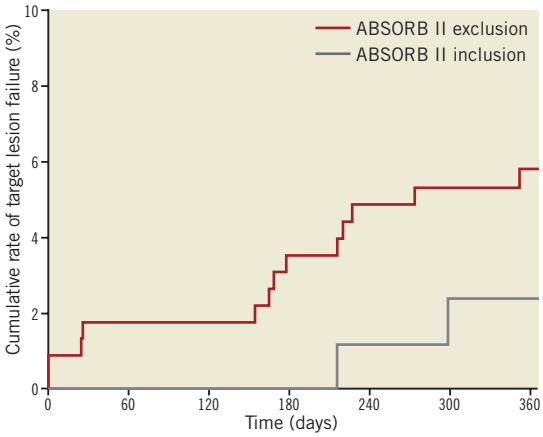

Figure 1. *One-year cumulative rates of target lesion failure in subgroups stratified according to ABSORB II trial inclusion and exclusion criteria.*

Kaplan-Meier cumulative ST incidence was 1.3% at one year. The first case of acute ST could probably be explained by residual distal edge dissection and on-treatment high platelet reactivity (HPR), as assessed by platelet function testing. The second case of acute ST occurred about one hour after PCI in a patient who had received the clopidogrel loading dose after the procedure, and who, at the time of ST, still had HPR. The subacute definite ST could be explained by DAPT cessation five days prior to ST. In the subacute probable ST, a scaffold underexpansion could be identified.

Discussion

One-year safety and efficacy data of BRS implantation in a real-world setting for the treatment of unselected populations with high proportions of complex coronary lesions typically encountered in routine clinical practice are still limited[10]. Indeed, the few one-year reports on Absorb outcomes have mostly focused on ACS patients[7,8] or have selective inclusion criteria[14]. We reported on the one-year clinical outcomes of patients enrolled in a prospective all-comers registry of Absorb from a single high-volume centre. Our data showed that Absorb were associated with reasonably low rates of TLF at one year (4.9%), particularly when considering the complexity of patients and lesions included. Four cases of definite/probable early (within one month) ST were observed, but no cases of late (>1 month) thrombosis occurred, resulting in an overall cumulative incidence of 1.3% at one year, quite similar to the incidence reported in contemporary all-comers trials and registries of second-generation DES[15,16]. For instance, in the ESTROFA-2 registry, the cumulative one-year incidences of definite/probable thrombosis were 1.3% and 1.4% for zotarolimus- and everolimus-eluting stents (EES), respectively[16]. Finally, the acute gain achieved in the present study was high and similar to that reported for DES, possibly explaining our favourable results.

Currently, the one-year outcomes of extended Absorb use in a real-world setting, including all-comers patients with a worse health status and higher proportion of complex lesions, while waiving the obligatory intravascular imaging guidance used in clinical trials, have been reported only by the ASSURE registry[10]. In this registry, very low rates (<3.0%) of device-related events were observed after Absorb implantation in 183 patients and 198 lesions. One-year rates of TLR and TVR were 2.8% and 2.2%, respectively. Moreover, there were no ST cases. The authors stated that high scaffold expansion pressure and slight oversizing seem to be the key factors in achieving good results. Despite similar procedural features, twofold higher incidences of device-related events were reported in our registry, most likely due to the more complex population treated compared with the ASSURE registry (i.e., longer lesions, higher proportions of bifurcations and CTO and inclusion of acute MI in our registry). Of note, our one-year results were similar to those reported in the first 512 patients of the ABSORB EXTEND registry, which reported a 4.9% TVF rate in a relatively selected population[14].

Recently, the results from the ABSORB II randomised trial comparing Absorb (n=335) versus XIENCE (Abbott Vascular) (n=166) have shown similar one-year rates of the device-oriented events (composite secondary endpoint) between the two devices (5% vs. 3%, respectively)[5]. Of note, patients of the present study had similar one-year outcomes to those included in the ABSORB II trial, who had relatively simpler lesions (4.9% vs. 5.0% of TLF, respectively). Interestingly, only 28% of patients included in the present registry had ABSORB II trial inclusion criteria. As expected, the one-year TLF rate was twofold higher within the group with ABSORB II exclusion criteria (5.8%) compared with the group with trial inclusion criteria, although this rate is similar to that reported for second-generation DES[15].

Unexpectedly high six-month incidences of definite/probable ST, 2.1% and 3%, have been reported among all-comers complex patients treated with Absorb in the multicentre GHOST-EU (1,189 patients) and in the single-centre Academic Medical Center (AMC, 135 patients) registries, respectively[6,7]. Importantly, in both registries, 70-75% of the ST cases occurred within 30 days after implantation, suggesting that procedural issues (i.e., residual dissection, stent malapposition or underexpansion) may be the underlying factors triggering most cases. In two out of four cases of the AMC registry, a residual distal edge dissection and an incomplete expansion of the distal scaffold edge were found. Similarly, in two of our four cases a residual distal edge dissection and underexpansion of the scaffold implanted on a severely calcified plaque were documented. Indeed, underexpansion has been identified as an important mechanism underlying ST[17]. These observations prompt the need for a more accurate lesion selection and for key implantation technique refinements, including a more accurate sizing, the systematic use of high-pressure post-dilatation with non-compliant balloons, and the more liberal use of intravascular imaging, especially in complex lesions. Of note, we observed a lower six-month ST rate (1.3%) compared with the GHOST-EU and AMC registries. This difference may be in part attributed to several technical differences, including greater post-dilatation rate, higher post-dilatation pressure, a more frequent use of intravascular imaging, especially among those with more complex lesions, and a slight scaffold oversizing in our registry. For instance, in the GHOST-EU registry, post-dilatation was performed in 49% of overall lesions versus 71.2% in our registry, and its use decreased as more experience was accumulated. By contrast, our post-dilation rate increased from around 60% in the first enrolment period (the cohort included in the GHOST-EU) to >95% thereafter.

In the blood flow, the presence of thick struts creates flow-dynamic alteration, resulting in high shear stress on top of the strut and low shear stress behind the strut, which may impact on vessel wall healing and trigger platelet aggregation[18]. In addition, in *ex vivo* studies thick-strut BRS showed higher acute thrombogenicity than thin-strut biodegradable polymer metallic EES[19]. Therefore, an adequate platelet inhibition is key to prevent ST. In the AMC registry, two out of four cases of ST occurred in patients

discontinuing DAPT. In our registry, DAPT-related issues were present in three out of four cases of ST. Whether the use of more potent antiplatelet agents (prasugrel or ticagrelor) after Absorb implantation might decrease ST is plausible but is not known and warrants dedicated investigations.

Study limitations

Our study suffers from the obvious limitations of an observational real-world registry, including patient selection bias and no independent event adjudication. Patients who received metallic stents together with Absorb represented about 22% of the overall population. To account for the potential influence of these patients on outcomes, the device-oriented composite endpoint was reported to represent the clinical performance of a new device[12]. Furthermore, the study lacks a control group. Finally, for the present general analysis we have not used a dedicated bifurcation QCA algorithm, which has recently been recommended[20].

Conclusions

The GHOST registry has shown that one-year "real-world" safety and efficacy outcomes of Absorb use for the treatment of unselected patients with high proportions of complex lesions are, overall, acceptable and comparable to those reported in the literature for second-generation DES. Several implantation technique features are key to achieve good angiographic and clinical results with Absorb, especially in more complex settings. Nevertheless, longer follow-up and randomised comparisons versus best-in-class DES are needed to confirm the promising results.

Impact on daily practice

The present study provides favourable six-month and one-year safety and efficacy outcomes associated with the implantation of bioresorbable scaffolds (BRS) in an unselected population with a high proportion of complex lesions. These results provide additional supportive evidence for the use of BRS in daily practice under real-world conditions. In particular, the findings of the present study suggest a key positive association between good clinical results and an optimal implantation technique, which should be pursued in daily practice.

Conflict of interest statement

C. Tamburino has received honoraria/lecture fees from Medtronic, Abbott Vascular and Edwards Lifesciences. D. Capodanno has served on advisory boards of Eli Lilly/Daiichi Sankyo, AstraZeneca, The Medicines Company and Abbott Vascular. The other authors have no conflicts of interest to declare.

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Computing Methods for Composite Clinical Endpoints in Unprotected Left Main Coronary Artery Revascularization

A Post Hoc Analysis of the DELTA Registry

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ABSTRACT

OBJECTIVES The study sought to investigate the impact of different computing methods for composite endpoints other than time-to-event (TTE) statistics in a large, multicenter registry of unprotected left main coronary artery (ULMCA) disease.

BACKGROUND TTE statistics for composite outcome measures used in ULMCA studies consider only the first event, and all the contributory outcomes are handled as if of equal importance.

METHODS The TTE, Andersen-Gill, win ratio (WR), competing risk, and weighted composite endpoint (WCE) computing methods were applied to ULMCA patients revascularized by percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) at 14 international centers.

RESULTS At a median follow-up of 1,295 days (interquartile range: 928 to 1,713 days), all analyses showed no difference in combinations of death, myocardial infarction, and cerebrovascular accident between PCI and CABG. When target vessel revascularization was incorporated in the composite endpoint, the TTE ($p = 0.03$), Andersen-Gill ($p = 0.04$), WR ($p = 0.025$), and competing risk ($p < 0.001$) computing methods showed CABG to be significantly superior to PCI in the analysis of 1,204 propensity-matched patients, whereas incorporating the clinical relevance of the component endpoints using WCE resulted in marked attenuation of the treatment effect of CABG, with loss of significance for the difference between revascularization strategies ($p = 0.10$).

CONCLUSIONS In a large study of ULMCA revascularization, incorporating the clinical relevance of the individual outcomes resulted in sensibly different findings as compared with the conventional TTE approach. In particular, using the WCE computing method, PCI and CABG were no longer significantly different with respect to the composite of death, myocardial infarction, cerebrovascular accident, or target vessel revascularization at a median of 3 years. (J Am Coll Cardiol Intv 2016;9:2280–8) © 2016 by the American College of Cardiology Foundation.

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Percutaneous coronary intervention (PCI) is broadly accepted as an alternative to coronary artery bypass grafting (CABG) when patients with unprotected left main coronary artery (ULMCA) disease present with low-to-intermediate angiographic complexity, which reflects contemporary guidelines (1) and the results of a plethora of meta-analyses (2–4), trials (5–8), and registries (9–13). Over the years, these studies have mostly investigated the comparative efficacy of PCI and CABG with respect to a primary composite endpoint mixing disparate cerebrovascular outcomes (i.e., death, myocardial infarction [MI], and cerebrovascular accident [CVA] with or without repeat revascularization).

SEE PAGE 2289

In both randomized and nonrandomized studies, the rationale behind merging events into a single composite measure is that of increasing the power of the comparison between study groups, which is expected to reduce the chance of untruly negative results. However, an inherent limitation of using a composite endpoint in ULMCA studies is that all the contributory outcomes are handled as if of equal importance (14). This becomes problematic when the implications of a relatively soft event (i.e., repeat revascularization) are contrasted with those of other disabling nonfatal events (i.e., MI or CVA). In addition, when composite endpoints are used, time-to-event (TTE) statistics consider only the first event, and the outcomes are typically counted in a non-hierarchical order (i.e., if repeat revascularization occurs in 1 group before death, only the first contributes to the drop of the corresponding curve for event-free survival). Finally, death may exert a competing effect on the risk of nonfatal events (15).

To address these limitations, multiple statistical approaches have been introduced that consider all events occurring at follow-up, incorporate their clinical relevance, or account for the competing risk of death (16–19). The merit of these computing methods, and their impact on the results of contemporary studies comparing PCI and CABG for ULMCA disease, have never been systematically investigated. The aim of this study was to explore the attributes of different analytical strategies for composite endpoints using DELTA (Drug Eluting stent for LefT main coronary Artery disease), 1 of the largest contemporary registries of ULMCA disease, as an example.

METHODS

STUDY DESIGN AND POPULATION. The methods and definitions of the DELTA registry have been published previously (9). Briefly, DELTA included all-comers patients with ULMCA disease treated by PCI with drug-eluting stents or CABG between April 2002 and April 2006 at 14 international sites (9). The primary analysis was based on the composite of death, MI, or CVA, and a secondary analysis was based on the composite of death, MI, CVA, and target vessel revascularization (TVR), herein cumulatively referred as major adverse cardiac or cerebrovascular events (MACCE). In the present study, the death/MI/CVA and MACCE results of DELTA were used as a reference to explore the effect of applying 4 computing strategies other than the conventional TTE approach, namely: 1) Andersen-Gill; 2) win ratio (WR); 3) competing risk; and 4) weighted composite endpoint (WCE). Merits and limitations of these approaches are summarized in **Table 1**.

ANDERSEN-GILL. The Andersen-Gill counting process is an extension of the traditional Cox model in which a subject contributes to the risk set for an event as long as being under observation at the time the event occurs (20). At variance with the TTE approach, repeated events are described among all components of the primary endpoint for the overall period, assuming equal probability. To avoid too much weight for related events occurring at the same time, a 1-day blanking period was applied. The results were reported as hazard ratio (HR) and 95% confidence interval (CI).

ABBREVIATIONS AND ACRONYMS

CABG = coronary artery bypass grafting
CI = confidence interval
CVA = cerebrovascular accident
HR = hazard ratio
MACCE = major adverse cardiac or cerebrovascular event(s)
MI = myocardial infarction
PCI = percutaneous coronary intervention
TTE = time-to-event
TVR = target vessel revascularization
ULMCA = unprotected left main coronary artery
WCE = weighted composite endpoint
WR = win ratio

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WIN RATIO. The WR is a rank-based approach for assessing treatment superiority by first ranking and then pairing patients between treatment groups according to different scores, as described by Pocock et al. (17). To the purpose of the present study, 3 scores were used: 1) the propensity score built by logistic regression to match patients undergoing PCI or CABG in the first report of the DELTA registry (9); 2) the SYNTAX (Synergy between PCI with Taxus and Cardiac Surgery) score; and 3) the SYNTAX score II (PCI calculator). A multiple imputation strategy was used for patients missing data required to compute their SYNTAX and SYNTAX II-PCI scores, as previously described (21). In the 3 scenarios (propensity score, SYNTAX score, and SYNTAX II score), each patient pair was evaluated to establish whether one had a death event before the other. If this was not the case (i.e., both matched patients were alive at the end of follow-up), the remaining pairs were then evaluated for the occurrence of CVA, then subsequently MI, and finally TVR (the latter in the MACCE analysis only). When pairing patients by the use of the SYNTAX and SYNTAX II scores, the treatment groups were unbalanced in number; therefore, after ranking, patients in the larger group (i.e., PCI) were randomly removed if a matching for the score was not found with the CABG counterpart. When patients in the PCI group had the same score, a random one was selected. Once the pairs were created, the number of "wins" (i.e., pairs where the CABG group had the event first) were divided by the number of "losses" (i.e., pairs where the PCI group had the event first) to provide the WR for PCI versus CABG (i.e., with a WR >1 indicating PCI as the better revascularization strategy, and values <1 indicating PCI as worse). Corresponding 95% CIs and significance tests for the WRs were calculated.

COMPETING RISK. A competing risk is an event that either hinders the observation of the event of interest or modifies the chance that this event occurs. Competing risks methods take these issues into account and, for composite endpoints, allow disentangling the contribution of an intervention on each type of event (19). In this study, the competing risk of death for combined nonfatal outcomes (MI/CVA or MI/CVA/TVR) was accounted using the Fine-Gray model, with results reported as HR and 95% CI (22).

WEIGHTED COMPOSITE ENDPOINT. The WCE computing approach extends the traditional TTE methodology by determining a weight for each of the nonfatal events (16,23). Briefly, each patient was attributed a weight of 1.0, which remained unaltered if no events occurred at follow-up. Patients with nonfatal events were considered to have their contribution to the group size reduced in weight, such that the additional weight was lost for subsequent events and the full (or residual) weight was lost for a death event. Consistent with a previous study (16), we assigned weights of 0.47 and 0.38 for CVA and MI, respectively. For TVR, a Markov decisional analytical model was designed to identify the cut off value that offsets the anticipated increase in TVR with PCI compared with CABG (24). Data from available ULMCA trials, registries, and meta-analyses were used to inform the Markov model, which finally assigned a weight of 0.25 to TVR (2–13). On the basis of the previous values, patients without events were attributed a cumulative weighting of 1, patients with CVA had 0.53 (1.00 − 0.47), patients with MI had 0.62 (1.00 − 0.38), and patients with TVR had 0.75 (1.00 − 0.25). Patient with ≥2 events during the follow-up period, if any, were attributed a cumulative weight reduced by all events.

TABLE 1 Characteristics of Different Computing Methods for Composite Clinical Outcomes

	Time-to-Event	Andersen-Gill	Win Ratio	Competing Risk	WCE
Uses first event	Yes	Yes	No	Yes	Yes
Uses all events	No	Yes	No	No	Yes
Death as most relevant	No	No	Yes	No	Yes
Uses time-to-event	Yes	Yes	No	Yes	Yes
Distribute weights	No	No	No	No	Yes

WCE = weighted composite event(s).

STATISTICAL ANALYSIS. In the DELTA registry, the propensity score was calculated by means of a nonparsimonious multivariable logistic regression model that included age, gender, diabetes, smoking, family history of coronary artery disease, unstable angina, acute MI, chronic kidney disease, left ventricular ejection fraction, prior CABG, prior PCI, multivessel disease, and concurrent right coronary artery disease (9). Propensity score matching was performed 1:1 with a ±0.03 caliper and no replacement. A multivariable Cox proportional hazards regression model was used to obtain adjusted analyses, as previously described (9). Traditional TTE curves for propensity-matched patients were generated with the Kaplan-Meier method and compared by the log-rank test. WCE Kaplan-Meier curves were also plotted. The TTE risks of death/MI/CVA and MACCE were reported for PCI versus CABG as HRs and corresponding 95% CIs. All the analyses were performed using SPSS version 21.0 (SPSS Inc., Chicago, Illinois) and R version 2.16 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

The DELTA registry comprised a total of 2,775 patients with ULMCA disease (1,874 treated with PCI and 901 treated with CABG) (9). Baseline clinical characteristics of the study groups before and after propensity score matching of 602 pairs are reported in Table 2. The c-statistic of the propensity score model was 0.78, and the Hosmer-Lemeshow p value was 0.38, indicating good discrimination and calibration, respectively. At a median follow-up of 1,295 days (interquartile range: 928 to 1,713 days), in the unmatched cohort, there were 367 deaths, 108 MIs, 55 CVAs, and 334 TVRs (Table 3). In the matched cohort, there were 141 deaths, 23 MIs, 18 CVAs, and 102 TVRs, with only 4 patients experiencing a second event within the follow-up period (2 patients had MI and later had TVR, 1 patient had TVR and later had a CVA, and 1 patient had TVR and later had MI).

TIME-TO-EVENT. Using the TTE approach, there were no differences between PCI and CABG for death/MI/CVA in either unadjusted (HR: 1.11; 95% CI: 0.89 to 1.36; p = 0.38), multivariable-adjusted (HR: 1.11; 95% CI: 0.85 to 1.42; p = 0.47), or propensity score-matched (HR: 0.91; 95% CI: 0.66 to 1.26; p = 0.57) analyses. By contrast, CABG was superior to PCI with respect to MACCE in either unadjusted (HR: 1.58; 95% CI: 1.32 to 1.90; p < 0.0001), multivariable-adjusted (HR: 1.64; 95% CI: 1.33 to 2.03; p < 0.0001), or propensity score-matched (HR: 1.35; 95% CI: 1.03 to 1.76; p = 0.03) analyses, driven by a significant difference in TVR.

ANDERSEN-GILL. Applying the Andersen-Gill counting process to the outcomes of the propensity-matched cohort confirmed the results of the TTE analysis. In fact, the HRs for death/MI/CVA and MACCE were 1.01 (95% CI: 0.76 to 1.36; p = 0.93) and 1.41 (95% CI: 1.12 to 1.79; p = 0.04), respectively.

WIN RATIO. In the first scenario (propensity score, 602 pairs), the WRs for death/MI/CVA and MACCE were 1.04 (95% CI: 0.77 to 1.39; p = 0.82) and 0.75 (95% CI: 0.58 to 0.96; p = 0.025). In the second scenario (SYNTAX score, 901 pairs), the WRs for death/MI/CVA and MACCE were 0.98 (95% CI: 0.77 to 1.26; p = 0.90) and 0.79 (95% 0.64 to 0.97; p = 0.028). In the third scenario (SYNTAX II score, 901 pairs), the WRs for death/MI/CVA and MACCE were 0.94 (95% CI: 0.73 to 1.20; p = 0.611) and 0.71 (95% CI: 0.58 to 0.88; p = 0.001). Overall, all 3 scenarios—regardless of the score used for pairing—showed similar results that were consistent with the TTE analysis, suggesting CABG to represent the best strategy only when TVR was included in the composite endpoint (Figure 1).

TABLE 2 Baseline Characteristics of the Propensity-Matched Groups

	All (N = 1,204)	PCI (n = 602)	CABG (n = 602)	p Value
Male	797 (66.2)	406 (67.4)	391 (65.0)	0.36
Age, yrs	66.5 ± 11.0	66.3 ± 11.5	66.8 ± 10.5	0.41
Family history of CAD	327 (27.2)	162 (26.9)	162 (27.4)	0.85
Hypertension	808 (67.1)	398 (66.1)	398 (68.1)	0.46
Dyslipidemia	757 (62.9)	363 (60.3)	363 (65.6)	0.07
Smoker	512 (42.5)	253 (42.0)	253 (43.0)	0.73
Diabetes	374 (31.1)	184 (30.6)	184 (31.6)	0.71
CKD	62 (5.1)	30 (5.0)	32 (5.3)	0.79
Clinical presentation				
Unstable angina	532 (44.2)	532 (44.7)	532 (43.7)	0.73
Acute MI	178 (14.8)	178 (15.3)	178 (14.3)	0.63
Previous CABG	47 (3.9)	47 (4.3)	47 (3.5)	0.46
Previous PCI	198 (16.4)	198 (16.1)	198 (16.8)	0.76
LVEF, %	53.2 ± 11.3	53.2 ± 11.3	53.2 ± 11.4	0.96
EuroSCORE, n	5.0 ± 3.2	5.0 ± 3.6	5.1 ± 2.9	0.60
Multivessel disease	1,127 (93.6)	564 (93.7)	563 (93.5)	0.91
RCA disease	841 (69.9)	427 (70.9)	414 (68.8)	0.41
Distal lesion location	777 (64.5)	387 (64.5)	390 (64.8)	0.92

Values are n (%) or mean ± SD.

CABG = coronary artery bypass grafting; CAD = coronary artery disease; CKD = chronic kidney disease; EuroSCORE = European System for Cardiac Operative Risk Evaluation; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PCI = percutaneous coronary intervention; RCA = right coronary artery.

COMPETING RISK. After accounting for the competing risk of death, the HRs for combined nonfatal events were 0.85 (95% CI: 0.46 to 1.58; p = 0.61) with respect to MI/CVA and 1.89 (95% CI: 1.33 to 2.68; p < 0.001) with respect to MI/CVA/TVR.

WEIGHTED COMPOSITE ENDPOINTS. Kaplan-Meier curves using the TTE approach and modified

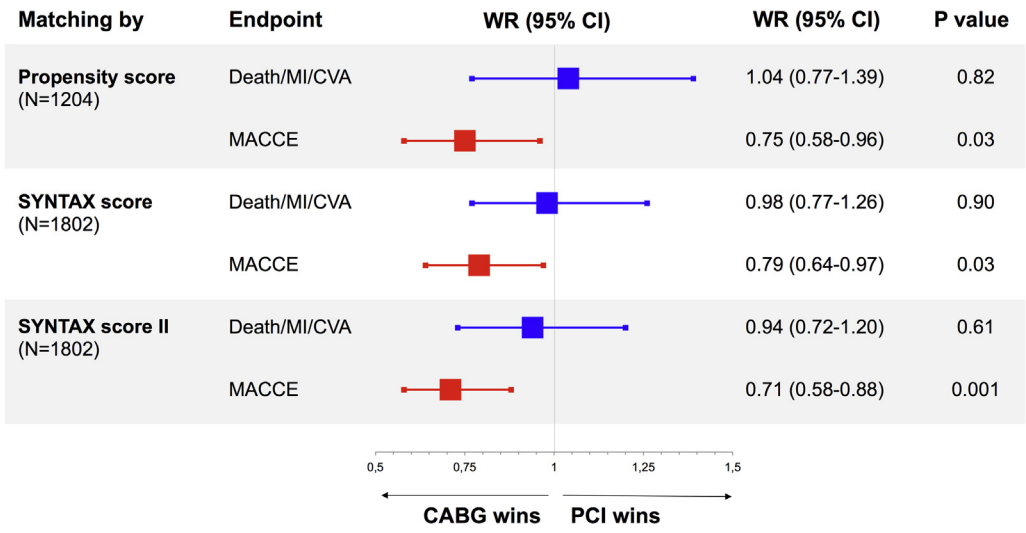
TABLE 3 Clinical Events in the Unmatched Cohorts

	PCI (n = 1,874)	CABG (n = 901)
In-hospital events		
Cardiac death	33 (1.7)	20 (2.2)
Noncardiac death	8 (0.5)	9 (1.0)
MI	88 (4.7)	213 (23.6)
CVA	4 (0.2)	12 (1.3)
TVR	15 (0.8)	3 (0.3)
MACCE	148 (7.9)	257 (28.4)
Events at follow-up		
Cardiac death	140 (7.5)	61 (6.8)
Noncardiac death	124 (6.6)	42 (4.6)
MI	75 (3.7)	33 (4.0)
CVA	30 (1.6)	25 (2.9)
TVR	290 (15.5)	44 (5.2)
MACCE	659 (34.9)	205 (23.5)

Values are n (%).

CVA = cerebrovascular accident; MACCE = major adverse cardiac or cerebrovascular event(s); TVR = target vessel revascularization; other abbreviations as in Table 2.

FIGURE 1 Win Ratio Estimates Based on Different Matching Criteria



Graphical representation of win ratio (WR) estimates and corresponding 95% confidence intervals (CIs) in patients from the DELTA (Drug Eluting stent for LefT main coronary Artery disease) registry for the comparison of percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG), based on different matching criteria. The results were confirmative of the corresponding traditional time-to-event analyses and did not appear to rely on the method chosen for matching (i.e., propensity score, SYNTAX [Synergy between PCI with Taxus and Cardiac Surgery] score, SYNTAX score II). CVA = cerebrovascular accident; MACCE = major adverse cardiac or cerebrovascular event(s); MI = myocardial infarction.

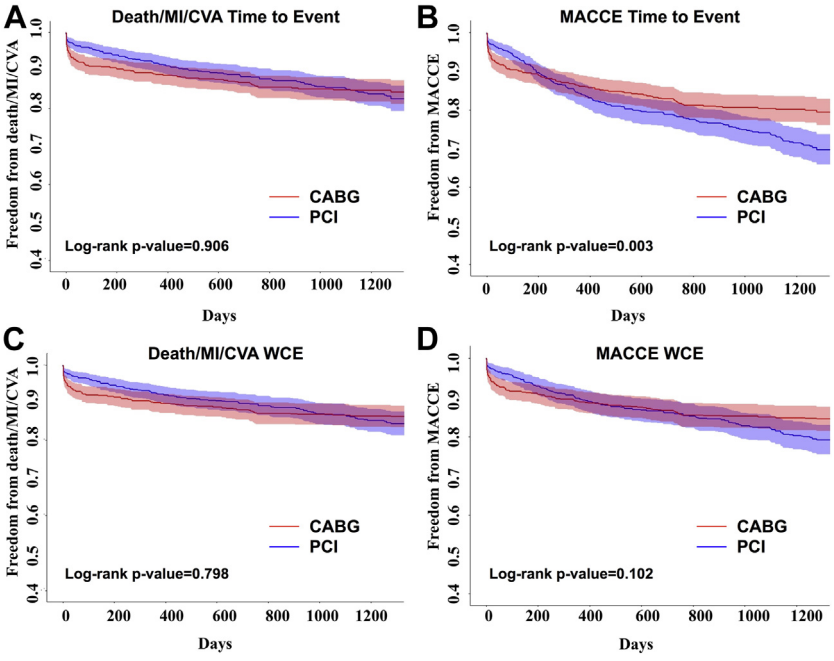
Kaplan-Meier curves using WCEs are shown for PCI and CABG groups of patients matched by propensity score in Figure 2. Table 4 reports corresponding 1-, 2-, and 3-year Kaplan-Meier estimates of PCI and CABG as reflected by the TTE and WCE analyses, as well as the absolute risk differences between PCI and CABG, and within PCI or CABG by using different computing methods. The profile of the TTE and WCE curves for death/MI/CVA was comparable (Figure 2), with the outcomes of PCI and CABG diverging during the first 100 days and the difference attenuating over time until the curves reached substantial overlap at the end of the follow-up period. Inclusion of TVR in the composite MACCE endpoint resulted in CABG being superior to PCI in the TTE analysis, with a progressive separation of the curves starting at 9 months ($p = 0.003$) (Figure 2). By contrast, this difference was markedly attenuated and no longer significantly different ($p = 0.10$) when the WCE computing method was used (Table 4). This finding was consistent in a sensitivity analysis where the weight given to TVR was 0.30 rather than 0.25 ($p = 0.08$).

EFFICIENCY OF EVENT USE. The distribution and use of events according to the TTE, Andersen-Gill, WR, competing risk, and WCE methods are reported in Table 5. The Andersen-Gill and WCE methods included all events, whereas the TTE, WR, and competing risk methods used fewer than all collected events.

DISCUSSION

TVR has been for years the driving force of the observed superiority of CABG over PCI in ULMCA studies (25). However, the true impact of repeat revascularization on patient well-being and quality-adjusted life-years has been questioned (26), and some interventional cardiologists argue that the reduction in revascularization with CABG does not outweigh the increased recovery time of cardiac surgery, and the higher risk of perioperative CVA (14). In the DELTA registry, there was evidence of substantial equipoise between PCI and CABG for death/MI/CVA, but not for MACCE (9). This is in line with the results of several meta-analyses (2-4), randomized clinical trials (5-8), and observational studies (9-13). On this background, we sought to explore whether applying alternative methods for assessing clinical outcomes within composite endpoints may depotentiate the confounding effect of TVR, and provide insights on potentially

FIGURE 2 Event-Survival Curves in the Propensity-Matched Cohorts



Survival curves with 95% CIs in PCI and CABG patients from the DELTA (Drug Eluting stent for LefT main coronary Artery disease) registry, matched by propensity score (602 pairs). Time-to-event freedom from **(A)** death/MI/CVA and **(B)** MACCE. WCE curves for **(C)** death/MI/CVA and **(D)** MACCE. WCE = weighted composite endpoint; other abbreviations as in Figure 1.

different interpretations to the results of contemporary ULMCA studies.

In our analysis, the use of a computing method that describes repeated events among all components of the primary endpoint (i.e., Andersen-Gill), prioritizes all follow-up events (i.e., WR), or accounts for the potential of death to obscure subsequent nonfatal outcomes (i.e., competing risk) determined no significant deviation from what was obtained by computing only the first event regardless of its fatality rate (i.e., TTE). By contrast, incorporating the clinical relevance of the individual outcomes (i.e., WCE) resulted in PCI and CABG being nonsignificantly different at a median of 3 years with respect to the composite endpoint of MACCE, which comes at variance with the propensity-matched TTE analysis of PCI and CABG in DELTA. Overall, these findings imply that the sizeable impact of TVR on MACCE in ULMCA studies may be corrected or attenuated by using an alternative computing approach that accounts for all events occurring at follow-up and incorporates their clinical relevance.

To the best of our knowledge, this is the first study to apply additional methods other than TTE for assessing clinical outcomes in the context of a study of PCI or CABG for ULMCA disease. The Andersen-Gill computing method was introduced in 1982, and is regarded as a meaningful approach to account for repeated events within the follow-up period (20). Indeed, a patient undergoing ULMCA revascularization may experience from repeated events during the subsequent years (i.e., multiple TVRs), but this was unlikely to happen in the propensity-matched cohort of the DELTA registry, where the number of repeated events was low, and the potential for events that may be under-reported or insufficiently captured by the extent of follow-up available cannot be entirely ruled out (9). These considerations may contribute to explain why in our study, the results of the Anderson-Gill analysis substantially replicated those of the TTE analysis, regardless of whether TVR was incorporated or not in the composite endpoint. In a population with multiple recurrent events, the results of the Andersen-Gill method could have been different. Also notably, the Andersen-Gill method assumes equal probabilities for first and subsequent events, which may be an unlikely assumption in a general population, although this issue has been likely minimal in this study due to the few number of repeated events. Alternative models have been

TABLE 4 Kaplan-Meier Estimates of Survival Free From Death/MI/CVA and MACCE Based on the TTE and WCE Computing Methods

	TTE		WCE		Δ	Δ	Δ	Δ
	PCI (A)	CABG (B)	PCI (A′)	CABG (B′)	PCI (A′-A)	CABG (B′-B)	TTE (B-A)	WCE (B′-A′)
Death/MI/CVA								
1 year	91.8%	88.9%	92.5%	89.9%	+0.7%	+1.0%	-2.9%	-2.6%
2 years	88.1%	86.4%	89.6%	87.9%	+1.5%	+1.5%	-1.7%	-1.7%
3 years	85.4%	84.9%	86.9%	86.7%	+1.5%	+1.8%	-0.5%	-0.2%
MACCE								
1 year	84.1%	86.0%	89.5%	88.8%	+5.4%	+1.8%	+1.9%	-0.7%
2 years	78.4%	82.4%	85.8%	86.4%	+7.4%	+4.0%	+4.0%	+0.6%
3 years	74.0%	80.3%	82.3%	84.9%	+8.3%	+4.5%	+6.3%	+2.6%

TTE = time-to-event; WCE = weighted composite event(s); other abbreviations as in Tables 2 and 3.

described that take the varying nature of risk for repeated events into account (27).

The WR analysis was introduced in 2012 and so far investigated only in few clinical scenarios (16,17). This approach allows prioritizing the hardest outcomes within a composite endpoint. Interestingly, with the WR, more of the component events are potentially included and computed in the analysis, whereas TTE retains only 1 event. However, because this method prioritizes and retains events, a number of nonfatal endpoints experienced by a subject are finally excluded. This explains why the largest proportion of events that went unused by the different computing methods was observed with the WR. Being a rank-based approach, calculation of the WR requires pairing of patients between treatment groups according to a risk score. The rationale for pairing patients by propensity score in our study was that of using one of the most accepted methodologies to adjust for baseline imbalances that could have influenced the patient attribution to a treatment group rather than the other in a large registry (28,29). For exploratory purposes, the SYNTAX and SYNTAX II scores were also used to reflect the underlying risk for the outcomes of interest and investigate their individual ability and implication as a matching criterion (21,30). Interestingly, all the 3 approaches provided similar results, which highlights the ability of the SYNTAX score and SYNTAX score II to capture and possibly maximize the control of major confounding factors affecting treatment selection in ULMCA disease.

Because death was the most frequent first event in the DELTA registry, we also explored whether a competing risk of mortality exists over the composite of nonfatal outcomes (i.e., MI/CVA and MI/CVA/TVR). Obviously, if a patient dies, there is no chance to experience subsequent nonfatal outcomes at later follow-up. The results of the competing risk analysis demonstrate that this bias was unlikely to affect the results of the DELTA registry, and confirmed the major role of TVR in driving the difference between PCI and CABG.

Using WCE allows attributing a weight to each type of event within a composite endpoint, differentiating its components on the basis of their severity and clinical impact. In addition, WCE allows including in the analysis multiple events occurring over time. Capturing the second event(s) is potentially relevant, as recurrences have clear implications for both health care costs and quality of life: this may be true especially when long-term follow-up is planned and the majority of events are nonfatal. Even more importantly, the attribution of a differential weight to each event addresses the problematic interpretation of mixing hard and soft outcomes within a composite endpoint, which frequently occurs in studies of ULMCA revascularization. Notably, the WCE method is different from the Andersen-Gill approach that also considers second events, because in that case, the weights of all recurrent events are considered equal. Our hypothesis of the WCE analysis displaying different results from the TTE computing method proved to be true once tested in the DELTA registry. In fact, PCI was no longer associated with worse outcomes compared with CABG when the lower prognostic weight of TVR over death, MI and CVA was taken into account. It can be speculated that weighting the lower risk of CVA compensates the excess in TVR with PCI compared with CABG patients (2). On this background, whether the use of second-generation drug-eluting stents—poorly represented in the DELTA registry—further modifies this equation, moving the pendulum toward PCI, may warrant future investigation.

The EXCEL (Evaluation of the Xience Everolimus-Eluting Stent Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) trial (NCT01205776) recently compared PCI with second-generation drug-eluting stents and CABG with respect to the composite of all-cause death, MI, or stroke at 3 years (31). By contrast, the NOBLE (Nordic-Baltic-British Left Main Revascularization Study) trial (NCT01496651) compared PCI with second-generation drug-eluting stents and CABG with respect to the 5-year combined endpoint of death, stroke, MI, and new revascularization (PCI or CABG) (32). Incorporation of repeat revascularization in the primary endpoint of the NOBLE trial is one of the potential explanations for the difference in the results and conclusions of the two trials (31,32). In this context, challenging the study findings of NOBLE by using WCE is of interest.

TABLE 5 Distribution and Weighting of MACCE by Computing Method

	All		Death		MI		CVA		TVR	
	PCI	CABG	PCI	CABG	PCI	CABG	PCI	CABG	PCI	CABG
All events*	169 (Ref)	115 (Ref)	75 (Ref)	66 (Ref)	13 (Ref)	10 (Ref)	6 (Ref)	12 (Ref)	75 (Ref)	27 (Ref)
TTE	166 (98.2)	114 (99.1)	75 (100.0)	66 (100.0)	13 (100.0)	9 (90.0)	5 (83.3)	12 (100.0)	73 (97.3)	27 (100.0)
Andersen-Gil	169 (100.0)	115 (100.0)	75 (100.0)	66 (100.0)	13 (100.0)	10 (100.0)	6 (100.0)	12 (100.0)	75 (100.0)	27 (100.0)
WR†	141 (83.4)	103 (89.5)	68 (90.7)	63 (95.5)	11 (84.6)	10 (90.9)	6 (100.0)	12 (100.0)	56 (75.7)	18 (69.2)
Competing risk	166 (98.2)	114 (99.1)	75 (100.0)	66 (100.0)	13 (100.0)	9 (90.0)	5 (83.3)	12 (100.0)	73 (97.3)	27 (100.0)
WCE	169 (100.0)	115 (100.0)	75 (100.0)	66 (100.0)	13 (100.0)	10 (100.0)	6 (100.0)	12 (100.0)	75 (100.0)	27 (100.0)

Values are n (%). *In the periprocedural period (i.e., within 72 h), there were 9 deaths, 3 MIs, 0 CVAs, and 1 TVR in the PCI group and 20 deaths, 2 MIs, 2 CVAs, and 2 TVRs in the CABG group. †With the win ratio (WR), more of the component events are potentially included and computed in the analysis, whereas TTE retains only 1 event. However, because this method prioritizes and retains events, a number of nonfatal endpoints experienced by a subject are finally excluded.

TVR = target vessel revascularization; Ref = reference; other abbreviations as in Tables 2, 3, and 4.

STUDY LIMITATIONS. We acknowledge some important limitations of our study. The impact of different computing strategies for composite endpoints was tested on a propensity-matched cohort from a large registry, rather than a randomized clinical trial. However, the propensity-matched results of the DELTA registry are in line with existing literature, including randomized trials, and the impact of confounding has been minimized—although not eliminated—by a well-calibrated and discriminative model. Indeed, using randomized data would have not necessarily been a better method for investigating the WR, which requires matching being performed by a risk score rather than the play of chance. The attribution of weights for the purposes of the WCE analysis might sound arbitrary. However, for MI and CVA, we used weights attributed on the basis of a rigorous consensus (16). Because such weights have not been determined for TVR, we developed a Markov model, and based on the available literature, we found a clinically plausible value of 0.25. A sensitivity analysis in which the weight was increased at 0.30 showed consistent results. We finally acknowledge that our results apply to the cohort of patients included in the DELTA registry, but could have been different in other settings with a higher rate of recurrent events or a larger disproportion between hard and soft endpoints.

CONCLUSIONS

Repeat revascularization is the major contributing factor to explain the superiority of CABG over PCI for MACCE in studies of ULMCA disease. In this post hoc analysis of the DELTA registry, incorporating the clinical relevance of individual outcomes within MACCE resulted in a sensible deviation from the results otherwise obtained by the conventional TTE analysis, with PCI and CABG being no longer different at a median of 3 years.

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PERSPECTIVES

WHAT IS KNOWN? Time-to-event statistics for composite outcome measures used in ULMCA studies consider only the first event, and all the contributory outcomes are handled as if of equal importance.

WHAT IS NEW? In ULMCA revascularization studies, weighting events is the most effective method to reduce the impact of TVR on the combined clinical endpoint, resulting in no difference between PCI and CABG at a median of 3 years.

WHAT IS NEXT? The weight of TVR should be taken into account in revascularization studies that use combined primary endpoints. The impact of computing methods for composite endpoints other than time-to-event statistics should be reappraised in populations with long-term follow-up and multiple repeated nonfatal events.

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KEY WORDS **Andersen-Gill, competing risk, left main, weighted composite event(s), win ratio**

ORIGINAL RESEARCH

Stent and Dual Antiplatelet Therapy Duration Comparisons in the Setting of a Multicenter Randomized Controlled Trial: Can the Operator Experience Affect the Study Results?

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Background—Operator experience influences outcomes after percutaneous coronary intervention, but this association in the controlled setting of a randomized, clinical trial is unclear.

Methods and Results—We investigated operator-related outcomes (30-day and 2-year efficacy and safety end points) among patients undergoing percutaneous coronary intervention and randomized to different dual antiplatelet therapy durations and stent types. A total of 2003 patients were analyzed, and 7 operator groups were compared. The majority of preprocedural and postprocedural characteristics were imbalanced. The primary end point of the study, the composite of death, myocardial infarction, or cerebrovascular accidents, did not differ among operators at 30 days or 2 years. There were no significant differences also for all other individual and composite end points analyzed at 30 days and 2 years, except for 2-year stent thrombosis (P=0.048) and bleeding events (P=0.022 for Bleeding Academic Research Consortium type 2, 3, or 5). Adjusted comparisons for the main end points showed slight differences among operators at 30 days, but not at 2 years. There was no interaction of operator with dual antiplatelet therapy duration (P=0.112) or stent type (P=0.300). Results remained entirely consistent when operators were stratified by their experience.

Conclusions—There was a weak signal of heterogeneity across study operators for the 30-day, but not the 2-year, main study outcomes. No clear effect of operator or operator experience was observed for the comparative efficacy and safety profile of the randomized stent types or dual antiplatelet therapy duration regimens.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00611286. **(*J Am Heart Assoc*. 2017;6: e007150. DOI: 10.1161/JAHA.117.007150.)**

Key Words: clinical outcomes • operator • percutaneous coronary intervention • randomized trial

Owing to innovations in device technology and improved operator techniques, percutaneous coronary intervention (PCI) has become a widely used and reproducible therapeutic procedure for the entire spectrum of coronary artery disease.[1,2]

Complications during and after PCI have dramatically declined during the past decades. Yet, periprocedural and postprocedural ischemic and bleeding adverse events still occur in a sizable proportion of patients. Although patient-related factors are known to play a key role for those

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Accompanying Tables S1 through S4 and Figures S1 through S5 are available at http://jaha.ahajournals.org/content/6/12/e007150/DC1/embed/inline-supplementary-material-1.pdf

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Clinical Perspective

What Is New?

- Observational studies suggest that operator volume/experience influences outcomes after percutaneous coronary intervention, but this is poorly explored in randomized, clinical trials, and there is ongoing debate on whether operator experience may influence reliability of trials findings.
- We compared operators in PRODIGY (Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia Study), a 4-by-2 randomized multicenter all-comer percutaneous coronary intervention trial comparing 4 stent types and 2 dual antiplatelet therapy duration regimens.
- We observed imbalances in the patient's and procedural characteristics and found weak differences in rates of clinical outcomes.
- After adjustment, there was a weak signal of heterogeneity across operators for 30-day, but not 2-year, main outcomes.
- When operators were stratified by their experience, no effect on clinical outcomes was observed.

What Are the Clinical Implications?

- No significant interactions were found between operators or operator experience and randomized dual antiplatelet therapy duration or stent type; thus, overall findings of the trial remained consistent.
- A prolonged dual antiplatelet therapy regimen failed to improve outcomes, irrespective of the operators.
- The routine collection of high-quality data sets should be encouraged to evaluate and improve operator competence and to allow investigation of operator as effect modifier of findings, especially for short-term outcomes after percutaneous coronary intervention, even in the controlled setting of a randomized, clinical trial.

occurrences, it is currently unknown to which degree these adverse events may be also operator dependent. Overall number of procedures performed and the operator experience may affect outcomes of patients undergoing PCI, but this evidence is mainly based on observational studies.[1–11] Randomized, controlled trials have played a major role in informing the community on the incidence, predictors, and implications of PCI-related adverse events. However, although the role of the center is often investigated or at least accounted for as a source of heterogeneity for the primary end point results, little is known on the potential impact of different operators on results of PCI studies. Operator expertise and the potential impact on outcomes has recently become a contentious topic for studies assessing access site.[12–16] Whether operators may also affect outcomes of studies assessing the performance of various stent platforms or durations of dual antiplatelet therapy (DAPT) after coronary stenting remains unclear. This analysis is frequently hampered by lack of proper data collection or inclusion of few cases by each single operator.

The aim of this study is to investigate whether an interoperator performance variation may exist in terms of efficacy and safety in the setting of the all-comer PRODIGY (Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia Study; NCT00611286) where patient recruitment was carried out by few interventional cardiologists, each recruiting a high number of patients.

Methods

The design and main findings of the PRODIGY trial have been previously reported.[17–19] PRODIGY is a 4-by-2 randomized, multicenter, open-label clinical trial designed to evaluate the efficacy and safety of prolonging the duration of clopidogrel therapy for up to 24 months in all-comer patients receiving a balanced mixture of stents with various anti-intimal hyperplasia potency and belonging to both first- and second-generation drug-eluting stent. Briefly, all-comer PCI patients (n=2013) were randomly allocated in a 1:1:1:1 fashion to 1 of 4 stent types, including everolimus-eluting stent, paclitaxel-eluting stent, zotarolimus-eluting Endeavor Sprint stent, or thin-strut bare metal stent. Patients alive at 30 days (n=1970) were then randomly allocated to either 6 or 24 months of DAPT. Selection criteria were broad, reflecting routine clinical practice. Randomization to 6- or 24-month DAPT was stratified by center, ongoing ST-segment-elevation myocardial infarction, presence of diabetes mellitus, and need for intervening for at least 1 in-stent restenotic lesion. The study was conducted in accord with the principles of the Declaration of Helsinki. The Ethics Committees of the 3 participating centers independently approved the protocol, and all participants gave written informed consent.

Operators

Interventional cardiologists of the 3 participating centers were trained operators, each with >500 cumulative PCI volume as first operator and all involved in the 24-hour on-call duty schedule at their referral institutions. During the trial, 6 operators performed PCI in the majority of patients enrolled, with each treating more than 50 patients. For the present study, each of them will represent an independent group. In order to explore the effect of PCI experience, operators were also further stratified in "More Experienced" and "Experienced" based on: (1) number of active years as first operator, (2) overall PCI volume, and (3) PCI volume/year in the 2 years before the trial initiation. "More experienced" operators were

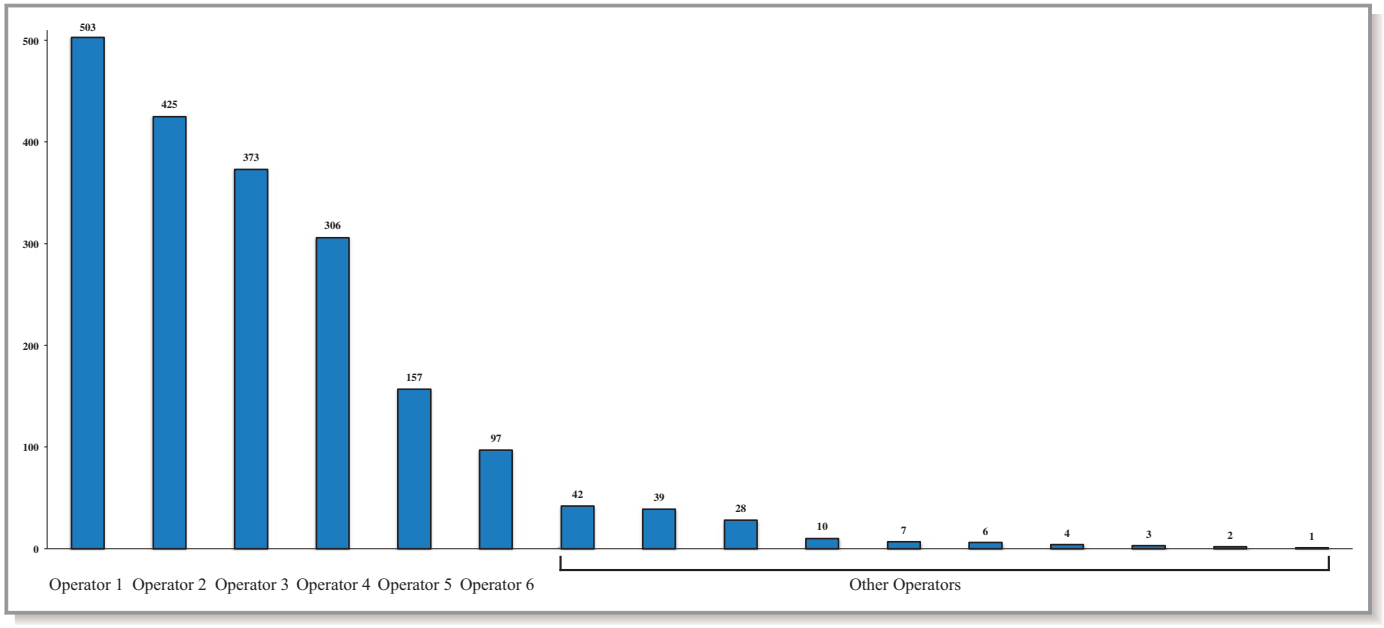

Figure 1. Operator procedure distribution.

those with >5 years, >1000 overall PCI, and >75 PCI/year, whereas "Experienced" were those with <5 years, 500 to 1000 overall PCI, and <75/year. Few other operators performed less than 50 procedures each, thus they were pooled in the seventh group named "other operators" overall including 142 patients/procedures (Figure 1).

Treatment Protocol and Follow-up

All patients received aspirin (80–160 mg orally indefinitely) and clopidogrel (75 mg/day) according to the randomization scheme as follows: for either 6 months in the short DAPT arm or 24 months in the prolonged DAPT arm irrespective of the previously implanted stent type or indication for PCI.

The randomized patients returned for study visits at 30 days and then every 6 months up to 2 years. During follow-up visits, patients were examined and assessed for adverse events, asked for the antiplatelet therapy compliance, and 12-lead ECG recordings were obtained.

Study End Points

The primary efficacy end point of the PRODIGY trial was the composite of death, MI, or cerebrovascular accident, whereas the key safety end point included Bleeding Academic Research Consortium (BARC) type 2, 3, or 5 bleeding. The net effect on the combined ischemic and bleeding complications was obtained by 2 net adverse clinical event (NACE) end points that were generated by combining the primary efficacy end point of death, MI, or cerebrovascular accident with either the primary safety end point of BARC type 2, 3, or 5 bleeding or with BARC type 3 or 5 events. Other end points included each component of the primary efficacy end point, cardiovascular death, stent thrombosis (ST) defined on the basis of the Academic Research Consortium criteria, and BARC type 3 or 5 bleeding. Other safety end points included bleeding events adjudicated according to the thrombolysis in myocardial infarction and global use of strategies to open occluded coronary arteries scales. All study end point definitions were previously reported.

All end points were confirmed on the basis of documentation collected at each hospital and were centrally adjudicated by the clinical events committee, whose members were unaware of the patients' treatment-group assignments. The time frame of interest for the primary end point was from 30 days (ie, after the primary end point randomization) to 24 months.

Statistical Analysis

The PRODIGY trial was designed to enroll at least 1700 patients to detect a 40% reduction in the relative risk of the primary end point in the 24-month clopidogrel group compared with 6-month duration of clopidogrel therapy, with statistical power of >80% at a 2-sided significance level of 0.05. The planned sample size was finally increased up to 2000 to allow for fatalities occurring within the first 30 days, noncompliance, and loss to follow-up as previously described.[17–19]

Categorical variables were expressed as frequency (percentage), whereas continuous variables were expressed as mean and SD. Baseline and procedural characteristics among

the 7 groups were compared using chi-square test for categorical variables and ANOVA F test for continuous variables. Crude events among groups were compared with likelihood ratio *P* values testing the shared frailty effect across operators using an inverse gamma distribution in Weibull time-to-event regression. Estimation of the cumulative major adverse cardiovascular event (MACE) rate, as well as of BARC bleeding and NACE, was performed by the Kaplan–Meier method.

In order to compare clinical outcomes among groups, hazard ratios with 95% confidence intervals were calculated from adjusted Weibull time-to-event regression comparing each operator (operator 2 to operator 6) versus operator 1 who was elected as reference because of the highest number of patients/procedures performed. The adjustment was performed including the following variables: age, sex, body mass index, hypertension, dyslipidemia, current smoking, family history of coronary artery disease, previous PCI, previous coronary artery bypass graft, peripheral arterial disease, creatinine clearance, left ventricular ejection fraction, acute coronary syndrome, femoral access, multivessel PCI, PCI performed by 2 or more operators (versus 1 operator only), 1 or more complex lesions, 1 or more restenotic lesions, randomized stent (4 categories), total stent length, and CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA Guidelines) score.

Proportional-hazards assumption was tested on the basis of Schoenfeld residuals after fitting a Cox regression model for each of the 4 end points ($P \geq 0.7$ in each case).

Univariate analysis was conducted to explore whether operator category may predict 2-year MACE, BARC type 2, 3, or 5, or NACE.

Interaction testing was performed to determine whether the effect of randomization to DAPT duration or to stent type on the primary end point was consistent irrespective of operator category or volume of PCI performed by each operator.

To explore the effect of operator experience, all the analyses were also computed contrasting “more experienced” versus “experienced” operators on study end points.

A 2-sided probability value of <0.05 was considered significant. All analyses were performed with Stata Statistical Software (release 14; StataCorp LP, College Station, TX).

Results

A total of 2013 patients were recruited into the study and randomly assigned to 1 of the 4 stent types. Ten patients withdrew consent. Thirty-three (1.6%) patients died within 30 days, thus 1970 patients were randomly allocated at 1 month to undergo 24-month versus 6-month duration of clopidogrel therapy. Seven operator groups were created by matching cases to first treating operator as follows: operator 1 (n=503), operator 2 (n=425), operator 3 (n=373), operator 4 (n=306), operator 5 (n=157), operator 6 (n=97), and other operators including 10 operators performing each less than 50 procedures and cumulatively recruiting 142 patients into the study (Figure 1).

Baseline and Procedural Characteristics

Table 1 reports baseline and procedural characteristics according to the operator groups. There were notable imbalances across operators that were mainly driven by the other operators group, which recruited patients who were slightly younger, more frequently affected by stable coronary artery disease (one fourth of patients in this group presented acute coronary syndrome as compared with three fourths of patients in all other operator groups), with preserved renal and left ventricular function, and lower bleeding risk. Operator 1 treated the highest rate of past MI or ST-segment-elevation myocardial infarction patients or those requiring more frequently left main coronary artery intervention, or presenting with the mean lowest mean left ventricular ejection fraction (Table 1). On the other hand, operator 6 treated the highest number of lesions per procedure, with at least 1 complex lesion per procedure as well as more patients with past coronary artery bypass graft. Multivessel or saphenous vein graft intervention was more frequently accomplished by operator 2, whereas operator 5 performed the lowest number of multivessel/multilesion interventions (Table 1). Radial access was the default access site across all operators.

Clinical Outcomes

At 30 days, there were no significant differences among operator groups for any analyzed individual or composite end points (Table 2). The highest rate of the primary end point was observed for operator 6, who experienced, however, the lowest number of any or access-site bleeding events. Operator 2 had the highest rate of cerebrovascular accident, BARC bleeding, as well as NACE. Operator 1 was the one experiencing the lowest rate of death and cerebrovascular accident, whereas operator 5 was associated with the lowest rate of MACE and NACE. Operator 1 and 2 were associated with the highest rate of access-site–related bleeding (Table 2). In the group of other operators, none of the patients died or had stroke or ST or target vessel revascularization or bleeding, and all events within 30 days were MI.

At 2-year follow-up, there were no significant differences among operators for the primary end point as well as the majority of secondary end points, except for ST, mainly driven by no event in the other operator group and for BARC type 2,

Table 1. Baseline and Procedural Characteristics

Characteristic	Operator 1 (N=503)	Operator 2 (N=425)	Operator 3 (N=373)	Operator 4 (N=306)	Operator 5 (N=157)	Operator 6 (N=97)	Other Operators (N=142)	*P* Value	*P* Value Without Other Operators
Age, y	68.79±11.23	68.10±11.82	68.50±11.18	66.39±11.31	68.35±11.73	68.50±11.68	66.57±9.44	0.061	0.096
Male	380 (75.5%)	330 (77.6%)	277 (74.3%)	227 (74.2%)	119 (75.8%)	75 (77.3%)	124 (87.3%)	0.065	0.874
Body mass index, kg/m^2	27.51±4.42	26.67±3.72	27.07±3.97	26.54±3.64	27.86±4.70	28.74±5.12	27.36±2.68	<0.001	<0.001
Diabetes mellitus	128 (25.4%)	97 (22.8%)	93 (24.9%)	72 (23.5%)	39 (24.8%)	24 (24.7%)	35 (24.6%)	0.982	0.956
Insulin dependent	31 (6.2%)	28 (6.6%)	24 (6.4%)	17 (5.6%)	9 (5.7%)	8 (8.2%)	4 (2.8%)	0.687	0.955
Hypertension	372 (74.0%)	288 (67.8%)	274 (73.5%)	226 (73.9%)	101 (64.3%)	76 (78.4%)	101 (71.1%)	0.059	0.033
Hyperlipidemia	268 (53.3%)	222 (52.2%)	191 (51.2%)	180 (58.8%)	75 (47.8%)	43 (44.3%)	115 (81.0%)	<0.001	0.098
Current smoker	113 (22.5%)	121 (28.5%)	83 (22.3%)	73 (23.9%)	45 (28.7%)	21 (21.6%)	21 (14.8%)	0.022	0.172
Family history of CAD	159 (31.6%)	120 (28.2%)	119 (31.9%)	61 (19.9%)	32 (20.4%)	30 (30.9%)	36 (25.4%)	0.002	0.001
Past MI	150 (29.8%)	106 (24.9%)	103 (27.6%)	74 (24.2%)	40 (25.5%)	25 (25.8%)	37 (26.1%)	0.607	0.483
Past PCI	85 (16.9%)	84 (19.8%)	68 (18.2%)	38 (12.4%)	33 (21.0%)	16 (16.5%)	43 (30.3%)	0.001	0.122
Past CABG	44 (8.7%)	50 (11.8%)	45 (12.1%)	21 (6.9%)	14 (8.9%)	16 (16.5%)	23 (16.2%)	0.012	0.036
Peripheral arterial disease	75 (14.9%)	47 (11.1%)	49 (13.1%)	29 (9.5%)	20 (12.7%)	9 (9.3%)	23 (16.2%)	0.184	0.211
Creatinine clearance, mL/min	78.36±31.98	76.82±31.96	75.84±29.93	79.42±30.85	77.31±29.83	76.64±33.63	87.62±77.32	0.058	0.722
LVEF, %	49.53±10.86	49.78±10.44	51.20±9.98	50.70±10.18	50.32±9.35	48.61±10.40	56.75±8.83	<0.001	0.097
Clinical presentation									
Stable angina	90 (17.9%)	92 (21.6%)	111 (29.8%)	62 (20.3%)	33 (21.0%)	15 (15.5%)	103 (72.5%)	<0.001	0.001
ACS	413 (82.1%)	333 (78.4%)	262 (70.2%)	244 (79.7%)	124 (79.0%)	82 (84.5%)	39 (27.5%)	<0.001	0.001
STEMI	107 (21.3%)	71 (16.7%)	65 (17.4%)	50 (16.3%)	32 (20.4%)	19 (19.6%)	23 (16.2%)	0.464	0.398
NSTEMI	123 (24.5%)	93 (21.9%)	96 (25.7%)	80 (26.1%)	36 (22.9%)	21 (21.6%)	11 (7.7%)	0.001	0.722
Unstable angina	183 (36.4%)	169 (39.8%)	101 (27.1%)	114 (37.3%)	56 (35.7%)	42 (43.3%)	5 (3.5%)	<0.001	0.003
Access site								<0.001	<0.001
Radial	307 (61.0%)	254 (59.8%)	239 (64.1%)	264 (86.3%)	89 (56.7%)	88 (90.7%)	NA	<0.001	<0.001
Femoral	107 (21.3%)	96 (22.6%)	58 (15.5%)	29 (9.5%)	45 (28.7%)	6 (6.2%)	NA	<0.001	<0.001
Other or missing	89 (17.7%)	75 (17.6%)	76 (20.4%)	13 (4.2%)	23 (14.6%)	3 (3.1%)	NA	<0.001	<0.001
Angiographic features									
Multivessel disease	351 (69.8%)	303 (71.3%)	264 (70.8%)	201 (65.7%)	115 (73.2%)	66 (68.0%)	102 (71.8%)	0.628	0.534
No. of diseased vessels								0.815	0.693
Single-vessel disease	152 (30.2%)	122 (28.7%)	109 (29.2%)	105 (34.3%)	42 (26.8%)	31 (32.0%)	40 (28.2%)	0.628	0.534
Two-vessel disease	168 (33.4%)	150 (35.3%)	138 (37.0%)	111 (36.3%)	60 (38.2%)	33 (34.0%)	51 (35.9%)	0.917	0.846
Three-vessel disease	183 (36.4%)	153 (36.0%)	126 (33.8%)	90 (29.4%)	55 (35.0%)	33 (34.0%)	51 (35.9%)	0.549	0.437

Continued

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Table 1. Continued

Characteristic	Operator 1 (N=503)	Operator 2 (N=425)	Operator 3 (N=373)	Operator 4 (N=306)	Operator 5 (N=157)	Operator 6 (N=97)	Other Operators (N=142)	*P* Value	*P* Value Without Other Operators
Multivessel intervention	145 (28.8%)	131 (30.8%)	94 (25.2%)	73 (23.9%)	26 (16.6%)	28 (28.9%)	37 (26.1%)	0.02	0.010
No. of treated lesions								<0.001	<0.001
1 lesion	290 (57.7%)	260 (61.2%)	254 (68.1%)	196 (64.1%)	123 (78.3%)	52 (53.6%)	82 (57.7%)	<0.001	<0.001
2 lesions	150 (29.8%)	121 (28.5%)	98 (26.3%)	69 (22.5%)	25 (15.9%)	22 (22.7%)	33 (23.2%)	0.011	0.007
3 lesions	44 (8.7%)	28 (6.6%)	12 (3.2%)	27 (8.8%)	5 (3.2%)	14 (14.4%)	13 (9.2%)	<0.001	<0.001
≥4 lesions	19 (3.8%)	16 (3.8%)	9 (2.4%)	14 (4.6%)	4 (2.5%)	9 (9.3%)	14 (9.9%)	0.001	0.050
Treated vessel(s)									
LAD	286 (56.9%)	215 (50.6%)	169 (45.3%)	168 (54.9%)	83 (52.9%)	54 (55.7%)	78 (54.9%)	0.034	0.021
LCX	140 (27.8%)	153 (36.0%)	133 (35.7%)	98 (32.0%)	36 (22.9%)	32 (33.0%)	53 (37.3%)	0.009	0.009
Right coronary artery	191 (38.0%)	158 (37.2%)	127 (34.0%)	104 (34.0%)	59 (37.6%)	36 (37.1%)	47 (33.1%)	0.809	0.789
Left main artery	34 (6.8%)	27 (6.4%)	20 (5.4%)	18 (5.9%)	3 (1.9%)	6 (6.2%)	5 (3.5%)	0.318	0.348
Saphenous vein graft	6 (1.2%)	17 (4.0%)	7 (1.9%)	2 (0.7%)	4 (2.5%)	3 (3.1%)	3 (2.1%)	0.038	0.021
At least one complex lesion*	374 (74.4%)	289 (68.0%)	202 (54.2%)	185 (60.5%)	111 (70.7%)	73 (75.3%)	99 (69.7%)	<0.001	<0.001
At least 1 restenotic lesion	21 (4.2%)	28 (6.6%)	17 (4.6%)	9 (2.9%)	2 (1.3%)	4 (4.1%)	15 (10.6%)	0.002	0.069
Type of randomized stent								0.008	0.009
Bare metal stent	120 (23.9%)	109 (25.6%)	109 (29.2%)	84 (27.5%)	39 (24.8%)	16 (16.5%)	25 (17.6%)	0.046	0.146
Paclitaxel-eluting stent	125 (24.9%)	112 (26.4%)	100 (26.8%)	63 (20.6%)	34 (21.7%)	29 (29.9%)	37 (26.1%)	0.368	0.266
Zotarolimus-eluting stent	124 (24.7%)	115 (27.1%)	61 (16.4%)	82 (26.8%)	47 (29.9%)	30 (30.9%)	41 (28.9%)	0.002	0.001
Everolimus-eluting stent	134 (26.6%)	89 (20.9%)	103 (27.6%)	77 (25.2%)	37 (23.6%)	22 (22.7%)	39 (27.5%)	0.347	0.281
No. of implanted stents	1.97±1.22	1.93±1.19	1.62±0.95	1.87±1.32	1.39±0.78	2.15±1.33	2.20±1.81	<0.001	<0.001
Overall stent length, mm	42.65±31.75	40.82±28.57	34.32±22.41	39.95±30.41	28.56±16.94	44.58±29.44	47.02±40.34	<0.001	<0.001
Mean stent diameter, mm	2.93±0.43	3.06±0.45	2.95±0.41	2.98±0.46	2.95±0.44	3.00±0.48	3.11±0.48	<0.001	0.001
PCI performed by 2 senior operators	143 (28.4%)	109 (25.6%)	112 (30.0%)	17 (5.6%)	26 (16.6%)	9 (9.3%)	34 (23.9%)	<0.001	<0.001
CRUSADE score	27.43±12.87	27.41±13.13	27.21±13.07	26.36±12.86	25.44±12.61	27.61±15.14	22.22±10.86	0.001	0.543
Randomized DAPT regimen at 30 d								0.562	0.672
Short DAPT	245 (48.7%)	213 (50.1%)	176 (47.2%)	150 (49.0%)	78 (49.7%)	50 (51.5%)	71 (50.0%)	0.983	0.962
Long DAPT	254 (50.5%)	206 (48.5%)	186 (49.9%)	150 (49.0%)	75 (47.8%)	45 (46.4%)	71 (50.0%)	0.987	0.968
Not randomized	4 (0.8%)	6 (1.4%)	11 (2.9%)	6 (2.0%)	4 (2.5%)	2 (2.1%)	0 (0.0%)	0.135	0.245

P values are omnibus comparisons across the 7 operator categories (chi-square test for categories, ANOVA F test for continuous variables). ACC indicates American College of Cardiology; ACS, acute coronary syndrome; AHA, American Heart Association; CABG, coronary artery bypass graft; CAD, coronary artery disease; DAPT, dual antiplatelet therapy; LAD, left anterior descending artery; LCX, left circumflex artery; LVEF, left ventricle ejection fraction; MI, myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; RCA, right coronary artery; STEMI, ST-elevation myocardial infarction.

*Type B2 or C lesion according to the ACC/AHA coronary lesion classification.

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Table 2. Clinical Outcomes at 30 Days

Event	Operator 1 (N=503)	Operator 2 (N=425)	Operator 3 (N=373)	Operator 4 (N=306)	Operator 5 (N=157)	Operator 6 (N=97)	Other Operators (N=142)	*P* Value	*P* Value Without Other Operators
Primary efficacy end point									
All-cause death, MI, or CVA	46 (9.1)	54 (12.7)	35 (9.4)	38 (12.4)	13 (8.3)	13 (13.4)	18 (12.7)	0.420	0.401
Secondary efficacy end points									
All-cause death or MI	45 (8.9)	47 (11.1)	34 (9.1)	37 (12.1)	12 (7.6)	12 (12.4)	18 (12.7)	1.000	1.000
All-cause death	4 (0.8)	6 (1.4)	11 (2.9)	6 (2.0)	4 (2.5)	2 (2.1)	0 (0.0)	0.211	0.279
Cardiovascular death	4 (0.8)	6 (1.4)	11 (2.9)	6 (2.0)	4 (2.5)	2 (2.1)	0 (0.0)	0.211	0.279
Stroke or TIA	1 (0.2)	8 (1.9)	2 (0.5)	1 (0.3)	3 (1.9)	1 (1.0)	0 (0.0)	0.057	0.074
Myocardial infarction	43 (8.5)	43 (10.1)	27 (7.3)	32 (10.5)	8 (5.1)	10 (10.3)	18 (12.7)	1.000	1.000
Definite ST	5 (1.0)	4 (0.9)	1 (0.3)	4 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	1.000	1.000
Definite or probable ST	7 (1.4)	6 (1.4)	4 (1.1)	7 (2.3)	1 (0.6)	1 (1.0)	0 (0.0)	1.000	1.000
Definite probable or possible ST	7 (1.4)	6 (1.4)	5 (1.4)	7 (2.3)	1 (0.6)	1 (1.0)	0 (0.0)	1.000	1.000
TVR	6 (1.2)	5 (1.2)	3 (0.8)	4 (1.3)	1 (0.7)	0 (0.0)	0 (0.0)	1.000	1.000
Safety end points									
Access-site related bleeding*	8 (1.6)	7 (1.6)	2 (0.5)	2 (0.7)	1 (0.6)	0 (0.0)	1 (0.7)	0.065	0.047
BARC classification									
Key safety end point—type 2, 3, or 5	12 (2.4)	10 (2.4)	5 (1.4)	5 (1.6)	3 (2.0)	0 (0.0)	0 (0.0)	1.000	1.000
Type 3 or 5	4 (0.8)	4 (0.9)	2 (0.5)	2 (0.7)	1 (0.7)	0 (0.0)	0 (0.0)	1.000	1.000
TIMI classification									
Minor	3 (0.6)	1 (0.2)	2 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1.000	1.000
Major	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0.145	0.153
Minor or major	3 (0.6)	1 (0.2)	2 (0.5)	2 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1.000	1.000
GUSTO classification									
Moderate	2 (0.4)	3 (0.7)	1 (0.3)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	1.000	1.000
Severe	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0.145	0.153
Moderate or severe	2 (0.4)	3 (0.7)	1 (0.3)	2 (0.7)	1 (0.7)	0 (0.0)	0 (0.0)	1.000	1.000
Net clinical adverse events (NACE)									
All-cause death, MI, CVA, or BARC 2, 3, or 5	58 (11.5)	63 (14.8)	40 (10.7)	41 (13.4)	16 (10.2)	13 (13.4)	18 (12.7)	1.000	1.000
All-cause death, MI, CVA, or BARC 3 or 5	50 (9.9)	58 (13.6)	37 (9.9)	39 (12.7)	14 (8.9)	13 (13.4)	18 (12.7)	0.453	0.419

Likelihood ratio *P* value testing the shared frailty effect across operators using an inverse gamma distribution in Weibull time-to-event regression. BARC indicates Bleeding Academic Research Consortium; CVA, cerebrovascular accident; GUSTO, global use of strategies to open occluded coronary arteries; MI, myocardial infarction; ST, stent thrombosis; TIA, transient ischemic attack; TIMI, thrombolysis in myocardial infarction; TVR, target vessel revascularization.
*Access-site related bleeding analyzed with mixed effects logistic regression.

3, or 5, mainly driven by difference for BARC 2 across operator groups (Table 3). ST was more frequently observed with operator 2, whereas operator 5 was associated with the highest rate of overall and most severe bleeding events. On the other hand, operator 5 was associated with the lowest rate of MI, ST, and target vessel revascularization. Operator 6 was the one with highest rate of the primary end point, as well as NACE, predominantly driven by the highest rates of death and MI (Table 3), whereas the primary end point was lowest for operator 3. Overall, the group of other operators who treated more stable patients was associated with lowest rates of death, bleeding, and composite end points (Table 3).

Adjusted comparisons for the main efficacy and safety end points at 30 days and 2 years are shown in Table 4. At 30 days, MACE and NACE were significantly increased with operator 2 compared with operator 1. Trends toward higher risk of MACE (49–56%) and NACE (45–52%) were also noted for Operator 4 and 6 as compared with operator 1, mainly attributable to increased risk of ischemic events. At 2 years, there was, however, no notable difference in operators'

Table 3. Clinical Outcomes at 2 Years

Event	Operator 1 (N=503)	Operator 2 (N=425)	Operator 3 (N=373)	Operator 4 (N=306)	Operator 5 (N=157)	Operator 6 (N=97)	Other Operators (N=142)	*P* Value	*P* Value Without Other Operators
Primary efficacy end point									
All-cause death, MI, or CVA	108 (21.5)	93 (21.9)	64 (17.2)	61 (20.0)	28 (17.8)	25 (25.8)	24 (17.0)	1.000	1.000
Secondary efficacy end points									
All-cause death or MI	100 (19.9)	83 (19.5)	62 (16.6)	58 (19.0)	28 (17.8)	24 (24.8)	23 (16.2)	1.000	1.000
All-cause death	40 (8.0)	36 (8.5)	33 (8.8)	21 (6.9)	16 (10.2)	11 (11.4)	6 (4.3)	1.000	1.000
Cardiovascular death	29 (5.8)	23 (5.5)	23 (6.2)	10 (3.3)	10 (6.4)	8 (8.4)	3 (2.2)	1.000	1.000
Stroke or TIA	14 (2.9)	15 (3.6)	6 (1.7)	4 (1.4)	5 (3.2)	3 (3.2)	1 (0.7)	0.386	0.486
Myocardial infarction MI	75 (15.1)	61 (14.5)	38 (10.3)	41 (13.5)	13 (8.4)	15 (15.9)	18 (12.7)	0.349	0.300
Definite ST	11 (2.2)	10 (2.4)	2 (0.5)	6 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.042	0.126
Definite or probable ST	18 (3.7)	17 (4.1)	5 (1.4)	9 (3.0)	1 (0.6)	3 (3.3)	0 (0.0)	0.048	0.195
Definite probable or possible ST	35 (7.1)	31 (7.4)	15 (4.1)	14 (4.7)	6 (3.9)	6 (6.5)	3 (2.2)	0.158	0.310
TVR	70 (14.4)	47 (11.5)	50 (14.1)	26 (8.7)	11 (7.4)	9 (10.0)	10 (7.1)	0.054	0.115
Safety end points									
BARC classification									
Key safety end point—type 2, 3, or 5	39 (8.0)	40 (9.7)	25 (7.0)	16 (5.4)	16 (10.6)	5 (5.7)	1 (0.7)	0.022	0.421
Type 3 or 5	13 (2.7)	20 (4.9)	15 (4.2)	8 (2.7)	7 (4.6)	2 (2.3)	1 (0.7)	0.340	0.494
TIMI classification									
Minor	9 (1.9)	7 (1.7)	6 (1.7)	1 (0.3)	1 (0.7)	2 (2.3)	0 (0.0)	1.000	1.000
Major	3 (0.6)	8 (2.0)	5 (1.4)	3 (1.0)	4 (2.6)	0 (0.0)	1 (0.7)	0.467	0.449
Minor or major	12 (2.5)	15 (3.7)	11 (3.1)	4 (1.3)	5 (3.3)	2 (2.3)	1 (0.7)	1.000	1.000
GUSTO classification									
Moderate	8 (1.6)	9 (2.2)	8 (2.2)	5 (1.7)	2 (1.4)	2 (2.3)	0 (0.0)	1.000	1.000
Severe	5 (1.0)	9 (2.2)	5 (1.4)	3 (1.0)	4 (2.6)	0 (0.0)	1 (0.7)	1.000	1.000
Moderate or severe	13 (2.7)	18 (4.4)	13 (3.7)	8 (2.7)	6 (4.0)	2 (2.3)	1 (0.7)	1.000	1.000
Net clinical adverse events (NACE)									
All-cause death, MI, CVA, or BARC 2, 3, or 5	136 (27.1)	120 (28.3)	77 (20.6)	72 (23.6)	40 (25.5)	28 (29.0)	24 (17.0)	0.120	0.227
All-cause death, MI, CVA, or BARC 3 or 5	116 (23.1)	101 (23.8)	69 (18.5)	66 (21.6)	32 (20.4)	26 (26.9)	24 (17.0)	1.000	1.000

Likelihood ratio *P* value testing the shared frailty effect across operators using an inverse gamma distribution in Weibull time-to-event regression. BARC indicates Bleeding Academic Research Consortium; CVA, cerebrovascular accident; GUSTO, global use of strategies to open occluded coronary arteries; MI, myocardial infarction; ST, stent thrombosis; TIA, transient ischemic attack; TIMI, thrombolysis in myocardial infarction; TVR, target vessel revascularization.

performances. Operator category did not predict 2-year MACE (*P*=0.74), BARC type 2, 3, or 5 (*P*=0.31), or NACE (*P*=0.66 and 0.85 for NACE with BARC 2, 3, or 5, and BARC 3 or 5, respectively).

Operator Interaction With DAPT and Stent Randomized Groups for the Primary Outcome

When the primary end point of all-cause death, MI, or cerebrovascular accident was stratified according to the operators, no significant interaction emerged between operator and DAPT randomization (*P*=0.112; Figure 2), and this was confirmed at 6-month landmark analysis (from 6 months to 2 years: *P*=0.425; Figure S1).

Similarly, interaction testing between operator and stent type (*P*=0.300; Figure 2) was negative. Also, no interaction was observed between operator and DAPT or randomized stent at stratified analysis by operator volume (Figures S2 and S3). Three-way interaction among operator-randomized DAPT duration-randomized stent was similarly negative (*P*=0.210).

Table 4. Adjusted Hazard Ratios

Event	Operator n vs Operator 1 (Reference)												Overall *P* Value*
	Operator 1 (N=503)	*P* Value	Operator 2 (N=425)	*P* Value	Operator 3 (N=373)	*P* Value	Operator 4 (N=306)	*P* Value	Operator 5 (N=157)	*P* Value	Operator 6 (N=97)	*P* Value	
At 30 d													
All-cause death, MI, or CVA	1	Ref.	1.58 (1.05–2.37)	0.029	1.38 (0.86–2.21)	0.179	1.56 (0.97–2.53)	0.069	1.09 (0.54–2.21)	0.802	1.49 (0.76–2.92)	0.245	0.224
BARC 2, 3, or 5	1	Ref.	0.82 (0.33–2.04)	0.672	0.95 (0.30–2.95)	0.923	0.72 (0.22–2.37)	0.593	0.57 (0.14–2.28)	0.431	…	0.231†	1.000
All-cause death, MI, CVA, or BARC 2, 3, or 5	1	Ref.	1.42 (0.98–2.05)	0.064	1.28 (0.83–1.96)	0.267	1.31 (0.84–2.04)	0.240	0.95 (0.51–1.76)	0.858	1.32 (0.69–2.53)	0.409	0.435
All-cause death, MI, CVA, or BARC 3 or 5	1	Ref.	1.57 (1.06–2.33)	0.024	1.36 (0.86–2.14)	0.189	1.52 (0.95–2.44)	0.078	1.07 (0.54–2.09)	0.849	1.45 (0.74–2.82)	0.280	0.244
At 2 y													
All-cause death, MI, or CVA	1	Ref.	1.10 (0.83–1.48)	0.504	0.96 (0.69–1.33)	0.791	1.18 (0.84–1.68)	0.342	0.91 (0.57–1.46)	0.700	1.37 (0.85–2.20)	0.199	1.000
BARC 2, 3, or 5	1	Ref.	1.14 (0.72–1.80)	0.573	0.98 (0.58–1.68)	0.954	0.73 (0.39–1.38)	0.340	1.40 (0.75–2.63)	0.291	0.73 (0.27–1.95)	0.527	1.000
All-cause death, MI, CVA, or BARC 2, 3, or 5	1	Ref.	1.11 (0.86–1.44)	0.415	0.89 (0.66–1.21)	0.466	1.07 (0.78–1.46)	0.687	1.01 (0.68–1.50)	0.949	1.17 (0.75–1.82)	0.487	1.000
All-cause death, MI, CVA, or BARC 3 or 5	1	Ref.	1.11 (0.84–1.46)	0.480	0.95 (0.69–1.30)	0.731	1.19 (0.85–1.67)	0.303	0.98 (0.63–1.52)	0.927	1.27 (0.79–2.02)	0.322	1.000

Hazard ratios from adjusted Weibull time-to-event regression comparing each operator n (2–6) vs Operator 1. Adjusted for: PCI performed by 2 or more operators (vs 1 operator only), age, sex, body mass index, hypertension, dyslipidemia, current smoking, family history coronary artery disease, previous percutaneous coronary intervention (PCI), coronary artery bypass graft, peripheral arterial disease, creatinine clearance, LVEF, acute coronary syndrome, femoral access, multivessel PCI, 1 or more complex lesions, 1 or more restenotic lesions, randomized stent (4 categories), total stent length, and CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines) score. BARC indicates Bleeding Academic Research Consortium; CVA, cerebrovascular accident; GUSTO, global use of strategies to open occluded coronary arteries; MI, myocardial infarction; PCI, percutaneous coronary intervention; ST, stent thrombosis; TIA, transient ischemic attack; TIMI, thrombolysis in myocardial infarction; TVR, target vessel revascularization.

*Likelihood ratio *P* value testing the shared frailty effect across operators using a Gaussian distribution in Adjusted Weibull time-to-event regression.

†No BARC 2, 3, or 5 bleedings in Operator 6: Fisher's exact test *P* value on raw counts reported instead comparing Operator 6 vs 1.

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Operator Experience

When analyses were conducted comparing "More experienced" with "Experienced" operators, no significant effect emerged on clinical outcomes at 30-day or 2-year and no interaction was noted with respect to randomized DAPT duration or stent type (Tables S1 through S4; Figures S4 and S5).

Discussion

The present study explored the interoperator impact on clinical outcomes of patients undergoing PCI in the setting of a randomized, clinical trial. Across each operator stratum, there were several differences for patient and procedural characteristics, making interpretation of unadjusted clinical outcomes problematic. After adjustment, there were some differences for 30-day outcomes, mainly owing to different risks of ischemic events across operators. However, adjusted analyses failed to show heterogeneous outcomes across operator groups at 2 years, and operators did not impact on the comparative efficacy or safety profile of different DAPT durations or stent types. Therefore, the present analysis provides reassurance that operator per se or operator experience/operator volume was not a significant effect modifier of our study findings.

The optimal duration of DAPT after PCI is a matter of ongoing discussion, attributed to a clear trade-off between benefits and risks. A prolonged DAPT regimen prevents recurrent or new MI related or not to stent thrombosis. Furthermore, procedural complexity has emerged as an important driver of DAPT duration, with prolonged DAPT being beneficial in more-complex procedures.[20] Accordingly, it is plausible that different operators with different technical skills, expertise, and case volume, as well as different procedural tactics (predilatation and postdilatation, duration and pressure of dilatation, stent implantation sizing and technique, use of intravascular imaging modalities, etc) may be associated with different clinical outcomes. In this respect, however, we did not find significant interaction between operator, type of stent, and DAPT regimen, suggesting that our overall study results were consistent across operators, which has notable implications for the external validity of our findings. There was, however, signal that operator may impact

	events/nr of patients	events/nr of patients	Hazard Ratio (95% CI)	p-value	interaction p-value
Randomized DAPT*:	**Short DAPT**	**Long DAPT**	**Long vs Short**		
All-cause Death, MI or CVA from 30 to 720 days					**0.112**
Operator 1	36/254	28/245	0.79 (0.48-1.29)	0.340	
Operator 2	16/206	27/213	1.68 (0.91-3.12)	0.099	
Operator 3	17/186	14/176	0.87 (0.43-1.76)	0.692	
Operator 4	16/150	7/150	0.41 (0.17-1.01)	0.052	
Operator 5	7/ 75	10/ 78	1.42 (0.54-3.73)	0.476	
Operator 6	5/ 45	8/ 50	1.51 (0.49-4.63)	0.468	
Other Operators***	3/ 71	4/ 71	1.36 (0.31-6.10)	0.684	
Randomized to any DES or BMS:**	**DES****	**BMS**	**DES vs BMS**		
All-cause Death, MI or CVA from 0 to 720 days					**0.300**
Operator 1	75/383	33/120	0.69 (0.46-1.04)	0.079	
Operator 2	65/316	28/109	0.80 (0.51-1.24)	0.314	
Operator 3	45/264	19/109	0.98 (0.57-1.67)	0.937	
Operator 4	49/222	12/ 84	1.59 (0.85-2.99)	0.150	
Operator 5	20/118	8/ 39	0.79 (0.35-1.80)	0.575	
Operator 6	19/ 81	6/ 16	0.61 (0.24-1.52)	0.287	
Other Operators***	20/117	4/ 25	1.05 (0.36-3.06)	0.936	

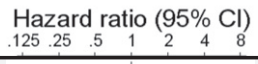

Figure 2. Stratified effect of operators on the primary comparisons of the primary outcome in the PRODIGY trial. Hazard ratios from Weibull time-to-event regression on the composite of all-cause death, MI, or CVA comparing the randomized DAPT durations or randomized stents and testing for effect modification by the Operators n (1–6). *Short DAPT randomized to 6 months of DAPT, Long DAPT randomized to 24 months of DAPT. **ZES-S (zotarolimus-eluting Endeavor Sprint stent), PES (paclitaxel-eluting stent), and EES (everolimus-eluting stent) combined. ***The Other Operators are shown for completeness, but not used for interaction testing. BMS indicates bare metal stent; CVA, cerebrovascular accidents; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; MI, myocardial infarction.

on outcomes in the early period after PCI when indeed operator and procedural factors are more likely to play a role. On the contrary, at 2 years, we did not observe significant differences across operator groups, likely as a reflection that procedural technicalities adopted by each operator have limited impact on long-term outcomes.

Physician competence is a critical component in the provision of optimal health care. All physicians must have the appropriate training, fund of knowledge, clinical decision making, and technical skills. In the setting of PCI, operators must perform these procedures at a requisite level of proficiency and competency.

Patients treated by high-volume operators and at high-volume centers have been shown to experience a higher rate of procedural success and lower rates of mortality and postprocedural complications.[1–11] As a consequence, standards of assistance have been recommended for PCI operators.[1,2,6] Recently, in an observational study, operator experience has emerged as an important prognostic factor in a complex intervention, such as left main PCI, where patients treated by high-volume and experienced operators had better outcomes.[9] Operators were shown to impact on outcomes in the setting of different complex procedures, such as chronic total occlusions,[21] the implantation of specific devices as bioresorbable vascular scaffolds,[22] and structural interventions.[23]

During the past decades, the cardiology community has been largely informed in terms of clinical practice by the results of many randomized trials. In order to achieve enough of a number of observations, and to reduce the bias related to single-center studies, multicenter studies are frequently performed and currently regarded as the study design allowing for the greatest external validity. Multicenter PCI studies can, however, also critically depend on expertise and proficiency of the multiple operators involved. Although subgroup analyses are frequently performed to explore the consistency of study results across different geographical locations, and sometimes randomization is stratified by center, the role of each operator within each center is almost never appropriately investigated. Operators are very rarely matched with the corresponding treated patients within each multicenter study, and even when this information is available, each study operator generally contributes with a limited number of patients within each study. There are, however, relevant exceptions. Interoperator variation was previously investigated in 1071 patients enrolled in the TAPAS (Thrombus Aspiration During Percutaneous Coronary Intervention in Acute Myocardial Infarction Study) trial.[16] The primary end point of the study, which was myocardial blush grade 3, was analyzed across 6 operator groups, and it was shown to significantly differ across operators after adjustment for baseline and procedural imbalances. This post-hoc analysis suggested that, even in a controlled setting, significant interoperator variation might exist in the efficacy of primary PCI.[16] Interestingly, however, no data on patient outcomes were available across operators at long-term follow-up.

More recently, the operator experience, and its potential impact on outcomes, has become a matter of debate in the comparison of radial versus femoral access site for PCI. In the MATRIX-Access (Minimizing Adverse Haemorrhagic Events by TRansradial Access Site and Systemic Implementation of angioX),[12] the benefit of radial versus femoral access appeared consistent across major patient subgroups including tertiles of the centers' annual volume of PCI. However, positive tests for trend were found across tertiles of the centers' percentage of radial PCI for both co-primary end points and all-cause mortality at 30 days, suggesting a more-pronounced benefit of radial access in centers that did 80% or more-radial PCI,[12] and this generated great interest.[13–15,24,25] Whether these differences will remain detectable also at longer-term follow-up remains currently unclear.

All together, our results are consistent with previous observations that operators may impact on procedural or PCI short-term (ie, 30-day) clinical outcomes whereas such an effect seems to vanish at time frames more remote from the index intervention. This may reflect the existence in contemporary practice of well-standardized percutaneous techniques and improved biomedical technologies for the treatment of patients with coronary artery disease. In this context, factors, which are largely unrelated to the revascularization procedure per se, such as adherence to and optimal titration of secondary prevention medication as well as comorbidities and disease progression, may affect long-term outcomes more than procedural technical features. On the other hand, the effect of operator on PCI outcomes seemed to be, at best, minimal, and when operators were stratified for their volume/experience before the trial initiation, this effect disappeared. The absence of a definite experience-outcome relationship for individual operators should not be regarded as surprising in such a context where centers and operators were at high volume of PCI. However, volume per se might not be an appropriate marker of quality (high volume may not correspond to high quality because practice/volume by itself is of little value if the procedure is not properly executed).[2,26]

Therefore, our current findings extends previous results of the PRODIGY trial by suggesting that the impact of stent selection or DAPT durations on ischemic and bleeding outcomes remained consistent across study operators.

Limitations

This is a post hoc analysis sharing limitations of other not prespecified and not powered analyses. PRODIGY is a

3-center trial, and it cannot be excluded that, in larger trials with many different centers and operators involved, a certain degree of interoperator variation may exist and may have a significant interaction with safety and efficacy end points.

Although the comparisons between operators were adjusted for main variables, it cannot be excluded that other confounders may affect these findings.

The number of events in some cases (ie, stroke or ST) was too low to allow an appropriate adjusted comparison among 6 or 7 groups.

Conclusions

After adjustment for multiple patient- and procedure-related imbalances, there was a weak signal of heterogeneity across individual study operators for the 30-day, but not the 2-year, main study outcomes, and no differences were observed across operators' past PCI volumes. Accordingly, no clear effect of the operator was observed for the comparative efficacy and safety profile of the randomized stent types or DAPT duration regimens in our study, which has notable implications for the external validity of the PRODIGY study results.

Disclosures

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Impact of angiographic coronary artery disease complexity on ischemic and bleeding risks and on the comparative effectiveness of zotarolimus-eluting vs. bare-metal stents in uncertain drug-eluting stent candidates☆

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ABSTRACT

Background: The impact of coronary artery disease (CAD) extension/complexity on outcomes and on the comparative benefits/risks of zotarolimus-eluting stent (ZES) versus bare-metal stents (BMS) remains unclear in patients at high risk of bleeding or thrombosis or at low restenosis risk.
Methods: We performed a post-hoc analysis of the ZEUS trial. The impact of coronary anatomic complexity measured by the SYNTAX score on the differences in outcomes following ZES and BMS was assessed at 1 year.
Results: The mean SYNTAX score was 16.3 ± 13.1 with a median of 12 (IQR: 7 to 22). We stratified patients according to SYNTAX tertiles (0–8: $n = 563$; >8–19 $n = 532$; >19: $n = 511$), and observed that the higher the score, the correspondingly higher was the rate of the primary endpoint of major adverse cardiovascular events (MACE) and other ischemic events, but not bleeding after adjustment. The superior efficacy of ZES versus BMS for MACE was consistent across SYNTAX tertiles (tertile 1: HR 0.71, 95% CI 0.44–1.13; tertile 2: HR 0.71, 95% CI 0.46–1.09; tertile 3: HR 0.83, 95% CI 0.61–1.10) without significant heterogeneity (p for trend = 0.55). This between-groups difference mainly reflected a reduction in MI and TVR without effect on mortality. There was no significant interaction between the SYNTAX score and allocated stent type with respect to ischemic and bleeding endpoints.

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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Conclusions: The SYNTAX score was predictor of major adverse cardiovascular events but not bleeding and ZES provided superior efficacy and safety than BMS across the whole spectrum of CAD complexity. SYNTAX score may be routinely used for the assessment of the ischemic risk (but not bleeding) after PCI and should not guide the decision-making for DES versus BMS in patients undergoing PCI.

1. Introduction

The Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) score is an angiographic scoring system that was developed to quantify the complexity and extension of coronary artery disease (CAD) in patients undergoing coronary revascularization. It has become an important tool to assist in deciding the optimal revascularization strategy in patients with complex CAD [1–4]. The score has been found to predict ischemic event recurrences and mortality during long-term follow-up percutaneous coronary intervention (PCI) in various patient populations, including all-comers, those with multivessel/complex disease, for whom the score was originally developed, or with ST-segment elevation myocardial infarction (STEMI) [2,5–8].

The ZEUS trial included patients at high bleeding risk, high thrombotic risk or low restenosis risk to assess the efficacy and safety of drug-eluting stent (DES) implantation using a stent with a biocompatible polymer and fast drug-eluting characteristics, instead of a bare-metal stent (BMS), followed, in all patients, by an abbreviated, tailored dual antiplatelet therapy (DAPT) [9]. In this context of selected patients, it remains unclear if CAD extension and/or complexity impacts on outcomes in terms of ischemic and bleeding risks and how it may affect the comparative safety and effectiveness of the two allocated stent types.

2. Methods

2.1. Study population

The design and main study findings of the ZEUS trial (NCT01385319) were previously reported [9–11]. Briefly, it was a multinational, randomized single-blinded trial which was conducted at 20 sites in 4 European countries (Italy, Switzerland, Portugal, and Hungary) and included patients with at least 1 qualifying criterion among the pre-specified uncertain DES recipients (high bleeding risk, high thrombosis risk or low restenosis risk) undergoing elective, urgent, or emergent PCI with intended stent implantation. Patients were randomly allocated 1:1 to receive Endeavor Sprint zotarolimus-eluting stent (*E*-ZES) or a thin-strut (thickness < 100 mm) BMS followed by a DAPT regimen independent of stent type, but clinical-profile–driven.

The study was conducted in accordance with the principles of the Declaration of Helsinki. The ethics committees of all participating centers independently approved the protocol, and all participants gave written informed consent.

2.2. Devices and therapy

The E-ZES (Medtronic Vascular, Minneapolis, Minnesota) is a cobalt-based alloy stent (91-μm strut thickness) with a phosphorylcholine polymer (4.8 μm) loaded with zotarolimus at a dose concentration of 10-μg/mm stent length. Approximately 95% of the zotarolimus is eluted from the stent within 15 days of implantation, although drug concentrations within surrounding vascular tissue may be detected as late as 30 days after stent deployment. All commercially available thin-strut BMS were allowed by the protocol.

All patients received aspirin (160 to 325 mg orally or 500 mg intravenously as a loading dose and then 80 to 160 mg orally per day) and clopidogrel (300 to 600 mg orally as loading dose followed by 75 mg/day), or prasugrel (60 mg as loading dose followed by 10 or 5 mg/day) or ticagrelor (180 mg as loading dose followed by 90 mg twice a day).

Duration of antiplatelet therapy was pre-specified on the basis of the inclusion criteria. Patients at high bleeding risk had a pre-specified 30-day DAPT regimen. Patients at high thrombosis risk had a pre-specified tailored duration of therapy on the basis of the specific condition conferring the high risk of thrombosis. This included a single antiplatelet regimen for patients intolerant of aspirin or available P2Y12 inhibitors, and a 30-day regimen in stable patients, or 6 to 12 months in unstable patients, in low restenosis risk patients.

As anticoagulation during PCI, unfractionated heparin or bivalirudin were used according to guidelines.

Staged procedures were allowed by protocol; in patients allocated to a 30-day course of DAPT who underwent staged intervention(s), therapy had to be prolonged or restarted for 30 additional days.

2.3. Study endpoints and follow-up

The aim of the ZEUS trial was to assess whether ZES implantation followed by a shorter than the currently recommended course of DAPT, tailored to the patient's clinical profile (tailored DAPT) and independent of stent type, would decrease the incidence of 12-month major adverse cardiovascular events (MACE), including all-cause death, non-fatal myocardial infarction (MI), or any target vessel revascularization (TVR), compared with BMS [9].

Secondary efficacy endpoints included each component of the primary endpoint, cardiovascular death, the composite of death and MI, the composite of cardiovascular death and MI; target lesion revascularization (TLR), ischemic stroke, and Academic Research Consortium–defined stent thrombosis (ST). Type of MI was also adjudicated according to the third universal definition of MI. Secondary safety endpoints comprised bleeding events according to both Bleeding Academic Research Consortium (BARC) and Thrombolysis In Myocardial Infarction (TIMI) classifications. Study endpoint definitions were previously reported [9]. All endpoints were confirmed on the basis of the documentation collected at each site and were centrally adjudicated by the clinical events committee, whose members were unaware of treatment assignment.

Thirty-day and 6- and 12-month follow-up visits were performed according to study protocol to evaluate potential adverse events and compliance with medications and to record a 12-lead electrocardiogram.

2.4. SYNTAX score

A single senior interventional cardiologist (AP), blinded to clinical data, clinical presentation, and outcomes calculated the SYNTAX score at baseline for each patient by scoring all coronary lesions with a diameter stenosis ≥50%, in vessels ≥1.5 mm, using the SYNTAX score algorithm available online (http://www.syntaxscore.com).

2.5. Statistical analysis

Categorical variables were expressed as frequency and percentage, and compared using the Fisher exact test, whereas continuous variables were expressed as median and interquartile range, and compared with the Wilcoxon rank sum test.

The population was stratified according to SYNTAX score tertiles and sensitivity analyses were performed using different cutoff values. Estimation of the cumulative incidence of events was performed by the Kaplan-Meier method, and hazard ratios (HRs) with 95% confidence intervals (CIs) and *p* values were calculated using the Cox regression model. The proportionality assumptions were checked by visual estimation after plotting the log cumulative hazard versus (log) time at follow-up after index procedure and by applying a test for nonproportional hazards using the Schoenfeld residuals. Cox-regression analysis with interaction testing was performed to determine whether the effect of stent type on the primary efficacy endpoint was consistent across SYNTAX subgroups. The interaction between treatment effect and SYNTAX score was also explored modelling the score as a continuous variable and was analyzed with a fractional polynomial interaction [12].

We also evaluated the effect of SYNTAX score on clinical outcomes in the overall population irrespective of stent randomization. We analyzed rates of clinical events according to SYNTAX tertiles, and we also modulated the score as a continuous variable testing the risk of ischemic and bleeding events in the overall population by means of both unadjusted and multivariable-adjusted, restricted cubic splines with three knots of the distribution (10th, 50th, and 90th percentiles). Multivariable adjustment of MACE and BARC type 2 to 5 bleeding was performed by including in the model all variables with a *p* value <0.1 at univariable analysis.

Sensitivity analyses were also performed testing the consistency of study results according to pre-defined 3 major criteria qualifying patients for inclusion (i.e. HBR, HTR, LRR).

A 2-sided p value <0.05 was considered significant. All analyses were performed on the basis of the intention-to-treat principle using SPSS version 23.0 (SPSS, Chicago, Illinois) and Stata 13.

3. Results

From June 2011 to September 2012, a total of 5288 patients were screened and 1606 were finally randomized. Approximately one-half

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of the patients ($n = 828$) entered the study due to HBR criteria, mainly due to age 80 years or older in 425 (26.5%) patients and/or need for oral anticoagulation in 311 (19.4%) patients. A high thrombotic risk and a low-restenosis risk were detected in 285 (17.7%) and in 941 (58.6%) patients, respectively. The median age was 74, nearly two-thirds of patients presented with acute coronary syndromes (acute STEMI in 20%). In total, the SYNTAX score ranged from 0 to 81, with a mean ± SD of 16.3 ± 13.1 and a median of 12 (interquartile range: 7 to 22) (**Supplementary Fig. 1**). In the main analysis, the overall population was stratified according to SYNTAX tertiles (0 to 8: $n = 563$; >8 to 19 $n = 532$; >19: $n = 511$), and the ZES and BMS groups remained well balanced with regard to baseline clinical and angiographic characteristics (**Supplementary Tables 1 and 2**). Patients in the highest SYNTAX tertile were older, more frequently with diabetes, renal dysfunction, history of MI or CABG, multivessel disease and more frequently received multivessel intervention, had complex lesions, and received multiple stents, reflecting the higher CAD complexity.

3.1. SYNTAX score and clinical outcomes

During follow-up, 71 patients (12.6%) in the first SYNTAX tertile, 87 patients (16.4%) in the second SYNTAX tertile, and 160 patients (31.3%) in the third SYNTAX tertile reached the primary endpoint ($p < 0.0001$; Fig. 1, Table 1). Similarly, all-cause death (p < 0.0001), cardiovascular death (p < 0.0001), MI (p < 0.0001), TVR (p < 0.0001), TLR (p < 0.0001), and definite ST ($p = 0.001$), as well as BARC bleeding ($p = 0.011$) were significantly higher according to SYNTAX score tertiles (Fig. 1, Table 1). When analyzing SYNTAX score as a continuous variable, or after multivariable adjustment for possible confounders, the SYNTAX score remained an independent predictor of the primary outcome, as well as of all additional secondary ischemic endpoints but stroke, whereas it did not remain associated to bleeding events (Fig. 2, **Supplementary Tables 3 and 4**).

3.2. SYNTAX score and the comparative effectiveness of ZES vs. BMS

The superior efficacy of ZES versus BMS for the primary endpoint was consistent across SYNTAX teriles (tertile 1: HR 0.71, 95% CI 0.44–1.13; tertile 2: HR 0.71, 95% CI 0.46–1.09; tertile 3: HR 0.83, 95% CI 0.61–1.10) with no signal of heterogeneity (p for trend = 0.55). The difference between ZES and BMS groups mainly reflected a reduction in MI (tertile 1: HR 0.23, 95% CI 0.07–0.83; tertile 2: HR 0.20, 95% CI 0.06–0.70; tertile 3: HR 0.45, 95% CI 0.25–0.79; p for trend = 0.21), and TVR (tertile 1: HR 0.29, 95% CI 0.12–0.68; tertile 2: HR 0.66, 95% CI 0.35–1.27; tertile 3: HR 0.60, 95% CI 0.36–0.98; p for trend = 0.21), but not mortality (tertile 1: HR 1.15, 95% CI 0.62–2.15; tertile 2: HR 0.81, 95% CI 0.47–1.42; tertile 3: HR 1.01, 95% CI 0.67–1.52; p for trend = 0.84) (**Supplementary Table 5**). When MI types were further considered, both type 1 and type 4b were significantly higher according to SYNTAX tertiles ($p < 0.0001$ for both) and were reduced in the ZES as compared to BMS arm, consistently across SYNTAX score tertiles (**Supplementary Table 6**). The rate of definite, definite/probable and definite/probable/possible stent thrombosis trended lower in the ZES group in all the SYNTAX tertiles without heterogeneity. No heterogeneity was observed across SYNTAX tertiles for all ischemic and bleeding outcomes (**Supplementary Table 5**), nor for MACE and BARC type 2–5 when SYNTAX score was modelled as a continuous variable (Fig. 3).

3.3. Additional analyses

The consistency of ZES benefits over BMS, irrespective of angiographic CAD complexity, was confirmed when the study population was stratified based on the median SYNTAX score value (i.e. 12), when the first two tertiles were combined and contrasted to the third one or based on the SYNTAX score boundaries which were generated in the context of the SYNTAX trial of 0–22, 23–32, ≥33) (data not shown). Similarly, when population was stratified according to single or multivessel disease (**Supplementary Table 7**).

Finally, there was no signal of heterogeneity for ZES benefits over BMS across SYNTAX tertiles when main outcomes (the primary endpoint of death from any cause, MI, or TVR, as well the secondary endpoint of death from any cause or MI or the individual endpoints of MI and TVR) were separately appraised across patients at high risk of bleeding or thrombosis or at low risk of restenosis (**Supplementary Table 8**).

4. Discussion

The ZEUS study focused on a unique patient population composed of patients with high bleeding risk, high thrombotic risk, or low restenosis risk who were largely excluded from the pivotal DES trials that led to regulatory approval. The main findings of the present analysis can be summarized as follows:

1. Anatomic complexity as assessed by the SYNTAX score independently predicted major adverse cardiovascular events, and death, MI, TVR or ST in the overall population as well as in each of the three patient categories which were included.

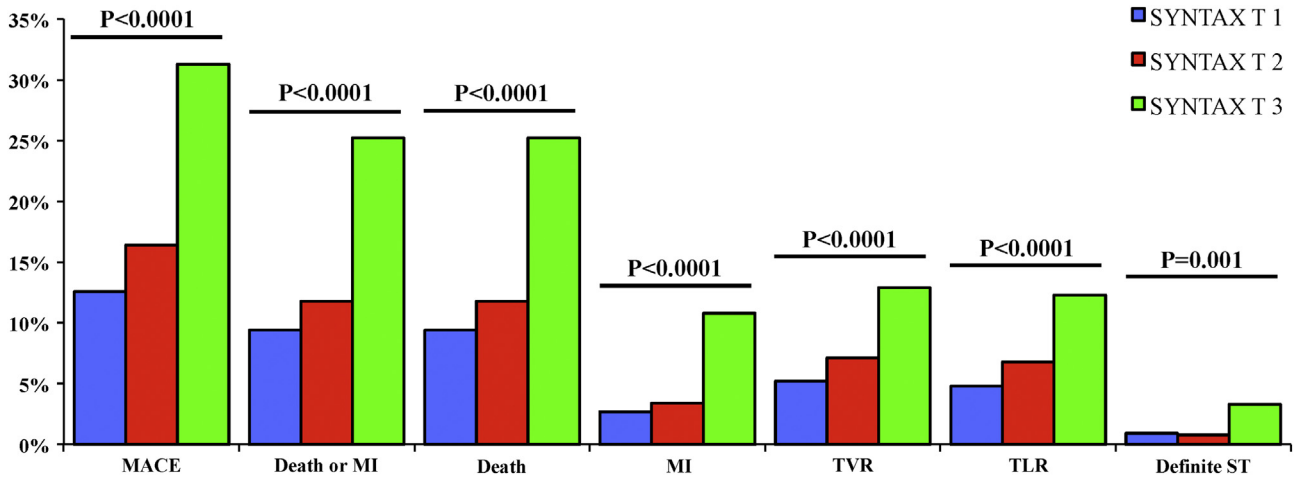

Fig. 1. Ischemic events according to SYNTAX score tertiles.

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Table 1
Clinical Outcomes at 12 months according to SYNTAX score tertiles.

	SYNTAX Low Tertile 1 (0–8) (*N* = 563)	SYNTAX Intermediate Tertile 2 (>8–19) (*N* = 532)	SYNTAX High Tertile 3 (>19) (N = 511)	P value
Primary efficacy endpoint				
Death from any cause, MI or TVR	71 (12.6)	87 (16.4)	160 (31.3)	<0.0001
Secondary efficacy endpoints				
Death from any cause or MI	53 (9.4)	63 (11.8)	129 (25.2)	<0.0001
Death from cardiovascular cause or MI	36 (6.4)	46 (8.6)	113 (22.1)	<0.0001
Death from any cause	40 (7.1)	50 (9.4)	91 (17.8)	<0.0001
Death from cardiovascular cause	23 (4.1)	32 (6.0)	73 (14.3)	<0.0001
MI	15 (2.7)	18 (3.4)	55 (10.8)	<0.0001
TVR	29 (5.2)	38 (7.1)	66 (12.9)	<0.0001
TLR	27 (4.8)	36 (6.8)	63 (12.3)	<0.0001
Ischemic stroke	6 (1.1)	6 (1.1)	9 (1.8)	0.55
Definite ST	5 (0.9)	4 (0.8)	17 (3.3)	0.001
Probable ST	4 (0.7)	5 (0.9)	14 (2.7)	0.01
Possible ST	8 (1.4)	12 (2.3)	27 (5.3)	<0.0001
Definite or probable ST	9 (1.6)	9 (1.7)	31 (6.1)	<0.0001
Definite, probable, or possible ST	17 (3.0)	21 (3.9)	58 (11.4)	<0.0001
Safety endpoints				
TIMI classification				
Major or minor	6 (1.1)	11 (2.1)	14 (2.7)	0.13
Major	5 (0.9)	6 (1.1)	9 (1.8)	0.42
Minor	1 (0.2)	5 (0.9)	5 (1.0)	0.19
Requiring medical attention	14 (2.5)	22 (4.1)	27 (5.3)	0.06
BARC classification				
Type 5 or 3	10 (1.8)	14 (2.6)	23 (4.5)	0.027
Type 5, 3 or 2	22 (3.9)	30 (5.6)	42 (8.2)	0.011
Type 5	3 (0.5)	5 (0.9)	3 (0.6)	0.68
Type 5A	1 (0.2)	4 (0.8)	2 (0.4)	0.35
Type 5B	2 (0.4)	1 (0.2)	1 (0.2)	0.82
Type 4	0	0	0	–
Type 3	7 (1.2)	9 (1.7)	20 (3.9)	0.007
Type 3A	3 (0.5)	3 (0.6)	5 (1.0)	0.62
Type 3B	3 (0.5)	5 (0.9)	14 (2.7)	0.005
Type 3C	1 (0.2)	1 (0.2)	1 (0.2)	0.99
Type 2	12 (2.1)	16 (3.0)	19 (3.7)	0.30

Abbreviations: BARC=Bleeding Academic Research Consortium; MI = Myocardial infarction; ST = Stent thrombosis; TIMI = Thrombolysis in myocardial infarction; TLR = Target lesion revascularization; TVR = Target vessel revascularization.

2. The SYNTAX score appeared at univariable analysis to be marginally but significantly associated to bleeding events. However, after adjustment, the SYNTAX score did not remain associated to the bleeding risk across different bleeding scales in the overall population as well as in high bleeding risk, high thrombotic risk, or low restenosis risk patients when separately appraised.
3. The SYNTAX score did not show significant interaction with the randomly allocated treatment suggesting that ZES remains superior to BMS across the whole spectrum of CAD complexity.

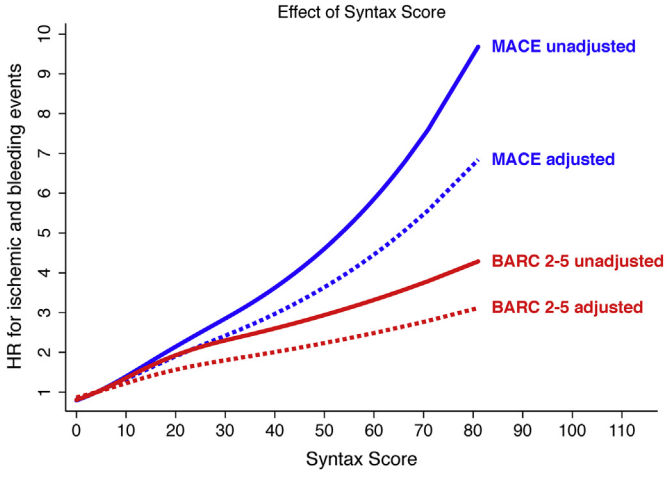

Fig. 2. Spline curves for the HR of the MACE and BARC type 2–5 bleeding vs. SYNTAX score modelled as a continuous variable. Patients with SYNTAX score in the first decile (corresponding to score value ≤4; $n = 211$) represent the referent group with the HR set to 1. The variables used for the adjustments are listed in the Table 4. BARC: Bleeding Academic Research Consortium; HR: hazard ratio; MACE: major adverse cardiovascular events.

Optimal DAPT regimen and stent selection remain topics of great debate [13,14]. The *E*-ZES is a hydrophilic polymer-based second-generation device with a unique drug fast-release profile which results in less powerful inhibition of intimal hyperplasia, but also in a rapid and/or complete stent strut coverage. This property allows shortening DAPT duration while maintaining superior efficacy compared with BMS. The ZEUS study, which mandated a tailored DAPT duration based on patients' characteristics, showed a lower incidence of MACE after E-ZES as compared with BMS in uncertain DES recipients [9]. E-ZES implantation provided superior efficacy and safety as compared with conventional BMS also among high bleeding risk patients (>50% of the patients fulfilled at least 1 criterion) who were to be treated with a 30-day course of DAPT only [11].

The present study is the first to assess the impact of SYNTAX score in uncertain DES candidates undergoing PCI. It confirms the ability of the SYNTAX score to identify patients who are at highest risk of adverse events also in the specific subsets of high bleeding risk, high thrombotic risk and low restenosis risk patients. This provides further evidence supporting the potential utility of the SYNTAX score in the assessment of ischemic risk in patients undergoing PCI.

When comparing DES and BMS performance, angiographic characteristics and complexity of CAD might have an important role,

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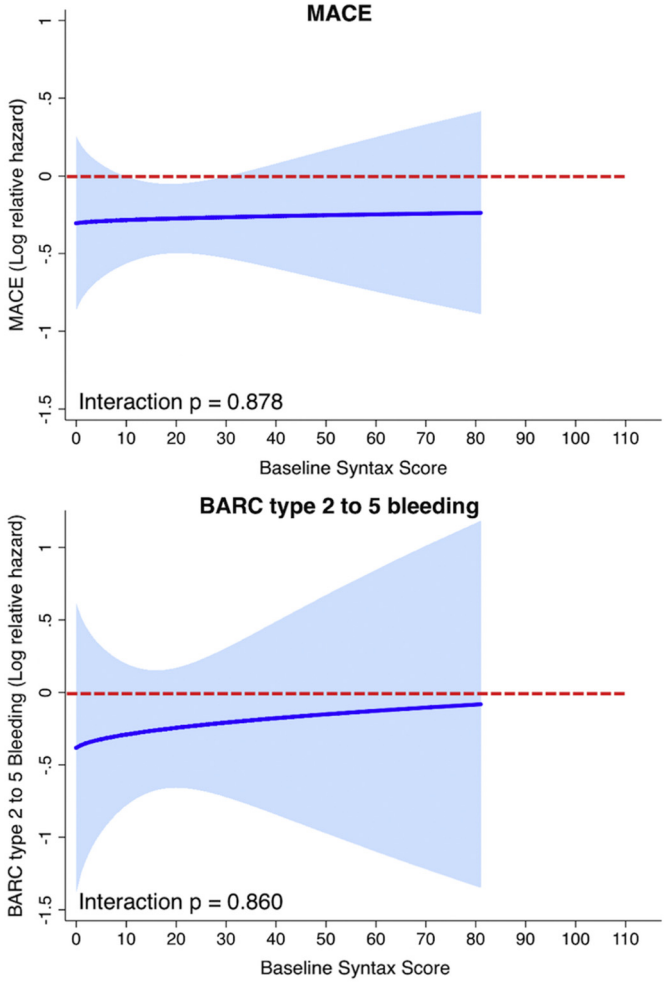

Fig. 3. Fractional polynomial interaction between randomized stent and SYNTAX score for the MACE and BARC type 2–5 bleeding. The treatment-by-SYNTAX interaction is analyzed by considering SYNTAX score as a continuous variable. The red line represents the treatment effect of ZES vs. BMS and the area represents the 95% CI of treatment effect. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

particularly when a very short (30-day) course of DAPT is required, therefore we explored whether the benefits of ZES over BMS were consistent across SYNTAX score strata. Although SYNTAX score properly identifies patients at higher risk of events and could be hypothesized to help deciding the stent selection in uncertain DES candidates, we found that ZES was superior to BMS irrespective of CAD extension and complexity. Thus, a very short (30-day) course of DAPT in the ZES group did not pose a significant risk, whereas it achieved superior clinical efficacy even in patients with intermediate-to-high angiographic complexity of CAD as compared to BMS. Interestingly, we noted that higher SYNTAX score seemed also to be associated with increased risk of bleeding. This predictive feature of the score, however, was not attributable to the score per se but was rather influenced by concomitant patients' characteristics; indeed, this effect was not significant after adjustment. This analysis carries new important implications as it confirms the specific ability of this score to predict ischemic but not bleeding recurrences after PCI and provides strong rational for combining in future analyses this score with dedicated algorithms modelled to predict the bleeding risk [15,16].

An additional intriguing observation in our current analysis merits further discussion. A trend towards lower bleeding risk was previously noted in the ZES vs BMS groups with respect to BARC 2, 3, or 5 bleeding in the overall population or in HBR patients [9,11], despite the randomized nature of the comparison and the fact that both patient groups received a similarly short/tailored course of DAPT after index intervention. This was justified by higher TVR rate in the BMS group over the course of follow-up, owing to the need to re-institute a DAPT regimen thereafter. When the SYNTAX score was modelled as a continuous variable, the benefits towards lower BARC 2, 3 or 5 bleeding occurrences were apparently more evident in patients with low SYNTAX score value. However, interaction testing with respect to the bleeding risk and the SYNTAX score, modelled as continuous variable, was negative and when BARC 3 or 5 events were considered across SYNTAX score tertiles, the greatest relative risk reduction for bleeding in favour of the ZES arm was noted in the highest tertile. Hence, there is clear signal that the use of a ZES instead of a BMS in our patient population has potential to mitigate the bleeding risk consistently across angiographic CAD complexity strata.

There is evidence suggesting that the use of DES, instead of BMS, leads not only to TVR but also MI, ST and cardiac mortality benefits [9,11,17,18]. Indeed, an intriguing finding of the ZEUS trial is that ZES compared with BMS significantly reduced TVR as expected, but also provided a significant reduction of MI, owing to a significant reduction of both type I (spontaneous) and type 4b (ST-related) MI, and here we confirmed that this effect was consistent in all SYNTAX score tertiles. The reduction of ST antagonizes previous concerns about DES-related ST and further confirms large evidence accumulated in last years that new-generation DES are associated with lower ST than BMS. Lower rates of spontaneous MI might be interpreted in light of the fact that DES reduces restenosis, which has historically been considered a benign process presenting in most cases with recurrent stable angina, while today is well known to be also related to MI occurrence. Conversely, in the Norwegian coronary stent trial (NORSTENT), which recruited 9013 patients with stable or unstable CAD and assigned them to PCI with the implantation of either contemporary DES (96% received either everolimus- or zotarolimus-eluting stents) or BMS [19], the composite outcome of death from any cause and nonfatal spontaneous MI, or quality of life, did not differ in-between groups. It was therefore suggested that, based on the excellent results achieved with BMS in NORSTENT, contemporary BMS still should be considered a viable alternative for some setting of patients, such as those who need anticoagulation, those who cannot complete the longer DAPT period because of a need for noncardiac surgery or other medical conditions with increased bleeding risk, those who have cancer and those with low restenosis rates [14]. On this scenario, our study adds to the current knowledge and could contribute to this debate by showing that DES is superior to BMS in specific clinical settings (still considered from someone "uncertain" candidates to DES) and irrespective of the angiographic complexity of the coronary disease. This finding further supports the most recent European guidelines recommending the use of new-generation DES over BMS in all patients undergoing PCI [4].

4.1. Study limitations

The present study has some limitations. First, the ZEUS study was not powered to explore SYNTAX subgroups, thus, it should be considered hypothesis-generating only. Yet, our results may not apply to patients with very high SYNTAX score who were only marginally represented in our study population; however, the absence of heterogeneity across SYNTAX subgroups was consistently observed even when different cutoffs were used or when the score was modelled as continuous. Second, it had a single-blind design, and no specific safeguards were adopted to ensure that patients and treating physicians remained unaware of treatment allocation beyond formal recommendations in the protocol, therefore it should be considered as an open-label study with evident limitations. Third, the findings apply to the studied ZES (Endeavor Sprint, which is no longer on the market) and cannot be expended to other new-generation DES. Fourth, longer follow-up is required to confirm durability of these findings. However, given the proven superior efficacy of other DES to inhibit intimal hyperplasia as

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compared to the Endeavor-ZES, it remains likely that other DES would have resulted in even greater efficacy as compared to BMS in preventing the need for re-intervention in the previously instrumented vessel(s). Fifth, the present findings should be interpreted considering that the majority of patients received a clopidogrel-based DAPT (prasugrel or ticagrelor at discharge were in <1%). Finally, we did not test intra/inter-observer variability in the SYNTAX score calculation, however, the single observer performing the blinded angiographic analysis was an experienced interventionalist and was well trained for SYNTAX score calculation.

5. Conclusion

Among patients with high bleeding risk, high thrombotic risk, or low restenosis risk undergoing PCI, anatomic complexity as assessed by the SYNTAX score predicted major adverse cardiovascular but no bleeding events. The SYNTAX score did not show significant interaction with treatment effect suggesting that in these patient categories ZES remains superior to BMS, both with similar short courses of DAPT, across the whole spectrum of CAD complexity.

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Conflict of interest

Dr. Gargiulo reports research grant support from Cardiopath PhD program. Dr. Roffi reports institutional research grants from Medtronic, Biotronik, Boston Scientific, Terumo, Abbott Vascular, outside the submitted work. Dr. Ferlini reports individual payment as consultant or for advisory board or as a speaker from Eli Lilly, Astra Zeneca, Biosensors, Chiesi, The Medicines Company, Daiichi Sankyo, MSD, outside the submitted work. Dr. Liistro reports personal fees from Medtronic, outside the submitted work. Dr. Vranckx reports personal fees from Bayer Health Care and Daicchi Sankyo, outside the submitted work. Dr. Windecker reports research contract to the institution from Amgen, Abbott, Biotronik, Boston Scientific, St Jude, outside the submitted work. Dr. Valgimigli reports grants from The Medicines Company and Terumo, during the study, grants from Astra Zeneca, personal fees from Abbott, Amgen, and Bayer, outside the submitted work. Other authors have nothing to disclose.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.09.120.

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Part 1

Trade-off for ischemia and bleeding during and immediately after percutaneous coronary interventions:

Pharmacological strategies to prevent the risk of AKI

Preventive Strategies for Contrast-Induced Acute Kidney Injury in Patients Undergoing Percutaneous Coronary Procedures

Evidence From a Hierarchical Bayesian Network Meta-Analysis of 124 Trials and 28 240 Patients

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Background—The effectiveness of currently available effective preventive strategies for contrast-induced acute kidney injury (CIAKI) is a matter of debate.

Methods and Results—We performed a Bayesian random-effects network meta-analysis of 124 trials (28 240 patients) comparing a total of 10 strategies: saline, statin, N-acetylcysteine (NAC), sodium bicarbonate ($NaHCO_3$), NAC+$NaHCO_3$, ascorbic acid, xanthine, dopaminergic agent, peripheral ischemic preconditioning, and natriuretic peptide. Compared with saline, the risk of CIAKI was reduced by using statin (odds ratio [OR], 0.42; 95% credible interval [CrI], 0.26–0.67), xanthine (OR, 0.32; 95% CrI, 0.17–0.57), ischemic preconditioning (OR, 0.48; 95% CrI, 0.26–0.87), NAC+$NaHCO_3$ (OR, 0.50; 95% CrI, 0.33–0.76), NAC (OR, 0.68; 95% CrI, 0.55–0.84), and $NaHCO_3$ (OR, 0.66; 95% CrI, 0.47–0.90). The benefit of statin therapy was consistent across multiple sensitivity analyses, whereas the efficacy of all the other strategies was questioned by restricting the analysis to high-quality trials. Overall, high heterogeneity was observed for comparisons involving xanthine and ischemic preconditioning, although the impact of NAC and xanthine was probably influenced by publication bias/small-study effect. Hydration alone was the least effective preventive strategy for CIAKI. Meta-regressions did not reveal significant associations with baseline creatinine and contrast volume. In patients with diabetes mellitus, no strategy was found to reduce the incidence of CIAKI.

Conclusions—In patients undergoing percutaneous coronary procedures, statin administration is associated with a marked and consistent reduction in the risk of CIAKI compared with saline. Although xanthine, NAC, $NaHCO_3$, NAC+$NaHCO_3$, ischemic preconditioning, and natriuretic peptide may have nephroprotective effects, these results were not consistent across multiple sensitivity analyses. **(*Circ Cardiovasc Interv*. 2017;10:e004383. DOI: 10.1161/CIRCINTERVENTIONS.116.004383.)**

Key Words: acetylcysteine ■ acute kidney injury ■ chronic kidney disease ■ contrast media ■ creatinine ■ meta-analysis ■ percutaneous coronary intervention

Over the past 25 years, the number of percutaneous procedures requiring contrast media administration has increased exponentially.[1] Contrast-induced acute kidney injury (CIAKI) is not an infrequent complication of coronary angiography and percutaneous coronary intervention and has been associated with increased mortality and cardiovascular events.[2,3]

See Editorial by Bangalore and Briguori

The optimal CIAKI prevention strategy for patients with suspected or confirmed coronary artery disease undergoing percutaneous coronary procedures is unknown. A wide array of medications and hydration regimens have been investigated in recent years.[4–6] Indeed, the large variety of available

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The Data Supplement is available at http://circinterventions.ahajournals.org/lookup/suppl/doi:10.1161/CIRCINTERVENTIONS.116.004383/-/DC1.

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WHAT IS KNOWN

- CIAKI is a relatively common complication of percutaneous coronary procedures, which has been associated with increased mortality and cardiovascular events.
- True effectiveness of several preventive strategies for CIAKI continues to be matter of debate as consequence of the extreme heterogeneity of available evidence.

WHAT THE STUDY ADDS

- This Bayesian network meta-analysis of 124 randomized clinical trials and 28 240 patients simultaneously compares the 10 most representative CIAKI preventive strategies tested in the past 25 years.
- When compared with saline hydration alone, periprocedural administration of a statin was associated with a significant CIAKI risk reduction with consistent results across multiple analyses, whereas the notable benefit of xanthine seemed to be significantly influenced by between-trial heterogeneity and disappeared after pooling only of patients with moderate-to-severe chronic kidney disease and trials with highest quality.
- NAC, $NaHCO_3$, NAC+$NaHCO_3$, and ischemic preconditioning reduced the risk of CIAKI when compared with saline hydration alone, but results were highly inconsistent across sensitivity analyses; hydration with saline was found to be the least effective strategy without significant variations after pooling only of trials ensuring an intense and prolonged infusion.

comparative trials provided extremely contradictory conclusions that has made it difficult to ascertain the best strategy for CIAKI prevention in clinical practice. Moreover, differences in the baseline clinical and procedural characteristics that are responsible for the interindividual susceptibility to CIAKI (ie, chronic kidney disease, diabetes mellitus, and contrast media volume) have significantly confounded the results of these studies.[7,8]

Network meta-analyses are extensions of standard pairwise meta-analyses that allow for simultaneous pooling of data related to multiple interventions, combination of direct and indirect components of the evidence in a single estimate, and comparison of treatments without a direct connection on the basis of indirect information.[9,10] We performed a comprehensive network meta-analysis of randomized clinical trials comparing preventative strategies for CIAKI in patients with suspected or confirmed coronary artery disease undergoing contrast media administration in the setting of a percutaneous coronary procedure.

Methods

This study was conducted in keeping with the PRISMA consensus (Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Protocols)[11] (PRISMA checklist, Appendix in the Data Supplement), the PRISMA extension statement for network meta-analyses,[12] and the Cochrane Collaboration recommendations.[13]

Search Strategy and Selection Criteria

PubMed, Embase, Scopus, Cochrane Library, and Web of Knowledge databases were searched for randomized clinical trials investigating the effects of preventive strategies for CIAKI, from the date of database inception to November 15, 2016. Additional specifications are reported in the Methods in the Data Supplement.

Inclusion and Exclusion Criteria

Studies were considered for inclusion only if they were randomized controlled trials of patients undergoing percutaneous coronary procedures (ie, coronary angiography with or without intervention) comparing ≥2 preventive strategies for CIAKI. Conference proceedings, unpublished reports, and trials with unclear treatments posology and CIAKI definition were excluded. Screening and data extraction are reported in the Methods in the Data Supplement.

End Points

The end point of interest was CIAKI, defined according to the most common definition as a relative ≥25% or an absolute ≥0.5 mg/dL serum creatinine increase within 48 to 72 hours from the procedure.[3,7] In some studies, CIAKI was defined as either a relative ≥25% or an absolute ≥0.5 mg/dL serum creatinine increase from baseline to 48 to 72 hours from the procedure. Some studies used definitions with time ≤1 week from the procedure. The rare studies (n=6) using only an AKIN (Acute Kidney Injury Network)/RIFLE-derived (Risk, Injury, Failure, Loss of Function, End Stage Renal Disease) definition of CIAKI were retained only in the main analysis. Trials using CIAKI definitions other than those listed above, mostly including definitions based on alternative biomarkers (ie, cystatin C, neutrophil gelatinase–associated lipocalin, urine creatinine, etc), were excluded.

Statistical Analyses

We performed a hierarchical Bayesian network meta-analysis using random-effects consistency models and noninformative priors.[14–16] After arm-level data imputation, the models were computed by Markov chain Monte Carlo simulations using 3 chains with overdispersed initial values, and Gibbs sampling was based on 100 000 iterations following discard of 50 000 (burn-in). Convergence was appraised according to Brooks and Gelman.[17] Posterior inference was summarized as odds ratio (OR) and 95% credible interval (CrI). Treatments were ranked to define the probability associated to each one to be the best strategy.[18] Inconsistency was assessed by comparing the deviance information criterion of consistency and inconsistency models and by contrasting direct and indirect evidence from the network (node-split).[15] Direct estimations represent the summary effects of Bayesian meta-analyses of trials comparing 2 strategies. Heterogeneity was graded based on I^2 statistics with values <25%, 25% to 50%, and >50%, representing mild, moderate, and severe heterogeneity, respectively.[19] All analyses were performed using R (version 3.1.1), WinBUGS (version 1.4), and STATA (version 12.1).

Sensitivity Analyses

Several sensitivity analyses according to different CIAKI definitions, moderate-to-advanced chronic kidney disease, diabetes mellitus, methodological characteristics of included trials (sample size, global qualitative assessment, blinding, and independent event adjudication), imputation of patients lost at follow-up, trial design, and treatment posology were run to investigate the robustness of the results and explore potential sources of inconsistency. Two network sensitivity analyses were also performed: (1) detachment of complex nodes of the primary network to the individual components and (2) selection of a network including only consistent comparisons and nodes with acceptable balance. The full methodology relevant to all these sensitivity analyses is more extensively described in the Methods in the Data Supplement.

Meta-Regression

The results of the main analysis were adjusted for baseline creatinine and contrast volume (see the Methods in the Data Supplement for further details).

Qualitative Assessment

Qualitative trial assessment was performed according to the 7-domain tool of the Cochrane Collaboration, whereas publication bias/small-study effect was inspected by comparison-adjusted funnel plot.[13] A description of qualitative assessment and comparison-adjusted funnel plot is provided in the Methods in the Data Supplement.

Results

Figure 1 illustrates the selection process and the geometry of the network. A total of 124 trials (n=28 240 patients) investigating 10 different preventive strategies (saline, statin, N-acetylcysteine [NAC], sodium bicarbonate [$NaHCO_3$], NAC+$NaHCO_3$, ascorbic acid, xanthine, dopaminergic agent, peripheral ischemic preconditioning, and natriuretic peptide) were finally selected (Figure I in the Data Supplement; Methods in the Data Supplement). References of the included trials and key trial–level methodological and clinical characteristics are reported in the Appendix in the Data Supplement (Trials List, Tables I and II in the Data Supplement). In about 95% of trials, CIAKI was reported according to the main definition or its 2 variants, although a 48 to 72 hours adjudication time was available in about 80%. Trial-level baseline creatinine and contrast volume values were significantly variable across trials.

Network Meta-Analysis

The incidence of CIAKI ranged from about 4% to 24% across strategies. Forest plots and rankograms of the network meta-analysis are illustrated in Figure 2. Compared with saline, the risk of CIAKI was reduced by statin (OR, 0.42; 95% CrI, 0.26–0.67), xanthine (OR, 0.32; 95% CrI, 0.17–0.57), ischemic preconditioning (OR, 0.48; 95% CrI, 0.26–0.87), NAC (OR, 0.68; 95% CrI, 0.55–0.84), $NaHCO_3$ (OR, 0.66; 95% CrI, 0.47–0.90), and NAC+$NaHCO_3$ (OR, 0.50; 95% CrI, 0.33–0.76). When comparing these strategies head to head, statin reduced the risk of CIAKI by 49% compared with NAC, whereas xanthine reduced the risk of CIAKI by 53%, 52%, 56%, and 59% compared with NAC, $NaHCO_3$, ascorbic acid, and dopaminergic agent, respectively (Figure 2). At treatments ranking, xanthine and statin emerged as the best strategies, whereas dopaminergic agent and saline were the worst.

Inconsistency Analysis, Node-Split, and Heterogeneity

The deviance information criterion was lower in the consistency model but to a small extent. Sources of inconsistency in specific segments of the network were inspected by node-split (Figure II in the Data Supplement). A significant inconsistency was detected only for the comparisons of NAC+$NaHCO_3$ versus saline (P=0.017) and xanthine versus NAC (P=0.039). Heterogeneity was extremely variable across comparisons, ranging from mild-to-extreme degree (Figure II in the Data Supplement). The comparison of statin versus saline presented a mild degree of heterogeneity (I^2=23.4%), whereas the comparison of xanthine versus saline showed a high degree of heterogeneity (I^2=66.0%). The comparisons of preconditioning versus saline and preconditioning versus NAC showed extreme heterogeneity.

Sensitivity Analyses

Figure 3 and Tables III through VI in the Data Supplement show the risk distribution of different strategies using saline

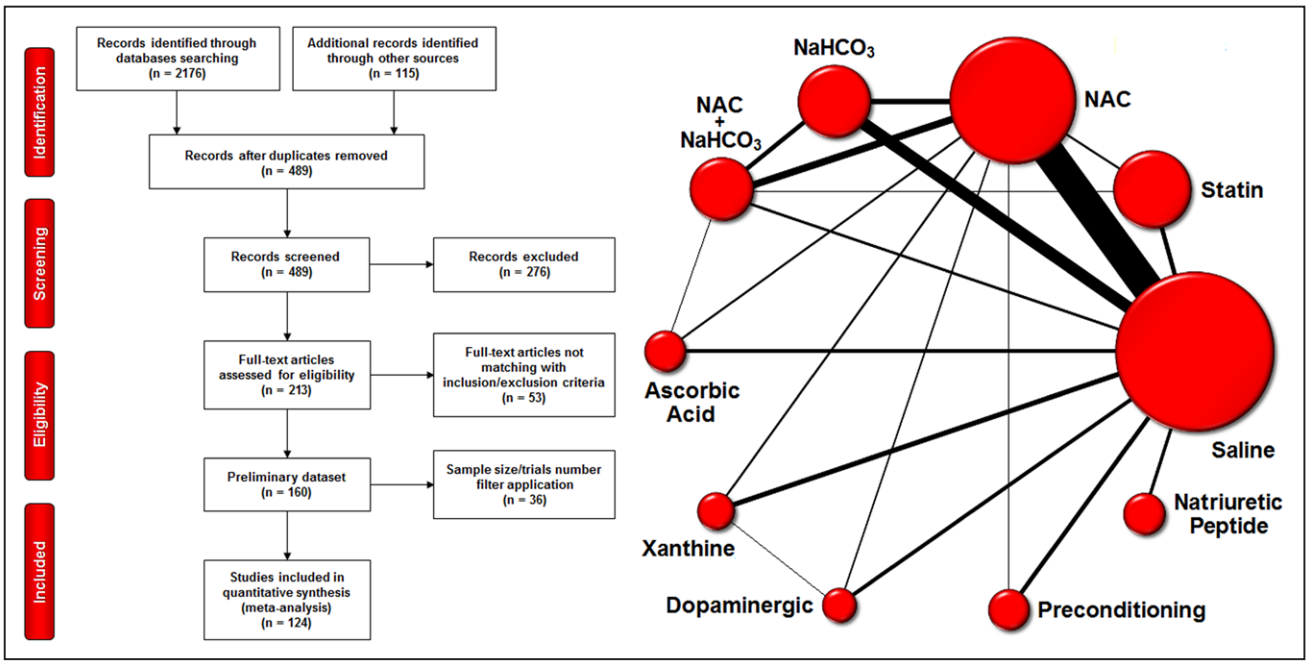

Figure 1. Flow diagram and network geometry**. Left**, The flow diagram describes the trials screening process. **Right**, Network of contrast-induced acute kidney injury preventive strategies. The node size is proportional to the number of patients included, and solid black lines define direct comparisons among strategies with thickness proportional to the number of trials involved. NAC indicates N-acetylcysteine; and $NaHCO_3$, sodium bicarbonate.

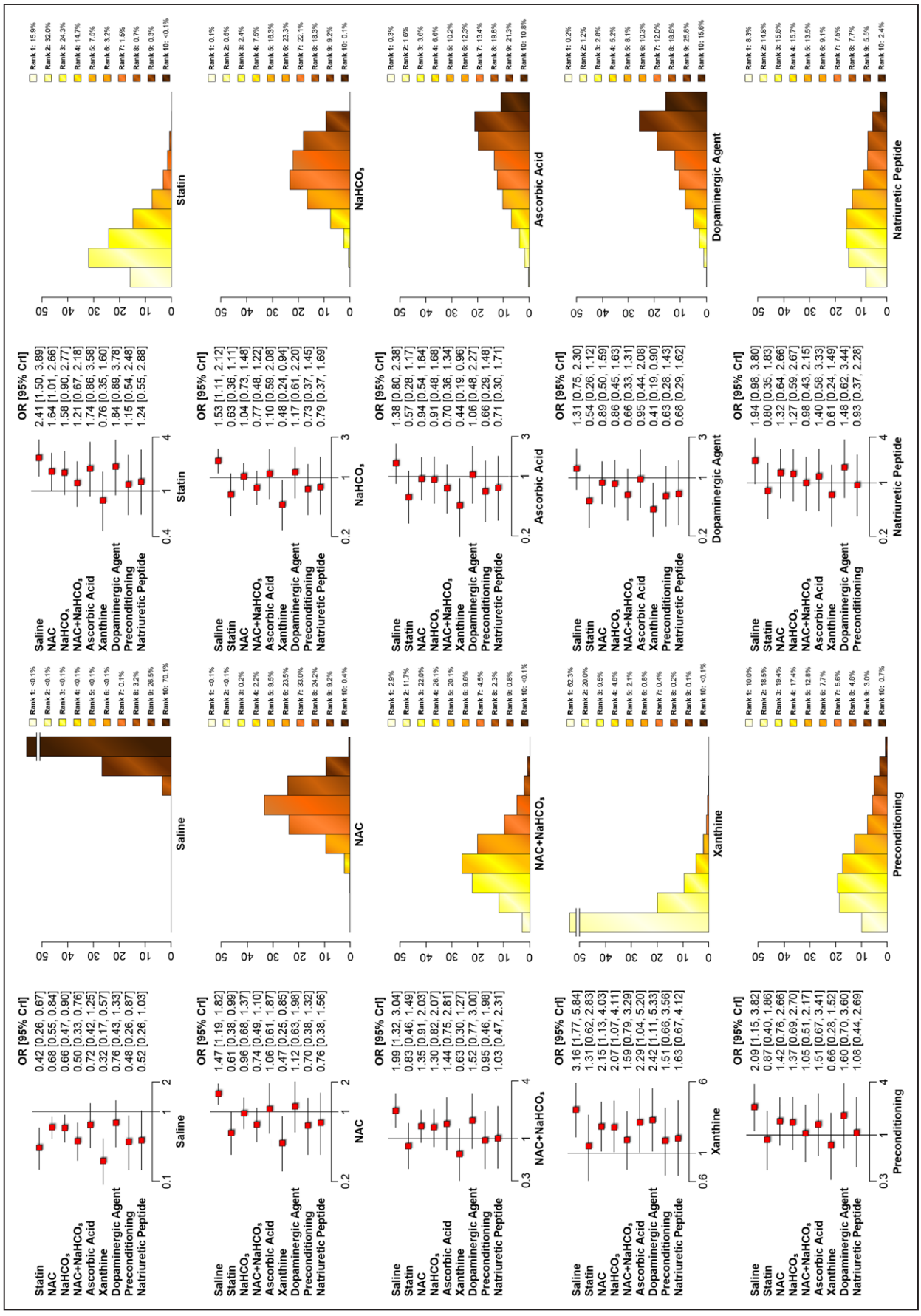

Figure 2. Continued

Figure 2 Continued. Main analysis**. Left**, The forest plots illustrate the risk distribution across the included strategy referred to a different common reference at a time. **Right**, Treatments are ranked according to the relative probability to be the first, the second, the third, etc., most effective. CrI indicates credible interval; NAC, N-acetylcysteine; $NaHCO_3$, sodium bicarbonate; and OR, odds ratio.

as the common reference after stratification by type of CIAKI definition. In trials reporting CIAKI events using both relative (≥25%) and absolute (≥0.5 mg/dL) serum creatinine criteria and trials using only relative criteria, the benefit of xanthine was no longer observable. Many strategies, including statin, xanthine, NAC, $NaHCO_3$, and NAC+$NaHCO_3$, were not sensitive to the different definitions.

Figure 4 and Tables VII and VIII in the Data Supplement show the risk distribution of different strategies using saline as common reference in analyses restricted to patients with moderate-to-severe chronic kidney disease or diabetes mellitus. In patients with estimated glomerular filtration rate ≤60 mL/min per 1.73 m^2 (or, when not available, estimated creatinine clearance ≤60 mL/min) or serum creatinine ≥1.5 mg/dL, statin, NAC, and ischemic preconditioning were associated with a risk reduction. In patients with diabetes mellitus, none of the strategies were found to reduce the risk of CIAKI compared with saline.

Figure 5 and Tables IX through XII in the Data Supplement show the risk distribution according to study quality assessment. After exclusion of smaller trials, the benefit of NAC, $NaHCO_3$, and NAC+$NaHCO_3$ over saline was reduced but persisting, whereas the superiority of statin and xanthine remained unchanged. By contrast, in analysis restricted to higher-quality trials, the effect associated with xanthine compared with saline was comparable, whereas statin and NAC continued to reduce the risk of CIAKI. Although in this analysis ischemic preconditioning and natriuretic peptide were associated with a notable risk reduction, they were supported by few trials, and high heterogeneity was noticed for ischemic preconditioning. Xanthine was no longer beneficial in trials with patient blinding or independent event adjudication. Only the risk reduction associated with statin and ischemic preconditioning compared with saline resulted unchanged or enhanced after pooling of trials with independent event adjudication, and NAC, $NaHCO_3$, and NAC+$NaHCO_3$ showed similar efficacy compared with saline. No trials investigating natriuretic peptide effectiveness were available for this analysis. The results remained consistent after imputation of the number of patients lost to follow-up and exclusion of the 3- or 4-arm trials which theoretically could have lost the benefit of randomization after removal of 1 arm testing a treatment that was not of interest (6.5%) or combination of 2 arms investigating the same treatment with different posology (4.0%; Figure III in the Data Supplement; Table XIII in the Data Supplement). Pooling only trials with a more generous and prolonged periprocedural 0.9% saline hydration regime and a intermediate-to-intense posology for each strategy (Figure 6; Table XIV in the Data Supplement) showed that statin and xanthine were the only 2 strategies associated with a marked CIAKI risk reduction compared with saline. However, whereas no heterogeneity was detected for statin versus saline, the comparison of xanthine versus saline showed high heterogeneity (I^2=76.3%).

Overall, the heterogeneity across these analyses showed a distribution generally similar to that of the main analysis (Table III in the Data Supplement). Although comparisons involving preconditioning showed extreme I^2 values and the xanthine versus saline comparison showed moderate-to-high heterogeneity, only a mild-to-moderate degree of heterogeneity was detected for statin versus saline.

After detaching complex nodes of the primary network (Figure IV in the Data Supplement), statin—both alone and combined with NAC and $NaHCO_3$—consistently reduced the risk of CIAKI compared with saline. Among xanthines, only theophylline—alone and in combination with NAC—was associated with a risk reduction. However, comparisons involving theophylline+NAC were inconsistent (Figure IV in the Data Supplement). Excluding nodes affected by significant *P* values at node-split and applying a minimum number of studies per node/sample size filter, the risk of CIAKI was reduced only in patients receiving statin, NAC, and $NaHCO_3$ (Figure V in the Data Supplement; Table XV in the Data Supplement).

Meta-Regressions

Bayesian network meta-regressions using weighted trial–level mean values of baseline creatinine (mg/dL) and contrast volume (mL) did not reveal significant changes for all the strategies other than ischemic preconditioning which resulted more effective than saline (Figure VI in the Data Supplement).

Qualitative Assessment

Bias assessment is schematically illustrated in Figures VII and VIII in the Data Supplement. Approximately 50% of trials did not ensure any blinding, and approximately 55% did not properly describe the process of random sequence generation. In addition, significant concerns arose from the high proportion of trials with unclear performance of allocation concealment (about 60%–65%) and blinded events adjudication (about 80%). Although the comparison-adjusted funnel plot did not display an asymmetrical distribution of the estimates for most strategies (Figure IX in the Data Supplement), a moderate asymmetry favoring treatment efficacy compared with control and a possible small-study effect was observed for NAC and xanthine.

Discussion

The main findings of this network meta-analysis can be summarized as follows. First, treatment with statin, xanthine, and—to a lesser extent—NAC, $NaHCO_3$, and NAC+$NaHCO_3$ is associated with a significant reduction in the risk of CIAKI compared with saline. Second, in contrast to xanthine, the benefit of statin was robust and consistent in multiple sensitivity analyses. Third, diabetes mellitus may offset the benefit of preventive strategies for CIAKI. Fourth, although often promoted as the best strategy against CIAKI, periprocedural hydration alone resulted to be the least effective preventive treatment without significant variation after inclusion of only trials ensuring an intense and prolonged infusion. In aggregate, these findings underscore the prominent role of statin and the possible role of xanthine as the best treatment options

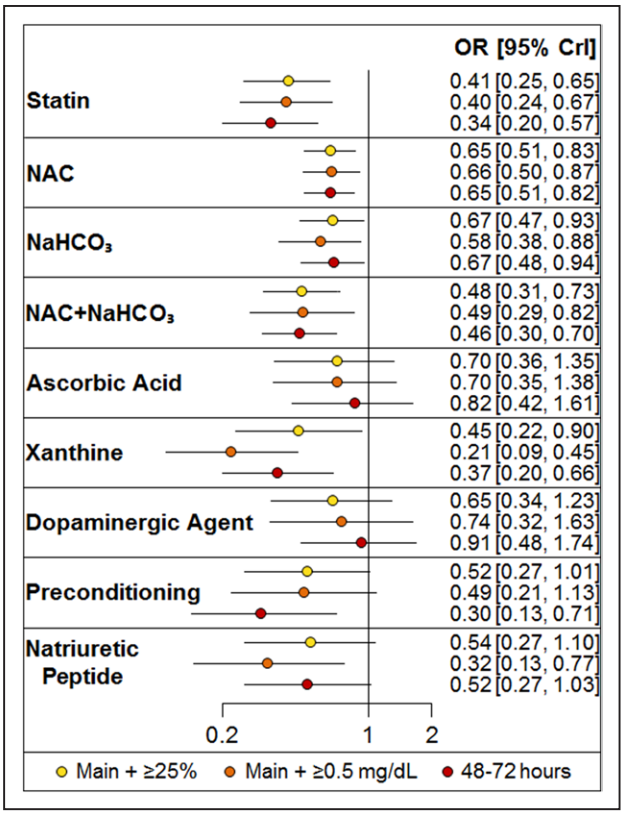

Figure 3. Subgroup analyses according to different contrast-induced acute kidney injury definitions. Trials and contrast-induced acute kidney injury events were pooled according to 3 different criteria: (1) main definition+contrast-induced acute kidney injury as serum creatinine increase ≥25%; (2) main definition+contrast-induced acute kidney injury as serum creatinine increase ≥0.5 mg/dL; and (3) events occurring between 48 and 72 h. CrI indicates credible interval; NAC, N-acetylcysteine; $NaHCO_3$, sodium bicarbonate; and OR, odds ratio.

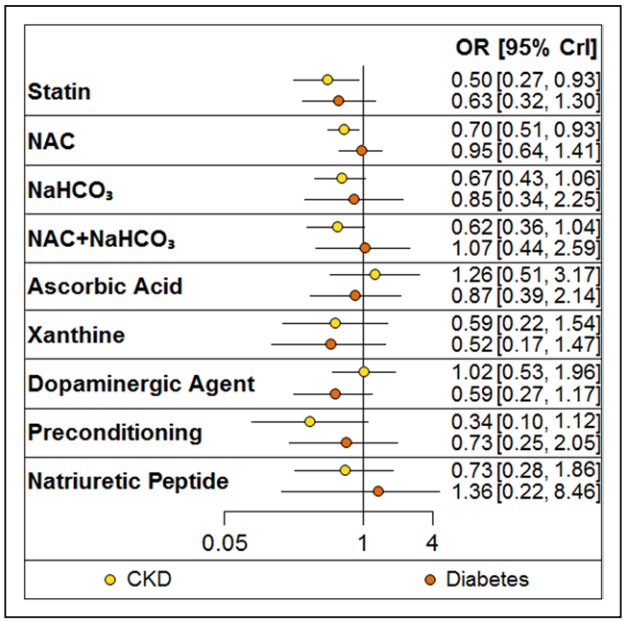

Figure 4. Subgroup analyses according to moderate-to-advanced chronic kidney disease and diabetes mellitus. In 2 different subgroup analyses, patients with advanced chronic kidney disease, defined as estimated glomerular filtration rate ≤60 mL/min per 1.73 m^2 (or, when not available, estimated creatinine clearance ≤60 mL/min) or serum creatinine ≥1.5 mg/mL and diabetes mellitus were pooled. CKD indicates chronic kidney disease; CrI, credible interval; NAC, N-acetylcysteine; $NaHCO_3$, sodium bicarbonate; and OR, odds ratio.

for preventing CIAKI in patients undergoing percutaneous coronary procedures with contrast media administration.

Inflammation, oxidative stress, direct tubular injury, osmotic loading, and medullary hypoxia play a significant role in the pathogenesis of CIAKI.[20,21] Preventive strategies have been tested on the assumption of a significant effect on one or more of these mechanisms.[5,6] Statins have known pleiotropic effects that act by decreasing local and systemic inflammation, improving endothelial function, and modulating regulatory mechanisms of cell survival.[22–24] Statins may be particularly effective in CIAKI prevention if patients present with a high expression of inflammation biomarkers[25] but can also play a beneficial role downstream by counteracting one of the possible common final pathways of the CIAKI process, namely contrast-induced tubular cells apoptosis.[24,26] In a recent in vitro study, statins reduced the activation of apoptosis in human kidney cells, with a lower phosphorylation of JNK and p53 and a lower expression of caspase 3.[26] Results on rats were comparable.[27] Although these findings are preliminary, they are consistent with a biologically plausible mechanism. In our study, the renoprotective effects observed in patients receiving preprocedural statin administration were marked and consistent regardless of the different CIAKI definitions used across trials, the presence of baseline moderate-to-severe chronic kidney disease, and the quality of the studies analyzed. Because the methodological quality of trials included in a meta-analysis can significantly influence pooled estimate,[13] we inspected the consistency of results associated with statin after pooling only trials with larger sample size, blinding, independent adjudication of the events, and higher cumulative methodological quality as defined by the Cochrane Collaboration[13] without detecting any significant change. In addition, heterogeneity across analyses was overall acceptable, and no asymmetry in trial-level estimates distribution was observed. Finally, meta-regression analyses did not suggest significant associations with basal creatinine and contrast volume variations across trials.

Theophylline or aminophylline (theophylline–ethylenediamine) and pentoxifylline are nonselective A_1 and A_2 adenosine receptors antagonists that produce renal vasodilation by blocking A_1 adenosine receptor–mediated vasoconstriction and induce diuresis by reducing sodium reabsorption in the proximal tubules.[28,29] We found a marked risk reduction in CIAKI with xanthine when compared with saline. However, although not sensitive to the definition of CIAKI and variations in posology, this effect was significantly mitigated in critical subsets, such as advanced chronic kidney disease and diabetes mellitus, and in trials with higher quality, blinding, and independent event adjudication. In addition, results associated with xanthine were supported only by 11 small trials (nearly 600 patients), and inspection of local inconsistency of the network showed that direct evidence significantly contrasted with indirect evidence for the comparison of xanthine

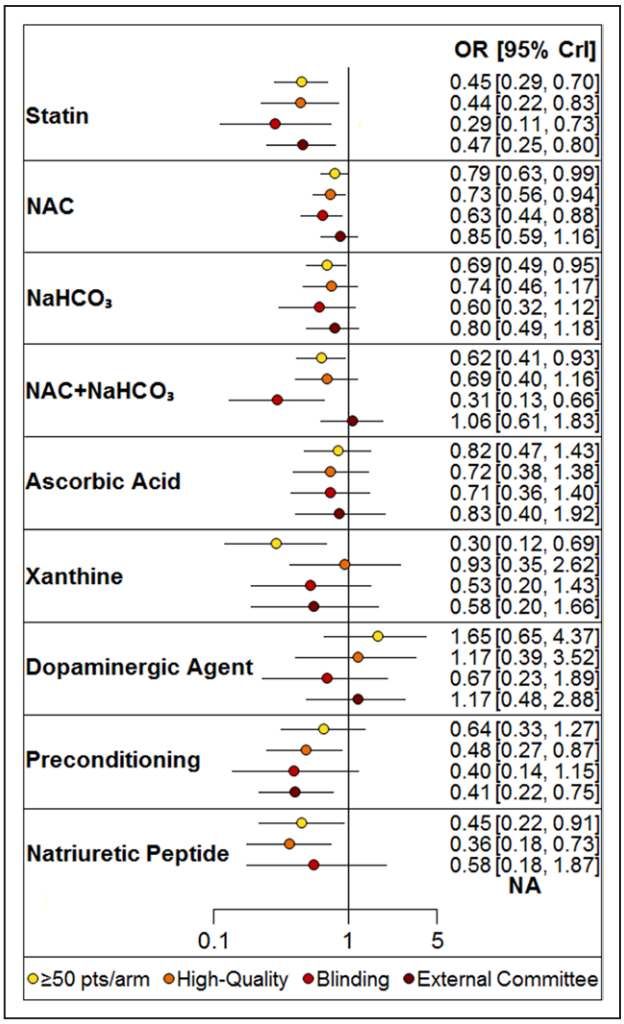

Figure 5. Subgroup analyses according to trials quality. Trials and contrast-induced acute kidney injury events were pooled according to 4 different methodological aspects: (1) trials with ≥50 patients per arm; (2) trials with high methodological quality, defined as a cumulative score ≥5.5 by combining components of the Cochrane Collaboration tool[13]; (3) trials planning at least patients blinding; and (4) trials having a blinded committee for contrast-induced acute kidney injury events adjudication. CrI indicates credible interval; NA, not available; NAC, N-acetylcysteine; $NaHCO_3$, sodium bicarbonate; and OR, odds ratio.

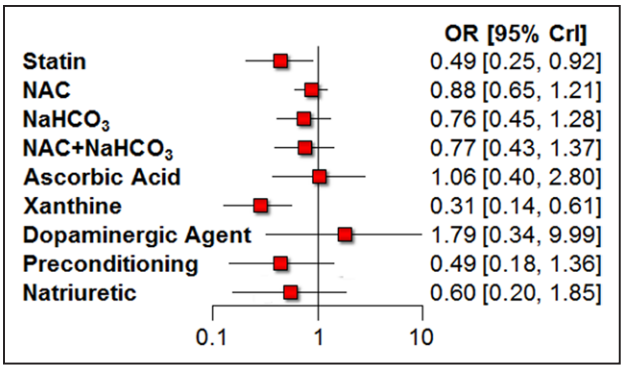

Figure 6. Sensitivity analysis of trials with intense posology. In this sensitivity analysis, only trials with systematic intense 0.9% (≥1 mL kg^{-1} h^{-1}) saline hydration regimens, from at least 6 h before to at least 6 h after the procedure, medium-to-high dose of medications, and reasonable periprocedural application (cycles for peripheral ischemic preconditioning) were considered. This sensitivity analysis sought to minimize the influence of trials including patients not hydrated or receiving saline solution with limited amount or duration. Secondary objective was to remove the influence of trials using low dose of medications, by including only trials using medium-to-high doses (ie, atorvastatin ≥40 mg, rosuvastatin ≥20 mg, simvastatin ≥20 mg, etc). CrI indicates credible interval; NAC, N-acetylcysteine; $NaHCO_3$, sodium bicarbonate; and OR, odds ratio.

versus NAC. After detachment of the network to individual strategies, we found that the benefit of xanthine is mostly attributable to theophylline and not pentoxifylline. Finally, concerns about the xanthine strategy arose from the high degree of heterogeneity detected across analyses, and funnel plot inspection showed a moderate asymmetry in the distribution of trial-level estimates likely with the presence of a small-study effect.

When compared with saline, we also observed a reduced risk of CIAKI with NAC, $NaHCO_3$, and NAC+$NaHCO_3$. The trials investigating these therapies included about 40% of patients included in the meta-analysis. The available data on the efficacy of NAC for CIAKI prevention, including several meta-analyses, provided contradictory conclusions.[5,30,31] Indeed, although NAC reduced CIAKI without significant variations across definitions, we found that these results could be influenced by trials with lower global quality and absence of independent event adjudication. These findings are in agreement with a systematic review appended to the ACT trial (Acetylcysteine for Contrast-Induced Nephropathy Trial),[31] in which deficiencies in allocation concealment and blinding provided partial explanation for the extreme variability in results across trials. In addition to these findings, low doses of NAC with or without inadequate hydration regimens may have introduced heterogeneity, and a publication bias/small-study effect amplifying NAC efficacy cannot be excluded. Interestingly, the removal of all trials with at least 1 arm, including <50 patients, produced a pooled effect comparable with saline.

Infusion of $NaHCO_3$ is another traditional strategy tested over time with mixed results.[32,33] $NaHCO_3$ was more effective than saline in the main analysis and was associated with efficacy similar to NAC. However, $NaHCO_3$ exhibited marked variations across subanalyses and was no longer effective in patients with moderate-to-severe chronic kidney disease or diabetes mellitus and trials of higher methodological quality. The exclusion of trials without systematic and adequate hydration regimens and medium-to-intense $NaHCO_3$ posology confuted the main analysis conclusions.

The combination of NAC+$NaHCO_3$ in a single strategy was explored in several trials in the attempt to amplify the effects of individual treatment components, but the results were not univocal.[34,35] In the main analysis, we observed a notable risk reduction associated with NAC+$NaHCO_3$ compared with saline, which had higher extent than the individual components of NAC+$NaHCO_3$ potentially indicating a cumulative effect. However, we revealed by network node-split a significant inconsistency for NAC+$NaHCO_3$ versus saline, with direct estimation reporting a similar effect of the 2 strategies. Finally, although the combination of statin with

NAC+$NaHCO_3$ was associated with the highest effect among statin-based strategies, this result was supported only by 1 trial,[26] which demands additional confirmation.

Ischemic preconditioning and natriuretic peptide showed a notable risk reduction when compared with saline in several analyses. Although these results are promising and deserve further attention in future, they should be considered with caution because, when compared with other strategies, the ischemic preconditioning and natriuretic peptide nodes included fewer patients and fewer trials. The limited data can explain the variable findings across analyses, where the selection of some trial having strong influence on pooled estimate could have driven the results. Moreover, some of the included trials investigating ischemic preconditioning were primarily conducted for other purpose. This consideration may explain the extreme heterogeneity constantly observed.

By node-split, we provided updated direct evidence estimates of different CIAKI prevention strategies (Figure II in the Data Supplement). Indeed, we are able to supplement considerably the latest frequentist meta-analyses of CIAKI[5,33,36–38] because in our study the direct component of evidence deriving from each available pair of preventive strategies is similar to a standard meta-analysis.

In aggregate, the results of our meta-analysis generate 2 additional considerations. First, although few studies have directly addressed volume expansion against CIAKI, intense hydration is commonly advocated as the cornerstone preventive strategy.[3,5–7] However, in our meta-analysis, hydration with saline solution alone was the least effective strategy, and the inclusion only of trials ensuring a more generous and prolonged periprocedural infusion did not modify this conclusion. On the one hand, our results do not contradict the central role of saline infusion, taking into consideration that all arms of included trials received a similar regimen, but on the other hand highlight the limitations of a preventive strategy based only on hydration. Second, comparisons between strategies other than saline tended to produce limited differences that can be only partially explained by the number of direct comparison in the network. The differential relative effectiveness across nonsaline-based strategies reflects the real magnitude of required advances against CIAKI.

Finally, in our study, we observed a significant negative impact of diabetes mellitus on the effectiveness of CIAKI preventive strategies, including statin and xanthine. Diabetes mellitus is an important cause of nephropathy and, although these conditions can be observed in the same patient, both can independently predispose to CIAKI.[2,3,7] However, on the one hand, according to our findings more information is needed to identify effective preventive strategies against CIAKI in diabetic patients, and on the other hand, the absence of individual patient data and event reporting in a significant proportion of trials limited our sample size.

Limitations

As with any meta-analysis, this study shares the limitations of the original trials included, and despite the multiple sensitivity analyses conducted, some remaining questions would only be addressed by individual patient data. More specifically, the results of our meta-analysis should be interpreted taking the following limitations into account. First, some of the included trials were heterogeneous, with differences in definitions, methods, and posology. Although our sensitivity analyses detected a modest influence of these variables, the influence of other unmeasured confounding factors cannot be ruled out. Moreover, as with any meta-analysis, the results of some restrictive analyses might be influenced by the reduction of included trials. Second, the estimation of a cutoff value to exclude underemployed strategies (ie, adding heterogeneity without producing any relevant additional finding) may imply a possible selection bias. However, as observable in the Figure I in the Data Supplement, this was necessary because about 50% of treatments identified before applying our ad hoc filter included <100 patients and as such would have been compared with strategies including several thousands of patients (ie, saline, statin, NAC, and $NaHCO_3$). Similarly, the exclusion of treatments investigated in <5 trials was empirical but preserved from the risk of considering strategies in which the evidence was supported only by a single large trial or unequally shared across few trials. As a matter of fact, the impact of this filter was not marked because it led to removal of only 1 strategy (ie, furosemide), and about 85% of patients treated with furosemide came only from a single medium-quality trial. A threshold for a minimum population size assigned to each identified treatment was also established using nonconservative parameters, which allowed for the inclusion of a large number of strategies, while excluding at the same time poorly represented and noninformative treatments. Third, analysis of treatment combinations implies per se a risk of bias (lumping). However, by detaching the network into the most elementary variants of strategies, the results remained unchanged and supported a similar effect within nodes, including similar treatments, with the exception of xanthine, as described earlier. Fourth, although our results apply to patients with suspected or confirmed coronary artery disease undergoing coronary diagnostics or procedures, about 10% of the trials enrolled a minor (<35%) proportion of patients who also underwent contrast administration for peripheral angiography or intervention sometimes performed in the same setting of the coronary procedures. Conversely, we deliberately excluded patients undergoing contrast media administration in the setting of computed tomographic diagnostics, transcatheter aortic valve replacement, and fully endovascular procedures because these procedures potentially entail different patient profiles and mechanisms of acute kidney injury. Fifth, the lack of specific trial-level outcomes did not enable exploring the influence of clinical presentation (ie, acute coronary syndrome, stable angina, silent angina, etc.) on the results of the meta-analysis. However, the posology subanalysis, including only trials requiring an intense hydration regimen for an adequate interval of time before the procedure, led to the exclusion of patients presenting with ST-segment–elevation myocardial infarction or undergoing emergency coronary procedure. Finally, detaching the statin node according to statin type (ie, atorvastatin, rosuvastatin, simvastatin, etc.) was not feasible. However, in 2 recent frequentist pairwise meta-analyses, no difference between statin types in terms of CIAKI risk reduction was observed.[36,38]

Conclusions

A preventive approach with statin was found to reduce the risk of CIAKI in patients undergoing coronary catheterization compared with saline. A xanthine-based strategy also proved effective compared with saline, but these results could be influenced by the presence of moderate-to-severe chronic kidney disease and the inclusion of lower-quality and small trials exaggerating the benefit of this strategy. NAC, $NaHCO_3$, and NAC+$NaHCO_3$ administration may be associated with a mild CIAKI risk reduction compared with saline, although the benefit of these strategies was attenuated in some sensitivity analyses. Ischemic preconditioning and natriuretic peptide may present a nephroprotective effect but larger and high-quality trials are required to draw conclusions. In patients with diabetes mellitus, none of the investigated strategies reduced the incidence of CIAKI.

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Dr Giacoppo conceived and designed the study; Drs Gargiulo, Buccheri, and Aruta collected and abstracted the data; Dr Giacoppo undertook the statistical analysis; Drs Giacoppo and Capodanno drafted the article; all authors had full access to all the data, including statistical reports and tables; all authors analyzed and interpreted the data; all the authors critically revised the article for important intellectual content; and Dr Capodanno is the guarantor and the supervisor of the study. All authors have reported that they have no relationships relevant to the contents of this article to disclose. Data used were extracted from literature.

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Disclosures

None.

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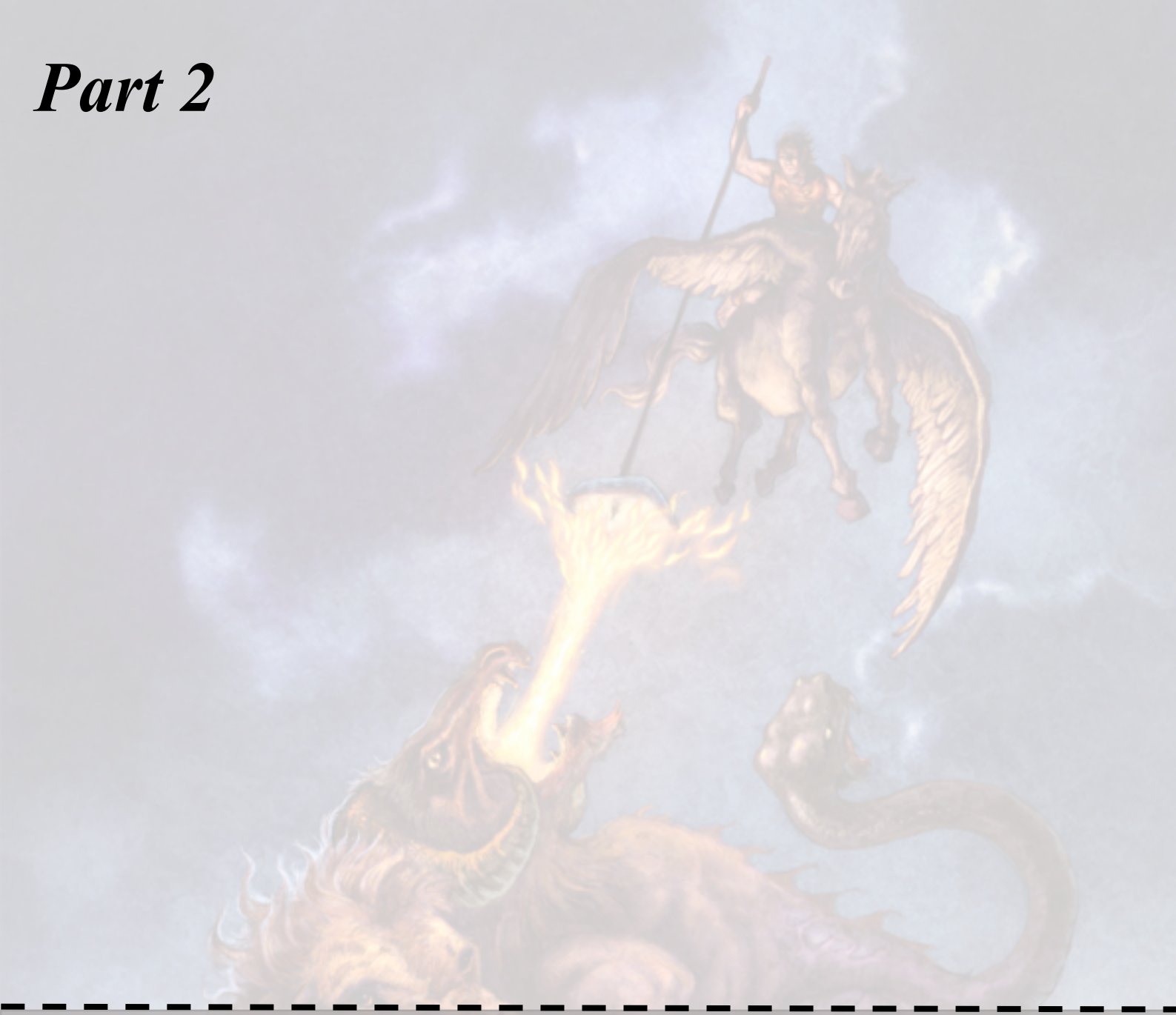
Part 2



Trade-off for ischemia and bleeding after percutaneous coronary interventions: which is the optimal regimen of antiplatelet therapy?

Impact of residual platelet aggregation and concomitant therapies on ischemic and bleeding events in patients receiving dual antiplatelet therapy (DAPT)

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Impact of residual platelet reactivity on reperfusion in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention

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Abstract

Aim: Whether high platelet reactivity (HPR) immediately after diagnostic angiography is associated with worse coronary reperfusion prior to and after primary percutaneous coronary intervention (PPCI) for ST-segment elevation myocardial infarction (STEMI) is unknown. This study aimed to assess the impact of $P2Y_{12}$-mediated HPR on angiographic outcomes in patients with STEMI undergoing PPCI.

Methods: STEMI patients undergoing PPCI and pretreated with a $P2Y_{12}$ receptor antagonist underwent platelet function testing with the VerifyNow™ assay at the time of angiography. Light transmission aggregometry (LTA) was performed in a subgroup. HPR was defined according to expert consensus definitions. Pre-PCI coronary patency, thrombotic burden and indices of impaired post-PCI reperfusion were compared between HPR and non-HPR patients.

Results: Among 164 patients, the prevalence of VerifyNow™-derived HPR was 71.3% at a median (interquartile range (IQR)) of 55 (40–75) minutes after a $P2Y_{12}$ inhibitor loading dose. Compared with non-HPR patients, those with HPR had significantly lower rates of pre-PCI Thrombolysis in Myocardial Infarction (TIMI) flow grades 2 or 3 (51.1% vs. 32.5%, $p = 0.04$), higher rates of thrombus score (TS) grade 3/4 (29.8% vs. 52.1%, $p = 0.015$) and 4 (14.9% vs. 32.5%, $p = 0.037$) and lower median (IQR) corrected TIMI frame count (cTFC; 23.2 (15.8–32.5) vs. 26.0 (21.0–35.0), $p = 0.02$), respectively. These findings were consistent using LTA-based data. HPR and TS grade 4 were predictors of higher cTFC.

Conclusions: In patients with STEMI undergoing PPCI pretreated with $P2Y_{12}$ receptor inhibitors, pre-PPCI HPR was found to be associated with lower pre-PCI coronary patency, higher thrombotic burden and a worse index of post-PCI coronary reperfusion.

Keywords

Platelet reactivity, ST-elevation myocardial infarction, percutaneous coronary intervention

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Introduction

Primary percutaneous coronary intervention (PPCI) is the recommended method of coronary reperfusion in patients with ST-segment elevation myocardial infarction (STEMI).[1,2] Given the pivotal pathophysiologic role of activated platelets in thrombotic coronary artery occlusion, dual-antiplatelet therapy (DAPT), consisting of aspirin plus an oral adenosine diphosphate (ADP) receptor ($P2Y_{12}$)

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antagonist (clopidogrel, prasugrel or ticagrelor), has been established as an important adjunct to PPCI.[1,2] Despite the lack of clear supporting evidence, current guidelines recommend that a $P2Y_{12}$ inhibitor should be given as early as possible to patients with STEMI and planned PPCI in order to favor and sustained reperfusion of the infarct-related artery (IRA), preventing peri-procedural thrombotic complications.[1,2]

Recently, the ATLANTIC (Administration of Ticagrelor in the Cath-Lab or in the Ambulance for New ST-Elevation Myocardial Infarction to Open the Coronary Artery) study showed that prehospital (in the ambulance) versus in-hospital (in the catheterization laboratory) treatment with ticagrelor does not improve pre-PCI coronary reperfusion.[3,4] In the era of fast-transfer protocols and short-time access to PPCI, this may be attributed to the lack of effective platelet inhibition at the time of angiography, given the known delay to the onset of action of oral antiplatelet agents in STEMI.[5–7] However, the link between coronary reperfusion and the varying degrees of $P2Y_{12}$ inhibition reached at the time of angiography is unknown in STEMI patients undergoing PPCI. Indeed, while there is convincing evidence showing that the risk of ischemic events after PCI increases in patients with high platelet reactivity (HPR) on treatment, there is limited evidence assessing the association between the level of residual $P2Y_{12}$-mediated platelet reactivity and angiographic outcomes of PPCI for STEMI.[8–10] Given the association between pre-PCI IRA patency, thrombotic burden and post-PCI coronary perfusion with improved survival,[11–13] understanding the effect of HPR on these surrogate endpoints would provide important insights into the clinical impact of achieving adequate $P2Y_{12}$ inhibition as early as possible in the setting of PPCI. Therefore, the objective of this pharmacodynamic study conducted in STEMI patients undergoing PPCI who were pretreated with a $P2Y_{12}$ receptor inhibitor was to investigate the impact of pre-PCI HPR on: 1) pre-PCI IRA patency; 2) thrombus burden; and 3) angiographic indices of coronary reperfusion.

Methods

Patient population

STEMI patients undergoing PPCI and platelet function testing from October 2012 to August 2014 at the Ferrarotto Hospital-University of Catania, Catania, Italy, were collected as part of the prospective, observational PROMETHEUS (Platelet Reactivity of STEMI Patients on Antithrombotic Therapy Undergoing Primary Angioplasty) registry. Patients were enrolled if they were older than 18 years of age, admitted with symptoms of ischemia lasting at least 30 minutes with an electrocardiographic ST-segment elevation >1 mm in two or more contiguous electrocardiogram leads or presenting with a new left bundle branch block and if they were undergoing PCI at <12 hours of symptoms onset and were pretreated with a $P2Y_{12}$ antagonist. Any of the oral $P2Y_{12}$ antagonists (clopidogrel, prasugrel or ticagrelor) was permitted because the present study aimed to evaluate the association between the absolute degree of $P2Y_{12}$ inhibition reached at the time of angiography and the coronary reperfusion, regardless of which agent was used to reach this inhibition. Patients were excluded in case of the following: administration of fibrinolytics and/or glycoprotein IIb/IIIa inhibitors (GPIs) upstream for <30 days; presentation with stent thrombosis; culprit lesion located in a coronary bypass graft or in a vessel segment <2.0 mm; spontaneous dissection; cardiogenic shock; chronic DAPT; concomitant use of other antithrombotic drugs (i.e., oral anticoagulant, dipyridamole, cilostazol or non-steroid anti-inflammatory drugs); aspirin allergy or intolerance; platelet count $<100 \times 10^6$/mL; hematocrit <25%; liver disease (bilirubin level >2 mg/dL); active bleeding; recent or chronic infective or inflammatory diseases; any malignancy; recent stroke; surgery or trauma in the previous 30 days.

All patients underwent platelet function testing with the VerifyNow™ assay (Accumetrics, Inc., San Diego, CA, USA). From the beginning of the study in October 2012 to August 2013, only STEMI patients presenting during weekdays during regular working hours (8:00 a.m. to 8:00 p.m.) were included in the registry due to logistics related to performing platelet function testing, also including light transmission aggregometry (LTA), at nights and weekends. After August 2013, only the VerifyNow™ assay was used, and all STEMI patients, including those presenting off-hours, were also screened.

For the purpose of the present study, in order to define pre-PPCI HPR and to assess the associations between the latter and both pre- and post-PPCI angiographic outcomes, we used pharmacodynamic data derived from the VerifyNow™ assay measured before PPCI, immediately after diagnostic coronary angiography. Multiple angiographic endpoints, as described below, were compared between patients with and without HPR measured at this time point. The local hospital Ethics Committee approved the study and informed consent was obtained from all patients. The study complied with the Declaration of Helsinki. The authors had full access to the data and take responsibility for its integrity.

Study medications and interventions

Upon presentation, all patients received aspirin 150 mg intravenously and an anticoagulant including unfractionated heparin and weight-adjusted, low-molecular-weight heparin. All patients were pretreated in the emergency department or at the referring center with a loading dose of clopidogrel (600 mg), prasugrel (60 mg) or ticagrelor (180 mg). The choice of the $P2Y_{12}$ antagonist was left to the discretion of the referring physician. The antithrombotic

regimen during procedure, the use of thrombus aspiration and the type of stent were left to the discretion of the interventional cardiologist. PPCI was performed according to standard techniques.

Blood sampling and platelet function analysis

Blood samples for platelet function testing were collected from an antecubital vein immediately after coronary angiography, before intra-procedural administration of any antithrombotic drug. The first 2–4 mL of blood were discarded in order to avoid spontaneous platelet activation, and samples were processed for functional assessments within 1 hour after blood drawing.

The VerifyNow™ $P2Y_{12}$ assay was performed in order to assess platelet function, as previously described,[14] and was used to define HPR.[8] This assay reports the results as $P2Y_{12}$ reaction units (PRU), with higher values representing higher platelet reactivity. HPR was defined as PRU >208, in keeping with current standards.[9]

LTA was performed by the turbidimetric method in a two-channel aggregometer (Chrono-Log 490 Model, Chrono-Log Corp., Havertown, PA, USA) according to standard protocols.[14] Platelet-rich plasma was obtained as a supernatant after centrifugation of citrated blood at 195 *g* for 10 minutes, and platelet-poor plasma was obtained by a second centrifugation of the blood fraction at 1528 *g* for 10 minutes. Aggregation curves were recorded for 6 minutes. Maximum platelet aggregation (MPA) was measured at peak, following challenge with ADP (5 and 20 μM).[14] Based on the LTA findings, HPR was defined as MPA-ADP (20 μM) >59% and MPA-ADP (5 μM) >46%.[8]

Angiographic analysis

The angiographic images were acquired with a General Electric Innova 2100 single-plane system. For the angiographic assessment after the procedure, a long final run at 30 frames/second was acquired in specific projections in order to minimize the superimposition of the perfusion territories of different arteries. Two experienced interventional cardiologists (BF and YO), who were blinded to platelet function testing, adjudicated the angiographic outcomes. All angiograms were assessed with respect to Thrombolysis in Myocardial Infarction (TIMI) flow scale of the IRA prior to and after PCI.[15] The corrected TIMI frame count (cTFC) and the myocardial blush grade (MBG) were determined on the post-PCI final angiogram, as previously described.[16,17]

The thrombus score (TS) was used as an angiographic index of thrombotic burden at the site of stenosis and calculated on the pre-PCI angiogram. Intracoronary thrombus was scored in five grades as previously described.[12] In brief, in TS grade 0, no cine-angiographic characteristics of thrombus are present; in TS grade 1, possible thrombus is present (i.e., reduced contrast density, haziness, irregular lesion contour or a smooth, convex "meniscus" at the site of total occlusion suggestive, but not diagnostic of thrombus); in TS grade 2, definite thrombus is present, with the greatest dimension at less than or equal to half of the vessel diameter; in TS grade 3, definite thrombus is present, but with the greatest linear dimension at greater than half but less than two vessel diameters; in TS grade 4, definite thrombus is present, with the largest dimension at greater than or equal to two vessel diameters; finally, in TS grade 5, there is a total occlusion (i.e., inability to assess thrombus burden due to total vessel occlusion).[12] Since TS grade 5 is essentially a classification of flow and not of thrombus, patients initially presenting in this group were reclassified into one of the other four categories after vessel recanalization by either wire crossing or passage/dilatation of a small (1.5-mm diameter) balloon.[12]

Study endpoints and sample size calculation

The primary endpoint was the rate of coronary artery patency prior to PCI, defined as TIMI flow grade 2 or 3. Assuming an incidence of 66% of TIMI flow grade 2 or 3 in patients without HPR,[10] we calculated that at least 46 patients in each group (HPR and no-HPR) were needed to detect a relative difference of 50% in the rate of TIMI flow grade 2 or 3 between groups, assuming 90% power and a two-sided significance level of 0.05. This assumption was based on the results of the only available study assessing the impact of HPR on pre-procedural IRA patency.[10]

Secondary endpoints included: i) the rates of pre-PCI TIMI flow grade 3; ii) the rates of pre-PCI TS grade 3/4 or 4 (high thrombus burden); iii) the rates of post-PCI TIMI flow grade <3 or MBG 0/1 (indices of impaired coronary perfusion); and iv) post-PCI cTFC (an angiographic index of myocardial perfusion used as a continuous variable).

Other secondary non-angiographic endpoints included ⩾70% resolution of ST-segment elevation at 60 minutes after PCI and levels of cardiac enzymes (creatine kinase-MB and troponin T) at peak.

Cardiac magnetic resonance

A cardiac magnetic resonance (CMR) assessment of infarct size and microvascular obstruction (MVO) was proposed for only the first 50 consecutive patients due to hospital resources and logistics. All CMR studies were performed from 7 to 10 days after the index event with a 1.5-Tesla MRI scanner (Achieva, Philips Medical Systems, The Netherlands). Long- and short-axis images were acquired using a standard cine steady-state free precession (SSFP), T2-weighted and inversion recovery fast gradient echo (IR-GRE) late gadolinium enhancement sequences. Anonymized images were independently assessed by an

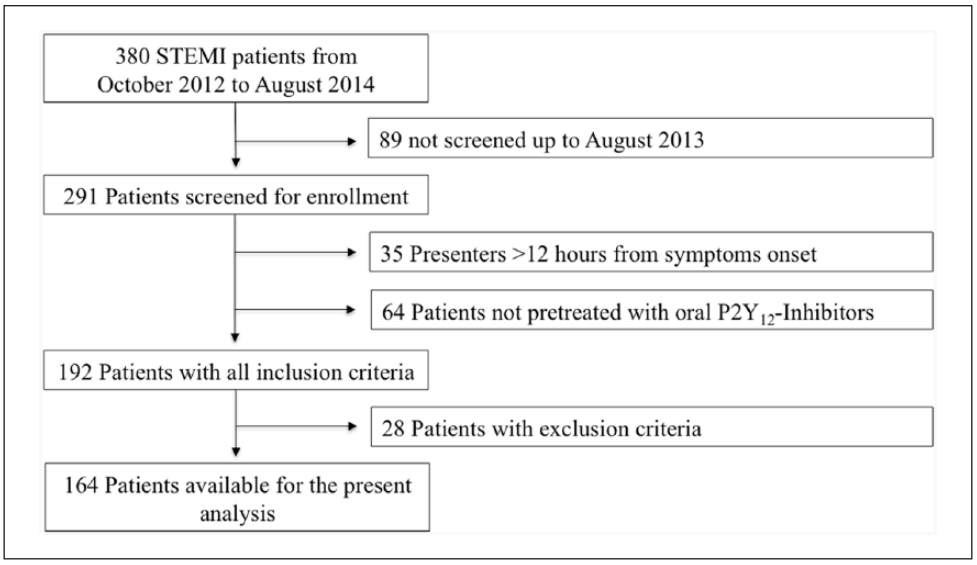

Figure 1. Study flow chart.

external CMR core laboratory (CMR Unit, Bristol Heart Institute, Bristol, UK). The images were analyzed with a commercially available software program (CMR42, Circle Cardiovascular Imaging, Canada). Semi-automated computer-aided threshold detection was used to identify regions of myocardium at risk, MVO, myocardial hemorrhage and infarcted myocardium, as previously described.[18] The myocardial edema and infarct size were expressed as a mass in grams (g).

Statistical analysis

Categorical variables are expressed as frequencies and percentages and were compared with the use of the chi-square test or Fisher's exact test, as appropriate. Continuous variables were expressed as means ± standard deviations or as medians and inter-quartile ranges (IQRs), and were compared by non-paired t-tests or Mann–Whitney's U tests, as appropriate. To assess independent predictors of the primary endpoint, a multivariate binary logistic regression model was used for estimating the odds ratio (OR) and the corresponding 95% confidence interval (95% CI). First, a univariate exploratory analysis was performed to test for the association of the primary endpoint with HPR and several potentially impacting variables. Next, only those variables with a p-value of $\leqslant 0.10$ were entered en-bloc into the multivariate models. Tested variables included: age, male gender, hypertension, hyperlipidemia, diabetes mellitus, prior myocardial infarction Killip's class, left anterior descending as culprit vessel, culprit vessel reference diameter, time from symptom onset to $P2Y_{12}$ loading dose, time from the $P2Y_{12}$ inhibitor administration to coronary angiography, total ischemic time and the use of clopidogrel and morphine. Furthermore, univariate linear regression analysis was performed with cTFC as the dependent variable. The tested variables were the same entered into the binary logistic regression model as covariates, plus culprit vessel stent length, thrombus aspiration and high thrombotic burden as previously defined. Next, a multivariate linear regression analysis included those variables with a p-value of $\leqslant 0.10$ at the univariate analysis plus thrombectomy.

A p-value of <0.05 was considered statistically significant. Statistical analysis was performed using SPSS version 15.0 software (SPSS Inc., Chicago, IL, USA).

Results

A total of 164 patients who fulfilled the eligibility criteria were included in the study (Figure 1). At a median time of 55 (IQR 40–75) minutes from the loading dose administration to angiography, the mean PRU value was 227.9 ± 82.0, and a PRU value >208 was observed in 117 (71.3%) patients.

Clinical and procedural characteristics of patients with and without HPR are listed in Tables 1 and 2, respectively. There were no significant differences in patient demographics and clinical characteristics according to HPR, except for the type of PY_{12} inhibitor, with clopidogrel and ticagrelor being more often administered to patients with and without HPR, respectively (Table 1). Clopidogrel was only used in 14 patients overall. No significant differences between groups were noted with respect to all procedural variables, with the exception of manual thrombus aspiration, which was more frequently performed in the HPR group, and the mean culprit vessel reference diameter, which was slightly higher in patients with HPR.

Key time intervals according to HPR status are listed in Table 3, with no evidence of significant differences

Table 1. Baseline clinical characteristics of study patients according to pre-procedural HPR status.

Variable	Overall population ($n=164$)	No-HPR PRU ⩽208 ($n=47$)	HPR PRU >208 ($n=117$)	*p*-value
Age, years	61.2 ± 11.8	61.8 ± 11.2	61.0 ± 12.0	0.68
Male gender, n (%)	120 (73.2)	35 (74.5)	85 (72.6)	0.97
Body mass index, kg/m^2	27.4 ± 4.1	27.1 ± 4.1	27.5 ± 4.2	0.61
Hypertension, n (%)	95 (57.9)	22 (46.8)	73 (62.4)	0.10
Hyperlipidemia, n (%)	57 (34.8)	17 (36.2)	40 (34.2)	0.95
Diabetes, n (%)	31 (18.9)	7 (14.9)	24 (20.5)	0.54
Smoking, n (%)	107 (65.2)	35 (74.5)	72 (61.5)	0.16
Killip's class, n (%)				0.33
I	135 (82.3)	36 (76.6)	99 (84.6)	
II	28 (17.1)	11 (23.4)	17 (14.5)	
III	1 (0.6)	0	1 (0.9)	
$P2Y_{12}$ inhibitor LD, n (%)				0.03
Clopidogrel	14 (8.5)	1 (2.1)	13 (11.1)	
Prasugrel	63 (38.4)	14 (29.8)	49 (41.9)	
Ticagrelor	87 (53.0)	32 (68.1)	55 (47.0)	
Anticogulation at ED, n (%)				0.91
UFH bolus	137 (83.5)	40 (85.1)	97 (82.9)	
LMWH	27 (16.5)	7 (14.9)	20 (17.1)	
Morphine use	42 (25.6)	11 (23.4)	31 (26.5)	0.83
Time of blood sampling, n (%)				0.38
6 a.m.–12 p.m.	46 (28.0)	13 (27.7)	33 (28.2)	
12 p.m.–18 p.m.	65 (39.6)	23 (48.9)	42 (35.9)	
18 p.m.–24 a.m.	33 (20.1)	7 (14.9)	26 (22.2)	
24 a.m.–6 a.m.	20 (12.2)	4 (8.5)	16 (13.7)	

HPR: high platelet reactivity; ED: emergency department; LD: loading dose; LMWH: low molecular weight heparin; UFH: unfractionated heparin.

Table 2. Procedural characteristics of study patients according to pre-procedural HPR status.

Variable	Overall population ($n=164$)	No-HPR PRU ⩽208 ($n=47$)	HPR PRU >208 ($n=117$)	*p*-value
Culprit vessel, n (%)				0.26
LAD	84 (51.2)	21 (44.7)	63 (53.8)	
LCx	19 (11.6)	4 (8.5)	15 (12.8)	
RCA	61 (37.2)	22 (46.8)	39 (33.3)	
Intervention, n (%)				0.84
Bare metal stent	27 (16.5)	8 (17.0)	19 (16.2)	
Drug-eluting stent	129 (78.7)	36 (76.6)	93 (79.5)	
Balloon angioplasty	8 (4.9)	3 (6.4)	5 (4.3)	
Manual thrombus aspiration, n (%)	93 (56.7)	18 (38.3)	75 (64.1)	0.004
Mean vessel diameter	3.3 ± 0.48	3.2 ± 0.46	3.4 ± 0.48	0.04
Mean stent length	27.4 ± 12.2	27.1 ± 12.4	27.5 ± 12.1	0.86
GPI use, n (%)	64 (39.0)	14 (29.8)	50 (42.7)	0.17
GPI bailout, n (%)	19 (11.6)	4 (8.5)	15 (12.8)	0.61
Bivalirudin use, n (%)	16 (9.8)	6 (12.8)	10 (8.5)	0.59

HPR: high platelet reactivity; LAD: left anterior descending; LCx: left circumflex artery; RCA: right coronary artery; GPI: glycoprotein IIb/IIIa inhibitor. Data are presented as mean ± standard deviation when appropriate.

between the two groups, except for the time interval from $P2Y_{12}$ inhibitor loading dose administration to angiography (65 [IQR 50–90] minutes vs. 50 [IQR 40–70] minutes, $p=0.0002$), and for the total ischemic time (220 [IQR 160–365] minutes vs. 190 [IQR 145–242] minutes, $p=0.02$), which were slightly longer in patients without HPR. After excluding the seven patients receiving the $P2Y_{12}$ inhibitor more than 2 hours before angiography, there were no more

Table 3. Timing intervals of study patients according to pre-procedural HPR status.

Variable	Median (interquartile range), min			
	Overall population ($n=164$)	No-HPR PRU ⩽208 ($n=47$)	HPR PRU >208 ($n=117$)	*p*-value
Symptom onset to $P2Y_{12}$ inhibitor	120 (70–190)	120 (80–240)	110 (70–180)	0.21
Symptom onset to PPCI	193 (145–264)	220 (160–335)	190 (145–242)	0.02*
ED to PPCI	100 (85–138)	100 (85–160)	100 (85–121)	0.33
Heparin to angiography	73 (60–108)	70 (60–125)	75 (60–100)	0.73
$P2Y_{12}$ inhibitor loading to angiography	55 (40–75)	65 (50–90)	50 (40–70)	0.002*

HPR: high platelet reactivity; PPCI: primary percutaneous coronary intervention; ED: emergency department;
*These differences were no more significant after excluding the seven patients receiving the $P2Y_{12}$ inhibitor at >2 hours before angiography.

the significant differences in the time from $P2Y_{12}$ inhibitor loading dose administration to angiography and in total ischemic time between the HPR and no-HPR groups.

There were no significant differences in demographic and clinical characteristics according to HRP defined using LTA. No significant differences between HPR and no-HPR groups as defined with LTA were found for all procedural variables, except for manual thrombus aspiration and for bare metal stent implantation, which were both more frequently performed in the HPR group. Finally, with regards to the key time intervals according to HPR status defined with LTA, no evidence of significant differences between the two groups was found, except for the time intervals from $P2Y_{12}$ inhibitor loading dose administration to angiography and from symptom onset to PPCI, which were slightly longer in patients without HPR.

HPR and pre-PCI angiographic parameters

Pre-PCI TIMI flow grades 2/3 or 3 at the baseline angiogram were found in 65 (39.6%) and 41 (25.0%) patients, respectively. A significantly lower rate of the primary endpoint of pre-PCI TIMI flow grades 2 or 3 was observed in the HPR group compared with the no-HPR group (32.5% vs. 51.1%, $p=0.04$) (Figure 2). Similar findings were replicated in the subgroup in which HPR was defined using LTA (Table 4). The rate of pre-PCI TIMI flow grade 3 was numerically, albeit not significantly, lower in the HPR group compared with the no-HPR group (22.2% vs. 31.9%, $p=0.27$) (Figure 2).

In the binary logistic multivariate analysis, HPR was negatively associated with the primary endpoint (OR 0.43, 95% CI 0.20–0.94, $p=0.03$) (Table 5). Other independent predictors of lower rates of the primary endpoint included Killip's class on admission and morphine use (Table 5).

Half of the population ($n=83$, 50.6%) presented with an occluded vessel (TS grade 5) and reclassification into a thrombus grade 0–4 was feasible in all of these patients after recanalization. TS grades 3/4 or 4 at baseline angiogram were found in 75 (45.7%) and 45 (27.4%) patients, respectively. Higher rates of patients with a TS grade 3/4

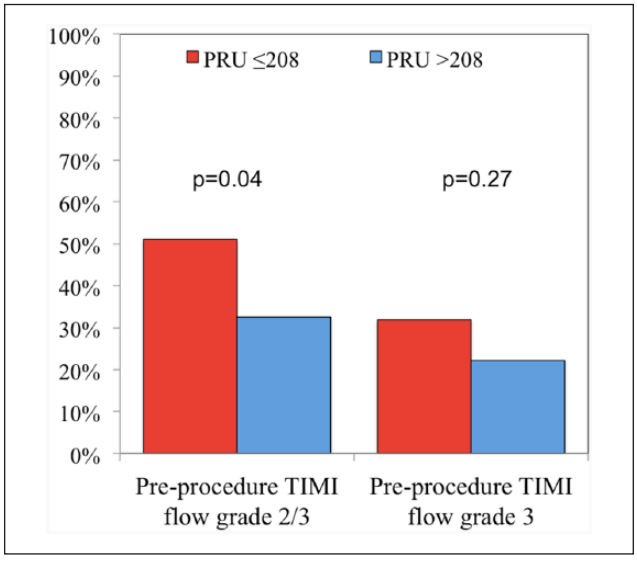

Figure 2. Rates of pre-procedure TIMI flow grades 2/3 or 3 according to the HPR status defined using PRU.
Bars represent the percentages of patients with pre-PCI TIMI flow grades 2/3 or 3 among the subgroups without HPR (red bars) and with HPR (blue bars).
TIMI: Thrombolysis in Myocardial Infarction; HPR: high platelet reactivity; PRU: $P2Y_{12}$ reaction units.

(52.1% vs. 29.8%, $p=0.015$) and TS grade 4 (32.5% vs. 14.9%, $p=0.037$) were observed in the HPR group compared with the no-HPR group, respectively (Figure 3). Among patients with TS grade 4 ($n=45$), 85.7% vs. 18.4% of those without and with HPR, respectively, had received a $P2Y_{12}$ inhibitor loading dose at >3 hours from symptom onset.

Similar findings were found after excluding the 14 patients receiving clopidogrel. Moreover, the results were consistent after excluding seven patients receiving the $P2Y_{12}$ inhibitor at more than two hours before angiography.

HPR and post-PCI outcomes

Post-PCI TIMI flow grades 0/1, 2 and 3 were observed in 6 (3.7%), 31 (18.9%) and 127 (77.4%) patients, respectively. The rates of final TIMI flow grade <3 or MBG 0/1

Table 4. Angiographic outcomes according to the pre-procedural HPR status defined using light transmission aggregometry.

Variable	No-HPR MPA-ADP (5 μM) ⩽46% (*n* = 36)	HPR MPA-ADP (5 μM) >46% (*n* = 50)	*p*-value	No-HPR MPA-ADP (20 μM) ⩽59% (*n* = 22)	HPR MPA-ADP (20 μM) >59% (*n* = 64)	*p*-value
Pre-PCI TIMI flow grades 2 or 3, n (%)	19 (52.8)	14 (28.0)	0.04	12 (54.5)	21 (32.8)	0.12
Thrombus score grade 3/4, n (%)	13 (36.1)	28 (56.0)	0.11	8 (36.4)	33 (51.6)	0.33
Thrombus score grade 4, n (%)	5 (13.9)	15 (30.0)	0.14	2 (9.1)	18 (28.1)	0.13
Post-PCI TIMI flow grade <3, n (%)	9 (25.0)	15 (30.0)	0.79	6 (27.3)	18 (28.1)	1.00
Post-PCI MBG 0/1, n (%)	6 (16.7)	18 (36.0)	0.08	4 (18.2)	20 (31.2)	0.37
Corrected TIMI frame count*	25 (18.5–34.8)	30 (22–48.2)	0.01	25 (7.5–33.5)	30 (22.0–44.6)	0.04

HPR: high platelet reactivity; MPA: maximum platelet aggregation; ADP: adenosine diphosphate; PCI: percutaneous coronary intervention; TIMI: Thrombolysis in Myocardial Infarction; MBG: myocardial blush grade.
*Expressed as median (interquartile range).

Table 5. Univariate and multivariate models for predicting pre-PCI TIMI flow grade 2 or 3 (primary endpoint).

Variable	Univariate OR (95% CI)	*p*-value	Multivariate OR (95% CI)	*p*-value
Age	0.98 (0.95–1.01)	0.11	–	–
Male gender	1.38 (0.67–2.84)	0.38	–	–
Hypertension	0.36 (0.19–0.69)	0.002	0.56 (0.27–1.16)	0.12
Hyperlipidemia	0.52 (0.26–1.04)	0.06	0.73 (0.33–1.61)	0.43
Diabetes	0.56 (0.24–1.31)	0.18	–	–
Prior myocardial infarction	0.33 (0.11–1.04)	0.06	0.87 (0.23–3.30)	0.84
Killip's class on admission	0.26 (0.10–0.72)	0.01	0.23 (0.07–0.75)	0.01
LAD culprit	1.24 (0.66–2.32)	0.50	–	
Vessel diameter	0.48 (0.24–0.96)	0.04	0.58 (0.27–1.26)	0.17
Symptom onset to $P2Y_{12}$ inhibitor	0.99 (0.99–1.02)	0.43	–	–
$P2Y_{12}$ to angiography	1.00 (0.99–1.01)	0.84	–	–
Symptom onset to PPCI	0.99 (0.94–1.00)	0.37	–	–
Heparin to angiography	1.00 (0.99–1.01)	0.99	–	–
Clopidogrel	0.91 (0.30–2.84)	0.87	–	–
Morphine	0.49 (0.23–1.07)	0.08	0.42 (0.18–0.99)	0.05
HPR >208	0.52 (0.26–1.03)	0.06	0.43 (0.19–0.94)	0.03

PCI: percutaneous coronary intervention; TIMI: Thrombolysis in Myocardial Infarction; OR: odds ratio; CI: confidence interval; LAD: left anterior descending; PPCI: primary percutaneous coronary intervention; HPR: high platelet reactivity.

(no-reflow) were 22.6% and 21.3%, respectively. No significant differences in the rates of post-PCI TIMI flow grade <3 (23.9% vs. 19.1%, $p=0.65$) and MBG grade 0/1 (23.1% vs. 17.0%, $p=0.52$) were observed between the HPR and no-HPR groups, respectively.

In the overall population, the median of cTFC was 25.9 (IQR 20.0–34.6), with significantly lower values in the no-HPR group compared with the HPR group, 23.2 (IQR 15.8–32.5) vs. 26.0 (IQR 21.0–35.0), $p=0.02$, respectively) (Figure 4). Consistent results with regards to the rates of post-PCI TIMI flow grade <3 or MBG 0/1 and cTFC were found when HPR was defined using LTA (Table 4).

After adjusting for potential confounders, age (β 0.19, $p=0.01$), diabetes (β 0.16, $p=0.03$), TS grade 4 (β 0.31, $p<0.001$) and HPR (β 0.15, $p=0.05$) were independently associated with higher cTFC (Table 6).

In addition, similar findings were observed after excluding the 14 patients receiving clopidogrel and among patients only receiving the $P2Y_{12}$ inhibitor at 2 hours before angiography.

The proportion of patients with ⩾70% resolution of ST-segment elevation at 60 minutes was numerically higher in the no-HPR group compared with the HPR group (72.3% vs. 58.1%, respectively, $p=0.12$), although this difference did not reach statistical significance.

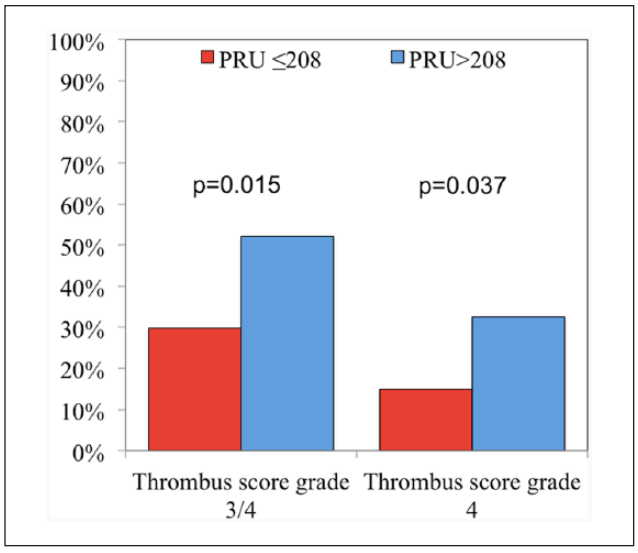

Figure 3. Rates of thrombus score grades 3/4 or 4 according to the HPR status defined using PRU.
Bars represent the percentages of patients with thrombus score grades 3/4 or 4 among the subgroups without HPR (red bars) and with HPR (blue bars).
HPR: high platelet reactivity; PRU: $P2Y_{12}$ reaction units.

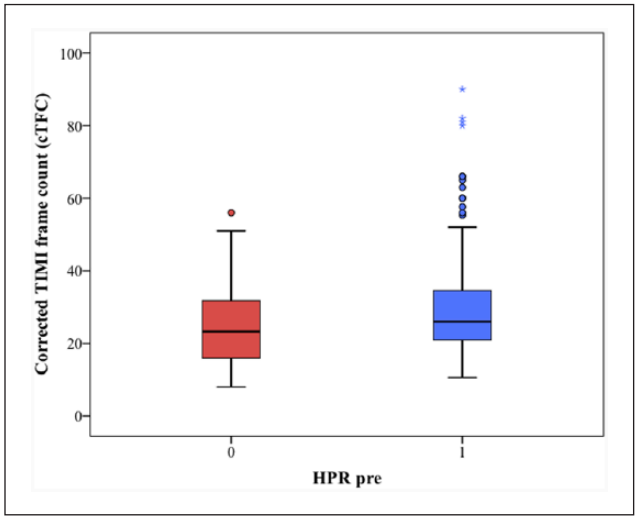

Figure 4. cTFC according to the HPR status defined using PRU.
Values of cTFC are reported among the subgroups without HPR ("0") and with HPR ("1"). The central box represents the values from the lower to upper quartile (25th–75th percentile). The middle horizontal line represents the median (50th percentile). The vertical line extends from the minimum to the maximum value within 1.5 box heights from the top or bottom of the box. Outliers are displayed as separate points.
cTFC: corrected TIMI frame count; TIMI: Thrombolysis in Myocardial Infarction; HPR: high platelet reactivity; PRU: $P2Y_{12}$ reaction units.

The peak levels of creatine kinase-MB (133 ± 110 vs. 166 ± 90 ng/mL, $p=0.045$) and troponin T (3217 ± 2657 vs. 4272 ± 3130 ng/L, $p=0.044$) were significantly lower in the no-HPR group compared with the HPR group, respectively.

Seven (4.3%) clinical adverse events occurred in-hospital. These included four cardiovascular death (2.4%) and three (1.8%) non-fatal acute stent thromboses. Six of these events occurred in patients with HPR; only one event (death) occurred in a patient without HPR.

CMR findings

Among the 50 first patients enrolled in the registry, CMR was performed in 41 (82%), and quantified imaging analysis was possible in 36 (72%) patients. Among these 36 patients included in the analysis, 20 (55.5%) had HPR and 16 (44.4%) had no-HPR. No relevant significant differences between these HPR and no-HPR subgroups were found for clinical characteristics, procedural variables and time intervals. Compared with no-HPR patients, those with HPR had a significantly higher area at risk (30 g [IQR 18.3–41] vs. 13 g [IQR 1–36.3], $p=0.04$) and a trend towards higher infarct mass (23 g [IQR 11.8–38.5] vs. 13.5 [IQR 5–27.5], $p=0.07$), respectively. MVO was observed in five cases (13.9%): four (20%) with HPR and one (6.3%) with no HPR. Intra-myocardial hemorrhage was found in two patients: one with HPR (but receiving GPI in bailout) and one with no HPR.

Discussion

The impact on coronary reperfusion of different degrees of residual $P2Y_{12}$-mediated platelet reactivity, regardless of the type of oral antagonist given in order to achieve this inhibition, has been poorly investigated in the setting of PPCI for STEMI.[19] In an attempt to fill this gap, the present observational study prospectively assessed ADP-induced platelet reactivity prior to PPCI in patients with STEMI who were pretreated with a loading dose of an oral $P2Y_{12}$ receptor antagonist and reported on their angiographic outcomes according to the achieved level of residual $P2Y_{12}$-mediated platelet reactivity. The main findings of our study can be summarized as follows: 1) at the time of initial angiography, after pretreatment with a loading dose of any $P2Y_{12}$ inhibitor, approximately two-thirds of patients were found to have HPR; 2) pre-PCI IRA patency, defined as TIMI flow grade 2 or 3, was more commonly observed in patients without HPR; 3) HPR, as well as Killip's class on admission and morphine use, were independently associated with lower pre-PCI TIMI grade 2 or 3, even after adjustment for clopidogrel use and time from $P2Y_{12}$ administration to angiography; 4) high thrombus burden prior to PCI, which emerged as a predictor of lower cTFC, was significantly lower in the no-HPR group; 5) HPR was independently associated with higher cTFC, an index of impaired myocardial perfusion; 6) no significant differences in the rates of no-reflow were found between the two groups; 7) stent thrombosis resolution was numerically lower in the HPR group without reaching statistical significance; and 8) HPR patients tended to

Table 6. Univariate and multivariate predictors of corrected TIMI frame count.

Variables	Univariate β coefficient	*p*-value	Multivariate β coefficient	*p*-value
Age	0.22	0.005	0.19	0.02
Male gender	0.02	0.78	–	–
Hypertension	0.05	0.54	–	–
Hyperlipidemia	0.01	0.91	–	–
Diabetes	0.23	0.004	0.18	0.02
Prior myocardial infarction	0.04	0.63	–	–
Killip's class on admission	0.03	0.67	–	–
LAD culprit	0.04	0.62	–	–
Thrombus aspiration	0.11	0.18	0.10	0.21
Vessel diameter	0.12	0.15	–	–
Stent length	0.05	0.53	–	–
Symptom onset to $P2Y_{12}$ inhibitor	0.03	0.74	–	–
$P2Y_{12}$ to angiography	0.10	0.22	–	–
Symptom onset to PPCI	0.08	0.31	–	–
Clopidogrel	0.09	0.27	–	–
Morphine	0.08	0.31	–	–
HPR >208	0.18	0.02	0.16	0.04
Thrombus burden grade 4	0.33	<0.001	0.29	<0.001

TIMI: Thrombolysis in Myocardial Infarction; LAD: left anterior descending; PPCI: primary percutaneous coronary intervention; HPR: high platelet reactivity.

have higher infarct sizes and areas at risk, as assessed by CMR. Overall, these observations support the hypothesis that in patients with STEMI undergoing PPCI, achieving an adequate level of $P2Y_{12}$-mediated platelet inhibition at the time of initial angiography may be beneficial in terms of better pre- and post-PCI angiographic outcomes.

The optimal timing of $P2Y_{12}$ inhibitor initiation in the setting of PPCI for STEMI has not been established yet. Current guidelines on STEMI management recommend that a loading dose of a $P2Y_{12}$ receptor antagonist should be given as early as possible.[1,2] However, this recommendation is not supported by strong clinical evidence.[3,20–26] Observational investigations evaluating pre-hospital versus peri-interventional clopidogrel administration in PPCI for STEMI[20–26] suggested that clopidogrel pretreatment was associated with improved pre-PCI patency and post-PCI myocardial perfusion[21] and some degree of clinical benefit.[21–23] Conversely, in two small randomized studies, clopidogrel pretreatment in the ambulance was not shown to improve pre- and post-PCI reperfusion, most likely because of too short (about 1 hour) clopidogrel loading-to-angiography time.[24,25] The recently published ATLANTIC trial has found no benefit in terms of pre-PCI coronary reperfusion of prehospital treatment with ticagrelor in STEMI patients undergoing PPCI.[3] In light of our observations suggesting a negative association between HPR and pre-PCI patency and myocardial perfusion, the lack of benefit in reperfusion with pretreatment in these latter randomized studies might be explained by the failure to achieve a difference between the compared groups (pretreatment vs. no pretreatment) in the proportions of patients with adequate platelet inhibition over a too-short time difference in $P2Y_{12}$ antagonist loading dose-to-angiography (the median loading dose-to-angiography time difference between the two treatment strategies was 31 minutes in the ATLANTIC study). Indeed, in the 37 patients undergoing platelet function testing in the ATLANTIC study, platelet reactivity at the time of angiography was similarly high between prehospital and in-hospital administration of ticagrelor, being above the threshold defining HPR.[3] Therefore, based on our results, we speculate that pretreatment with agents with faster onsets of action could be associated with better reperfusion outcomes compared with no pretreatment or very short pretreatment times with currently approved oral $P2Y_{12}$ inhibitors.

Recently published data have shown that prasugrel compared with clopidogrel provided better coronary reperfusion after PPCI for STEMI, implying a beneficial effect of achieving more potent $P2Y_{12}$ inhibition.[26,27] In addition to this, our observation that pre-PCI IRA patency and post-PCI myocardial perfusion are better in patients without HPR prior to PPCI suggests that there is a need to achieve effective inhibition of ADP-mediated pathways as soon as possible. Although the novel $P2Y_{12}$ antagonists prasugrel and ticagrelor are faster and more potent inhibitors than clopidogrel, recent studies have shown that both drugs exhibit an initial delay in the onset of their antiplatelet action in patients with STEMI undergoing PPCI,[5–7] with a consistent proportion of patients, ranging from 35% to 50%, persisting with a PRU of >208 at 2 hours after ticagrelor or prasugrel loading doses.[5–7] These latter observations provide a basis for investigating alternative antiplatelet agents with faster onsets of action.

An option for achieving rapid and effective $P2Y_{12}$ inhibition is represented by cangrelor, which is a direct-acting, intravenously administered, highly selective $P2Y_{12}$ antagonist with a short half-life (≈2.6 minutes) and a rapid onset and offset (30–60 minutes) of action.[28] The pharmacologic profile of cangrelor makes it an attractive strategy when fast $P2Y_{12}$ inhibition is needed. A recent trial (CHAMPION-PHOENIX) showed that cangrelor compared with clopidogrel significantly reduced ischemic events at 48 hours in about 11,000 subjects undergoing PCI for stable angina or acute coronary syndrome, including STEMI.[29] However, in this latter study, cangrelor was not given upstream and patients did not receive pretreatment with other $P2Y_{12}$ inhibitors. Cangrelor was recently approved in Europe and the USA in patients undergoing PCI. The effects of cangrelor on reperfusion indices remain to be determined, and further dedicated studies with cangrelor in the setting of STEMI will be conducted.

An intriguing finding of our study is represented by the evidence of a significant independent association between HPR and a well-validated angiographic index of microvascular dysfunction, namely cTFC.[30] Several mechanisms can explain this association. Distal embolization of atherothrombotic debris during PCI leading to mechanical occlusion of microvessels and to activation of coagulation and inflammation pathways is one of the key mechanisms underlying microvascular dysfunction.[31] Higher thrombus burden has been correlated to distal embolization leading to microvascular dysfunction.[32] Consistently, in our study, a TS of grade 4 emerged as an independent predictor of lower cTFC, regardless of thrombectomy, which was higher in the HPR group. The observed association between HPR and increased rates of high TS may explain the impact of HPR on microvascular dysfunction. Furthermore, it has been suggested that intracoronary platelet-derived microparticles (PMPs) have a direct role in the pathogenesis of microvascular impairment, perhaps favoring thrombus generation in the coronary microcirculation.[33] As PMPs are released upon platelet activation, $P2Y_{12}$-mediated platelet inhibition might decrease levels of intracoronary PMPs and thus, in turn, improve microvascular perfusion independently of the thrombotic burden.[34]

Study limitations

Owing to the sample size, a single-center prospective investigation such as this should be regarded as exploratory and hypothesis generating, especially with regards to post-PCI outcomes. While the single-center design may limit the generalizability of the present results, it allows for a reduction of procedure heterogeneity, potentially introducing fewer confounding variables. Nevertheless, our results need to be confirmed in larger multicenter studies. Although we have performed a multivariate analysis, due to the observational design of our investigation, the direct effects of several confounders, such as the use of morphine, cannot be completely excluded. The association between HPR and clinical outcomes was not evaluated in the present analysis, which focused on angiographic endpoints. Ultimately, for the sake of the feasibility of conducting platelet function testing using multiple assays, in the first study period, when LTA was also performed, only patients who presented on weekdays during regular working hours were recruited. However, the clinical characteristics and time intervals of off-hours and on-hours patients were not significantly different (data not shown). In addition, it appears unlikely that the time of enrollment will have impacted on the association between the absolute levels of platelet inhibition and reperfusion, which was the primary focus of the present study. In any case, no significant differences were observed between the no-HPR and HPR groups in the 6-hour time intervals of the day in which blood was collected. Finally, although angiography is limited in terms of accurately assessing thrombus, the angiographic estimation of thrombus burden according to the applied classification is practical in an urgent setting such as STEMI and has been related to survival.

Conclusions

In patients undergoing PPCI for STEMI who were pretreated with a $P2Y_{12}$ receptor inhibitor, an adequate level of ADP-induced platelet reactivity inhibition assessed at the time of initial coronary angiography was found to be associated with higher pre-PCI IRA patency and significantly lower thrombotic burden. Regarding post-PCI coronary reperfusion, only one index (cTFC) of angiographic reperfusion was improved in the no-HPR group, while there were no significant differences in categorical variables such as no-reflow and stent thrombosis resolution. Moreover, the CMR assessment (performed only in a subgroup of patients) showed trends towards reduced area at risk and infarct size in the no-HPR group. Overall, our findings suggest that achieving effective $P2Y_{12}$ inhibition as early as possible in STEMI might be useful for pre-PCI patency and probably for post-PCI outcomes. In addition, these observations may have relevant therapeutic implications for patients presenting with STEMI and planned PPCI. Indeed, given current fast-transfer protocols and rapid access to PPCI, along with the known delay to the onset of action of oral $P2Y_{12}$ antagonists in STEMI, faster-acting intravenous agents such as cangrelor might be useful in the STEMI setting in order to potentially improve reperfusion and achieve better clinical outcomes, but data are needed in order to assess this latter claim. Nevertheless, our results need confirmation in adequately powered studies, especially for post-PCI reperfusion outcomes.

Conflict of interest

Piera Capranzano served on advisory boards of Eli-Lilly/Daiichi Sankyo and The Medicines Company. Davide Capodanno served

on advisory boards of Eli-Lilly/Daiichi Sankyo and AstraZeneca and received speaker's honoraria from Eli-Lilly/Daiichi Sankyo, AstraZeneca and Bayer. Dominick J Angiolillo received payment as an individual for: a) consulting fees or honoraria from Bristol-Myers Squibb, Sanofi-Aventis, Eli Lilly/Daiichi Sankyo, The Medicines Company, AstraZeneca, Merck, Abbott Vascular, Bayer and PLx Pharma; and b) participation in review activities from CeloNova, Johnson & Johnson, St. Jude and Sunovion. He has received institutional payments for grants from Bristol-Myers Squibb, Sanofi-Aventis, GlaxoSmithKline, Otsuka, Eli Lilly/Daiichi Sankyo, The Medicines Company and AstraZeneca. Corrado Tamburino has received honoraria/lecture fees from Medtronic, Abbott Vascular Edwards Lifesciences and Eli-Lilly. None of the other authors have conflicts of interest to report.

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Impact of proton pump inhibitors on clinical outcomes in patients treated with a 6- or 24-month dual-antiplatelet therapy duration: Insights from the PROlonging Dual-antiplatelet treatment after Grading stent-induced Intimal hyperplasia studY trial

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Background Proton pump inhibitors (PPIs) are frequently prescribed in combination with clopidogrel, but conflicting data exist as to whether PPIs diminish the efficacy of clopidogrel. We assessed the association between PPI use and clinical outcomes for patients treated with percutaneous coronary intervention (PCI) and dual-antiplatelet therapy (DAPT) with clopidogrel plus aspirin.

Methods and results In the PRODIGY trial, 1,970 patients were randomized to 6- or 24-month DAPT at 30 days from index procedure. Among them, 738 patients (37.5%) received PPI (mainly lansoprazole; 90.1%) at the time of randomization. Proton pump inhibitor users were older, were most likely to be woman, had a lower creatinine clearance, presented more frequently with acute coronary syndrome, and had a higher CRUSADE bleeding score. After adjustment, the primary efficacy end point (composite of all-cause death, myocardial infarction, and cerebrovascular accident) was similar between no PPI and PPI users (9.2% vs 11.5%, adjusted hazard ratio [HR] 1.051, 95% CI 0.788-1.400, $P = .736$). Bleeding rates did not differ between the 2 groups (Bleeding Academic Research Consortium type 2, 3, or 5: adjusted HR 0.996, 95% CI 0.672-1.474, $P = .980$). Net clinical adverse events were also similar in no PPI and PPI patients (12.9% vs 14.9%, adjusted HR 0.99, 95% CI 0.772-1.268, $P = .93$). Results remained consistent at sensitivity analysis when focusing on the 548 patients who remained on PPI for the whole study duration.

Conclusions The current findings suggest that the concomitant use of PPIs, when clinically indicated, in patients receiving clopidogrel is not associated with adverse clinical outcome. (Am Heart J 2016;174:95-102.)

Dual-antiplatelet therapy (DAPT) is the cornerstone of antithrombotic treatment in patients undergoing percutaneous coronary intervention (PCI), although its optimal duration still remains debated.[1-3] Notably, these patients are frequently treated with a proton pump inhibitor (PPI) to prevent gastrointestinal (GI) complications such as ulceration and bleeding or due to preexisting gastric disease.[4-7] However, clopidogrel is a prodrug that requires metabolic transformation in the liver by cytochrome P-450 isoenzyme (mainly CYP2C19) to elicit its antiplatelet effect. Proton pump inhibitors are also metabolized by CYP enzymes, leading to a potential inhibition of CYP2C19 (mainly omeprazole and esomeprazole) translating into reduced metabolic activation of clopidogrel when taken together. Indeed, some pharmacodynamic studies demonstrated a reduction of clopidogrel-induced antiplatelet effect when a PPI, mainly omeprazole, was concomitantly administered.[8-11] The Food and Drug Administration and the European Medicine Agency discourage the

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concomitant use of omeprazole and clopidogrel.[12,13] The clinical impact of the combined administration has been studied, but results have been discordant, with some studies reporting an increased risk of cardiovascular adverse events, whereas others did not confirm this concern.[5-7,11,14-23] Pooled analyses also provided inconclusive results, owing to the risk of misinterpretation related to poor-quality observational studies, thus supporting the need for high-quality studies.[14,15]

Therefore, the purpose of the present subanalysis of the PRODIGY randomized trial is to assess whether medical therapy with PPI compared to that without PPI may impact clinical outcomes in the setting of an all-comer population undergoing PCI and with a randomly allocated short (6 months) or prolonged (24 months) DAPT regimen, consisting of clopidogrel and aspirin.

Methods

The design and main findings of the PRODIGY have been previously reported.[1,24] Briefly, all-comer PCI patients receiving a balanced mixture of stents with varying anti-intimal hyperplasia potency and belonging to both first- and second-generation drug-eluting stent (DES) at 3 Italian sites were randomly allocated at 30 days to either 6 or 24 months of DAPT. Selection criteria were broad, reflecting routine clinical practice. Randomization to 6- or 24-month DAPT was stratified by center, ongoing ST-segment elevation myocardial infarction (MI), the presence of diabetes mellitus, and need for intervening of at least 1 in-stent restenotic lesion. The study was conducted in accordance with the principles of the Declaration of Helsinki. The Ethics Committees of the 3 participating centers independently approved the protocol, and all participants gave written informed consent.

Treatment protocol

All patients received aspirin (75-100 mg orally indefinitely) and clopidogrel (75 mg/d) according to the randomization scheme as follows: for either 6 months in the short DAPT arm or 24 months in the prolonged DAPT arm irrespective of the previously implanted stent type or indication for PCI.

Follow-up

The randomized patients returned for study visits at 30 days and then every 6 months up to 2 years. During follow-up visits, patients were examined and assessed for adverse events and asked for the antiplatelet therapy compliance, and 12-lead electrocardiogram recordings were obtained.

Proton pump inhibitor use

The decision to start the treatment with a PPI as well as the type of PPI to be used was left at the physician's discretion and was not randomly assigned or mandated by protocol. Proton pump inhibitor use was identified both at study baseline and at each study follow-up visit, along with other concomitant medication use. For the present analysis, patients were defined as PPI users if on treatment at 30-day follow-up visit, at the time point when the randomization to short- versus long-term DAPT was performed. We performed sensitivity analyses to investigate the effect of PPI versus no PPI on clinical outcomes after excluding patients who had changed their initial status (no PPI or PPI) during the follow-up.

Table I. Baseline characteristics in PPI-treated versus non–PPI-treated patients

	No PPI (n = 1232)	PPI (n = 738)	*P*
Age (y)	68.1 (59.0-75.4)	71.2 (63.2-77.3)	<.0001
Male sex	79.2% (976)	72.5% (535)	.001
Body mass index (kg/m^2)	26.9 (24.7-29.4)	26.2 (24.2-29.3)	.923
Diabetes	24.8% (305)	23.3% (172)	.461
Insulin dependent	5.7% (70)	6.0% (44)	
Hypertension	71.3% (879)	72.5% (535)	.486
Hyperlipidemia	55.3% (681)	53.8% (397)	.596
Current cigarette use	24.4% (301)	22.6% (167)	.380
Creatinine clearance (mL/min)	77.7 (58.3-99.2)	69.5 (53.3-91.0)	<.0001
Prior MI	26.1% (321)	27.0% (199)	.520
Prior PCI	18.6% (229)	16.1% (119)	.180
LVEF	55.0 (45-60)	50.0 (43-60)	.080
Clinical presentation			
Stable angina pectoris	30.5% (376)	17.5% (129)	<.0001
ACS	69.5% (856)	82.5% (609)	
STEMI	30.2% (372)	37.4% (276)	.001
NSTEMI	21.3% (262)	25.5% (188)	.031
Unstable angina	18.0% (222)	19.6% (145)	.369
Multivessel disease	70.5% (868)	69.2% (511)	.569
No. of treated lesions	1 (1-2)	1 (1-2)	.370
≥2 treated lesions	37.3% (459)	37.5% (277)	.900
≥3 treated lesions	11.8% (145)	10.6% (78)	
Multivessel intervention	26.5% (327)	27.0% (199)	.837
At least 1 complex lesion (type B2 or C)*	67.0% (825)	65.2% (481)	.416
Total ACC/AHA score†	3 (2-5)	3 (2-4)	.600
CRUSADE score	24 (16-34)	27 (18-38)	<.0001
Aspirin	100% (1232)	100% (738)	>.999
Clopidogrel	98.8% (1230)	99.9% (737)	.882
Statin	90.3% (1093)	90.9% (671)	.627

Abbreviations: *LVEF*, Left ventricular ejection fraction; *STEMI*, ST-segment elevation myocardial infarction; *NSTEMI*, non–ST-segment elevation myocardial infarction; *ACC*, American College of Cardiology; *AHA*, American Heart Association.

*According to the American College of Cardiology/American Heart Association coronary lesion classification.

†Type A stenoses were coded 1 point; type B1 stenoses, 2 points; type B2 stenoses, 3 points; and type C stenoses, 4 points.

Study end points

The primary efficacy end point of the PRODIGY trial was the composite of death, MI, or cerebrovascular accident (CVA), whereas the key safety end point included Bleeding Academic Research Consortium (BARC) type 2, 3, or 5 bleeding. The net effect on the combined ischemic and bleeding complications was obtained by 2 net adverse clinical event (NACE) end points that were generated by

Table II. Baseline characteristics in PPI versus no PPI treated patients stratified for the randomly allocated DAPT duration

	24-m clopidogrel			6-m clopidogrel		
	No PPI (n = 612)	PPI (n = 375)	*P*	No PPI (n = 620)	PPI (n = 363)	*P*
Age (y)	67.9 (58.9-74.5)	71.8 (63.8-77.7)	<.0001	68.1 (59.2-76.6)	70.1 (61.7-76.9)	.04
Male sex	80.6% (493)	72.3% (271)	.003	77.9% (483)	72.7% (264)	.070
Body mass index (kg/m^2)	27.0 (24.9-29.4)	26.0 (23.9-29.3)	.450	26.8 (24.2-29.2)	26.4 (24.2-29.3)	.200
Diabetes	24.7% (151)	24.8% (93)	.900	24.9% (154)	21.8% (79)	.290
Insulin dependent	6.2% (38)	5.6% (21)		5.2% (32)	6.3% (23)	
Hypertension	71.4% (437)	75.7% (284)	.140	71.3% (442)	69.1% (251)	.410
Hyperlipidemia	56.5% (346)	55.2% (207)	.680	54.0% (335)	52.3% (190)	.640
Current cigarette use	23.9% (146)	20.3% (176)	.200	25.3% (156)	25.1% (91)	.450
Creatinine clearance (mL/min)	77.7 (58.1-102.7)	68.9 (53.0-91.9)	.001	77.8 (58.4-96.5)	70.7 (53.8-90.6)	.002
Prior MI	28.3% (173)	25.9% (97)	.410	24.8% (154)	28.1% (102)	.300
Prior PCI	20.9% (128)	16.3% (61)	.070	17.7% (110)	16.5% (60)	.490
LVEF	54.0 (43-60)	55.0 (45-60)	.520	55.0 (45-60)	50.0 (40-60)	.002
Clinical presentation						
Stable angina pectoris	31.2% (191)	17.1% (64)	<.0001	29.8% (185)	17.9% (65)	<.0001
ACS	68.8% (421)	82.9% (311)		70.2% (435)	82.1% (298)	
STEMI	31.0% (190)	34.9% (131)	.210	29.4% (182)	39.9% (145)	.001
NSTEMI	21.1% (129)	25.9% (97)	.080	21.5% (133)	25.1% (91)	.190
Unstable Angina	16.7% (102)	22.1% (83)	.03	19.4% (120)	17.1% (62)	.370
Multivessel disease	70.4% (431)	70.4% (264)	.990	70.5% (437)	68.0% (247)	.420
No. of treated lesions	1 (1-2)	1 (1-2)	.320	1 (1-2)	1 (1-2)	.780
≥2 treated lesions	37.4% (229)	36.3% (136)	.720	37.1% (230)	38.8% (141)	.590
≥3 treated lesions	11.4% (70)	10.1% (38)	.520	12.1% (75)	11.0% (40)	.610
Multivessel intervention	25.8% (158)	25.3% (95)	.870	27.3% (169)	28.7% (104)	.640
At least 1 complex lesion (type B2 or C)*	67.3% (412)	61.3% (230)	.060	66.6% (413)	69.1% (251)	.410
Total ACC/AHA score†	3 (2-4)	3 (2-4)	.600	3 (2-5)	3 (2-5)	.840
CRUSADE score	24 (15-35)	28 (19-38)	<.0001	24 (18-33)	27 (18-38)	.004
Aspirin	100% (612)	100% (375)	>.999	100% (620)	100% (365)	>.999
Clopidogrel	99.8% (611)	99.7% (374)	.726	99.8% (619)	100% (363)	.444
Statin	89.2% (539)	90.4% (339)	.560	91.3% (554)	91.5% (332)	.920

* According to the ACC/AHA coronary lesion classification.
† Type A stenoses were coded 1 point; type B1 stenoses, 2 points; type B2 stenoses, 3 points; and type C stenoses, 4 points.

combining the primary efficacy end point of death, MI, or CVA with either the primary safety end point of BARC type 2, 3, or 5 bleeding or with BARC type 3 or 5 events. Other end points included each component of the primary efficacy end point, cardiovascular death, stent thrombosis (ST) defined based on the Academic Research Consortium criteria, and BARC type 3 or 5 bleeding. Other safety end points included bleeding events adjudicated according to the Thrombolysis in Myocardial Infarction (TIMI) and Global Use of Strategies to Open Occluded Coronary Arteries scales. All study end point definitions were previously reported.

All end points were confirmed based on documentation collected at each hospital and were centrally adjudicated by the clinical events committee, whose members were unaware of the patients' treatment-group assignments. The time frame of interest for the primary end point was from 30 days (ie, after the primary endpoint randomization) to 24 months.

Statistical analysis

Categorical variables were expressed as frequency (percentage), whereas continuous variables were expressed as median (interquartile range). Continuous variables were compared between randomized groups using the Wilcoxon rank sum test, whereas for binary variables the χ^2 test was used.

Hazard ratios (HRs) with 95% CIs were calculated for no PPI versus PPI treated patients (ie, values >1 indicated increased hazard in the PPI group) with a proportional hazards model. Cox regression was used for multivariate analysis. Clinical and angiographic characteristics that were imbalanced at a nominal 5% significance level between the 2 groups treated or not treated with PPI were identified and included the final adjusted model; these included sex, age, creatinine clearance, clinical presentation, and CRUSADE score. As sensitivity analyses, adjusted outcomes were also evaluated after excluding patients who had modified their PPI status (assumption of PPI in those with no PPI therapy at 30 days or interruption of PPI in those with PPI therapy at 30 days) during follow-up. Further sensitivity analyses included the assessment of adjusted outcomes with landmark analysis at 6 to 24 months and the analysis restricted to those patients treated with lansoprazole as PPI type (exclusion of other PPI types).

Interaction testing was performed to determine whether the effect of DAPT duration was consistent irrespective of PPI treatment on the primary and secondary end points of the study. This was performed with likelihood ratio tests of the null hypothesis that the interaction coefficient was zero. A 2-sided *P* value of <.05 was considered significant. All analyses were based on the intention-to-treat principle and were performed with SPSS, version 21.0 (SPSS, Inc, Chicago, IL).

For the present analysis, no extramural funding was used to support this work. The authors are solely responsible for the design and conduct of this study, all study analyses, and drafting and editing of the manuscript.

Results

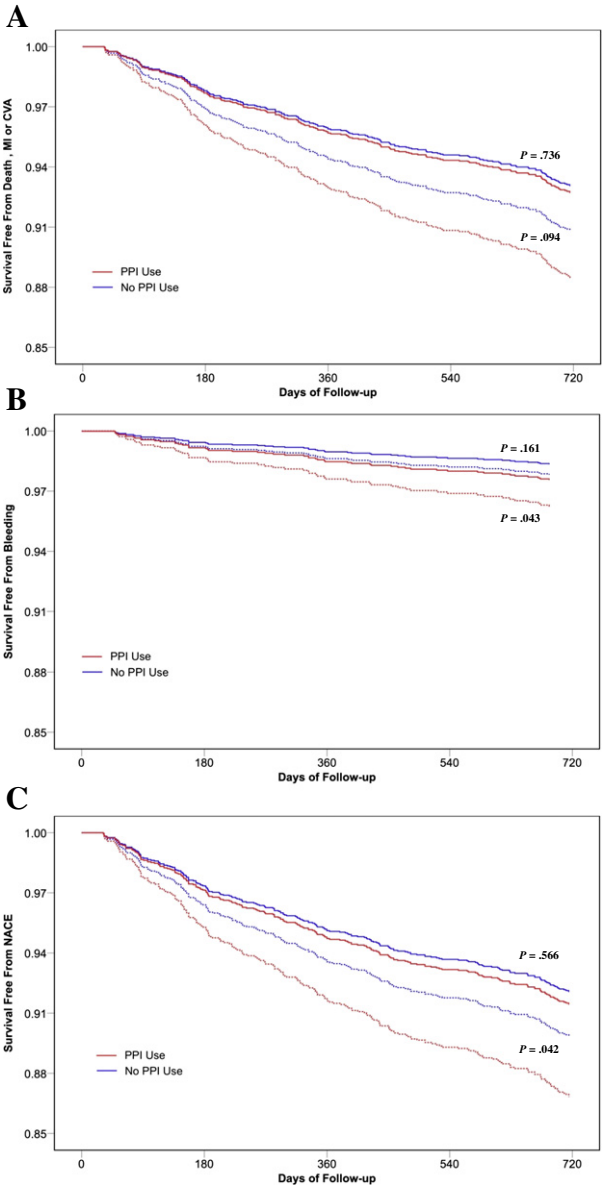
Among 1,970 patients randomized to 6- versus 24-month DAPT at 30 days from the PCI, 738 patients (37.5%) were receiving a PPI. Most of them were treated with lansoprazole (671 patients, 90.9%), whereas the others received pantoprazole (56 patients, 7.6%) and few patients received other PPI types (omeprazole, esomeprazole, and rabeprazole, 1.5%).

Baseline characteristics of population with PPI and without PPI are summarized in Table I, whereas Table II describes their characteristics in the setting of the 2 randomized arms of DAPT regimens (24 vs 6 months). Compared with patients who did not receive PPI, those receiving PPI were older, were more likely female, had a lower creatinine clearance, presented more frequently with acute coronary syndrome (ACS), and had a higher CRUSADE bleeding score (Tables I and II). The primary efficacy end point (composite of all-cause death, MI, and CVA) was similar between patients with PPI and without PPI use (9.2% vs 11.5%, adjusted HR 1.051, 95% CI 0.788-1.400, *P* = .736) (Figure 1). Results were consistent across other secondary end points as reported in Table III. Safety end points of bleeding did not differ between the 2 groups (BARC type 2, 3, or 5: adjusted HR 0.996, 95% CI 0.672-1.474, *P* = .980; BARC type 3 or 5: adjusted HR 1.478, 95% CI 0.856-2.553, *P* = .160) (Figure 1 and Table III). Overall, major bleeding evaluated with different definitions was more frequent in PPI users compared with those without PPI (BARC 3 or 5: 3.7% vs 2.1%, TIMI major 1.5% vs 0.9%, GUSTO moderate or severe 3.7% vs 1.9%); however, after adjustment for confounding factors, none of them remained significant (Table III). The composite of efficacy and safety end points in the NACE was also similar in no PPI and PPI patients (12.9% vs 14.9%, adjusted HR 0.99, 95% CI 0.772-1.268, *P* = .93) (Figure 1 and Table III).

Finally, there was no signal for heterogeneity between PPI use and explored clinical end points with respect to randomized DAPT duration (Figure 2, Supplementary Figure 1, Table IV, and Supplementary Tables I-III).

At sensitivity analyses, PPI therapy during follow-up was taken into account (1 month: 738 PPI patients 37%, 6 months: 685 PPI patients 35%, 12 months: 690 PPI patients 35%, 18 months: 709 PPI patients 36%, 24 months: 734 PPI patients 37%). A specific analysis of clinical outcomes was also performed in patients who remained consistently on a PPI throughout the follow-up period and excluding those who had started or interrupted PPI

Figure 1



Survival free from ischemic and bleeding events according to PPI treatment. Cox proportional model plot for the primary end point of death for all causes, MI, and CVA (**A**), bleeding defined as BARC class 3 or 5 (**B**), and NACEs (**C**) in patients treated or not treated with PPI. Dashed lines represent the unadjusted risk model. Solid lines represent the adjusted risk model.

Table III. Clinical outcomes in PPI-treated versus non–PPI-treated patients

	No PPI (n = 1232)	PPI (n = 738)	Unadjusted HR (95% CI)	*P*	Adjusted HR (95% CI)	*P*
Primary efficacy end point						
Death for any cause, MI, or CVA	113 (9.2)	85 (11.5)	1.272 (0.960-1.685)	.094	1.051 (0.788-1.400)	.736
Secondary efficacy end points						
Death for any cause or MI	107 (8.7)	75 (10.2)	1.178 (0.877-1.582)	.278	0.957 (0.708-1.293)	.773
Death for any cause	77 (6.2)	53 (7.2)	1.150 (0.811-1.632)	.433	0.918 (0.642-1.311)	.636
Death for cardiovascular cause	44 (3.6)	29 (3.9)	1.101 (0.689-1.759)	.688	0.865 (0.534-1.400)	.554
MI	48 (3.9)	32 (4.3)	1.115 (0.713-1.744)	.633	0.941 (0.597-1.485)	.790
Definite or probable ST	19 (1.5)	9 (1.2)	0.780 (0.353-1.723)	.539	0.682 (0.306-1.523)	.350
Definite, probable, or possible ST	47 (3.8)	37 (5.0)	1.320 (0.858-2.030)	.207	1.028 (0.662-1.597)	.900
Safety end points						
BARC classification						
Key safety end point (type 2, 3, or 5)	64 (5.2)	43 (5.8)	1.127 (0.766-1.659)	.545	0.996 (0.672-1.474)	.980
Type 3 or 5	26 (2.1)	27 (3.7)	1.746 (1.019-2.992)	.043	1.478 (0.856-2.553)	.161
TIMI classification						
Minor	10 (0.8)	10 (1.4)	1.680 (0.699-4.036)	.246	1.434 (0.589-3.492)	.428
Major	11 (0.9)	11 (1.5)	1.679 (0.728-3.873)	.224	1.465 (0.627-3.421)	.378
Minor or major	21 (1.7)	21 (2.8)	1.684 (0.920-3.084)	.091	1.453 (0.786-2.687)	.234
GUSTO classification						
Moderate	13 (1.1)	14 (1.9)	1.803 (0.848-3.836)	.126	1.449 (0.676-3.110)	.341
Severe	12 (1.0)	13 (1.8)	1.820 (0.830-3.988)	.135	1.626 (0.732-3.613)	.232
Moderate or severe	24 (1.9)	27 (3.7)	1.893 (1.092-3.281)	.023	1.582 (0.905-2.763)	.107
NACE						
Death for any cause; MI; CVA; or BARC 2, 3, or 5 bleeding	159 (12.9)	110 (14.9)	1.172 (0.919-1.494)	.202	0.989 (0.772-1.268)	.933
Death for any cause, MI, CVA, or BARC 3 or 5 bleeding	125 (10.1)	97 (13.1)	1.317 (1.010-1.717)	.042	1.083 (0.826-1.419)	.566

Abbreviations: *GUSTO*, Global Use of Strategies to Open Occluded Coronary Arteries.

therapy. Results remained robust showing the absence of significant differences for ischemic and bleeding events (Supplementary Table IV). This was further confirmed by landmark analyses (Supplementary Table V) and by restriction of analysis to lansoprazole as PPI (Supplementary Table VI).

Discussion

The present post hoc analysis from the PRODIGY randomized trial investigated the impact of concomitant PPI use on clinical outcomes in all-comer patients undergoing PCI and receiving DAPT with clopidogrel as thienopyridine component.

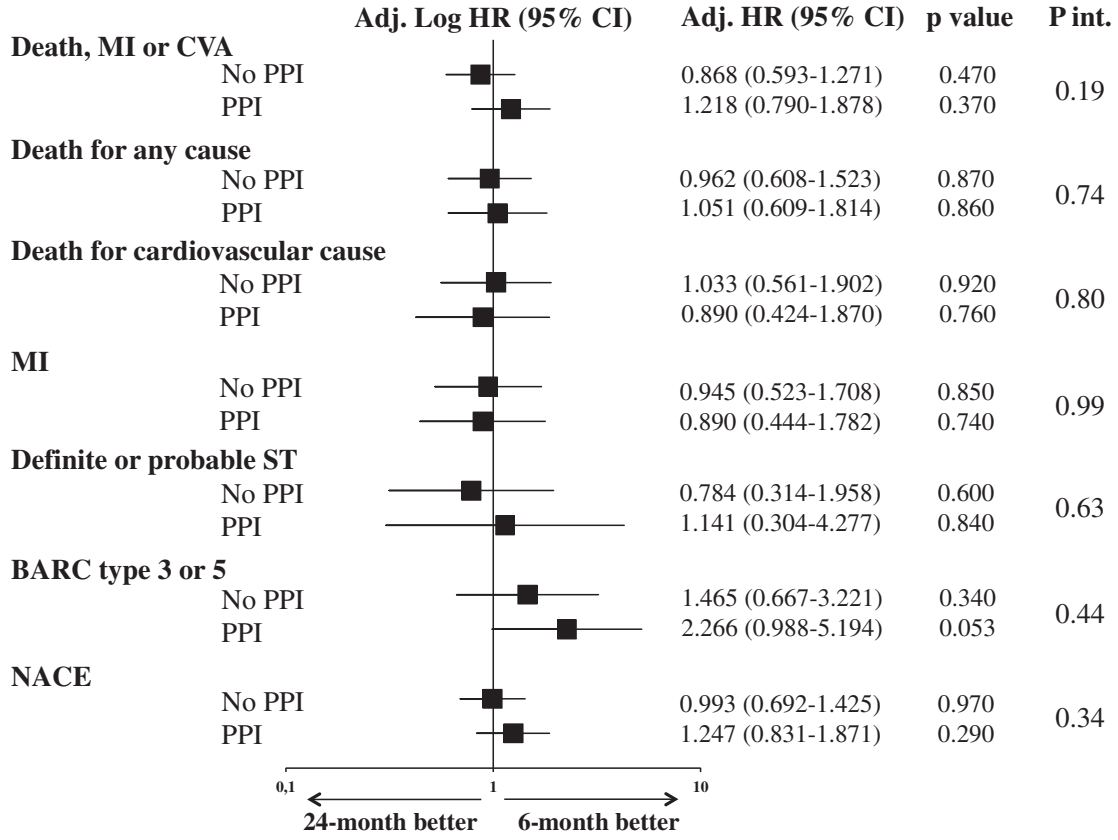
Although, at univariate analysis, PPI use was associated with an increased risk of ischemic and bleeding events, after multivariate adjustment, PPI therapy was no longer related to different rates of ischemic events, bleeding, or NACE at 2 years irrespective of the short or prolonged regimen of DAPT. The findings of our study are consistent with the results of the COGENT trial, showing thus no association of PPI use with increased risk of ischemic events.

Several studies assessing the inhibition of platelet aggregation suggested that PPIs may significantly reduce the antiplatelet effect of clopidogrel when the 2 drugs are coadministered.[8-11] In particular, some PPIs (omeprazole and esomeprazole) highly inhibit CYP2C19 isoenzyme, whereas other PPIs are weak inhibitors (lansoprazole) or do not inhibit this isoenzyme (pantoprazole). However, the findings from pharmacodynamic studies may not necessarily translate into differences in clinical outcomes, and the design and quality of studies might be the major determinant of such contrasting evidence.[14,15] Indeed, most studies supporting an increased risk of cardiovascular ischemic events when using any type of PPI in patients on clopidogrel are observational studies. Conversely, randomized trials and propensity score–matched studies did not support such concerns. Nonetheless, new evidence from a recent US analysis of >60,000 patients with gastroesophageal reflux disease exposed to PPIs raised new questions by reporting a 1.2-fold increased risk of MI and a 2-fold increased risk of cardiovascular mortality, irrespective of clopidogrel use.[20]

Proton pump inhibitor use was associated with an increased risk of Major Adverse Cardiovascular Events and MI but not death and target vessel revascularization in the subgroup analysis of the BASKET trial.[22] Similarly, the CAPRIE trial showed a higher rate of ischemic events among patients treated with PPIs and clopidogrel, whereas the most recent subanalysis from the ADAPT-DES trial showed increased rate of Major Adverse Cardiovascular Events due to death and target vessel revascularization rather than MI or ST.[17,23]

In contrast, the dedicated COGENT trial did not support these findings.[16] This trial randomly assigned patients with an indication for DAPT to receive clopidogrel in combination with either omeprazole or placebo, in addition to

Figure 2



Forest plots for clinical outcomes in short versus prolonged DAPT duration according to PPI treatment. Proton pump inhibitor and no-PPI subgroups are shown, with HRs and 95% CIs, for the primary end point of death for any cause, MI, or CVA; death for any cause; cardiovascular death; MI; definite or probable stent thrombosis; BARC type 3 or 5 bleeding; and NACEs among patients randomly assigned to either the 6- or 24-month DAPT.

aspirin. The composite of cardiovascular death, MI, revascularization, or stroke did not differ, but GI events were less frequent in the omeprazole group.[16]

In the subgroup analyses of the PRINCIPLE and TRITON-TIMI 38 trials, a significant impact of PPI therapy on reducing the effect of clopidogrel on platelet aggregation was further substantiated. However, the pharmacodynamic changes did not translate into adverse clinical outcomes.[11]

Our study is in line with and importantly adds to previous evidence indicating that the use of PPIs, largely consisting of lansoprazole, in conjunction with clopidogrel is safe. In addition, this observation held true in the 2 randomized groups of short- versus long-term DAPT, indicating that PPI therapy does not increase ischemic events irrespective of whether clopidogrel is administered for short periods (ie, 6 months) or prolonged times (ie, 24 months). The incidence of ST was low and did not differ in patients with or without concomitant PPI use.

In the subgroup analysis of the PLATO trial on PPI use, the association between PPI use and clinical adverse events in patients treated with clopidogrel was likely due to confounding (observed also in those receiving ticagrelor and in those receiving non-PPI GI drugs), with PPI use emerging as a marker for, rather than a cause of higher rates of cardiovascular adverse events.[18] Interestingly, the role of confounding factors appeared to also be relevant in the present study as the PPI population showed an increased risk of both ischemic and bleeding events. However, after multivariate adjustment, differences in outcomes were no longer present.

Proton pump inhibitors are often prescribed in patients with DAPT to reduce bleeding complications or due to specific clinical indication (ie, gastric disease). Generally, the PPI use is left to the discretion of clinicians, and often, a selection of patients is performed with those receiving PPI being at increased risk for ischemic and bleeding events. This explains at least in part the results of observational

Table IV. Adjusted clinical outcomes in PPI-treated versus non–PPI-treated patients stratified for the randomly allocated DAPT duration

	24-m clopidogrel				6-m clopidogrel				
	No PPI (n = 612)	PPI (n = 375)	Adjusted HR (95% CI)	*P*	No PPI (n = 620)	PPI (n = 363)	Adjusted HR (95% CI)	*P*	P_{int}
Primary efficacy end point									
Death for any cause, MI, or CVA	52 (8.5)	48 (12.8)	1.375 (0.916-2.064)	.125	61 (9.8)	38 (10.2)	0.852 (0.562-1.291)	.449	.19
Secondary efficacy end points									
Death for any cause or MI	48 (7.8)	40 (10.7)	1.218 (0.789-1.881)	.372	59 (9.5)	35 (9.6)	0.824 (0.538 -1.261)	.372	.33
Death for any cause	37 (6.0)	28 (7.5)	1.070 (0.645-1.777)	.792	40 (6.5)	25 (6.9)	0.865 (0.519-1.441)	.578	.74
Death for cardiovascular cause	22 (3.6)	14 (3.7)	0.877 (0.437-1.757)	.711	22 (3.5)	15 (4.1)	0.974 (0.494-1.923)	.941	.80
MI	23 (3.8)	16 (4.3)	0.980 (0.505-1.904)	.953	25 (4.0)	16 (4.4)	0.923 (0.490-1.739)	.803	.99
Definite or probable ST	8 (1.3)	5 (1.3)	0.718 (0.231-2.225)	.566	11 (1.8)	4 (1.1)	0.652 (0.204-2.085)	.471	.63
Definite, probable, or possible ST	19 (3.1)	19 (5.1)	1.431 (0.743-2.755)	.283	28 (4.5)	18 (5.0)	0.868 (0.473-1.593)	.647	.34
Safety end points									
BARC classification									
Key safety end point (type 2, 3, or 5)	41 (6.7)	32 (8.5)	1.227 (0.762-1.977)	.400	23 (3.7)	11 (3.0)	0.661 (0.321-1.362)	.261	.34
Type 3 or 5	15 (2.5)	19 (5.1)	1.881 (0.937-3.777)	.076	11 (1.8)	8 (2.2)	1.048 (0.418-2.627)	.920	.44
TIMI classification									
Minor	7 (1.1)	4 (1.1)	0.741 (0.212-2.592)	.639	3 (0.5)	6 (1.7)	3.572 (0.861-14.827)	.080	.15
Major	6 (1.0)	10 (2.7)	2.569 (0.905-7.290)	.076	5 (0.8)	1 (0.3)	0.264 (0.031-2.265)	.225	.11
Minor or major	13 (2.1)	14 (3.7)	1.559 (0.717-3.391)	.262	8 (1.3)	7 (1.9)	1.388 (0.479-3.739)	.579	.91
GUSTO classification									
Moderate	8 (1.3)	9 (2.4)	1.487 (0.562-3.934)	.424	5 (0.8)	5 (1.4)	1.488 (0.424-5.222)	.535	.96
Severe	6 (1.0)	10 (2.7)	2.569 (0.905-7.288)	.076	6 (1.0)	3 (0.8)	0.705 (0.175-2.843)	.623	.26
Moderate or severe	13 (2.1)	19 (5.1)	2.079 (1.007-4.292)	.048	11 (1.8)	8 (2.2)	1.050 (0.419-2.633)	.917	.31
NACE									
Death for any cause; MI; CVA; or BARC 2, 3, or 5 bleeding	87 (14.2)	65 (17.3)	1.140 (0.818-1.589)	.440	72 (11.6)	45 (12.4)	0.875 (0.599-1.277)	.489	.60
Death for any cause, MI, CVA, or BARC 3 or 5 bleeding	61 (10.0)	55 (14.7)	1.329 (0.911-1.939)	.141	64 (10.3)	42 (11.6)	0.928 (0.625-1.379)	.712	.34

studies on PPI use and increased ischemic risk. In the present study, PPIs were prescribed to patients with a greater bleeding risk, as indicated by a more advanced age, more female patients, and ACS, a worse renal function and a higher CRUSADE score. However, after adjustment for these confounding factors, the differences between PPI and no-PPI populations were not clinically relevant for most clinical outcomes. Although the COGENT trial excluded patients with prior indication for PPI use or H2-receptor antagonists and patients at higher risk for GI bleeding, the results of the present study can be extended to an all-comer population of patients undergoing PCI and DAPT therapy.

Limitations

This is a post hoc not randomized and not prespecified analysis of the PRODIGY trial, and the prescription of a PPI was left to the physician's discretion.

Rates of overall but not specifically GI bleeding were evaluated and available for this analysis, so potential benefits of PPI on reducing GI bleeding events could not be analyzed.

Although multivariate adjustment was performed, it cannot be excluded that unknown/unmeasured factors may have impacted findings.

Data on PPI dosage were not prospectively collected, so it was not possible to make specific analysis on dose-dependent effects.

"In the PRODIGY, lansoprazole was by far the most frequently used PPI. Hence, it remains unclear whether our findings may be extrapolated to other PPIs such as omeprazole or esmoprazole."

Genetic analysis to test the predisposition for reduced clopidogrel responsiveness was not available. Therefore, it cannot be excluded that PPIs may have a different impact on outcomes in this subgroup of patients.

Conclusion

Overall, PPI use was not associated with an increased risk of cardiovascular events in all-comer patients undergoing PCI and receiving DAPT. Our findings do not support the need to avoid concomitant use of PPIs and DAPT with aspirin plus clopidogrel, when clinically indicated.

Appendix. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ahj.2016.01.015.

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Editorial

Long-term dual antiplatelet therapy and concomitant optimal medical therapy following percutaneous coronary intervention

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The dual antiplatelet therapy (DAPT) consisting of aspirin and a P2Y12 inhibitor exerts protection against ischemic myocardial recurrences. During last two decades, DAPT has become the mainstay for treating patients with coronary artery disease (CAD) undergoing percutaneous coronary intervention (PCI), following the initial demonstration that DAPT was superior to anticoagulant therapy in these patients. Initially, and for many years, DAPT was prescribed for 2 to 6 months after PCI in important trials of stent implantation leading to the approval of early-generation drug-eluting stents (DES) by the US Food and Drug Administration. However, the subsequent increasing safety concerns related to the potential occurrence of late and very late stent thrombosis (ST) after implantation of early-generation DES lead to the recommendation of prolonging DAPT to 12 months by the American guidelines (1).

On this background, different studies have specifically investigated the comparison of different DAPT regimens after PCI and the optimal duration of DAPT still remains matter of discussion (2-9).

From one hand, some trials explored the effects of a short DAPT regimen (3 to 6 months) compared with 12 months DAPT supporting that such approach is as effective and safer being associated with similar ischemic events but reduced risk of bleeding. In patients with clinical characteristics such as to be considered at high bleeding risk, a 1-month DAPT was also found to be safe and effective after new-generation DES (10,11). On the other hand, other trials, consisting mainly of patients treated with elective DES implantation, compared prolonged DAPT (total therapy duration: 18 to 48 months) with 6 to 12 months of DAPT to determine whether extended therapy reduces late and very late stent thrombosis and prevents ischemic events associated with disease progression and plaque rupture at other nonstented sites. The majority of these trials (PRODIGY, ITALIC, DES-LATE, OPTIDUAL, ARCTIC Interruption) did not support the hypothesized benefits of DAPT prolongation, rather underlying concerns in terms of bleeding events (8,9,12). In contrast, the largest of these trials, the DAPT study, found that prolonging DAPT was associated with reduction of ischemic events, although this was mainly proven for the larger population of patients receiving DES implantation (n=9,961) rather than in those receiving a bare metal stent (n=1,687) (13,14). In the DAPT study, patients treated with DES or BMS implantation who received DAPT for 12 months and were without ischemic or bleeding events during this period were randomized to an additional 18 months of DAPT or to aspirin monotherapy. In the overall cohort and in the DES subgroup, extended DAPT resulted in a significant reduction in very late ST, myocardial infarction (MI), major adverse cardiac and cerebrovascular events (MACCE defined as death or MI or stroke), and increased risk of moderate or severe bleeding. In the patients receiving BMS, the DAPT prolongation did

not reduce significantly ischemic outcomes but increased bleeding events, however, it should be noted that there was no significant interaction between subgroups (DES and BMS) and the BMS subset may have been underpowered to identify such differences (14).

Some have hypothesized that "the longer, the better", however, this remains a matter of ongoing debate with many concerns on this approach. Indeed, a major issue that emerged from the DAPT study was the increase of non-cardiovascular mortality observed in patients prolonging DAPT and subsequently this was further confirmed in meta-analyses (5,8,9,13).

The large body of contrasting evidence accumulated during last years on the optimal duration of DAPT after stent implantation has led to growing discussion. Currently, the common consensus among opinion leaders is that there is no "*one size fits all*" approach and no common rule for the duration of DAPT after implantation of coronary stents (4,5,15). Consequently, a tailored approach may be advisable, wherein the personalized risks of ischemic versus bleeding events are carefully considered for each patient. A realistic estimation of the long-term ischemic and bleeding risk in each patient undergoing PCI is of paramount importance to tailor the optimal DAPT duration.

Accordingly, DAPT prolongation after the mandatory period seems to be more appropriate in patients at high risk for ischemic events but with relatively low risk of bleeding. In opposite, a 3- to 6-month DAPT regimen may be the ideal approach for patients with increased risk of bleeding based on the relatively high incidence of late bleeding events during DAPT therapy with harmful effect on survival. A shorter DAPT (i.e., 1-month) has been found to be safe and effective in patients with high risk of bleeding (i.e., elderly, need for oral anticoagulation, need for major noncardiac surgery, severe anemia, history of bleeding or transfusion, non-skin cancer, renal failure, severe liver disease, thrombocytopenia, planned long-term use of steroids or nonsteroidal anti-inflammatory drugs). Thus, there is a great interest in exploring specific clinical conditions that can identify patients in whom the benefit-risk ratio could be in favor or disfavor of DAPT continuation. Some subgroups have shown to benefit from extending DAPT due to their increased ischemic risk, such as patients with ACS at presentation (16), prior myocardial infarction (17), peripheral arterial disease (18) or those with multivessel disease or complex lesions (19,20). On the contrary, other conditions, such as diabetes (21), gender (22,23), chronic kidney disease (24), and elderly patients (25) did not emerge to be per se relevant drivers of the DAPT prolongation.

In line with the strategy to search for factors helping to individualize the optimal DAPT regimen patient-by-patient, Resor and colleagues recently investigated the impact of optimal medical therapy (OMT) on the treatment effect of DAPT (26). This analysis was conducted in the setting of all patients enrolled in the randomized DAPT study, including those treated with DES or BMS.

OMT was defined at the time of randomization as a combination of any dose statin, β-blocker, and ACE inhibitor/ARB use in patients with class I indication for each medication in agreement with American guidelines: (I) statin: all patients were considered to have an indication; (II) β-blocker: reduced ejection fraction, congestive heart failure, previous MI or ACS; (III) ACE inhibitor/ARB: hypertension, diabetes mellitus, reduced ejection fraction, or chronic kidney disease (26).

The overall finding of the study that DAPT prolongation provided ischemic benefits at the cost of increased bleeding was confirmed irrespective of OMT status, therefore, this analysis suggested that the decision to continue or interrupt DAPT beyond 12 months should not be based on the OMT.

OMT is recommended in patients with CAD due to the evidence of being associated with decrease of ischemic events and death. However, it is unknown whether the reduced risk in OMT patients may be also associated with a reduced or ischemic benefit related to prolongation of DAPT exposing thus the patient only to the increased bleeding risk related to such a strategy. The present subanalysis of the DAPT study seems to support the concept that there is no interaction between OMT and DAPT, rather suggesting that they may act synergistically through different mechanisms in order to reduce ischemic events (26). The authors also explored predictors of being or not on OMT and found that younger patients or those presenting with ACS or receiving clopidogrel instead of prasugrel were associated with higher rates of OMT. It is, however, an important concern that delicate categories such as patients with previous MI, previous PCI, renal insufficiency or hypertension more frequently were associated with lower rates of OMT. Although potentially interesting, these observations may have been related, at least in part, to different regional patterns of drug management, indeed, suboptimal OMT was mainly observed in North America compared with other sites.

The study is interesting, original, well conducted,

includes a large number of patients, and almost complete data on concomitant medication.

The findings, however, require some important considerations to allow an appropriate interpretation:

- First, the study was not prespecified and should be considered hypothesis-generating only;
- Second, OMT was a binary definition and the two groups (on OMT and off OMT) were attributed on the basis of therapy at enrollment, but OMT status is actually dynamic and in individual patients may have been modified throughout the study;
- Third, the definition of OMT status was performed without considering real reasons for not assuming a specific drug (contraindication, allergy, etc.) or taking into account lipid and blood pressure levels (did patients defined to be on OMT really reach the recommended targets for OMT?) or the dosage of drugs (i.e., this is particularly relevant for patients with reduced ejection fraction and indication to b-blockers);
- Fourth, the impact of OMT was only tested for the period of randomized treatment to DAPT versus aspirin alone between 18–30 months. In the DAPT analysis restricted to DES implantation, an important rebound effect was observed after DAPT interruption from 30 to 33 months and it would be interesting to know if OMT did not play a relevant role also in this phenomenon;
- Finally, there was a selective reporting of outcomes. Although mortality, stent thrombosis and stroke outcomes were included in the MACCE, they were not individually reported, thus a potential interaction of OMT status with these endpoints cannot be excluded. Especially in the DAPT study, all-cause mortality has emerged as an important and debated issue in the group of patients receiving DAPT prolongation and it would be interesting if this outcome had been reported. Indeed, we do not know whether OMT would have mitigated or not the increased risk of mortality described in those patients.

OMT represents a crucial but often underestimated aspect of post-procedural PCI care (26,27). The control of multiple cardiovascular risk factors decreases the incidence of cardiovascular events (27,28). OMT is a broad term that includes specific pharmacotherapy to control arterial hypertension, hyperlipidemia, and chronic hyperglycemia as well as the control of lifestyle risk factors (weight loss, smoking cessation, dietary regimen, exercise, and life rhythms). Importantly, the European Society of Cardiology guidelines highlighted that OMT should not be considered an alternative but a synergistic approach to revascularization (28).

In our opinion, from a practical point of view, the most relevant and also worrisome aspect emerged from this study, irrespective of DAPT regimen, and confirming other previous evidence, is the suboptimal frequency of OMT, indeed, approximately 37% of patients were not on OMT. Importantly, this appears to be even more alarming when we consider that the patients enrolled in the DAPT study represented a selected population of patients that were assumed to be at low risk of altered adherence to medical therapy; indeed, 12 months after PCI, only patients event-free and with appropriate compliance to thienopyridine therapy (defined as having taken 80% to 120% of the drug without stopping it for >14 days) were eligible for randomization. Although adherence to therapy was not assessed individually in each group, the overall good adherence of the enrolled patients to the medical treatment was confirmed by consistency of the rates of patients assuming statin, β-blocker, ACEi/ARB and OMT at randomization (12 months after PCI) and at end of the study (30 months after PCI). We may therefore assume that the rates of those without OMT in real practice might be much higher, which should raise a red flag for all practitioners. Notably, patients without OMT had higher rates of MI, MACCE and moderate or severe bleeding compared with patients on OMT. Therefore, given that the proportion of patients not on OMT still remains large, this study underlines a major unmet need in current practice: more and more organized efforts are needed to increase adherence and adherence awareness in our community and within our patients.

The real challenge in the 21-century seems to be finding ways to let the community apply established evidence even more than identifying new treatment venues.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Effects of Carvedilol Versus Metoprolol on Platelet Aggregation in Patients With Acute Coronary Syndrome: The PLATE-BLOCK Study

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Platelet aggregation plays a pivotal role in acute coronary syndrome (ACS). In this setting, β-blockers (BBs) are used to counteract the effects of catecholamines on heart. Circulating catecholamines can also potentiate platelet reactivity, mainly through α_2- and β_2-adrenoceptors on human platelets' surface, thus BB may affect platelet aggregation; however, the effects of different BBs on platelet aggregation in contemporary-treated patients with ACS have been poorly investigated. One hundred patients with ACS on dual antiplatelet therapy with aspirin and ticagrelor were randomized to receive treatment with carvedilol, a nonselective BB (n = 50), or metoprolol, a selective β_1-blocker (n = 50), at maximum tolerated dose. Light transmission aggregometry was performed at randomization (T0) and at 30-day follow-up (T30), and the results were expressed as a percentage of maximum platelet aggregation (MPA). The primary end point was epinephrine-induced MPA at 30 days. Patients were predominantly men (80%), and mean age was 57.3 ± 9.7 years. The 2 randomized groups were well balanced for baseline characteristics. At T0, mean MPA was similar between the groups (18.96 ± 9.05 vs 18.32 ± 9.21 with 10 μM epinephrine, 14.42 ± 9.43 vs 15.98 ± 10.08 with 20 μM adenosine diphophate (ADP), and 13.26 ± 9.83 vs 14.30 ± 9.40 with 10 μM ADP for carvedilol and metoprolol, respectively, all p = NS). At 30 days, platelet aggregation induced by epinephrine was significantly lower in the carvedilol group than in the metoprolol group (23.52 ± 10.25 vs 28.72 ± 14.37, p = 0.04), with a trend toward the lower values of ADP-induced MPA (20 μM ADP 19.42 ± 13.84 vs 24.16 ± 13.62, p = 0.09; 10 μM ADP 19.12 ± 12.40 vs 22.57 ± 13.59, p = 0.19). In conclusion, carvedilol, a nonselective BB, reduces residual platelet reactivity in patients with ACS compared with the selective BB, metoprolol. **(Am J Cardiol 2018;122:6–11)**

Platelet aggregation plays a pivotal role in the pathogenesis of ischemic events during and after acute coronary syndrome (ACS).[1–3] Myocardial ischemia is associated with a high activity of the sympathetic nervous system, which is reflected by increased plasma levels of epinephrine and norepinephrine. In patients with ACS, β-blocker (BB) drugs are important to counteract the effects of catecholamines on heart, and many compounds are available (some with selective β_1-adrenoceptor blockade and some with nonselective α- and β-inhibition properties[4]), but there is no molecule recommended over the other.[5–7] Besides their effects on heart, circulating catecholamines have also demonstrated to affect platelet reactivity in different manners, such as potentiating the proaggregant effect of other substances, influencing the response to antiplatelet agents, directly interacting with platelets' surface adrenergic receptors (α_{2A} subtype is the most abundant, but β_2 type is also present).[8–12] Additionally, nonselective BB seem also able to decrease plasma catecholamine levels more than selective ones,[13] and their lipophilicity can increase the ability to indirectly affect platelet aggregation by a chemical interaction with platelet's cell membrane.[14] A recent meta-analysis suggested that nonselective lipophilic BB reduced platelet aggregation more effectively than selective nonlipophilic BB, but included studies were well outdated (mainly conducted in 1970s to 1980s), and none of them included patients with ACS treated with contemporary dual antiplatelet therapy (DAPT).[8] The aim of our study was to compare the effects of the nonselective BB, carvedilol, with the selective metoprolol on platelet aggregation induced by epinephrine and adenosine diphosphate (ADP) in the contemporary setting of patients with ACS receiving DAPT with aspirin and ticagrelor.

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See page 10 for disclosure information.

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Methods

The PLATE-BLOCK study is an investigator-initiated, single-center, open-label, prospective randomized trial. Consecutive patients hospitalized for an ACS (ST-segment elevation myocardial infarction [STEMI], non–ST-segment elevation myocardial infarction [NSTEMI], unstable angina) presented at the coronary care unit of University Federico II of Naples, undergoing acid acetylsalicylic and ticagrelor treatment and percutaneous coronary intervention, were screened. Exclusion criteria were as follows: age <18 years; contraindication to BB therapy; ongoing prasugrel, ticlopidine, or clopidogrel therapy; creatinine clearance <30 ml/min; moderate to severe anemia (hemoglobin <10 mg/dl); platelet count >600,000/mm^3 or <130,000/mm^3; hematocrit >50% or <25%; known blood dyscrasia or bleeding diathesis; concomitant neoplastic or immune-mediated pathologies; ongoing oral anticoagulation therapy. Patients were treated with aspirin (loading dose of 150 to 300 mg orally or 75 to 150 mg intravenously, and 100 mg once a day as maintenance dose) and ticagrelor (180 mg loading dose, 90 mg twice daily as maintenance dose). All patients eligible for enrollment who accepted to participate provided written informed consent and were randomly assigned to carvedilol or metoprolol treatment at maximum tolerated dosage. Randomization occurred using concealed table that was previously generated using Research Randomizer (https://www.randomizer.org). The study complied with the Declaration of Helsinki. The local institutional ethics committee approved the study protocol, and all patients gave written informed consent to participate. The trial protocol is registered within ClinicalTrials.gov, number NCT02809820.

Clinical events occurring within 30 days were recorded. Any death, unless an unequivocal noncardiovascular cause could be established, was defined as death from cardiovascular causes. Myocardial infarction was defined in accordance with the third universal definition proposed in 2012.[15] Stent thrombosis was defined according to the Academic Research Consortium criteria.[16] Stroke was defined as focal loss of neurologic function caused by an ischemic or hemorrhagic event, with residual symptoms lasting at least 24 hours or leading to death. Bleeding was defined according to Thrombolysis In Myocardial Infarction (TIMI) and Bleeding Academic Research Consortium criteria.[17]

Samples for platelet function testing were taken at baseline (within 48 hours after coronary angiography after diagnosis of ACS) and at 30 days. The measurements were performed in the morning just before the administration of the morning ticagrelor dose. When GPIIb/IIIa inhibitors were prescribed, an interval of 18 to 24 hours after completion of the infusion was required before platelet function testing was performed, to avoid interference with aggregation assay. Platelet aggregation was measured by light transmission aggregometry (LTA) using a dual channel lumi-aggregometer (model 700; Chrono-Log, Havertown, Pennsylvania). Platelet-rich plasma was prepared from blood that was drawn from the antecubital vein by venipuncture into 3.8% trisodium citrate (w/v) Vacutainer blood collection tubes. Platelet-rich plasma was obtained by centrifugation of blood at 180 *g* at 25°C for 10 minutes. Platelet-poor plasma was obtained by centrifugation of the rest of the blood at 1,500 *g* at 25°C for 10 minutes.[3] Platelet aggregation was monitored at 37°C with constant stirring (1,200 rpm) and measured as the increase in light transmission for 6 minutes, with the addition of epinephrine (10 μM) and ADP (10 and 20 μM) as a proaggregatory stimulus. All measurements were obtained within 2 hours of sample collection, and the results are reported as percentage of maximum platelet aggregation (MPA).

The primary end point of the study was to evaluate the effects of metoprolol versus carvedilol after 30 days of treatment on platelet aggregation induced by 10 μM epinephrine, in patients with ACS on DAPT. Epinephrine test was elected to be the primary end point given the anticipated effects of BB on reducing catecholamine-induced platelet aggregation. Secondary end points were the evaluation of ADP-induced platelet aggregation (10 and 20 μM) and adverse clinical events, including ischemic and bleeding complications at 30 days.

The primary hypothesis of the study is that the % MPA with epinephrine at 30 days will be reduced in the carvedilol group compared with the metoprolol group. Based on previous studies, standard deviation (SD) of MPA is quite variable, and probably different timing, different drugs, and different methodologies contribute to this.[18,19] Assuming an SD of at least 8% and that an absolute 5% would be a clinically relevant difference in the % MPA induced by epinephrine, a sample size of at least 100 subjects (50 for each group) would detect a true difference between groups with statistical power ≥80% at an alpha significance level of 0.05. The planned sample size was then increased up to 120 to allow occurrence of new contraindications or adverse events or incomplete aggregometry data. Variables were expressed as absolute numbers and percentage or mean ± SD. Comparisons were made by chi-square test or Student *t* test, as appropriate. Statistical analyses were performed using IBM-SPSS, version 23 (SPSS Inc, Chicago, Illinois).

Results

Between June 2016 and December 2016, 204 patients with ACS (STEMI, NSTEMI, and unstable angina) were assessed for eligibility. Of these, 84 did not meet the study entry criteria or refused to consent, whereas 120 provided their written informed consent to participate in the study; of these, 111 were randomized (metoprolol, n = 55; carvedilol, n = 56), representing the enrolled population. A total of 100 patients (metoprolol, n = 50; carvedilol, n = 50) were the primary population and finally analyzed (Figure 1). Baseline clinical characteristics are shown in Table 1. The mean age was 57.3 ± 9.7, and the majority of patients were males and smokers, 18% had diabetes, and 16% had history of myocardial infarction. At clinical presentation, 62% had STEMI, with an average left ventricle ejection fraction at transthoracic echocardiogram of about 45% and a relatively stable hemodynamic profile. The 2 randomized groups were homogenous in terms of cardiovascular risk factors, routine laboratory variables, or medications (Table 1). Angiographic and procedural characteristics of the 2 study groups are shown in Table 1. The culprit lesion was the left anterior descending artery in half of patients, and 1/3 of patients had multivessel disease. The majority of patients received percutaneous coronary intervention with stent implantation and had a final TIMI 3 flow.

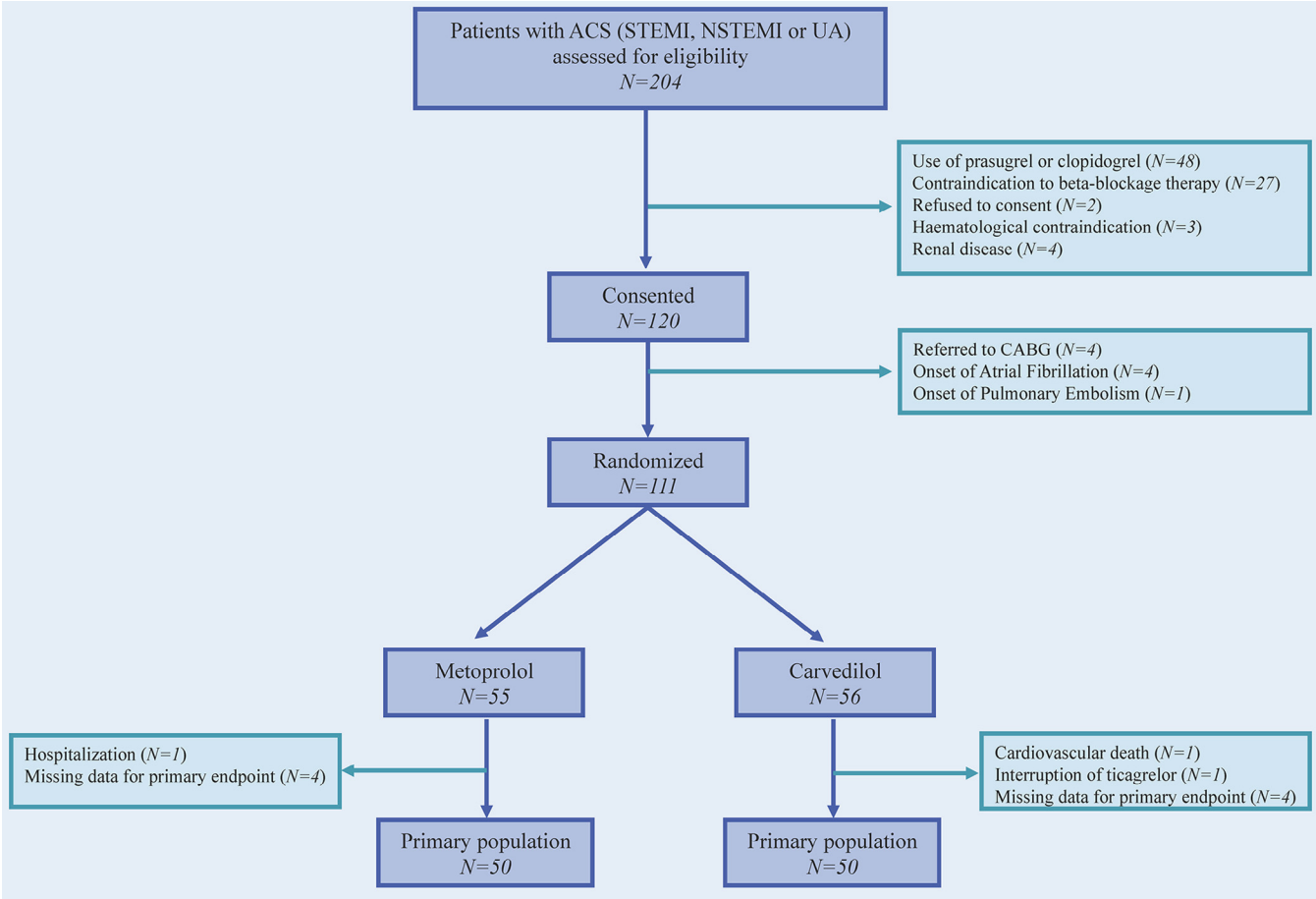

Figure 1. Flowchart of the study. ACS, acute coronary syndrome; STEMI = ST-segment elevation myocardial infarction; NSTEMI = non–ST-segment elevation myocardial infarction; UA = unstable angina.

Table 2 lists the mean value and SD of MPA induced by epinephrine and ADP in the 2 groups, at baseline (T0) and at 30 days (T30). At baseline, results of the platelet assessment were comparable between the 2 groups, with the expected platelet inhibition as a result of the DAPT. At T30, the results of MPA were significantly higher than baseline in the 2 groups for all proaggregative stimuli. Interestingly, patients in the carvedilol group showed an epinephrine-induced MPA at T30 significantly lower than that observed in the metoprolol population (23.5 ± 10.2 vs 28.7 ± 14.3, p = 0.040) (Figure 2). In secondary analyses, when ADP was used as proaggregative stimulus, a trend toward reduction in the carvedilol group compared with metoprolol group was observed and was more pronounced with higher ADP concentration (10 μM ADP 19.12 ± 12.40 vs 22.57 ± 13.59, p = 0.19; 20 μM ADP 19.42 ± 13.84 vs 24.16 ± 13.62, p = 0.088). Overall, no patient, but one in the metoprolol group, showed a high on-treatment residual platelet reactivity (MPA >59% with ADP stimulation).

Clinical outcomes at 30 days, in terms of ischemic and bleeding end points, are shown in Table 2. No death, myocardial infarction, or urgent revascularization occurred. Two patients in the carvedilol group underwent a new hospitalization within 30-day follow-up, both of them for heart failure. Notably, 1 minor bleeding was observed in the metoprolol group (blood loss from pre-existing hemorrhoids) without need for modification of DAPT and no major bleeding events were reported.

Discussion

There is evidence that BB can inhibit the catecholamine-induced platelet aggregability, but there is limited evidence regarding the role of specific BB agents to affect platelet activity and there are no data on ACS patients treated with contemporary DAPT including aspirin and a new more potent P2Y12 inhibitor. To our knowledge, this is the first randomized, open-label study on patients with ACS receiving aspirin and ticagrelor to compare carvedilol, a nonselective BB, with metoprolol, a selective β_1-blocker. We found that carvedilol significantly reduced residual platelet aggregation 30 days after the index event compared with metoprolol. Notably, this benefit was additional to DAPT and was observed despite the therapy with a new potent P2Y12 inhibitor (i.e., ticagrelor). This finding might have important clinical implications in the daily practice when choosing the type of BB agent to be used in this setting of patients.

BBs competitively inhibit the myocardial effects of circulating catecholamines and reduce myocardial oxygen consumption by lowering heart rate, blood pressure, and myocardial contractility. They are recommended for secondary

Table 1
Baseline, angiographic, and procedural characteristics according to beta-blockage therapy

Variable	Carvedilol (n = 50)	Metoprolol (n = 50)	P value
Age (years)	57.8 ± 9.5	56.8 ± 9.8	0.600
Men	41 (82%)	39 (78%)	0.617
Smoker	36 (72%)	36 (72%)	1.000
Hypertension	29 (58%)	25 (50%)	0.422
Hypercholesterolemia*	23 (46%)	17 (34%)	0.221
Diabetes Mellitus	10 (20%)	8 (16%)	0.603
BMI (kg/m^2)	27.9 ± 4.9	28.5 ± 4.5	0.596
Previous MI	10 (20%)	6 (12%)	0.275
Previous PCI	9 (18%)	6 (12%)	0.401
Previous TIA/Stroke	1 (2%)	1 (2%)	0.977
Previous coronary bypass	2 (4%)	1 (2%)	0.558
Creatinine (mg/dl)	0.92 ± 0.23	0.87 ± 0.16	0.199
Creatinine clearance (ml/min)†	100.8 ± 32.4	109.8 ± 31.7	0.165
COPD	8 (16%)	7 (14%)	0.779
Clinical presentation			
Killip class >1	7 (14%)	7 (14%)	1.000
LVEF (%)	45.0 ± 6.3	44.9 ± 5.7	0.921
RWMS	1.6 ± 0.3	1.7 ± 0.3	0.559
Heart rate (bpm)	71.8 ± 9.1	74.4 ± 10.6	0.196
Systolic BP (mm Hg)	122.6 ± 17.2	123.0 ± 17.4	0.921
Diastolic BP (mm Hg)	79.1 ± 9.3	76.7 ± 11.3	0.256
STEMI	31 (62%)	31 (62%)	1.000
NSTEMI	18 (36%)	19 (38%)	0.836
Unstable angina pectoris	1 (2%)	0 (0%)	0.315
Laboratory parameters			
Hemoglobin (g/dl)	13.8 ± 1.5	14.0 ± 1.5	0.520
Hematocrit (%)	41.7 ± 4.6	41.8 ± 4.1	0.984
Platelet count (×10^3/ml)	210.2 ± 56.1	230.2 ± 62.9	0.097
Cardiovascular medications			
Proton Pump Inhibitors	49 (98%)	50 (100%)	0.315
ACEi/ARBs	25 (50%)	32 (64%)	0.157
Statins	49 (98%)	48 (96%)	0.558
Diuretics	3 (6%)	2 (4%)	0.630
Insulin	4 (8%)	2 (4%)	0.371
Oral antidiabetics	8 (16%)	6 (12%)	0.509
Thrombolysis	5 (10%)	2 (4%)	0.240
Randomized beta-blocker dosage			
Mean (standard deviation)	13.5 ± 6.5	98.0 ± 26.6	-
Median (range)	12.5 (6.25–25)	100 (50–200)	-
Periprocedural antithrombotics			
UFH	49 (98%)	47 (94%)	0.307
Bivalirudin	0 (0%)	1 (2%)	0.315
Glycoprotein IIb/IIIa inhibitors	15 (30%)	20 (40%)	0.366
Culprit coronary artery			
Left main	0 (0%)	1 (2%)	0.315
Left anterior descending artery	23 (46%)	29 (58%)	0.230
Left circumflex	12 (24%)	7 (14%)	0.202
Right coronary artery	13 (26%)	13 (26%)	>0.999
Multi-vessel coronary disease	13 (26%)	17 (34%)	0.383
TIMI flow pre-PCI			
0	20 (40%)	16 (32%)	0.405
1	5 (10%)	7 (14%)	0.538
2	12 (24%)	9 (18%)	0.461
3	13 (26%)	18 (36%)	0.280
TIMI flow post-PCI			
0	0 (0%)	0 (0%)	-
1	0 (0%)	0 (0%)	-
2	1 (2%)	0 (0%)	0.315
3	49 (98%)	50 (100%)	0.315
Procedural details			
Stent	47 (94%)	49 (98%)	0.307
Diameter of stent (mm)	3.11 ± 0.47	3.12 ± 0.35	0.828
Length of stent (mm)	21.93 ± 7.37	20.31 ± 7.01	0.270

Values are n (%) or mean ± SD.

ACEi = angiotensin-converting enzyme inhibitors; ARB = angiotensin receptor blocker; BMI = body mass index; BP = blood pressure; COPD = chronic obstructive pulmonary disease; HR = heart rate; LVEF = left ventricle ejection fraction; MI = myocardial infarction; NSTEMI = non–ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; RWMS = regional wall motion score; STEMI = ST-segment elevation myocardial infarction; TIA = transient ischemic attack; TIMI = Thrombolysis In Myocardial Infarction; UFH = unfractionated heparin.

* Hypercholesterolemia refers to patients receiving lipid-lowering therapy at baseline (before index event).

† Estimated creatinine clearance was calculated according to Cockcroft-Gault formula.

Table 2
Results of platelet aggregation induced by epinephrine and ADP with LTA and 30-day clinical outcomes

	Carvedilol (n = 50)	Metoprolol (n = 50)	p
Epinephrine 10 µmol/L			
T0	18.96 ± 9.05	18.32 ± 9.21	0.727
T30	23.52 ± 10.25*	28.72 ± 14.37*	0.040
ADP 10 µmol/L			
T0	13.26 ± 9.83	14.30 ± 9.40	0.590
T30	19.12 ± 12.40*	22.57 ± 13.59*	0.190
ADP 20 µmol/L			
T0	14.42 ± 9.43	15.98 ± 10.08	0.426
T30	19.42 ± 13.84*	24.16 ± 13.62*	0.088
Clinical outcomes			
Death	0	0	-
Myocardial Infarction	0	0	-
Stent Thrombosis	0	0	-
Stroke	0	0	-
Urgent TVR	0	0	-
Intracranial bleeding	0	0	-
TIMI major bleed	0	0	-
TIMI minor bleed	0	1 (2%)	0.315
BARC type 3 or 5	0	0	-
BARC type 2	0	1 (2%)	0.315
Hospitalization	2 (4%)	0	0.153

Values are expressed as % of maximum platelet aggregation (MPA) ± SD.

* p <0.05 versus T0.

BARC = Bleeding Academic Research Consortium; TIMI = Thrombolysis In Myocardial Infarction; TVR = target vessel revascularization.

prevention in patients with ACS, regardless of reperfusion therapy, given their beneficial effects on prognosis.[5–7] Nowadays, many BB compounds are available, with different pharmacologic profiles. Generally, BBs without intrinsic sympathomimetic activity are suggested, especially β-1 blockers such as sustained release metoprolol succinate, bisoprolol, or the β-1 and α-1 blocker carvedilol, which are also the ones demonstrating mortality benefits in patients with heart failure and systolic dysfunction.[5] Among them, often β-1 blockers

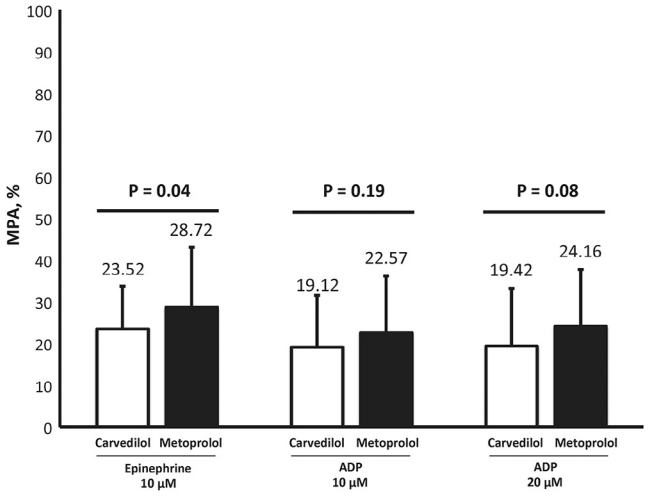

Figure 2. Maximum platelet aggregation 30 days after acute coronary syndrome according to the randomized treatment with carvedilol or metoprolol. MPA = maximum platelet aggregation.

are chosen to reduce pulmonary complications related to bronchospasm; however, there is no preferential guideline recommendation of 1 molecule over the other;[5–7] thus, our study could be relevant to provide useful insights on this topic and to help guide the selection of the optimal BB type. The early administration of BB agents in myocardial infarction is supported by several studies that demonstrated favorable effect in reducing blood pressure, heart rate, arrhythmias, and improving left ventricle systolic function. Different studies and a recent meta-analysis have suggested that, besides these well-known beneficial clinical effects, BBs could exert their protective action by also inhibiting platelet aggregation.[8–10]

The effects of circulating catecholamines on platelet reactivity have been extensively investigated, reporting an increased ADP- and collagen-induced platelet aggregation in conditions of elevated adrenergic system activity, such as myocardial infarction and angina. Catecholamines are supposed to exhibit their proaggregating effects, interacting mainly with α_{2A} adrenoceptors, whose stimulation determines the inhibition of adenylate cyclase through G_i protein.[11,20] Platelet surface also exhibits a small amount of β_2-receptor, whose activation results in AMP cyclic (cAMP) formation, which is known to inhibit platelet aggregation through mechanisms involving Ca^{++}.[12] β_2-receptor could be targeted by nonselective BB, with a consequent inhibition of platelets cAMP formation, decrease of calcium availability, and in turn platelet activation. Conversely, the use of selective β_1-blockers would protect from this mechanism, as suggested by Winther et al[21] that showed higher levels of plasma and platelet cAMP and lower platelet aggregation in patients treated with metoprolol compared with propranolol. However, compared with placebo, metoprolol did not show any reduction of ADP-induced platelet aggregation in patients with myocardial infarction.[22] Therefore, the antiplatelet effect of BB is only partially explained by the direct interaction with the platelet adrenoceptors, but there are also other indirect mechanisms. Indeed, it is known that BBs are able to decrease plasma levels of catecholamines, with a more pronounced effect of nonselective compounds.[23,24] In particular, in patients with heart failure, the long-term therapy with carvedilol but not metoprolol reduced coronary sinus norepinephrine levels.[13]

In addition, some nonselective BBs, such as carvedilol and propranolol, have shown a membrane-stabilizing effect that affects Ca^{++} availability in the platelets and inhibits platelet aggregation.[14,25] Petrikova et al[26,27] investigated the antiplatelet activity of carvedilol and showed that, besides the antagonistic effects on α-adrenoceptors, carvedilol, thanks to its lipophilicity, inhibits platelet aggregation and thromboxane B2 formation through the interaction with membrane macromolecules, such as phospholipids, ion channels, enzymes, and other molecules.

In accordance with the available data, our study demonstrates that patients receiving carvedilol showed lower epinephrine-induced platelet aggregation than those treated with metoprolol after ACS. Based on the results of LTA, carvedilol was not able to significantly reduce ADP-induced platelet aggregation. Also, this finding is in accordance with previous studies[27,28] that demonstrated an in vitro dose-dependent reduction of aggregation when epinephrine was used as stimulus, whereas carvedilol was least effective in platelets stimulated with ADP even at high concentrations.

Notably, the baseline level of platelet aggregation is lower than T30 values. This finding seems to be consistent with pharmacodynamic studies of patients treated with ticagrelor, which showed that, after 6 weeks of treatment, the inhibitor effect on platelet aggregation measured with LTA was slightly lower than 24 hours after the loading dose.[19] In our study, baseline aggregation was performed within 24 to 48 hours since the coronary angiography, so platelet aggregation could be still influenced by different kinds of medications.

This study explored platelet aggregation and was not powered to assess clinical events. However, the 2 BBs investigated are routinely used in the daily practice and none of them is expected to significantly impact on ischemic and bleeding events compared with the other. Additionally, it is well known that DAPT with more potent P2Y12 inhibitors is the standard of care after ACS and percutaneous coronary intervention,[29,30] and platelet reactivity is associated with thrombotic events; thus, its reduction could be beneficial in reducing thrombotic complications.[2] Our data were focused on ticagrelor-based DAPT and cannot be extended to patients receiving different DAPT regimens (i.e., prasugrel or clopidogrel) or single antiplatelet therapy associated with anticoagulation therapy (i.e., patients with atrial fibrillation or mechanic valves).

In conclusion, our study showed that in patients with ACS receiving contemporary DAPT with aspirin and ticagrelor, the use of carvedilol, a nonselective BB, is associated with a reduced residual platelet aggregation compared with metoprolol, a selective β_1-blocker. This finding might have important clinical implications, given the enhanced adrenergic signaling in the setting of ACS and its known association with platelet reactivity, thrombotic events, and long-term outcomes. However, further studies are needed to evaluate the translational effect of this benefit on clinical outcomes.

Disclosures

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Part 2

Trade-off for ischemia and bleeding after percutaneous coronary interventions: which is the optimal regimen of antiplatelet therapy?

Personalizing type and duration of DAPT

EuroIntervention 2017;13:717-733

State of the art: duration of dual antiplatelet therapy after percutaneous coronary intervention and coronary stent implantation – past, present and future perspectives

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KEYWORDS

- dual antiplatelet therapy
- percutaneous coronary intervention
- randomised trials

Abstract

Evidence from studies published more than 10 years ago suggested that patients receiving first-generation drug-eluting stents (DES) needed dual antiplatelet therapy (DAPT) for at least 12 months. Current evidence from randomised controlled trials (RCT) reported within the past five years suggests that patients with stable ischaemic heart disease who receive newer-generation DES need DAPT for a minimum of three to six months. Patients who undergo stenting for an acute coronary syndrome benefit from DAPT for at least 12 months, but a Bayesian network meta-analysis confirms that extending DAPT beyond 12 months confers a trade-off between reduced ischaemic events and increased bleeding. However, the network meta-analysis finds no credible increase in all-cause mortality if DAPT is lengthened from three to six months to 12 months (posterior median odds ratio [OR] 0.98; 95% Bayesian credible interval [BCI]: 0.73-1.43), from 12 months to 18-48 months (OR 0.87; 95% BCI: 0.64-1.17), or from three to six months to 18-48 months (OR 0.86; 95% BCI: 0.63-1.21). Future investigation should focus on identifying scoring systems that have excellent discrimination and calibration. Although predictive models should be incorporated into systems of care, most decisions about DAPT duration will be based on clinical judgement and patient preference.

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Abbreviations

ACS	acute coronary syndrome
ARCTIC-Interruption	Assessment by a double Randomisation of a Conventional antiplatelet strategy versus a monitoring-guided strategy for drug-eluting stent implantation and, of Treatment Interruption versus Continuation 1 year after stenting
BES	biolimus-eluting stent
BMS	bare metal stent(s)
CAD	coronary artery disease
CAPRIE	a randomised, blinded, trial of Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events
CHARISMA	Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance
CLASSICS	Clopidogrel Aspirin Stent International Cooperative Study
CREDO	Clopidogrel for the Reduction of Events During Observation
CURE	Clopidogrel in Unstable angina to prevent Recurrent Events
DAPT	dual antiplatelet therapy
DES	drug-eluting stent(s)
DES-LATE	Optimal Duration of Clopidogrel Therapy with DES to Reduce Late Coronary Arterial Thrombotic Events
EXCELLENT	Efficacy of Xience/Promus Versus Cypher in rEducing Late Loss After stENTing
FANTASTIC	Full Anticoagulation Versus Aspirin and Ticlopidine
I-LOVE-IT 2	Evaluate Safety and Effectiveness of the Tivoli® DES and the Firebird DES for Treatment of Coronary Revascularization
ISAR	Intracoronary Stenting and Antithrombotic Regimen study
ISAR-SAFE	Intracoronary Stenting and Antithrombotic Regimen: Safety And EFficacy of 6 Months Dual Antiplatelet Therapy After Drug-Eluting Stenting
ITALIC	Is There A LIfe for DES after discontinuation of Clopidogrel
IVUS-XPL	Impact of Intravascular Ultrasound Guidance on Outcomes of Xience Prime Stents in Long Lesions
LEADERS-FREE	Prospective Randomised Comparison of the BioFreedom Biolimus A9 Drug-Coated Stent Versus the Gazelle Bare-Metal Stent in Patients at High Bleeding Risk
MACCE	major adverse cardiac and cerebrovascular events
MATTIS	Multicentre Aspirin and Ticlopidine Trial after Intracoronary Stenting
MI	myocardial infarction
NIPPON	Nobori Dual Antiplatelet Therapy as Appropriate Duration
OPTIDUAL	OPTImal DUAL antiplatelet therapy after drug-eluting stent implantation
OPTIMIZE	Optimised Duration of Clopidogrel Therapy Following Treatment with the Endeavor Zotarolimus-Eluting Stent in Real-World Clinical Practice
PCI	percutaneous coronary intervention
PRODIGY	PROlonging Dual-antiplatelet treatment after Grading stent-induced Intimal hyperplasia studY
RCT	randomised controlled trial(s)
RESET	REal Safety and Efficacy of 3-month dual antiplatelet Therapy following Endeavor zotarolimus-eluting stent implantation
SECURITY	Second-generation Drug-eluting Stent Implantation Followed by 6- versus 12-month dual antiplatelet therapy
ST	stent thrombosis
STARS	Stent Anticoagulation Restenosis Study
ZEUS	Zotarolimus-eluting Endeavor sprint stent in Uncertain DES candidates

Introduction

In its 40th anniversary, percutaneous coronary intervention (PCI) has achieved excellent early and late outcomes thanks to advances in technologies, operator expertise, and antithrombotic therapy. Although the advent of drug-eluting stents (DES) has been crucial for the overall success of PCI, stent thrombosis (ST) and myocardial infarction may occur unless patients adhere to a strict regimen of dual antiplatelet therapy (DAPT), which consists of concurrent use of aspirin and a $P2Y_{12}$ platelet receptor blocker. The use of DAPT, however, confers an increased risk of major bleeding that in some instances is fatal.

The purpose of the current report is to review the early developments that have led to replacement of anticoagulation therapy with DAPT after stent implantation, current recognition of the prognostic significance of major bleeding, and ultimate awareness that the duration of DAPT after DES implantation must be prescribed on an individual basis.

The past

On 16 September 1977, Andreas Grüntzig performed the first coronary balloon angioplasty in a 37-year-old man with a proximal stenosis in the left anterior descending artery. The result was successful and durable[1,2]. However, in the series of 624 patients undergoing coronary angioplasty between 1977 and 1981 in Zurich and Atlanta, emergency operations due to sudden closure or spasm of the artery occurred in 5% and Q-wave myocardial infarction (MI) in 3%, but no in-hospital deaths occurred[1]. At that time, the optimal pharmacotherapy to prevent failure and complications remained uncertain[3]. Early investigators recommended the use of warfarin as long-term adjunctive therapy after femoropopliteal transluminal angioplasty and its use was also adopted for the treatment of acute MI, whereas other studies demonstrated benefit

from the administration of aspirin after MI[4]. In a randomised comparison of aspirin and coumadin in 248 PCI patients, aspirin did not reduce recurrent stenoses as compared with coumadin at nine months of follow-up (27% vs. 36%; p=not significant)[4].

In subsequent studies, evidence supported benefits of aspirin therapy after MI or PCI[5], but at the same time balloon angioplasty seemed to be limited by a high incidence of abrupt vessel closure after dilatation and requirement for reintervention for restenosis. The implantation of an expandable metal stent to maintain vessel patency after balloon dilatation emerged as the solution to these problems[6,7]. Nevertheless, the inherent thrombogenicity of metal stents that were in contact with circulating blood resulted in thrombotic stent occlusion despite aggressive anticoagulant therapy. In a pivotal trial, angiographic follow-up after placement of a self-expanding coronary artery stent showed that early occlusion occurred in approximately 20% of cases[8]. Additionally, haemorrhagic and peripheral vascular complications due to the intensive anticoagulation adopted for the first few weeks after the procedure seriously limited the benefits of PCI.

Two studies in 1995 were the first to suggest that the combination of aspirin and ticlopidine was a safe replacement for anticoagulant therapy after coronary stent implantation[9,10]. In 1996, ISAR suggested advantages of DAPT over anticoagulation by showing that combined antiplatelet therapy (aspirin plus ticlopidine) after the placement of coronary stents reduced the incidence of both cardiac events and haemorrhagic and vascular complications compared with conventional anticoagulation-based therapy (intravenous heparin, phenprocoumon, and aspirin)[11]. Later, STARS demonstrated that DAPT was superior to anticoagulant therapy after implantation of bare metal stents (BMS) and reduced ST by 85% as compared with aspirin alone[12]. In the FANTASTIC study, which studied both elective and unplanned coronary stenting, DAPT with aspirin and ticlopidine significantly reduced rates of bleeding and subacute stent occlusion compared with conventional anticoagulation[13]. In the MATTIS study, high-risk patients receiving aspirin and ticlopidine after coronary stenting had significantly reduced bleeding and vascular complications and there was a marked trend towards decreased cardiac events compared with aspirin and anticoagulation[14]. At the same time, clopidogrel appeared, which was a new thienopyridine derivative that had fewer side effects than ticlopidine. The CAPRIE trial suggested that clopidogrel could be used in place of aspirin to prevent ischaemic stroke, MI or vascular death in patients at risk of ischaemic events[15]. Then the CLASSICS study supported replacement of ticlopidine by clopidogrel after coronary stenting due its safer profile[16]. The CURE study confirmed the efficacy and safety of clopidogrel added to aspirin in patients with ACS and in those undergoing PCI[17,18].

Evidence from early studies thus suggested that a strategy based on aspirin and a thienopyridine was substantially more effective and better tolerated than anticoagulation, thus facilitating a widespread adoption of stenting in clinical practice. Indeed, the last two decades have established the pivotal role of DAPT in preventing both stent- and non-stent-related ischaemic events after PCI compared with single antiplatelet therapy or anticoagulation. Recently, new hypotheses have been studied or are still under evaluation (i.e., very short DAPT regimens and aspirin interruption during follow-up)[5]. However, the optimal duration of DAPT after stent implantation has been a matter of contention for years. Indeed, in parallel with the evolution of the DAPT regimens, stent technology has evolved from BMS to first-generation DES, a change that has implications for DAPT regimens. When clopidogrel was approved in 1997 by the U.S. Food and Drug Administration (FDA), it was recommended for two weeks after BMS implantation[19] and then later for four weeks[16]. When sirolimus-eluting stents were approved in 2003, the labelling recommended three months of clopidogrel because that is how the agent had been used in clinical trials[20]. When paclitaxel-eluting stents were approved in 2004, the labelling recommended six months of clopidogrel, again based on how it had been used in trials[21]. Later, this DAPT duration was seriously questioned due to increasing safety concerns that were initially related to late and very late ST in first-generation DES, but also to an increase in death and MI. Indeed, 2006 was a critical year for evidence on first-generation DES, but an expert FDA panel concluded that DES appeared to increase the risk of late stent thrombosis, but not the risk of death or MI[22]. At that time, the concerns about DES led to the empirical recommendation of 12 months of DAPT. The panel also agreed on the urgent need for studies on ST and the duration of DAPT[22].

The recommendation of 12 months of DAPT was maintained in the following few years with the sole exception of patients in whom the risk of bleeding outweighed the anticipated benefit. Based on previous findings from the PCI-CURE (stenting comprised 80% of the PCI cases, but all stents were BMS and the mean duration of DAPT was nine months) and CREDO studies (all BMS; only 63% of patients assigned to clopidogrel finished one year of therapy)[18,23], and observational studies reporting a persistent risk of ST beyond six months after stenting, particularly in the context of DAPT cessation[24-26], the 2011 American guideline recommended a minimum DAPT duration of at least 12 months after DES implantation[27]. The European guidelines in 2010 recommended one month of DAPT after BMS in stable patients, but six to 12 months after DES, and 12 months in the case of ACS[28]. An additional relevant milestone of DAPT history was the introduction of the new $P2Y_{12}$ inhibitors, prasugrel in 2007[29] and ticagrelor in 2009[30], which further improved outcomes of ACS patients undergoing PCI and receiving DAPT.

Figure 1 shows the main steps in the advent and evolution of DAPT, and **Figure 2** shows the mechanism of action of DAPT.

The present

GUIDELINES, TRIALS AND META-ANALYSES OF DAPT DURATION

The guidelines from the European Society of Cardiology recommend at least one month of DAPT for stable ischaemic heart disease (SIHD) treated with BMS and at least six months if

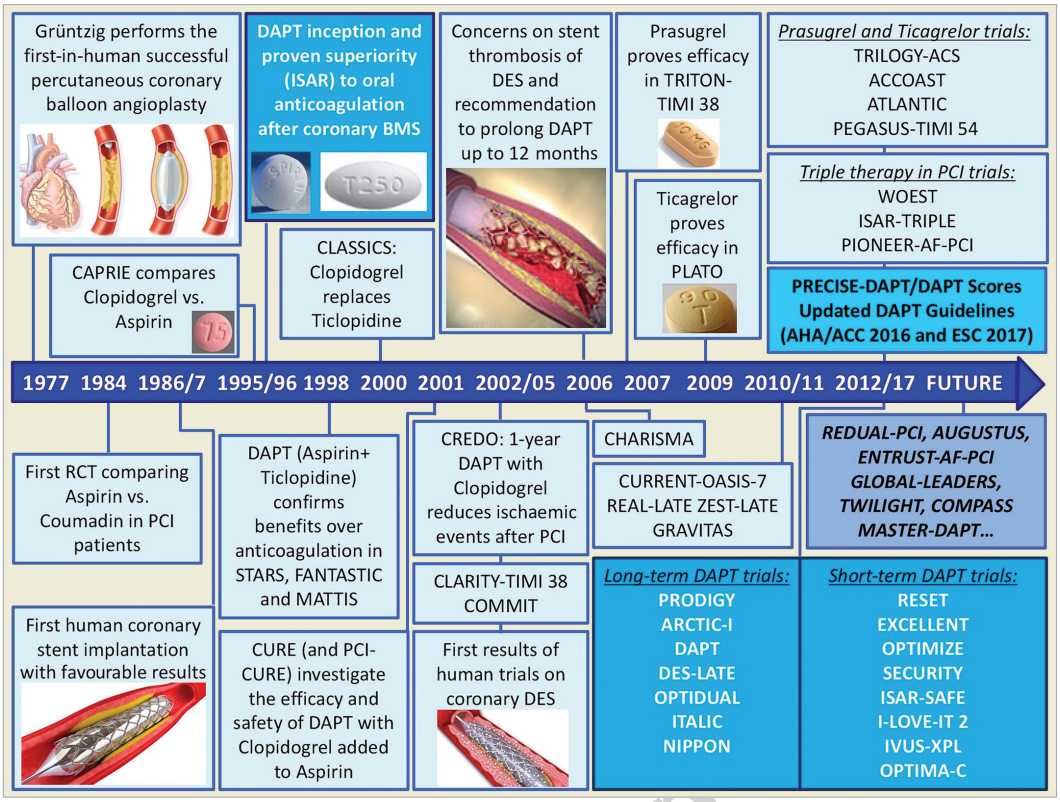

Figure 1. *History of DAPT in PCI.*

treated with DES, while in ACS patients a 12-month DAPT was recommended, suggesting that shorter courses in patients with SIHD or longer courses in patients with a history of ACS may be considered[31,32]. A 2016 focused update on DAPT from the American College of Cardiology/American Heart Association[33] recommended a minimal mandatory duration of DAPT of six months after implantation of newer-generation DES in patients with SIHD and replaced the 2011 guideline recommendation of at least 12 months[27]. The abbreviated course of therapy for patients with SIHD seemed reasonable, because the risk of ST with newer-generation DES was lower than it was with first-generation DES[34].

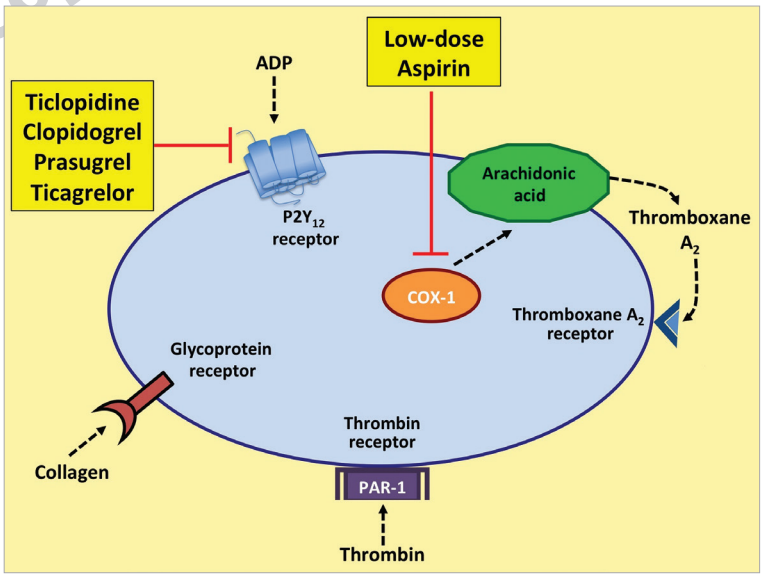

Figure 2. *Sites of action of DAPT. DAPT includes aspirin, a cyclooxygenase-1 (COX-1) inhibitor, and a $P2Y_{12}$ receptor inhibitor (ticlopidine, clopidogrel, prasugrel, or ticagrelor). ADP: adenosine diphosphate; PAR-1: protease-activated receptor-1*

Since publication of the DAPT update, new evidence regarding DAPT duration has emerged. Data from 14 RCT **(Figure 3)** of patients undergoing implantation of DES, with more than two thirds of subjects receiving newer-generation stents **(Table 1)**, and randomised to either prolonged or short-course DAPT, have been published[35-50]. The largest RCT of DAPT duration, the DAPT trial[43], randomly assigned 9,961 patients to prolonged DAPT of 2.5 years or to short-course DAPT of 12 months after DES implantation. Prolonged DAPT was associated with a reduced rate of ST (0.4% vs. 1.4%; HR 0.29, 95% CI: 0.17-0.48, p<0.001), MACCE (4.3% vs. 5.9%; HR 0.71, 95% CI: 0.59-0.85, p<0.001) and reduced MI (2.1% vs. 4.1%, HR 0.47, p<0.001) but was associated with a borderline increased risk of death from any cause (2.0% vs. 1.5%, HR 1.36, 95% CI: 1.00-1.85, p=0.05) and increased moderate or severe bleeding (2.5% vs. 1.6%, p=0.001).

When aggregate data from the 14 RCT including the DAPT trial are pooled **(Appendix)**, short compared with prolonged DAPT is associated with no significant difference in mortality (odds ratio [OR] 0.85; 95% CI: 0.72-1.01) and reduced major bleeding (OR 0.68, 95% CI: 0.55-0.82). On the other hand, as shown in **Figure 4**, shorter courses of DAPT are associated with more cases of MI (OR 1.37, 95% CI: 1.12-1.67) and ST (OR 1.69, 95% CI: 1.13-2.54).

The absence of a mortality benefit from prolonged DAPT may seem counterintuitive given the reductions in MI and ST, but these findings may reflect a temporal attenuation in mortality risk attributable to ST. While acute and subacute ST are associated with mortality rates approaching 50%, late and very late ST are associated with mortality rates of about 10%[51]. As a result, it is possible that extension of DAPT beyond 12 months may simultaneously reduce both MI and ST without influencing mortality. On the other hand, major bleeding may be more dangerous than non-fatal MI[52-57]. Taken together, the reductions in mortality from lowering thrombosis with prolonging DAPT may be counterbalanced by an increase in mortality from bleeding complications[58].

Although a large number of meta-analyses of the DAPT RCT have been published[37,59-63], they have produced mixed results. Apparent discrepancies may have arisen because traditional meta-analyses comparing outcomes use a binary short-versus-long definition of DAPT duration. This poses a problem, even for

Trials of DAPT duration after PCI

14 studies, ~40,000 patients randomised

	Study	Patients	Hypothesis	Result
Trials of short-term DAPT	RESET	N=2,117	3 months non-inferior to 12 months	✔
	OPTIMIZE	N=3,199	3 months non-inferior to 12 months	✔
	EXCELLENT	N=1,443	6 months non-inferior to 12 months	✔
	SECURITY	N=1,399	6 months non-inferior to 12 months (stopped)	✔
	ISAR-SAFE	N=4,000	6 months non-inferior to 12 months (stopped)	✔
	I-LOVE-IT 2	N=1,829	6 months non-inferior to 12 months	✔
	IVUS-XPL	N=1,400	6 months non-inferior to 12 months	✔
Trials of long-term DAPT	PRODIGY	N=1,970 (DES=1,501)	24 months superior to 6 months	✖
	ARCTIC-I	N=1,259	>12 months (median 17) superior to 12 months	✖
	DAPT	N=9,961	30 months superior to 12 months	✔
	DES-LATE	N=5,045	36 months superior to 12 months	✖
	OPTIDUAL	N=1,385	48 months superior to 12 months (stopped)	✖
	ITALIC	N=1,850	6 months non-inferior to 12 and 24 months (stopped)	✔
	NIPPON	N=3,307	6 months non-inferior to 18 months (stopped)	✔

Figure 3. *Trials of DAPT after PCI. Trial result is reported according to whether the hypothesis was demonstrated (✔, green colour) or not (✖, red colour). Five trials are reported with yellow colour due to premature interruption of planned enrolment.*

Table 1. RCT summaries.

Study duration (comparison)	Year	Age	Diabetes (%)	Follow-up (mo)	Newer-generation stents (%)	Trial completion	Primary endpoint	Proportion with prior MI (%)	Proportion with current MI (%)	Expected event rate in control group (%)	Observed event rate in control group (%)
DES-LATE (36 vs. 12 mo)[35]	2010	62	28	24	30.0	Enrolment completed	Cardiac death, MI or stroke <24 hrs	3.9	23.3	2.7	2.6
PRODIGY (24 vs. 6 mo)[36,37]	2012	68	24	24	50.0	Enrolment completed	Death, MI or stroke	27.3	55.7	8.0	10.1
EXCELLENT (12 vs. 6 mo)[38]	2012	63	38	12	75.0	Enrolment completed	Cardiac death, MI, or ischaemia-driven TVR	5.1	27.4	10.0	4.5
RESET (12 vs. 3 mo)[39]	2012	62	29	12	85.0	Enrolment completed	Cardiac death, MI, ST, revasc, or bleeding	1.7	14.3	10.5	4.7
OPTIMIZE (12 vs. 3 mo)[40]	2013	62	35	12	100.0	Enrolment completed	NACCE - death, MI, stroke, or bleed	23.8	11.0	9.0	6.0
ARCTIC (17 vs. 12 mo)[41]	2014	64	33	12	63.0	Enrolment completed	Death, MI, ST, stroke, or urgent TVR	30.4	0.0	6.0	4.0
SECURITY (12 vs. 6 mo)[42]	2014	65	31	12	100.0	Stopped after 1,399 of 2,740 planned	Cardiac death, MI, ST, or stroke	20.7	0.0	6.0	4.5
DAPT (30 vs. 12 mo)[43]	2014	62	31	18	59.0	Enrolment completed	Coprimary: ST and MACCE	21.3	26.0	0.5/2.9	0.5/2.4
ITALIC (24 vs. 6 mo)[44,45]	2015	62	37	12	100.0	Stopped after 2,031 of 2,475 planned	Death, MI, urgent TVR, stroke, or major bleeding	15.1	7.5	3.0	1.5
ISAR-SAFE (12 vs. 6 mo)[46]	2015	67	25	12	72.0	Stopped after 4,005 of 6,000 planned	Death, MI, ST, stroke, or TIMI major bleed	25.2	18.4	10.0	1.5
OPTIDUAL (48 vs. 12 mo)[47]	2016	64	31	36	65.0	Stopped after 1,385 of 1,966 planned	Death, MI, stroke, or major bleeding	17.4	26.9	7.0	7.5
I-LOVE-IT 2 (12 vs. 6 mo)[48]	2016	60	23	18	100.0	Enrolment completed	Cardiac death, TVMI or TVR	16.9	24.5	8.3	5.9
IVUS-XPL (12 vs. 6 mo)[49]	2016	64	37	12	100.0	Enrolment completed	Cardiac death, MI, stroke, or TIMI major bleeding	5.0	15.6	7.0	2.2
NIPPON (18 vs. 6 mo)[50]	2017	67	38	12	100.0	Stopped after 3,307 of 4,598 planned	All-cause mortality, MI, stroke, and major bleeding	12	13.7	4.5	2.1

the traditional meta-analysis presented here **(Figure 4)**, because 12 months of DAPT was defined as "short" in four trials[35,41,43,47] and as "long" in seven trials[38-40,42,46,48,49]. Comparing outcomes at 12 months with outcomes at 12 months in a meta-analysis may unintentionally introduce noise in the statistical models. An alternative approach is to avoid 12-month versus 12-month comparisons, as was done by Navarese and colleagues in a stratified meta-analysis[62], but a Bayesian network meta-analysis may take advantage of the complete evidence base and provide an optimal approach to compare outcomes after short (three to six months), intermediate (12 months), and prolonged (18-48 months) durations of DAPT.

The use of network meta-analysis clarifies the differences in outcomes after short durations of three to six months, the standard comparator of 12 months, and prolonged durations of 18-48 months of DAPT **(Figure 5)** and reveals no credible reductions in mortality when DAPT was used for three to six months as compared with 12 months (posterior OR 0.98; 95% Bayesian credible interval [BCI]: 0.73-1.43), when DAPT was used for 12 months as compared with 18-48 months (OR 0.87; 95% BCI: 0.64-1.17), or when DAPT was used for three to six months as compared with 18-48 months (OR 0.86, 95% BCI: 0.63-1.21). Moreover, no difference in any major outcome was seen between three to six months and 12 months of DAPT, but bleeding was lower when DAPT was used for three to six months as compared with 18-48 months (OR 0.53, 95% BCI: 0.33-0.81), a finding that is counterbalanced by increased MI (OR 1.72, 95% BCI: 1.18-2.42) and ST (OR 2.56, 95% BCI: 1.23-5.03).

ISCHAEMIC AND BLEEDING RISKS OF DAPT AND DECISION MAKING ON DAPT DURATION

DAPT with aspirin and a $P2Y_{12}$ inhibitor reduces ischaemic recurrences but increases bleeding risk, which is related to the treatment

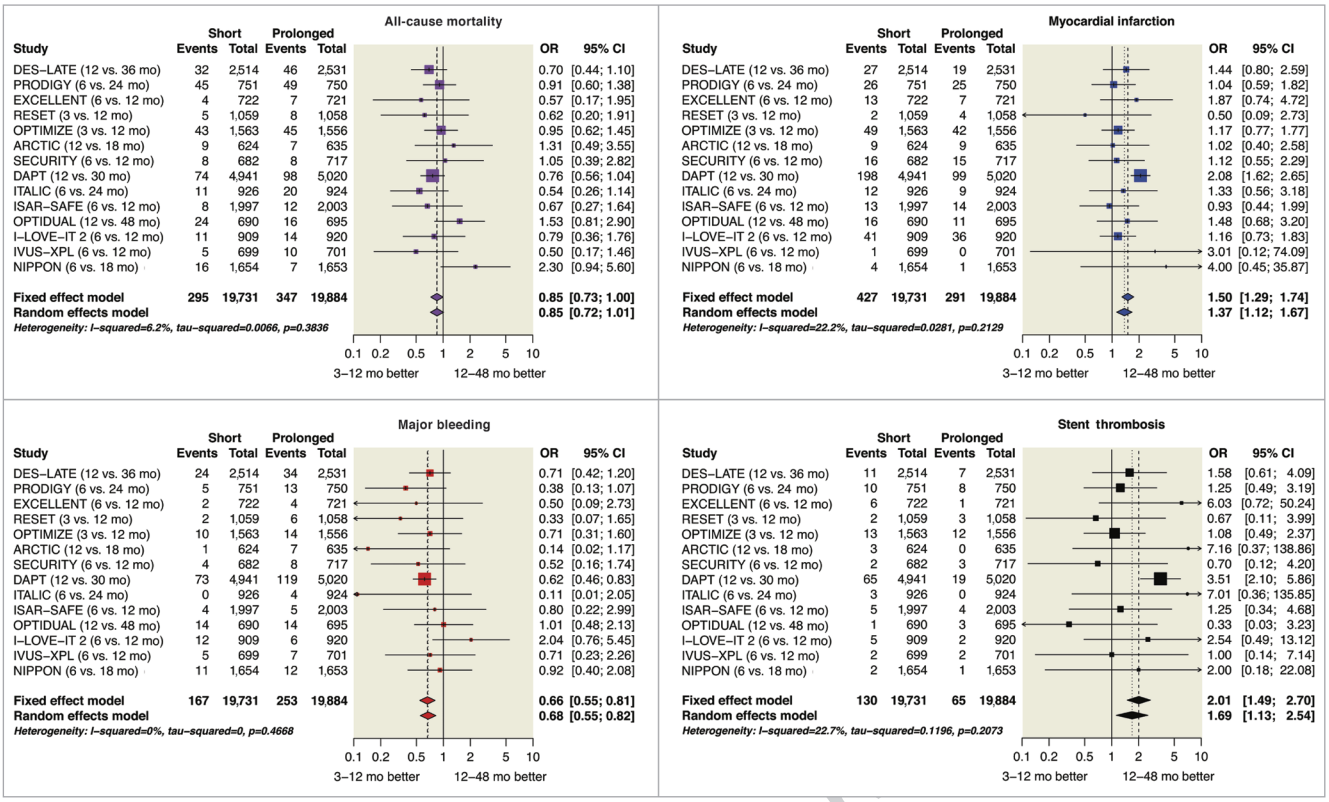

Figure 4. *Forest plot of event rates after prolonged or short course of DAPT after drug-eluting stent implantation. Original figures created with the open-source statistical program [R] 3.0.3 [85] and library package "meta" 3.8-0 [86]. Note: OPTIMA-C trial (6 vs. 12-month DAPT) was completed in 2015, presented orally in 2015 but not yet published, recently registered on clinicaltrials.gov (NCT03056118), and therefore not included here. Adapted with permission from the American Heart Association[87]. CI: confidence interval; OR: odds ratio*

duration. It is now clear that both ischaemic and bleeding risks can negatively impact on prognosis[52-58]. Therefore, the decision as to whether DAPT should be continued beyond one year after PCI requires preliminary clarification of the relative weight of ischaemic and bleeding events on mortality. Choosing between these two negative outcomes with similar frequencies and prognostic implications remains a great challenge. Tailored treatment algorithms maximising benefits over risks represent the only sensible way forward.

Some subgroups of patients undergoing DES implantation may benefit from extending DAPT, such as patients with prior MI[64,65], ACS at presentation[66,67], complex PCI[68] or peripheral arterial disease[69,70]. On the other hand, other patient characteristics may not benefit from extending DAPT, such as diabetes[71], chronic kidney disease[72], or advanced age[73]. In patients with high bleeding risk, a course of DAPT as short as one month has been found to be feasible[74,75].

Against this background, recently proposed tools derived from randomised studies, namely the DAPT and PRECISE-DAPT scores[76,77], may help to guide the decision making. The DAPT score was proposed for patients who tolerated 12 months of DAPT to select those eligible for treatment prolongation[78]. It was derived from 11,648 patients randomised in the entire DAPT database and is based on ischaemic and bleeding risk factors to help identify patients with greater expected benefit versus greater expected harm from prolonging DAPT over one year after stenting. It assigns 1 point each for MI at presentation, prior MI or PCI, diabetes, stent diameter less than 3 mm, smoking, and paclitaxel-eluting stent; 2 points each for history of congestive heart failure/low ejection fraction and vein graft intervention; −1 point for age 65 to 74 years; and −2 points for age ≥75 years. In patients with clinical predictive scores of 2 or higher, continued thienopyridine therapy was associated with an absolute risk reduction in MI or ST that was 8.2 times greater than the absolute risk increase in moderate or severe bleeding. On the other hand, among patients with scores lower than 2, DAPT prolongation was associated with an absolute increase in bleeding that was 2.4 times the absolute reduction in MI or ST[79]. Of note, the DAPT score is only applicable to patients who have completed one year of DAPT after coronary stent treatment without a major ischaemic or bleeding event and cannot be applied earlier, at the time of PCI, to select less than 12 months of treatment in patients at high bleeding risk.

More recently, a novel risk score (PRECISE-DAPT) has been proposed for the prediction of out-of-hospital bleeding in patients treated with DAPT using age, creatinine clearance, white blood cell count, haemoglobin, and history of bleeding[77]. High bleeding risk

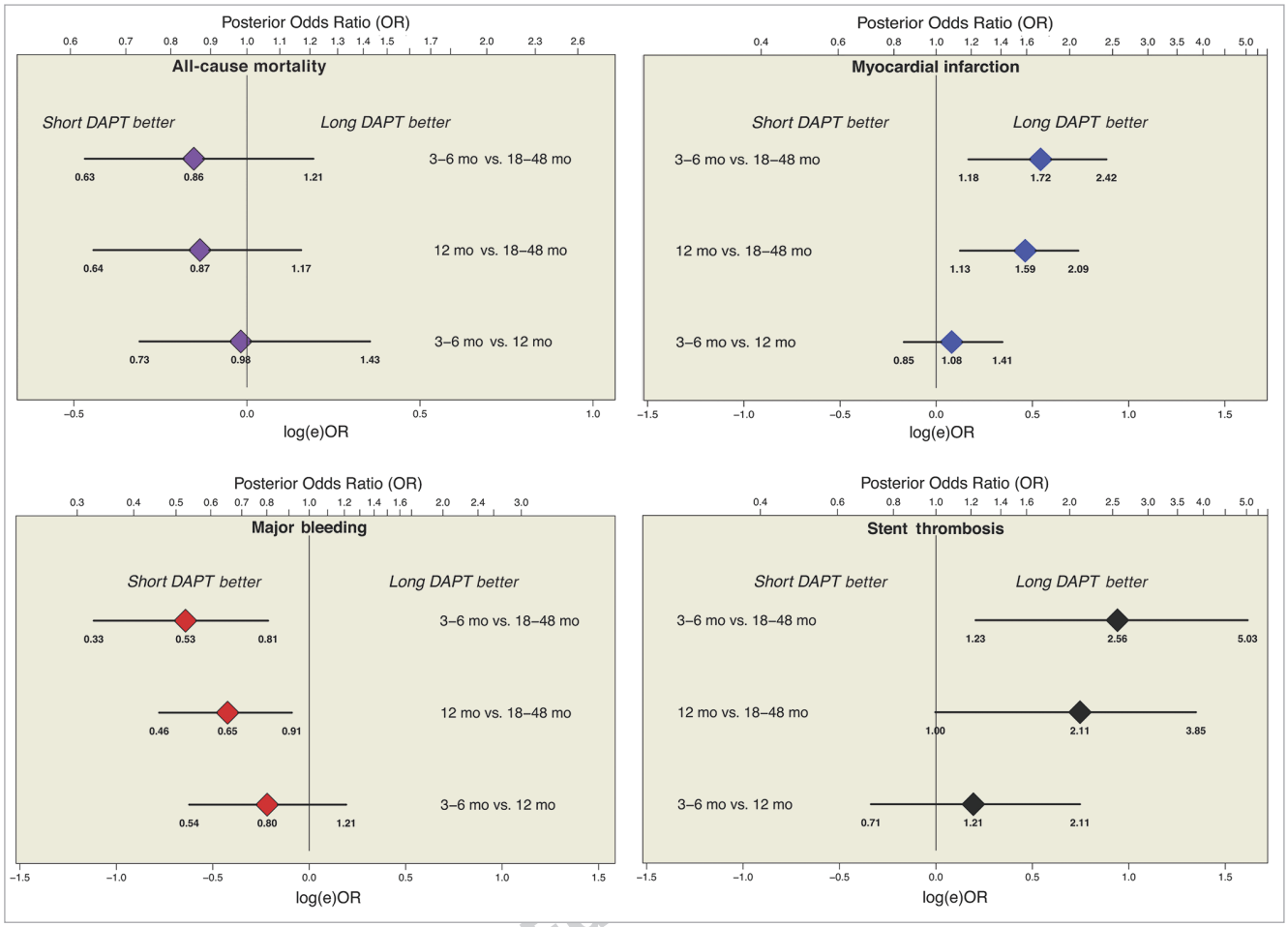

Figure 5. *Caterpillar plot of event rates and duration of DAPT. In a network meta-analysis, the number of events after each duration of DAPT was modelled using a binomial distribution, and the logit of each rate had a non-informative prior distribution to ensure that the posterior inference would be dominated by the likelihood of the data. Data presented as posterior mean odds ratio and 95% Bayesian credible intervals. Original figures were created with OpenBUGS (Bayesian inference using Gibbs sampling) and Markov chain Monte Carlo modelling, starting with non-informative priors centred at 0.000 with precision of 0.0001 and using 10,000 draws of the Gibbs chain, to ensure that the posterior distribution would be dominated by the likelihood, using described methods (Figure 7)* [85,87-89]*. Adapted with permission from the American Heart Association*[87]

patients (score ≥25) can be easily detected and might benefit from a shortened (i.e., <12 months) DAPT duration. Conversely, patients not at high bleeding risk (score <25) might receive a standard (i.e., 12 months) or prolonged (i.e., >12 months) treatment without being exposed to significant bleeding liability. The PRECISE-DAPT score is a simple bedside risk assessment tool, which can be easily implemented in everyday clinical practice and might be useful at the time of treatment initiation. A suggested algorithm for decision making based on these two scores is shown in **Figure 6**.

Authors' perspectives

We believe that, in low-risk patients who have undergone newer-generation DES implantation, a minimum DAPT duration of three to six months is sufficient to prevent stent-related thrombotic events. On the other hand, patients at high risk of thrombotic events[79] and low risk of bleeding[77] may derive a benefit from extension of DAPT beyond six to 12 months. Several scoring systems have appeared, but additional prospective investigation will be required to define their utility in everyday practice[80]. Future studies will need to identify optimal DAPT duration in patients who receive bioresorbable scaffolds[81].

In accordance with a personalised approach, patients at high bleeding risk on DAPT need special attention. The multicentre randomised open-label MASTER-DAPT trial (NCT03023020) is currently enrolling 4,300 high bleeding risk patients in >100 international centres to compare one-month DAPT with a more prolonged regimen consisting of at least three or six months of DAPT depending on whether the patient has or has not a concomitant indication to oral anticoagulation.

The future role of aspirin is also a matter of ongoing investigation[5]. Historical evidence comparing aspirin with placebo showed a great reduction in thrombotic risk and supports current

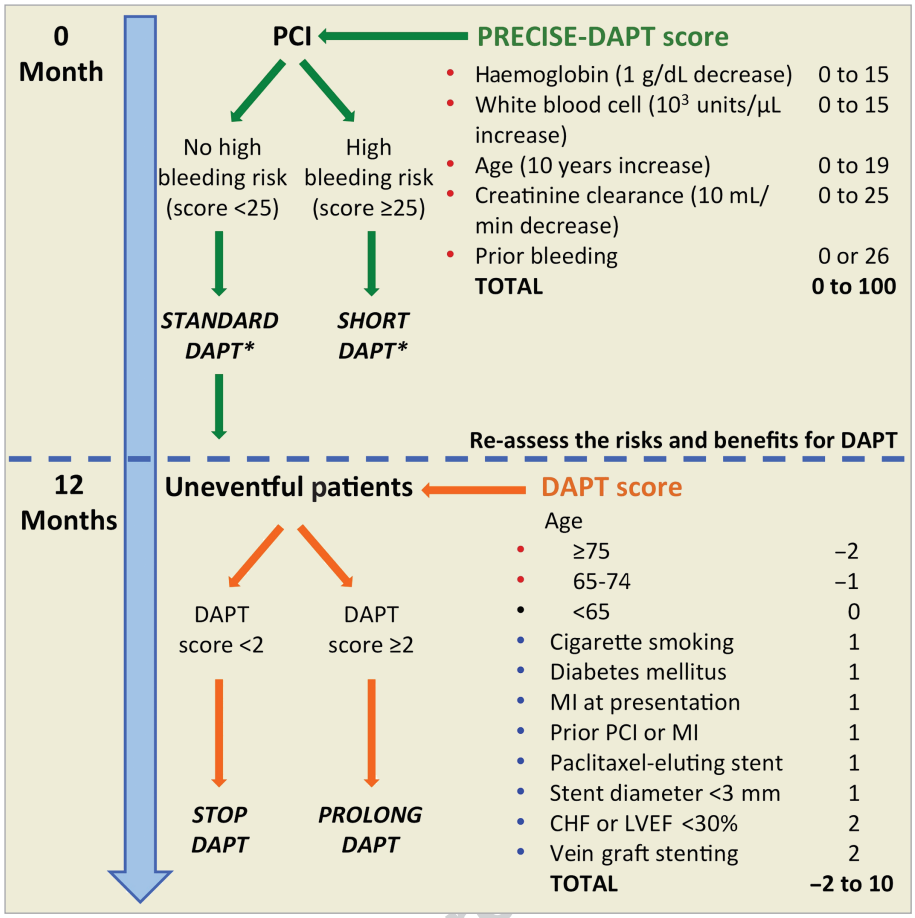

Figure 6. *Decision making on DAPT duration based on PRECISE-DAPT and DAPT scores. Variables included in the scores are associated with increased bleeding risk (red dot), increased ischaemic risk (blue dot) or neutral effect (black dot). *In the validation study, short-term DAPT consisted of three to six months of therapy and standard DAPT consisted of at least 12 months of DAPT.*

recommendations. However, $P2Y_{12}$ inhibitors have mostly been studied as adjuncts to aspirin; the comparison of single antiplatelet therapy with new $P2Y_{12}$ inhibitors alone versus DAPT after ACS or PCI for secondary prevention of atherothrombotic events is a new field of research. While up-to-date research has focused on DAPT and its duration, an alternative and original approach is the "less is more" paradigm exploring the role of monotherapy with new $P2Y_{12}$ inhibitors for efficacy and also for the reduction in risk of bleeding. The GLOBAL LEADERS (NCT01813435) trial is designed to assess the role of ticagrelor as a single antiplatelet agent after a short course of DAPT for the long-term prevention of adverse cardiac events, across a wide spectrum of patients, following BES implantation[82].

The subject of several ongoing trials is the comparison of treatment regimens combining an oral anticoagulant (warfarin or novel oral anticoagulants) with single or dual antiplatelet therapy for patients with atrial fibrillation and ACS or coronary stents[5,83,84]. The role of long-term secondary prevention with novel oral anticoagulant (NOAC)-based regimens (i.e., NOAC alone or in combination with aspirin) will be re-assessed and will probably impact on our future practice. The routine use of platelet function testing or genotyping to guide clinical decisions is not currently recommended, but future evidence may eventually provide new insights on this topic.

Finally, only selected DES have received CE mark approval for one-month DAPT for patients in need; however, this was based on limited data. Whether DAPT should be stent-specific or whether the newer-generation DES have different DAPT requirements remains a matter of ongoing investigation.

Conclusions

No single DAPT recommendation applies to every patient. In low-risk patients who receive a newer-generation DES, a minimum DAPT duration of three to six months may be sufficient to prevent early and largely stent-related thrombotic events. Patients who undergo stenting for acute coronary syndrome may benefit from DAPT for at least 12 months. Extension of DAPT beyond 12 months entails a trade-off between increased bleeding and reduced ischaemic events. Because RCT can only elucidate broad principles and scoring systems only consider a small number of risk factors for bleeding or ischaemic risk, the fine details of DAPT duration must be defined by clinicians for each patient on an individual basis.

Appendix. Methods

Aggregate data from 14 randomised controlled trials (RCT) of patients undergoing implantation of predominantly newer-generation drug-eluting stents (DES) and randomised to either shorter or longer courses of dual antiplatelet therapy (DAPT)[35-50] comprise the evidence base for the analysis of DAPT duration after DES implantation. As described previously[63,89], data from each trial had been abstracted in duplicate by two reviewers (J.A. Bittl and U. Baber). The present review uses the previously abstracted data to create the original forest plots and caterpillar plots using procedures and data shown here (**Table 2** and **Figure 7**).

BAYESIAN NETWORK META-ANALYSIS

Because each RCT performed two-way DAPT comparisons of DAPT durations that varied widely, an indirect three-way comparison of outcomes after short, medium or long durations of DAPT was carried out using Bayesian network meta-analysis. As described in detail, we modelled the number of deaths after short courses of DAPT in the seven studies that had both three- to six-month and 12-month arms[38-40,42,46,48,49] by using a binomial distribution. We assumed that the difference of log odds between a short (S) duration of DAPT and a 12-month duration (M) of DAPT from each study $\delta_{i,SM}$ followed a normal random effects dis-

Table 2. Data on mortality.

	s[]	t[]	r[]	nn[]	b[]
DES-LATE (36 vs. 12 mo)	1	2	32	2,514	1
DES-LATE (36 vs. 12 mo)	1	3	46	2,531	1
PRODIGY (24 vs. 6 mo)	2	1	45	751	1
PRODIGY (24 vs. 6 mo)	2	3	49	750	1
EXCELLENT (12 vs. 6 mo)	3	1	4	722	1
EXCELLENT (12 vs. 6 mo)	3	2	7	721	1
RESET (12 vs. 3 mo)	4	1	5	1,059	1
RESET (12 vs. 3 mo)	4	2	8	1,058	1
OPTIMIZE (12 vs. 3 mo)	5	1	43	1,563	1
OPTIMIZE (12 vs. 3 mo)	5	2	45	1,556	1
ARCTIC (18 vs. 12 mo)	6	2	9	624	1
ARCTIC (18 vs. 12 mo)	6	3	7	635	1
SECURITY (12 vs. 6 mo)	7	1	8	682	1
SECURITY (12 vs. 6 mo)	7	2	8	717	1
DAPT (30 vs. 12 mo)	8	2	74	4,941	1
DAPT (30 vs. 12 mo)	8	3	98	5,020	1
ITALIC (24 vs. 6 mo)	9	1	8	912	1
ITALIC (24 vs. 6 mo)	9	3	7	910	1
ISAR-SAFE (12 vs. 6 mo)	10	1	8	1,997	1
ISAR-SAFE (12 vs. 6 mo)	10	2	12	2,003	1
OPTIDUAL (48 vs. 12 mo)	11	2	24	690	1
OPTIDUAL (48 vs. 12 mo)	11	3	16	695	1
I-LOVE-IT 2 (12 vs. 6 mo)	12	1	11	909	1
I-LOVE-IT 2 (12 vs. 6 mo)	12	2	14	920	1
IVUS-XPL (12 vs. 6 mo)	13	1	5	699	1
IVUS-XPL (12 vs. 6 mo)	13	2	10	701	1
NIPPON (18 vs. 6 mo)	14	1	16	1,654	1
NIPPON (18 vs. 6 mo)	14	3	7	1,653	1

ARCTIC[41]: assessment by a double randomisation of a conventional antiplatelet strategy versus a monitoring-guided strategy for drug-eluting stent implantation and of treatment interruption versus continuation 1 year after stenting; CI: confidence interval; DAPT[43]: dual antiplatelet therapy; DES-LATE[35]: Optimal Duration of Clopidogrel Therapy with DES to Reduce Late Coronary Arterial Thrombotic Events; EXCELLENT[38]: Efficacy of Xience/Promus Versus Cypher in rEducing Late Loss After stENTing; I-LOVE-IT 2[48]: Evaluate Safety and Effectiveness of the Tivoli® DES and the Firebird DES for Treatment of Coronary Revascularization; ISAR-SAFE[46]: Intracoronary Stenting and Antithrombotic Regimen: Safety And EFficacy of 6 Months Dual Antiplatelet Therapy After Drug-Eluting Stenting; ITALIC[44,45]: Is There A LIfe for DES after discontinuation of Clopidogrel; IVUS-XPL: Impact of Intravascular Ultrasound Guidance on Outcomes of Xience Prime Stents in Long Lesions; NIPPON[50]: Nobori Dual Antiplatelet Therapy as Appropriate Duration; OPTIDUAL[47]: OPTImal DUAL antiplatelet therapy after drug-eluting stent implantation; OPTIMIZE: Optimized Duration of Clopidogrel Therapy Following Treatment with the Endeavor Zotarolimus-Eluting Stent in Real-World Clinical Practice; OR: odds ratio; PRODIGY[36,37]; PROlonging Dual-antiplatelet treatment after Grading stent-induced Intimal hyperplasia studY; RESET[39]: REal Safety and Efficacy of 3-month dual antiplatelet Therapy following Endeavor zotarolimus-eluting stent implantation; SECURITY[38-40,42,46,48,49]: Second-generation Drug-eluting Stent Implantation Followed by 6- versus 12-month dual antiplatelet therapy

```
#Export data from Excel in comma-separated format containing a csv suffix, which is the best way to
input data into [R]. Remember that "E:" is a common designation of the hard disk on a Mac running
Windows, but "C:" is used on a PC. Remember also to replace "johnbittl" with your user name on your
computer, "Dropbox" and "EuroInterventionDAPT" with your folder names, and "NetworkDAPTDeath.csv" with
your file name (see Bittl JA, He Y: Bayesian analysis: practical approach to interpret clinical trials
and create clinical practice guidelines. Circulation Cardiovasc Qual Outcomes 2017;10:1-11)[87].
DDdat<-read.csv("Z:/Users/johnbittl/Dropbox/EuroInterventionDAPT/NetworkDAPTDeath.csv",as.is=TRUE,
header=T)
str(DDdat)
s<-c(DDdat$s)
t<-c(DDdat$t)
r<-c(DDdat$r)
nn<-c(DDdat$nn)
b<-c(DDdat$b)
#Specify the model in BUGS language, but save it as a string in [R]
modelString="
model
{ # i counts the two arms of all 14 studies
for (i in 1:28)
{
r[i] ~ dbin(p[i], nn[i]);
logit(p[i]) <- mu[s[i]]+delta[i]*(1-equals(t[i],b[i]));
delta[i] ~ dnorm(md[i], prec);
md[i] <- d[t[i]]-d[b[i]];
}
# j represents the CABG arm
for (j in 1:14)
{
mu[j] ~ dnorm(0, .001);
}
prec ~ dgamma(0.001, 0.001);
d[1] <- 0;
# K represents the relative treatment comparator: k1 = Short, k=2 is 12 mo, k=3 is Long
for (k in 2:3)
{
d[k] ~ dnorm(0, .001)
}
for (c in 1:2)
{
for (k in (c+1):3)
{
lor[c,k] <- d[k]-d[c];
log(or[c,k]) <- lor[c,k];
}
}
}
  "
# Write the modelString to a file
writeLines (modelString,con="model.txt")
# Use BRugs to check model
modelCheck ("model.txt")
#load data
dataList = list(s=c(s),
     t=c(t),
     r=c(r),
     nn=c(nn),
     b=c(b)
)

#Use BRugs commands to put the data into a file and ship the file to BUGS
modelData(bugsData(dataList))
#Initialize the chains
nChain=1
modelCompile(numChains = nChain) #Compile the model
initsList = list(d=c(NA,0,0), prec=1, mu=c(0,0,0,0,0,0,0,0,0,0,0,0,0,0))
modelInits(bugsData(initsList))
modelGenInits()
#R defines a new variable to specify an arbitrary chain length
chainLength1 = 5000
#BRugs tells BUGS to generate a MCMC chain
modelUpdate (chainLength1)
#BRugs keeps a record of parameters
samplesSet(c("lor"))
#BRugs asks BUGS for summary statistics
chainLength2 = 10000
thinStep = 2
modelUpdate (chainLength2)
thetaSummaryObs = samplesStats (c("lor")); thetaSummaryObs
thetaSummaryObs<-thetaSummaryObs[order(thetaSummaryObs$mean),]
expTheta<-exp(thetaSummaryObs)
print(thetaSummaryObs)
print(expTheta)
#############################################################################################################
#caterpillar plot
x<-seq(from=-0.8,to=0.6,by=0.01)
#Short vs. 12 mo
x<--thetaSummaryObs$mean
y<-c(3,2,1)
plot(x,y,xlim=c(-0.6,1.0),ylim=c(3.5,0),pch=23,cex=4,ylab="",yaxt="n",col="black",bg="purple",
cex.axis=1.0, xlab="log(e)OR", cex.lab=1.6)
axis (4, pos=0.0, tck = 0, labels=FALSE, col="black")
text (0.73,3,"3-6 mos vs. 12 mos", cex= 1.4)
text (0.75,1,"3-6 mos vs. 18-48 mos",cex = 1.4)
text (0.75,2, "12 mos vs. 18-48 mos", cex = 1.4)
text (0, 0,"All-Cause Mortality",cex = 1.6,font =2)
text (0.4, 0.6, "Long DAPT Better",cex=1.6,font=3)
text (-0.4, 0.6, "Short DAPT Better",cex=1.6,font=3)
text (-thetaSummaryObs$mean[3], 1.2, font=2, round(1/expTheta$mean[3],2))
text (-thetaSummaryObs$val2.5pc[3], 1.2, font=2,round(1/expTheta$val2.5pc[3],2))
text (-thetaSummaryObs$val97.5pc[3], 1.2, font=2,round(1/expTheta$val97.5pc[3],2))
text (-thetaSummaryObs$mean[1],3.2,font=2,round(1/expTheta$mean[1],2))
text (-thetaSummaryObs$val2.5pc[1], 3.2, font=2,round(1/expTheta$val2.5pc[1],2))
text (-thetaSummaryObs$val97.5pc[1], 3.2, font=2,round(1/expTheta$val97.5[1],2))
text (-thetaSummaryObs$mean[2], 2.2,  font=2,round(1/expTheta$mean[2],2))
text (-thetaSummaryObs$val2.5pc[2], 2.2,  font=2,round(1/expTheta$val2.5pc[2],2))
text (-thetaSummaryObs$val97.5pc[2], 2.2,  font=2,round(1/expTheta$val97.5pc[2],2))
segments(-thetaSummaryObs$val2.5pc[3], 1, -thetaSummaryObs$mean[3]+0.027, 1, lty=1, col="black", lwd=3)
segments(-thetaSummaryObs$val97.5pc[3], 1, -thetaSummaryObs$mean[3]-0.029, 1, lty=1, col="black", lwd=3)
segments(-thetaSummaryObs$val2.5pc[1], 3, -thetaSummaryObs$mean[1]+0.027, 3, lty=1, lwd=3)
segments(-thetaSummaryObs$val97.5pc[1], 3, -thetaSummaryObs$mean[1]-0.029, 3, lty=1,  lwd=3)
segments(-thetaSummaryObs$val2.5pc[2], 2, -thetaSummaryObs$mean[2]+0.027, 2, lty=1,  lwd=3)
segments(-thetaSummaryObs$val97.5pc[2], 2, -thetaSummaryObs$mean[2]-0.029, 2, lty=1,  lwd=3)
mtext ("Posterior Odds Ratio (OR)",3, line =2, cex = 1.6)
axis (3, at=c(-0.91,-0.69, -0.51,-0.35, -0.22, -0.105,0.0, 0.095,0.182, 0.262,0.336,
0.405,0.47,0.531,0.588,0.693, 0.833, 0.956, 1.10,1.19, 1.281,1.386,1.46,1.53,1.61,1.67,1.72,1.79),
labels=c(0.4,0.5,0.6, 0.7, 0.8,0.9, "1.0", 1.1,1.2, 1.3,1.4,1.5, 1.6,1.7, 1.8, "2.0", 2.3, 2.6, "3.0",
3.3,3.6,"4.0",4.3,4.6,"5.0",5.3,5.6,"6.0"))
#To create good margins
mar.default <- c(5,4,4,2) + 0.0
par(mar = mar.default + c(0, 2, 0, 0))
#To copy in eps and pdf formats to your original folder. (Change the date each time or you will
overwrite.)
dev.copy2eps(file="NetworkDAPTDeathMay20Caterpillar.eps")
dev.copy2pdf(file="NetworkDAPTDeathMay20Caterpillar.pdf")
```

Figure 7. *R Code for Figure 5: network meta-analysis for DAPT mortality and caterpillar plot.*

tribution with mean d_{SM} and variance τ^2_{SM}, where d_{SM} characterised the comparative effectiveness between a short duration of DAPT and 12 months of therapy. Similarly, we modelled the number of deaths after prolonged DAPT in the four studies that had treatment arms comparing 12 months (M) of DAPT with long (L) durations of DAPT of 18-48 months[35,41,43,47,49] as a binomial distribution. We assumed that the difference of log odds from each study $\delta_{i,ML}$ followed a normal random effects distribution with mean d_{ML} and variance τ^2_{ML}, where d_{ML} characterised the comparative effectiveness between prolonged DAPT and 12 months of therapy.

The difference between d_{SM} and d_{ML} can be denoted by $d_{SL}=d_{SM}-d_{ML}$ to describe the comparative effectiveness between short and long durations of DAPT under the model. Finally, we completed the model specification by imposing the following prior distributions to the parameters:

$$d_{SM} \sim N[0,10^3]$$
$$d_{ML} \sim N[0,10^3],$$
$$\tau^2_{SM} \sim IG[10^{-3},10^{-3}],$$
$$\tau^2_{ML} \sim IG[10^{-3},10^{-3}],$$

where d is the mean difference in the log odds of an outcome after S, M or L DAPT and τ^2 is the associated variance modelled using a normal (N) or inverse gamma (IG) distribution, based on the complete model described in other reports[87].

Conflict of interest statement

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Editorial

Time for science to catch up with clinical practice?

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Siddiqi *et al.* performed a retrospective analysis of the large Veterans database to explore the effect of clopidogrel prolongation beyond 12 months compared with 12 months or less after coronary stenting (1). Patients treated between 2002 and 2006 were divided in two groups: normal renal function (n=18,162) or chronic kidney disease (CKD, n=4,880) based on an estimated glomerular filtration rate (eGFR) cut-off of ≥ or <60 mL/min, respectively. A further stratification was made to compare patients treated with bare metal stents (BMS) and those treated with drug-eluting stents (DES). Outcomes were evaluated in patients free from ischemic or bleeding events within the first 12 months after percutaneous coronary intervention (PCI), at a follow-up ranging from 1 to 4 years after PCI. The primary endpoint was the combined outcome of death or acute myocardial infarction (MI), which was significantly increased in patients with CKD in both DES and BMS subgroups. However, CKD was also associated with an increased risk of disabling or life-threatening bleeding after DES and BMS implantation.

The authors reported that clopidogrel use of more than 12 months after PCI in patients with CKD receiving DES was associated with lower risk of death or MI (18% *vs.* 24%, HR=0.74; 95% CI, 0.58 to 0.95), and death (15% *vs.* 23%, HR=0.61; 95% CI, 0.47 to 0.80). At multivariate and propensity-score adjusted analyses, however, results were confirmed for death but not for the composite of death or MI. Furthermore, the potential benefits of prolonged dual antiplatelet therapy (DAPT) on the primary endpoint did not apply to patients treated with BMS. No significant increase of life-threatening bleeding was observed by prolonging DAPT administration after both DES or BMS implantation in patients with CKD at multivariate or propensity analyses, however: (I) a trend of increased risk was present (significant at univariate analysis in DES subgroup); (II) the rates of major bleeding were not reported and (III) the number of life-threatening bleeding events was probably too low to detect a significant difference between subgroups.

Finally, in patients with normal renal function, the authors observed consistent findings but the magnitude of ischemic risk reduction was lower than that observed in CKD patients treated with DES.

Although affected by some inherent critical limitations, this large retrospective study is well conducted and of interest to the community because it deals with a specific patient population (i.e., patients affected by CKD) in whom few data from randomized trials are available.

DAPT administration aims to reduce the risk of stent thrombosis (ST) after coronary stent implantation and prevent coronary atherothrombotic events at sites outside of the stented segment. However, the optimal duration of DAPT after stent implantation in general, and following DES implantation in particular, is matter of ongoing debate (2,3).

Does this study help in identifying the target population in which DAPT should be prolonged well beyond 12 months? We believe the reader should apply caution while interpreting study results. Beyond the obvious limitations carried by a retrospective and non-randomized analysis, these findings should be critically contrasted with the results of randomized controlled studies, which showed a clear effect of DAPT prolongation on non-fatal ischemic endpoints, i.e., MI and very late ST, in the absence of a mortality benefit. How can we reconcile those with the observed reduction in mortality but not mortality or MI risk in the current analysis? A plausible interpretation is that in clinical practice clinicians are able to identify patients

who benefit from prolonged DAPT duration and using sophisticated statistical tools, no adjustment can be made for baseline or updated covariates that are not routinely captured, and perhaps not even capturable, in registries.

Drug eluting stents have consistently reduced in-stent restenosis as compared with BMS but at the expense of safety concerns duo to an increase in late and very late ST. In particular, first-generation DES were associated with a four- to five-fold higher risk of very late ST as compared with BMS, which fueled "the longer the better" recommendation for DAPT duration in patients treated with DES (4). Conversely, second-generation devices were shown to be safer in terms of ST as compared with both first-generation DES and BMS (5).

Recent trials, reviews and meta-analyses (2,6-12) compared efficacy and safety of short (<12 months) and long term (≥12 months) DAPT after first- and second-generation DES implantation with respect to the currently recommended 12-month therapy (13,14). A short course of DAPT was associated with a significant reduction in major bleeding without significant differences in ischemic or thrombotic outcomes. Moreover, patients associated with high risk of bleeding events were recently evaluated in two different trials (15,16) in which DAPT was stopped very early (1 month) after second-generation DES implantation without safety concerns in terms of ischemic events. In particular, the ZEUS trial (15) compared Zotarolimus-eluting Endeavor sprint stent followed by 30-day DAPT with BMS followed by the same DAPT regimen, while the LEADERS FREE trial (16) compared a polymer-free Biolimus-eluting stent with a very similar BMS platform followed by 1-month DAPT. Both studies demonstrated that a treatment strategy consisting of second-generation DES implantation followed by a shorter than currently recommended DAPT regimen (30 days) resulted in a lower risk of MACE as compared with BMS in high-bleeding risk patients.

Conversely, prolonging DAPT over 12 months yielded a significant reduction in terms of MI and ST, in particular in trials including first-generation DES use (10,17), but at the price of a substantial increasing in major bleeding. Moreover, all-cause mortality was also significantly increased in the long-term DAPT population (10,11,18). Actually, bleeding and ST may have a different impact on mortality as highlighted in a recent meta-analysis reporting a significant association between bleeding and non-cardiovascular death but not between ST and cardiovascular death (19).

As a result, a personalized DAPT duration based on patient's bleeding and ischemic risk seems to be a more logical strategy in order to reach maximum benefits with limited side effects.

Patients with CKD represent a sizable proportion of patients (between 33% and 50%) with myocardial ischemia undergoing percutaneous coronary stent implantation (20), although frequently excluded or marginally represented in major randomized trials evaluating clopidogrel duration after coronary stenting. Siddiqi *et al.* included a high number of patients with eGFR <60 mL/min in whom primary and secondary outcomes were evaluated with multivariate and propensity analyses (1). The sensitivity analyses using the CKD-Epi equation, which seems to be more precise in estimating renal function, supported the consistency of their results. Unfortunately, due to the small number of subjects with eGFR < 30 mL/min, the differences across different degrees of CKD have not been evaluated in this study (1).

In early-stage CKD population the risk for premature cardiovascular disease is increased by 25% to 30% while in end-stage CKD patients it is more than 30- to 50-fold higher. On the other hand, also the bleeding risk is increased in patients with renal dysfunction (1,20). Indeed, renal disease was identified to be commonly used in the clinical practice to weigh the bleeding risk after DES implantation in a recent survey (3), and it is also included in the most relevant available bleeding risk scores (i.e., CRUSADE and HAS-BLEED).

Siddiqui *et al.* concluded that: "in patients with CKD, prolonging clopidogrel beyond 12 months after PCI may decrease the risk of death or MI only in patients receiving first-generation DES as compared with BMS". Key questions remains with respect to whether and how much these results may be applicable to patients with more severely reduced renal function (i.e., eGFR <30 mL/min) or to patients treated with contemporary devices, such as newer generation DES.

The observation that prolonged DAPT did not increase bleeding risk, a finding which has been remarkably consistent across all randomized controlled studies and meta-analyses, further raising concerns on the adequacy of adjustment for biases in the current analysis.

Conclusions

Prolongation of DAPT still remains highly debated, irrespective of specific subgroups of patients, because it

is associated with ischemic benefits, but also with a time-dependent risk of major and clinically relevant bleeding complications, which in turn significantly affect morbidity and mortality.

The present study offers data for additional debate as it focuses on a large sub-population of patients with high ischemic and bleeding risks, who are frequently under-represented in randomized trials on DAPT duration and/or stent types. The key lesson here is that perhaps clinicians seem to be able to select the ideal CKD population in whom DAPT may and should be prolonged, better than conventional inclusion or exclusion criteria so far employed in clinical trials. Hence, once more trialists and device or drug manufacturing companies need to learn from clinicians more than vice versa.

Randomized trials of new generation DES and reliable $P2Y_{12}$ inhibitors (ticagrelor or prasugrel) are needed to help clinicians to perform even better.

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Footnote

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Impact of Sex on 2-Year Clinical Outcomes in Patients Treated With 6-Month or 24-Month Dual-Antiplatelet Therapy Duration

A Pre-Specified Analysis From the PRODIGY Trial

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ABSTRACT

OBJECTIVES The aim of this study was to assess the impact of sex on 2-year outcomes after percutaneous coronary intervention (PCI) in patients randomly allocated to 24-month versus 6-month dual-antiplatelet therapy (DAPT).

BACKGROUND The optimal duration of DAPT after PCI is highly debated. Whether sex per se should drive decision making on DAPT duration remains unclear.

METHODS The primary efficacy endpoint of PRODIGY (Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia Study) was the composite of death, myocardial infarction, or cerebrovascular accident at 24-month follow-up. The key safety endpoint was type 2, 3, or 5 bleeding according to the Bleeding Academic Research Consortium criteria.

RESULTS Women (n = 459 [23.3%]) were older and more likely to have hypertension, lower creatinine clearance, and acute coronary syndrome but had a lower severity of coronary artery disease. After adjustment, prolonged DAPT, compared with 6-month treatment, did not reduce the primary endpoint in both men (adjusted hazard ratio: 1.080; 95% confidence interval: 0.766 to 1.522; p = 0.661) and women (adjusted hazard ratio: 1.013; 95% confidence interval: 0.588 to 1.748; p = 0.962) (interaction p = 0.785). No sex disparity was identified across multiple secondary ischemic endpoints, including overall or cardiovascular mortality, myocardial infarction, and stent thrombosis. There was also no clear sex-related effect on clinically relevant bleeding, including Bleeding Academic Research Consortium type 3 or 5, TIMI (Thrombolysis in Myocardial Infarction), and GUSTO (Global Use of Strategies to Open Occluded Coronary Arteries) scales.

CONCLUSIONS The present findings suggest that men and women undergoing PCI have similar adjusted 2-year ischemic and bleeding outcomes, despite being characterized by different clinical presentation. Sex failed to emerge as a treatment modifier with respect to DAPT duration, suggesting that decision making on DAPT duration in female patients should weigh ischemic versus bleeding risks. (J Am Coll Cardiol Intv 2016;9:1780–9) © 2016 by the American College of Cardiology Foundation.

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Percutaneous coronary intervention (PCI) is the most frequently performed revascularization procedure for coronary artery disease (CAD) in both male and female patients. Sex influences age, cardiovascular risk factors, clinical presentation, and angiographic features, including extension of disease and vessel size. However, the impact of sex on clinical outcomes after PCI remains debated. Although female sex has been identified as an independent predictor of adverse outcomes after PCI in some studies (1-4), it had no or minimal impact on outcomes in others (5-10).

Dual-antiplatelet therapy (DAPT) is the cornerstone of antithrombotic treatment in patients undergoing PCI, although its optimal duration remains controversial (11-17). Whether sex should be taken into account when selecting the DAPT regimen is still unknown. Female sex per se was recently proposed as a single covariate to identify patients in whom short DAPT duration would be advisable (18). Yet the evidence appraising the role of sex in the choice of the optimal DAPT duration is limited.

The aim of this subanalysis of the PRODIGY (Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia Study) randomized trial was to compare 2-year clinical outcomes in male and female patients and to assess the impact of sex in the setting of an all-comer population undergoing PCI and with a randomly allocated short (6-month) or prolonged (24-month) DAPT regimen, consisting of clopidogrel and aspirin.

METHODS

The present study is a pre-specified analysis of PRODIGY (NCT00611286). The design and main findings have been previously reported (11,19). Briefly, all-comer PCI patients (n = 2,013) were randomized to 4 types of stent (bare-metal, zotarolimus-eluting, paclitaxel-eluting, or everolimus-eluting stents) with varying anti-intimal hyperplasia potency and belonging to both the first and second generations of drug-eluting stent at 3 Italian sites. At 30 days, patients (n = 1,970) were randomly allocated to either 6 or 24 months of DAPT. Selection criteria were broad, reflecting routine clinical practice. Randomization to 6- or 24-month DAPT was stratified by center, ongoing ST-segment elevation myocardial infarction (MI), the presence of diabetes mellitus, and need for intervening on at least 1 in-stent restenotic lesion. The study was conducted in accordance with the principles of the Declaration of Helsinki. The ethics committees of the 3 participating centers independently approved the protocol, and all participants gave written informed consent.

TREATMENT PROTOCOL. All patients received aspirin (80 to 160 mg orally indefinitely) and clopidogrel (75 mg/day) according to the randomization scheme as follows: for either 6 months in the short-DAPT arm or 24 months in the prolonged-DAPT arm, irrespective of the previously implanted stent type or indication for PCI.

FOLLOW-UP. The randomized patients returned for study visits at 30 days and then every 6 months up to 2 years. During follow-up visits, patients were examined and assessed for adverse events and asked about antiplatelet therapy compliance, and 12-lead electrocardiographic recordings were obtained.

ABBREVIATIONS AND ACRONYMS

BARC = Bleeding Academic Research Consortium
CAD = coronary artery disease
CI = confidence interval
CVA = cerebrovascular accident
DAPT = dual-antiplatelet therapy
HR = hazard ratio
MI = myocardial infarction
PCI = percutaneous coronary intervention
ST = stent thrombosis

TABLE 1 Baseline Characteristics in Male and Female Patients

	Male (n = 1,511)	Female (n = 459)	p Value
Age (yrs)	67.8 (58.8-75.1)	73.6 (66.2-79.3)	<0.0001
Body mass index (kg/m^2)	26.8 (24.6-29.4)	26.2 (23.5-28.9)	0.950
Diabetes	24.0% (362)	25.1% (115)	0.631
Insulin dependent	5.8% (87)	5.9% (27)	
Hypertension	69.2% (1,045)	80.4% (369)	<0.0001
Hyperlipidemia	54.6% (825)	55.1% (253)	0.845
Current cigarette use	25.5% (385)	18.3% (84)	0.002
Creatinine level (mg/dl)	1.0 (0.9-1.2)	0.9 (0.7-1.1)	0.002
Creatinine clearance (ml/min)	80.6 (59.8-99.8)	60.5 (46.5-79.8)	<0.0001
Prior myocardial infarction	28.4% (429)	21.1% (97)	0.006
Prior PCI	19.5% (295)	13.9% (64)	0.013
LVEF	50.0 (45-60)	52.4 (45-60)	0.521
Clinical presentation			
Stable angina pectoris	26.9% (406)	21.6% (99)	0.023
Acute coronary syndrome	73.1% (1,105)	78.4% (360)	
STEMI	32.9% (497)	32.9% (151)	0.998
NSTEMI	22.7% (343)	23.3% (107)	0.785
Unstable angina	17.5% (265)	22.2% (102)	0.024
Multivessel disease	72.1% (1,089)	63.2% (290)	<0.0001
Number of treated lesions	1 (1-2)	1 (1-2)	0.005
≥2 treated lesions	39.1% (591)	31.6% (145)	0.004
≥3 treated lesions	12.0% (181)	9.2% (42)	0.094
Multivessel intervention	28.1% (424)	22.2% (102)	0.013
At least 1 complex lesion (type B2 or C)*	67.3% (1,017)	63.0% (289)	0.085
Total ACC/AHA score†	3 (2-5)	3 (2-4)	0.027
Aspirin	100% (1,511)	100% (459)	>0.999
Clopidogrel	99.9% (1,510)	99.6% (457)	0.075
Warfarin	1.8% (27)	1.5% (7)	0.716
Statin	90.8% (1,360)	89.4% (404)	0.351

Values are median (interquartile range) or % (n). *According to the ACC/AHA coronary lesion classification. †Type A stenoses were coded 1 point, type B1 stenoses 2 points, type B2 stenoses 3 points, and type C stenoses 4 points.

ACC = American College of Cardiology; AHA = American Heart Association; LVEF = left ventricular ejection fraction; NSTEMI = non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

TABLE 2 Baseline Characteristics According to Randomization for Dual-Antiplatelet Therapy Duration

	Male (n = 1,511)			Female (n = 459)		
	24-Month Clopidogrel (n = 764)	6-Month Clopidogrel (n = 747)	p Value	24-Month Clopidogrel (n = 223)	6-Month Clopidogrel (n = 236)	p Value
Age (yrs)	68.2 (58.8–74.8)	67.5 (58.7–75.6)	0.627	74.0 (66.7–79.1)	73.0 (64.2–79.4)	0.365
Body mass index (kg/m^2)	26.7 (24.8–29.4)	26.9 (24.5–29.4)	0.599	26.2 (23.9–29.1)	26.2 (23.4–28.5)	0.277
Diabetes	24.7% (189)	23.2% (173)	0.472	24.7% (55)	25.4% (60)	0.851
Insulin dependent	5.9% (45)	5.6% (42)		6.3% (14)	5.5% (13)	
Hypertension	70.5% (539)	67.9% (506)	0.237	81.6% (182)	79.2% (187)	0.851
Hyperlipidemia	56.8% (434)	52.3% (391)	0.081	53.4% (119)	56.8% (134)	0.521
Current cigarette use	24.6% (188)	26.4% (197)	0.431	15.2% (34)	21.2% (50)	0.100
Creatinine level (mg/dl)	1.0 (0.9–1.2)	1.0 (0.9–1.2)	0.674	0.9 (0.8–1.1)	0.9 (0.7–1.0)	0.028
Creatinine clearance (ml/min)	80.1 (59.1–103.3)	81.1 (60.8–96.6)	0.157	60.3 (45.0–79.6)	61.4 (47.2–80.1)	0.280
Prior myocardial infarction	29.7% (227)	27.1% (202)	0.250	19.3% (43)	22.9% (54)	0.345
Prior PCI	21.1% (161)	18.0% (134)	0.124	12.6% (28)	15.3% (36)	0.404
LVEF	50.0 (45–60)	50.0 (44–60)	0.780	55.0 (45–60)	50.0 (45–60)	0.080
Clinical presentation						
Stable angina pectoris	27.4% (209)	26.4% (197)	0.666	20.6% (46)	22.5% (53)	0.634
Acute coronary syndrome	72.6% (555)	73.6% (550)	0.666	79.4% (177)	77.5% (183)	0.634
STEMI	32.6% (249)	33.2% (248)	0.801	32.3% (72)	33.5% (79)	0.787
NSTEMI	22.5% (172)	22.9% (171)	0.861	24.2% (54)	22.5% (53)	0.656
Unstable angina	17.5% (134)	17.5% (131)	0.999	22.9% (51)	21.6% (51)	0.746
Multivessel disease	72.9% (557)	71.2% (532)	0.465	61.9% (138)	64.4% (152)	0.575
Number of treated lesions	1 (1–2)	1 (1–2)	0.024	1 (1–2)	1 (1–2)	0.393
≥2 treated lesions	37.8% (289)	40.4% (302)	0.300	34.1% (76)	29.2% (69)	0.265
≥3 treated lesions	11.3% (86)	12.7% (95)	0.382	9.9% (22)	8.5% (20)	0.605
Multivessel intervention	25.9% (198)	30.3% (226)	0.061	24.7% (55)	19.9% (47)	0.221
At least 1 complex lesion (type B2 or C)*	65.7% (502)	68.9% (515)	0.180	62.8% (140)	63.1% (149)	0.937
Total ACC/AHA score†	3 (2–4)	3 (3–5)	0.036	3 (2–4)	3 (2–4)	0.627
Aspirin	100% (764)	100% (747)	>0.999	100% (223)	100% (236)	>0.999
Clopidogrel	99.9% (763)	100% (747)	0.323	99.6% (222)	99.6% (235)	0.968
Warfarin	1.3% (10)	2.3% (17)	0.153	1.4% (3)	1.7% (4)	0.756
Statin	90.0% (683)	91.7% (677)	0.241	88.6% (195)	90.1% (209)	0.617

Values are median (interquartile range) or % (n). *According to the ACC/AHA coronary lesion classification. †Type A stenoses were coded 1 point, type B1 stenoses 2 points, type B2 stenoses 3 points, and type C stenoses 4 points.

Abbreviations as in Table 1.

STUDY ENDPOINTS. The primary efficacy endpoint of the PRODIGY trial was the composite of death, MI, or cerebrovascular accident (CVA), while the key safety endpoint included Bleeding Academic Research Consortium (BARC) type 2, 3, or 5 bleeding. The net effect on the combined ischemic and bleeding complications was obtained by 2 net adverse clinical event endpoints that were generated by combining the primary efficacy endpoint of death, MI, or CVA with either the primary safety endpoint of BARC type 2, 3, or 5 bleeding or BARC type 3 or 5 events. Other endpoints included each component of the primary efficacy endpoint, cardiovascular death, stent thrombosis (ST) defined on the basis of the Academic Research Consortium criteria, and BARC type 3 or 5 bleeding. Other safety endpoints included bleeding events adjudicated according to the TIMI (Thrombolysis in Myocardial Infarction) and GUSTO (Global Use of Strategies to Open Occluded Coronary Arteries) scales. All study endpoint definitions were previously reported.

All endpoints were confirmed on the basis of documentation collected at each hospital and were centrally adjudicated by the clinical events committee, whose members were unaware of the patients' treatment group assignments. The time frame of interest for the primary endpoint was from 30 days (i.e., after the primary endpoint randomization) to 24 months.

STATISTICAL ANALYSIS. Categorical variables are expressed as frequency (percentage), whereas continuous variables are expressed as median (interquartile range). Continuous variables were compared between randomized groups using the Wilcoxon rank sum test, whereas for binary variables, the chi-square test was used. Multiple imputation (the iterative Markov-chain Monte Carlo algorithm [fully conditional specification or chained equations imputation]

TABLE 3 Clinical Outcomes in Female and Male Patients

	Male (n = 1,511)	Female (n = 459)	Unadjusted Hazard Ratio (95% CI)	p Value	Adjusted Hazard Ratio (95% CI)	p Value
Primary efficacy endpoint						
Death from any cause, MI, or CVA	140 (9.3)	58 (12.6)	0.716 (0.527–0.972)	0.032	0.912 (0.658–1.262)	0.577
Secondary efficacy endpoints						
Death from any cause or MI	124 (8.2)	58 (12.6)	0.631 (0.462–0.863)	0.004	0.792 (0.568–1.103)	0.168
Death from any cause	89 (5.9)	41 (8.9)	0.650 (0.449–0.941)	0.023	0.834 (0.564–1.234)	0.365
Death from cardiovascular cause	48 (3.2)	25 (5.4)	0.576 (0.355–0.933)	0.025	0.775 (0.467–1.286)	0.324
Stroke or TIA	25 (1.7)	7 (1.5)	1.083 (0.468–2.504)	0.852	1.363 (0.569–3.268)	0.487
MI	53 (3.5)	27 (5.9)	0.588 (0.370–0.934)	0.025	0.698 (0.424–1.150)	0.158
Definite ST	11 (0.7)	4 (0.9)	0.822 (0.262–2.581)	0.737	1.161 (0.244–5.520)	0.851
Definite or probable ST	21 (1.4)	7 (1.5)	0.914 (0.389–2.150)	0.837	1.224 (0.491–3.055)	0.664
Definite, probable, or possible ST	59 (3.9)	25 (5.4)	0.705 (0.442–1.126)	0.144	0.963 (0.583–1.588)	0.881
Safety endpoints						
BARC classification						
Key safety endpoint (type 2, 3, or 5)	77 (5.1)	30 (6.5)	0.763 (0.500–1.163)	0.209	0.927 (0.588–1.462)	0.745
Type 3 or 5	38 (2.5)	15 (3.3)	0.756 (0.416–1.374)	0.358	1.005 (0.531–1.899)	0.989
Type 2	39 (2.6)	15 (3.3)	0.775 (0.427–1.406)	0.402	0.883 (0.456–1.710)	0.711
TIMI classification						
Minor	14 (0.9)	6 (1.3)	0.695 (0.267–1.808)	0.456	0.858 (0.298–2.467)	0.776
Major	17 (1.1)	5 (1.1)	1.017 (0.375–2.758)	0.973	1.384 (0.488–3.919)	0.541
Minor or major	31 (2.1)	11 (2.4)	0.840 (0.422–1.671)	0.619	1.103 (0.526–2.313)	0.795
GUSTO classification						
Moderate	18 (1.2)	9 (2.0)	0.596 (0.268–1.327)	0.205	0.820 (0.346–1.941)	0.651
Severe	20 (1.3)	5 (1.1)	1.199 (0.450–3.194)	0.717	1.641 (0.594–4.532)	0.339
Moderate or severe	37 (2.4)	14 (3.1)	0.789 (0.427–1.460)	0.450	1.104 (0.573–2.126)	0.767
Net adverse clinical events						
Death from any cause, MI, CVA, or BARC type 2, 3 or 5 bleeding	189 (12.5)	80 (17.4)	0.696 (0.536–0.904)	0.007	0.835 (0.633–1.102)	0.203
Death from any cause, MI, CVA, or BARC type 3 or 5 bleeding	153 (10.1)	69 (15.0)	0.654 (0.493–0.870)	0.003	0.833 (0.615–1.128)	0.238

Values are n (%) unless otherwise indicated. Multivariate adjustment for age, hypertension, smoking, creatinine level, prior MI, ACS, multivessel intervention, and total ACC/AHA score.

BARC = Bleeding Academic Research Consortium; CI = confidence interval; CVA = cerebrovascular accident; GUSTO = Global Use of Strategies to Open Occluded Coronary Arteries; MI = myocardial infarction; ST = stent thrombosis; TIA = transient ischemic attack; TIMI = Thrombolysis In Myocardial Infarction; other abbreviations as in Table 1.

implemented in SPSS [IBM, Armonk, New York] was used to create 5 datasets with imputation of missing values on the basis of their potential predictors) was used for missing values of creatinine levels at baseline (n = 21) and ejection fraction (n = 136).

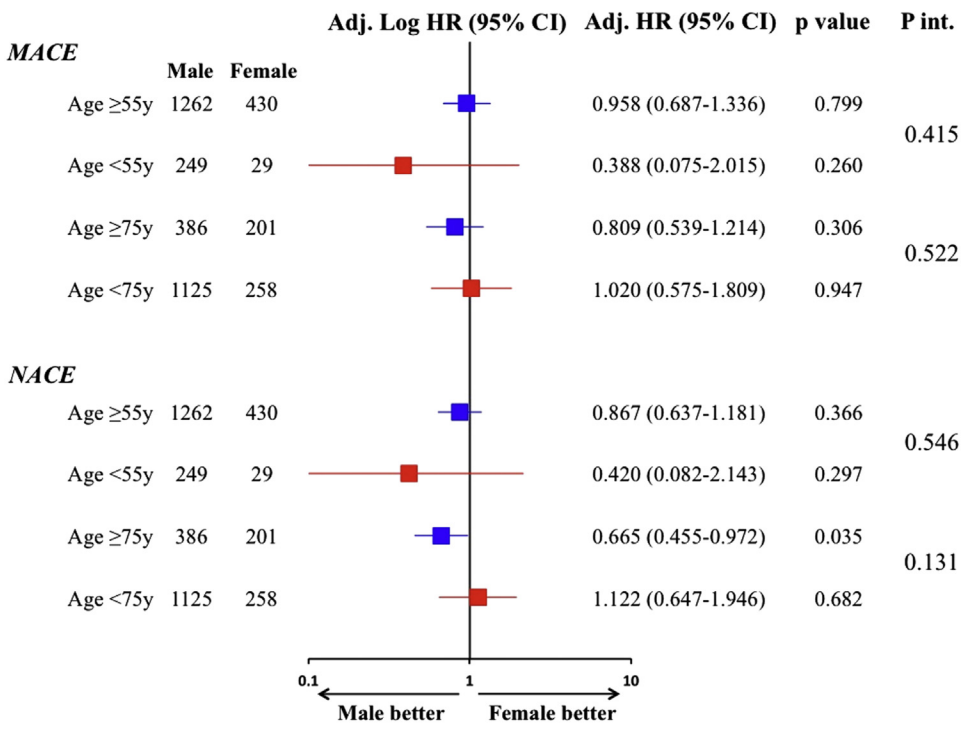
Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated for male versus female (values >1 indicated increased hazard in the male group) and 24-month versus 6-month DAPT (values >1 indicated increased hazard with 24-month DAPT) with a proportional hazards model. Cox regression was used for multivariate analysis. Clinical and angiographic characteristics that were imbalanced at a nominal 5% significance level between the 2 groups were identified and included the final adjusted model; these included age, hypertension, smoking, baseline creatinine level, prior MI, clinical presentation, multivessel intervention and total American College of Cardiology/American Heart Association score.

Interaction testing was performed to determine whether the effect of DAPT duration was consistent irrespective of sex on the primary and secondary endpoints of the study. This was performed with likelihood ratio tests of the null hypothesis that the interaction coefficient was zero. A 2-sided p value <0.05 was considered to indicate statistical significance. All analyses were based on the intention-to-treat principle and were performed with SPSS version 23.0.

RESULTS

Among 1,970 patients randomized to 6- versus 24-month DAPT at 30 days from PCI, 1,511 (76.7%) were men, and 459 (23.3%) were women. Baseline characteristics are summarized in Table 1, while Table 2 describes baseline characteristics of the 2 randomized arms of DAPT regimens (24 vs. 6 months) in male and female patients. Compared with men, women were older, had a higher prevalence of

FIGURE 1 Interaction Between Age and Sex on 2-Year Composite Endpoints



Male and female patients were compared on the basis of age subgroups, with hazard ratios (HRs) and 95% confidence intervals (CIs), for the primary endpoint of death from any cause, myocardial infarction, or cerebrovascular accident and net adverse clinical events (NACEs). MACE = major adverse cardiovascular event.

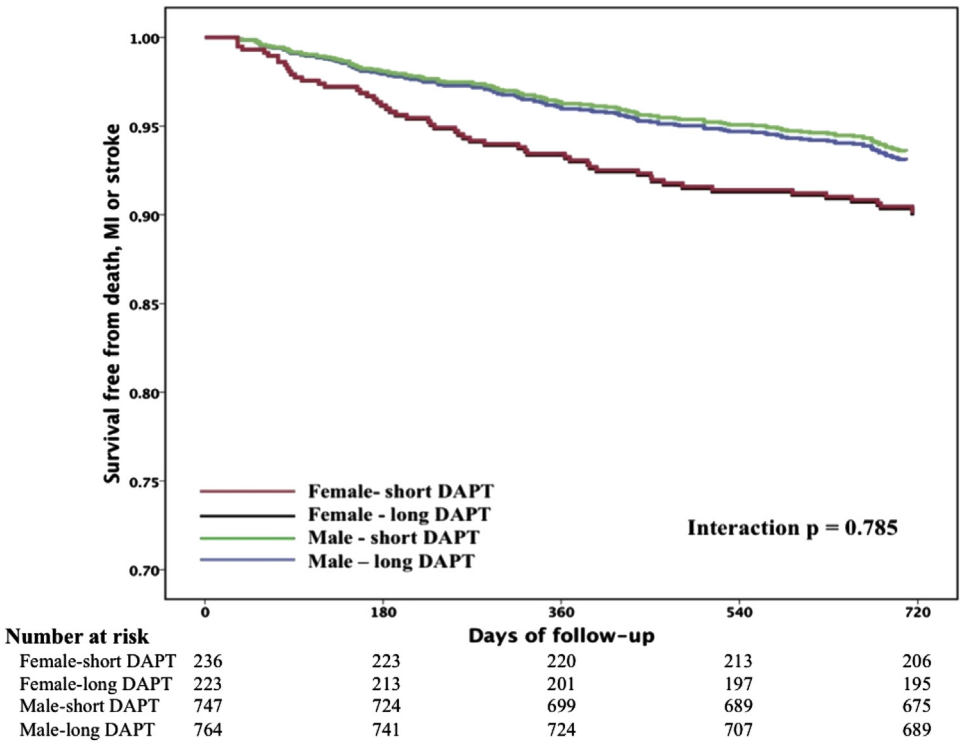
hypertension, had lower creatinine clearance, presented more frequently with acute coronary syndrome, were less likely smokers, and had a lower prevalence or extension of CAD with less need for multivessel intervention (**Table 1**). Overall, baseline characteristics were well balanced in patients randomized to 24-month or 6-month DAPT in both male and female subgroups (**Table 2**).

At 2 years, crude events and unadjusted HRs showed that women had higher rates of death, MI, and the composite of ischemic events or ischemic and bleeding events (**Table 3**). The primary efficacy endpoint (death, MI, or CVA) occurred in 58 women (12.6%) and 140 men (9.3%) (HR: 0.716; 95% CI: 0.527 to 0.972; p = 0.032) (**Table 3**). After multivariate adjustment for baseline imbalances, no significant difference was noted between men and women in the primary efficacy endpoint (adjusted HR: 0.912; 95% CI: 0.658 to 1.262; p = 0.577) (**Table 3**). Consistent results were observed across all other ischemic or bleeding endpoints between sexes (**Table 3**). In an age-matched sensitivity analysis, major adverse cardiovascular events and net adverse clinical events were not affected by sex (all interaction p values > 0.05) (**Figure 1**) or by stent type (Online Table 1).

In both randomized DAPT groups, the primary endpoint was similar in female and male patients after adjustment (24-month DAPT: adjusted HR: 0.923; 95% CI: 0.586 to 1.453; p = 0.729; 6-month DAPT: adjusted HR: 0.828; 95% CI: 0.515 to 1.331; p = 0.436; p for interaction = 0.785) (**Figure 2**, Online Table 2). Accordingly, event rates did not differ with respect to DAPT duration in male (adjusted HR: 1.080; 95% CI: 0.766 to 1.522; p = 0.661 (**Figure 3**, **Table 4**) and female (adjusted HR: 1.013; 95% CI: 0.588 to 1.748; p = 0.962) (**Figure 3**, **Table 4**) patients.

The key safety endpoint of BARC type 2, 3, or 5 bleeding occurred in 30 women (6.5%) and 77 men (5.1%). Men treated with longer DAPT experienced higher rates of bleeding events (adjusted HR: 3.506; 95% CI: 2.013 to 6.104; p < 0.0001) (**Table 4**), whereas women did not (adjusted HR: 0.827; 95% CI: 0.382 to 1.794; p = 0.631) (**Table 4**), with positive interaction testing (p for interaction = 0.002). This difference appeared to be driven mainly by BARC 2 bleeding

FIGURE 2 Survival Free From Death, Myocardial Infarction, or Cerebrovascular Accident According to Sex and Dual-Antiplatelet Therapy Duration



Number at risk					
Female-short DAPT	236	223	220	213	206
Female-long DAPT	223	213	201	197	195
Male-short DAPT	747	724	699	689	675
Male-long DAPT	764	741	724	707	689

Cox proportional model plot for the primary endpoint of death from all causes, myocardial infarction (MI), or cerebrovascular accident. DAPT = dual-antiplatelet therapy.

events (men: adjusted. HR: 6.651; 95% CI: 2.592 to 17.065; $p < 0.0001$; women: adjusted HR: 0.764; 95% CI: 0.240 to 2.431; $p = 0.649$; p for interaction = 0.003) (Table 4). Accordingly, when bleeding was assessed in terms of BARC type 3 or 5, prolonged versus short DAPT did not differ with respect to clinical outcomes in men (adjusted HR: 1.969; 95% CI: 0.965 to 4.019; $p = 0.063$) (Figure 3, Table 4) or women (adjusted HR: 0.971; 95% CI: 0.331 to 2.851; $p = 0.957$) (Figure 3, Table 4) separately appraised, with negative interaction testing (p for interaction = 0.237). Assessing the impact of sex across TIMI and GUSTO bleeding scales provided consistent results (Table 4).

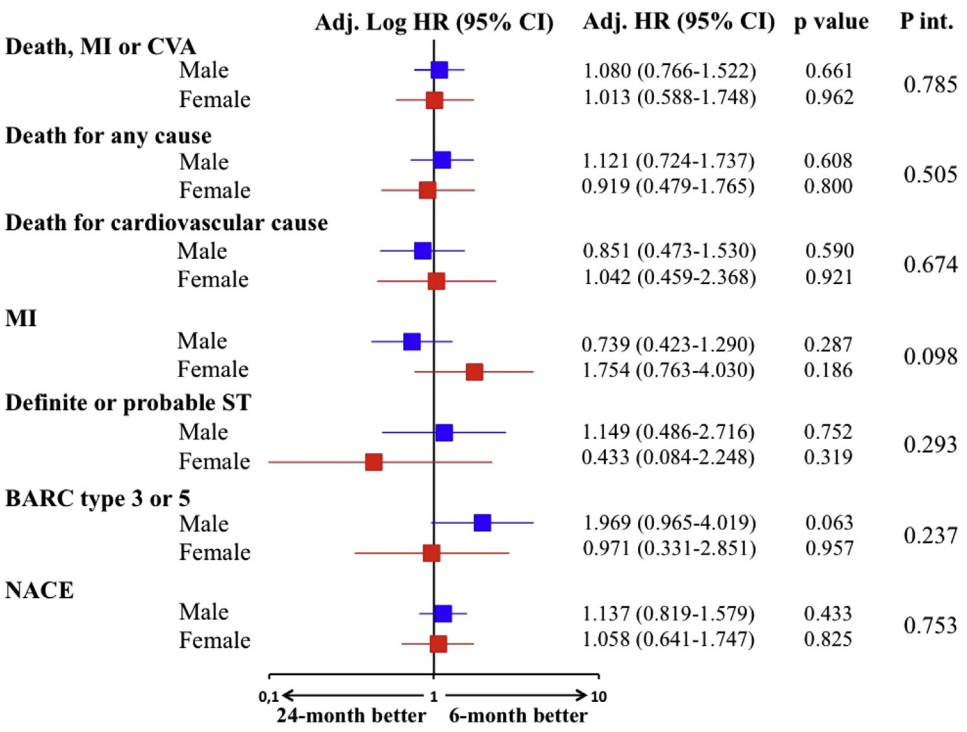
According to major adverse cardiovascular event and BARC results, the rates of net adverse clinical events did not show a significant interaction between DAPT duration and sex (BARC type 2, 3, or 5: p for interaction = 0.091; BARC type 3 or 5: p for interaction = 0.753) (Figure 4, Table 4). No relevant interaction was found between age or stent type and sex in DAPT arms (Online Tables 3 and 4).

DISCUSSION

In the present analysis from the PRODIGY trial, we assessed the impact of sex on clinical outcomes in all-comer patients undergoing PCI and receiving different durations of DAPT. The main findings can be summarized as follows. 1) Twenty-four-month DAPT duration was not associated with ischemic benefits in male and female patients, consistent with the overall PRODIGY results. 2) Male but not female patients had a significantly increased risk for bleeding events with prolonged DAPT according to the key safety endpoint of BARC type 2, 3 or 5 bleeding. However, the rate of bleeding did not differ between male and female patients when treated with 6- or 24-month DAPT duration after exclusion of BARC type 2 events.

This is the first dedicated sex-based analysis of a randomized trial comparing a short with a prolonged DAPT regimen. Our analysis suggests that the overall results of the PRODIGY trial can be extended with confidence to both sexes.

FIGURE 3 Interaction Between Sex and Randomization to 24-Month or 6-Month Dual-Antiplatelet Therapy on 2-Year Clinical Outcomes



Male and female subgroups are shown, with hazard ratios (HRs) and 95% confidence intervals (CIs), for the primary endpoint of death from any cause, myocardial infarction (MI), or cerebrovascular accident (CVA), death from any cause, cardiovascular death, MI, definite or probable stent thrombosis (ST), Bleeding Academic Research Consortium (BARC) type 3 or 5 bleeding, and net adverse clinical events (NACEs) among patients randomly assigned to either 6-month or 24-month dual-antiplatelet therapy.

PRODIGY was designed to detect a 40% reduction in the composite endpoint of death, MI, or CVA in the prolonged-DAPT arm but failed to support such a benefit in largely unselected patients (25.6% with stable CAD and 74.4% with acute coronary syndrome) undergoing PCI with a balanced mixture of stent types, including both first- and second-generation drug-eluting stents. Overall, these results are consistent with those of other trials exploring the impact of DAPT prolongation (12,14-17), which either showed no benefit of prolonged DAPT or benefit on recurrent MI and very late ST but no significant impact on death or cardiovascular death. The PEGASUS-TIMI 54 (Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis In Myocardial Infarction 54) study was the only trial to observe a significant reduction of stroke in patients treated with 60 mg but not in those taking a 90-mg twice-daily ticagrelor regimen compared with aspirin only (20). All studies consistently observed increases in bleeding events, depending on study power and bleeding endpoint definitions.

When taken together, currently available studies suggest that decision making regarding DAPT duration toward either shorter or longer than the conventional 12-month time frame should involve a "patient-by-patient" approach, aiming at balancing ischemic versus bleeding risks. With that respect, whether sex per se should be taken into account in tailoring patient's therapy is still unclear.

Although many studies support sex differences in cardiovascular outcomes (1-4), an equally large body of evidence suggests that women treated for CAD are older and have a higher prevalence of comorbidities, and as a result significant differences in outcomes between male and female patients are no longer demonstrated following adjustment for these baseline differences (5-10). Consistent with the latter studies, the results of the current analysis show that in an all-comer population of patients treated with stent implantation, men and women feature similar ischemic as well as clinically relevant bleeding risks when baseline confounders are accounted for in the multivariate model.

TABLE 4 Adjusted Clinical Outcomes in Patients Randomized to 24-Month Versus 6-Month Dual-Antiplatelet Therapy Stratified by Sex

	Male (n = 1,511)				Female (n = 459)				
	24-Month Clopidogrel (n = 764)	6-Month Clopidogrel (n = 747)	Adjusted Hazard Ratio (95% CI)	p Value	24-Month Clopidogrel (n = 223)	6-Month Clopidogrel (n = 236)	Adjusted Hazard Ratio (95% CI)	p Value	p Value for Interaction
Primary efficacy endpoint									
Death from any cause, MI, or CVA	72 (9.4)	68 (9.1)	1.080 (0.766–1.522)	0.661	28 (12.6)	30 (12.7)	1.013 (0.588–1.748)	0.962	0.785
Secondary efficacy endpoints									
Death from any cause or MI	60 (7.9)	64 (8.6)	0.962 (0.668–1.386)	0.835	28 (12.6)	30 (12.7)	1.013 (0.588–1.748)	0.962	0.972
Death from any cause	46 (6.0)	43 (5.8)	1.121 (0.724–1.737)	0.608	19 (8.5)	22 (9.3)	0.919 (0.479–1.765)	0.800	0.505
Death from cardiovascular cause	23 (3.0)	25 (3.3)	0.851 (0.473–1.530)	0.590	13 (5.8)	12 (5.1)	1.042 (0.459–2.368)	0.921	0.674
MI	23 (3.0)	30 (4.0)	0.739 (0.423–1.290)	0.287	16 (7.2)	11 (4.7)	1.754 (0.763–4.030)	0.186	0.098
Stroke or TIA	19 (2.5)	6 (0.8)	3.609 (1.344–9.765)	0.011	1 (0.4)	6 (2.5)	0.170 (0.020–1.448)	0.105	0.010
Definite ST	6 (0.8)	5 (0.7)	1.182 (0.355–3.939)	0.785	2 (0.9)	2 (0.8)	>10 (0–>1,000)	0.968	0.935
Definite or probable ST	11 (1.4)	10 (1.3)	1.149 (0.486–2.716)	0.752	2 (0.9)	5 (2.1)	0.433 (0.084–2.248)	0.319	0.293
Definite, probable, or possible ST	26 (3.4)	33 (4.4)	0.735 (0.433–1.246)	0.253	12 (5.4)	13 (5.5)	0.969 (0.412–2.278)	0.943	0.471
Safety endpoints									
BARC classification									
Key safety endpoint (type 2, 3, or 5)	60 (7.9)	17 (2.3)	3.506 (2.013–6.104)	<0.0001	13 (5.8)	17 (7.2)	0.827 (0.382–1.794)	0.631	0.002
Type 3 or 5	26 (3.4)	12 (1.6)	1.969 (0.965–4.019)	0.063	8 (3.6)	7 (3.0)	0.971 (0.331–2.851)	0.957	0.237
Type 2	34 (4.5)	5 (0.7)	6.651 (2.592–17.065)	<0.0001	5 (2.2)	10 (4.2)	0.764 (0.240–2.431)	0.649	0.003
TIMI classification									
Minor	7 (0.9)	7 (0.9)	0.822 (0.285–2.374)	0.718	4 (1.8)	2 (0.8)	1.407 (0.219–9.051)	0.719	0.674
Major	14 (1.8)	3 (0.4)	6.054 (1.355–27.043)	0.018	2 (0.9)	3 (1.3)	0.712 (0.144–4.410)	0.716	0.071
Minor or major	21 (2.7)	10 (1.3)	1.946 (0.882–4.294)	0.099	6 (2.7)	5 (2.1)	1.060 (0.298–3.762)	0.929	0.328
GUSTO classification									
Moderate	11 (1.4)	7 (0.9)	1.348 (0.519–3.501)	0.540	6 (2.7)	3 (1.3)	1.550 (0.353–6.794)	0.561	0.953
Severe	14 (1.8)	6 (0.8)	2.293 (0.813–6.466)	0.117	2 (0.9)	3 (1.3)	0.712 (0.114–4.440)	0.716	0.242
Moderate or severe	24 (3.1)	13 (1.3)	1.687 (0.837–3.399)	0.143	8 (3.6)	6 (2.5)	1.162 (0.379–3.562)	0.792	0.484
Net adverse clinical events									
Death from any cause, MI, CVA, or BARC type 2, 3, or 5 bleeding	113 (14.8)	76 (10.2)	1.548 (1.147–2.091)	0.004	39 (17.5)	41 (17.4)	0.994 (0.626–1.578)	0.979	0.091
Death from any cause, MI, CVA, or BARC type 3 or 5 bleeding	81 (10.6)	72 (9.6)	1.137 (0.819–1.579)	0.443	35 (15.7)	34 (14.4)	1.058 (0.641–1.747)	0.825	0.753

Multivariate adjustment for age, hypertension, smoking, creatinine level, prior MI, ACS, multivessel intervention, and total ACC/AHA score.
Abbreviations as in Tables 1 and 3.

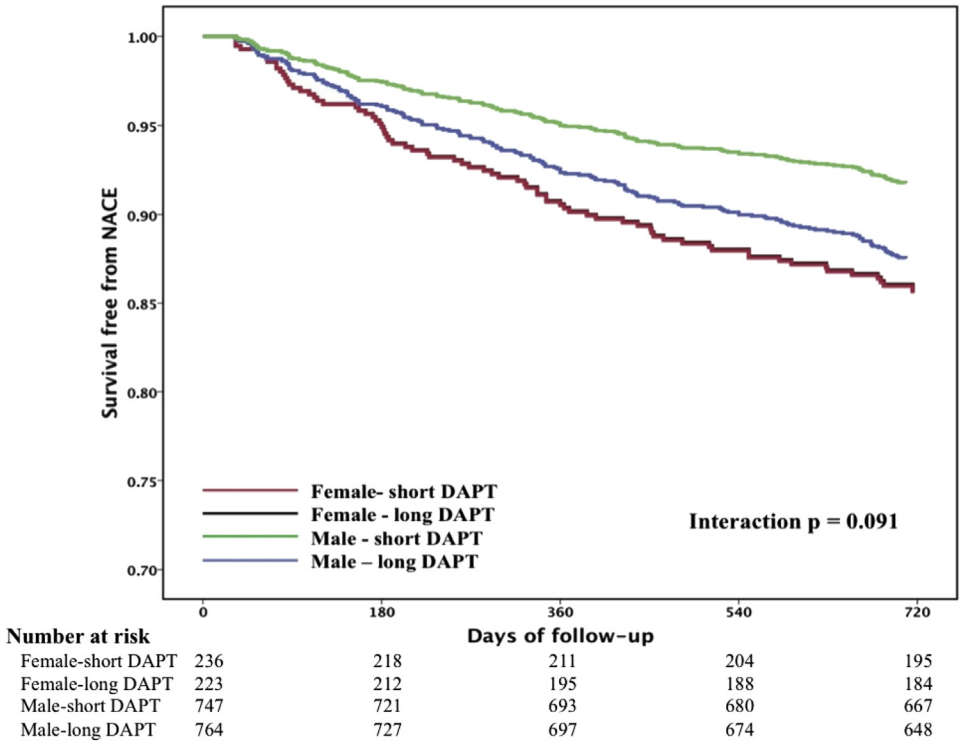
Age is a major confounder when analyzing outcomes stratified for sex (21,22). Hence, in our analysis, we also compared women and men on the basis of age subcategories, which confirmed the results of the adjusted analysis.

Some evidence suggests that women undergoing PCI are at increased risk for bleeding. Hence, it could be speculated that DAPT prolongation should be avoided in women, who are on average older (18). However, the increased bleeding risk in women compared with men appears to be restricted largely to the periprocedural period, with sex failing to predict long-term bleeding risk (7,10,23,24). This is consistent with our study findings, which suggest that clinically relevant bleeding occurring from 30 days onward after intervention is not affected by sex.

The DAPT trial showed that DAPT prolongation significantly reduced both MI and definite or probable ST in men but not in women (sex interaction 0.03 and 0.04 for MI and ST, respectively). However, the sex interaction for bleeding (GUSTO moderate or severe) or major adverse cardiovascular and cerebrovascular events was not significant (25). Sex subgroup analysis in the ARCTIC Interruption trial did not show differences between sexes in the primary (composite of all-cause death, MI, stroke or transient ischemic attack, urgent coronary revascularization, and ST) and secondary (composite of ST or urgent revascularization) endpoints (26). Similarly, the DES-LATE trial confirmed consistency between men and women for the primary endpoint (composite of cardiac death, MI, or stroke 24 months after randomization) (27), as did the PEGASUS-TIMI 54 trial (20).

Hence, the results of our dedicated analysis are consistent with the results of subgroup analysis of other major DAPT studies and support the concept that sex is not a treatment modifier with respect to DAPT duration.

FIGURE 4 Survival Free From Net Adverse Clinical Events According to Sex and Dual-Antiplatelet Therapy Duration



Number at risk					
Female-short DAPT	236	218	211	204	195
Female-long DAPT	223	212	195	188	184
Male-short DAPT	747	721	693	680	667
Male-long DAPT	764	727	697	674	648

Cox proportional model plot for net adverse clinical events (NACEs). DAPT = dual-antiplatelet therapy.

STUDY LIMITATIONS. Although this was a prespecified analysis of the PRODIGY trial, sex was not used for stratification at the time of randomization. The female study population was smaller compared with the male group, as observed in most trials investigating patients with CAD. Yet this analysis suffered from both type I and type II errors. This study should be regarded as exploratory and hypothesis generating.

CONCLUSIONS

Women undergoing PCI differed from their male counterparts in that they were typically older, more often had hypertension and reduced renal function, but less frequently were smokers and had a lower degree of CAD complexity. However, after adjustment, 2-year ischemic and clinically relevant bleeding outcomes did not differ. DAPT prolongation did not mitigate the high risk at baseline; indeed, compared with short-term DAPT, a prolonged DAPT regimen did not benefit both male and female patients, suggesting that sex should not be a primary covariate to be considered in decision making on DAPT duration after coronary stenting.

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PERSPECTIVES

WHAT IS KNOWN? Contrasting evidence exists on the optimal DAPT duration and on the impact of sex on long-term clinical outcomes after PCI.

WHAT IS NEW? Women and men have similar rates of long-term ischemic and bleeding events. Prolonged DAPT did not reduce ischemic events in both sexes.

WHAT IS NEXT? Sex should not be a primary covariate to be considered in decision making on DAPT duration after coronary stenting.

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KEY WORDS bleeding, clopidogrel, DAPT, ischemic events, sex

APPENDIX For supplemental tables, please see the online version of this article.

JAMA Cardiology | Original Investigation

Prolonged vs Short Duration of Dual Antiplatelet Therapy After Percutaneous Coronary Intervention in Patients With or Without Peripheral Arterial Disease

A Subgroup Analysis of the PRODIGY Randomized Clinical Trial

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IMPORTANCE Patients with concomitant peripheral arterial disease (PAD) experience worse cardiovascular outcomes after percutaneous coronary intervention (PCI).

OBJECTIVE To assess the efficacy and safety of prolonged (24 months) vs short (≤6 months) dual antiplatelet therapy (DAPT) in patients with PAD undergoing PCI.

DESIGN, SETTING, AND PARTICIPANTS This subanalysis of the randomized Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia Study (PRODIGY) trial assessed unselected patients from tertiary care hospitals with stable coronary artery disease or acute coronary syndromes with or without concomitant PAD from December 2006 to December 2008. Data analysis was performed from January 7 to April 4, 2016.

INTERVENTIONS Percutaneous coronary intervention.

MAIN OUTCOMES AND MEASURES Rates of the primary efficacy end point, composite of death, myocardial infarction, or cerebrovascular accidents, and occurrence of the key safety end point, a composite of Bleeding Academic Research Consortium type 2, 3, or 5.

RESULTS This analysis comprised 246 and 1724 patients with and without PAD, respectively. In the patients with PAD, mean (SD) age was 73.2 (9.2) in the prolonged group and 75.7 (8.7) years in the short DAPT group, and 97 (82.2%) were male in the prolonged group and 92 (71.9%) were male in the short DAPT group. In the patients without PAD, mean (SD) age was 67.1 (11.2) years in the prolonged group and 66.8 (11.3) years in the short DAPT group, and 667 (76.8%) were male in the prolonged group and 655 (76.6%) were male in the short DAPT group. Status of PAD was associated with a higher risk of death and ischemic events (hazard ratio [HR], 2.80; 95% CI, 2.05-3.83; $P < .001$). Prolonged vs short DAPT conveyed a lower risk of the primary efficacy end point in patients with PAD (19 [16.1%] vs 35 [27.3%]; HR, 0.54; 95% CI, 0.31-0.95; $P = .03$) but not in patients without PAD (81 [9.3%] vs 63 [7.4%]; HR, 1.28; 95% CI, 0.92-1.77; $P = .15$), with positive interaction ($P = .01$). The risk of definite or probable stent thrombosis was significantly lower in patients with PAD treated with prolonged compared with short DAPT (HR, 0.07; 95% CI, 0-1.21; $P = .01$). Bleeding Academic Research Consortium type 2, 3, or 5 bleeding occurred in 6 patients with PAD (5.2%) receiving prolonged DAPT relative to 8 (6.9%) of those receiving short DAPT (HR, 0.77; 95% CI, 0.27-2.21; $P = .62$), with a significant interaction ($P = .04$) compared with patients without PAD.

CONCLUSIONS AND RELEVANCE Peripheral artery disease confers a poor prognosis in patients undergoing PCI in the setting of stable coronary artery disease or acute coronary syndromes. Prolonged DAPT lowers the risk of ischemic events with no apparent bleeding liability in this high-risk group.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT00611286.

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Invited Commentary

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Concomitant peripheral arterial disease (PAD) is increasingly recognized as an important risk factor among patients with coronary artery disease (CAD).[1,2] Clinically relevant atherosclerosis that affects the peripheral vascular circulation is detected in up to 40% of patients with CAD,[3-5] with an adverse effect on clinical outcomes.[6-8] Among patients with CAD who require percutaneous coronary intervention (PCI), those with concomitant PAD have a 2-fold increase in the early and long-term risk of death.[2]

Antiplatelet therapy is pivotal to prevent cardiovascular events in patients with isolated PAD.[9,10] Evidence suggests that extended duration of dual antiplatelet therapy (DAPT) after PCI provides more effective protection against atherothrombotic events compared with short-term regimens, at the risk of more frequent bleeding.[11] Whether the duration of DAPT in patients undergoing PCI should be tailored based on concomitant PAD is currently unknown, to our knowledge. In a survey initiated by the European Association of Percutaneous Cardiovascular Interventions that assessed DAPT prescription patterns after coronary stenting, concomitant PAD was not identified as a clinically important factor affecting the decision regarding treatment duration in 1134 responders from 92 countries.[12] Against this background, we performed a subgroup analysis of the Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia Study (PRODIGY) trial[13] to evaluate the effect of PAD on ischemic and bleeding events and to assess the efficacy and safety of a prolonged (24-month) vs a short (≤6-month) DAPT duration according to the presence of concomitant PAD.

Key Points

Question What is the ideal duration of dual antiplatelet therapy (DAPT) after coronary stenting in patients with concomitant coronary and peripheral arterial disease?

Findings In this subanalysis of a randomized clinical trial, peripheral arterial disease emerged as a treatment modifier in terms of DAPT duration in patients undergoing percutaneous coronary intervention, with a prolonged regimen (up to 24 months) associated with a significantly lower risk of death and atherothrombotic events and unaffected risk of bleeding.

Meaning The significant prognostic effect of concomitant peripheral arterial disease should be taken into account when managing the duration of DAPT after percutaneous coronary intervention.

Methods

The randomized, multicenter, open-label PRODIGY trial compared the safety and efficacy profile of prolonged vs short duration of DAPT in a minimally selected population of patients undergoing coronary stenting from December 2006 to December 2008.[13] Data analysis was performed from January 7 to April 4, 2016. All participants gave written informed consent, and their data were deidentified. The Cardiology Department at University of Ferrara (Ferrara, Italy) led the study, and the protocol was independently approved by the ethics committees of the participating centers. The study design and primary results of the PRODIGY trial have been previously described[14] and are summarized in the eMethods in the Supplement.

Study Population

For the purpose of this intention-to-treat analysis, the study population was stratified according to PAD status. At baseline, patients with intermittent claudication or prior amputation or percutaneous or surgical peripheral revascularization were identified as having PAD. All patients were followed up through clinic visits at 30 days and up to 2 years after PCI.

Study End Points

Definitions of study outcomes have been previously reported.[13] The primary efficacy end point was a composite of death, myocardial infarction (MI), or cerebrovascular accident (CVA) up to 2 years. The primary key safety end point included a composite of type 2, 3, or 5 bleeding according to the Bleeding Academic Research Consortium (BARC) criteria.[15] Other end points were death, cardiovascular death, MI, and stent thrombosis, defined according to the Academic Research Consortium criteria.[16] A net adverse clinical events (NACE) end point combining the primary efficacy end point of death, MI, or CVA with BARC type 3 or 5 bleeding was additionally analyzed. All study end points were adjudicated by a clinical events committee unaware of treatment allocation.

Statistical Analysis

Categorical baseline variables were presented as frequencies and percentages with *P* values calculated with unpaired *t* tests, χ^2 tests, or Fisher exact tests. Continuous variables were expressed as mean (SD) and compared with the independent-samples *t* test. The effect of PAD on clinical outcomes was evaluated by Cox proportional hazards regression analyses by adjusting for baseline variables associated with the primary efficacy and key safety end point at the univariate analysis with a significance level of $P < .20$. The efficacy and safety of prolonged DAPT vs short DAPT for patients with vs without PAD was evaluated at 24 months and from 6 to 24 months. Clinical events were expressed as counts with rates computed according to the Kaplan-Meier method. Cox proportional hazards regression analysis was used to calculate hazard ratios (HRs) with 95% CIs, and an interaction test was provided to evaluate the effect of treatment in patients with vs without PAD. As sensitivity analysis, the efficacy and safety of different durations of DAPT in patients with PAD were evaluated by adjusting for baseline variables that significantly differ between patients randomized to prolonged vs short DAPT. Analyses were performed with STATA statistical software, release 13 (StataCorp).

Results

Of 1970 patients enrolled in the PRODIGY trial, a history of PAD was present in 246 participants (12.5%). Among the

Table. Baseline Characteristics According to PAD and DAPT Duration[a]

Characteristic	Patients With PAD			Patients Without PAD			*P* Value for Interaction
	Prolonged DAPT (n = 118)[b]	Short DAPT (n = 128)[c]	*P* Value	Prolonged DAPT (n = 869)[b]	Short DAPT (n = 855)[c]	*P* Value	
Age, mean (SD), y	73.2 (9.2)	75.7 (8.7)	.03	67.1 (11.2)	66.8 (11.3)	.53	.06
Male	97 (82.2)	92 (71.9)	.07	667 (76.8)	655 (76.6)	.95	.08
BMI, mean (SD)	27.5 (5.0)	26.3 (3.5)	.04	27.8 (13.0)	27.7 (10.3)	.91	.47
Hypertension	103 (87.3)	112 (87.5)	.96	618 (71.1)	581 (68.0)	.16	.67
Dyslipidemia	60 (50.8)	80 (62.5)	.07	493 (56.7)	445 (52.0)	.05	.02
Smoking	18 (15.3)	20 (15.6)	.94	204 (23.5)	227 (26.5)	.15	.71
Diabetes, type 1 or 2	36 (30.5)	47 (36.7)	.34	208 (23.9)	186 (21.8)	.30	.17
Insulin-treated diabetes	14 (11.9)	13 (10.2)	.69	45 (5.2)	42 (4.9)	.83	.80
Family history of CAD	33 (28.0)	22 (17.2)	.05	256 (29.5)	242 (28.3)	.63	.08
Previous MI	47 (39.8)	53 (41.4)	.90	223 (25.7)	203 (23.7)	.37	.55
Previous PCI	24 (20.3)	35 (27.3)	.23	165 (19.0)	135 (15.8)	.09	.06
Previous CABG	16 (13.6)	28 (21.9)	.10	94 (10.8)	75 (8.8)	.17	.03
Creatinine clearance, mean (SD), mL/min/1.73 m^2	62.4 (29.0)	60.7 (24.9)	.61	81.6 (43.6)	80.2 (29.2)	.41	.95
Previous stroke	2 (1.7)	2 (1.6)	.99	4 (0.5)	6 (0.7)	.54	.67
Congestive HF or LV dysfunction	9 (7.6)	7 (5.5)	.61	31 (3.6)	33 (3.9)	.80	.45
Indication of PCI			.64			.82	.58
Stable CAD	29 (24.6)	38 (29.7)		226 (26.0)	212 (24.8)		
NSTE-ACS	65 (55.1)	64 (50.0)		346 (39.8)	342 (40.0)		
STEMI	24 (20.3)	26 (20.3)		297 (34.2)	301 (35.2)		
Acute MI at presentation	62 (52.5)	62 (48.4)	.53	485 (55.8)	489 (57.2)	.59	.42
Drug therapy at 30 d							
ACE inhibitors or receptor blockers	100 (84.7)	104 (81.2)	.50	767 (88.3)	721 (84.3)	.02	.81
β-Blockers	94 (79.7)	96 (77.4)	.75	734 (85.2)	715 (84.5)	.68	.82
Statins	105 (89.0)	107 (83.6)	.26	781 (89.9)	792 (92.6)	.05	.05
Diuretics	48 (40.7)	57 (46.0)	.43	203 (23.6)	234 (27.7)	.05	.99
Proton pump inhibitors	50 (42.4)	45 (35.2)	.29	325 (37.4)	318 (37.2)	.96	.29

Abbreviations, ACE, angiotensin-converting enzyme inhibitor; BMI, body mass index (calculated as the weight in kilograms divided by the square of height in meters); CABG, coronary artery bypass grafting; CAD, coronary artery disease; DAPT, dual antiplatelet therapy; HF, heart failure; LV, left ventricular; MI, myocardial infarction; NSTE-ACS, non–ST-segment elevation acute coronary syndrome; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

SI conversion factors: To convert creatinine clearance to milliliters per second per square meters, multiply by 0.0167.

[a] Data are presented as number (percentage) of patients unless otherwise indicated.

[b] 24 months.

[c] 6 months or less.

PAD group, 118 and 128 patients were randomized to the prolonged and short DAPT groups, respectively. A total of 869 and 855 patients without PAD were randomized to the prolonged and short DAPT groups, respectively (**Table**).

Baseline Clinical and Angiographic Characteristics

Patients with PAD were older and more often had hypertension, type 1 or type 2 diabetes, previous MI, and previous coronary artery bypass grafting than patients without PAD. In addition, they were more likely to present with non–ST-segment elevation MI, had more complex CAD, and more frequently underwent multivessel intervention. At 30 days, patients with PAD were more often taking diuretics, whereas the use of β-blockers and statins was higher among patients without PAD (eTable 1 and eTable 2 in the Supplement).

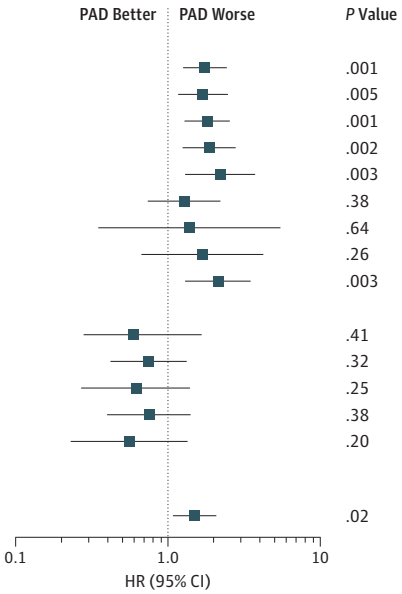
Patients with PAD randomized to prolonged DAPT were younger, had a higher body mass index, and less frequently underwent PCI of the left main coronary artery than those allocated to short DAPT. Otherwise, the baseline and periprocedural characteristics were well matched between the study groups (Table and eTable 3 in the Supplement).

Clinical Outcomes According to PAD Status

Patients with PAD experienced higher rates of ischemic events at 2-year follow-up compared with patients without PAD: the composite of death, MI, or CVA occurred in 54 patients with PAD (21.9%) vs 144 patients without PAD (8.4%) (adjusted HR, 1.75; 95% CI, 1.26-2.44; *P* = .001). Mortality was higher among patients with PAD (39 [15.8%] vs 91 patients without PAD [5.3%]; adjusted HR, 1.87; 95% CI,

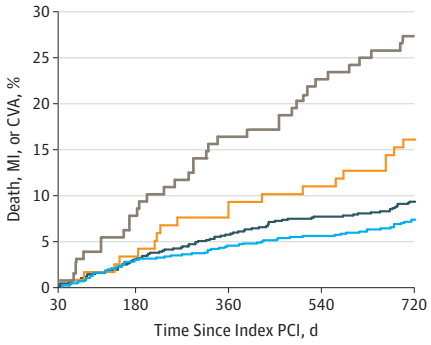
Figure 1. Effect of Peripheral Artery Disease (PAD) on Clinical Outcomes at 24-Month Follow-up

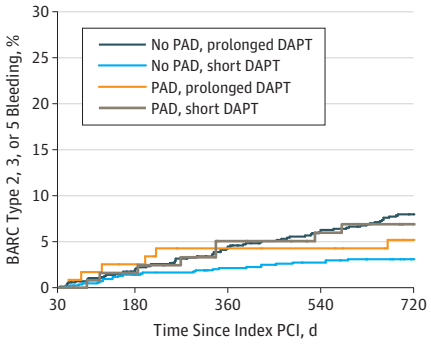
Bleeding Event	Patients With PAD, No. (%) (n = 246)	Patients Without PAD, No. (%) (n = 1724)	Crude Analysis HR (95% CI)	Crude Analysis *P* Value	Adjusted Analysis HR (95% CI)	Adjusted Analysis *P* Value
Ischemic events						
Death, MI, or CVA	54 (21.9)	144 (8.4)	2.80 (2.05-3.83)	<.001	1.75 (1.26-2.44)	.001
Cardiac death, MI, or CVA	42 (17.4)	115 (6.7)	2.72 (1.91-3.88)	<.001	1.70 (1.17-2.48)	.005
Death or MI	51 (20.7)	131 (7.6)	2.89 (2.09-4.00)	<.001	1.82 (1.29-2.56)	.001
Death	39 (15.8)	91 (5.3)	3.15 (2.16-4.58)	<.001	1.87 (1.25-2.79)	.002
Cardiac death	24 (10.0)	49 (2.9)	3.58 (2.19-5.83)	<.001	2.21 (1.30-3.76)	.003
MI	18 (7.5)	62 (3.6)	2.09 (1.24-3.54)	.006	1.28 (0.74-2.22)	.38
Definite ST	3 (1.3)	12 (0.7)	1.82 (0.51-6.46)	.35	1.39 (0.35-5.50)	.64
Definite or probable ST	7 (3.0)	21 (1.2)	2.43 (1.03-5.72)	.04	1.69 (0.67-4.23)	.26
Definite, probable, or possible ST	27 (11.4)	57 (3.3)	3.48 (2.20-5.50)	<.001	2.14 (1.30-3.50)	.003
Bleeding events						
TIMI minor or major	6 (2.6)	36 (2.1)	1.22 (0.51-2.89)	.66	0.69 (0.28-1.67)	.41
BARC type 2, 3, 5	14 (6.0)	93 (5.5)	1.11 (0.63-1.94)	.73	0.75 (0.42-1.33)	.32
BARC type 3 or 5	7 (3.0)	46 (2.7)	1.11 (0.50-2.46)	.79	0.62 (0.27-1.40)	.25
BARC type 2 or 3	12 (5.2)	81 (4.8)	1.09 (0.59-2.00)	.78	0.76 (0.40-1.41)	.38
GUSTO moderate or severe	6 (2.6)	45 (2.7)	0.97 (0.41-2.28)	.95	0.56 (0.23-1.35)	.20
Net adverse clinical events						
Death, MI, or CVA or BARC type 3 or 5 bleeding	54 (21.9)	168 (9.8)	1.64 (1.20-2.25)	.002	1.50 (1.08-2.08)	.02



Ischemic end points were adjusted for age, sex, hypertension, smoking, type 1 or 2 diabetes, family history of coronary artery disease (CAD), previous myocardial infarction (MI), previous percutaneous coronary intervention (PCI), previous coronary artery bypass graft, creatinine level, left ventricular ejection fraction, and indication to PCI. Bleeding end points were adjusted for age, previous MI, previous PCI, creatinine level, and left ventricular ejection fraction. BARC indicates Bleeding Academic Research Consortium; CVA, cerebrovascular accident; GUSTO, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries; HR, hazard ratio; ST, stent thrombosis; TIMI, Thrombolysis in Myocardial Infarction.

Figure 2. Kaplan-Meier Curves at 24 Months





No. at risk					
No PAD, prolonged DAPT	869	840	816	799	785
No PAD, short DAPT	855	829	812	803	788
PAD, prolonged DAPT	118	114	109	105	99
PAD, short DAPT	128	118	107	99	93

No. at risk					
No PAD, prolonged DAPT	869	834	802	778	756
No PAD, short DAPT	855	833	816	806	794
PAD, prolonged DAPT	118	114	109	108	102
PAD, short DAPT	128	118	107	103	98

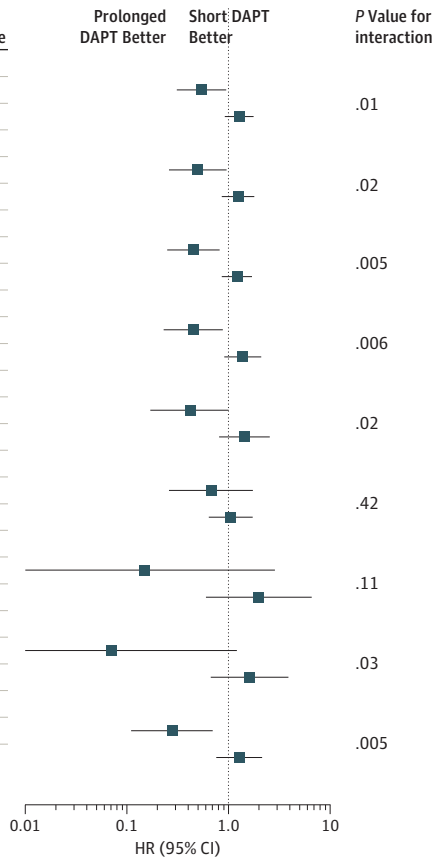
Kaplan-Meier curves are shown for the composite of death, myocardial infarction (MI), or cerebrovascular accident (CVA) and for Bleeding Academic Research Consortium (BARC) type 2, 3, or 5 bleeding. DAPT indicates dual antiplatelet therapy; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention. Prolonged DAPT refers to 24 months and short DAPT, 6 months or less.

1.25-2.79; *P* = .002); cardiac death was specifically reported in 24 patients with PAD (10.0%) compared with 49 patients without PAD (2.9%) (adjusted HR, 2.21; 95% CI, 1.30-3.76; *P* = .003) (**Figure 1** and eFigure 1A in the Supplement).

BARC type 2, 3, or 5 bleeding was not increased among patients with PAD compared with those without PAD (14 [6.0%] vs 93 [5.5%]; adjusted HR, 0.75; 95% CI, 0.42-1.33; *P* = .32) (Figure 1 and eFigure 1B in the Supplement). Similar results were obtained by applying other bleeding definitions. The risk of NACE was significantly increased in patients with PAD compared with those without PAD (54 [21.9%] vs 168 [9.8%]; adjusted HR, 1.50; 95% CI, 1.08-2.08; *P* = .02).

Figure 3. Ischemic Events at 24 Months According to Randomized Dual Antiplatelet Therapy (DAPT) and Peripheral Arterial Disease (PAD) Status

Bleeding Event	Patients Receiving Prolonged DAPT, No. (%)	Patients Receiving Short DAPT, No. (%)	HR (95% CI)	*P* Value	*P* Value for interaction
Death, MI, or CVA					
PAD	19 (16.1)	35 (27.3)	0.54 (0.31-0.95)	.03	.01
No PAD	81 (9.3)	63 (7.4)	1.28 (0.92-1.77)	.15	
Cardiac death, MI, or CVA					
PAD	14 (12.1)	28 (22.3)	0.50 (0.26-0.96)	.04	.02
No PAD	64 (7.4)	51 (6.0)	1.25 (0.86-1.80)	.24	
Death or MI					
PAD	16 (13.6)	35 (27.3)	0.45 (0.25-0.82)	.008	.005
No PAD	72 (8.3)	59 (6.9)	1.21 (0.86-1.71)	.28	
Death					
PAD	12 (10.2)	27 (21.1)	0.45 (0.23-0.88)	.02	.006
No PAD	53 (6.1)	38 (4.5)	1.39 (0.91-2.10)	.12	
Cardiac death					
PAD	7 (6.1)	17 (13.7)	0.42 (0.17-1.00)	.051	.02
No PAD	29 (3.4)	20 (2.4)	1.44 (0.81-2.55)	.21	
MI					
PAD	7 (6.0)	11 (8.9)	0.68 (0.26-1.74)	.42	.42
No PAD	32 (3.7)	30 (3.5)	1.05 (0.64-1.73)	.84	
Definite ST					
PAD	0 (0.0)	3 (2.7)	0.15 (0.01-2.87)[a]	.25	.11
No PAD	8 (0.9)	4 (0.5)	1.99 (0.60-6.61)	.26	
Definite or probable ST					
PAD	0 (0.0)	7 (6.0)	0.07 (0.00-1.21)[a]	.01	.03
No PAD	13 (1.5)	8 (1.0)	1.62 (0.67-3.90)	.28	
Definite, probable, or possible ST					
PAD	6 (5.2)	21 (17.2)	0.28 (0.11-0.70)	.006	.005
No PAD	32 (3.7)	25 (3.0)	1.27 (0.76-2.15)	.36	



CVA indicates cerebrovascular accident; HR, hazard ratio; MI, myocardial infarction; ST, stent thrombosis. Prolonged DAPT refers to 24 months and short DAPT, 6 months or less.

[a] Continuity corrected relative risk with Fisher exact test for zero events.

Efficacy of Prolonged DAPT According to PAD

As shown in **Figure 2** and **Figure 3**, among patients with PAD, prolonged DAPT was associated with a lower risk of the primary efficacy end point compared with short DAPT (19 [16.1%] vs 35 [27.3%]; HR, 0.54; 95% CI, 0.31-0.95; *P* = .03). In contrast, no significant difference was found in the risk of the primary end point between the 2 DAPT regimens among patients without PAD (81 [9.3%] in the prolonged-duration regimen vs 63 [7.4%] in the short-duration regimen; HR, 1.28; 95% CI, 0.92-1.77; *P* = .15), resulting in a significant qualitative interaction (*P* = .01). This difference was mainly driven by a significant interaction for death (*P* = .006), which was lower in the group of patients with PAD treated with prolonged DAPT (12 [10.2%] in the prolonged-duration regimen vs 27 [21.1%] in the short-duration regimen; HR, 0.45; 95% CI, 0.23-0.88; *P* = .02) compared with patients without PAD (53 [6.1%] in the prolonged-duration regimen vs 38 [4.5%] in the short-duration regimen; HR, 1.39; 95% CI, 0.91-2.10; *P* = .12). In the landmark analysis, the interaction test for the occurrence of the primary efficacy end point remained significant (*P* = .02), with a lower risk of events in patients with PAD allocated to prolonged DAPT compared with patients in the short DAPT group (15 [13.2%] vs 25 [21.2%]; HR, 0.59; 95% CI, 0.31-1.12; *P* = .10) (eTable 4 in the Supplement).

Definite or probable stent thrombosis was significantly reduced in patients with PAD randomized to prolonged DAPT compared with short DAPT (0 [0%] vs 7 [6.0%]; HR, 0.07; 95% CI, 0-1.21; *P* = .01), with significant interaction (*P* = .03) compared with patients without PAD, in whom prolonged DAPT had no effect (13 [1.5%] vs 8 [1.0%]; HR, 1.62; 95% CI, 0.67-3.90; *P* = .28) (Figure 3).

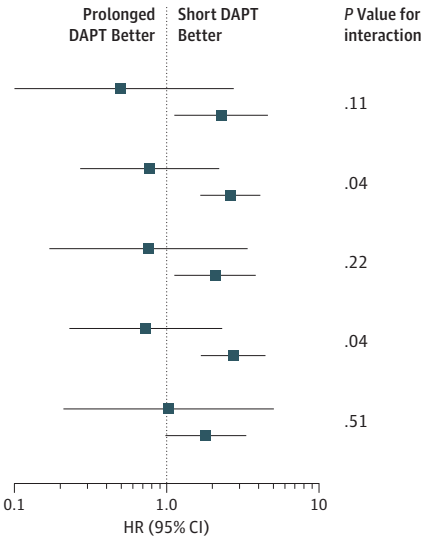
Baseline clinical characteristics of patients experiencing stent thrombosis with PAD or without PAD were comparable (eTable 5 in the Supplement), although multivessel disease and multiple treated lesions were more frequently observed in patients with PAD (eTable 6 in the Supplement).

Safety of Prolonged DAPT According to PAD

The cumulative time-to-event curves for the key safety end point are shown in Figure 2. BARC type 2, 3, or 5 bleeding was not significantly affected by DAPT duration in the PAD cohort (6 [5.2%] in the prolonged-duration regimen vs 8 [6.9%] in the short-duration regimen; HR, 0.77; 95% CI, 0.27-2.21, *P* = .62), whereas patients without PAD receiving prolonged DAPT

Figure 4. Bleeding Events at 24 Months According to Randomized Dual Antiplatelet Therapy (DAPT) and Peripheral Arterial Disease (PAD) Status

Bleeding Event	Patients Receiving Prolonged DAPT, No. (%)	Patients Receiving Short DAPT, No. (%)	HR (95% CI)	*P* Value
TIMI major or minor				
PAD	2 (1.8)	4 (3.5)	0.50 (0.09-2.74)	.43
No PAD	25 (3.0)	11 (1.3)	2.27 (1.12-4.61)	.02
BARC type 2, 3, or 5				
PAD	6 (5.2)	8 (6.9)	0.77 (0.27-2.21)	.62
No PAD	67 (8.0)	26 (3.1)	2.61 (1.66-4.11)	<.001
BARC type 3 or 5				
PAD	3 (2.6)	4 (3.4)	0.76 (0.17-3.40)	.72
No PAD	31 (3.7)	15 (1.8)	2.07 (1.12-3.83)	.02
BARC type 2 or 3				
PAD	5 (4.4)	7 (6.0)	0.73 (0.23-2.31)	.60
No PAD	59 (7.1)	22 (2.6)	2.72 (1.67-4.44)	<.001
GUSTO moderate or severe				
PAD	3 (2.6)	3 (2.6)	1.02 (0.21-5.04)	.98
No PAD	29 (3.4)	16 (1.9)	1.81 (0.98-3.33)	.06



BARC indicates Bleeding Academic Research Consortium; GUSTO, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries; HR, hazard ratio; TIMI, Thrombolysis in Myocardial Infarction. Prolonged DAPT refers to 24 months and short DAPT, 6 months or less.

experienced higher rates of bleeding events according to BARC and other prespecified criteria compared with patients in the short DAPT group (**Figure 4**). These findings were confirmed in the landmark analysis with focus between 6 and 24 months (eTable 4 in the Supplement).

Net Adverse Clinical Events

Cumulative incidence curves of NACE according to DAPT duration among patients with and without PAD are shown in eFigure 2 in the Supplement. The risk of NACE was significantly decreased in the prolonged DAPT group compared with the short DAPT group in the PAD population (19 [16.1%] in the prolonged-duration regimen vs 35 [27.3%] in the short-duration regimen; HR, 0.54; 95% CI, 0.31-0.95; *P* = .03). Among patients without PAD, NACE occurred in 97 patients (11.2%) in the prolonged DAPT group and 71 patients (8.3%) in the short DAPT group (HR, 1.36; 95% CI, 1.00-1.85; *P* for interaction = .047).

Safety and Efficacy of Prolonged DAPT According to Clinical Presentation

As reported in eTable 7 in the Supplement, among patients with PAD presenting with stable CAD, no significant difference in the rate of the primary efficacy end point at 2 years was found between those receiving prolonged and short DAPT (4 [13.8%] vs 6 [15.8%], *P* = .82). Among patients with PAD and acute coronary syndromes at presentation, the primary end point arose in 15 patients (16.9%) randomized to prolonged DAPT compared with 29 (32.2%) of those randomized to short DAPT (HR, 0.46; 95% CI, 0.25-0.87; *P* = .02; *P* for interaction = .36). BARC type 2, 3, or 5 bleeding were not significantly different between the prolonged and short DAPT groups in patients with PAD with stable CAD (2 [6.9%] vs 2 [5.4%], *P* = .77) or acute coronary syndromes (4 [4.6%] vs 6 [7.7%], *P* = .44).

Sensitivity Analysis

After adjustment for age, body mass index, and left main PCI, the adjusted HR for the primary efficacy end point was 0.66 (95% CI, 0.37-1.16; *P* = .15), with positive interaction testing (*P* = .05). Furthermore, prolonged DAPT in patients with PAD was still associated with a reduction in the composite of death or MI (16 [13.6%] in the prolonged-duration regimen vs 35 [27.3%] in the short-duration regimen; adjusted HR, 0.51; 95% CI, 0.28-0.94; *P* = .02) and overall stent thrombosis (6 [5.2%] in the prolonged-duration regimen vs 21 [17.2%] in the short-duration regimen; adjusted HR, 0.33; 95% CI, 0.13-0.82; *P* = .01).

Discussion

The salient findings of the present analysis are as follows. First, in patients undergoing PCI, concomitant PAD was associated with a 2-fold increased risk of ischemic events, whereas the risk of bleeding was unaffected. Second, prolonged DAPT duration of 24 months after PCI reduced the risk of the primary efficacy end point of death, MI, or CVA compared with short DAPT of 6 months or less in patients with PAD. The improved efficacy of prolonged DAPT in patients with PAD was not offset by an increased risk of actionable bleeding episodes.

Atherosclerosis of peripheral vessels portends a higher burden of CAD, accounting for impaired survival and worse cardiovascular outcomes. In a pooled analysis of 19 867 patients from 8 randomized clinical trials, PAD was a significant predictor of the composite of death, MI, and target-vessel revascularization 6 months after PCI (HR, 1.17; 95% CI, 1.05-1.31; *P* = .005) and was independently associated

with an increased risk of mortality throughout follow-up.[2] Among outpatients with stable CAD included in the REACH (Reduction of Atherothrombosis for Continued Health) registry, the 1-year rate of cardiovascular death, MI, stroke, or hospitalization for atherothrombotic events was 23.1% in patients with concomitant PAD compared with 13% among patients with isolated PAD and 17% among patients with isolated CAD.[17] Consistently, the GRACE (Global Registry of Acute Coronary Events) registry reported higher in-hospital mortality among patients with acute coronary syndromes and concomitant PAD, with a 6-month rate of major cardiovascular events of 14.6% compared with 7.2% in patients without PAD.[8]

Several pathophysiologic and clinical observations support the detrimental association of CAD and PAD. A multivessel coronary involvement, along with a proinflammatory status, is more common among patients with concomitant CAD and PAD.[18,19] Moreover, the onset of clinical symptoms and the identification of CAD are frequently camouflaged by PAD owing to the impaired functional status of patients.[6,20] Finally, the underestimation of this high-risk condition in clinical practice accounts for a well-described tendency to withhold pharmacologic therapies for secondary prevention in these patients.[21] Our study lends further support to the notion of an increased risk of ischemic events in patients with CAD and concomitant PAD. More specifically, the risks of NACE and cardiovascular mortality were more than doubled among patients with concomitant PAD.

Although patients with PAD experienced higher rates of ischemic events, they did not have a parallel increase in the risk of bleeding. These results are difficult to interpret because they conflict with other studies,[6,22,23] hence, potentially reflecting a power issue. Nonetheless, because we assessed bleeding events starting from 30 days after PCI, it may be possible that the exclusion of periprocedural events, which are more common in patients with PAD,[24] may explain the lack of association noted in our study between PAD status and bleeding risk. In addition, the high burden of mortality observed in patients with PAD may have camouflaged the occurrence of bleeding events. In the PEGASUS-TIMI 54 (Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis In Myocardial Infarction 54) study, PAD status was not associated with bleeding, and ticagrelor compared with placebo did not result in a higher risk of major or minor bleeding at both the 60-mg and 90-mg doses.[25] Furthermore, there is evidence demonstrating an increased platelet reactivity in patients with multisite atherosclerosis as a consequence of the larger amount of diseased endothelium and diffuse high shear stress.[26] An inverse association between platelet reactivity and bleeding exists.[27,28]

Antiplatelet therapy has the potential to mitigate the risk of atherothrombotic events in patients with PAD. In the CAPRIE (Clopidogrel vs Aspirin in Patients at Risk of Ischemic Events) trial,[29] clopidogrel monotherapy conveyed higher cardiovascular ischemic protection and low major bleeding in patients with stable PAD vs aspirin. The CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance) trial[10] tested the benefit of DAPT with aspirin and clopidogrel in patients with established stable atherosclerotic vascular disease or multiple atherothrombotic risk factors. Overall, DAPT was not superior to aspirin monotherapy for the primary end point of death, MI, or stroke (534 of 7802 [6.8%] vs 773 of 7801 [7.3%], $P = .22$). However, DAPT was associated with lower rates of MI and hospitalization for ischemic events without increasing the risk of major bleeding among patients with PAD. The addition of vorapaxar, an antagonist of protease-activated receptor 1 of thrombin, to aspirin and clopidogrel significantly reduced acute limb ischemia and peripheral revascularization but increased the risk of serious (intracranial) bleeding among patients with PAD included in the TRA2°P-TIMI 50 trial (Trial to Assess the Effects of SCH 530348 in Preventing Heart Attack and Stroke in Patients With Atherosclerosis).[30]

To our knowledge, this is the first study to evaluate the safety and efficacy of different DAPT durations in patients with concomitant CAD and PAD after PCI. Although in the overall population of the PRODIGY trial prolonged DAPT was not more effective, the relative risk of the primary efficacy end point was approximately halved by prolonged DAPT in patients with PAD with an interaction testing suggesting heterogeneity of treatment effect according to PAD status. Despite a high residual burden of risk in this patient population (the composite end point still occurred in roughly 16% of patients allocated to prolonged DAPT), a positive interaction was found for all-cause mortality, cardiovascular mortality, and definite or probable stent thrombosis. These results should be interpreted in the context of the DAPT study[11] that demonstrated a significantly reduced risk of stent thrombosis and major adverse cardiovascular and cerebrovascular events among 9961 patients randomly assigned to continue thienopyridine treatment or to receive placebo beyond 1 year after PCI.

Nevertheless, the implementation of prolonged DAPT in clinical practice remains controversial because of the higher risk of bleeding invariably reported in studies[11,14] comparing different DAPT durations. Although prolonged DAPT increased the bleeding risk compared with short DAPT among patients without PAD, we did not observe a significant effect of prolonged DAPT on bleeding risk among patients with PAD. The disconnect between PAD status and bleeding risk remains difficult to explain and could have been in part related to the exceedingly high incidence of ischemic events and the modest sample size. However, it is consistent with previous reports.[10,25] Overall, our results should be considered hypothesis generating for future dedicated randomized clinical trials.

We acknowledge the following limitations. First, this was not a prespecified analysis and therefore has all the potential shortcomings of such studies, including limited number of patients and events. Furthermore, because the randomization was not stratified by PAD status, our results may be attributable to differences in baseline variables. Second, PAD status was ascertained solely on the basis of clini-

cal history; therefore, underreporting cannot be excluded. Third, we were unable to indicate the peripheral vascular district primarily diseased and the rates of subsequent limb-related outcomes. Furthermore, we did not ascertain the safety and efficacy of different DAPT durations according to the clinical presentation (claudication, previous peripheral revascularization) of PAD. Fourth, DAPT in the PRODIGY trial was based on the use of aspirin and clopidogrel administration. Therefore, whether new P2Y12 receptor inhibitors may further improve clinical outcomes in this high-risk subset remains unanswered. This issue will be ascertained in part by the ongoing EUCLID (Examining Use of Ticagrelor in PAD) trial, testing the superiority of ticagrelor compared with clopidogrel monotherapy in reducing the risk of cardiovascular events among 13 500 patients with PAD (clinicaltrials.gov, NCT01732822).[31]

Conclusions

The coexistence of PAD and CAD conveyed higher risks of cardiovascular morbidity and mortality among patients undergoing PCI. A prolonged DAPT duration (up to 24 months) resulted in a lower risk of atherothrombotic events, including a mortality benefit, than short DAPT. The apparent neutral effect of longer DAPT on bleeding risk of patients with PAD requires further evaluation in adequately powered studies.

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ISCHEMIC HEART DISEASE (D MUKHERJEE, SECTION EDITOR)

Long-Term Use of Ticagrelor in Patients with Coronary Artery Disease

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Abstract
Purpose of Review This review aims to summarize and discuss safety and effectiveness of the long-term use of ticagrelor in patients with coronary artery disease (CAD).
Recent Findings Ticagrelor is an orally administered, direct, and reversible inhibitor of the $P2Y_{12}$-platelet receptor. Long-term use of ticagrelor in patients with previous myocardial infarction (MI) has been investigated in the PEGASUS-TIMI-54 trial. Overall, 21,162 patients with a spontaneous MI 1 to 3 years before randomization were randomly assigned to ticagrelor 90 mg bid, ticagrelor 60 mg bid, or placebo. Compared with placebo, both doses of ticagrelor showed that they were capable of significantly reducing the primary efficacy endpoint, although with a significant increase in TIMI major bleeding. Intracranial hemorrhage or fatal bleeding did not differ across groups.
Summary These findings establish clear benefit of DAPT extension with ticagrelor beyond 1 year of treatment, which comes with a tradeoff of clinically meaningful bleeding. Altogether, current evidence suggests that the duration of DAPT remains a patient-by-patient decision based on thrombotic and bleeding risk profiles.

Keywords Antiplatelet therapy · $P2Y_{12}$ inhibitor · Ticagrelor · Coronary artery disease · Ischemic events · Bleeding events

Abbreviations

ACS	Acute coronary syndrome
ARCTIC Interruption	Assessment by a Double Randomisation of a Conventional Antiplatelet Strategy Versus a Monitoring-Guided Strategy for Drug-Eluting Stent Implantation and of Treatment Interruption Versus Continuation 1 Year After Stenting
ATP	Adenosine triphosphate
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CHARISMA	Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance
CKD	Chronic kidney disease
DAPT	Dual antiplatelet therapy
DES	Drug-eluting stent
DES-LATE	Optimal Duration of Clopidogrel Therapy With Drug Eluting Stents to Reduce Late Coronary Arterial Thrombotic Events
EUCLID	Examining Use of Ticagrelor in PAD
EXCELLENT	Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting
HR	Hazard ratio
I-LOVE-IT 2	Evaluate Safety and Effectiveness of the Tivoli DES and the Firebird DES for Treatment of Coronary Revascularization

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ISAR-SAFE	Intracoronary Stenting and Antithrombotic Regimen: Safety and Efficacy of 6 Months Dual Antiplatelet Therapy After Drug-Eluting Stenting
ITALIC	Is There A Life for DES After Discontinuation of Clopidogrel
IVUS-XPL	Impact of Intravascular Ultrasound Guidance on Outcomes of XIENCE PRIME Stents in Long Lesions
MACCE	Major adverse cardiovascular or cerebrovascular events
MACE	Major adverse cardiovascular events
MI	Myocardial infarction
NACE	Net adverse clinical events
OPTIDUAL	Optimal Dual Antiplatelet Therapy
OPTIMIZE	Optimized Duration of Clopidogrel Therapy Following Treatment with the Zotarolimus-Eluting Stent in Real-World Clinical Practice
PAD	Peripheral arterial disease
PCI	Percutaneous coronary intervention
PEGASUS-TIMI-54	Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin—Thrombolysis In Myocardial Infarction 54
PLATO	PLATelet inhibition and patient Outcomes
PRODIGY	Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia
RESET	Real Safety and Efficacy of 3-month Dual Antiplatelet Therapy Following Endeavor Zotarolimus-Eluting Stent Implantation
RR	Risk ratio
SECURITY	Second Generation Drug-Eluting Stent Implantation Followed by Six- Versus Twelve-Month Dual Antiplatelet Therapy
TIA	Transient ischemic attach
TRA2P-TIMI 50	Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events—Thrombolysis in Myocardial Infarction 50

Introduction

The synergistic effect of aspirin and a $P2Y_{12}$-receptor inhibitor has been investigated in several trials, showing a greater reduction in platelet reactivity as compared to that achieved by each drug separately [1–4]. For more than 10 years, dual antiplatelet therapy (DAPT) with aspirin and clopidogrel has remained the cornerstone of treatment for patients with stable coronary artery disease (CAD) as well as acute coronary syndrome (ACS), including unstable angina (UA), non-ST-elevation myocardial infarction (NSTEMI), and ST-elevation myocardial infarction (STEMI). Two new and more potent oral $P2Y_{12}$-receptor inhibitors, prasugrel and ticagrelor, were approved in 2009 and 2011, respectively, by the FDA for clinical use in the setting of ACS, and more recently also, an intravenous agent named cangrelor was added to this scenario (Table 1) [5, 6].

Ticagrelor is a cyclopentyl-triazolopyrimidine that directly and reversibly inhibits the platelet $P2Y_{12}$-receptor through allosteric modulation. Ticagrelor is orally administrated twice daily; it is not a prodrug and does not require metabolic activation. Furthermore, 30–40% of its antiplatelet activity is mediated by an active metabolite (AR-C124910XX) coming from hepatic CYP3A4 and CYP3A5 processing. When related with clopidogrel, ticagrelor exhibits a more potent and more predictable antiplatelet effect with a faster onset and offset of action. In the PLATO trial [7], ticagrelor was compared with clopidogrel in terms of safety and efficacy in ACS patients who were intended for either invasive or non-invasive treatment. Ticagrelor reduced the primary endpoint, a composite of death from vascular causes, myocardial infarction (MI), and stroke at 12 months, mainly through a decrease in cardiovascular death and MI. The number needed to treat for benefit was in the range of 54. Ticagrelor did not increase overall or fatal bleeding. However, there was a higher risk of bleeding unrelated to coronary artery bypass grafting (CABG), with a number needed to treat for harm in the range of 167. Ticagrelor therapy showed a superior efficacy also in specific patient subsets such as those with recurrences of cardiovascular events [8], STEMI [9], diabetes mellitus [10], chronic kidney disease (CKD) [11], age >75 years, a body weight <60 kg [7], and a history of stroke or transient ischemic attack (TIA) [12].

Unlike other $P2Y_{12}$ inhibitors, ticagrelor exerts off-target cardiovascular effects, mainly related to its capability in increasing adenosine plasma levels [13, 14]. Adenosine is released in the plasma after ischemia, hypoxia, or oxidative stress and quickly taken up by red blood cells through sodium-dependent and sodium-independent equilibrative nucleoside transporters or converted into inosine by adenosine deaminase. Ticagrelor therapy was associated with increased adenosine plasma levels by inhibition of sodium-independent equilibrative nucleoside transporter-1 (ENT-1). Moreover, ticagrelor induces adenosine triphosphate (ATP) release from human red blood cells in a dose-dependent manner [15]. The combined effects of ticagrelor on both ATP release and adenosine reuptake may result in circulating plasma levels of adenosine which may determine (1) vasodilation, (2) reduction in ischemia/reperfusion injury and electrical conduction, (3) increase in platelet inhibition, (4) decrease of glomerular filtration rate, (5) dyspnea, and (6) improvement in microcirculation. In a recent non-randomized trial, ticagrelor therapy was

Table 1 Principal characteristics of $P2Y_{12}$ inhibitors

	Clopidogrel	Prasugrel	Ticagrelor	Cangrelor
Chemical class	Thienopyridine	Thienopyridine	Cyclopentyl-triazolopyrimidine	Stabilized ATP analogue
Administration	Oral	Oral	Oral	Intravenous
$P2Y_{12}$ blocking	Irreversible	Irreversible	Reversible	Reversible
Regimen	300–600 mg then 75 mg a day	60 mg then 10 mg a day	180 mg then 90 mg twice a day	30 μg/kg bolus then 4 μg/kg/min infusion
Dose in CKD				
eGFR 15–60 ml/min/1.73 m^2	No adjustment	No adjustment	No adjustment	No adjustment
eGFR < 15 ml/min/1.73m^2	Use only for selected indications (e.g., ST prevention)	Not recommended	Not recommended	No adjustment
Activation	Prodrug, with variable liver metabolism	Prodrug, with predictable liver metabolism	Active drug, with additional active metabolite	Active drug
Onset of loading dose action[a]	2–6 h[b]	30 min[b]	30 min[b]	2 min[b]
Offset of action	3–10 days	7–10 days	3–5 days	30–60 min
Withdrawal before surgery	5 days	7 days	5 days	1 h
Plasma half-life of active drug	30–60 min	30–60 min[c]	6–12 h	5–10 min
Adenosine reuptake inhibition	No	No	Yes	Yes (the inactive metabolite only)
Interaction with CYP-targeted drugs	CYP2C19	No	CYP3A4/5	No

ATP adenosine triphosphate, *CKD* chronic kidney disease, *eGFR* estimated glomerular filtration rate

[a] 50% inhibition of ADP-induced platelet aggregation

[b] Onset of action may be delayed if intestinal absorption is delayed (e.g., by opiate)

[c] The distribution phase half-life is reported since it most likely reflects duration of clinically relevant plasma levels, while the corresponding elimination phase half-life is approximately 7 h

associated with improved endothelial function in patients who experienced an ACS as compared with prasugrel, clopidogrel, or no $P2Y_{12}$ inhibitors [16]. A prospective crossover randomized trial is currently ongoing to confirm or dispute these findings (clinicaltrials.gov, NCT02587260).

The aim of this review is to summarize and discuss the safety and effectiveness of the long-term use of ticagrelor in patients with CAD.

Long-Term DAPT Approach: a Contemporary Update

The optimal duration of DAPT in patients with CAD or after percutaneous coronary intervention (PCI) remains a matter of ongoing debate [17–23, 24•, 25•, 26, 27••, 28, 29]. During the last two decades, several trials have explored this issue in patients undergoing PCI, with some investigating the benefit/risk profile of a shortened DAPT duration regimen of 3–6 months (RESET, OPTIMIZE, EXCELLENT, SECURITY, ISAR-SAFE, I-LOVE-IT 2, IVUS-XPL, NIPPON, PRODIGY, ITALIC) [30–38], while others are comparing 12-month DAPT versus a prolonged regimen (DAPT, ARCTIC Interruption, OPTIDUAL, DES-LATE) [39–41, 42••, 43]. The rationale of investigating a longer than 12-month treatment duration is strong, as the evidence that patients with CAD, especially after ACS, remain at long-term risk of new ischemic events is mounting [44]. Nevertheless, the results of long-term DAPT trials have shown contrasting findings. Both PRODIGY and ITALIC trials have demonstrated that 24-month DAPT did not provide benefits compared with 6-month DAPT. The PRODIGY failed indeed to demonstrate the superiority of 24-month DAPT in terms of death, MI, or cerebrovascular events, but rather showed that this prolonged regimen did not decrease ischemic events while increasing bleeding, the need for transfusion as well as the composite of ischemic and bleeding events (net clinical adverse events, NACE) [31]. The ITALIC trial showed the non-inferiority of 6-month DAPT compared with 24-month DAPT with no significant differences in each safety, ischemic, or composite endpoint [30].

The ARCTIC Interruption, DES-LATE, and OPTIDUAL trials supported the concept that there is no apparent benefit but instead potential harm with extension of DAPT beyond 1 year after coronary stenting. In the ARCTIC Interruption trial, at 1 year after DES implantation, 1259 patients were randomized to interruption of DAPT where the thienopyridine was interrupted and a single aspirin antiplatelet treatment was

maintained (interruption group) or a strategy of DAPT continuation for 6–18 months (continuation group) [39]. The majority of patients in DAPT received clopidogrel, while less than 10% received prasugrel. After a median follow-up of 17 months, the primary endpoint (composite of death, myocardial infarction, stent thrombosis, stroke, or urgent revascularization) did not differ between groups (hazard ratio [HR] 1.17 [95% CI 0.68–2.03]; $p = 0.58$), while bleeding events occurred more often in the continuation group compared with the interruption group (major bleeding: HR 0.15 [0.02–1.20]; $p = 0.073$; major or minor bleeding: HR 0.26 [0.07–0.91]; $p = 0.04$) [39]. In the DES-LATE, 5045 patients who received DES and were free of major adverse cardiovascular events (MACE) and major bleeding for at least 12 months after stent placement were randomly allocated to additional 24 months of DAPT (clopidogrel plus aspirin, overall 36 months) versus aspirin alone but DAPT prolongation did not reduce the risk of the composite endpoint of death from cardiac causes, myocardial infarction, or stroke [41]. In the OPTIDUAL trial, 1385 patients free of major cardiovascular/cerebrovascular events (MACCE) or major bleeding and on aspirin and clopidogrel 12 months after stenting were randomized to continuing clopidogrel 75 mg daily (extended DAPT group) or discontinuing clopidogrel (aspirin group) [40]. Median follow-up after stenting was 33.4 months, and the primary outcome (NACE: composite of death, MI, stroke, or major bleeding) as well as single endpoints were similar between the two groups. Although DAPT prolongation failed to demonstrate superiority, this trial was underpowered due to premature interruption [40]. On the other hand, the DAPT trial clearly demonstrated that prolonging DAPT beyond 1 year offers ischemic benefits [42••]. Continued treatment (30-month DAPT) with thienopyridine, as compared with placebo, reduced the rates of stent thrombosis (HR 0.29 [0.17–0.48]; $p < 0.001$), MACCE (HR 0.71 [0.59–0.85]; $p < 0.001$), and MI (HR 0.47 [0.37–0.61]; $p < 0.001$). The rate of death from any cause was 2.0% in the group that continued thienopyridine therapy and 1.5% in the placebo group (HR 1.36 [1.00–1.85]; $p = 0.05$), and the rate of moderate or severe bleeding was increased with continued thienopyridine treatment (2.5% vs. 1.6%, $p = 0.001$) [42••]. Although the trial supported ischemic advantages of 30-month DAPT compared with 12-month DAPT, some concerns were raised in terms of safety. While the increase of bleeding was expected in the prolonged DAPT group, the increase of all-cause death was unexpected and has become a matter of great discussion [42••]. The higher mortality in the DAPT trial was putatively attributed to increased non-cardiovascular death due to cancer, bleeding, and trauma-related deaths; however, an imbalance in the baseline number of patients with a history of cancer might have partly contributed to this risk.

In order to address this issue, a recent meta-analysis of ten randomized trials including 31,666 patients found a reduction of MI and stent thrombosis with treatment with DAPT beyond 1 year after DES implantation, but also an increase of major bleeding and all-cause mortality, owing to higher non-cardiovascular mortality, not offset by a decrease in cardiac mortality [21]. In this meta-analysis, the large patient cohort provided sufficient statistical power and 351 (67%) of the 523 total deaths were recorded in trials other than DAPT [21]. This meta-analysis was different from a prior one by Elmariah et al. that included 14 trials and 69,644 randomly assigned patients concluding that DAPT prolongations were not associated with increased mortality [20]. The latter indeed included a heterogeneous population of patients with atherosclerotic disease (patients treated with PCI but also patients with peripheral artery disease, atrial fibrillation, and CAD managed medically) and did not include the ISAR-SAFE and ITALIC trials that were included in the meta-analysis by Palmerini et al. and these differences may contribute to explain opposite results.

Altogether, studies of long-term DAPT for an additional 18 to 36 months after DES found an absolute decrease in late stent thrombosis and ischemic complications of 1–2% and an absolute increase in bleeding complications of ≈1% [45••]. A weighted risk-benefit analysis of studies with patients treated with DES found 6 fewer MIs and 3 fewer stent thrombosis but 5 additional major bleeds per 1000 patients treated with prolonged DAPT per year [45••].

Based on this evidence described, a general approach may be suggested considering a short-term (3 or 6 months) DAPT strategy in patients at low risk of recurrent coronary events (i.e., stable CAD), in those at low risk of stent thrombosis (especially after treatment with contemporary DES), and in those at high risk of bleeding. Conversely, an extended DAPT strategy (>1 year) might still be considered in some patients in whom prevention of stent and non-stent-related coronary events is likely to counterbalance its potential adverse events, thus resulting in reduced or a neutral effect on mortality.

Long-Term Ticagrelor-Based DAPT in Patients with Prior Myocardial Infarction

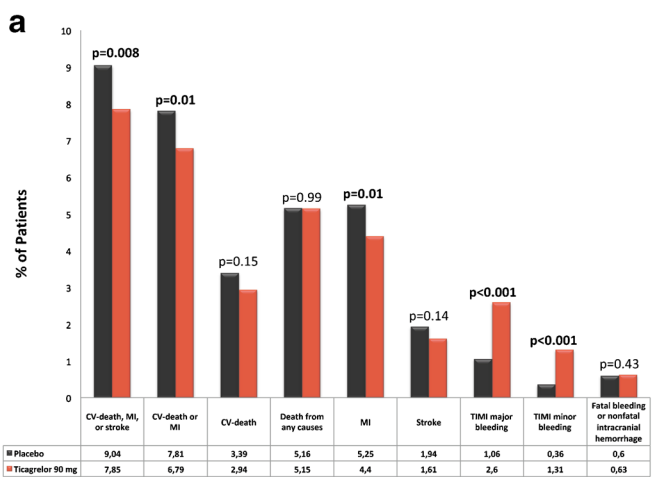
The use of long-term DAPT with ticagrelor in patients with previous MI has been investigated only in the PEGASUS-TIMI-54 trial [46••]. A total of 21,162 patients who experienced a spontaneous myocardial infarction 1 to 3 years earlier were randomly assigned, in a double-blind 1:1:1 fashion, to ticagrelor 90 mg twice a day, ticagrelor 60 mg twice a day, or placebo. All patients were also treated with low-dose aspirin. The primary efficacy endpoint, at a median follow-up of 33 months, was a composite of cardiovascular death, myocardial infarction, or stroke, while the primary safety endpoint was the rate of major bleedings using the TIMI classification.

At 3 years, the primary efficacy endpoint was significantly reduced using each of the two doses of ticagrelor as compared with placebo: 9.04% in the placebo group, 7.85% in the 90-mg ticagrelor group (HR 0.85 [0.75–0.96], $p = 0.008$), and 7.77% in the 60-mg ticagrelor group (HR 0.84 [0.74–0.95], $p = 0.004$) (Fig. 1). On the contrary, the primary safety endpoint was significantly increased in ticagrelor-treated patients as compared with placebo: 1.06% in the placebo group, 2.60% in the 90-mg ticagrelor group ($p < 0.001$), and 2.30% in the 60-mg ticagrelor group ($p < 0.001$) (Fig. 1). Nevertheless, intracranial hemorrhage or fatal bleeding did not differ across groups. Moreover, there was a trend towards a reduction of cardiovascular death alone using both doses of ticagrelor as compared with placebo, even if a statistical significance was not achieved. An exploratory analysis showed a significant decrease in the rate of MI with both doses of ticagrelor as compared to placebo as well as a significant reduction in the stroke rate using ticagrelor 60 mg twice daily. In the intention-to-treat analysis, both doses of ticagrelor showed that they have the same magnitude of efficacy, while the 60-mg dose twice daily was associated with a lower rate of bleedings and dyspnea, showing a more attractive benefit-risk profile. The results of the PEGASUS-TIMI-54 trial suggested that patients with a previous ACS, mainly those in whom the risk of ischemic events and cardiovascular death outweighs the risk of major or life-threatening bleedings, might benefit from prolonged ticagrelor-based DAPT. In fact, the new update of the European Society of Cardiology (ESC) NSTE-ACS guidelines [47], published on 2016, now include a recommendation that DAPT beyond 1 year may be considered depending on the ischemic and bleeding patient risk (tailored prolonged DAPT).

In order to explore the pharmacokinetics and pharmacodynamics of the two doses of ticagrelor, an analysis of the PEGASUS-TIMI-54 has found that ticagrelor 60 mg bid achieved similar levels of peak and trough platelet inhibition in nearly all patients as compared with the 90-mg bid dosage [43]. Yet, the 60-mg ticagrelor regimen was associated with a better safety profile in the trial, and regulatory agencies both in the USA and EU have granted approval to the ticagrelor 60-mg regimen only for DAPT extension in the form of aspirin and ticagrelor beyond 1 year.

In the PEGASUS-TIMI-54, the adherence to the study drug in patients treated with ticagrelor was significantly lower as compared to placebo [48]. Non-adherence is a common issue in clinical trials as well as in routine clinical practice, which significantly affects clinical outcomes and health costs. In the 90-mg ticagrelor group, the rate of drug discontinuation was 32%, in the 60-mg ticagrelor group 29%, and in the placebo group 21% ($p < 0.001$). The treatment discontinuation was mainly driven by non-serious adverse events, such as non-major bleeding and mild to moderate dyspnea, with a high rate early after initiation of the study drug and a low rate for patients completing 1 year of treatment. These data showed how defined "non-serious" adverse events in a clinical trial may influence the quality of life, reducing the patient's adherence to the medical treatment and requiring heedful counseling after the start of ticagrelor administration, in order to maximize drug effectiveness. Importantly, from a practical point of view, another substudy has recently shown that when considering the prolongation of $P2Y_{12}$ inhibitor therapy in high-risk patients, there is a greater benefit in the continuation of such therapy without interruption after MI, rather than re-initiating such therapy in patients who have remained stable for an extended period [49], highlighting the importance of avoiding temporary or permanent DAPT discontinuation.

The results of the PEGASUS-TIMI-54 trial were consistent in the subgroups of patients deemed to be at very



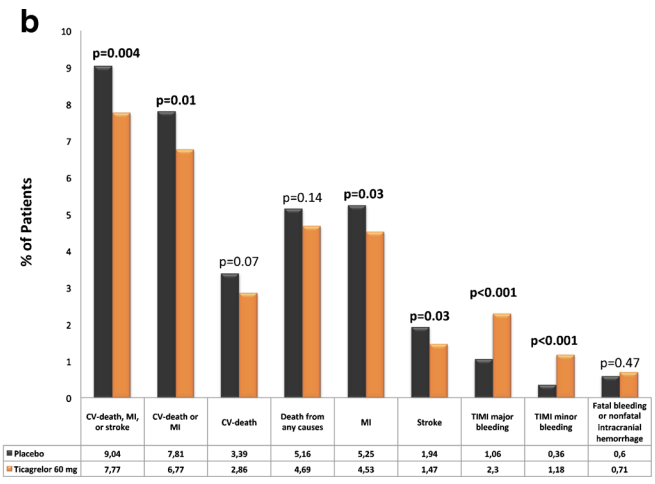


Fig. 1 Three-year safety and efficacy outcomes of the PEGASUS-TIMI-54 trial. **a** Reports 3-year safety and efficacy outcomes related to the comparison between ticagrelor 90 mg twice daily vs. placebo within the PEGASUS-TIMI-54 trial. **b** Reports 3-year safety and efficacy outcomes related to the comparison between ticagrelor 60 mg twice daily vs. placebo within the PEGASUS-TIMI-54 trial. *CV* cardiovascular, *MI* myocardial infarction, *TIMI* thrombolysis in myocardial infarction

high ischemic risk. The addition of ticagrelor to aspirin in patients with diabetes mellitus and prior MI significantly reduced the risk of recurrent ischemic events, including cardiovascular death and coronary heart disease [50], as well as in patients with chronic kidney disease [51]. PAD is known to be more frequent in CAD patients. The presence of PAD in CAD patients worsens prognosis [52–54]. A recent subanalysis of the PEGASUS-TIMI-54 has demonstrated that among stable patients with prior MI, those with concomitant PAD have heightened ischemic risk and ticagrelor in these patients reduced MACE, with a large absolute risk reduction, as well as major adverse limb events [55]. In the PRODIGY trial, PAD patients (approximately 12.5%) were confirmed to be at increased risk of ischemic events and interestingly they benefited by DAPT prolongation up to 24 months with no apparent greater bleeding risk compared with patients without PAD [56]. The effects of ticagrelor in patients with PAD will be definitively assessed by the ongoing EUCLID trial (clinicaltrials.gov, NCT01732822), including 13,500 patients with PAD and testing the superiority of ticagrelor over clopidogrel monotherapy in the reduction of the risk of cardiovascular events.

Finally, a recent analysis of the PEGASUS-TIMI-54 showed that high-risk patients with prior MI are at concomitant high risk for stroke, approximately one third of which are fatal or lead to moderate-to-severe disability [57]. Patients treated with ticagrelor 60 mg twice daily had a significant decrease of stroke risk without an increase of hemorrhagic stroke but with more major bleeding [57].

After PEGASUS-TIMI-54 publication, the topic of cancer-related increased mortality risk after long-term antithrombotic therapy has emerged once more as matter of discussion within the community [58]. Bonaca et al. reported higher rates of cancer-related death among patients receiving either 90 or 60 mg of ticagrelor than among those receiving placebo (1.10% and 0.92% vs. 0.76%), and when these findings were pooled with those of the DAPT trial, a significant relative increase of 41% in the number of cancer-related deaths among patients who were treated with extended DAPT [58] was shown. Also, in the case of PEGASUS-TIMI-54, however, it seems that an imbalance of cancer patients in the randomized groups may contribute to partly explain this issue. Future studies are needed to shed light on this matter [58]. However, unlike the null effect of long-term thienopyridine administration, which tended to increase non-CV mortality and exerted a null effect on CV mortality, the long-term treatment of ticagrelor in the PEGASUS-TIMI-54 trial was associated with a numerical (even if not statistically significant) decrease of CV deaths, which overcompensated a small yet consistent increase of non-CV deaths (Costa F. et al. IJC 2015).

Long-Term DAPT in Patients with Prior Myocardial Infarction

The search for a tailored approach to the decision-making for the DAPT duration has moved the interest towards subgroups that may benefit by long-term DAPT with no or acceptable bleeding risk. An initial trial on clopidogrel, the CHARISMA, enrolled patients with established atherosclerosis or at high risk of clinical atherosclerotic disease and randomized them to either DAPT or aspirin monotherapy [59]. At a median follow-up of 28 months, the DAPT arm had no significant reduction in ischemic events but a 0.4% absolute increase in severe bleeding was observed [59]. Notably, a post hoc analysis of patients enrolled in the study with previous MI showed a 1.7% absolute reduction of the composite endpoint (cardiovascular death, MI, or stroke) with DAPT, with no benefit in those with CAD without prior MI [60]. In accordance with the interesting findings of the PEGASUS-TIMI-54 trial in this specific setting of patients, a recent meta-analysis has explored the role of long-term DAPT for secondary prevention in patients with previous MI [27••]. In particular, 6 trials were pooled together (PEGASUS-TIMI-54, PRODIGY, CHARISMA, DAPT, ARCTIC Interruption, and DES-LATE) including 33,435 patients followed over a mean of 31 months [27••]. Of these patients, only those from the PEGASUS-TIMI-54 received ticagrelor as $P2Y_{12}$ inhibitor. Long-term DAPT reduced the risk of MACE compared with aspirin alone (risk ratio, RR, 0.78 [0.67–0.90]; $p = 0.001$) and cardiovascular death (RR 0.85 [0.74–0.98]; $p = 0.03$), without differences in non-cardiovascular death (RR 1.03 [0.86–1.23]; $p = 0.76$) or all-cause mortality (RR 0.92 [0.83–1.03]; $p = 0.13$). Long-term DAPT also reduced MI (RR 0.70 [0.55–0.88]; $p = 0.003$), stroke (RR 0.81 [0.68–0.97]; $p = 0.02$), and stent thrombosis (RR 0.50 [0.28–0.89]; $p = 0.02$), but at the cost of an increased risk of major bleeding (RR 1.73 [1.19–2.50]; $p = 0.004$), although not fatal bleeding was similar in the two regimens (RR 0.91 [0.53–1.58]; $p = 0.75$). Therefore, this study supported the concept that despite increased major bleeding, long-term DAPT, irrespective of type of $P2Y_{12}$ inhibitor used, may offer benefits in terms of ischemic events without increasing mortality in patients with prior MI [27••]. Interestingly, this study did not show a significant reduction in all-cause mortality; thus, Bonaca and Sabatine recently expanded this meta-analysis also including the cohort of patients with prior MI in the TRA2P-TIMI-50 trial (excluding patients with stroke/TIA because vorapaxar is not approved for them) and focused only on the ticagrelor 60-mg group of the PEGASUS-TIMI-54 which is the dose currently approved [61]. They obtained a significant 11.5% decrease of all-cause mortality, which was attributable to reduction of cardiovascular mortality without reduction or increase of non-cardiovascular death. They concluded that long-term intensive DAPT was beneficial in

patients with prior MI and no high risk of bleeding [61]. However, this study did not include the OPTIDUAL trial, another long-term negative trial, and was also criticized based on the concept that post hoc mixing of different trials with different antiplatelet drugs, different overall findings, and different follow-ups introduces clinical heterogeneity in the analysis [62]. It was argued, indeed, that it is not reliable to estimate all-cause mortality from pooling subgroups with negative or inconclusive findings from underpowered studies due to the high risk of false-positive conclusions, which alter the possibility to translate these findings into health care and daily practice [62]. Therefore, although patients with prior MI seem to benefit from DAPT prolongation, current evidence is not sufficient to support survival advantages with this approach, which on the contrary can be obtained with other recommended strategies including drugs (aspirin, statins, beta-blockers, and ACE inhibitors) or lifestyle changes (i.e., stop smoking, regular exercise) [62].

How to Select the Optimal Candidates for a Long-Term DAPT in Contemporary Clinical Practice

The translation of trial findings into clinical practice is a complex process that needs to take always into account the single patient features. A tailored approach is the most often recommended strategy in order to select the DAPT duration in each patient based on the patient's risk of ischemic and bleeding events. In line with this concept, a dedicated algorithm would be helpful to properly select the best candidates for a long-term use of DAPT. A pre-specified analysis of the DAPT trial population has recently proposed a 9-item score [63••], named DAPT score (Table 2), which comprised age (≥75 years or 65 to 74 years), prior MI or PCI, stent diameter <3 mm, congestive heart failure or left ventricular ejection fraction (LVEF) <30%, MI at presentation, paclitaxel-eluting stent, smoking, and diabetes. In this exploratory analysis, the composite endpoint of stent thrombosis or MI in patients with DAPT score <2 was not significantly different in the long-term DAPT arm as compared with aspirin alone (1.7% vs. 2.3%, respectively; $p = 0.07$), while GUSTO moderate or severe bleeding occurred more frequently in the long-term DAPT group (3.0% vs. 1.4%; $p < 0.001$). Contrarily, patients with a DAPT score ≥2 treated with prolonged thienopyridines had a significantly lower rate of ST or MI compared with aspirin alone (2.7% vs. 5.7%; $p < 0.001$) and no significant difference in terms of GUSTO moderate to severe bleedings (1.8% vs. 1.4%; $p = 0.26$). Similar results were confirmed also in the subpopulation of patients with previous MI of the DAPT trial [64]. Main limitations of this score are the following: (a) It comes from a post hoc analysis; (b) it is not powered to examine differences in outcomes between subgroups; (c) unmeasured confounders cannot be excluded.

Table 2 DAPT score

Items	Points
Age	
<65 years	0
65–75 years	−1
>75 years	−2
Vein graft stent	2
Cigarette smoking within last 2 years	1
Diabetes mellitus	1
Myocardial Infarction at presentation	1
Stent diameter <3 mm	1
History of CHD or LVEF <30%	2
Prior MI or prior PCI	1
Paclitaxel-eluting stent	1

CHD chronic heart disease, *LVEF* left ventricle ejection fraction, *MI* myocardial infarction, *PCI* percutaneous coronary intervention

Moreover, the score is applicable to patients with clinical characteristics similar to those enrolled in the trial, but the translation and the generalizability to all patients with CAD treated with PCI or with prior MI are limited and not a plausible scenario for daily practice. For example, the DAPT score is not applicable to the PEGASUS-TIMI-54 patient population due to the different design of the two trials, the inclusion of PCI procedural items in the score (approximately 20% of patients in the PEGASUS-TIMI-54 did not receive PCI), and the $P2Y_{12}$ inhibitor used (mainly clopidogrel in the DAPT study with approximately 30% of patients receiving prasugrel, while ticagrelor only in the PEGASUS-TIMI-54; patients receiving ticagrelor or other antiplatelet combinations could have a different risk/benefit ratio). Additionally, the use of the DAPT score has not yet demonstrated to improve patient outcomes. The future validation of the DAPT score in contemporary datasets is mandatory to assess the prediction rule of this score in other cohorts and its potential usefulness on patient treatment in daily clinical practice. Thus, it should be used with caution until further validation is performed, and optimal clinical and procedural care to reduce overall bleeding and ischemic risks should be performed irrespective of the patient's score.

Conclusion

Results of recent trials, in particular the PEGASUS-TIMI-54 trial, seem to encourage the long-term use of ticagrelor in patients with CAD who are deemed at high thrombotic and/or low bleeding risks. Whether long-term use of ticagrelor is able to reduce mortality remains to be clarified. Doubtless, it is associated with lower thrombotic risks but also with an

increased risk of bleeding, although not fatal or intracranial ones. Therefore, tailoring therapy remains the optimal approach to be recommended and selecting patients at high risk of ischemic events but low risk of bleeding may be a potential strategy to identify patients who may benefit by a more aggressive long-term DAPT regimen.

Compliance with Ethical Standards

Conflict of Interest Sara Ariotti declares that she has no conflict of interest. Giuseppe Gargiulo receives research grant support from Cardiopath PhD program (Federico II University). Marco Valgimigli receives speakers' bureau and institutional research grant from AstraZeneca.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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•• of Major Importance

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Short term versus long term dual antiplatelet therapy after implantation of drug eluting stent in patients with or without diabetes: systematic review and meta-analysis of individual participant data from randomised trials

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ABSTRACT

OBJECTIVE

To compare clinical outcomes between short term (up to 6 months) and long term (12 months) dual antiplatelet therapy (DAPT) after placement of a drug eluting stent in patients with and without diabetes.

DESIGN

Individual participant data meta-analysis. Cox proportional regression models stratified by trial were used to assess the impact of diabetes on outcomes.

DATA SOURCE

Medline, Embase, and Cochrane databases and proceedings of international meetings searched for randomised controlled trials comparing durations of DAPT after placement of a drug eluting stent. Individual patient data pooled from six DAPT trials.

PRIMARY OUTCOME

Primary study outcome was one year risk of major adverse cardiac events (MACE), defined as cardiac death, myocardial infarction, or definite/probable stent thrombosis. All analyses were conducted by intention to treat.

RESULTS

Six trials including 11 473 randomised patients were pooled. Of these patients, 3681 (32.1%) had diabetes and 7708 (67.2%) did not (mean age 63.7 (SD 9.9) and 62.8 (SD 10.1), respectively), and in 84 (0.7%) the information was missing. Diabetes was an independent predictor of MACE (hazard ratio 2.30, 95% confidence interval 1.01 to 5.27; P=0.048 At one year follow-up, long term DAPT was not associated with a decreased risk of MACE compared with short term DAPT in patients with (1.05, 0.62 to 1.76; P=0.86) or without (0.97, 0.67 to 1.39; P=0.85) diabetes (P=0.33 for interaction). The risk of myocardial infarction did not differ between the two DAPT regimens (0.95, 0.58 to 1.54; P=0.82; for those with diabetes and 1.15, 0.68 to 1.94; P=0.60; for those without diabetes (P=0.84 for interaction). There was a lower risk of definite/probable stent thrombosis with long term DAPT among patients with (0.26, 0.09 to 0.80; P=0.02) than without (1.42, 0.68 to 2.98; P=0.35) diabetes, with positive interaction testing (P=0.04 for interaction), although the landmark analysis showed a trend towards benefit in both groups. Long term DAPT was associated with higher rates of major or minor bleeding, irrespective of diabetes (P=0.37 for interaction).

CONCLUSIONS

Although the presence of diabetes emerged as an independent predictor of MACE after implantation of a drug eluting stent, compared with short term DAPT, long term DAPT did not reduce the risk of MACE but increased the risk of bleeding among patients with stents with and without diabetes.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Dual antiplatelet therapy (DAPT) is the standard of care among patients undergoing percutaneous coronary intervention, but its optimal duration is debated, particularly after implantation of a drug eluting stent

Some trials have shown that short term (up to 6 months) DAPT is not inferior to 12 months of treatment

As diabetes is a well known risk factor for cardiovascular disease as well as for disease progression and ischaemic complications after percutaneous coronary intervention, patients might benefit from prolonged DAPT

WHAT THIS STUDY ADDS

After percutaneous coronary intervention with implantation of a drug eluting stent, patients with diabetes, including those receiving treatment with insulin, were confirmed to be at higher risk of ischaemic events compared with patients without diabetes, though long term compared with short term DAPT did not reduce ischaemic or composite endpoints and slightly increased the risk of bleeding in patients with and without diabetes

Short term DAPT after implantation of a drug eluting stent is as effective as long term DAPT in patients with or without diabetes and might reduce risks and costs of prolonged treatment

Introduction

Dual antiplatelet therapy (DAPT) represents the evidence based standard of care among patients undergoing percutaneous coronary intervention. Treatment aims to reduce the risk of stent thrombosis after implantation of a coronary stent and prevent coronary atherothrombotic events at sites outside the stented segment. The optimal duration of DAPT after stent implantation in general, and particularly after implantation of a drug eluting stent, however, remains a matter of controversy.[1-7] Currently, a minimum duration of six months has been advocated in professional guideline documents and adopted worldwide for

management of patients receiving drug eluting stents, irrespective of type.[8-10]

Diabetes mellitus is a widely recognised risk factor for atherosclerosis, disease progression, and restenosis after percutaneous coronary intervention.[11-14] Although new generation drug eluting stents have also been shown to provide improved safety and efficacy compared with balloon angioplasty, bare metal stents, and early generation drug eluting stents among patients with diabetes, such patients, particularly when they need treatment with insulin, have a high ischaemic risk.[15-18] Increased platelet and thrombin reactivity and decreased response to therapeutic agents including aspirin and clopidogrel have been described in patients with diabetes.[19 20]

Whether diabetes should be taken into consideration in the selection of the most appropriate duration of DAPT remains unclear. Recently, it was proposed that the presence of diabetes can identify patients who benefit from prolonged DAPT because of the increased related ischaemic risk.[4 6 21] Yet the evidence appraising the role of diabetes in the choice of the optimal duration is limited.[22]

We assessed the impact of diabetes status on outcomes after implantation of drug eluting stents in patients treated with short term (≤6 months) or long term (12 months) DAPT. We conducted a patient level pooled analysis of randomised trials comparing clinical outcomes between short term and long term treatment after implantation of a drug eluting stent and stratified outcomes according to diabetes status.

Methods

Study design

The present study was an individual participant data (IPD) meta-analysis of randomised controlled trials designed to investigate the efficacy and safety of long versus short term DAPT in patients with or without medically treated diabetes. The present meta-analysis was performed according to the PRISMA-IPD statements.[23]

In November 2015, we searched Medline, Embase, Cochrane controlled trials register databases, and main international websites and meetings for randomised controlled trials directly comparing short term (3-6 months) and long term (≥12 months) DAPT among patients undergoing percutaneous coronary intervention with drug eluting stents. We excluded trials that looked at DAPT for 12 months compared with more than 12 months. The following keywords were used: "randomized clinical trial", "drug-eluting stent", "dual antiplatelet therapy", "clopidogrel", "aspirin", "thienopyridines" (see appendix for supplementary methods). No language or publication date restrictions were imposed. The most recent data for a given study were abstracted. The internal validity of randomised controlled trials was assessed by evaluating concealment of allocation, blind adjudication of events, and inclusion of all randomised patients in the analysis. The quality of trials included in the meta-analysis was appraised with Cochrane methods (selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias).

Three investigators (GG, MV, and TP) independently did the systematic search and critically identified studies to ensure satisfaction of the collected studies.

Among qualifying trials, those for which we obtained patient level data from the principal investigators were finally included in the present meta-analysis and combined in a single pooled database. In addition to the four previously included randomised controlled trials,[24-28] we included the SECURITY[29] and the ITALIC[30] trials (fig 1; tables A-D in appendix). The intention to treat population was used for these analyses, including all patients according to randomised treatment arm regardless of actual treatment. Data beyond one year were censored to preserve analysis homogeneity. Furthermore, we excluded a quarter of patients randomised to bare metal stents from the PRODIGY population to restrict the analysis to patients receiving a drug eluting stent.[25 31] Characteristics of the included studies are described in tables A-D in the appendix.

Definitions end endpoints

Our primary endpoint was the one year rate of major adverse cardiac events (MACE), including the composite of cardiac death, myocardial infarction, or definite/probable stent thrombosis, as previously described.[24] Secondary endpoints included the one year rate of major and minor bleeding, all cause death, cardiac death, stroke, myocardial infarction, stent thrombosis (definite, probable, and definite/probable), and target vessel revascularisation, and combinations of these endpoints.

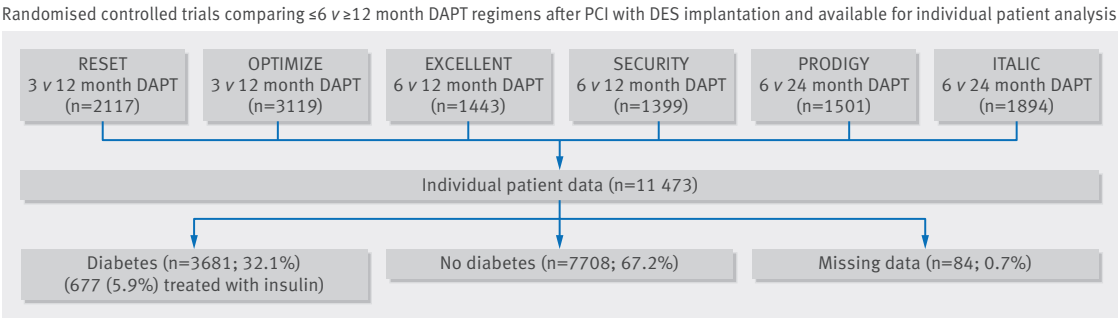

Fig 1 | Studies and patients included in analysis of individual patient data. PCI=percutaneous coronary intervention; DES=drug eluting stent

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We incorporated the endpoint definitions as applied in each trial. Stent thrombosis was defined according to criteria from the academic research consortium.[32] Four of the included trials defined bleeding according to TIMI (thrombolysis in myocardial infarction) criteria.[33] One trials used the modified REPLACE-2/GUSTO criteria,[26] while another trial used the BARC (bleeding academic research consortium) criteria.[34] In each trial a blinded clinical event committee adjudicated events (table B in appendix). Table C in the appendix reports endpoint definitions in each included trial.

Patient involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in the design and implementation of the study. There are no plans to involve patients in dissemination.

Statistical analysis

We report categorical variables as count and percentages and compared them with a conditional regression analysis stratified by trial. Continuous variables are reported as means and standard deviation and were compared with a two way analysis of variance stratified by trial. We carried out an individual patient data meta-analysis with a one stage approach.

Results are reported as hazard ratios with 95% confidence intervals. We used a mixed effects Cox regression model that took into account the variation between trials in baseline hazard and hazard ratios to derive an overall hazard ratio across trials (see supplementary methods in appendix).[35 36] We used Cox regression for formal interaction testing to evaluate consistency of treatment effect between the groups with and without diabetes. Cumulative survival curves were constructed with the Kaplan-Meier model.

From the pooled patient level database, we also investigated all endpoints in the subgroup of patients with diabetes who were receiving treatment with insulin. We also examined the risk of MACE with long term versus short term DAPT in prespecified subgroups: by clinical presentation (acute coronary syndrome or stable), age (<65 or ≥65), sex, and presence of multivessel disease.

As a sensitivity analysis, we compared long term versus short term DAPT for MACE, myocardial infarction, definite/probable stent thrombosis, and major or minor bleeding after censoring clinical events occurring before the landmark time point (landmark analyses at time of DAPT discontinuation) and excluding patients who prematurely discontinued DAPT (defined by stopping at least one month before the period scheduled by randomisation, unless caused by an adverse event such as bleeding).

We performed a further sensitivity analysis including the two randomised controlled trials for which we did not have patient level data.[37 38] In this case, we compared ≤6 month versus 12 month DAPT in patients with and without diabetes for net clinical adverse events (NACE; defined as the composite of all cause death, myocardial infarction, stroke, or major bleeding) because the published data ffom these two randomised controlled trials only reported hazard ratios for this endpoint in patients with or without diabetes. We used a two stage approach for this analysis. We calculated hazard ratios and 95% confidence intervals from the individual patient data available from the six randomised controlled trials and used the hazard ratios and risk ratios published in the subgroup analyses for the ISAR-SAFE and I-LOVE-IT 2 trials, respectively (see table E in appendix).[37 38] We then combined all the estimates of effectiveness using standard meta-analysis methods.

We assessed heterogeneity with τ^2 statistic, with values <0.04, 0.04-0.36, and >0.36 representing mild, moderate, and severe heterogeneity, respectively.[39]

Values of P<0.05 were considered significant for all analyses. We used Stata version 14 (StataCorp, College Station, TX), R (R Foundation for Statistical Computing, Vienna, Austria), and Reviewer Manager version 5.2 (RevMan; Nordic Cochrane Centre, Copenhagen).

Results

Figure 1 shows the study population (the study flow diagram is shown in fig A in the appendix). Six trials were included in the final analysis, comprising PRODIGY,[25] OPTIMIZE,[26] EXCELLENT,[27] RESET,[28] SECURITY,[29] and ITALIC[30] (tables A-C in appendix). Among these randomised controlled trials, two studies compared 3 month with 12 month DAPT (RESET and OPTIMIZE), two studies compared 6 month with 12 month DAPT (EXCELLENT and SECURITY), and two studies compared 6 month with 24 month DAPT (PRODIGY and ITALIC) (fig 1). The risk of bias was generally low, although the treatment was open label in all trials, and SECURITY and ITALIC were stopped early because of recruitment problems (table D in appendix). When we checked the individual patient data, we did not identify any relevant issues undermining the data integrity.

Patient population

Among the 11 473 randomised patients identified, 3681 (32.1%) had diabetes (mean age 63.7, SD 9.9), 7708 (67.2%) did not have diabetes (mean age 62.8, SD 11.0), and the information was missing in 84 (0.7%) (fig 1). Among patients with diabetes, 677 patients (mean age 62.8, SD 10.1) were treated with insulin (18.4% of those with diabetes; 5.9% of the overall population). The numbers randomised to long term versus short term DAPT were, respectively, 1853 and 1828 in the group with diabetes, 340 and 337 in the group with diabetes treated with insulin, and 3848 and 3860 in the group without diabetes.

Baseline characteristics

Baseline characteristics were well balanced between long term and short term DAPT arms within the groups with and without diabetes (table 1). There were, however, distinct differences in almost every variable between patients with and without diabetes (table F in appendix). Patients with diabetes were older, more likely to be women, and had higher rates of

Table 1 | Baseline characteristics according to randomisation for duration of dual antiplatelet therapy (DAPT) after implantation of drug eluting stent in randomised controlled trials according to diabetes status. Figures are percentages (numbers) of patients unless specified otherwise

	Diabetes (n=3681)			No diabetes (n=7708)		
Characteristic	Long DAPT (n=1853)	Short DAPT (n=1828)	P value	Long DAPT (n=3848)	Short DAPT (n=3860)	P value
Mean (SD) age (years)	63.7 (10.0)	63.6 (9.9)	0.60	62.8 (11.1)	62.8 (10.8)	0.73
Men	64.0 (1186/1853)	65.8 (1202/1828)	0.27	72.0 (2770/3848)	72.2 (2787/3860)	0.83
Hypertension	87.4 (1618/1852)	87.0 (1591/1828)	0.76	75.1 (2889/3846)	74.5 (2873/3856)	0.54
Hypercholesterolaemia	72.3 (1326/1834)	71.9 (1302/1810)	0.81	60.7 (2308/3803)	60.1 (2296/3821)	0.59
Smoking	17.6 (274/1558)	19.5 (301/1543)	0.17	23.6 (799/3381)	24.0 (816/3403)	0.74
Previous myocardial infarction	22.6 (371/1638)	25.2 (416/1652)	0.09	21.2 (742/3505)	20.2 (706/3501)	0.30
Previous PCI	19.5 (321/1646)	21.4 (354/1658)	0.19	15.7 (550/3511)	16.6 (585/3516)	0.27
Previous CABG	7.7 (126/1645)	7.3 (121/1657)	0.70	5.6 (196/3507)	5.4 (190/3518)	0.73
Previous stroke	4.4 (54/1230)	6.2 (78/1257)	0.05	3.3 (81/2457)	3.1 (78/2482)	0.76
Creatinine >106.08 μmol/L	10.9 (79/725)	8.2 (59/720)	0.08	7.4 (133/1804)	6.9 (125/1812)	0.58
Clinical presentation:						
Stable angina pectoris	62.5 (1159/1853)	59.8 (1094/1828)	0.09	56.6 (2178/3847)	57.7 (2227/3860)	0.34
Acute coronary syndrome	37.5 (694/1853)	40.2 (734/1828)		43.4 (1669/3847)	42.3 (1633/3860)	
STEMI	3.3 (61/1853)	3.0 (55/1828)	—	6.4 (247/3847)	6.9 (265/3860)	—
NSTEMI	7.4 (137/1853)	7.2 (131/1828)	—	9.0 (348/3847)	8.5 (328/3860)	—
Unstable angina	26.8 (496/1853)	30.0 (548/1828)	—	27.9 (1074/3847)	26.9 (1040/3860)	—
Discharge drugs:						
Aspirin	99.9 (1292/1293)	99.9 (1277/1278)	0.99	99.5 (2693/2706)	99.8 (2694/2699)	0.06
Clopidogrel	99.8 (1290/1293)	99.6 (1273/1278)	0.47	99.7 (2699/2706)	99.6 (2688/2699)	0.49
β blockers	71.5 (765/1070)	70.8 (759/1072)	0.72	70.0 (1555/2222)	68.4 (1527/2232)	0.26
ACEI/ARB	60.3 (645/1070)	62.6 (671/1072)	0.27	56.9 (1265/2222)	57.1 (1275/2232)	0.90
Statins	86.5 (926/1070)	87.7 (940/1072)	0.43	86.8 (1928/2222)	88.1 (1966/2232)	0.19
Mean (SD) diseased vessels/patient	1.53 (0.9)	1.54 (0.9)	0.79	1.48 (0.8)	1.49 (0.8)	0.81
Mean (SD) No of treated vessels/patient	1.22 (0.5)	1.25 (0.5)	0.15	1.21 (0.4)	1.20 (0.4)	0.41
Mean (SD) No of stents/patient	1.58 (0.9)	1.60 (0.9)	0.64	1.51 (0.8)	1.48 (0.8)	0.31
Mean (SD) No of lesions stented/patient	1.33 (0.6)	1.34 (0.6)	0.83	1.26 (0.5)	1.26 (0.5)	0.53
Mean (SD) total stent length/patient (mm)	39.0 (26.1)	39.3 (26.7)	0.85	34.6 (22.9)	33.9 (23.1)	0.35
Mean (SD) smallest stent implanted (mm)	3.0 (0.5)	3.0 (0.4)	0.35	3.1 (0.8)	3.1 (0.5)	0.78
Type of drug eluting stent:						
PES	4.1 (75/1844)	4.2 (76/1820)	<0.001	4.8 (182/3831)	4.8 (183/3840)	<0.001
SES	4.3 (80/1844)	3.7 (68/1820)		11.1 (425/3831)	2.5 (96/3840)	
EES	39.4 (727/1844)	34.7 (631/1820)		35.4 (1357/3831)	30.9 (1185/3840)	
ZES	47.5 (875/1844)	52.9 (962/1820)		44.1 (1689/3831)	57.0 (2190/3840)	
BES	4.0 (74/1844)	3.8 (70/1820)		4.0 (154/3831)	4.2 (160/3840)	
Mixed	0.5 (9/1844)	0.4 (8/1820)		0.5 (19/3831)	0.3 (13/3840)	
Other	0.2 (4/1844)	0.3 (5/1820)		0.1 (5/3831)	0.3 (13/3840)	
Stented coronary artery:						
Left main	2.3 (23/998)	2.7 (27/1002)	0.58	2.3 (54/2369)	2.2 (52/2372)	0.84
LAD	62.5 (726/1161)	65.5 (763/1165)	0.14	62.8 (1657/2639)	62.3 (1656/2659)	0.70
LCx	35.1 (381/1087)	33.0 (358/1085)	0.31	31.2 (778/2497)	30.7 (758/2472)	0.71
RCA	39.7 (428/1078)	39.8 (434/1091)	0.97	34.5 (862/2497)	30.6 (868/2508)	0.95
Bifurcation	18.4 (115/624)	18.8 (115/612)	0.87	16.0 (225/1410)	14.3 (203/1424)	0.21
Chronic total occlusion	2.0 (22/1084)	2.7 (29/1083)	0.32	2.3 (51/2240)	2.4 (55/2247)	0.71

BES=biolimus eluting stent; CABG=coronary artery bypass graft; EES=everolimus eluting stent; GFR=glomerular filtration rate; LAD=left anterior descending artery; NSTEMI=non-ST elevation myocardial infarction; PCI=percutaneous coronary intervention; PES=paclitaxel eluting stent; SES=sirolimus eluting stent; STEMI= ST elevation myocardial infarction; SVG=saphenous vein graft; ZES=zotarolimus eluting stent.

cardiovascular disease (hypertension, hypercholesterolaemia, previous myocardial infarction, previous percutaneous coronary intervention, previous coronary artery bypass grafting, previous stroke, and renal dysfunction) than those without diabetes (table F in appendix). Stable angina was more often the clinical presentation in both those with and without diabetes. Patients with diabetes had more extensive coronary artery disease, as evidenced by the higher number of diseased vessels, treated vessels and lesions, bifurcation treatment, stents implanted, and longer total stent length but smaller stent diameter implanted (table F in appendix).

Impact of diabetes on the primary endpoint

Diabetes (P=0.046), number of diseased vessels (P=0.004), and total stent length per patient (P=0.002) were independent predictors of MACE. Compared with patients without diabetes, those with diabetes had significantly higher rates of MACE (adjusted hazard ratio 2.30, 95% confidence interval 1.01 to 5.27; P=0.048) (fig 2).

Long term *v* short term DAPT for primary endpoint according to diabetes status

The rates of MACE at one year were similar among patients treated with long term versus short term DAPT in each subgroup (hazard ratio 1.05, 95% confidence

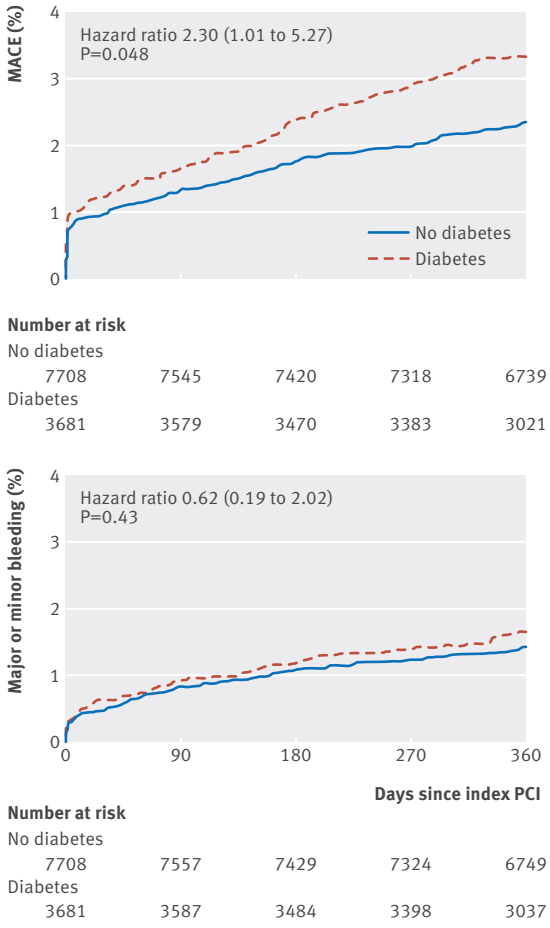

Fig 2 | **Ischaemic and bleeding events in patients with and without diabetes. PCI=percutaneous coronary intervention**

interval 0.62 to 1.76, P=0.86, τ^2=0.16, for those with diabetes; 0.97, 0.67 to 1.39, P=0.85, τ^2=0.06, for those without diabetes; interaction P=0.33) (fig 3, table 2).

Within the group of patients with diabetes, there were no significant differences in MACE between long term and short term DAPT at one year among prespecified subgroups (sex, age ≥65, acute coronary syndrome, multivessel disease) as well as in patients without diabetes (table 3). Even in subgroups there was no significant interaction between diabetes and DAPT regimen (table 3).

Bleeding events

There were no significant differences in terms of bleeding in patients with or without diabetes (adjusted hazard ratio 0.62, 95% confidence interval 0.19 to 2.02; P=0.43) (fig 2; table G in appendix). Conversely, 12 month DAPT was associated with a significantly higher rate of major or minor bleeding compared with short term DAPT in patients with diabetes (1.89, 1.10 to 3.27; P=0.02; τ^2=0.02) and a non-significant increase in those without diabetes (1.43, 0.96 to 2.11; P=0.08; τ^2=0.01; interaction P=0.37) (fig 3, table 2). Major bleeding events were consistently increased with long term DAPT in both populations, though significantly only in patients without diabetes (1.72, 0.72 to 4.10, P=0.22, τ^2=0.00, for those with diabetes; 2.56, 1.08 to 6.07, P=0.03, τ^2=0.43, in those without diabetes; interaction P=0.69; table 2).

Other clinical outcomes

The risk of myocardial infarction was significantly increased among patients with diabetes compared with those without diabetes (adjusted hazard ratio 3.66, 95% confidence interval 1.25 to 10.69; P=0.018), and it was the major determinant of the overall increase of MACE (table G in appendix). There were, however, no significant differences in the risk of myocardial infarction between long term versus short term DAPT (0.95, 0.58 to 1.54, P=0.82, τ^2=0.03, for those diabetes; 1.15, 0.68 to 1.94, P=0.60, τ^2=0.19, for those without diabetes; interaction P=0.84; table 2).

The risk of definite or probable stent thrombosis was numerically but not significantly increased among patients with diabetes compared with those without (adjusted hazard ratio 1.89, 95% confidence interval 0.31 to 11.38; P=0.49; table G in appendix). There was a reduction in the risk of definite/probable stent thrombosis with long term compared with short term DAPT among patients with diabetes but with severe heterogeneity (0.26, 0.09 to 0.80; P=0.02; τ^2=0.47), whereas no such effect was observed in patients without diabetes (1.42, 0.68 to 2.98; P=0.35; τ^2=0.00), with positive interaction testing (interaction P=0.04; table 2).

Table 2 (and table G in appendix) reports all other endpoints. No significant differences emerged between patients treated with long term versus short term DAPT in patients with and without diabetes.

Sensitivity analyses

Consistent with the main analysis, rates of MACE were similar with long term or short term DAPT in both patients with and without diabetes in a landmark analysis in which we censored events encountered before DAPT discontinuation and excluding patients who stopped DAPT early (table H in appendix). This analysis confirmed the absence of differences observed in terms of myocardial infarction and the trend towards an increased risk of bleeding with DAPT for 12 months. In contrast with the main analysis, the rates of definite/probable stent thrombosis showed a trend towards reduced event rates in both patients with and without diabetes treated with DAPT for 12 months compared with short term treatment.

The overall results suggesting similar outcomes with short term and long term DAPT, irrespective of diabetes status, were further confirmed when we carried out the meta-analysis including published results from the ISAR-SAFE[38] and I-LOVE-IT 2[37] trials. The composite of all cause death, myocardial infarction, stroke, or major bleeding was similar between short term and long term DAPT in both patients with diabetes (5074 patients; hazard ratio 0.92, 95% confidence interval 0.69 to 1.23; P=0.56; I^2=12%; fig 4) and without diabetes (12 141 patients; 0.99, 0.78 to 1.25; P=0.69; I^2=15%; fig 4), without significant heterogeneity between these subgroups (P=0.69; I^2=0%; fig 4).

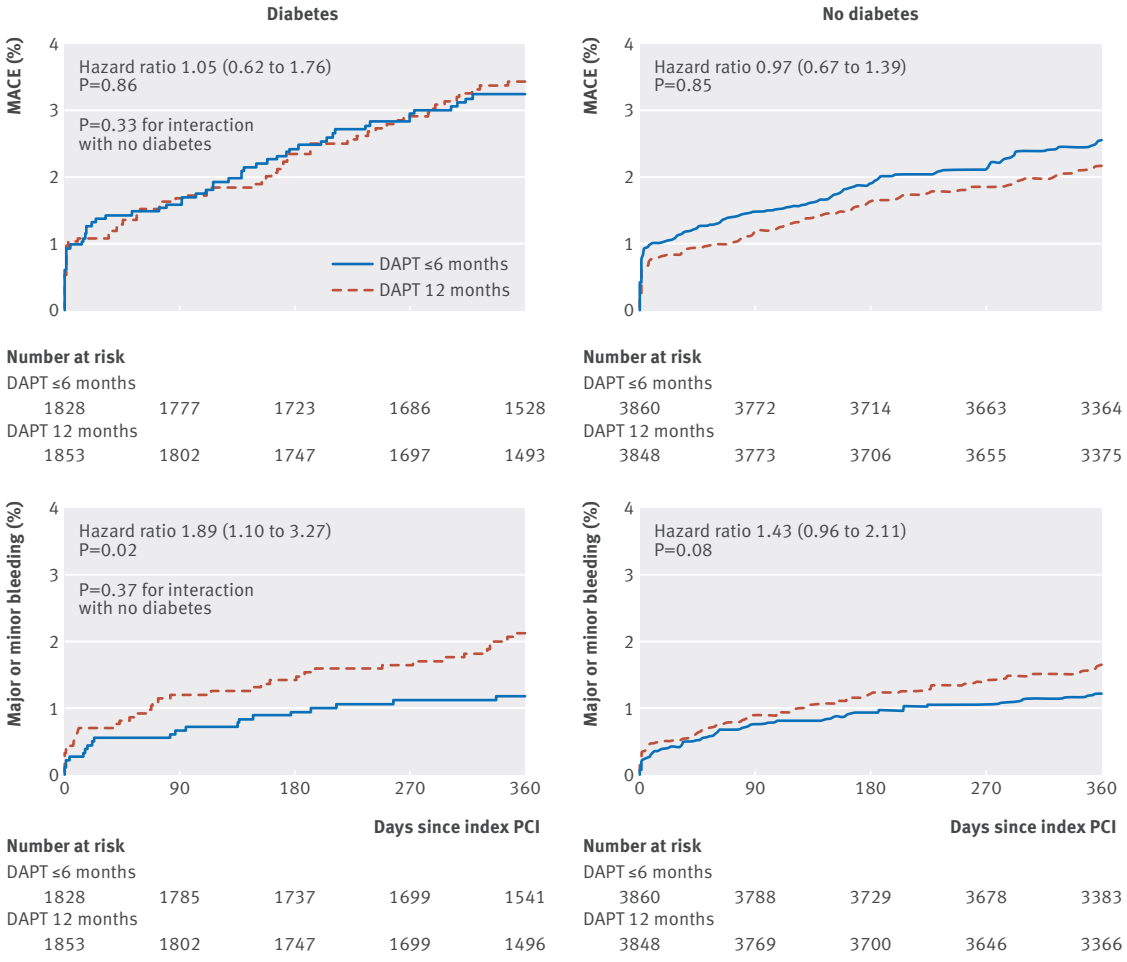

Fig 3 | **Ischaemic and bleeding events in patients with or without diabetes according to long term and short term DAPT. PCI=percutaneous coronary intervention**

Discussion

This patient level analysis of six randomised trials assessed clinical outcomes of long term versus short term DAPT in patients with or without diabetes. It showed that patients with diabetes, including those treated with insulin, had a higher baseline risk profile and showed an increased risk of MACE but not of bleeding, even after adjustment. Compared with short term DAPT, long term DAPT was associated with similar rates of MACE in patients with and without diabetes, although stent thrombosis was reduced. The risk of MACE did not differ across the prespecified subgroups of patients (by acute coronary syndrome, sex, multivessel disease, and age ≥65). Short term DAPT was associated with reduced risks of bleeding, irrespective of diabetes status.

To date, nine randomised controlled trials have looked at 3 or 6 months compared with 12 or more months of DAPT after implantation of a drug eluting stent.[25-30 37 38 40] To our knowledge, this is the first comprehensive study to explore the comparison of clinical outcomes of short term (≤6 months) with long term (12 months) DAPT after drug eluting stent implantation according to diabetes status. The strength of our analysis is represented by the inclusion of individual patient level data from a large patient population from six multicentre multinational randomised trials. Individual patient level meta-analysis overcomes important limitations of study level meta-analysis and improves internal validity and allows for time to event, subgroup, and covariable adjusted analyses.

Drug eluting stents and DAPT

Compared with bare metal stents, drug eluting stents have consistently reduced the risk of restenosis and repeat revascularisation at the expense of safety concerns because of an increase in late and very late stent thrombosis.[41 42] In particular, first generation drug eluting stents were associated with a four to fivefold higher risk of late and very late stent thrombosis compared with bare metal stents, leading to the concept of "the longer the better" regarding duration of DAPT in patients with drug eluting stents. Of note, new generation stents have been shown to be safer in terms of stent thrombosis than both early generation stents and bare metal stents.[43-45] Prolonged DAPT, however, is associated with increased risks of bleeding and death, as well as healthcare costs.[3 46] Therefore, the optimal duration is of paramount clinical relevance, although still a matter of debate.

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Table 2 | Clinical outcomes in long term versus short term dual antiplatelet therapy (DAPT) after implantation of drug eluting stent stratified by diabetes

	Diabetes (n=3681)					No diabetes (n=7708)					
	Long DAPT (n=1853)	Short DAPT (n=1828)	HR (95% CI)	P value	τ^2	Long DAPT (n=3848)	Short DAPT (n=3860)	HR (95% CI)	P value	τ^2	P for interaction
MACE	62 (3.3)	58 (3.2)	1.05 (0.62 to 1.76)	0.86	0.16	82 (2.1)	97 (2.5)	0.97 (0.67 to 1.39)	0.85	0.06	0.33
All cause death, MI, or stroke	74 (4.0)	66 (3.6)	1.10 (0.79 to 1.54)	0.58	0.00	93 (2.4)	99 (2.6)	1.02 (0.72 to 1.46)	0.91	0.07	0.48
Cardiac death, MI, or stroke	69 (3.7)	59 (3.2)	1.12 (0.79 to 1.60)	0.52	0.01	90 (2.3)	106 (2.7)	1.01 (0.68 to 1.49)	0.97	0.11	0.16
All cause death, MI, stroke, or major bleeding	81 (4.4)	69 (3.8)	1.16 (0.83 to 1.60)	0.39	0.01	109 (2.8)	107 (2.8)	1.12 (0.76 to 1.66)	0.56	0.12	0.58
Cardiac death, MI, stroke, or major bleeding	81 (4.4)	71 (3.9)	1.10 (0.79 to 1.53)	0.57	0.01	117 (3.0)	120 (3.1)	1.23 (0.77 to 1.96)	0.38	0.22	0.46
All cause death or MI	68 (3.7)	59 (3.2)	1.16 (0.78 to 1.72)	0.46	0.04	83 (2.2)	90 (2.3)	1.02 (0.71 to 1.47)	0.91	0.07	0.39
Cardiac death or MI	60 (3.2)	56 (3.1)	1.05 (0.65 to 1.69)	0.85	0.11	80 (2.1)	93 (2.4)	1.08 (0.69 to 1.70)	0.73	0.16	0.37
All cause death	49 (2.6)	39 (2.1)	1.34 (0.87 to 2.06)	0.19	0.02	59 (1.5)	57 (1.5)	1.05 (0.73 to 1.51)	0.81	0.00	0.53
Cardiac death	30 (1.6)	23 (1.3)	1.29 (0.75 to 2.23)	0.36	0.00	37 (1.0)	35 (0.9)	1.17 (0.72 to 1.91)	0.53	0.03	0.58
Stroke	13 (0.7)	10 (0.5)	1.29 (0.56 to 2.97)	0.55	0.02	15 (0.4)	16 (0.4)	0.94 (0.47 to 1.90)	0.87	0.00	0.57
MI	37 (2.0)	39 (2.1)	0.95 (0.58 to 1.54)	0.82	0.03	55 (1.4)	62 (1.6)	1.15 (0.68 to 1.94)	0.60	0.19	0.84
Definite ST	4 (0.2)	11 (0.6)	0.34 (0.11 to 1.08)	0.07	0.04	13 (0.3)	8 (0.2)	1.63 (0.67 to 3.97)	0.28	0.02	0.04
Probable ST	3 (0.2)	5 (0.3)	0.59 (0.14 to 2.48)	0.47	0.00	4 (0.1)	4 (0.1)	0.87 (0.21 to 3.62)	0.85	0.10	0.61
Definite/probable ST	7 (0.4)	16 (0.9)	0.26 (0.09 to 0.80)	0.02	0.47	17 (0.4)	12 (0.3)	1.42 (0.68 to 2.98)	0.35	0.00	0.04
MI or definite/probable ST	42 (2.3)	46 (2.5)	0.90 (0.55 to 1.46)	0.66	0.06	60 (1.6)	71 (1.8)	0.94 (0.64 to 1.38)	0.75	0.04	0.79
TVR	56 (3.0)	71 (3.9)	0.82 (0.57 to 1.90)	0.30	0.02	107 (2.8)	115 (3.0)	0.86 (0.63 to 1.16)	0.32	0.03	0.42
Major or minor bleeding	38 (2.1)	21 (1.1)	1.89 (1.10 to 3.27)	0.02	0.02	62 (1.6)	46 (1.2)	1.43 (0.96 to 2.11)	0.08	0.01	0.37
Major bleeding	14 (0.8)	8 (0.4)	1.72 (0.72 to 4.10)	0.22	0.00	30 (0.8)	14 (0.4)	2.56 (1.08 to 6.07)	0.03	0.43	0.69
Minor bleeding	24 (1.3)	13 (0.7)	3.91 (1.24 to 12.40)	0.02	0.87	33 (0.9)	35 (0.9)	0.82 (0.49 to 1.37)	0.45	0.04	0.11

MACE=major adverse cardiac events (cardiac death, myocardial infarction (MI), or definite/probable stent thrombosis (ST)); TVR=target vessel revascularisation.

Diabetes mellitus and DAPT

Diabetes mellitus is a key risk factor for atherosclerosis, disease progression, and restenosis during follow-up, particularly if patients are insulin dependent, even after coronary revascularisation.[11 12 15-18] Notably, the detrimental metabolic state that accompanies diabetes is responsible for abnormalities in endothelial and platelet function that can contribute to accelerated atherosclerosis and increase the risk of adverse cardiovascular events.[19 20] A large body of evidence has described the role of increased platelet activity and adhesion in the progression of vascular complications observed in patients with diabetes, characterised by a high incidence of cardiovascular events and lower antithrombotic efficacy of treatment with aspirin and clopidogrel.[19 20] Indeed, patients with diabetes mellitus might have a smaller than expected response to aspirin (because of accelerated renewal of platelets and alteration of thromboxane pathway) and clopidogrel (the lower response to the drug in those with diabetes is mainly caused by abnormalities in the active metabolite pharmacokinetic profile, with only a minor contribution of platelet dysfunction related to the P2Y12 signalling pathway). Therefore, the clinical translation of these findings could lead to the concept that prolonged DAPT in patients with diabetes might be the rational approach, although it has not been clearly demonstrated.

A recent large observational study has suggested that extending the duration of clopidogrel treatment beyond 12 months could decrease rates of very late death or myocardial infarction only in patients with diabetes who had been treated with a first generation drug eluting stent compared with either patients without diabetes or those who had other stent types, although the latter group had an overall event rate higher than patients with a drug eluting stent.[21] This study, however, like other retrospective studies, has relevant limitations, and appropriate adjustment is unlikely to eliminate selection bias.[22] Randomised studies comparing different DAPT regimens have provided results of subgroup analyses. Interestingly, some contrasting evidence emerged from these analyses on the role of diabetes, although dedicated studies on the impact of diabetes, including in patients treated with insulin, have not been published to date.

In the EXCELLENT trial, there was a significant interaction between diabetes status and duration of DAPT (interaction P<0.001) for the primary endpoint (composite of cardiac death, myocardial infarction, or ischaemia driven target vessel revascularisation at 12 months), with patients with diabetes having a significant benefit with DAPT for 12 months compared with 6 months, whereas patients without diabetes had a significantly lower event rate with short term DAPT.[27] Also the DAPT trial showed a significant interaction between diabetes and treatment arm (interaction P=0.01), although patients with diabetes did not benefit from prolonged DAPT (30 months) compared with patients without diabetes who experienced a lower risk of MACCE (major adverse cardiovascular and cerebrovas-

Table 3 | Major adverse cardiac events (MACE) for long term versus short term dual antiplatelet therapy (DAPT) after implantation of drug eluting stent in subgroups of patients with or without diabetes

	Diabetes (n=3681)				No diabetes (n=7708)				
	HR (95% CI)	P value	τ^2	P for interaction	HR (95% CI)	P value	τ^2	P for interaction	P for interaction for diabetes/DAPT
Age (years):									
<65	1.26 (0.33 to 4.77)	0.74	1.87	0.84	0.84 (0.52 to 1.34)	0.46	0.04	0.50	0.58
≥65	1.09 (0.68 to 1.76)	0.71	0.00		1.05 (0.68 to 1.63)	0.82	0.05		0.91
Sex:									
Women	1.32 (0.78 to 2.21)	0.30	0.03	0.09	1.25 (0.65 to 2.37)	0.50	0.14	0.20	0.90
Men	0.67 (0.38 to 1.21)	0.90	0.08		0.77 (0.55 to 1.10)	0.15	0.00		0.69
Clinical presentation:									
Stable CAD	1.10 (0.63 to 1.92)	0.74	0.09	0.84	1.21 (0.79 to 1.85)	0.38	0.03	0.20	0.79
ACS	0.98 (0.37 to 2.58)	0.97	0.83		0.76 (0.43 to 1.33)	0.34	0.16		0.66
Multivessel disease:									
No	1.74 (0.91 to 3.32)	0.09	0.17	0.09	1.27 (0.82 to 1.96)	0.28	0.06	0.12	0.43
Yes	0.75 (0.36 to 1.57)	0.44	0.38		0.69 (0.37 to 1.28)	0.24	0.20		0.87

ACS=acute coronary syndrome; CAD=coronary artery disease.

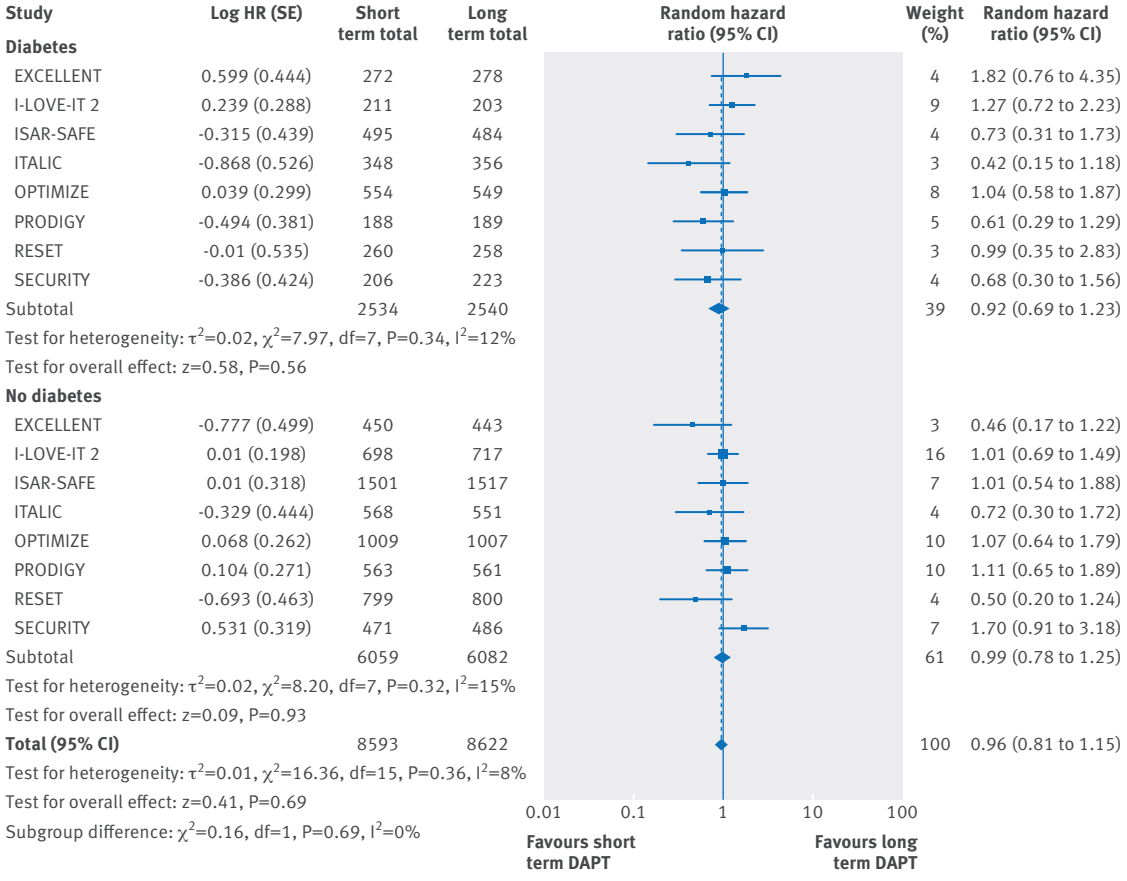

Fig 4 | Net adverse clinical events in patients with and without diabetes according to long term and short term DAPT in eight randomised trials

cular events) (mainly because of a decreased risk of myocardial infarction and stent thrombosis).[46] The recent dedicated subanalysis of the DAPT trial showed that prolonged DAPT reduced the risk of myocardial infarction, but this benefit was attenuated in patients with diabetes compared with those without diabetes.[47] Similarly, in the DES-LATE, patients with diabetes showed a trend towards benefit from interrupting DAPT at 12 months, although the P value for interaction was borderline (P=0.07).[48] Conversely, other trials, including OPTIMIZE,[26] RESET,[28] I-LOVE-IT 2,[37] ISAR-SAFE,[38] ARCTIC Interruption,[49] and the recently published IVUS-XPL[40] did not show significant heterogeneity between subgroups with and without diabetes. Even if characterised by a different design not matching with eligibility criteria of our meta-analysis (inclusion of patients with a history of myocardial infarction one to three years before, irrespective of percutaneous coronary intervention performed or drug eluting stent implanted), the recent substudy by the PEGASUS-TIMI

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54 trial also confirmed the absence of potential significant heterogeneity related to diabetes status.[50] Indeed, consistent with the findings in patients without diabetes, those with diabetes had long term benefits in terms of ischaemia and cardiovascular death but increased risk of bleeding with ticagrelor compared with placebo in addition to a background treatment with aspirin.[50]

Perspectives for clinical practice

Our study shows that compared with short term DAPT, long term DAPT does not provide benefits in terms of ischaemic protection but rather increases the risk of bleeding, irrespective of diabetes status. Although patients with diabetes are at increased risk for ischaemic events, and prolonged DAPT is often advised in these patients, our analysis indicates that prolonged treatment is not associated with improved outcomes among patients with stents with and without diabetes, even when we restricted the analysis to the subgroup of patients with diabetes treated with insulin (see supplementary results in appendix). Although we observed a lower risk of definite/probable stent thrombosis with DAPT for 12 months in patients with diabetes, this finding should be interpreted in the context of high heterogeneity between trials, hampering definitive conclusions; moreover the absence of consistent benefit in terms of composite endpoints of ischaemic events (adding stent thrombosis to myocardial infarction or death (cardiac or all cause)) as well as at the landmark analyses (in which we excluded events occurring in the first three to six months when both randomised treatments were, by study design, identical) was reassuring on the clinical implications of this small excess of stent thrombosis in such patients. On the contrary, the relevance of our overall findings should be interpreted in light of the baseline characteristics of the included patients, particularly concerning the risk of bleeding. Indeed, compared with studies dedicated to patients with high risk (such as LEADERS-FREE with 18.6% of all bleeding and 7.3% of major bleeding (BARC type 3 or 5) at one year[51]), our study population can be considered at low risk given that the overall rate of major or minor bleeding events was about 1.5% at one year, of which major bleeding was 0.6% compared with 0.4%, 0.4%, 2.6%, 0.7%, 0.9%, and 0.3% in RESET, EXCELLENT, PRODIGY, OPTIMIZE, SECURITY, and ITALIC trials, respectively. Furthermore, a recent meta-regression analysis of DAPT trials underlined the concept that in the contemporary era of drug eluting stents, bleeding has a stronger impact on mortality than stent thrombosis.[5] In line with this, the absence of benefit at the expense of an increased risk of bleeding in patients with diabetes treated with long term compared with short term DAPT is relevant and underlines the opportunity to shorten DAPT in this subset of patients.

Limitations

Our study shares limitations of other meta-analyses, although the analysis of patient level data mitigates some of them. As the six randomised controlled trials we included were not specifically designed to investigate outcomes in the subgroup of patients with diabetes, our study has intrinsic limitations of subgroup analyses and should be considered as hypothesis generating. The pooling of data, however, allowed us to obtain a large number of patients with diabetes (n=3681) as well as insulin treated diabetes (n=677) to be compared with patients without diabetes. Even though we collected individual data from randomised controlled trials, the post hoc nature of this analysis introduces biases. Furthermore, it remains unclear if our findings could be applicable to all patients with diabetes irrespective of its type (type 1 or 2) as this information was not available.

The results described cannot be extended to all types of drug eluting stent because zotarolimus and everolimus eluting stents were more commonly implanted. Similarly, as all patients received clopidogrel, our findings could have differed if novel anti-platelet agents such as prasugrel or ticagrelor had been used. Definitions of some clinical endpoints differed slightly across trials, potentially introducing effect modifiers. Although the meta-analysis of eight randomised controlled trials confirmed the findings of short versus long term DAPT, this was conducted without patient level data from two randomised controlled trials, and net clinical adverse events was the only endpoint that we were able to analyse from the published data in the subgroups for diabetes status. Finally, most of the trials randomised patients at the time of the percutaneous coronary intervention or a month later, before the three to six months planned discontinuation of DAPT. Differences in events occurring within three to six months of DAPT are chance effects, but the sensitivity analysis that excluded those events confirmed the findings of the main analysis.

Conclusions

Although the presence of diabetes emerged as an independent predictor of MACE, long term compared with short term DAPT did not reduce the risk of MACE but increased the risk of bleeding among patients with and without diabetes. This study might have relevant implications for clinicians and patients and could modify current daily clinical practice. A shorter DAPT regimen was found to be effective and safe in patients with and without diabetes. Diabetes per se should not be a driver for prolonging DAPT over the mandatory period after implantation of a drug eluting stent because of increased risks compared with potential benefits of this strategy. Future studies should be specifically designed and powered to deal with patients with diabetes and should explore the optimal duration of DAPT according to the type of diabetes and its medical management.

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Appendix 1: Supplementary material

A Critical Appraisal of Aspirin in Secondary Prevention

Is Less More?

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"The unexamined life is not worth living."
—Socrates[1]

ABSTRACT: Aspirin represents the *sine qua non* for antiplatelet pharmacotherapy in patients with cardiovascular diseases because of its well-established role in secondary prevention and its widespread availability and affordability. Historical studies, conducted in an era that bears little resemblance to contemporary clinical practice, demonstrated large reductions in thrombotic risk when aspirin was compared with placebo, thus forming the evidence base promulgated in practice guidelines and recommendations. $P2Y_{12}$ inhibitors have mostly been studied in addition to aspirin; dual-antiplatelet therapy proved superiority compared with aspirin monotherapy for the prevention of ischemic events, despite increased bleeding risks. An alternative approach currently under investigation includes evaluation of single-antiplatelet therapy with $P2Y_{12}$ inhibitors alone versus dual-antiplatelet therapy after acute coronary syndromes or coronary stent implantation. As the availability of more effective antiplatelet agents increases, it is time to revisit the existing and long-standing paradigm supporting aspirin use for secondary prevention of atherothrombotic events. Ongoing trials will provide new evidence whether the less-is-more strategy is justified.

Every year millions of patients worldwide undergo percutaneous coronary intervention (PCI) for treatment of coronary artery disease (CAD). To date, dual-antiplatelet therapy (DAPT), consisting of low-dose acetylsalicylic acid (ASA or aspirin) and an inhibitor of the adenosine diphosphate (ADP) $P2Y_{12}$ platelet receptor, is mandatory to prevent thrombosis among patients with stable CAD after stent implantation and following acute coronary syndromes (ACS), irrespective of final management (invasive or noninvasive).[2–6] An alternative approach currently under investigation includes evaluation of single-antiplatelet therapy with $P2Y_{12}$ inhibitors alone after ACS or coronary stent implantation.

The aim of this article is to critically review the available evidence for aspirin use after ACS and PCI and to discuss the scientific rational for ongoing studies testing the risks and benefits of omission or early discontinuation of aspirin in favor of $P2Y_{12}$ inhibitor monotherapy.

PLATELET PATHOPHYSIOLOGY AND ROLE OF ANTIPLATELET AGENTS

Platelets are critical modulators of hemostasis following tissue trauma and vascular injury. Thus, inhibition of platelet adhesion and aggregation consistently resulted in an

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increased risk of bleeding.[7] Platelet activation plays a crucial role in the development of atherosclerosis and ACS; thus, its inhibition is pivotal to prevent ischemic complications after stent implantation, including stent thrombosis (ST). Platelets adhere to the injured endothelium of blood vessels at sites of endothelial cell activation and contribute to the development of chronic atherosclerotic plaques. Moreover, platelets trigger the acute onset of arterial thrombosis in response to atherosclerotic plaque rupture.[7] Although platelet adhesion and activation is a physiological response to the fissuring or rupture of atherosclerotic plaques, eventually contributing to repair, uncontrolled progression of this process, through a series of self-sustaining amplification loops, may lead to intraluminal thrombus formation and vascular occlusion.[8] Platelet activation determines several responses, including shape change; dense granule secretion of ATP, 5-hydroxytryptamine, and ADP (it binds to $P2Y_{12}$ receptors that have a potent effect on amplification of platelet activation); α-granule secretion of chemokines (leading to activation of leukocytes and endothelial cells) and coagulation factors; and procoagulant changes in the platelet surface membrane supporting thrombin generation and activation of GPIIb/IIIa leading to platelet aggregation and outside-in signaling further amplifying platelet activation.[8] Consequently, platelet inhibition is the mainstay in the prevention of recurrent ischemic events (Figure 1), and current guidelines recommend a period of DAPT ranging from a minimum of 1 month to well beyond 1 year among patients undergoing PCI.[2–6,9] The pharmacopeia of $P2Y_{12}$ antagonists has rapidly expanded in recent years. [10,11] In comparison with clopidogrel, which has been shown to improve outcomes vis-à-vis placebo on a background therapy of aspirin[12] as well as aspirin monotherapy,[13] the new $P2Y_{12}$ inhibitors, prasugrel and ticagrelor, are characterized by faster onset of action and more consistent and potent inhibition of platelet function. Unlike aspirin, $P2Y_{12}$ inhibitors block the amplification process of platelet activation.[7,11] Both prasugrel and ticagrelor have been tested thus far in clinical trials involving ACS patients with ASA serving as background therapy. Accordingly, the safety and efficacy of monotherapy with these potent agents remains unknown. Prasugrel, an irreversible inhibitor of $P2Y_{12}$ receptor, was associated with a lower risk of major adverse cardiovascular events (MACE), largely driven by reduction in myocardial infarction (MI), but a higher risk of spontaneous and coronary artery bypass grafting (CABG)–related major bleeding compared with clopidogrel among ACS patients[14] already on background ASA therapy. Notably, fatal bleeding was slightly but significantly increased in prasugrel in comparison with clopidogrel-treated patients.

The direct and reversible $P2Y_{12}$ antagonist ticagrelor offers at least similar inhibition of the $P2Y_{12}$ receptor as prasugrel,[15] but yields faster offset of platelet inhibition in comparison with prasugrel and clopidogrel. Ticagrelor significantly reduced the risk of MACE, but also all-cause and cardiovascular mortality in comparison with clopidogrel in ACS patients, irrespective of the final management strategy (invasive or noninvasive).[16] Ticagrelor increases nonprocedural but not CABG-related or fatal bleeding in comparison with clopidogrel. Prasugrel or ticagrelor, when used with background aspirin therapy, are therefore preferred over clopidogrel in ACS patients, based on superior prevention of ischemic events despite both carrying higher risk of spontaneous (ie, nonprocedural) bleeding hazard.[2,3,5]

Given the delicate balance between ischemic and bleeding risks in patients receiving DAPT and notwithstanding the recent evidence that long-term DAPT further decreases the risk of MACE, [17,18] there remains uncertainty on the optimal DAPT duration after ACS or stent implantation.[19] As a result, a personalized approach to administration and duration of DAPT therapy is advocated, integrating anticipated ischemic over bleeding risks. Remarkably, such a treatment strategy has never been tested prospectively. At the time of DAPT discontinuation, current guidelines recommend indefinite aspirin monotherapy as a secondary prevention measure.[2–6]

Recently, exploration of novel strategies for patients with ACS has yielded mixed results. The use of low-dose rivaroxaban at 2.5 mg twice daily in the ATLAS-ACS 2 trial (Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects With Acute Coronary Syndrome ACS 2),[20] and vorapaxar in the TR A2°P-TIMI50 (Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events-Thrombolysis in Myocardial Infarction 50)[21] and TRACER (Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome)[22] trials have been shown to reduce the risk of ischemic adverse events at the cost of greater bleeding in comparison with DAPT consisting of aspirin and clopidogrel. Conversely, less favorable results were observed for rivaroxaban at a dose of 5 mg twice daily (ATLAS-ACS), for dabigatran (twice daily administration of 50, 75, 110, or 150 mg) in the RE-DEEM study (Dabigatran Versus Placebo in Patients With ACS on DAPT: A Randomized, Double-Blind, Phase II Trial),[23] apixaban (5 mg twice daily) in the APPRAISE-2 study (Apixaban for Prevention of Acute Ischemic and Safety Events),[24] and darexaban (all doses) in the RUBY-1 trial (Study Evaluating Safety, Tolerability and Efficacy of YM150 in Subjects With Acute Coronary Syndromes).[25] More specifically, these trials generally showed a magnitude of incremental bleeding risk that was not counterbalanced by a concordant reduction in thrombotic events thereby rendering a neutral or negative net benefit. Because these strategies were examined by adding the novel agent to a background of DAPT, inferences surrounding the omission of ASA in the experimental arm are not possible based on these studies.

Given the well-recognized trade-off between ischemic prevention and bleeding risk in patients receiving DAPT

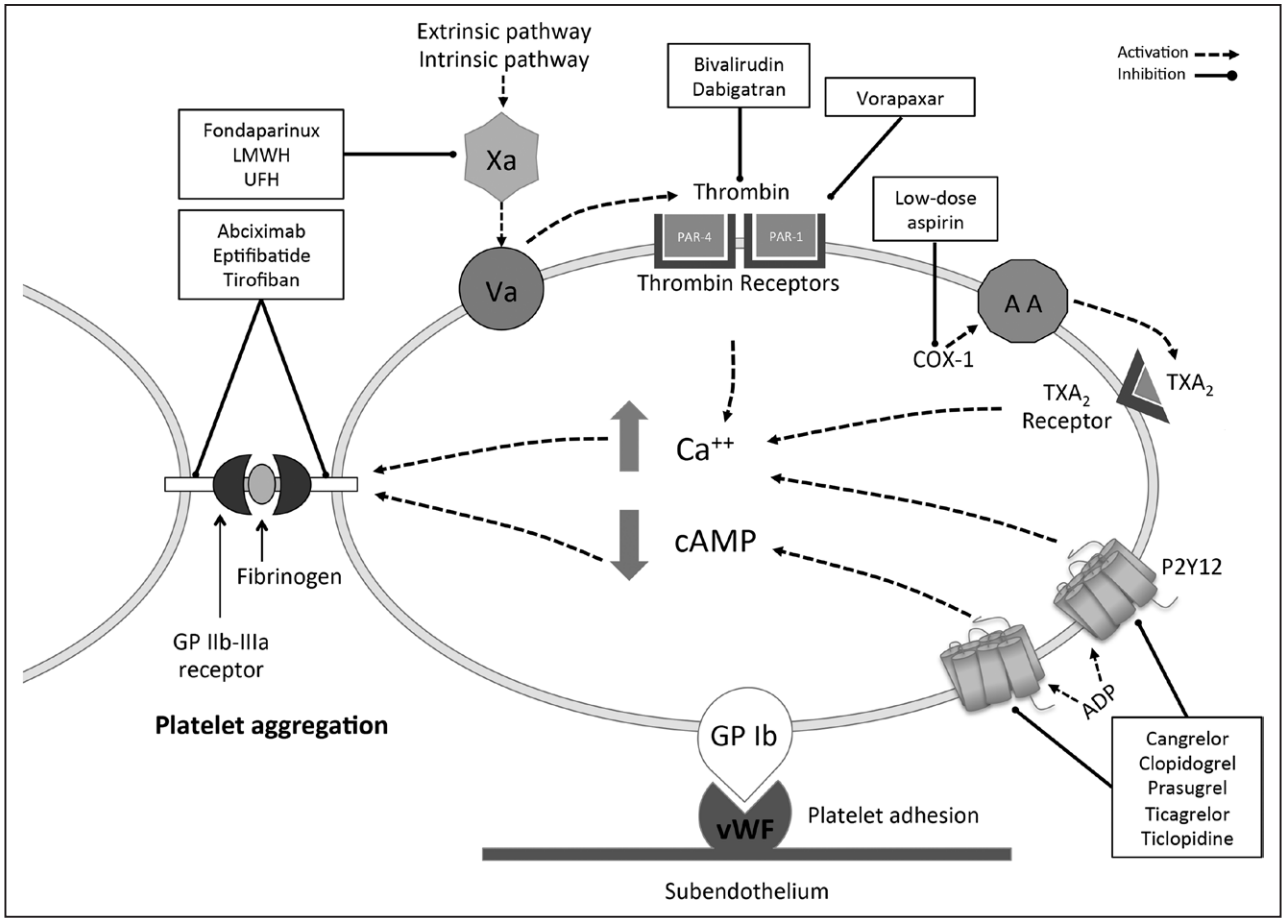

Figure 1. Antithrombotic agents.
Illustration of the process of platelet aggregation and the mechanism of actions of the main antithrombotic agents. AA indicates arachidonic acid; ADP, adenosine diphosphate; Ca, calcium; COX, cyclooxygenase; GP, glycoprotein; LMWH, low-molecular-weight heparin; PAR, protease-activated receptor; TXA_2, thromboxane A_2; UFH, unfractionated heparin; and vWF, von Willebrand factor.

or triple therapy, alternative strategies that optimize net clinical benefit by preserving ischemic reduction without increasing bleeding harm are needed. An intriguing and emerging area of research is to avoid aspirin therapy altogether in favor of long-term $P2Y_{12}$ inhibitor monotherapy. Ongoing studies aim to discern whether monotherapy with a $P2Y_{12}$ inhibitor can safely and effectively replace conventional DAPT regimens after ACS or PCI, or even replace ASA for long-term secondary prevention.

ASPIRIN

Mechanism of Action

ASA was synthesized in 1897 and then commercialized as aspirin in 1899. It was used worldwide because of its anti-inflammatory/analgesic effects until the 1970s when its antiplatelet effects became apparent. For this latter mechanism of action, aspirin has become the cornerstone in the antithrombotic therapy for the prevention and treatment of wide range of cardiovascular diseases worldwide.

Arachidonic acid is released from membrane phospholipids by several isoforms of phospholipase A2 (Figure 2). Free arachidonic acid is converted to the unstable intermediates prostaglandin G2 and prostaglandin H2 by cytosolic prostaglandin H synthases through its cyclooxygenase (COX) and hydroperoxidase activities, respectively.[26–29] Prostaglandin H2 is converted by tissue-specific isomerases to multiple prostanoids that activate specific cell membrane receptors. Although high-dose aspirin inhibits both COX-1 and COX-2, low-dose aspirin selectively and irreversibly inhibits COX-1 in the arachidonic acid pathway (Figure 2), subsequently blocking the production of thromboxane A2 (TXA2), a platelet agonist (rapidly transformed in TXB2), thereby reducing thrombus formation.[26,29] More specifically, aspirin first binds to an arginine 120 residue, as do other nonsteroidal anti-inflammatory drugs, but unlike these, aspirin then acetylates the serine 529 residue of human COX-1 (serine 516 in human COX-2 for higher doses of aspirin) located in the narrowest section of the channel, irreversibly inhibiting access to the COX catalytic site by

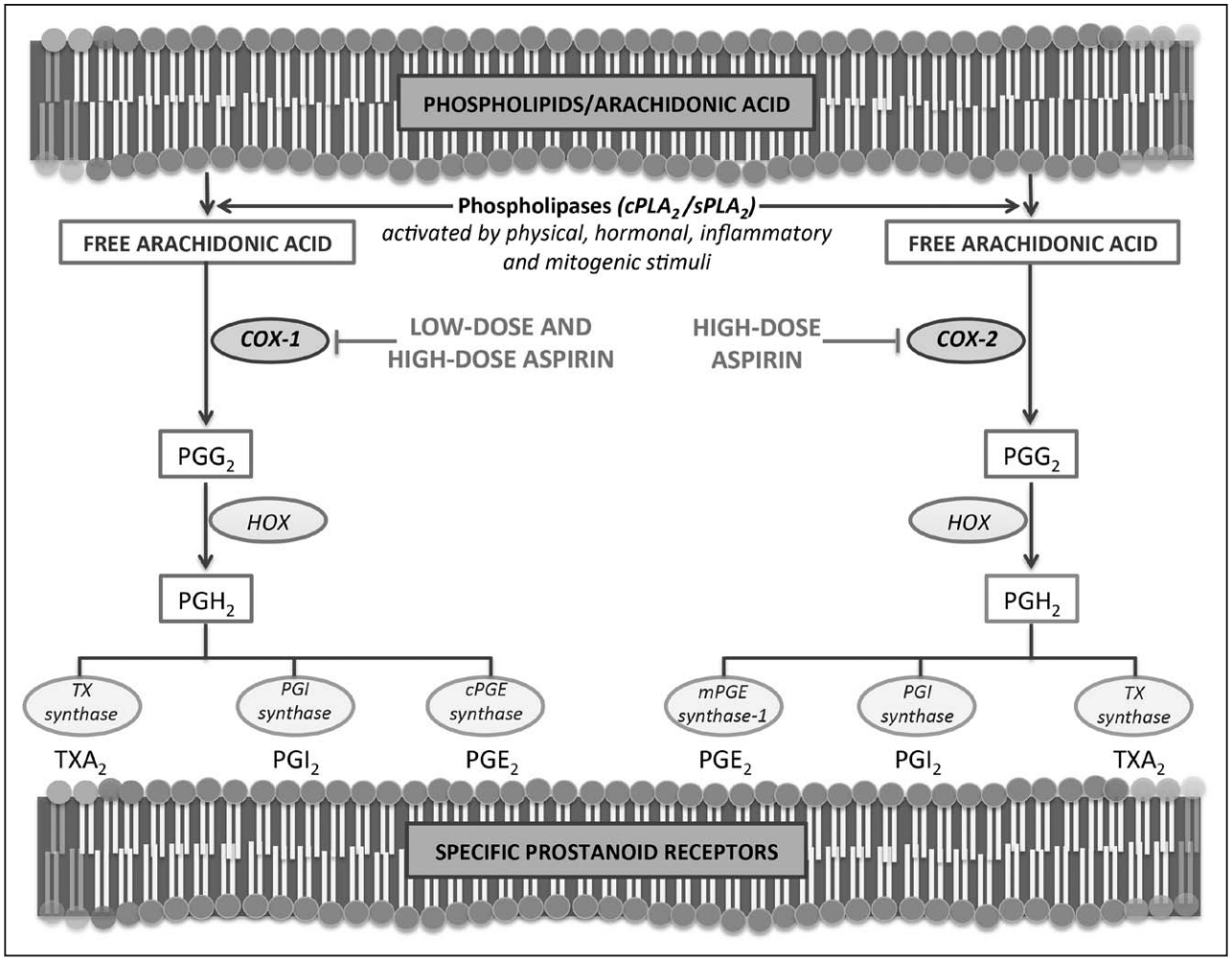

Figure 2. Aspirin mechanism of antiplatelet action.
Illustration of the process of formation and action of prostanoids and the mechanism of action of aspirin. COX indicates cyclooxygenase; cPGE, cytosolic prostaglandin E; $cPLA_2$, cytosolic phospholipase A_2; HOX, hydroperoxidase; mPGE, microsomal prostaglandin E; PG, prostaglandin; $sPLA_2$, secretory phospholipase A_2; and TX, thromboxane.

arachidonic acid.[26,29] This antiplatelet effect persists for the lifespan of platelets because the permanent inactivation of the platelet COX-1 can be reversed only through the generation of new platelets.[28] Although aspirin is characterized by a very short half-life (≈15 minutes in plasma), it needs to be administered only once daily for the purpose of platelet inhibition.

Importantly, there is a nonlinear relationship between low-dose aspirin-induced inactivation of platelet COX-1 and inhibition of TXA2-dependent platelet function.[8] This translates into crucial implications: (1) a less than maximal inactivation of COX-1 determines a significant reduction in platelet inhibition; (2) after aspirin discontinuation, the recovery of platelet function is disproportionately rapid, occurring within 3 to 4 days; (3) most traditional nonsteroidal anti-inflammatory drugs are not able to completely and persistently inhibit platelet COX-1. Additionally, the selective inhibition by ASA of TXA2-dependent platelet function alone, without any effect on other pathways of platelet activation (ADP-$P2Y_{12}$, thrombin-protease–activated receptor-1) forms the physiological rationale for dual- or triple-antiplatelet therapy in high-risk settings where further platelet inhibition is necessary (Figure 1).[8]

The gastrointestinal adverse effects of aspirin and nonsteroidal anti-inflammatory drugs (erosive gastritis and bleeding) are mainly a result of COX-1 inhibition.[29] Indeed, COX-1 is ubiquitous, constitutively expressed in the human body and able to produce prostaglandins involved in platelet aggregation (mainly TXA2), but also in the maintenance of gastrointestinal mucosal integrity (mainly prostaglandin E_2 and prostaglandin I_2).[29]

Clinical Outcomes

Numerous studies have clearly demonstrated that low-dose aspirin reduces cardiovascular morbidity and mortality in patients with ACS or previous MI and confers

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a durable long-term benefit.[30,31] Most randomized trials have been summarized by the Antithrombotic Trialists' Collaboration, which included 16 secondary prevention randomized trials (17 000 individuals at high-risk, 43 000 person-years, 3306 serious vascular events) and compared long-term aspirin versus control.[30] Aspirin significantly reduced the risk of serious vascular events (6.7% versus 8.2% per year, $P<0.0001$), with a nonsignificant increase in intracranial hemorrhage but reductions in total stroke (2.08% versus 2.54% per year, $P=0.002$) and coronary events (4.3% versus 5.3% per year, $P<0.0001$). Among the 16 secondary prevention trials, only 6 included post-MI patients (overall 10 859 patients), whereas the other 10 trials enrolled post–transient ischemic attack (TIA)/stroke patients. Convincing results notwithstanding, these findings must be interpreted within the context of several important limitations that might limit generalizability to contemporary clinical practice. First and perhaps most relevant, most studies were conducted several decades ago and do not reflect the modern-day clinical settings, therapeutics, and event rates (Tables 1 and 2).[31] Second, most included young and predominantly male patients. Third, the ASA regimens used in most of these studies differ significantly from current clinical norms in terms of dosing frequency and amount. As a result, it is unclear whether the benefits associated with ASA use in these studies would be replicated in the contemporary era.

Further evidence supporting the preventive role of aspirin was yielded by a meta-analysis exploring the hazards inherent to aspirin withdrawal or noncompliance in subjects at risk for, or with established, CAD.[32] Overall, the nonadherence or withdrawal of aspirin was associated with a 3-fold increased risk of MACE. However, reasons for aspirin discontinuation were not accounted for in this aggregate data analysis, which may explain the higher ischemic hazards at least as much as aspirin withdrawal.

Resistance and Hypersensitivity

Treatment with aspirin confers a long-lasting functional defect in platelets, which is detectable with laboratory tests for platelet reactivity[26,33] and also prolongs the bleeding time. The effect of ASA on platelet COX-1 has also been characterized through measurements of serum TXB2 and urinary metabolites of TXB2.[33–35] Given that the maximal biosynthetic capacity of human platelets is several thousand times as high as the basal rate of TXA2 biosynthesis in healthy subjects, the relationship between the inhibition of platelet COX-1 activity and TXA2 biosynthesis in vivo is nonlinear. The inhibition of platelet COX-1 has functional relevance when a reduction by at least 95% in the maximal capacity to generate TXA2 is reached. However, it should be noted that, recently, the nonlinear relationship between COX-1 inhibition and platelet function has been questioned.[36] In this study, a linear relationship was observed between aggregation and TXA2 production for all combinations of arachidonic acid or collagen and aspirin, and similar relationships were found in combinations of aspirin-treated and naïve platelets, and in blood from individuals taking an antithrombotic dose of aspirin.[36]

The term aspirin resistance has been used to describe the inability of aspirin to produce a measurable response on ex vivo tests of platelet function, to inhibit TXA2 biosynthesis in vivo, or to protect individual patients from thrombotic complications. A large body of data has reported lower-than-expected inhibition of platelet function in a variable proportion of patients treated with aspirin.[35,37] Some data showed that patients defined to have aspirin resistance were found to be at increased risk for recurrent cardiovascular events with greater clinically relevant long-term morbidity and mortality.[38,39]

The interpatient variability in aspirin response (aspirin resistance) has been mainly attributed to the variable turnover rate of its target receptor (platelet COX-1). Remarkably, the dosage of TXB2 serum levels at different time points was used to identify patients with a faster recovery of COX-1 activity and consequently characterized by aspirin resistance.[40] In this study, some factors were associated with resistance: younger age, higher mean platelet volume and body mass index in diabetic patients, whereas only higher body mass index was a predictor in patients without diabetes mellitus. A twice-daily regimen of low-dose aspirin was originally proposed for patients with high platelet turnover rates,[41] this has also been shown to rescue the limited duration of the antiplatelet effect in patients with aspirin resistance.[40,42]

Although several studies have been published on the topic of aspirin resistance, its definition, diagnosis, causes, and clinical consequences remain controversial.[43] The term resistance should be used when the drug is unable to bind to its pharmacological target, either because of the inability to reach it (as a consequence of reduced bioavailability, in vivo inactivation, or negative interaction with other substances) or alterations of the target.[43] Accordingly, it is inappropriate to consider all patients experiencing atherothrombotic events while on aspirin treatment to be resistant. This phenomenon has been called clinical resistance, but it should be more properly named treatment failure.[43] Given that arterial thrombosis is multifactorial, an arterial thrombotic event in a patient may reflect treatment failure rather than resistance.[44] Additionally, the finding of high residual platelet reactivity in vitro in patients on aspirin treatment has often been confused with aspirin resistance, but may not necessarily imply that these patients are resistant to treatment, particularly if platelet function is measured through laboratory tests that are not specific for the effect of aspirin on its pharmacological target. Doubtless, unspecific tests are useful to

Table 1. Secondary Prevention Trials of Aspirin Versus Control in Patients With Previous Myocardial Infarction

Trial Name	Starting Year	Publication Year	Aspirin Daily Dose, mg	No. of Patients	Study Duration	Age	Male, %	Htn, %	Diabetes Mellitus, %	β-Blocker, %	Time From MI to Enrollment	Revascularization (PCI/CABG), %
Prior MI												
Cardiff I	1971	1974	300	1239	13 mo	55	100	NA	NA	NA	10 wk	0
Cardiff II	NA	1979	900	1725	12 mo	56	85	NA	0.5	NA	95% <7days	0
PARIS I*	1975	1980	972	1216	41 mo	56	87	NA	10	15.4	8 wk to 60 mo	0
AMIS	1975	1980	1000	4524	38 mo	55	89	NA	11	12	8 wk to 60 mo	0
CDP-A†	1972	1976	972	1529	22 mo	56	100	NA	14	NA	75% >60 mo	0
GAMIS‡	1970	1980	1500	626*	24 mo	59	78	19	20	NA	30–42 days	0
Micristin	NA	1979	1500	1340	24 mo	NA	NA	NA	NA	NA	NA	NA
Acute MI												
ISIS-pilot§	1983	1987	162.5	619	1 mo	60	80	22	5	40	<24 h	0
ISIS-2‖	1985	1988	162.5	17187	35 days	NA	NA	NA	NA	NA	<24 h	0
Dutch-aspirin	NA	1990	100	100	3	62.5	74	NA	NA	32	<12 h	Rare, none within 1 wk
Huddinge	NA	1988	167 (500 every 3 days)	20	1 mo (12 mo)	63	80	NA	NA	20	<24 h	10
Frankfurt	NA	1976	1320	39	14 days	NA	NA	NA	NA	NA	NA	NA
APRICOT¶	NA	1993	325	192	3 mo	57	81	NA	NA	43	48 h	10.4
Unstable angina												
VA-pilot	1974	1986	324	50	3 mo	NA	100	NA	NA	NA	NA	NA
VA-main	1974	1983	324	1266	3 mo	56	100	41	17	74	48 h	3.5
RISC	1985	1990	75	796	12 mo	58	100	30	8	88	72 h	3.9
ALDUSA-pilot#	NA	1987	324–340	84	12 mo	NA	NA	NA	NA	NA	NA	NA
Thèroux**	1986	1988	650	479	6 days (3 mo)	58	71	38	13	96	<24 h	48
ATACS-pilot††	1987	1990	325–380	93	3 mo	62	60	49	37	39	<48 h	50
Coronary angioplasty												
Perth‡‡	1986	1991	100	212	6 mo	55	84	34	4	58	–	100% PCI for stable CAD
M-HEART III‖‖	NA	1995	325	503	6 mo	58	83	50	18	NA	–	100% PCI for stable CAD
Stable CAD												
SAPAT¶¶	1985	1992	75	2035	50	67	52	41	7	100	–	3.9
VA bypass IV-B##	1983	1989	325	502	24	58	100	46	NA	NA	–	100% enrolled after CABG

ALDUSA-pilot indicates Aspirin at Low Dose in Unstable Angina; AMIS, Aspirin Myocardial Infarction Study; APRICOT, Antithrombotics in the Prevention of Reocclusion In Coronary Thrombolysis; ASA, aspirin; ATACS-pilot, Antithrombotic Therapy in Acute Coronary Syndromes; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CDP-A, Coronary Drug Project-Aspirin; GAMIS, German-Austrian Myocardial InfarctionStudy; Htn, hypertension; ISIS, International Studies of Infarct Survival; M-HEART II, Multi-Hospital Eastern Atlantic Restenosis Trialists II; MI, myocardial infarction; NA, not available; PARIS I, Persantine-Aspirin Reinfarction Study I; PCI, percutaneous coronary intervention; RISC, Research Group on Instability in Coronary Artery Disease; SAPAT, Swedish Angina Pectoris Aspirin Trial; and VA, Veterans Administration.

*PARIS I included 3 groups (ASA+dipyridamole=810; ASA=810; placebo=406).

†Patients enrolled were all those previously enrolled in the CDP study that included 3 groups (dextrothyroxine, estrogen 5 mg/d and estrogen 2.5 mg/d)

‡GAMIS included 3 groups (ASA=317, placebo=309, phenprocoumon=320).

§ISIS-pilot: patients with suspected acute MI were randomly assigned to receive either a high-dose short-term intravenous infusion of streptokinase or placebo. Using a 2×2×2 factorial design, patients were also randomly assigned to receive either oral ASA (325 mg on alternate days for 28 days) or placebo, and separately randomly assigned to receive either intravenous heparin (1000 IU h^{-1} for 48 h) or no heparin.

‖Patients up to 24 h after the onset of suspected acute MI were randomly assigned to 4 groups: 1-hour intravenous infusion of streptokinase; 1 month of 162.5 mg/d enteric-coated ASA; both active treatments or neither.

¶Patients treated with intravenous thrombolytic therapy followed by intravenous heparin were eligible when a patent infarct-related artery was demonstrated at angiography <48 h. Patients were randomly assigned to either 325 mg ASA daily (n=102) or placebo (n=90) with discontinuation of heparin or to Coumadin (n=92).

#ALDUSA-pilot: In the 40-mg arm, patients were to receive ASA 120 mg on day 1 and 40 mg daily thereafter.

**Patients were randomly assigned to 4 groups: ASA (n=121), heparin (n=118), ASA+heparin (n=122) or placebo (n=118).

††Patients were randomly assigned to receive ASA (325 mg daily; n=32), or full-dose heparin followed by warfarin (n=24), or the combination of ASA (80 mg/d) plus heparin and then warfarin (n=37).

‡‡After angioplasty of a previously untreated native coronary artery and after 2 wk of ASA therapy, 216 subjects (aged <70 y without acute MI) were randomly assigned to treatment with soluble ASA (n=108), 100 mg/d, or placebo (n=104) to study the effect on restenosis.

‖‖Patients were randomly assigned to ASA (325 mg daily; n=248), sulotroban (800 mg 4 times a day; n=249), or placebo (n=255), started within 6 h before PTCA and continued for 6 mo.

¶¶Patients with symptoms of chronic stable angina pectoris treated with increasing doses of sotalol were randomly assigned to ASA 75 mg daily (n=1009) or placebo (1026).

##The study determined how to improve saphenous vein graft patency after coronary artery bypass grafting by comparing ASA (325 mg once daily; n=104), ASA (325 mg 3 times daily; n=96), ASA+dipyridamole (325 mg and 75 mg, respectively, 3 times daily; n=99), sulfinpyrazone (267 mg 3 times daily; n=96), and placebo (3 times daily; n=107).

Table 2. Individual Results of Trials of Aspirin Versus Control

Trial Name	Treatment Regimen	Patients		Nonfatal MI		Nonfatal Stroke		Vasc Deaths		Vasc Events		Nonvasc Deaths		Major Bleeds			
		APT	Ctrl	APT	Ctrl	APT	Ctrl	APT	Ctrl	APT	Ctrl	APT	Ctrl	APT		Ctrl	
Prior MI																	
Cardiff-I	A300	615	624	10	15	–	–	47	61	57	76	2	4	–	(0)	–	(0)
Cardiff-II	A900	847	878	31	65	0	0	98	122	129	187	5	5	–	(0)	–	(0)
PARIS-I	A972 + D225	1620	406	105	34	15	3	147	45	265	82	26	7	–	(0)	–	(0)
AMIS	A1000	2267	2257	140	173	29	49	214	199	379	411	32	20	–	(0)	–	(0)
CDP-A	A972	758	771	27	32	7	9	43	61	76	102	2	4	–	(0)	–	(0)
GAMIS	A1500	317	309	11	15	0	0	22	30	33	45	5	2	–	(0)	–	(0)
Micristin	A1500	672	668	22	35	9	15	34	56	65	106	15	15	2	(1)	2	(1)
Acute MI																	
ISIS-pilot	A325 (SK), A325, A325 (H), A325 (H + SK)	313	306	7	9	1	2	25	35	33	46	0	0	1	(0)	1	(0)
ISIS-2	A162.5 (SK), A162.5	8587	8600	74	161	29	52	815	1026	915	1236	2	7	24	(2)	18	(3)
Dutch-aspirin	A100 (H)	50	50	2	6	1	0	9	12	12	18	0	0	0	(0)	0	(0)
Huddinge	A167	10	10	0	0	0	0	0	0	0	0	0	1	0	(0)	0	(0)
Frankfurt	A1320 + D300, A1320	25	14	0	0	0	0	1	1	1	1	0	0	0	(0)	0	(0)
APRICOT	A325 (H + FIB)	107	95	3	10	0	0	1	2	4	12	0	0	–	(–)	–	(–)
Unstable angina																	
VA-pilot	A324	26	24	0	1	0	0	1	3	1	4	0	0	0	(0)	0	(0)
VA-main	A324	661	677	27	49	3	2	15	24	45	75	0	0	0	(0)	0	(0)
RISC	A75	474	471	36	69	0	0	9	16	45	85	2	2	0	(0)	0	(0)
ALDUSA-pilot	A325, A40	56	28	5	0	1	0	1	1	7	1	0	0	–	(0)	–	(0)
Théroux	A650, A650 (H)	243	236	6	12	0	0	0	2	6	14	0	0	4	(0)	2	(0)
ATACS-pilot	A80 (H + W)	37	24	0	3	–	–	0	1	0	4	0	0	1	(0)	0	(0)
Coronary angioplasty																	
Perth	A100	124	128	0	2	–	–	–	–	0	2	–	–	–	(–)	–	(–)
M-HEART II	A325, ST	497	255	5	10	–	–	1	1	6	11	–	–	–	(–)	–	(–)
Stable CAD																	
SAPAT	A75	1009	1026	40	61	21	27	53	71	111	159	29	35	18	(9)	11	(5)
VA bypass IV-B	A325	161	173	3	3	–	–	3	4	6	7	0	0	–	(–)	–	(–)

The number of patients per group or the total number of patients could not correspond to Table 1 because ATT had access to individual patient data for many of the trials. Numbers of nonfatal major (extracranial) bleeds are shown first, with fatal bleeds in parentheses. Nonfatal stroke includes ischemic and hemorrhagic strokes, together with strokes of unknown etiology. Vascular deaths includes deaths that were known to have a vascular cause, and deaths of unknown cause. A indicates aspirin; ALDUSA-pilot, Aspirin at Low Dose in Unstable Angina; AMIS, Aspirin Myocardial Infarction Study; APRICOT, Antithrombotics in the Prevention of Reocclusion In Coronary Thrombolysis; APT, antiplatelet; ATACS-pilot, Antithrombotic Therapy in Acute Coronary Syndromes; CAD, coronary artery disease; CDP-A, Coronary Drug Project-Aspirin; Ctrl, control; D, dipyridamole; FIB, fibrinolytic therapy; GAMIS, German-Austrian Myocardial Infarction Study; H, heparin; ISIS, International Studies of Infarct Survival; M-HEART II, Multi-Hospital Eastern Atlantic Restenosis Trialists II; MI, myocardial infarction; Nonvasc, nonvascular; PARIS-I, Persantine-Aspirin Reinfarction Study I; RISC, Research Group on Instability in Coronary Artery Disease; SAPAT, Swedish Angina Pectoris Aspirin Trial; SK, streptokinase; ST, sulotroban; W, warfarin; VA, Veterans Administration; Vasc, vascular; and –, data unavailable.

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identify patients with high residual platelet reactivity, but only specific tests measuring the pharmacological effect of aspirin can clarify whether platelet hyperreactivity is attributable to insufficient pharmacological effect of aspirin or to other causes. Consequently, resistance to aspirin should be limited to situations in which aspirin is unable to inhibit COX-1–dependent TXA2 production (and thus, TXA2-dependent platelet functions). Measuring the capacity of platelets to directly synthesize TXA2 has been recommended to monitor the effect of aspirin.[45] The measurement of serum TXB2 to assess aspirin response showed that the prevalence of poor responders is extremely low.[45] Confounding problems may contribute to inappropriate use of the term resistance. The most frequent and plausible cause of insufficient inhibition of COX-1 by aspirin is probably poor patient compliance to therapy. Furthermore, genetic considerations, increased platelet turnover in some diseases (with a more rapid recovery of COX-1–dependent platelet function) and interference with the aspirin mechanism (ie, competition of aspirin with other nonsteroidal anti-inflammatory drugs, such as ibuprofen, can prevent aspirin irreversible acetylation and inactivation of the COX-1) could also account for interindividual variability of response to aspirin.[45]

Currently, aspirin resistance is not evaluated in routine clinical practice and efforts to enhance susceptibility to ASA, for instance, by increasing the aspirin daily regimen, should not be pursued given the lack of outcome data in this specific population.[30,31]

Aspirin may also be associated with hypersensitivity or intolerance, challenging secondary prevention.[46–49] Hypersensitivity refers to a history of respiratory, cutaneous, or systemic reactions, whereas the term intolerance refers to a history of severe indigestion incurred by low-dose aspirin.[47] Aspirin intolerance may be frequent, varying from 6% to 20%, whereas true hypersensitivity is rare at 0.6% to 2.4% of the general population.[47] These patients may be managed via desensitization protocols, which have been shown to be effective, but remain underused.[47–49] However, potentially fatal systemic reactions are rare and the number of patients with a true contraindication to low-dose aspirin is rather low.[47] In a study of patients with CAD undergoing cardiac catheterization and coronary stent implantation, Rossini et al[50] found that 2.6% reported histories of aspirin sensitivity characterized by respiratory or cutaneous manifestations (no anaphylactic reactions). The authors tested a novel rapid desensitization procedure (6 sequential doses of aspirin [1, 5, 10, 20, 40, and 100 mg] over 5.5 hours without corticosteroids or antihistamines) before cardiac catheterization (ST-segment–elevation MI patients underwent desensitization before hospital discharge) and found that this was safe and effective (success in 89%, during 1-year follow-up aspirin was tolerated well, without developing allergic reactions).[50]

Dosage

It is known that aspirin inhibition of platelet TXA2 is cumulative on repeated daily dosing and saturable at low doses (daily administration of ASA 30 mg determines a virtually complete suppression of platelet TXA2 after 1 week) in healthy individuals because of its irreversible nature, but some clinical conditions (diabetes mellitus, metabolic syndrome, CABG, etc) are associated with suboptimal antiplatelet inhibition by aspirin.[26] Thus, typical regimens of 75 to 100 mg daily clearly exceed the minimal effective dose required for a full pharmacodynamic effect, but accommodate some degree of interindividual variability.[26]

It has been suggested that aspirin doses <75 mg daily may be more effective than higher doses because they spare prostacyclin (an antiplatelet and vasodilator) and cause less gastrointestinal toxicity. In the Antithrombotic Trialists' meta-analysis, no significant differences in outcomes were observed when ASA ≥75 mg was compared with ASA <75 mg among 3570 patients in 3 trials.[31] However, aspirin doses of <75 mg have been less widely assessed than doses of 75 to 150 mg daily, and uncertainty remains as to whether such low doses are as effective as daily doses of ≥75 mg. Among trials evaluating higher daily doses of ASA versus no-ASA, the relative reduction in vascular events was 19% with doses of 500 to 1500 mg daily, 26% with doses of 160 to 325 mg daily, and 32% with doses of 75 to 150 mg daily, whereas daily doses <75 mg seemed to have a somewhat smaller effect (proportional reduction 13%).[31] In trials comparing ASA with control, the proportional increase in the risk of a major extracranial bleed was similar with all daily aspirin doses <325 mg (odds ratios 1.7 [95% confidence interval [CI] 0.8–3.3] for <75 mg; 1.5 [1.0–2.3] for 75–150 mg; and 1.4 [1.0–2.0] for 160–325 mg). Two trials that compared 75 with 325 mg aspirin daily with <75 mg daily also found no significant difference in major extracranial bleeds (2.5% with 75–325 mg versus 1.8% with <75 mg; *P*=nonsignificant).

A systematic review of clinical trials in 2007 suggested that available clinical data did not support the routine, long-term use of aspirin dosages >75 to 81 mg daily in the setting of cardiovascular disease prevention and that higher dosages, which were commonly prescribed, were not more effective at preventing events, but rather were associated with increased risks of gastrointestinal bleeding.[51] A subanalysis of the CURE trial (Clopidogrel in Unstable Angina to Prevent Recurrent Events) stratified patients based on ASA dosage (≤100, 101–199, and ≥200) demonstrating that the higher ASA doses did not reduce ischemic events but significantly increased the risk of major or life-threatening bleeding.[52] The CURRENT-OASIS 7 trial (Double-Dose Versus Standard-Dose Clopidogrel And High-Dose Versus Low-Dose Aspirin in Individuals Undergoing PCI for ACS) confirmed no sig-

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nificant differences in MACE between patients with ACS randomly assigned to high-dose (300–325 mg) versus low-dose (75–100 mg) ASA.[53] Although overall bleeding complications were nonsignificantly different, there was a higher incidence of gastrointestinal bleeding with high-dose ASA.[53] Interestingly, in the PLATO trial (Platelet Inhibition and Patient Outcomes), variation in ASA dose emerged as a possible explanation for observed regional differences (lower effect of ticagrelor in North America than in the rest of the world) and the lowest risk of cardiovascular death, MI, or stroke with ticagrelor in comparison with clopidogrel was associated with a low maintenance dose of concomitant aspirin.[54] Importantly, high-dose ASA also reduced the benefits of ticagrelor outside the United States.[54] On the contrary, an analysis from the TRITON–TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel–Thrombolysis in Myocardial Infarction 38) showed that, although North American patients received high-dose ASA more frequently than in other countries, the bleeding and ischemic events of prasugrel in comparison with those of clopidogrel were directionally consistent regardless of ASA dose.[55]

More recent data from US clinical practice still reflects uncertainty regarding the optimal aspirin dose for secondary prevention.[56] Indeed, despite previous data supporting lower doses of ASA, an analysis from 2014 showed that ≈60% of US patients with heart disease were discharged with 325-mg aspirin doses, whereas most of the remainder received lower doses (81 mg daily in 36%). Even among patients who experienced major in-hospital bleeding, 57% received the 325-mg dose. Furthermore, high-dose ASA was also commonly adopted in patients treated without revascularization (45%), in those treated with CABG (48%), or in those prescribed triple therapy (44%).[56] Similarly, the recent analysis from the Treatment with ADP Receptor Inhibitors: Longitudinal Assessment of Treatment Patterns and Events after Acute Coronary Syndrome study (TRANSLATE-ACS) showed that among 10 213 patients with MI who underwent PCI, 63% were discharged on ASA 325 mg and 37% with ASA 81 mg daily.[57] The adjusted risk of MACE was nonsignificantly different between the 2 regimens, but high-dose ASA was associated with greater risk of any Bleeding Academic Research Consortium–defined bleeding, driven mostly by minor Bleeding Academic Research Consortium type 1 or 2 events not requiring hospitalization.[57]

Recently, American guidelines have incorporated the low-dose ASA recommendation stating that a daily aspirin dose of 81 mg (range 75–100 mg) is recommended in patients treated with DAPT.[6] However, the ADAPTABLE trial (Aspirin Dosing: A Patient-Centric Trial Assessing Benefits and Long-term Effectiveness; NCT02697916) is expected to offer additional information on optimal ASA dosages. This study is funded by a Patient-Centered Outcomes Research Institute Award and will be conducted through PCORnet (National Patient-Centered Clinical Research Network).[58] The primary composite outcome (death, hospitalization for nonfatal MI, or stroke) and a primary safety end point of major bleeding complications were chosen with input from patients. The trial will compare a daily dose of ASA 81 versus 325 mg in 20 000 high-risk patients with atherosclerotic heart disease (defined as MI, or catheter ≥75% stenosis of ≥1 epicardial vessel, or PCI/CABG) and at least one of the following: age >65 years, creatinine 1.5 mg/dL, diabetes mellitus, 3-vessel disease, cerebrovascular disease or peripheral arterial disease, ejection fraction <50% (by echocardiogram, catheter or nuclear imaging), or current smoking. Patients will be excluded if they are <18 years of age, have a documented ASA allergy or contraindication (including pregnancy or nursing), a significant gastrointestinal bleed within the past 12 months, a significant bleeding disorder, need warfarin or non-Vitamin K oral anticoagulants or ticagrelor. Enrollment is planned to occur over 24 months, and the maximum follow-up will be 30 months.

Dual-Antiplatelet Therapy

The activation of platelets by a primary agonist, such as exposed collagen or thrombin at a site of vessel injury or plaque rupture, triggers platelet production of TXA2 and the release of ADP from platelet-dense granules, as well. TXA2 and ADP then act as autocrine and paracrine agonists via activation of platelet thromboxane-prostanoid and ADP ($P2Y_1$ and $P2Y_{12}$) receptors, respectively. By targeting both COX-1 and $P2Y_{12}$ pathways of platelet activation, aspirin and $P2Y_{12}$ inhibitors yield an additive or even synergistic effect when used in concert.[59]

Twenty years ago, the ISAR study (Intracoronary Stenting and Antithrombotic Regimen) first demonstrated that DAPT was superior to anticoagulant therapy in patients undergoing to PCI.[60,61] Subsequently, the CURE trial showed the benefits of adding clopidogrel to ASA monotherapy in ACS patients and also in those undergoing PCI, although at the cost of increased bleeding.[12,62] Over the past 2 decades, the coadministration of $P2Y_{12}$ inhibitors with aspirin has been shown to further reduce the risk of acute thrombotic events in several clinical settings, albeit always at the price of greater bleeding.[2,8,12] As a result, equipoise and controversy persist surrounding the optimal duration of DAPT after PCI.[63] Multiple studies have consistently shown the feasibility of reducing DAPT duration to 6 (PRODIGY, EXCELLENT, SECURITY, ITALIC, ISAR-SAFE, I-LOVE-IT 2, IVUS-XPL, NIPPON) or even 3 months (OPTIMIZE, RESET), resulting in lower bleeding hazards without any incremental increase in ischemic events.[64] Nevertheless, other trials investigated the value of prolonging DAPT beyond 12 months (ARCTIC Interruption, DAPT, DES-LATE, OPTIDUAL), providing partially conflicting results as it relates to

the benefit to reduce nonfatal ischemic events including MI and very late ST at the expense of greater bleeding and potentially fatal outcomes. A meta-analysis of 10 thienopyridine trials including 31 666 patients showed that shorter DAPT was associated with a lower risk of major bleeding, but a higher risk of MI and ST.[63] Notably, this analysis also demonstrated that longer DAPT was associated with a significantly increased risk of all-cause mortality that was attributable to noncardiac mortality.[63] The caveat of this analysis, however, is that by pooling all available thienopyridine studies, a 12-month DAPT duration was included in both control and experimental groups, thereby failing to provide information on optimal DAPT duration. As an alternative approach, these 10 thienopyridine trials have been stratified more recently based on DAPT duration in the control group, by keeping 12 months as the control therapy and contrasting it to either a shortened (ie, 6 or 3 months) or a prolonged (ie, ≥18 months) DAPT regimen.[19] This analysis showed that DAPT discontinuation before 12 months after PCI with drug-eluting stent (DES) yielded fewer bleeding events without an apparent increase of ischemic complications. DAPT continuation beyond 12 months reduced ischemic and thrombotic events at the expense of more frequent major bleeding and all-cause mortality. Hence, it has been suggested that the currently recommended 12-month DAPT duration after DES implantation is a compromise between ischemic and bleeding risk of uncertain value, and it highlights the challenge of identifying a uniformly ideal DAPT duration across patient ischemic and bleeding risk profiles in practice.

Although it has been suggested that early-generation DES, in comparison with new-generation DES, may amplify the need for prolonged DAPT,[65] an emerging new paradigm is that the benefit of prolonged DAPT may largely be stent independent. DAPT consisting of aspirin and clopidogrel beyond 12 months has been shown to reduce the risk of MI not related to stented segments.[18] The benefits and risks of aspirin and ticagrelor at doses of 60 mg twice daily and 90 mg twice daily beyond 1-year treatment was investigated in patients with established CAD, revealing a reduced risk of ischemic events, including myocardial infarction and stroke, again at the expense of increased bleeding risk. The paradigm shift (from stent to patient protection) supports the notion of extending DAPT beyond the vulnerability window intrinsic to and related to stents (subacute or late ST). Yet this benefit must be interpreted in the context of the continuous increase in bleeding risk observed during the course of DAPT duration. Previous evidence that, in patients on DAPT bleeding, may decrease over time (ie, CHARISMA) has been challenged by recent studies (DAPT, PRODIGY, PEGASUS [Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin]) suggesting a linear relationship between DAPT duration and bleeding risk. Although a high risk of bleeding is somewhat expected soon after the initiation of DAPT, multiple long-term DAPT studies have clearly shown that this risk never abates over time, even after several years of treatment. A recent subanalysis from PEGASUS explored the reasons for and timing of discontinuation of ticagrelor among stable patients with prior MI and found that bleeding was the main cause of discontinuation. The rate of treatment discontinuation because of bleeding was 3.5% in the ticagrelor 60 mg arm and 5% in the ticagrelor 90 mg arm (in comparison with <1% in the placebo group) and it increased to ≈5% and 6.5%, respectively, at an average 3-year follow-up (in comparison with ≈1.2% in the placebo group).[66]

In a pooled analysis of trials comparing short versus prolonged DAPT durations, bleeding was potentially more causally associated with all-cause mortality than ST, which highlights the need to minimize the risks of bleeding to optimize the fatality rate.[67] This appears consistent with the results of a large survey capturing DAPT prescription practices, where attempts to individualize DAPT duration based on conventional ischemic and bleeding risk factors emerged as the most common prescription pattern.[68]

It remains unclear whether the type of DAPT (ie, the type of $P2Y_{12}$ inhibitor paired with aspirin) affects the comparative effectiveness/safety profile of a shortened versus a prolonged DAPT duration.

The PEGASUS study randomly assigned 21 162 patients with an MI 1 to 3 years earlier to ticagrelor 90 mg twice daily, ticagrelor 60 mg twice daily, or placebo.[17] All patients received low-dose aspirin and were followed for a median of 33 months. In comparison with placebo, both ticagrelor doses reduced the rate of the primary efficacy end point, with cumulative event rates at 3 years of 7.85% in the 90 mg twice daily group, 7.77% in the 60 mg twice daily group, and 9.04% in the placebo group (hazard ratio [HR] for 90 mg of ticagrelor versus placebo, 0.85; 95% CI, 0.75–0.96; P=0.008; HR for 60 mg of ticagrelor versus placebo, 0.84; 95% CI, 0.74–0.95; P=0.004). Both ticagrelor doses significantly reduced rates of MI, whereas the 60 mg twice daily ticagrelor regimen also reduced the risk of stroke and trended toward a reduction in cardiovascular mortality. When pooling both doses, there was no signal of harm related to all-cause mortality, which is at variance with the previously discussed results of the pooled analysis using clopidogrel for DAPT.[69] Whether the observed heterogeneity with respect to overall mortality after prolonged DAPT reflects the characteristics of the $P2Y_{12}$ inhibitor used in the DAPT regimen (ie, a thienopyridine versus a nonthienopyridine agent) or rather different patient selections across studies (ie, a uniform post-MI population in PEGASUS versus a mix of stable and unstable CAD patients undergoing stent implantation in other thienopyridine trials) is unclear and warrants subsequent investigation.[69–72]

SINGLE-ANTIPLATELET $P2Y_{12}$ INHIBITOR THERAPY AFTER PCI

Rationale

Under the assumption that aspirin is the default antiplatelet therapy, all the studies in the past decades investigating, among others, $P2Y_{12}$ antagonists or oral anticoagulants, both in patients with or without an established indication to systemic anticoagulation, have been conducted as add-on therapy in the context of background aspirin treatment. A prolonged DAPT, despite being efficacious in mitigating the risks of MI and ST, may disproportionally increase bleeding liability, leading to unfavorable effects on noncardiovascular and total mortality. Although the addition of rivaroxaban to a DAPT regimen consisting of aspirin and clopidogrel was effective in reducing a composite ischemic end point, including a significant reduction in cardiovascular mortality, relevant increases in overall, life-threatening, and intracranial bleeding were also observed.

These findings may reflect the ceiling effect associated with further intensification of antithrombotic drugs wherein additional exposure increases bleeding toxicity without any reduction in thrombosis. Consequently, the less-is-more concept has been proposed in an effort to mitigate bleeding potential while preserving antithrombotic efficacy achieved through the concomitant inhibition of multiple platelet activation pathways, thereby optimizing net clinical benefit. Recently, a stand-alone $P2Y_{12}$ inhibition strategy has been proposed to replace long-term DAPT regimens for long-term secondary prevention. Interestingly, Rollini et al[73] compared the antiplatelet effect of aspirin monotherapy and clopidogrel monotherapy in patients with atherosclerotic disease in a prospective pharmacodynamics study and showed that clopidogrel was associated with increased platelet inhibition in heavy smokers.

Although the results of large randomized studies are awaited to validate this potentially new treatment modality, 3 large-scale studies testing different anticoagulants in ACS patients have shown that bleeding prevention may be causally linked to mortality benefit, despite slightly higher risks of ST or catheter thrombosis.[74–76] The net clinical effect of adding aspirin in patients receiving newer more potent $P2Y_{12}$ antagonists is unknown and aspirin may increase bleeding while not further mitigating the ischemic risk. This may be particularly true in patients treated with newer $P2Y_{12}$ antagonists,[11] which unlike ticlopidine[77] or clopidogrel,[78,79] exert a predictable inhibition of the target receptor.

Biochemical Considerations

Several lines of evidence suggest that $P2Y_{12}$ antagonists might also affect TXA2 platelet production, thereby minimizing any additional antiplatelet effect realized with aspirin use.[80–85] Experiments with platelet-rich plasma from healthy volunteers have shown that prasugrel active metabolites inhibit platelet release of both TXA2 and ATP+ADP, and the addition of aspirin to prasugrel failed to provide any additional inhibition of platelet aggregation.[82] However, the study had some limitations, particularly in how the effect of aspirin was assessed. These findings are related to the strong $P2Y_{12}$ inhibition, so they also can be extended to ticagrelor. Indeed, in a recent pharmacodynamics study in diabetic patients, both prasugrel and ticagrelor were associated with inhibitory effects on measures of non–ADP-induced platelet reactivity (ie, thromboxane-, collagen-, and thrombin-induced).[86] Nevertheless, it remains to be proven whether these in vitro and ex vivo observations will translate into clinical implications. However, the overall effect of adding aspirin (particularly at daily doses >100 mg) to new $P2Y_{12}$ antagonists could be deleterious because of its inhibition of protective prostanoids in other cells and tissues, including vascular endothelium, stomach, and kidney.[80] High-dose aspirin does not provide greater treatment efficacy but increases bleeding risks in comparison with a low-dose aspirin regimen.[54,87] In the PLATO trial, geographical differences in clinical outcomes were observed, namely, an apparent lack of superior treatment effect of ticagrelor over clopidogrel in the study cohort recruited in the United States.[15,54] Of the 37 baseline and postrandomization factors explored, aspirin maintenance dose was found to be the most important covariate explaining at least in part these regional differences.[54] In particular, the lowest risk of cardiovascular death, MI, or stroke with ticagrelor in comparison with clopidogrel, was associated with a low maintenance dose of concomitant aspirin, whereas the higher maintenance dose of aspirin used in the United States in comparison with other regions (≥300 mg/d in 53.6% versus 1.7% of patients, respectively) seemed to be responsible for these geographic differences. This study suggested that high-dose aspirin added to ticagrelor could be deleterious and could blunt ticagrelor benefits, in the United States, and in the as non-United States, as well.[54] Notably, 2 small studies showed that aspirin had no direct effect on ticagrelor pharmacokinetics or its platelet inhibition.[88]

Evidence contradicting the possible biochemical interaction between $P2Y_{12}$ and COX-1 inhibition has also been provided. Cattaneo et al[89] assessed whether $P2Y_{12}$ antagonists have off-target/indirect inhibitory effects on platelet TXA2 production. They studied 3 patients with inherited deficiency of $P2Y_{12}$ receptors and 33 healthy subjects, demonstrating that $P2Y_{12}$ inhibition did not affect the platelet capacity to synthesize TXA2: (1) serum TXB2 (TXA2 metabolite) levels were similar in $P2Y_{12}$R-deficient patients and healthy subjects and were not decreased by $P2Y_{12}$ antagonists in vitro; (2) serum TXB2 levels did not decrease in patients treated with prasugrel

(10 mg) or placebo for 14 days; (3) ASA inhibited TXB2 production more effectively than a $P2Y_{12}$ antagonist, and only the combination of ASA plus $P2Y_{12}$ antagonist inhibited platelet aggregation induced by high concentrations of collagen.

Clinical guidelines supporting the prophylactic use of aspirin for purposes of secondary prevention acknowledge the cardiovascular benefits, weighed against the potential risks of bleeding.

However, it should be mentioned that new aspirin formulations have a better pharmacokinetic/pharmacodynamic profile and gastrointestinal tolerability that may open new avenues for aspirin in the future.

Furthermore, there is also relevant evidence supporting other benefits related to low-dose aspirin use, including chemoprevention and reduced risk of dementia, and these effects would be lost in case of long-term treatment with new $P2Y_{12}$ antagonists instead of aspirin.[90–93] It has been suggested that low-dose aspirin is associated with decreased incidence and mortality for colorectal cancer, potentially because of its interference with neoplastic transformation of a normal intestinal epithelium (mainly in the colorectal region) toward a sporadic adenoma and its progression to cancer.[90–92] It has also been speculated that even a 10% reduction in overall cancer incidence starting in the first 10 years of treatment may favorably tip the balance of benefits and risks in average-risk populations.[91] Preliminary evidence also suggests that low-dose aspirin reduces cognitive decline in the elderly, possibly by reducing brain inflammation (inhibition of platelet-related inflammation and release of lipoxins).[93] Long-term studies comparing aspirin versus $P2Y_{12}$ inhibitors alone would be required to confirm or disprove these potential aspirin-specific effects.

Clinical Evidence

Initial experience supporting the use of $P2Y_{12}$ inhibitors over aspirin was provided by the TASS (Ticlopidine Aspirin Stroke Study) and the CAPRIE (Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events) trials.[13,94] Ticlopidine was more effective than aspirin in preventing strokes in a high-risk population with similar bleeding risk.[94] In the CAPRIE trial, long-term administration of clopidogrel among patients with atherosclerotic vascular disease was as safe as, but more effective than aspirin in reducing the combined risk of ischemic stroke, MI, or vascular death.[13] The recent SOCRATES (Acute Stroke or TIA Treated with Aspirin or Ticagrelor and Patient Outcomes) was an international double-blind controlled trial in 674 centers in 33 countries, in which 13199 patients with a nonsevere ischemic stroke or high-risk TIA were randomly assigned within 24 hours after symptom onset, in a 1:1 ratio, to receive either ticagrelor (180 mg loading dose on day 1 followed by 90 mg twice daily for days 2–90) or aspirin (300 mg on day 1 followed by 100 mg daily for days 2–90).[95] The primary end point (stroke, MI, or death within 90 days) occurred in 442 of the 6589 patients (6.7%) treated with ticagrelor, versus 497 of the 6610 patients (7.5%) treated with aspirin (HR, 0.89; 95% CI, 0.78–1.01; P=0.07).[95] Approximately 32% of patients were taking aspirin before randomization, and the prespecified subgroup analysis of the primary end point showed that these patients tended to derive greater benefit from ticagrelor (previous aspirin patients: HR, 0.76; 95% CI, 0.61–0.95; no previous aspirin patients: HR, 0.96; 95% CI, 0.82–1.12), although the interaction P value was nonsignificant (interaction P=0.10). Interestingly, major bleeding occurred in 0.5% of patients treated with ticagrelor and in 0.6% of patients treated with aspirin, intracranial hemorrhage in 0.2% and 0.3%, respectively, and fatal bleeding in 0.1% and 0.1%.[95] This study failed to conclusively show superiority of ticagrelor versus aspirin in poststroke/TIA patients; however, it adds to the growing evidence that a $P2Y_{12}$ inhibitor monotherapy strategy may result in greater protection from ischemic recurrences than aspirin, with a similar bleeding profile.

Further evidence supporting the use of $P2Y_{12}$ inhibitors without aspirin in patients with established atherosclerotic disease was provided in the context of the MATCH trial (Molecular Analysis for Therapy Choice).[96] In MATCH, 7599 high-risk patients with recent ischemic stroke or TIA and at least 1 additional vascular risk factor, who were already receiving clopidogrel 75 mg/d, were randomly assigned to aspirin 75 mg/d or placebo.[96] This study showed that adding aspirin to clopidogrel did not decrease major vascular events but increased the risk of major and life-threatening, including intracranial, bleeding complications.[96] This supported the concept that adding ASA to clopidogrel was more dangerous than adding clopidogrel to ASA as was previously observed in the CURE trial.

Finally, evidence suggesting an improved safety profile of aspirin omission after PCI comes from the proof-of-concept WOEST study (What Is the Optimal Antiplatelet and Anticoagulant Therapy in Patients With Oral Anticoagulation and Coronary Stenting) that compared the use of clopidogrel alone in patients on vitamin K antagonist and showed fewer bleeding complications without an apparent increase of thrombotic events, including a lower mortality risk in comparison with triple therapy.[97] It should be emphasized, however, that concomitant oral anticoagulant therapy largely increases bleeding risk, but it also mitigates thrombotic risks, including the reduction of ST incidence. Therefore, caution should be used in extrapolating the effect of aspirin removal in patients taking oral anticoagulants to those not in need of such therapy (ie, who have indication to DAPT only) after ACS or PCI.

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Table 3. Characteristics of Trials Assessing Anticoagulation Therapy in Patients With AF Undergoing PCI

	REDUAL-PCI	PIONEER AF-PCI	AUGUSTUS	ENTRUST-AF-PCI
Title	A Prospective Randomised, Open Label, Blinded End point (PROBE) Study to Evaluate DUAL Antithrombotic Therapy With Dabigatran Etexilate (110 mg and 150 mg BID) Plus Clopidogrel or Ticagrelor vs Triple Therapy Strategy With Warfarin (INR 2.0–3.0) Plus Clopidogrel or Ticagrelor and Aspirin in Patients With Non Valvular Atrial Fibrillation (NVAF) That Have Undergone a Percutaneous Coronary Intervention (PCI) With Stenting	An Open-label, Randomized, Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention	An Open-label, 2×2 Factorial, Randomized Controlled, Clinical Trial to Evaluate the Safety of Apixaban vs Vitamin K Antagonist and Aspirin vs Aspirin Placebo in Patients With Atrial Fibrillation and Acute Coronary Syndrome or Percutaneous Coronary Intervention	Evaluation of the Safety and Efficacy of an Edoxaban-based Compared to a Vitamin K Antagonist-based Antithrombotic Regimen in Subjects With Atrial Fibrillation Following Successful Percutaneous Coronary Intervention (PCI) With Stent Placement
ClinicalTrials.gov identifier	NCT02164864	NCT01830543	NCT02415400	NCT02866175
Sponsor	Boehringer Ingelheim	Janssen Scientific Affairs, LLC	Bristol-Myers Squibb	Daiichi Sankyo Inc.
Estimated enrollment	2502	2127	4600	1500
Study start date	July 2014	May 2013	June 2015	February 2017
Estimated completion date	March 2017	July 2016	September 2017	February 2019
Allocation	Randomized	Randomized	Randomized	Randomized
End point classification	Safety/efficacy study	Safety study	Safety study	Safety/efficacy study
Intervention model	Parallel assignment	Single-group assignment	Factorial assignment	Parallel assignment
Masking	Open label	Open label	Open label	Open label
Active comparator	Warfarin 5 or 3 or 1 mg plus aspirin plus clopidogrel or ticagrelor	Dose-adjusted VKA once daily (target INR 2.0–3.0) plus low-dose aspirin, 75 to 100 mg/d, and clopidogrel 75 mg once daily (or prasugrel 10 mg once daily or ticagrelor 90 mg twice daily) followed by dose-adjusted VKA once daily (target INR 2.0–3.0 or 2.0–2.5 at the investigator discretion) plus low-dose aspirin for 12 mo	VKA orally once daily plus aspirin film-coated tablet orally once daily (81 mg or placebo)	VKA plus clopidogrel 75 mg once daily (or in the presence of a documented clinical need prasugrel [5 mg or 10 mg once daily] or ticagrelor [90 mg twice daily] may be used).

(*Continued*)

Table 3. Continued

	REDUAL-PCI	PIONEER AF-PCI	AUGUSTUS	ENTRUST-AF-PCI
Experimental comparator	Dabigatran etexilate 110 mg plus clopidogrel or ticagrelor Dabigatran etexilate 150 mg plus clopidogrel or ticagrelor	Rivaroxaban 2.5 mg twice daily plus low-dose aspirin 75–100 mg once daily and clopidogrel 75 mg once daily (or prasugrel 10 mg once daily or ticagrelor 90 mg twice daily) followed by rivaroxaban 15 mg (10 mg if moderate CKD) once daily plus low-dose aspirin for 12 mo Rivaroxaban 15 mg (10 mg if moderate CKD) once daily plus clopidogrel 75 mg once daily (or prasugrel 10 mg once daily or ticagrelor 90 mg twice daily) for 12 mo	Apixaban 2.5 or 5 mg orally twice per day plus aspirin film coated tablet orally once daily (81 mg or placebo)	Edoxaban 60 mg once daily or 30 mg once daily in selected subjects
Primary outcome	First ISTH major or CRNM bleeding (up to 30 mo)	Clinically significant bleeding at 12 mo (composite of TIMI major bleeding, minor bleeding, and bleeding requiring medical attention)	Occurrence of ISTH major or CRNM bleeding during the time the patient is taking the medicine which is 6 mo (between apixaban and VKA; between aspirin and no-aspirin)	Number of ISTH major or CRNM bleeding (≤12 mo)
Secondary outcome	At 30 mo: Undetermined cause of death; noncardiovascular death; cardiovascular death; all death; MI; stroke; ST; SE; death+MI+stroke; unplanned revascularization (PCI or CABG); death or first thrombotic event (all death, MI, stroke/SE); death or first thrombotic event or unplanned revascularization	Clinically significant bleeding and adverse cardiovascular events, and adverse events at 10 d, 30 d, 3 mo, 6 mo, 9 mo, 12 mo. Composite of clinically significant bleeding and adverse cardiovascular events at the end of DAPT period (1 mo or 6 mo or 12 mo) and at 12 mo	Superiority on major+CRNM bleeding between apixaban versus VKA at 6 mo Composite of death and ischemic events (stroke, MI, ST, urgent revascularization) between apixaban versus VKA and between aspirin and no-aspirin at 6 mo First rehospitalization for any cause between apixaban versus VKA and between aspirin and no-aspirin at 6 mo	At 12 mo: composite number of cardiovascular death, stroke, SE, MI, and ST events; composite number of cardiovascular death, stroke, SE, MI, ST events, and ISTH-defined bleeding events; Number of ISTH major bleeding
Inclusion criteria	1. Male or female patients aged ≥18 y 2. Patients with nonvalvular AF 3. Patient presenting with: an ACS (STEMI, NSTEMI, or UA) that was successfully treated by PCI and stenting (either BMS or DES) or stable coronary artery disease with at least 1 lesion eligible for PCI that was successfully treated by elective PCI and stenting (either BMS or DES) 4. The patient must be able to give informed consent	1. History of paroxysmal, persistent, or permanent nonvalvular AF 2. Have undergone PCI with stent placement for primary atherosclerotic disease 3. INR of ≤2.5 to be randomized 4. Women must be postmenopausal before entry or practicing a highly effective method of birth control when heterosexually active 5. Be willing and able to adhere to the prohibitions and restrictions specified in the study protocol	1. Adults with either active or a history of nonvalvular AF or flutter with the planned or existing use of an oral anticoagulant for prophylaxis of thromboembolism. In addition, subjects must have had an ACS or PCI with a stent within the previous 14 days 2. Planned use of antiplatelet agents for at least 1 to 6 mo 3. Men and women ≥18 y 4. Women of childbearing potential must have a negative serum or urine pregnancy test within 24 h before the start of study drug	Oral anticoagulant therapy indication for AF for a period of at least 12 mo following successful PCI with stenting. Eligibility is assessed 4 h after sheath removal and within 5 days after successful PCI with stent placement. If a staged PCI is planned, eligibility is assessed after completion of the last stage.

(*Continued*)

Circulation. 2016;134:1881–1906. DOI: 10.1161/CIRCULATIONAHA.116.023952

Table 3. Continued

	REDUAL-PCI	PIONEER AF-PCI	AUGUSTUS	ENTRUST-AF-PCI
Exclusion criteria	1. Mechanical or biological heart valve prosthesis 2. Cardiogenic shock during current hospitalization 3. Stroke within 1 mo before screening visit 4. Major surgery within the month before screening 5. Gastrointestinal hemorrhage within 1 mo before screening, unless, in the opinion of the Investigator, the cause has been permanently eliminated 6. Major bleeding episode including life-threatening bleeding episode in 1 mo before screening visit 7. Anemia (Hb <10g/dL) or thrombocytopenia including heparin-induced thrombocytopenia (platelet count <100×109/L) at screening 8. Severe CKD (estimated CrCl by Cockcroft-Gault <30 mL/min at screening 9. Active liver disease	1. Any condition that contraindicates anticoagulant or antiplatelet therapy or would have an unacceptable risk of bleeding, such as, but not limited to: platelet count <90 000/μL at screening, history of intracranial hemorrhage, 12 mo history of clinically significant gastrointestinal bleeding, non-VKA-induced elevated prothrombin time (PT) at screening 2. Anemia of unknown cause with a Hb level <10 g/dL 3. History of stroke or TIA 4. Calculated CrCl <30 mL/min at screening 5. Known significant liver disease or liver function test abnormalities 6. Any severe condition that would limit life expectancy to <12 mo	1. Conditions other than AF that require chronic anticoagulation (eg, prosthetic mechanical heart valve) 2. Severe CKD (serum creatinine >2.5 mg/dL or a calculated CrCl < 30 mL/min 3. History of intracranial hemorrhage 4. Patients have had or will undergo CABG for their index ACS event 5. Known ongoing bleeding or coagulopathies 6. Any contraindications or allergies to VKA, apixaban, or to intended $P2Y_{12}$ antagonists or to aspirin	1. Bleeding risks or systemic conditions 2. Known bleeding diathesis, including but not limited to: a. Uncontrolled active bleeding, encompassing both ISTH major and clinically relevant nonmajor bleeding, preceding randomization. Lesion or condition, if considered to be a significant risk for major bleeding. This may include but is not limited to: unresolved gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding (eg, malignancies with metastasis), recent unresolved brain or spinal injury, recent brain, spinal, or ophthalmic surgery, any intracranial hemorrhage, known or suspected esophageal varices, arteriovenous malformations, vascular aneurysms (of >3.5 cm) or major intraspinal or intracerebral vascular abnormalities. b. Medication-related 3. INR > 2.5 (the subject can be reconsidered at a later time, but within 5 days of sheath removal). 4. Contraindication to edoxaban, VKA, ASA. and $P2Y_{12}$ antagonists; 5. Concomitant treatment with other antithrombotic agents, fibrinolytic therapy. and chronic nonsteroidal anti-inflammatory drugs (NSAIDs). 6. Critically ill or hemodynamically unstable subjects (at the time of randomization) including: a. Cardiogenic shock or acute decompensated heart failure, with the requirement for vasopressor agents or inotropic support or mechanical support to support circulation b. Respiratory failure requiring endotracheal intubation and mechanical ventilation. 7. Any prior mechanical valvular prosthesis; 8. Planned coronary or vascular intervention or major surgery within 12 mo; Randomization must be deferred to the last stage in a multistep, multivessel PCI procedure; 9. Moderate or severe mitral stenosis; 10. Ischemic stroke within 2 wk before randomization;

(*Continued*)

Table 3. Continued

	REDUAL-PCI	PIONEER AF-PCI	AUGUSTUS	ENTRUST-AF-PCI
Exclusion criteria (Continued)				11. Uncontrolled severe hypertension with a systolic blood pressure (BP) ≥180 mm Hg and diastolic BP≥120 mm Hg; 12. Severe renal impairment with estimated CrCl <15 mL/min or on dialysis; 13. Known abnormal liver function before randomization (including hepatic disease or biochemical evidence of significant liver derangement known before randomization). 14. Any of the following abnormal local laboratory results prior to randomization: a. Platelet count < 50×109/L b. Hemoglobin <8 mg/dL 15. Unable to provide written IC; Female subjects of childbearing potential without using adequate contraception (female of childbearing potential is defined as one who has not been postmenopausal for at least 1 y, or has not been surgically sterilized, or has not had a hysterectomy at least 3 mo before the start of this study [Visit 1]). Females taking oral contraceptives should have been on therapy for at least 3 mo. Adequate contraceptives include hormonal intrauterine devices, hormonal contraceptives (oral, depot, patch, or injectable), and double-barrier methods such as condoms or diaphragms with spermicidal gel or foam. 16. Pregnant or breastfeeding subjects; 17. Assessment that the subject is not likely to comply with the study procedures or have complete follow-up; 18. Participating in another clinical trial that potentially interferes with the current study; 19. Previous randomization in this study; 20. Known drug or alcohol dependence within the past 12 mo as judged by the Investigator; 21. Life expectancy <12 mo.

ACS indicates acute coronary syndrome; AF, atrial fibrillation; BID, twice daily; BMS, bare metal stent; CABG, coronary artery bypass graft; CKD, chronic kidney disease; CrCl, creatinine clearance; CRNM, clinically relevant nonmajor; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; Hb, hemoglobin; IC, informed consent; INR, international normalized ratio; ISTH, international society on thrombosis and hemostasis; MI, myocardial infarction; NSTEMI, non–ST-segment–elevation myocardial infarction; PCI, percutaneous coronary intervention; SE, systemic embolism; ST, stent thrombosis; STEMI, ST-segment–elevation myocardial infarction; TIA, transient ischemic attack; UA, unstable angina; and VKA, vitamin-K antagonist.

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Table 4. Characteristics of GLOBAL LEADERS, TWILIGHT, and TICO Trials

	GLOBAL LEADERS	TWILIGHT	TICO
Title	Comparative Effectiveness of 1 mo of Ticagrelor Plus Aspirin Followed by Ticagrelor Monotherapy Versus a Current-day Intensive Dual Antiplatelet Therapy in All-comers Patients Undergoing Percutaneous Coronary Intervention With Bivalirudin and BioMatrix Family Drug-eluting Stent Use	Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention	Ticagrelor Monotherapy After 3 mo in the Patients Treated With New Generation Sirolimus Stent for Acute Coronary Syndrome
ClinicalTrials.gov identifier	NCT01813435	NCT02270242	NCT02494895
Sponsor	European Cardiovascular Research Institute (ECRI)	Mount Sinai School of Medicine	Yonsei University
Estimated enrollment	16 000	9000	3056
Study start date	May 2013	July 2015	July 2015
Estimated completion date	June 2016	October 2018	July 2020
Allocation	Randomized	Randomized	Randomized
End point classification	Safety/efficacy study	Safety/efficacy study	Safety/efficacy study
Intervention model	Parallel assignment	Parallel assignment	Parallel assignment
Masking	Open label	Double blind	Open label
Active comparator	Aspirin (≤100 mg qd) + Ticagrelor (90 mg bid) for 12 mo followed by aspirin monotherapy for 12 mo in case of ACS; Aspirin (≤100 mg qd) + clopidogrel (75 mg qd) for 12 mo followed by aspirin monotherapy for 12 mo in case of stable CAD	Aspirin (81 mg daily for 12 mo) + ticagrelor (90 mg bid for 15 mo)	Aspirin + ticagrelor
Experimental comparator	Aspirin (≤100 mg qd) + ticagrelor (90 mg bid) for 1 mo followed by 23 mo of ticagrelor monotherapy.	Placebo (daily for 12 mo)+ ticagrelor (90 mg bid for 15 mo)	Ticagrelor monotherapy at 3 mo after PCI
Primary outcome	Composite of all-cause mortality or nonfatal new Q-wave MI up to 2 y	Bleeding: the time to first occurrence of clinically relevant bleeding, defined as BARC types 2, 3, or 5 bleeding at 1 y (15 mo after PCI)	Major adverse cardiovascular clinical events (MACCE) 1 y after the procedure Major bleeding (TIMI) 1 y after the procedure
Secondary outcome	Bleeding: The composite of investigator-reported BARC3 or BARC5 bleeding up to 2 y	Ischemic episode: the time to first occurrence of confirmed cardiovascular death, nonfatal MI, ischemic stroke, or IDR at 1 y (15 mo after PCI)	

(*Continued*)

Table 4. Continued

	GLOBAL LEADERS	TWILIGHT	TICO
Inclusion criteria	All-comer patients: 1. Age ≥18 y; 2. Presence of ≥1coronary artery stenoses of ≥50% in a native coronary artery or in a saphenous venous or arterial bypass conduit suitable for coronary stent implantation. The vessel should have a reference vessel diameter of at least 2.25 mm (no limitation on the number of treated lesions, vessels, or lesion length); 3. Able to provide informed consent and willing to participate in 2-y follow-up period.	High-risk patients who have undergone successful elective or urgent PCI with at least one locally approved drug-eluting stent discharged on DAPT with aspirin and ticagrelor of at least 3 mo intended duration will be eligible. Enrollment into the study will require meeting at least one clinical inclusion, one angiographic inclusion, and none of the exclusion criteria. Clinical Inclusion Criteria: 1. Adult patients ≥ 65 y of age 2. Recent (≥3 days) presentation with acute coronary syndrome with clinical stabilization and decreasing cardiac enzymes 3. Established vascular disease defined as previous MI, documented PAD or CAD/PAD revascularization 4. Diabetes mellitus treated with medications (oral hypoglycemic, subcutaneous injection of insulin) 5. CKD defined as an eGFR <60 mL·min^{-1}·1.73m^{-2} or creatinine clearance (CrCl) <60 mL/min Angiographic Inclusion Criteria: 1. Multivessel CAD 2. Target lesion requiring total stent length >30 mm 3. SYNTAX score ≥23 4. Bifurcation lesions with Medina X:X:1 classification requiring at least 2 stents 5. Left main (≥50%) or proximal LAD (≥70%) lesion 6. Calcified target lesion requiring atherectomy	1. Patients ≥19 y old 2. Patients who received new-generation sirolimus-eluting (Osiro) stent implantation for treating ACS 3. Patients without significant clinical events such as MI, stent thrombosis, or revascularization until 3 mo after PCI 4. Provision of informed consent
Exclusion criteria	1. Known intolerance to aspirin, $P2Y_{12}$ inhibitors, bivalirudin, stainless steel, or biolimus; 2. Known intake of a strong CYP3A4 inhibitor (eg, ketoconazole, clarithromycin, nefazodone, ritonavir, and atazanavir), because coadministration may lead to a substantial increase in exposure to ticagrelor; 3. Known moderate to severe hepatic impairment (alanine-aminotransferase ≥3×ULN); 4. Planned surgery, including CABG as a staged procedure (hybrid) within 12 mo of the index procedure, unless dual-antiplatelet therapy is maintained throughout the perisurgical period;	1. Under 18 y of age 2. Contraindication to aspirin 3. Contraindication to ticagrelor 4. Planned surgery within 90 days 5. Planned coronary revascularization (surgical or percutaneous) within 90 days 6. Need for chronic oral anticoagulation 7. Prior stroke 8. Dialysis-dependent renal failure 9. Active bleeding or extreme risk for major bleeding (eg, active peptic ulcer disease, gastrointestinal pathology with a raised risk for bleeding, malignancies with a raised risk for bleeding)	1. Age > 80 y 2. Increased risk of bleeding, anemia, thrombocytopenia 3. A need for oral anticoagulation therapy 4. Pregnant women or women with potential childbearing 5. Life expectancy <1 y 6. Patients treated with strong CYP3A4 inhibitors (eg, ketoconazole, clarithromycin, nefazodone, ritonavir, or atazanavir) 7. Patients who had history of intracranial hemorrhage

(*Continued*)

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Table 4. Continued

	GLOBAL LEADERS	TWILIGHT	TICO
Exclusion criteria (Continued)	5. Need for chronic oral anticoagulation therapy; 6. Active major bleeding or major surgery within the past 30 days; 7. Known history of intracranial hemorrhagic stroke or intracranial aneurysm; 8. Known stroke (any type) within the past 30 days; 9. Known pregnancy at time of randomization; 10. Female who is breastfeeding at time of randomization; 11. Currently participating in another trial and not yet at its primary end point	10. Emergent or salvage PCI or STEMI presentation. 11. Liver cirrhosis 12. Life expectancy <1 y 13. Unable or unwilling to provide informed consent 14. Women of childbearing potential (as determined by hospital standard of care) 15. Fibrinolytic therapy within 24 h of index PCI 16. Concomitant therapy with a strong cytochrome P-450 3A inhibitor or inducer 17. Platelet count <100 000 mm^3 18. Requiring ongoing treatment with aspirin >325 mg daily	8. Moderate to severe hepatic dysfunction 9. Increased risk of bradycardia-related symptom (guidance and reference)

ACS indicates acute coronary syndrome; BARC, bleeding academic research consortium; bid, twice daily; CABG, coronary artery bypass graft; CAD, coronary artery disease; CKD, chronic kidney disease; DAPT, dual-antiplatelet therapy; eGFR, estimated glomerular filtration rate; IDR, ischemia-driven revascularization; LAD, left anterior descending artery; MI, myocardial infarction; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; qd, every day; STEMI, ST-segment–elevation myocardial infarction; SYNTAX, Synergy Between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery; and ULN, upper limit normal.

Ongoing Studies

Based on the considerations outlined above and to further evaluate the contemporary value of aspirin as a secondary prevention medication, numerous randomized trials are currently being conducted in patients with (Table 3) or without (Table 4) an established indication for concomitant oral anticoagulation.

Table 3 shows the trials testing the less-is-more approach (ie, clopidogrel monotherapy in the absence of concomitant aspirin therapy) after PCI in patients with atrial fibrillation.

Table 4 shows ongoing trials in patients without atrial fibrillation. The GLOBAL LEADERS (GLOBAL LEADERS: A Clinical Study Comparing Two Forms of Anti-platelet Therapy After Stent Implantation; NCT01813435) is a superiority all-comers (with the exception of patients with an indication for oral anticoagulant) study among patients undergoing PCI. It is designed to assess whether a 24-month antithrombotic regimen with ticagrelor and 1-month aspirin, in comparison with 12-month conventional DAPT followed by aspirin monotherapy, improves outcome.[98] This is an investigator-initiated, randomized, open-label, outcome trial, which recruited 16 001 patients admitted for stable CAD or ACS undergoing PCI under standardized treatment consisting of bivalirudin-supported biolimus-eluting stent implantation. Patients were enrolled in >100 interventional cardiology sites in Europe, Asia, Brazil, Australia, and Canada from July 2013 to November 2015. Patients were randomly assigned (1:1 ratio) to ticagrelor 90 mg twice daily for 24 months plus ASA ≤100 mg for 1-month versus conventional DAPT with either ticagrelor in ACS patients or clopidogrel for 12 months plus ASA ≤100 mg for 24 months in stable CAD patients (Figure 3). Under the assumption that less may be more, this study is powered to show the superiority of ticagrelor monotherapy in terms of all-cause mortality or Q-wave MI. Results are to be released in the first or second quarter of 2018.

The TWILIGHT (Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention; NCT02270242) is a double-blind, multicenter trial enrolling ≈9000 high-risk patients undergoing elective or urgent PCI (emergent or salvage PCI or ST-segment–elevation MI presentation is an exclusion criterion) with DES (Table 4). Subjects meeting eligibility criteria at 3 months after enrollment are randomly assigned to ticagrelor (90 mg twice daily) and aspirin (81–100 mg/d) or ticagrelor and placebo for an additional 12 months. It is powered to show a reduction of bleeding with ticagrelor monotherapy (Figure 4). The first patient was enrolled in July 2015, and results are expected in 2019.

In the TICO study (Ticagrelor Monotherapy After 3 Months in the Patients Treated With New Generation Sirolimus Stent for Acute Coronary Syndrome; NCT02494895), 3056 patients with ACS treated with new-generation sirolimus-eluting stent implantations are randomly assigned to ticagrelor monotherapy or ticagrelor plus aspirin at 3 months after PCI. The primary end point is the rate of major adverse cardiovascular

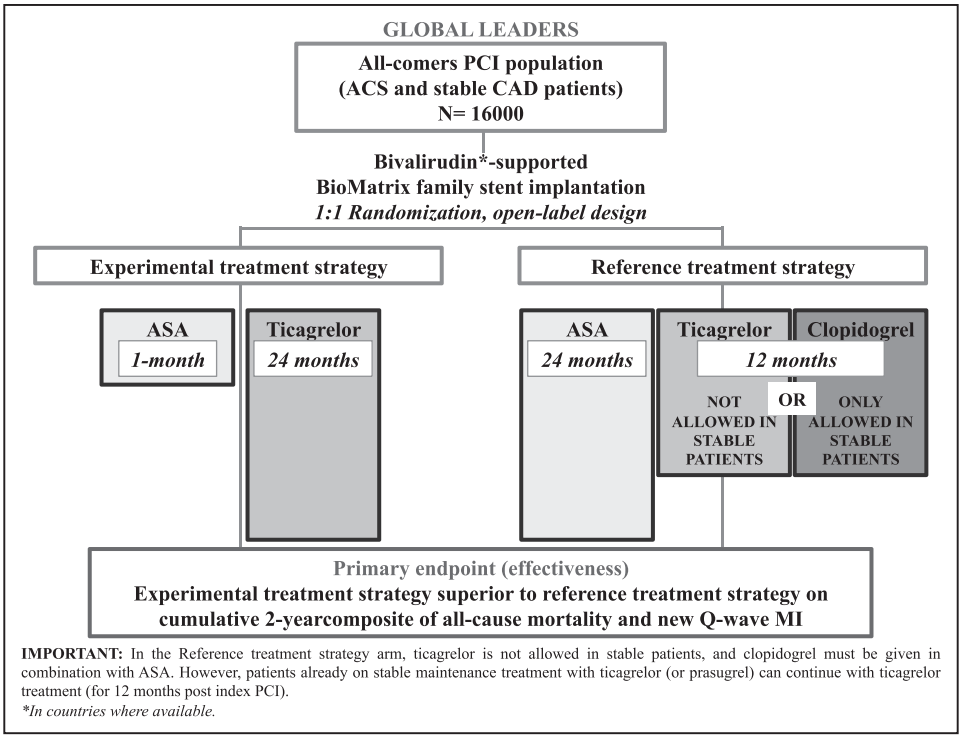

Figure 3. Design of the GLOBAL LEADERS trial.
Illustration of the study diagram of the GLOBAL LEADERS trial. Adapted from Figure 1 of Vranckx et al[97] with permission of the publisher. Copyright © 2016, Europa Digital & Publishing. ACS indicates acute coronary syndromes; ASA, aspirin; CAD, coronary artery disease; MI, myocardial infarction; and PCI, percutaneous coronary intervention.

clinical events and major bleeding at 1 year after the procedure (Table 4).

Following the encouraging results of a 2.5 mg twice daily rivaroxaban regimen added to aspirin and clopidogrel,[20] the COMPASS (Rivaroxaban for the Prevention of MACE in Coronary or Peripheral Artery Disease; NCT01776424) is recruiting (from February 2013 to March 2018) 27 400 patients with coronary or peripheral artery disease randomly allocated to rivaroxaban and aspirin or rivaroxaban alone in comparison with aspirin monotherapy for the prevention of recurrent ischemic events, stroke, or cardiovascular death. The primary

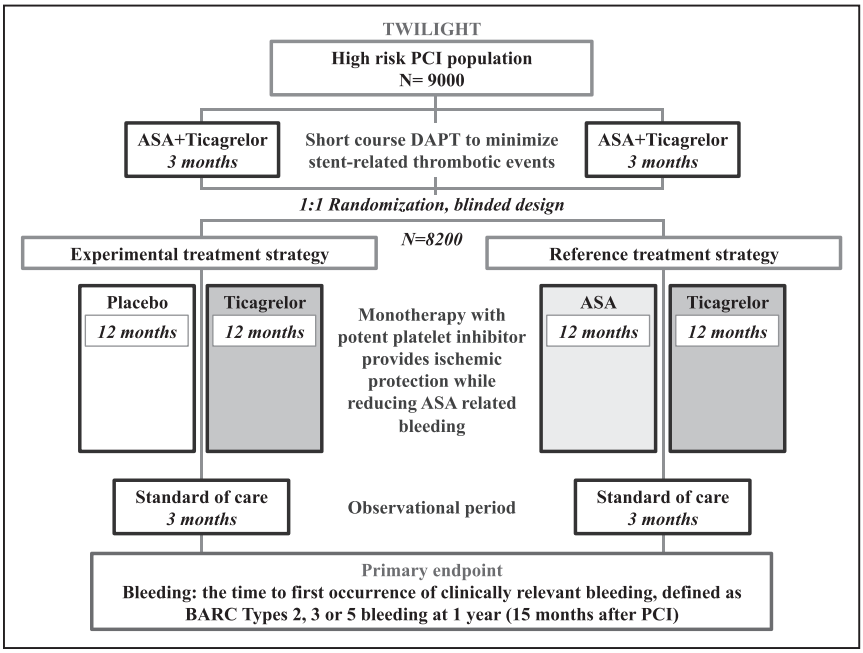

Figure 4. Design of the TWILIGHT trial.
Illustration of the study diagram of the TWILIGHT trial. ASA indicates aspirin; BARC, Bleeding Academic Research Consortium; DAPT, dual-antiplatelet therapy; and PCI, percutaneous coronary intervention.

efficacy end point is the occurrence of MI, stroke, or cardiovascular death at 5 years, and the occurrence of major bleeding is the primary safety end point. On the other hand, the GEMINI-ACS1 trial (A Study to Compare the Safety of Rivaroxaban Versus Acetylsalicylic Acid in Addition to Either Clopidogrel or Ticagrelor in Participants With Acute Coronary Syncrome; NCT02293395) is a phase II prospective, randomized, double-dummy, double-blind, active-controlled trial testing the safety of dual-antithrombotic therapy (rivaroxaban 2.5 mg twice daily plus $P2Y_{12}$ inhibitor) in comparison with DAPT (aspirin 100 mg plus $P2Y_{12}$ inhibitor) within 10 days of an ACS event in 3000 patients.[99] Patients will be randomly assigned in a 1:1 ratio stratified by intended $P2Y_{12}$ inhibitor use (clopidogrel 75 mg daily or ticagrelor 90 mg twice daily), with 1500 patients expected in each $P2Y_{12}$ inhibitor strata. The primary end point is TIMI clinically significant bleeding (major, minor, or requiring medical attention). The exploratory efficacy determination will be a composite of cardiovascular death, MI, ischemic stroke, and ST.

Similar to PCI setting, ASA alternatives are also being explored in patients undergoing transcatheter aortic valve implantation (ie, GALILEO, ATLANTIS, and POPULAR-TAVI trials), in whom the balance between ischemic and bleeding risks may be more challenging because of advanced age and comorbidities.[100]

CONCLUSION

Single-antiplatelet therapy with $P2Y_{12}$ inhibitors is being explored as a potential alternative to a DAPT regimen after ACS or coronary stent implantation, and a potentially more effective long-term treatment than aspirin monotherapy, as well. Given the well-established role of aspirin as a secondary prevention medication, its widespread availability and affordability, aspirin should remain a critical antithrombotic compound in patients with established coronary or cardiovascular disorders. However, as the availability of newer, potentially safer and more effective antiplatelet or antithrombotic agents increases, the quest for the ideal long-term secondary prevention medication mandates reappraising the value of aspirin, an historical antiplatelet agent whose efficacy was proven largely versus placebo in the setting of studies that appear largely outdated in comparison with contemporary cardiovascular practice.

The optimal duration of a DAPT regimen post-ACS or stent implantation remains unresolved and is most likely variable from patient to patient. The results of ongoing trials appraising the value of dropping aspirin in favor of $P2Y_{12}$ inhibitor monotherapy will soon shed new light on the less-is-more approach for long-term secondary prevention.

DISCLOSURES

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FOOTNOTES

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Ischaemic and bleeding outcomes in elderly patients undergoing a prolonged versus shortened duration of dual antiplatelet therapy after percutaneous coronary intervention: insights from the PRODIGY randomised trial

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KEYWORDS

- bleeding
- clinical trials
- elderly

Abstract

Aims: The aim of this study was to evaluate the efficacy and safety of 24-month vs. six-month dual antiplatelet therapy (DAPT) among elderly (≥75 years) and non-elderly patients (<75 years) undergoing percutaneous coronary intervention.

Methods and results: The primary efficacy endpoint of the PRODIGY trial was the composite of death, myocardial infarction, or cerebrovascular accident at 24-month follow-up. The key safety endpoint was type 2, 3 or 5 bleeding according to the BARC criteria. Of 1,970 participants, 587 (29.8%) were elderly and had a higher risk of adverse events compared with younger patients. The risk of the primary endpoint was not significantly reduced with 24-month compared to six-month DAPT among both elderly (HR 0.80, 95% CI: 0.55-1.16, p=0.24) and non-elderly patients (HR 1.48, 95% CI: 0.95-2.30, p=0.08), although interaction testing was significant (p=0.036). A 24-month versus six-month DAPT significantly increased the risk of BARC type 2, 3 or 5 bleeding in both older (HR 1.90, 95% CI: 1.06-3.38, p=0.03) and younger patients (HR 2.54, 95% CI: 1.43-4.53, p=0.002, p-interaction=0.48). However, measures of absolute risk difference indicated a less favourable safety profile of prolonged DAPT for older rather than younger patients.

Conclusions: In the PRODIGY trial, prolonging clopidogrel-based DAPT beyond six months in elderly patients increased the risk of bleeding, without affording a significant prevention of ischaemic events.

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Abbreviations

BARC Bleeding Academic Research Consortium
CVA cerebrovascular accident
DAPT dual antiplatelet therapy
GUSTO Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries
MI myocardial infarction
PCI percutaneous coronary intervention
TIMI Thrombolysis In Myocardial Infarction

Introduction

Elderly individuals account for an increasing proportion of patients with coronary artery disease undergoing percutaneous coronary intervention (PCI), due to the ageing of the population with increased life expectancy[1-3]. Dual antiplatelet therapy (DAPT) with aspirin and oral $P2Y_{12}$ adenosine diphosphate receptor inhibitors represents the standard of treatment to prevent new atherothrombotic events after PCI, yet its optimal duration remains controversial[4-6]. Results from randomised trials and meta-analyses indicate that extended (i.e., >12 months) duration of DAPT is associated with a lower risk of ischaemic events, even though this benefit is partly offset by a higher risk of clinically relevant bleeding[7-9]. However, extrapolating such findings to elderly patients is challenging in view of the increased risk of bleeding and ischaemic events occurring in this subgroup. In addition, elderly individuals have been underrepresented among randomised trials that evaluated different durations of DAPT following PCI. The Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia Study (PRODIGY) compared a strategy of DAPT extended to 24 months with a shorter course of DAPT up to six months in a broadly inclusive population of PCI patients, with the inclusion of a relatively high proportion of elderly participants[10].

Therefore, we sought to evaluate the impact of age in modulating the hazard of ischaemic and bleeding events and to investigate the outcomes of 24-month vs. six-month DAPT in elderly (≥75 years) vs. younger patients (<75 years) enrolled in the PRODIGY trial.

Methods

Details on study design and primary results of the PRODIGY trial have been reported elsewhere[10]. Briefly, all-comer patients undergoing treatment with a balanced mixture of stents were randomly allocated at 30 days to either up to six months or to 24 months of DAPT. The ethics committees of the participating centres independently approved the protocol and all participants gave written informed consent.

TREATMENT PROTOCOL

All patients received aspirin (80-160 mg orally indefinitely) and clopidogrel (75 mg/day) according to the randomisation scheme as follows: for either up to six months in the short DAPT group or to 24 months in the prolonged DAPT arm, irrespective of the previously implanted stent type or indication for PCI.

STUDY ENDPOINTS

The primary efficacy endpoint of the PRODIGY trial was the composite of death, myocardial infarction (MI), or cerebrovascular accident (CVA), whereas the key safety endpoint included Bleeding Academic Research Consortium (BARC) type 2, 3, or 5 bleeding. Other endpoints included each component of the primary efficacy endpoint, cardiovascular death, stent thrombosis defined on the basis of the Academic Research Consortium criteria, and BARC type 3 or 5 bleeding. Additional safety endpoints were bleeding events adjudicated according to the Thrombolysis In Myocardial Infarction (TIMI) and the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries (GUSTO) criteria. More detailed definitions of the endpoints have been provided previously[11]. A clinical events committee blinded to treatment allocation adjudicated all efficacy and bleeding events.

STATISTICAL ANALYSIS

Continuous variables are presented as mean±standard deviation and were compared with the Wilcoxon rank-sum test. Categorical variables are expressed as counts and percentages and were compared with chi-square or Fisher's exact tests as appropriate. We evaluated the effect of age, modulated as a continuous variable, on the risk of ischaemic and bleeding events in the overall population by means of multivariable-adjusted, restricted cubic splines with three knots of the distribution (10^{th}, 50^{th}, and 90^{th} percentiles)[12]. The effect of age on clinical events was analysed in the categories of patients <75 vs. ≥75 years by using Cox regression analyses. Both analyses were adjusted for baseline clinical variables associated with the primary efficacy and key safety endpoints at the univariate analysis with a significance level of $p<0.20$. The efficacy and safety of 24-month DAPT vs. six-month DAPT for elderly (≥75 years) vs. non-elderly (<75 years) patients was evaluated at 24 months. Clinical events were expressed as counts with rates computed according to the Kaplan-Meier method. Cox regression analysis was used to calculate hazard ratios (HRs) with 95% confidence intervals (CIs) and an interaction test was provided to evaluate the effect of treatment in the elderly vs. non-elderly. Sensitivity analyses were conducted to evaluate the efficacy and safety of DAPT from six to 24 months by using a landmark analysis and to assess whether results were consistent by applying the cut-off of 65 years to define the elderly status. In addition, we evaluated the risk of deaths associated or not with MI if they occurred within a seven-day window from MI onset. Risk difference and the number needed to treat for benefit or harm (NNTB or NNTH) with relative 95% CI were also provided in order to account for absolute risk estimates. Finally, the interaction between treatment effect and ageing, modelled as a continuous variable, was analysed with a fractional polynomial interaction[13]. All p-values are two-sided and statistical significance was assumed for $p<0.05$. All analyses were carried out with Stata Statistical Software, Release 13 (StataCorp LP, College Station, TX, USA).

Results

Of 1,970 participants enrolled in the PRODIGY trial, 587 (29.8%) patients were ≥75 years of age and 1,383 (70.2%) patients were <75 years of age. As shown in **Table 1** and **Table 2**, baseline and periprocedural features were largely comparable within the elderly vs. non-elderly groups between patients assigned to 24-month or six-month DAPT.

EFFECT OF AGEING ON CLINICAL OUTCOMES

There was a direct graded relationship between age and the risks of the primary efficacy or the key safety endpoint, with a steeper increase in the hazard trajectories beyond 70 years of age **(Figure 1)**. A similar direct association between age and bleeding events was observed for BARC type 3 or 5, TIMI minor or major, or GUSTO moderate or severe bleeding (data not shown). When dichotomised, patients with age ≥75 years compared with younger participants had a higher risk of death, MI or CVA and BARC type 2, 3 or 5 bleeding.

EFFICACY OF PROLONGED DAPT AMONG ELDERLY VS. NON-ELDERLY PATIENTS

Figure 2A shows the analysis of efficacy endpoints at two-year follow-up. There was a significant interaction (p=0.036) between

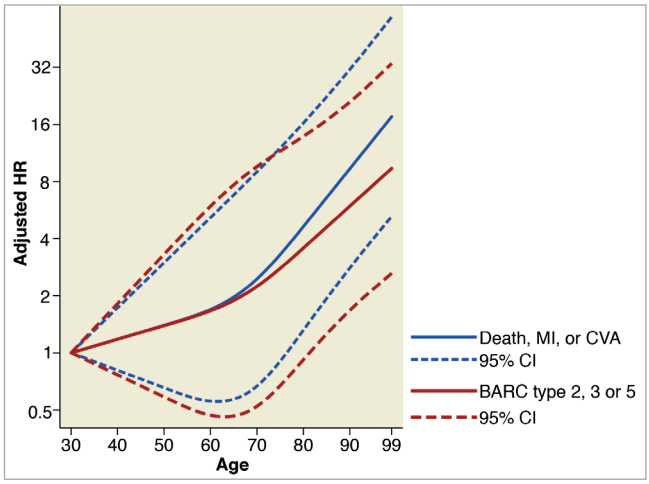

Figure 1. *Multivariable-adjusted spline curves for the HR of the primary ischaemic and bleeding endpoint vs. age modelled as a continuous variable. Patients with age ≤30 years represent the referent group with the HR set to 1. The dotted lines represent the 95% CI of the hazard function. The variables used for the adjustments are listed in the Methods section. BARC: Bleeding Academic Research Consortium; CI: confidence intervals; CVA: cerebrovascular accident; HR: hazard ratio; MI: myocardial infarction*

Table 1. Baseline characteristics.

	Age ≥75 years			Age <75 years			*p*-interaction
	24-month DAPT N=283	≤6-month DAPT N=304	*p*-value	24-month DAPT N=704	≤6-month DAPT N=679	*p*-value	
Age, years	80.2±3.7	80.6±4.3	0.47	62.9±9.1	62.3±8.7	0.07	0.19
Male	186 (65.7)	200 (65.8)	1.00	578 (82.1)	547 (80.6)	0.49	0.64
BMI, kg/m^2	26.8±9.5	26.4±3.6	0.58	28.1±13.3	28.1±11.4	0.22	0.78
Hypertension	232 (82.0)	237 (78.0)	0.26	489 (69.5)	456 (67.2)	0.39	0.54
Dyslipidaemia	142 (50.2)	149 (49.0)	0.81	411 (58.4)	376 (55.4)	0.28	0.70
Smoking	18 (6.4)	29 (9.5)	0.17	204 (29.0)	218 (32.1)	0.22	0.38
Diabetes	83 (29.3)	82 (27.0)	0.58	161 (22.9)	151 (22.2)	0.80	0.72
Insulin-treated diabetes	17 (6.0)	22 (7.2)	0.62	42 (6.0)	33 (4.9)	0.41	0.31
Family history of CAD	70 (24.7)	39 (12.8)	<0.001	219 (31.1)	225 (33.1)	0.42	<0.001
Previous MI	93 (32.9)	93 (30.6)	0.60	177 (25.1)	163 (24.0)	0.66	0.84
Previous PCI	47 (16.6)	64 (21.1)	0.17	142 (20.2)	106 (15.6)	0.03	0.018
Previous CABG	44 (15.5)	40 (13.2)	0.41	66 (9.4)	63 (9.3)	1.00	0.54
Creatinine clearance, mL/min	53.6±19.7	54.9±18.7	0.28	89.7±44.8	87.8±27.5	0.82	0.32
Peripheral artery disease	55 (19.4)	74 (24.3)	0.16	63 (8.9)	54 (8.0)	0.56	0.14
LVEF, %	49.8±10.6	48.5±11.0	0.12	51.5±10.0	51.4±10.1	0.92	0.20
Congestive HF or LV dysfunction	24 (8.5)	21 (6.9)	0.54	16 (2.3)	19 (2.8)	0.61	0.35
Indication to PCI			0.62			0.99	0.66
Stable CAD	56 (19.8)	58 (19.1)	0.84	199 (28.3)	192 (28.3)	1.00	
NSTE-ACS	149 (52.7)	151 (49.7)	0.51	262 (37.2)	255 (37.6)	0.91	
STEMI	78 (27.6)	95 (31.2)	0.37	243 (34.5)	232 (34.2)	0.91	
Acute MI at presentation	162 (57.2)	188 (61.8)	0.27	385 (54.7)	363 (53.5)	0.67	0.23

Values are n (%) or mean±SD. BMI: body mass index; CABG: coronary artery bypass graft; CAD: coronary artery disease; DAPT: dual antiplatelet therapy; HF: heart failure; LV: left ventricular; LVEF: left ventricular ejection fraction; MI: myocardial infarction; NSTE-ACS: non-ST-segment elevation acute coronary syndrome; STEMI: ST-segment elevation myocardial infarction.

Table 2. Angiographic and procedural characteristics.

	Age ≥75 years			Age <75 years			*p*-interaction
	24-month DAPT N=283	≤6-month DAPT N=304	*p*-value	24-month DAPT N=704	≤6-month DAPT N=679	*p*-value	
Angiographic features			0.09			0.73	0.08
Single-vessel disease	58 (20.5)	79 (26.0)		234 (33.2)	220 (32.4)		
Two-vessel disease	84 (29.7)	100 (32.9)		267 (37.9)	250 (36.8)		
Three-vessel disease	141 (49.8)	125 (41.1)		203 (28.8)	209 (30.8)		
Multivessel disease	225 (79.5)	225 (74.0)	0.12	470 (66.8)	459 (67.6)	0.78	0.13
Multivessel PCI	88 (31.1)	98 (32.2)	0.79	165 (23.4)	175 (25.8)	0.32	0.74
≥2 treated lesions	116 (41.0)	127 (41.8)	0.87	249 (35.4)	244 (35.9)	0.87	0.97
≥3 treated lesions	33 (11.7)	32 (10.5)	0.69	75 (10.7)	83 (12.2)	0.40	0.39
≥4 treated lesions	10 (3.5)	14 (4.6)	0.54	28 (4.0)	30 (4.4)	0.69	0.74
Treated vessel							
Left anterior descending artery	151 (53.4)	161 (53.0)	0.93	367 (52.1)	357 (52.6)	0.87	0.86
Left circumflex artery	113 (39.9)	93 (30.6)	0.02	208 (29.5)	225 (33.1)	0.16	0.006
Right coronary artery	86 (30.4)	113 (37.2)	0.10	260 (36.9)	250 (36.8)	1.00	0.14
Left main artery	24 (8.5)	24 (7.9)	0.88	31 (4.4)	32 (4.7)	0.80	0.71
Saphenous vein graft	7 (2.5)	7 (2.3)	1.00	16 (2.3)	10 (1.5)	0.32	0.59
At least one type B2/C lesion	185 (65.4)	221 (72.7)	0.06	457 (64.9)	443 (65.2)	0.91	0.12
At least one restenotic lesion	7 (2.5)	15 (4.9)	0.13	38 (5.4)	33 (4.9)	0.72	0.12
Randomised stent			0.58			0.88	0.45
Bare metal stent	82 (29.0)	80 (26.3)		164 (23.3)	166 (24.4)		
Paclitaxel-eluting stent	66 (23.3)	68 (22.4)		182 (25.9)	177 (26.1)		
Zotarolimus-eluting stent	59 (20.8)	78 (25.7)		186 (26.4)	167 (24.6)		
Everolimus-eluting stent	76 (26.9)	78 (25.7)		172 (24.4)	169 (24.9)		
Number of implanted stents	1.9±1.3	1.9±1.0	0.22	1.8±1.2	1.9±1.3	0.52	0.59
Overall stent length, mm*	38.6±28.8	39.3±24.3	0.26	39.3±30.8	40.5±30.5	0.53	0.87
Mean stent diameter, mm*	2.9±0.4	3.0±0.4	0.04	3.0±0.5	3.0±0.5	0.008	0.004

All data are shown per patient. *Information available in 1,964 patients. DAPT: dual antiplatelet therapy; PCI: percutaneous coronary intervention

age, dichotomised at age 75 years cut-off point, and the primary efficacy endpoint. Although the primary efficacy endpoint did not differ based on the randomly allocated DAPT duration among elderly patients, event rates were numerically lower for prolonged DAPT (HR 0.80, 95% CI: 0.55-1.16, p=0.24). Conversely, a trend towards an increased risk of the primary endpoint was observed among younger patients randomised to 24-month vs. six-month DAPT (HR 1.48, 95% CI: 0.95-2.30, p=0.08). This difference was mainly driven by cardiac mortality, which occurred more frequently among younger patients randomised to 24-month DAPT (HR 2.92, 95% CI: 0.94-9.05, p=0.06). However, the age-by-treatment interaction was significant for deaths not related to MI (p=0.043), but not for those related to MI (p=0.81). The test for interaction for the primary endpoint was not significant (p=0.10) from six to 24 months **(Figure 2B)**. By using a cut-off of 65 years, there was no significant interaction (p=0.09) with 24-month vs. six-month DAPT with respect to the primary ischaemic endpoint among patients ≥65 years (HR 0.89, 95% CI: 0.66-1.21, p=0.48) vs. those <65 years (HR 1.75, 95% CI: 0.86-3.58, p=0.13).

SAFETY OF PROLONGED DAPT AMONG ELDERLY VS. NON-ELDERLY PATIENTS

Figure 3A shows the analysis of safety endpoints at two-year follow-up. BARC type 2, 3 or 5 bleeding was significantly increased in both elderly (HR 1.90, 95% CI: 1.06-3.38, p=0.03) and non-elderly patients (HR 2.54, 95% CI: 1.43-4.53, p=0.002; p for interaction=0.48) randomised to 24-month versus six-month DAPT. The NNTH was lower for elderly (NNTH 18; 95%CI: NNTH 119 to NNTH 10) than for non-elderly patients (NNTH 29; 95%CI: NNTH 72 to NNTH 18). Although not significantly increased, bleeding events according to TIMI and GUSTO definitions were numerically higher in patients randomised to 24-month DAPT vs. six-month DAPT. In the analysis between six and 24 months **(Figure 3B)**, the relative risks of BARC type 2, 3 or 5 bleeding were consistently higher in both patients aged ≥75 years (HR 2.73, 95% CI: 1.26-5.89, p=0.01) and patients <75 years (HR 2.73, 95% CI: 1.37-5.44, p=0.004, p for interaction=0.99). The corresponding NNTH for the two groups was 18 (95%CI: NNTH 89 to NNTH 11) and 36 (95%CI: NNTH 107 to NNTH 21), respectively. After six months, moderate or severe

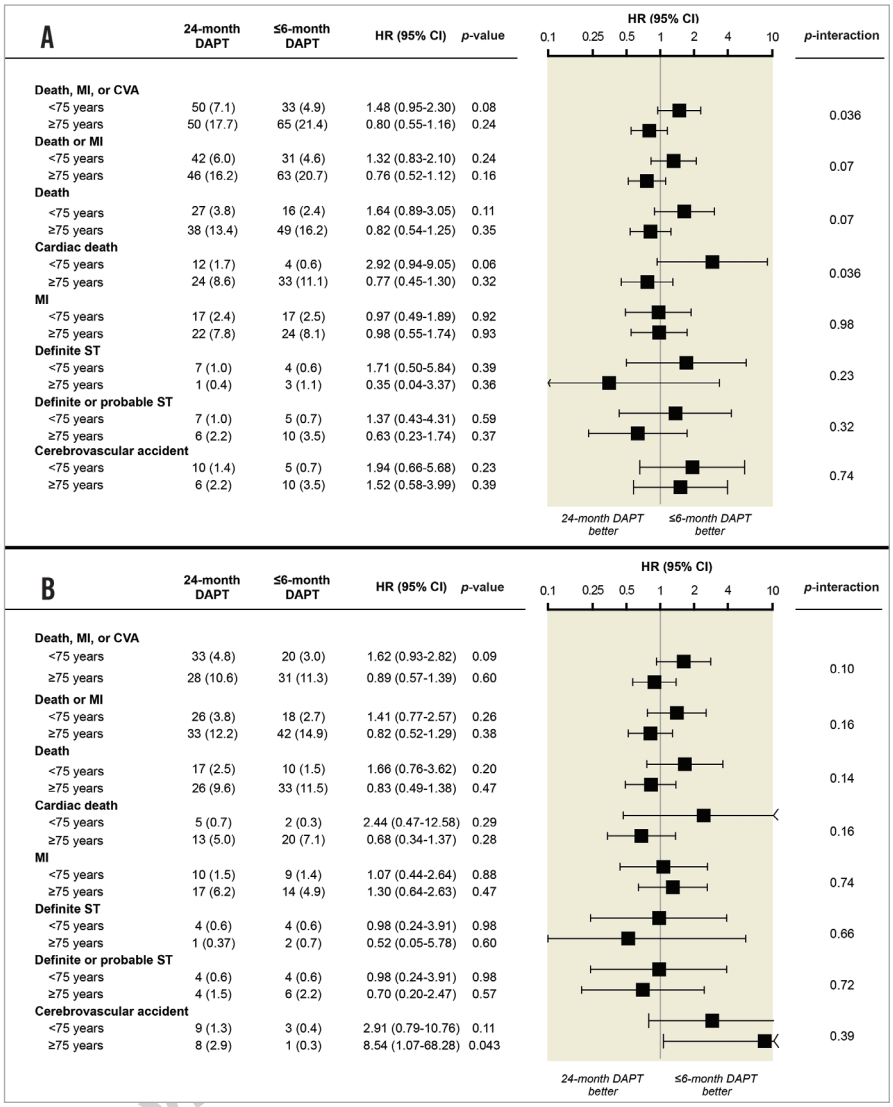

Figure 2. *Analysis of efficacy outcomes stratified by age. A) Ischaemic events at 24 months. B) Ischaemic events from six to 24 months. CI: confidence intervals; CVA: cerebrovascular accident; DAPT: dual antiplatelet therapy; HR: hazard ratio; MI: myocardial infarction; ST: stent thrombosis*

bleeding according to GUSTO criteria was significantly increased in elderly but not in younger patients treated with 24-month DAPT. The corresponding NNTH was NNTH 24 (95%CI: NNTH 78 to NNTH 13) for older vs. NNTH 194 (95%CI: NNTB 198 to NNTH 58) for younger patients. A significant interaction (p=0.007) for the absolute risk difference of moderate or severe GUSTO bleeding was present between older (3.9%, 95% CI: 1.1-6.8%) and younger groups (0.04%, 95% CI: -0.06%–1.5%) after six-month follow-up. By using a cut-off of 65 years, there was no significant interaction (p=0.49) with 24-month vs. six-month DAPT with respect to the primary bleeding endpoint among patients ≥65 years (HR 1.96, 95% CI: 1.23-3.31, p=0.004) vs. those <65 years (HR 2.92, 95% CI: 1.23-6.96, p=0.02).

INTERACTION BETWEEN AGEING AND TREATMENT EFFECT OF DAPT

The age-by-treatment interaction evaluated by fractional polynomial analyses was not significant for the primary efficacy (p=0.35) and key safety endpoints (p=0.73). For the composite of death, MI or CVA, the area representing the 95% CI treatment effect crossed the no effect line throughout all ages **(Figure 4A)**. In contrast, the area of treatment effect for the key safety endpoint was above the line of no effect for a wide range of ages, indicating a harmful effect of 24-month over six-month DAPT in terms of bleeding complications for most age values **(Figure 4B)**.

Discussion

The main findings of the present analysis of the PRODIGY trial can be summarised as follows.

1) Elderly patients undergoing PCI have a higher risk of ischaemic and bleeding events compared with younger patients, with a similar effect of ageing on the hazards of such events.
2) In both elderly and non-elderly patients, prolonging DAPT for 24 months did not reduce the risk of the primary efficacy endpoint of death, MI or CVA compared with a six-month DAPT.

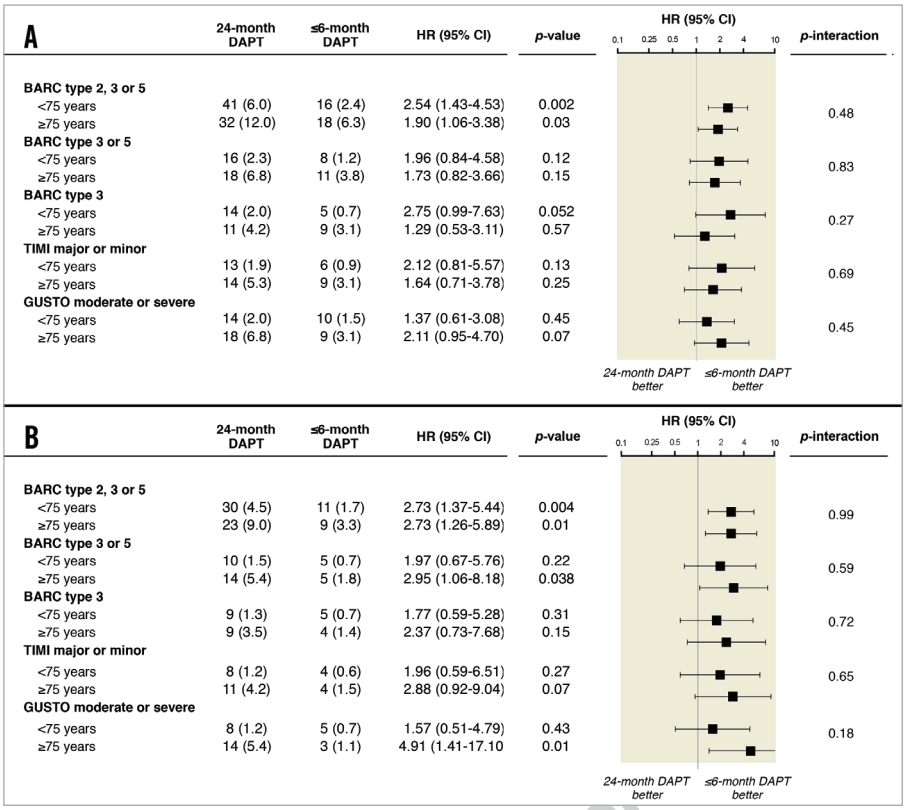

Figure 3. *Analysis of safety outcomes stratified by age. A) Bleeding events at 24 months. B) Bleeding events from six to 24 months. BARC: Bleeding Academic Research Consortium; GUSTO: Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries; TIMI: Thrombolysis In Myocardial Infarction*

3) A strategy of 24-month DAPT compared with six-month DAPT was associated with a greater risk of the key safety endpoint of BARC type 2, 3 or 5 bleeding in both elderly and non-elderly patients. Although the relative magnitude of treatment effect on bleeding was similar, the absolute risk difference with prolonged DAPT was greater in elderly compared with younger participants.

DAPT is an evidence-based, guideline-recommended, standard of care treatment after PCI[14]. Recently, two large randomised trials, DAPT and PEGASUS-TIMI 54 (Prevention of cardiovascular

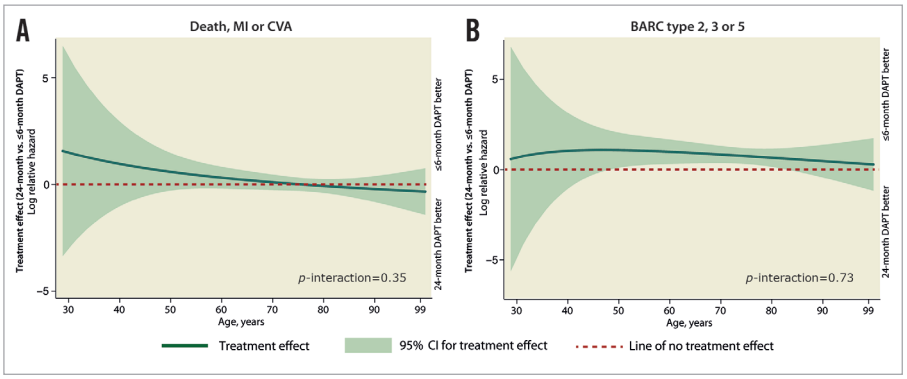

Figure 4. *Fractional polynomial interaction for the primary efficacy and key safety endpoints. A) Death, MI or CVA. B) BARC type 2, 3 or 5 bleeding. The treatment-by-age interaction is analysed by considering age as a continuous variable. The green line represents the treatment effect of 24-month vs. six-month DAPT and the area represents the 95% CI of treatment effect. The dotted red line represents the no treatment effect. The comparison of 24-month vs. six-month DAPT is significant for the age values where the green area does not cross the line of no treatment effect. In this case, the effect of prolonged DAPT in increasing the risk of the key safety endpoint was significant for the range of 50 to 80 years.*

events in patients with prior heart attack using ticagrelor compared to placebo on a background of aspirin–thrombolysis in myocardial infarction 54), showed a significant reduction in ischaemic events with long-term DAPT among patients undergoing PCI as well as among high-risk patients with prior myocardial infarction[7,9,15,16]. Nevertheless, the optimal treatment duration of DAPT remains controversial as the protection afforded by extended DAPT in terms of ischaemic events is counterbalanced by an increase in bleeding complications[7,8]. Although the PEGASUS-TIMI 54 trial reported consistent results in terms of the primary ischaemic endpoint according to age, elderly patients represented less than 15% of the overall population[15]. However, despite being formally not significant (p for interaction=0.09), elderly versus non-elderly patients derived less ischaemic benefit from 90 mg of ticagrelor vs. placebo. At variance, among participants allocated to ticagrelor 60 mg, elderly patients derived a similar magnitude of benefit to non-elderly patients with regard to the primary efficacy endpoint. A treatment-by-age heterogeneity for the primary endpoint according to age has been observed in the ISAR-SAFE (p for interaction=0.03) and IVUS-XPL trials (p for interaction=0.051), favouring the use of short-term DAPT in elderly rather than younger patients[17,18]. However, the primary endpoint in both trials included a composite of ischaemic and bleeding events, which did not allow complete assessment of the benefit-risk ratio associated with DAPT in elderly patients.

We found that elderly patients experienced a greater risk of both ischaemic and bleeding events, with risk trajectories proceeding similarly with ageing. Such a pattern is similar to that described by Roe and colleagues in a cohort of patients with acute coronary syndrome managed without revascularisation[19]. Prolonged DAPT did not reduce the risk of ischaemic events among both elderly and non-elderly patients, which is in keeping with the results in the overall finding of the PRODIGY trial. However, interaction testing showed heterogeneity in treatment effect for the primary efficacy endpoint, with a possible harmful effect with 24-month DAPT in non-elderly subjects. In this regard, the higher risk of cardiac instead of non-cardiac death among younger patients randomised to 24-month DAPT, although not related to MI, remains biologically counterintuitive and difficult to explain. Such a finding could also be the result of variable categorisation rather than a direct effect, because the age-by-treatment interaction on a continuous basis was not significant at the fractional polynomial analysis.

Our study provides a nuanced interpretation for the alleged difference in the risk of bleeding associated with DAPT use among elderly patients. We found that prolonged DAPT had a similar effect on the key bleeding endpoint of BARC type 2, 3 or 5 among elderly and non-elderly patients at 24-month follow-up. However, owing to the higher rate of bleeding events, elderly patients had a greater increase in the absolute risk of BARC 2, 3 or 5 bleeding with 24-month DAPT, resulting in a lower NNTH (18 vs. 29). During the period between six and 24 months, the absolute risk difference in BARC 2, 3 or 5 bleeding tended to increase, as well as the difference in the NNTH (18 vs. 36). Taken together, these findings suggest that relative and absolute risks of bleeding should be disentangled in the decision process for DAPT duration in elderly people, by factoring the similar relative risk of bleeding associated with prolonged DAPT with the higher absolute risk difference due to the increased event rate.

Limitations

The results of this study have to be interpreted in the light of several limitations. First, our observations are based on subgroup populations within an overall trial, which failed to show the superiority of prolonged DAPT in the main population. Second, although there is general agreement that people ≥75 years can be defined as "elderly", ageing is a continuous process and the cut-off of 75 years remains arbitrary. Nevertheless, we tried to accommodate this limitation by evaluating the age-by-treatment interaction also on a continuous basis. Furthermore, a cut-off of 65 years yielded similar results. Third, the group of elderly patients was relatively modest in size, and all the analyses should be considered as hypothesis-generating and exploratory in nature. However, it is noteworthy that the mean age in the PRODIGY trial was the highest across available trials with comparable design. This might explain the differential effect of elderly status on the risk of ischaemic events observed in this study compared with other trials enrolling relatively younger patients. Fourth, randomisation in the PRODIGY trial was not stratified by age.

Conclusions

In an all-comers population of PCI patients, elderly participants experienced a higher risk of ischaemic and bleeding events compared with their non-elderly counterparts with a comparable effect of ageing on the hazards of such events. Prolonging DAPT for 24 months was not associated with a significantly different risk of the primary efficacy endpoint among elderly and non-elderly patients. However, elderly patients seemed to derive a greater absolute risk of clinically relevant bleeding from prolonged DAPT than younger patients.

Impact on daily practice

Elderly status conveys a higher risk of both ischaemic and bleeding events. Although dual antiplatelet therapy increases the risk of bleeding in both elderly and non-elderly patients, the former group incurs a substantially higher event rate. The efficacy of prolonged dual antiplatelet therapy for the prevention of ischaemic events is not influenced by elderly status.

Conflict of interest statement

R. Piccolo has received a research grant from the Veronesi Foundation. G. Gargiulo has received a research grant from the European Association for Percutaneous Cardiovascular Interventions (EAPCI) and from the CardioPath PhD program. S. Windecker has received research grants to the institution from Abbott, Biotronik, Boston Scientific, Biosensors, Medtronic, Edwards, and St. Jude. The other authors have no conflicts of interest to declare.

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Impact of Chronic Kidney Disease on 2-Year Clinical Outcomes in Patients Treated with 6-Month or 24-Month DAPT Duration: An Analysis from the PRODIGY Trial

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Objectives: To assess whether moderate-to-severe CKD is a treatment modifier for benefit or harm in patients randomly allocated to 24-month versus 6-month DAPT. Background: It is still unclear whether chronic kidney disease CKD should impact on the decision-making on optimal duration of dual antiplatelet therapy (DAPT) after percutaneous coronary intervention (PCI). Methods and Results: PRODIGY trial randomized 1970 all-comer patients at 24-month versus 6-month DAPT after PCI. Patients with moderate-to-severe CKD ($n = 604$; 30.7%) were older, more likely to be women, to have hypertension, diabetes, prior MI or PCI, with higher severity of coronary artery disease (CAD), but were less frequently smokers or presenting with stable CAD. After adjustment, the 2-year rates of primary endpoint (composite of death, myocardial infarction and cerebrovascular accident), as well as bleeding and net adverse clinical events were higher in patients with moderate-to-severe CKD. DAPT prolongation at 24-month did not reduce the primary endpoint in both CKD (adj. HR: 0.957; 95% CI 0.652–1.407; $P = 0.825$) and no-CKD (adj. HR: 1.341; 95% CI 0.861–2.086; $P = 0.194$) groups (Pint = 0.249), but increased bleeding in both groups (CKD: adj. HR: 1.999; 95% CI 1.100–3.632; $P = 0.023$; no-CKD: adj. HR: 2.880; 95% CI 1.558–5.326; $P = 0.001$; Pint = 0.407). Conclusions: Moderate-to-severe CKD did not modify the effect of a prolonged or shortened DAPT duration in largely unselected patients undergoing stent implantation. Our analysis suggests that CKD should not be a major driver in the decision-making on the duration of DAPT after stent implantation. This exploratory study is underpowered and should be considered hypothesis-generating only. © 2017 Wiley Periodicals, Inc.

Key words: chronic kidney disease (CKD); clopidogrel; DAPT; cardiovascular events; bleeding

INTRODUCTION

Dual antiplatelet therapy (DAPT) is the antithrombotic of choice in patients with coronary artery disease (CAD) undergoing percutaneous coronary intervention (PCI) with stent implantation. However, its optimal duration is a matter of ongoing debate [1–9]. Guidelines recommend at least 6-12 months in patients with acute coronary syndrome (ACS) [1,2,9], but the evidence for this is weak, and some randomized

Additional Supporting Information may be found in the online version of this article.

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Conflict of interest: Nothing to report.

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controlled trials suggested that the risks of prolonging DAPT beyond 6 to 12 months outweigh the potential benefits [10–12]. On the other hand, a recent trial on DAPT duration has shown a relevant reduction in rates of stent thrombosis (ST) and myocardial infarction (MI) in patients free from bleeding or ischemic events in the 30-month versus 12-month DAPT duration groups [13].

It is still unknown whether the presence of CKD should drive the decision-making on optimal DAPT duration. CKD patients are at increased risk for both ischemic and bleeding complications [14–16], making the equation between possible ischemic benefits and bleeding risks more challenging. A recent study has suggested that clopidogrel prolongation over 12 months could be favorable in CKD patients receiving first-generation drug-eluting stent (DES) in terms of a significant reduction of death or myocardial infarction (MI), and no increase of severe bleeding [17,18].

We assessed whether moderate-to-severe CKD is a treatment modifier for benefit or harm in patients randomly allocated to 24-month versus 6-month DAPT.

METHODS

The design and main findings of the PRODIGY (Prolonging Dual- Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia Study; NCT00611286) have been previously reported [12,19,20]. Briefly, all-comer PCI patients receiving a balanced mixture of stents with varying anti-intimal hyperplasia potency and belonging to both first- and second-generation DES at three Italian sites were randomly allocated at 30 days to either 6 or 24 months of DAPT. Selection criteria were broad, reflecting routine clinical practice. Randomization to 6- or 24-month DAPT was stratified by center, ongoing ST-segment-elevation myocardial infarction (STEMI), presence of diabetes mellitus, and need for intervening for at least one in-stent restenotic lesion. The study was conducted in accordance with the principles of the Declaration of Helsinki. The Ethics Committees of the three participating centers independently approved the protocol, and all participants gave written informed consent.

Treatment Protocol

All patients received aspirin (80–160 mg orally indefinitely) and clopidogrel (75 mg/day) according to the randomization scheme as follows: for either 6 months in the short DAPT arm or 24 months in the prolonged DAPT arm irrespective of the previously implanted stent type or indication for PCI.

Follow-Up

The randomized patients returned for study visits at 30 days, and then every 6 months up to 2 years. During follow-up visits, patients were examined and assessed for adverse events, asked for the antiplatelet therapy compliance and 12-lead electrocardiogram recordings were obtained.

Study Endpoints

The primary efficacy endpoint of the PRODIGY trial was the composite of death, MI, or cerebrovascular accident (CVA), while the key safety endpoint included Bleeding Academic Research Consortium (BARC) type 2, 3, or 5 bleeding. The net effect on the combined ischemic and bleeding complications was obtained by two net adverse clinical event (NACE) endpoints that were generated by combining the primary efficacy endpoint of death, MI, or CVA with either the primary safety endpoint of BARC type 2, 3, or 5 bleeding or with BARC type 3 or 5 events. Other endpoints included each component of the primary efficacy endpoint, cardiovascular death, stent thrombosis (ST) defined on the basis of the Academic Research Consortium criteria, and BARC type 3 or 5 bleeding. Other safety endpoints included bleeding events adjudicated according to the TIMI and GUSTO scales. All study endpoint definitions were previously reported.

All endpoints were confirmed on the basis of documentation collected at each hospital and were centrally adjudicated by the clinical events committee, whose members were unaware of the patients' treatment-group assignments. The time frame of interest for the primary endpoint was from 30 days (i.e., after the primary endpoint randomization) to 24 months.

Renal Function Assessment

For this analysis, patients were divided into two groups according to their estimated creatinine clearance (Cockroft-Gault formula). Patients were defined as "Moderate-to-severe CKD" if having an estimated creatinine clearance <60 ml/min, while defined as "No/mild CKD" if creatinine clearance was >60 ml/min. As sensitivity analysis, the modification of diet in renal disease (MDRD) formula was also used to estimate glomerular filtration rate (eGFR) and CKD was defined if eGRF <60ml/min/1.73 m^2 (Supplementary Table I).

Statistical Analysis

The PRODIGY trial was designed to enroll at least 1700 patients to detect a 40% reduction in the relative risk of the primary endpoint in the 24-month clopidogrel group compared with 6-month duration of clopidogrel therapy, with statistical power of $>80\%$ at a 2-sided significance level of 0.05. The planned sample size was

TABLE I. Baseline Characteristics in Patients with or Without Moderate-to-Severe CKD

Characteristic	Moderate-to-severe CKD (N = 604)	No/Mild CKD (N = 1366)	P value
Age (yr)	76.9 ± 8.0	63.9 ± 10.1	<0.0001
	77.5 (73.3–82.3)	64.7 (57.2–71.4)	
Male (*n*)	63.1% (381)	82.7% (1130)	<0.0001
Body Mass Index (kg/m^2)	25.6 ± 3.4	28.6 ± 13.0	<0.0001
	25.3 (23.5–27.5)	27.4 (25.2–29.9)	
Diabetes	27.6% (167)	22.7% (310)	0.018
Insulin-dependent	6.5% (39)	5.5% (75)	
Hypertension	79.8% (482)	68.2% (932)	<0.0001
Hyperlipidemia	51.8% (313)	56.0% (765)	0.086
Current cigarette use	11.4% (69)	29.3% (400)	<0.0001
Creatinine levels (mg/dl)	1.5 ± 1.2	0.9 ± 0.2	<0.0001
	1.3 (1.0–1.5)	0.9 (0.8–1.1)	
Creatinine Clearance (ml/min)	45.4 ± 11.9	93.1 ± 34.2	<0.0001
	48.3 (38.7–54.9)	87.8 (72.8–105.3)	
Prior myocardial infarction	33.9% (205)	23.5% (321)	<0.0001
Prior PCI	20.5% (124)	17.2% (235)	0.078
LVEF	48.3 ± 10.8	51.8 ± 9.9	<0.0001
	50.0 (40–56)	55 (45–60)	
Clinical presentation			
Stable angina pectoris	20.2% (122)	28.0% (383)	<0.0001
Acute Coronary Syndrome	79.8% (482)	72.0% (983)	
STEMI	29.1% (176)	34.6% (472)	0.018
NSTEMI	30.0% (181)	19.7% (269)	<0.0001
Unstable Angina	20.7% (125)	17.7% (242)	0.117
Multivessel Disease	77.3% (467)	66.8% (912)	<0.0001
No. of treated lesions	1.54 ± 0.8	1.54 ± 0.9	0.996
	1 (1–2)	1 (1–2)	
≥2 treated lesions	40.7% (246)	35.9% (490)	0.040
≥3 treated lesions	11.1% (67)	11.4% (156)	0.832
Multivessel intervention	30.1% (182)	25.2% (344)	0.022
At least one complex lesion (Type B2 or C)[a]	69.5% (420)	64.9% (886)	0.043
Total ACC/AHA score[b]	4.0 ± 2.2	3.8 ± 2.3	0.014
	3 (3–5)	3 (2–4)	
Aspirin	100% (604)	100% (1366)	>0.999
Clopidogrel	99.5% (601)	100.0% (1366)	0.009
Statin	85.3% (505)	92.8% (1259)	<0.0001

ACC = American College of Cardiology; AHA = American Heart Association; CABG = Coronary Artery Bypass Graft; LVEF = Left Ventricle Ejection Fraction; NSTEMI = Non-ST-Elevation Myocardial Infarction; PCI = Percutaneous Coronary Intervention; STEMI= ST-Elevation Myocardial Infarction.

[a]According to the ACC/AHA coronary lesion classification.

[b]Type A stenoses were coded 1 point, type B1 stenoses 2 points, type B2 stenoses 3 points, and type C stenoses 4 points.

finally increased up to 2000 to allow for fatalities occurring within the first 30 days, noncompliance, and loss to follow-up as previously described [12].

Categorical variables were expressed as frequency (percentage), whereas continuous variables were expressed as mean (standard deviation) and median (interquartile range). Continuous variables were compared between randomized groups using the Wilcoxon's rank sums test, whereas for binary variables the $\chi 2$ test was used. Multiple imputations were used for missing values of creatinine levels ($n = 21$) and ejection fraction ($n = 136$).

Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated for moderate-to-severe CKD versus no/mild CKD (i.e., values >1 indicated increased hazard in the CKD group) and 24-month versus 6-month DAPT (i.e., values >1 indicated increased hazard in the 24-month DAPT) with a proportional hazards model. Cox-regression was used for multivariate analysis. Clinical and angiographic characteristics that were imbalanced at a nominal 5% significance level between the two groups were identified and included the final adjusted model; these included age, gender, body mass index (BMI), diabetes, hypertension, smoking, prior myocardial infarction (MI), left ventricular ejection fraction (LVEF), clinical presentation, multivessel intervention and total ACC/AHA score. Interaction testing was performed to determine whether the effect of

TABLE II. Baseline Characteristics in Patients with or Without Moderate-to-Severe CKD According to the Randomization for DAPT Duration

	Moderate-to-Severe CKD ($N = 604$)			No/Mild CKD ($N = 1366$)		
Characteristic	24-Month Clopidogrel ($N = 312$)	6-Month Clopidogrel ($N = 292$)	P value	24-Month Clopidogrel ($N = 675$)	6-Month Clopidogrel ($N = 691$)	P Value
Age (year)	77.0 (73.3–81.7)	78.3 (73.3–83.2)	0.194	64.6 (57.2–71.5)	64.8 (57.2–71.3)	0.824
Male	65.1% (203)	61.0% (178)	0.296	83.1% (561)	82.3% (569)	0.708
Body Mass Index (kg/m^2)	25.5 (23.5–27.7)	25.3 (23.4–27.4)	0.960	27.4 (25.3–30.4)	27.3 (24.8–29.7)	0.597
Diabetes	28.2% (88)	27.1% (79)	0.752	23.1% (156)	22.3% (154)	0.716
Insulin-dependent	5.8% (18)	7.2% (21)		6.1% (41)	4.9% (34)	
Hypertension	82.1% (256)	77.4% (226)	0.155	68.9% (465)	67.6% (467)	0.604
Hyperlipidemia	53.5% (167)	50.0% (146)	0.386	57.2% (386)	54.8% (379)	0.384
Current cigarette use	11.2% (35)	11.6% (34)	0.869	27.7% (187)	30.8% (213)	0.205
Creatinine levels (mg/dl)	1.3 (1.1–1.5)	1.2 (1–1.4)	0.152	0.9 (0.8–1.1)	1.0 (0.8–1.1)	0.578
Creatinine Clearance (ml/min)	48.1 (37.7–55.4)	48.6 (39.9–54.7)	0.433	88.0 (73.1–108)	87.7 (72.2–101.4)	0.026
Prior myocardial infarction	33.7% (105)	34.2% (100)	0.878	24.4% (165)	22.6% (156)	0.415
Prior PCI	21.8% (68)	19.2% (56)	0.426	17.9% (121)	16.5% (114)	0.484
LVEF	50.0 (40.4–56.1)	50.0 (40–55)	0.180	55.0 (45–60)	55.0 (45–60)	0.547
Clinical presentation						
Stable angina pectoris	20.5% (64)	19.9% (58)	0.842	28.3% (191)	27.9% (192)	0.834
Acute Coronary Syndrome	79.5% (248)	80.1% (234)	0.842	71.7% (484)	72.2% (499)	0.834
STEMI	27.6% (86)	30.8% (90)	0.379	34.8% (235)	34.3% (237)	0.841
NSTEMI	30.8% (96)	29.1% (86)	0.656	19.3% (130)	20.1% (139)	0.691
Unstable Angina	21.2% (66)	20.2% (59)	0.774	17.6% (119)	17.8% (123)	0.934
Multivessel Disease	78.2% (244)	76.4% (223)	0.590	66.8% (451)	66.7% (461)	0.969
No. of treated lesions	1 (1–2)	1 (1–2)	0.028	1 (1–2)	1 (1–2)	0.557
$\geq$2 treated lesions	37.8% (118)	43.8% (128)	0.133	36.6% (247)	35.2% (243)	0.583
$\geq$3 treated lesions	10.3% (32)	12.0% (35)	0.499	11.3% (76)	11.6% (80)	0.853
Multivessel intervention	26.9% (84)	33.6% (98)	0.076	25.0% (169)	25.3% (175)	0.902
At least one complex lesion (Type B2 or C)[a]	65.1% (203)	74.3% (217)	0.014	65.0% (439)	64.7% (447)	0.893
Total ACC/AHA score[b]	3 (2–4)	4 (3–6)	0.010	3 (2–4)	3 (2–4)	0.606
Aspirin	100% (312)	100% (292)	>0.999	100% (675)	100% (691)	>0.999
Clopidogrel	99.4% (310)	99.7% (291)	>0.999	100.0% (675)	100.0% (691)	0.602
Statin	83.4% (257)	87.5% (248)	0.183	92.5% (621)	93.0% (638)	0.746

ACC = American College of Cardiology; AHA = American Heart Association; CABG = Coronary Artery Bypass Graft; LVEF = Left Ventricle Ejection Fraction; NSTEMI = Non-ST-Elevation Myocardial Infarction; PCI = Percutaneous Coronary Intervention; STEMI= ST-Elevation Myocardial Infarction.

[a]According to the ACC/AHA coronary lesion classification.

[b]Type A stenoses were coded 1 point, type B1 stenoses 2 points, type B2 stenoses 3 points, and type C stenoses 4 points.

DAPT duration was consistent irrespective of CKD severity on the primary and secondary endpoints of the study. This was performed with likelihood ratio tests of the null hypothesis that the interaction coefficient was zero. Finally, the interaction between treatment effect and renal function, modeled as a continuous variable, was analyzed with a fractional polynomial interaction, as proposed by Royston and Sauerbrei, and the best fit for the interaction models was chosen according to the Akaike information criteria. A two-sided probability value of <0.05 was considered significant. All analyses were based on the intention-to-treat principle, and were performed with SPSS, version 21.0 (SPSS Inc., Chicago, IL, USA) and Stata Statistical Software, release 13 (StataCorp LP, College Station, Texas, US).

RESULTS

Among 1,970 patients randomized to 6 versus 24-month DAPT at 30 days from the PCI, 1366 (69.3%) had a creatinine clearance >60 ml/min and 604 (30.7%) had moderate-to-severe CKD, including 65 patients with creatinine clearance $\leq$30 ml/min. Baseline characteristics are summarized in Table I**.** Characteristics of patients randomized to 24-month or 6-month DAPT stratified for CKD are reported in Table II. Compared with no/mild CKD, patients with moderate-to-severe CKD were older, more likely to be women, to have hypertension, diabetes, prior MI or PCI, but had lower BMI, lower LVEF, and were less frequently smokers. They had a higher extension and severity of CAD, with increased need for multivessel intervention. Among CKD patients, PCI was more frequently indicated by non-ST-segment elevation ACS

TABLE III. Clinical Outcomes in Patients with or Without Moderate-to-Severe CKD

	Moderate-to-Severe CKD (N = 604)	No/Mild CKD (N = 1366)	Unadjusted Hazard Ratio (95%CI)	P value	Adjusted Hazard Ratio (95% CI)	P Value
Primary Efficacy Endpoint						
Death for any cause, MI or CVA	112 (18.5)	86 (6.3)	3.172 (2.395–4.202)	<0.0001	1.512 (1.042–2.194)	0.029
Secondary Efficacy Endpoints						
Death for any cause or MI	104 (17.2)	78 (5.7)	3.230 (2.408–4.333)	<0.0001	1.540 (1.044–2.273)	0.030
Death for any cause	79 (13.1)	51 (3.7)	3.819 (2.469–5.907)	<0.0001	1.153 (0.651–2.040)	0.626
Death for cardiovascular cause	46 (7.6)	27 (2.0)	4.034 (2.508–6.489)	<0.0001	1.268 (0.687–2.341)	0.447
Stroke or TIA	20 (3.3)	12 (0.9)	3.873 (1.893–7.923)	<0.0001	1.965 (0.785–4.918)	0.149
MI	44 (7.3)	36 (2.6)	2.872 (1.849–4.461)	<0.0001	1.454 (0.815–2.592)	0.205
Definite ST	7 (1.2)	8 (0.6)	2.094 (0.759–5.774)	0.153	2.004 (0.470–8.539)	0.347
Definite or Probable ST	9 (1.5)	19 (1.4)	1.078 (0.488–2.382)	0.853	0.552 (0.208–1.467)	0.234
Definite, Probable or Possible ST	50 (8.3)	34 (2.5)	3.512 (2.272–5.431)	<0.0001	1.349 (0.758–2.402)	0.308
Safety Endpoints						
BARC classification						
Key safety endpoint (Type 2, 3 or 5)	53 (8.8)	54 (4.0)	2.379 (1.628–3.475)	<0.0001	1.677 (1.025–2.743)	0.039
Type 3 or 5	33 (5.5)	20 (1.5)	3.971 (2.278–6.920)	<0.0001	2.373 (1.147–4.908)	0.020
TIMI classification						
Minor	11 (1.8)	9 (0.7)	2.956 (1.225–7.135)	0.016	2.199 (0.660–7.330)	0.200
Major	13 (2.2)	9 (0.7)	3.418 (1.461–7.997)	0.005	1.529 (0.514–4.550)	0.445
Minor or major	24 (4.0)	18 (1.3)	3.196 (0.734–5.888)	<0.0001	1.757 (0.782–3.949)	0.172
GUSTO classification						
Moderate	18 (3.0)	9 (0.7)	4.836 (2.173–10.766)	<0.0001	4.154 (1.437–12.011)	0.009
Severe	15 (2.5)	10 (0.7)	3.553 (1.596–7.909)	0.002	2.023 (0.734–5.578)	0.173
Moderate or severe	32 (5.3)	19 (1.4)	4.051 (2.296–7.148)	<0.0001	2.714 (1.293–5.694)	0.008
Net Clinical Adverse Events (NACE)						
Death for any cause, MI, CVA or BARC 2, 3 or 5 Bleeding	139 (23.0)	130 (9.5)	2.630 (2.071–3.341)	<0.0001	1.488 (1.087–2.036)	0.013
Death for any cause, MI, CVA or BARC 3 or 5 Bleeding	126 (20.9)	96 (7.0)	3.225 (2.473–4.206)	<0.0001	1.601 (1.128–2.274)	0.008

BARC = Bleeding Academic Research Consortium; CVA = Cerebrovascular Accident; GUSTO= Global Use of Strategies to Open Occluded Coronary Arteries; MI = Myocardial Infarction; ST = Stent Thrombosis; TIA = Transient Ischemic Attack; TIMI = Thrombolysis in Myocardial Infarction.

(NSTE-ACS) and less frequently by ST-segment elevation MI (STEMI) compared with no/mild CKD (Table I).

Baseline characteristics were well balanced in randomized DAPT arms in both moderate-to-severe CKD and no/mild CKD (Table II).

At 2-year, crude events and unadjusted HR suggested higher ischemic and bleeding risks in patients with moderate-to-severe CKD (Table III). The primary efficacy endpoint (death, MI or CVA) occurred in 112 (18.5%) of moderate-to-severe CKD and 86 (6.3%) of no/mild CKD. After adjustment, the primary efficacy endpoint was increased by roughly 50% in those with as compared to those without CKD (adj. HR:1.512; 95% confidence interval [CI] 1.042–2.194; $P = 0.029$; Table III). Similarly, bleeding and NACE were significantly higher in patients with CKD (Table III).

In both randomized groups of DAPT regimen (24 and 6-month DAPT), the primary endpoint was nonsignificantly increased in patients with CKD (24-month DAPT: adj. HR:1.497; 95% CI 0.901–2.488; $P = 0.120$; 6-month DAPT: adj. HR:1.427; 95% CI 0.814–2.501; $P = 0.214$; p for interaction = 0.249; Table IV, Fig. 1). Similarly, the risk of the primary efficacy endpoint did not differ with respect to DAPT duration in both moderate-to-severe CKD (17.6% in the 24-month vs. 19.5% in the 6-month DAPT arms; adj. HR:0.957; 95% CI 0.652–1.407; $P = 0.825$; Figs. 1 and 2, Table V, Supplementary Table I) and no/mild CKD patients (6.7% in the 24-month vs. 5.9% in the 6-month DAPT arms; adj. HR:1.341; 95% CI 0.861–2.086; $P = 0.194$; Figs. 1 and 2, Table V, Supplementary Table I). The absence of interaction between CKD and DAPT duration was further confirmed by analyzing renal function as a continuous variable with fractional polynomial analyses ($P = 0.558$; Supplementary Figure 1).

The key safety endpoint of BARC type 2, 3 or 5 bleeding occurred in 53 (8.8%) and 54 (4.0%) CKD and no-mild CKD respectively. Patients treated with longer DAPT experienced higher rate of bleeding events in both groups (CKD: adj. HR:1.999; 95% CI 1.100–3.632; $P = 0.023$; no/mild CKD: adj. HR:2.880; 95% CI 1.558–5.326; $P = 0.001$; Fig. 3, Table V,

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TABLE IV. Adjusted Clinical Outcomes in Patient with or Without Moderate-to-Severe CKD Stratified by DAPT Duration

	24-Month Clopidogrel (987)				6-Month Clopidogrel (983)				
	Moderate-to-severe CKD ($N = 312$)	No/Mild CKD ($N = 675$)	Adjusted Hazard Ratio (95% CI)	P value	Moderate-to-Severe CKD ($N = 292$)	No/Mild CKD ($N = 691$)	Adjusted Hazard Ratio (95%CI)	P value	P_{int}
Primary Efficacy Endpoint									
Death for any cause, MI or CVA	55 (17.6)	45 (6.7)	1.497 (0.901–2.488)	0.120	57 (19.5)	41 (5.9)	1.427 (0.814–2.501)	0.214	0.249
Secondary Efficacy Endpoints									
Death for any cause or MI	47 (15.1)	41 (6.1)	1.318 (0.765–2.271)	0.320	57 (19.5)	37 (5.4)	1.704 (0.958–3.030)	0.069	0.075
Death for any cause	37 (11.9)	28 (4.1)	1.123 (0.506–2.495)	0.776	42 (14.4)	23 (3.3)	1.101 (0.480–2.526)	0.821	0.557
Death for cardiovascular cause	21 (6.7)	15 (2.2)	1.278 (0.553–2.950)	0.566	25 (8.6)	12 (1.7)	1.092 (0.440–2.706)	0.850	0.299
MI	20 (6.4)	19 (2.8)	0.794 (0.355–1.778)	0.576	24 (8.2)	17 (2.5)	2.321 (0.983–5.470)	0.055	0.336
Stroke or TIA	13 (4.2)	7 (1.0)	2.214 (0.713–6.871)	0.169	7 (2.4)	5 (0.7)	1.297 (0.268–6.273)	0.747	0.996
Definite ST	4 (1.3)	4 (0.6)	1.916 (0.315–11.652)	0.480	3 (1.0)	4 (0.6)	0.634 (0.038–10.696)	0.752	0.256
Definite or Probable ST	6 (1.9)	7 (1.0)	1.238 (0.312–4.917)	0.761	3 (1.0)	12 (1.7)	0.286 (0.065–1.257)	0.097	0.149
Definite, Probable or Possible ST	21 (6.7)	17 (2.5)	1.484 (0.651–3.382)	0.348	29 (9.9)	17 (2.5)	1.112 (0.490–2.527)	0.799	0.330
Safety Endpoints									
BARC classification									
Key safety endpoint (Type 2, 3 or 5)	34 (10.9)	39 (5.8)	1.495 (0.832–2.685)	0.179	19 (6.5)	15 (2.2)	1.968 (0.760–5.095)	0.163	0.407
Type 3 or 5	23 (7.4)	11 (1.6)	2.837 (1.116–7.214)	0.029	10 (3.4)	9 (1.3)	1.520 (0.444–5.205)	0.505	0.310
TIMI classification									
Minor	7 (2.2)	4 (0.6)	3.214 (0.523–19.729)	0.207	4 (1.4)	5 (0.7)	1.528 (0.263–8.882)	0.637	0.379
Major	10 (3.2)	6 (0.9)	1.531 (0.443–5.290)	0.501	3 (1.0)	3 (0.4)	0.789 (0.081–7.684)	0.838	0.947
Minor or major	17 (5.4)	10 (1.5)	1.975 (0.710–5.489)	0.192	7 (2.4)	8 (1.2)	1.184 (0.292–4.805)	0.813	0.418
GUSTO classification									
Moderate	13 (4.2)	4 (0.6)	7.118 (1.496–33.860)	0.014	5 (1.7)	5 (0.7)	2.163 (0.430–10.889)	0.349	0.161
Severe	10 (3.2)	6 (0.9)	1.529 (0.442–5.283)	0.502	5 (1.7)	4 (0.6)	3.051 (0.504–18.461)	0.225	0.875
Moderate or severe	22 (7.1)	10 (1.5)	2.761 (1.052–7.247)	0.039	10 (3.4)	9 (1.7)	2.516 (0.755–8.387)	0.133	0.386
Net Clinical Adverse Events (NACE)									
Death for any cause, MI, CVA or BARC 2, 3 or 5 Bleeding	74 (23.7)	78 (11.6)	1.361 (0.904–2.048)	0.140	65 (22.3)	52 (7.5)	1.556 (0.940–2.577)	0.086	0.085
Death for any cause, MI, CVA or BARC 3 or 5 Bleeding	66 (21.2)	50 (7.4)	1.631 (1.013–2.628)	0.044	60 (20.5)	46 (6.7)	1.460 (0.858–2.485)	0.163	0.591

Abbreviations: BARC = Bleeding Academic Research Consortium; CVA = Cerebrovascular Accident; GUSTO= Global Use of Strategies to Open Occluded Coronary Arteries; MI = Myocardial Infarction; ST = Stent Thrombosis; TIA = Transient Ischemic Attack; TIMI = Thrombolysis in Myocardial Infarction.

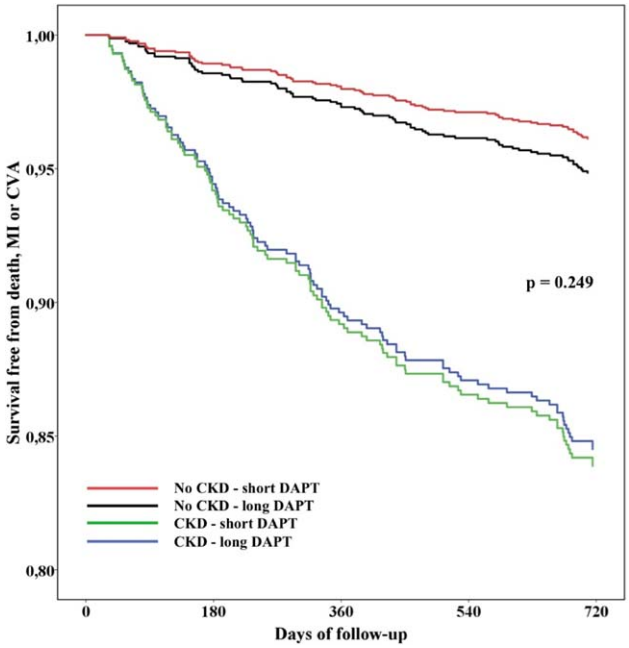

Fig. 1. Survival free from ischemic events according to CKD presence. Cox proportional model plot for the primary endpoint of all-cause death, myocardial infarction, and cerebrovascular accident.

Supplementary Table I), without significant interaction between CKD and bleeding outcomes (p for interaction = 0.407). This latter observation remained consistent when considering renal function as a continuous variable (P =0.476; Supplementary Figure 2).

When bleeding was restricted to BARC 3 or 5, the increased rate of bleeding with prolonged DAPT as compared with short-DAPT was higher in CKD patients (CKD: adj. HR:2.278; 95% CI 1.066–4.869; $P = 0.034$) but not in those with no/mild CKD: adj. HR:1.250; 95% CI 0.489–3.196; $P = 0.641$; Figs. 2 and 3, Table V, Supplementary Table I). Interaction testing however was negative between CKD and moderate-to-severe bleeding (p for interaction = 0.310).

The risk of NACE, consisting of death, MI, CVA or BARC 2, 3 or 5 bleeding, was similar between 24-month versus 6-month DAPT in CKD (adj. HR:1.162; 95% CI 0.822–1.643; $P = 0.395$; Fig. 4, Table V, Supplementary Table I), but significantly increased in no/mild CKD group (adj. HR:1.765; 95% CI 1.226–2.540; $P = 0.002$; Fig. 4, Table V, Supplementary Table I), with negative quantitative interaction testing (p for interaction = 0.085). When BARC 3 or 5 were used for NACE, there were no significant differences between 24-month versus 6-month DAPT in both groups (CKD: adj. HR:1.117;

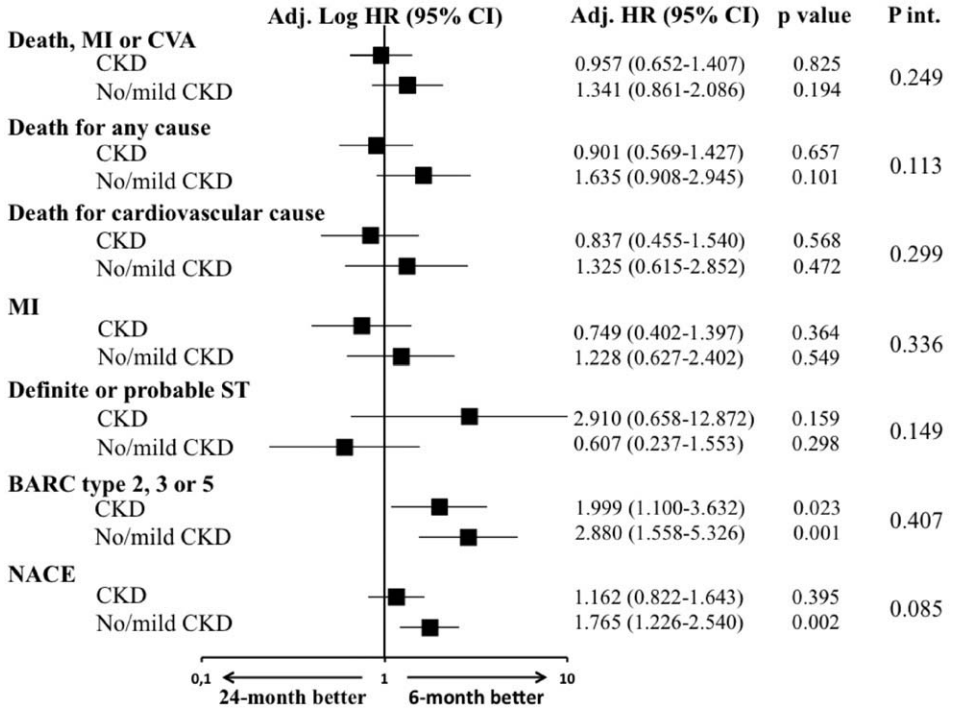

Fig. 2. Interaction between CKD and impact of randomization to 24-month or 6-month DAPT on 2-year clinical outcomes. CKD and no CKD subgroups are shown, with hazard ratios and 95% confidence intervals, for the primary endpoint of death for any cause, myocardial infarction (MI), or cerebrovascular accident (CVA), death for any cause, cardiovascular death, myocardial infarction, definite or probable stent thrombosis, BARC type 3 or 5 bleeding and net adverse clinical events (NACE) among patients randomly assigned to either the 6-month or the 24-month dual-antiplatelet therapy.

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TABLE V. Adjusted Clinical Outcomes in 24-Month Versus 6-Month DAPT Stratified by CKD

	Moderate-to-Severe CKD ($N = 604$)				No/Mild CKD ($N = 1366$)				
	24-Month Clopidogrel ($N = 312$)	6-Month Clopidogrel ($N = 292$)	Adjusted Hazard Ratio (95%CI)	P value	24-Month Clopidogrel ($N = 675$)	6-Month Clopidogrel ($N = 691$)	Adjusted Hazard Ratio (95%CI)	P value	P_{int}
Primary Efficacy Endpoint									
Death for any cause, MI or CVA	55 (17.6)	57 (19.5)	0.957 (0.652–1.407)	0.825	45 (6.7)	41 (5.9)	1.341 (0.861–2.086)	0.194	0.249
Secondary Efficacy Endpoints									
Death for any cause or MI	47 (15.1)	57 (19.5)	0.809 (0.541–1.208)	0.300	41 (6.1)	37 (5.4)	1.404 (0.881–2.238)	0.154	0.075
Death for any cause	37 (11.9)	42 (14.4)	0.901 (0.569–1.427)	0.657	28 (4.1)	23 (3.3)	1.635 (0.908–2.945)	0.101	0.557
Death for cardiovascular cause	21 (6.7)	25 (8.6)	0.837 (0.455–1.540)	0.568	15 (2.2)	12 (1.7)	1.325 (0.615–2.852)	0.472	0.299
MI	20 (6.4)	24 (8.2)	0.749 (0.402–1.397)	0.364	19 (2.8)	17 (2.5)	1.228 (0.627–2.402)	0.549	0.336
Stroke or TIA	13 (4.2)	7 (2.4)	1.809 (0.706–4.638)	0.217	7 (1.0)	5 (0.7)	1.631 (0.454–5.865)	0.454	0.996
Definite ST	4 (1.3)	3 (1.0)	3.308 (0.335–32.696)	0.306	4 (0.6)	4 (0.6)	0.936 (0.221–3.966)	0.928	0.256
Definite or Probable ST	6 (1.9)	3 (1.0)	2.910 (0.658–12.872)	0.159	7 (1.0)	12 (1.7)	0.607 (0.237–1.553)	0.298	0.149
Definite, Probable or Possible ST	21 (6.7)	29 (9.9)	0.701 (0.386–1.272)	0.243	17 (2.5)	17 (2.5)	1.080 (0.549–2.127)	0.824	0.330
Safety Endpoints									
BARC classification									
Key safety endpoint (Type 2, 3 or 5)	34 (10.9)	19 (6.5)	1.999 (1.100–3.632)	0.023	39 (5.8)	15 (2.2)	2.880 (1.558–5.326)	0.001	0.407
Type 3 or 5	23 (7.4)	10 (3.4)	2.278 (1.066–4.869)	0.034	11 (1.6)	9 (1.3)	1.250 (0.489–3.196)	0.641	0.310
TIMI classification									
Minor	7 (2.2)	4 (1.4)	1.773 (0.502–6.265)	0.374	4 (0.6)	5 (0.7)	0.604 (0.142–2.560)	0.494	0.379
Major	10 (3.2)	3 (1.0)	3.514 (0.933–13.240)	0.063	6 (0.9)	3 (0.4)	2.858 (0.561–14.565)	0.206	0.947
Minor or major	17 (5.4)	7 (2.4)	2.565 (1.040–6.321)	0.041	10 (1.5)	8 (1.2)	1.279 (0.472–3.466)	0.629	0.418
GUSTO classification									
Moderate	13 (4.2)	5 (1.7)	2.432 (0.847–6.979)	0.098	4 (0.6)	5 (0.7)	0.651 (0.154–2.761)	0.560	0.161
Severe	10 (3.2)	5 (1.7)	1.781 (0.595–5.326)	0.302	6 (0.9)	4 (0.6)	1.812 (0.444–7.468)	0.411	0.875
Moderate or severe	22 (7.1)	10 (3.4)	2.087 (0.974–4.473)	0.059	10 (1.5)	9 (1.7)	1.153 (0.440–3.020)	0.772	0.386
Net Clinical Adverse Events (NACE)									
Death for any cause, MI, CVA or BARC 2, 3 or 5 Bleeding	74 (23.7)	65 (22.3)	1.162 (0.822–1.643)	0.395	78 (11.6)	52 (7.5)	1.765 (1.226–2.540)	0.002	0.085
Death for any cause, MI, CVA or BARC 3 or 5 Bleeding	66 (21.2)	60 (20.5)	1.117 (0.777–1.607)	0.549	50 (7.4)	46 (6.7)	1.266 (0.834–1.922)	0.269	0.591

BARC = Bleeding Academic Research Consortium; CVA = Cerebrovascular Accident; GUSTO= Global Use of Strategies to Open Occluded Coronary Arteries; MI = Myocardial Infarction; ST = Stent Thrombosis; TIA = Transient Ischemic Attack; TIMI = Thrombolysis in Myocardial Infarction.

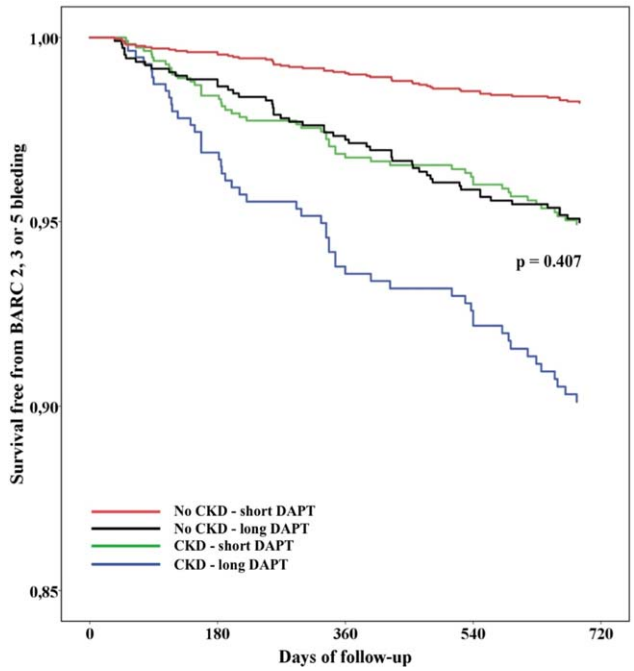

Fig. 3. Survival free from bleeding events according to CKD presence. Cox proportional model plot for BARC 2, 3, or 5 bleeding events.

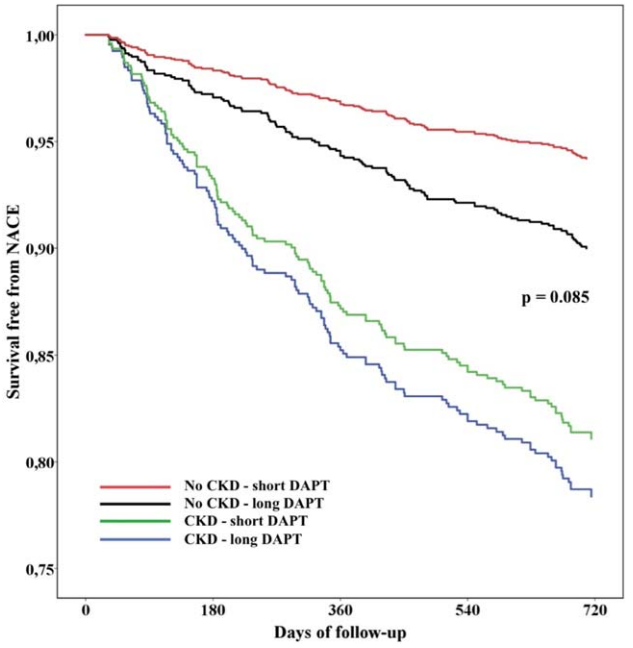

Fig. 4. Survival free from net clinical adverse events according to CKD presence. Cox proportional model plot for NACE including BARC 2, 3, or 5 bleeding events.

95% CI 0.777–1.607; $P = 0.549$; no/mild CKD: adj. HR:1.266; 95% CI 0.834–1.922; $P = 0.269$; p for interaction = 0.591; Figs. 2 and 4, Table V, Supplementary Table I).

DISCUSSION

This sub-analysis from the PRODIGY randomized trial assessed the impact of CKD on clinical outcomes in all-comer patients undergoing PCI and receiving DAPT with clopidogrel and aspirin. The main findings are as follows:

1. CKD was confirmed to be a risk factor for both ischemic and bleeding events;
2. Although patients with moderate-to-severe CKD had higher rates of ischemic events than those with no-mild CKD, DAPT prolongation at 24-month as compared with 6-month DAPT was not associated with ischemic benefits in both CKD and no-mild CKD sub-groups, which is a consistent observation with the overall results of the PRODIGY trial;
3. Patients with or without CKD experienced a significant increase of bleeding events when undergoing prolonged DAPT duration according to the key safety endpoint of the study, consisting of BARC 2, 3 or 5. When more stringent criteria for bleeding were applied (excluding BARC 2 events), only those with CKD had a significantly higher rate of bleeding events with DAPT prolongation; However, interaction testing was negative suggesting that CKD per se did not emerge as treatment modifier with respect to the risk of bleeding when a prolonged DAPT regimen is implemented.

The optimal DAPT duration after coronary stenting remains an ongoing matter of debate, but the more frequently suggested approach is tailoring therapy based on patient characteristics and avoiding prolonged DAPT regimens due to emerging risks in terms of bleeding and mortality [4,5,12].

Many studies have focused on the association between renal dysfunction and risk of ischemic events after PCI [17,21–23]. CKD patients are characterized by more frequent high platelet reactivity and higher rate of poor responsiveness to this drug have been previously observed [24–27].

However, a large body of evidence also supports the concept that CKD patients are also at higher bleeding risks after PCI [15,22,28,29]. Consistent with these observations, renal function is frequently taken into account in previously developed bleeding risk scores, including CRUSADE, HAS-BLEED and ACUITY.

The evidence from studies that specifically addressed the impact of DAPT regimen stratified for renal function is limited. To our knowledge, the current study is

the first dedicated CKD sub-analysis from a randomized trial comparing a short versus a prolonged DAPT regimen. In a retrospective analysis from Siddiqui et al, clopidogrel prolongation was found to be associated with reduction of MI and death in the absence of significant increase in severe bleeding [17,18]. However, that study suffered from important limitations, including the bleeding definition [18]. Conversely, our study prospectively collected baseline and follow-up information in the setting of a randomized clinical study specifically investigating the role of two different regimens of DAPT after stent implantation [12]. In the PEGASUS-TIMI 54 trial, there was no significant interaction between renal function and clinical ischemic events with both CKD and no-CKD patients having benefits from ticagrelor therapy, even if those with CKD had a higher risk of MACE and a higher absolute risk reduction [30].

Differently from previous suggestions, our findings support the concept that the presence of moderate-to-severe CKD should be considered as a condition in which bleeding risk outweighs ischemic risk, rather than the opposite [14,16,17]. Therefore, these patients would benefit more if not prolonging DAPT over the recommended period after PCI, although this decision should always be tailored at an individual level. Consequently, it seems plausible to extend the results generally observed by randomized trials (DAPT prolongation increases risks of bleeding and mortality, while a short course of DAPT was associated with a significant reduction in major bleeding without significant differences in ischemic or thrombotic outcomes) also to patients with CKD.

Limitations

This sub-analysis of the PRODIGY trial was not prespecified. This study was not designed or powered to specifically investigate on CKD differences, but it is an exploratory analysis that should be considered hypothesis generating and needs to be confirmed in further trials.

CONCLUSIONS

The present study suggests that in the setting of an unselected PCI population receiving a balanced distribution of coronary stents, including first and newer generation DES, CKD does not appear a treatment modifier with respect to the benefit or harm of a prolonged DAPT regimen. Moreover, CKD patients are exposed to a sizable bleeding risk when treated with a 24-month as compared with 6-month DAPT duration. Hence, our analysis does not suggest that CKD should be a major driver in the decision-making on the duration of DAPT after stent implantation.

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Invited Commentary

Deciding on the Duration of Dual Antiplatelet Therapy—When the Choice Between 2 Evils Is Still Evil

Marco Valgimigli, MD, PhD; Giuseppe Gargiulo, MD

The Dual Antiplatelet Therapy (DAPT) Study[1] was an international, blinded, placebo-controlled, randomized trial comparing 2 durations of thienopyridine therapy to prevent stent thrombosis (ST) or the composite end point of mortality, myocardial infarction (MI), or stroke among 9961 patients treated with drug-eluting stents. The study aimed to demonstrate that prolonged thienopyridine therapy (ie, for an additional 18 months) would be noninferior to standard therapy duration (ie, 1-year therapy after coronary stenting) with respect to moderate or severe bleeding as defined by the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries (GUSTO) classification.[1] A secondary cohort consisting of 1687 patients treated with bare metal stents was also included.

Related article

Prolonging DAPT for an additional 18 months compared with 1-year therapy in selected patients with no ischemic or bleeding recurrences at 12 months (in addition to other features) reduced the risks of major adverse cardiovascular events (4.3% vs 5.9%, $P < .001$) and ST (0.4% vs 1.4%, $P < .001$) but increased the risks of moderate to severe bleeding (2.5% vs 1.6%, $P = .001$).[1] While a trade-off between benefits and risks with continued thienopyridine therapy plus aspirin was anticipated based on previous findings,[2] an increased risk of all-cause mortality, a secondary end point, with continuation of thienopyridine therapy was unexpected and remains a matter of concern.[1] The higher risk of fatalities in the group with continued thienopyridine therapy was attributable to greater noncardiovascular mortality (1% vs 0.5%, $P < .002$), while cardiac death was comparable (0.9% vs 1.0%, $P = .98$).[1]

In the Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on the Background of Aspirin-Thrombolysis in Myocardial Infarction 54 (PEGASUS TIMI 54) trial,[3] patients after MI who were treated with ticagrelor in combination with aspirin experienced a 17% relative reduction in cardiovascular death, MI, or stroke compared with those who were treated with placebo and aspirin (4.47% vs 5.25%, $P = .005$). In a prespecified analysis of those who had not discontinued $P2Y_{12}$ inhibitor therapy or had only discontinued it within 30 days, the benefit was greatest (28% relative reduction [4.9% vs 6.2%], $P = .004$).[3] Yet, consistent with what was previously observed in the DAPT Study,[1] the rates of TIMI major bleeding were higher with ticagrelor (2.60% with 90 mg twice daily and 2.30% with 60 mg twice daily) than with placebo (1.06%) ($P < .001$ for each dose vs placebo).[3] While cardiovascular death trended lower, noncardiovascular death was increased with ticagrelor therapy.[4]

Both studies[1,3] established the superiority of prolonged DAPT over aspirin alone in preventing ischemic recurrence in stabilized patients after percutaneous coronary intervention or MI. However, despite apparently selecting subpopulations with low bleeding risk, both trials observed a worrisome increase in major bleeding with DAPT compared with no DAPT (placebo, which is aspirin alone), the magnitude of which appeared to be comparable to the difference in nonfatal ischemic end points seen between study arms. Therefore, the decision of whether DAPT should be continued 1 year from the event or coronary stenting requires preliminary clarification of the relative effect of ischemic and bleeding events on mortality.

In this issue of *JAMA Cardiology*, Secemsky et al[5] present findings that lend further support to end the one-size-fits-all era regarding the potency and duration of antithrombotic agents. Those believing that the DAPT Study[1] unconditionally supports the extension of DAPT beyond 1 year in all patients after coronary stenting should read their article with even greater attention.[6]

What are the lessons to be learned by practicing cardiologists? First, continuing DAPT beyond 12 months based on theoretical concerns about very late ST is unjustified. Even in the setting of the study by Secemsky et al,[5] in which 22.5% of patients received paclitaxel-eluting stents (which were confirmed to be independently associated with higher ischemic risk), ST was rare (22.5% of ischemic events), while most ischemic events were MI not related to ST (61.0% of ischemic events). Therefore, DAPT should be continued with the chief aim of preventing spontaneous MI rather than protecting the few previously stented millimeters of coronary arteries.

Second, the frequency of bleeding events after a prolonged course of DAPT, as well as their implications with respect to mortality, is dependent on the applied classification. The DAPT Study[1] prespecified a sensitive definition for recurrent MI based on troponin elevation beyond the upper limit of normal in conjunction with any compatible transient ischemia symptoms. This specification is in keeping with the universal MI definition (and with the somewhat insensitive GUSTO classification for bleeding events) that was developed in the thrombolysis era to compare in-hospital hemorrhagic complications across different lytic agents. In the study by Secemsky et al,[5] a total of 235 GUSTO moderate or severe bleeding events occurred in 232 of 11 648 patients (2.0%), which is roughly 50% lower than the 502 adjudicated ischemic end points that were observed in 478 (4.1%) of the patients. This observation led the authors to conclude that, while ischemic and bleeding events were both associated with a high mortality rate, ischemic events were more frequent than bleeding events.

However, delving deeper into the study results by Secemsky et al[5] reveals a broader and (we believe) more accurate set of observations. Patients with spontaneous MI had a 9.1-fold greater risk of dying during the study compared with

those without spontaneous MI. However, patients with GUSTO moderate to severe bleeding had an 18.1-fold greater probability of death compared with those without such GUSTO events throughout follow-up. Hence, a more appropriate conclusion is that, although bleeding events were less frequent than ischemic events according to prespecified classifications, they were associated with a 2-fold higher risk of death. Calculation of the attributable risk helps to factor in both prevalence and a measure of association with mortality. By doing so, the occurrence of spontaneous MI during the study would explain approximately 17% of the overall mortality, while the occurrence of GUSTO moderate to severe bleeding would explain as much as 25%. Therefore, prioritizing (to prevent) ischemic events over bleeding events does not definitively appear to be the right thing to do.

Third, the Bleeding Academic Research Consortium (BARC) classification appears to be much more suitable than the GUSTO classification to inform clinicians on the safety profile of any tested antithrombotic treatment in today's practice. Bleeding at BARC 2, 3, or 5 (ie, any actionable bleeding) occurred in 4.1% of the patients in the study by Secemsky et al,[5] which corresponds exactly to the event rate observed for ischemic events and which carried an almost identical risk of mortality compared with ischemic events.

Fourth, the analysis by Secemsky et al[5] confirmed previous observations that even a so-called minor yet actionable bleeding category, such as BARC 2, is associated with higher mortality risk.[7] This finding by Secemsky et al[5] is in agreement with the prior study[7] and is paramount because it derives from an analysis in which fatal bleeding events (ie, BARC 5) were analyzed separately instead of being distributed to other classes (ie, BARC 2 or 3) according to initial assessment by the clinical event committee (ie, before they became fatal). Hence, this scenario has most likely resulted in a dilution effect with respect to the measure of association between BARC 2 and 3 and fatal outcomes.

Fifth, as expected, while ischemic events in the study by Secemsky et al[5] were mainly associated with an increased risk of cardiovascular death (78.8% for with cardiovascular death among all deaths in patients with ischemic events), bleeding accounted for a more balanced distribution with respect to type of fatalities (of deaths after a bleeding event, 53.7% were cardiovascular and 46.3% were noncardiovascular). This finding possibly explains, at least in part, the overall results in terms of mortality and type thereof across major DAPT studies.[3]

In summary, choosing between 2 evils occurring at similar frequencies and carrying comparable prognostic implications is still evil. Personalized treatment algorithms maximizing benefits over risks represent the only sensible way forward. The DAPT Study investigators should be commended for their continued efforts to learn from and teach based on the powerful database they have amassed.

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Annals of Internal Medicine ORIGINAL RESEARCH

Use of the Dual-Antiplatelet Therapy Score to Guide Treatment Duration After Percutaneous Coronary Intervention

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Background: The dual-antiplatelet therapy (DAPT) score was developed to identify patients more likely to derive harm (score <2) or benefit (score ≥2) from prolonged DAPT after percutaneous coronary intervention (PCI).

Objective: To evaluate the safety and efficacy of DAPT duration according to DAPT score.

Design: Retrospective assessment of DAPT score–guided treatment duration in a randomized clinical trial. (ClinicalTrials.gov: NCT00611286)

Setting: PCI patients.

Patients: 1970 patients undergoing PCI.

Intervention: DAPT (aspirin and clopidogrel) for 24 versus 6 months.

Measurements: Primary efficacy outcomes were death, myocardial infarction, or cerebrovascular accident. The primary safety outcome was type 3 or 5 bleeding according to the Bleeding Academic Research Consortium definition. Outcomes were assessed between 6 and 24 months.

Results: 884 patients (44.9%) had a DAPT score of at least 2, and 1086 (55.1%) had a score less than 2. The reduction in the primary efficacy outcome with 24- versus 6-month DAPT was greater in patients with high scores (risk difference [RD] for score ≥2, −2.05 percentage points [95% CI, −5.04 to 0.95 percentage points]; RD for score <2, 2.91 percentage points [CI, −0.43 to 6.25 percentage points]; $P = 0.030$). However, the difference by score for the primary efficacy outcome varied by stent type; prolonged DAPT with high scores was effective only in patients receiving paclitaxel-eluting stents (RD, −7.55 percentage points [CI, −12.85 to −2.25 percentage points]). The increase in the primary safety outcome with 24- versus 6-month DAPT was greater in patients with low scores (RD for score ≥2, 0.20 percentage point [CI, −1.20 to 1.60 percentage points]; RD for score <2, 2.58 percentage points [CI, 0.71 to 4.46 percentage points]; $P = 0.046$).

Limitation: Retrospective calculation of the DAPT score.

Conclusion: Prolonged DAPT resulted in harm in patients with low DAPT scores undergoing PCI but reduced risk for ischemic events in patients with high scores receiving paclitaxel-eluting stents. Whether prolonged DAPT benefits patients with high scores treated with contemporary drug-eluting stents requires further study.

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Dual-antiplatelet therapy (DAPT) with aspirin and oral $P2Y_{12}$ adenosine diphosphate–receptor inhibitors is an evidence-based, guideline-recommended standard of care in patients with coronary artery disease undergoing percutaneous coronary intervention (PCI) (1–3). The pathobiological rationale for DAPT after PCI is to prevent atherothrombotic manifestations in the stented coronary segments before arterial healing and stent endothelialization are complete. However, although guidelines mandate a minimum course of 1 to 6 months after PCI, depending on clinical presentation and stent type (1, 3), the optimal duration of DAPT in the long term is controversial because the ischemic protection afforded by extended DAPT is largely offset by an increase in bleeding complications (4, 5). Prolonged DAPT has been estimated to prevent 8 myocardial infarctions per 1000 persons treated for 1 year, but at a cost of 6 major bleeding events (6, 7). In view of this tradeoff between efficacy and safety, as well as a possible lack of a mortality benefit due to an increase in noncardiovascular deaths with prolonged DAPT (4, 8), American and European guidelines recommend individualizing the duration of DAPT on the basis of ischemic versus bleeding risks (1, 3). This recommendation is also consistent with the results of a survey assessing contemporary clinical practice (9).

The DAPT score is a new standardized tool to identify patients who would derive benefit or harm from prolonged DAPT (10, 11). However, the efficacy and safety of DAPT duration as guided by the score have not been assessed outside the derivation cohort included in the DAPT (Dual Antiplatelet Therapy) Study (ClinicalTrials.gov: NCT00977938), in which all patients received DAPT for 12 months and were then randomly assigned to continue thienopyridine treatment or placebo on a background of aspirin (8). We therefore sought to apply the DAPT score to PRODIGY (Prolonging Dual-Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia Study), which enrolled a broadly inclusive sample of patients randomly assigned to a prolonged (24 months) versus a short (≤6 months) DAPT regimen after PCI (12).

See also:

Editorial comment 1

METHODS

Details on study design and primary results of PRODIGY have been reported elsewhere (12–14). Briefly, unselected patients undergoing PCI (n = 2013) were randomly assigned to receive 1 of 4 types of stent (bare-metal, zotarolimus-eluting, paclitaxel-eluting, or everolimus-eluting). At 30 days, 1970 patients were randomly allocated to either 6 or 24 months of DAPT. Randomization was stratified by center, ongoing ST-segment elevation myocardial infarction, presence or absence of diabetes mellitus, and presence or absence of in-stent restenosis. Selection criteria were broad in order to reflect routine clinical practice. The main exclusion criteria were known allergy to antiplatelet drugs, planned surgery within the next 24 months, history of bleeding diathesis, active bleeding or stroke in the previous 6 months, need for concomitant oral anticoagulation, pregnancy, and life expectancy less than 2 years.

Treatment Protocol

A maintenance dose of clopidogrel (75 mg/d) was administered for up to 6 or 24 months according to randomization. A low dose of aspirin (80 to 160 mg/d) was prescribed indefinitely in all patients.

Study End Points

The primary efficacy end point for this analysis was the composite of death, myocardial infarction, or cerebrovascular accident. Other efficacy outcomes included each component of the primary efficacy end point, cardiovascular death, and stent thrombosis according to the Academic Research Consortium criteria (15).

The primary safety end point was a composite of type 3 or 5 bleeding according to the Bleeding Academic Research Consortium (BARC) definitions, including overt bleeding with a decrease in hemoglobin level of at least 3 g/dL; bleeding requiring transfusion, intravenous vasoactive agents, or surgical intervention for control; bleeding resulting in cardiac tamponade; and intracranial or intraocular bleeding. Other safety end points were BARC type 2, 3, or 5 bleeding as well as bleeding that met the Thrombolysis in Myocardial Infarction (TIMI) and the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) criteria. The BARC, TIMI, and GUSTO criteria are detailed in **Appendix 1** (available at Annals.org). A clinical events committee blinded to treatment allocation adjudicated all efficacy and safety events.

Calculation of the DAPT Score

We calculated the DAPT score for each patient included in PRODIGY, as previously reported (10). The score ranges from −2 to 10 and is calculated by assigning points according to characteristics related to the patient (0 for age <65 years, −1 for age ≥65 and <75 years, −2 for age ≥75 years, 1 for diabetes mellitus, 1 for current smokers, 1 for prior PCI or myocardial infarction, and 2 for history of congestive heart failure or left ventricular ejection fraction <30%) and the index procedure (1 for acute myocardial infarction at presentation, 2 for PCI of saphenous vein graft, 1 for implantation of a paclitaxel-eluting stent, and 1 for stent diameter <3 mm). Overall, a low score (<2) identifies patients for whom bleeding risks outweigh ischemic benefits, and a high score (≥2) identifies patients for whom ischemic benefits outweigh bleeding risks. A calculator for the score is available at www.daptstudy.org/for-clinicians/calchome.htm.

Statistical Analysis

For calculation of the DAPT score, missing values for left ventricular ejection fraction (n = 136) were estimated using multiple imputation (**Appendix 2**, available at Annals.org). The reported percentages are Kaplan–Meier estimates of cumulative incidence at 24 months. Because the randomized treatment between groups began to diverge at 6 months, a landmark analysis was performed between 6 and 24 months by censoring patients if they experienced the event of interest, died, or were lost to follow-up before 6 months (16). The efficacy and safety of prolonged versus short DAPT were assessed in categories of high and low DAPT score. To account for data censoring, the pseudovalue approach was used to calculate absolute risk differences (RDs) and 95% CIs between prolonged and short DAPT (17). The treatment effect of prolonged versus short DAPT between patients with high and low scores was compared using a Z test for interaction (18). The efficacy of prolonged versus short DAPT within the high and low score groups was also explored across stent types, with heterogeneity assessed by the Q statistic.

Sensitivity analyses were conducted from 1 to 24 months after patients who received earlier-generation paclitaxel-eluting stents, which are associated with a higher risk for stent thrombosis and myocardial infarction, and those with missing values for left ventricular ejection fraction were excluded. A sensitivity analysis of safety outcomes accounting for the competing risk for death was also conducted (17). All P values were 2-sided, and those less than 0.05 indicated statistical significance. All analyses were done using Stata, version 13 (StataCorp). Further details on the statistical analysis are provided in **Appendix 2**.

Institutional Review Board Approval

The ethics committees of the participating centers independently approved the protocol, and all participants gave written informed consent.

Role of the Funding Source

This study received no funding.

RESULTS

DAPT Score Distribution and Baseline Characteristics

Of 1970 patients enrolled in PRODIGY, 884 (44.9%) had a high DAPT score (≥2) and 1086 (55.1%) had a low score (<2). The median score was 1 (interquartile range, 0 to 2; mean, 1.3 [SD, 1.5]) (**Appendix Figure 1**, available at Annals.org). Patients with high scores were

younger and more likely to be male; to be smokers; and to have diabetes, prior myocardial infarction, prior coronary revascularization, congestive heart failure or left ventricular dysfunction, and acute myocardial infarction at presentation. They also were less likely to have arterial hypertension or peripheral artery disease and had higher estimated glomerular filtration rates (Table 1). Patients with high scores more frequently had PCI for saphenous vein graft disease or in-stent restenosis and had a greater mean stent diameter (Table 2). Baseline and periprocedural characteristics were similar within high and low score groups between patients assigned to 24 versus 6 months of DAPT (Appendix Tables 1 and 2, available at Annals.org).

Efficacy Outcomes With Prolonged Versus Short DAPT, by DAPT Score

The reduction in the primary efficacy outcome of death, myocardial infarction, or cerebrovascular accident with 24 versus 6 months of DAPT was greater in patients with high scores than those with low scores (*P* for interaction = 0.030) (Figure, *top*).

Among patients with high scores, the primary ischemic outcome occurred in 4.2% randomly assigned to 24-month DAPT compared with 6.2% randomly assigned to 6-month DAPT (RD, −2.05 percentage points [95% CI, −5.04 to 0.95 percentage points]) (Table 3 and Appendix Figure 2, available at Annals.org). Compared with short DAPT, prolonged DAPT was associated with fewer cardiac deaths and myocardial infarctions (RD, −2.01 percentage points [CI, −4.53 to 0.51 percentage points]). Definite, probable, or possible stent thrombosis was also significantly reduced in patients with high scores who received prolonged versus short DAPT (RD, −2.44 percentage points [CI, −4.70 to −0.19 percentage points]). Among patients with low scores, the primary efficacy outcome occurred in 9.8% randomly assigned to 24-month DAPT compared with 6.8% randomly assigned to 6-month DAPT (RD, 2.91 percentage points [CI, −0.43 to 6.25 percentage points]) (Table 3 and Appendix Figure 2).

Safety Outcomes With Prolonged Versus Short DAPT, by Score

The increase in the primary safety outcome of BARC type 3 or 5 bleeding with 24- versus 6-month DAPT was greater in patients with low scores than those with high scores (*P* for interaction = 0.046) (Figure, *bottom*).

Among patients with high scores, BARC type 3 or 5 bleeding occurred in 1.2% randomly assigned to 24-month DAPT compared with 1.0% randomly assigned to 6-month DAPT (RD, 0.20 percentage point [CI, −1.20 to 1.60 percentage points]) (Table 4 and Appendix Figure 2). Consistently, there were no large differences between prolonged and short DAPT with regard

Table 1. Baseline Characteristics, by DAPT Score

Characteristic	DAPT Score					High vs. Low DAPT Score		
	<0 (*n* = 233)	0 (*n* = 394)	1 (*n* = 459)	2 (*n* = 461)	>2 (*n* = 423)	High (≥2) (*n* = 884)	Low (<2) (*n* = 1086)	Risk Difference (95% CI)
Mean age (SD), *y*	77.9 (5.4)	74.1 (8.2)	69.2 (9.9)	63.7 (10.4)	59.7 (10.6)	61.8 (10.6)	72.8 (9.1)	−11.0 (−11.9 to −10.2)
Male, *n (%)*	155 (66.5)	271 (68.8)	353 (76.9)	375 (81.3)	357 (84.4)	732 (82.8)	779 (71.7)	11.1 (7.3 to 14.8)
Mean BMI (SD), *kg/m²*	26.5 (3.4)	28.0 (18.8)	27.1 (3.9)	27.8 (10.8)	28.4 (9.6)	28.1 (10.2)	27.3 (11.7)	0.8 (−0.2 to 1.8)
Hypertension, *n (%)*	184 (79.0)	308 (78.2)	340 (74.1)	313 (67.9)	269 (63.6)	582 (65.8)	832 (76.6)	−10.8 (−14.7 to −6.8)
Dyslipidemia, *n (%)*	122 (52.4)	217 (55.1)	241 (52.5)	257 (55.7)	241 (57.0)	498 (56.3)	580 (53.4)	2.9 (−1.5 to 7.4)
Smoking, *n (%)*	2 (0.9)	21 (5.3)	75 (16.3)	144 (31.2)	227 (53.7)	371 (42.0)	98 (9.0)	32.9 (29.5 to 36.4)
Diabetes, *n (%)*	14 (6.0)	70 (17.8)	99 (21.6)	124 (26.9)	170 (40.2)	294 (33.3)	183 (16.9)	16.4 (12.7 to 20.1)
Insulin-treated diabetes, *n (%)*	4 (1.7)	15 (3.8)	21 (4.6)	27 (5.9)	47 (11.1)	74 (8.4)	40 (3.7)	4.7 (2.6 to 6.8)
Family history of CAD, *n (%)*	51 (21.9)	105 (26.6)	126 (27.5)	131 (28.4)	140 (33.1)	271 (30.7)	282 (26.0)	4.7 (0.7 to 8.7)
Previous MI, *n (%)*	26 (11.2)	81 (20.6)	111 (24.2)	136 (29.5)	172 (40.7)	308 (34.8)	218 (20.1)	14.8 (10.9 to 18.6)
Previous PCI, *n (%)*	18 (7.7)	54 (13.7)	90 (19.6)	96 (20.8)	101 (23.9)	197 (22.3)	162 (14.9)	7.4 (4.0 to 10.8)
Previous CABG, *n (%)*	26 (11.2)	42 (10.7)	35 (7.6)	46 (10.0)	64 (15.1)	110 (12.4)	103 (9.5)	3.0 (0.2 to 5.7)
Mean creatinine clearance (SD), *mL/min/1.73 m²**	60.6 (19.1)	65.9 (23.3)	77.0 (50.6)	85.5 (28.8)	94.0 (35.1)	89.6 (32.2)	69.5 (37.4)	20.1 (17.0 to 23.2)
Peripheral artery disease, *n (%)*	35 (15.0)	60 (15.2)	64 (13.9)	51 (11.1)	36 (8.5)	87 (9.8)	159 (14.6)	−4.8 (−7.7 to −1.9)
Mean LVEF (SD), %†	54.2 (8.6)	52.4 (9.9)	51.1 (9.8)	50.3 (10.1)	47.4 (11.5)	48.9 (10.9)	52.2 (9.7)	−3.3 (−4.2 to −2.4)
Congestive heart failure or left ventricular dysfunction, *n (%)*	0 (0)	0 (0)	7 (1.5)	20 (4.3)	53 (12.5)	73 (8.3)	7 (0.6)	7.6 (5.9 to 9.3)
Indication for PCI, *n (%)*								
Stable CAD	91 (39.1)	123 (31.2)	128 (27.9)	108 (23.4)	55 (13.0)	163 (18.4)	342 (31.5)	−13.1 (−16.9 to −9.2)
NSTE-ACS	105 (45.1)	179 (45.4)	173 (37.7)	183 (39.7)	177 (41.8)	360 (40.7)	457 (42.1)	−1.4 (−5.7 to 3.0)
STEMI	37 (15.9)	92 (23.4)	158 (34.4)	170 (36.9)	191 (45.2)	361 (40.8)	287 (26.4)	14.4 (10.3 to 18.5)
Acute MI at presentation, *n (%)*	60 (25.8)	175 (44.4)	246 (53.6)	289 (62.7)	328 (77.5)	617 (69.8)	481 (44.3)	25.5 (21.2 to 29.8)

BMI = body mass index; CABG = coronary artery bypass grafting; CAD = coronary artery disease; DAPT = dual-antiplatelet therapy; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NSTE-ACS = non–ST-segment elevation acute coronary syndrome; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.
* Missing in 21 patients.
† Missing in 136 patients.

Table 2. Angiographic Characteristics, by DAPT Score*

Characteristic	DAPT Score					High vs. Low DAPT Score		
	<0 (*n* = 233)	0 (*n* = 394)	1 (*n* = 459)	2 (*n* = 461)	>2 (*n* = 423)	High (≥2) (*n* = 884)	Low (<2) (*n* = 1086)	Risk Difference (95% CI)
Angiographic features, *n (%)*								
Single-vessel disease	66 (28.3)	119 (30.2)	156 (34.0)	127 (27.5)	123 (29.1)	250 (28.3)	341 (31.4)	−3.1 (−7.2 to 1.0)
2-vessel disease	82 (35.2)	130 (33.0)	153 (33.3)	184 (39.9)	152 (35.9)	336 (38.0)	365 (33.6)	4.4 (0.1 to 8.7)
3-vessel disease	85 (36.5)	145 (36.8)	150 (32.7)	150 (32.5)	148 (35.0)	298 (33.7)	380 (35.0)	−1.3 (−5.5 to 2.9)
Multivessel disease, *n (%)*	167 (71.7)	275 (69.8)	303 (66.0)	334 (72.5)	300 (70.9)	634 (71.7)	745 (68.6)	−2.5 (−6.4 to 1.5)
Multivessel PCI, *n (%)*	72 (30.9)	115 (29.2)	115 (25.1)	124 (26.9)	100 (23.6)	224 (25.3)	302 (27.8)	0.6 (−3.7 to 4.9)
≥2 treated lesions	91 (39.1)	154 (39.1)	158 (34.4)	174 (37.7)	159 (37.6)	333 (37.7)	403 (37.1)	0.6 (−3.7 to 4.9)
≥3 treated lesions	28 (12.0)	44 (11.2)	48 (10.5)	52 (11.3)	51 (12.1)	103 (11.7)	120 (11.0)	0.6 (−2.2 to 3.4)
≥4 treated lesions	12 (5.2)	16 (4.1)	15 (3.3)	20 (4.3)	19 (4.5)	39 (4.4)	43 (4.0)	0.5 (−1.3 to 2.2)
Treated vessel, *n (%)*								
Left anterior descending artery	141 (60.5)	209 (53.0)	247 (53.8)	238 (51.6)	201 (47.5)	439 (49.7)	597 (55.0)	−5.3 (−9.7 to −0.9)
Left circumflex artery	85 (36.5)	141 (35.8)	137 (29.8)	148 (32.1)	128 (30.3)	276 (31.2)	363 (33.4)	−2.2 (−6.4 to 2.0)
Right coronary artery	66 (28.3)	147 (37.3)	158 (34.4)	175 (38.0)	163 (38.5)	338 (38.2)	371 (34.2)	4.1 (−0.2 to 8.3)
Left main artery	15 (6.4)	24 (6.1)	29 (6.3)	24 (5.2)	19 (4.5)	43 (4.9)	68 (6.3)	−1.4 (−3.4 to 0.7)
Saphenous vein graft	0 (0)	1 (0.3)	3 (0.7)	6 (1.3)	30 (7.1)	36 (4.1)	4 (0.4)	3.7 (2.5 to 4.9)
≥1 type B2/C lesion, *n (%)*	150 (64.4)	249 (63.2)	317 (69.1)	291 (63.1)	299 (70.7)	590 (66.7)	716 (65.9)	0.8 (−3.4 to 5.0)
≥1 restenotic lesion, *n (%)*	6 (2.6)	8 (2.0)	18 (3.9)	36 (7.8)	25 (5.9)	61 (6.9)	32 (2.9)	4.0 (2.1 to 5.8)
Randomized stent, *n (%)*								
Bare-metal stent	85 (36.5)	130 (33.0)	109 (23.7)	98 (21.3)	70 (16.5)	168 (19.0)	324 (29.8)	−10.8 (−14.6 to −7.0)
Paclitaxel-eluting stent	7 (3.0)	42 (10.7)	106 (23.1)	145 (31.5)	190 (44.9)	335 (37.9)	155 (14.3)	23.6 (19.9 to 27.3)
Zotarolimus-eluting stent	71 (30.5)	102 (25.9)	124 (27.0)	119 (25.8)	77 (18.2)	196 (22.2)	297 (27.3)	−5.2 (−9.0 to −1.3)
Everolimus-eluting stent	70 (30.0)	120 (30.5)	120 (26.1)	99 (21.5)	86 (20.3)	185 (20.9)	310 (28.5)	−7.6 (−11.5 to −3.8)
Mean implanted stents (SD), *n*	1.9 (1.2)	1.9 (1.3)	1.8 (1.2)	1.9 (1.2)	1.9 (1.2)	1.9 (1.2)	1.9 (1.3)	0 (−0.1 to 0.1)
Mean overall stent length (SD), *mm*	40.2 (28.8)	38.1 (28.4)	38.3 (29.3)	40.9 (31.3)	40.7 (29.0)	40.8 (30.2)	38.6 (28.8)	2.2 (−0.4 to 4.8)
Mean stent diameter (SD), *mm*	3.0 (0.4)	3.0 (0.4)	3.0 (0.4)	3.0 (0.4)	3.0 (0.5)	3.0 (0.5)	2.95 (0.4)	0.1 (0 to 0.1)

DAPT = dual-antiplatelet therapy; PCI = percutaneous coronary intervention.
* Percentages may not sum to 100 due to rounding.

to GUSTO moderate or severe bleeding (RD, 0.20 percentage point [CI, −1.03 to 1.44 percentage points]) or TIMI minor or major bleeding (RD, 0.20 percentage point [CI, −1.20 to 1.60 percentage points]). In contrast, in the low score group, the risk for BARC type 3 or 5 bleeding was increased among patients randomly assigned to 24- versus 6-month DAPT (RD, 2.58 percentage points [CI, 0.71 to 4.46 percentage points]) (**Table 4** and **Appendix Figure 2**). The risks for GUSTO moderate or severe bleeding (RD, 2.57 percentage points [CI, 0.77 to 4.38 percentage points]) or TIMI minor or major bleeding (RD, 1.97 percentage points [CI, 0.37 to 3.56 percentage points]) were consistently increased in patients allocated to prolonged versus short DAPT.

Effect of Stent Type and Sensitivity Analysis

For the primary efficacy outcome in patients with high DAPT scores, risk estimates associated with 24- versus 6-month DAPT varied by stent type (*P* for interaction = 0.005), driven primarily by a lower risk for events with prolonged versus short DAPT among patients who received paclitaxel-eluting stents (RD, −7.55 percentage points [CI, −12.85 to −2.25 percentage points]) (**Figure** and **Appendix Table 3**, available at Annals.org). After patients with paclitaxel-eluting stents were excluded, the RDs for the primary ischemic outcome associated with randomized DAPT duration were similar in both the high (RD, 1.23 percentage points [CI, −2.41 to 4.86 percentage points]) and low (RD, 2.38 percentage points [CI, −1.12 to 5.87 percentage points]) score categories (*P* for interaction = 0.65) (**Figure** and **Appendix Tables 4** and **5**, available at Annals.org).

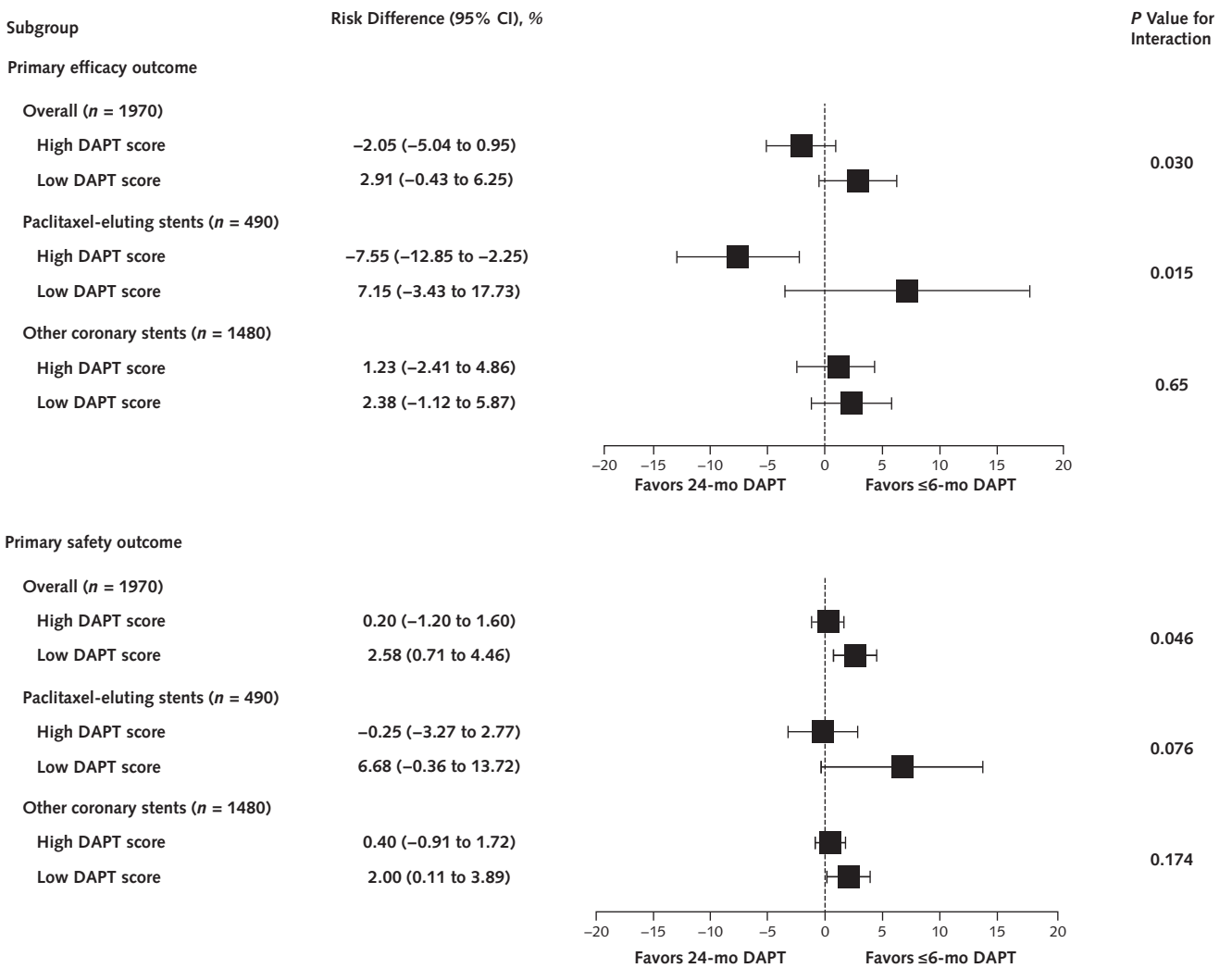
Clinical outcomes between 1 and 24 months according to DAPT duration and score category are shown in **Appendix Tables 6** and **7** (available at Annals.org). For the primary efficacy outcome, RDs between the high (−1.24 percentage points [CI, −4.95 to 2.47 percentage points]) and low (1.37 percentage points [CI, −2.40 to 5.14 percentage points]) DAPT score groups were less pronounced (*P* for interaction = 0.33). In contrast, the greater harmful effect of prolonged DAPT on the primary safety outcome remained more pronounced in patients with low scores (RD, 2.95 percentage points [CI, 0.72 to 5.18 percentage points])

versus high scores (RD, −0.05 percentage point [CI, −1.86 to 1.76 percentage points]) (*P* for interaction = 0.040). After patients with missing values for left ventricular ejection fraction were excluded, clinical outcomes stratified by score and DAPT duration were consistent with the main analyses (**Appendix Tables 8** and **9**, available at Annals.org). The analysis of safety outcomes after the competing risk for death was accounted for yielded results consistent with those of the main analysis (**Appendix Table 10**, available at Annals.org).

Discussion

The DAPT score integrates ischemic and bleeding risk factors to guide patient selection for optimal duration of therapy in patients free from ischemic or bleeding events who have received DAPT for 1 year after PCI. Similar to the DAPT Study, patients with high and low scores were roughly equally represented in PRODIGY (about 45% and 55%, respectively). We applied the score to unselected patients undergoing PCI and at an earlier time point (6 months) than in the DAPT Study (12 months). Given the findings from PRODIGY, our results suggest that the score may be useful in identifying patients who would derive harm from prolonged DAPT and could therefore be managed with a short course without incurring a higher risk for ischemic events. In addition, our findings suggest that the performance of the DAPT score may vary on the basis of the type of implanted stent. Prolonged therapy was effective in preventing ischemic events only among patients with a high score who received early-generation paclitaxel-eluting stents. However, prolonged DAPT was safe in patients with high scores, regardless of the type of stent received, because it was associated with a risk for bleeding similar to that of short DAPT.

Figure. Risk–benefit assessment of a DAPT score–guided strategy from 6 to 24 mo for the primary efficacy end point (*top*) and the primary safety end point (*bottom*).



DAPT = dual-antiplatelet therapy.

Table 3. Efficacy Outcomes With Prolonged Versus Short DAPT, by DAPT Score

Outcome	DAPT*		Risk Difference (95% CI), *percentage points*
	24 mo (*n* = 450)	≤6 mo (*n* = 434)	
High DAPT score (≥2)			
Death, MI, or CVA	18 (4.2)	26 (6.2)	−2.05 (−5.04 to 0.95)
Death	10 (2.3)	16 (3.8)	−1.50 (−3.81 to 0.81)
Cardiac death	4 (0.9)	9 (2.1)	−1.22 (−2.89 to 0.44)
MI	10 (2.3)	12 (2.9)	−0.59 (−2.72 to 1.54)
Cardiac death, MI, or CVA	12 (2.8)	20 (4.8)	−2.00 (−4.60 to 0.60)
Death or MI	17 (3.9)	25 (6.0)	−2.05 (−4.98 to 0.88)
Cardiac death or MI	11 (2.6)	19 (4.6)	−2.01 (−4.53 to 0.51)
Definite ST	4 (0.9)	5 (1.2)	−0.29 (−1.68 to 1.11)
Definite or probable ST	5 (1.2)	8 (1.9)	−0.79 (−2.47 to 0.89)
Definite, probable, or possible ST	7 (1.6)	17 (4.1)	−2.44 (−4.70 to −0.19)
MI or definite/probable ST	10 (2.3)	12 (2.9)	−0.60 (−2.78 to 1.58)
	DAPT*		
	24 mo (*n* = 537)	≤6 mo (*n* = 549)	
Low DAPT score (<2)			
Death, MI, or CVA	51 (9.8)	36 (6.8)	2.91 (−0.43 to 6.25)
Death	33 (6.3)	27 (5.0)	1.22 (−1.55 to 4.00)
Cardiac death	14 (2.7)	13 (2.5)	0.24 (−1.68 to 2.16)
MI	17 (3.2)	11 (2.1)	1.17 (−0.78 to 3.11)
Cardiac death, MI, or CVA	38 (7.4)	26 (5.0)	2.36 (−0.57 to 5.29)
Death or MI	42 (8.0)	35 (6.6)	1.39 (−1.76 to 4.54)
Cardiac death or MI	26 (5.0)	22 (4.2)	0.80 (−1.75 to 3.36)
Definite ST	1 (0.2)	1 (0.2)	0.01 (−0.52 to 0.53)
Definite or probable ST	3 (0.6)	2 (0.4)	0.20 (−0.63 to 1.04)
Definite, probable, or possible ST	13 (2.5)	15 (2.8)	−0.32 (−2.27 to 1.64)
MI or definite/probable ST	17 (3.3)	11 (2.1)	1.17 (−0.81 to 3.14)

CVA = cerebrovascular accident; DAPT = dual-antiplatelet therapy; MI = myocardial infarction; ST = stent thrombosis.
* Values are numbers of first events and percentages (Kaplan–Meier estimates of cumulative incidence at 24 mo).

In the DAPT Study, patients with high scores who were randomly assigned to continue therapy had fewer myocardial infarctions or stent thrombosis events (2.7% vs. 5.7%; $P < 0.001$) without incurring a significantly increased risk for GUSTO moderate or severe bleeding (1.8% vs. 1.4%; $P = 0.26$). In this high-risk category, prolonged DAPT was also associated with a significant reduction in the risk for myocardial infarction or death (2.7% vs. 5.7%; $P < 0.001$) and in the composite of death, myocardial infarction, or stroke (4.9% vs. 7.6%; $P < 0.001$) (10). Conversely, patients with low scores randomly assigned to prolonged DAPT had a higher risk for moderate or severe bleeding (3.0% vs. 1.4%; $P < 0.001$) without deriving significant benefit in the prevention of myocardial infarction or stent thrombosis (1.7% vs. 2.3%; $P = 0.07$) (10). The test for heterogeneity of the treatment effect yielded a significant interaction for the primary ischemic end point of myocardial infarction or stent thrombosis (P for interaction < 0.001) and GUSTO moderate or severe bleeding (P for interaction = 0.02) (10).

The present study provides additional evidence on use of the DAPT score in a less selective PCI population, in which randomization to DAPT duration was performed at 1 month without a priori knowledge about tolerability of a 12-month DAPT course (as was the case in the DAPT Study). In addition, although the DAPT Study excluded patients who had a major ischemic or bleeding event during the first year after PCI (8), PRODIGY had few exclusion criteria.

Long-term management of patients with established coronary artery disease should be targeted not only to secondary prevention of ischemic events but also to bleeding prevention given its independent association with mortality. An analysis of the ADAPT-DES (Assessment of Dual Antiplatelet Therapy with Drug-Eluting Stents) study showed that bleeding after hospital discharge occurs in nearly 7% of patients undergoing PCI within 2 years and is associated with a 5-fold increase in the adjusted risk for all-cause death (19). The primary safety outcome of this study was BARC type 3 or 5 bleeding, which has the potential to capture a greater proportion of clinically significant bleeding events than the GUSTO and TIMI criteria while maintaining the same prognostic value of bleeding on mortality (20). We found that DAPT for 6 months in patients with low scores was associated with an absolute difference of approximately 2.5 percentage points in BARC type 3 or 5 bleeding, with consistent findings when the GUSTO and TIMI criteria were applied. Dual-antiplatelet therapy for 6 instead of 24 months did not increase the risk for ischemic events in patients with low, suggesting that it could be implemented earlier (such as 6 months) to identify patients at high bleeding risk (score <2) in whom DAPT can be safely interrupted. Such a strategy could apply to a relevant proportion of patients undergoing PCI because at least 50% of patients included in the DAPT Study and PRODIGY had a low DAPT score, and roughly 20% of patients had been

excluded from the DAPT Study due to an intercurrent bleeding event before 12 months.

Among patients with high scores, our findings on the safety profile of DAPT are in line with the DAPT Study, as no increased bleeding risk was observed with prolonged DAPT. Of note, the cumulative incidence of BARC type 3 or 5 bleeding at 24 months was about 1% in both the prolonged and the short DAPT groups, suggesting that patients with high scores may be less susceptible to bleeding complications, regardless of DAPT duration. However, we believe that the issue of whether prolonged DAPT is beneficial in the subgroup of patients with high scores requires further investigation.

When analyzing the efficacy of prolonged DAPT in patients with high scores, we found evidence for an interaction between duration and the type of stent implanted. Prolonged DAPT in patients treated with paclitaxel-eluting stents resulted in significant absolute reductions of 7.55 percentage points in the risk for the primary ischemic outcome and 6.85 percentage points in the composite outcome of cardiac death or myocardial infarction. In contrast, there was no sign of a beneficial effect of prolonged DAPT for other types of coronary stents, even though CIs were wide. Paclitaxel-eluting stents are no longer used in clinical practice and have been superseded by new-generation drug-eluting stents because of safety concerns. Several trials and meta-analyses have shown a higher risk for stent thrombosis and myocardial infarction with paclitaxel-eluting stents than with bare-metal stents and new-generation drug-eluting stents (21–23). When data were analyzed after patients allocated to receive paclitaxel-eluting stents were excluded, interaction testing between DAPT duration and score categories was no longer significant for ischemic outcomes. This is consistent with a sensitivity analysis performed within the DAPT Study, where interaction testing for myocardial infarction or stent thrombosis was also no longer significant when only patients treated with new-generation everolimus-eluting stents were evaluated (10).

The results of this study should be interpreted in view of several limitations. First, although all variables included in the DAPT score were prospectively collected, the score was not available at enrollment and was therefore retrospectively calculated. Second, few ischemic events occurred and risk estimates were im-

Table 4. Safety Outcomes With Prolonged Versus Short DAPT, by DAPT Score

Outcome	DAPT*		Risk Difference (95% CI), *percentage points*
	24 mo (*n* = 450)	**≤6 mo (*n* = 434)**	
High DAPT score (≥2)			
BARC criteria			
Type 3 or 5 bleeding	5 (1.2)	4 (1.0)	0.20 (−1.20 to 1.60)
Type 2 bleeding	11 (2.6)	4 (1.0)	1.59 (−0.20 to 3.38)
Type 3 bleeding	5 (1.2)	4 (1.0)	0.20 (−1.20 to 1.60)
Type 2 or 3 bleeding	16 (3.8)	8 (2.0)	1.79 (−0.47 to 4.06)
Type 2, 3, or 5 bleeding	16 (3.8)	8 (2.0)	1.79 (−0.48 to 4.05)
TIMI criteria			
Minor or major bleeding	5 (1.2)	4 (1.0)	0.20 (−1.20 to 1.60)
Minor bleeding	5 (1.2)	4 (1.0)	0.21 (−1.19 to 1.60)
Major bleeding	0 (0)	0 (0)	−0.01 (−0.02 to 0)
GUSTO criteria			
Moderate or severe bleeding	4 (0.9)	3 (0.7)	0.20 (−1.03 to 1.44)
Moderate bleeding	5 (1.2)	3 (0.7)	0.44 (−0.88 to 1.76)
Severe bleeding	0 (0)	0 (0)	−0.01 (−0.02 to 0)
	DAPT*		
	24 mo (*n* = 537)	**≤6 mo (*n* = 549)**	
Low DAPT score (<2)			
BARC criteria			
Type 3 or 5 bleeding	19 (3.7)	6 (1.1)	2.58 (0.71 to 4.46)
Type 2 bleeding	18 (3.6)	6 (1.1)	2.42 (0.58 to 4.26)
Type 3 bleeding	13 (2.6)	5 (0.9)	1.61 (0.01 to 3.21)
Type 2 or 3 bleeding	31 (6.2)	11 (2.1)	4.10 (1.67 to 6.53)
Type 2, 3, or 5 bleeding	37 (7.4)	12 (2.3)	5.07 (2.46 to 7.69)
TIMI criteria			
Minor or major bleeding	14 (2.7)	4 (0.8)	1.97 (0.37 to 3.56)
Minor bleeding	4 (0.8)	3 (0.6)	0.21 (−0.79 to 1.20)
Major bleeding	10 (2.0)	1 (0.2)	1.76 (0.50 to 3.01)
GUSTO criteria			
Moderate or severe bleeding	18 (3.5)	5 (1.0)	2.57 (0.77 to 4.38)
Moderate bleeding	8 (1.6)	3 (0.6)	1.00 (−0.25 to 2.25)
Severe bleeding	10 (2.0)	2 (0.4)	1.57 (0.26 to 2.88)

BARC = Bleeding Academic Research Consortium; DAPT = dual-antiplatelet therapy; GUSTO = Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries; TIMI = Thrombolysis in Myocardial Infarction.
* Values are numbers of first events and percentages (Kaplan-Meier estimates of cumulative incidence at 24 mo).

precise. Third, several differences exist with respect to study design between PRODIGY and the DAPT Study. Patients included in the DAPT Study had to demonstrate the ability to tolerate 12 months of therapy without ischemic or bleeding complications, whereas randomization to DAPT in PRODIGY occurred 1 month after PCI and inclusion criteria were less restrictive. Moreover, duration differed between the trials—the DAPT Study randomly assigned patients to 12- versus 30-month DAPT, whereas PRODIGY randomly assigned patients to 6- versus 24-month DAPT. Despite these differences, evaluation of the score in a different population may support expanding the clinical application of this tool by adding novel information on its external validity. Fourth, although the interaction by stent type should be carefully interpreted because of the relatively small number of patients included in each stratum, in PRODIGY, unlike the DAPT Study, the type of stent was as per random allocation. Fifth, the applicability of the DAPT score to patients with high bleeding risk who may have been excluded from both trials remains unclear. Finally, left ventricular ejection fraction was imputed for 136 patients; however, a sensitivity analysis that excluded these patients showed consistent results.

In conclusion, our study supports the use of the DAPT score for unselected patients undergoing PCI to identify those who are at higher risk for bleeding and concomitantly less likely to derive benefit from prolonged therapy. The DAPT score correctly identified patients deriving benefit and no harm from prolonged therapy when patients receiving a paclitaxel-eluting stent were evaluated, but not when they were excluded in a sensitivity analysis. Further validation of the DAPT score is therefore needed in a large contemporary cohort of patients treated with newer-generation drug-eluting stents.

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Reproducible Research Statement: *Study protocol:* Available from Dr. Valgimigli (e-mail, marco.valgimigli@insel.ch). *Statistical code:* Available from Dr. Piccolo (e-mail, raffaele.piccolo@insel.ch). *Data set:* Not available.

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EDITORIAL COMMENT

DAPT Duration After Drug-Eluting Stent Implantation

No News Is Good News*

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This year, percutaneous coronary intervention (PCI) is living its 40th anniversary, which indicates the coming of age of a technique that has achieved low procedural risks and excellent clinical outcomes, providing similar (if not superior) results as compared with conventional coronary bypass surgery in many patient/lesion subsets.

The advent of coronary stents greatly contributed to make the results of PCI predictable, satisfactory, and durable. The risk of thrombotic stent occlusion led to the development of dual antiplatelet therapy (DAPT), which was originally conceived as a dedicated treatment regimen to prevent stent thrombosis (ST), a serious limitation of stent implantation.

Twenty years after the first study ascertained the efficacy of DAPT for ST prevention (1), and roughly 10 years after durable DAPT was mandated by consensus to avert the risks of very-late ST (2), DAPT investigations have reached a mature state, to which the 2-year results of the ITALIC (Is There a Life for Drug Eluting Stent (DES) After Discontinuation of Clopidogrel) study nicely contributes (3). The current evidence shows that there can be safe drug-eluting stent (DES) implantation without prolonged DAPT and that there is value for prolonged DAPT in some cases of DES implantation (**Table 1**).

Trials have explored the potential to safely reduce DAPT duration to 3 to 6 months and showed the noninferiority of this approach compared with 12 months DAPT (4). Recently, in high bleeding-risk patients, even 1-month DAPT was shown to be safe and effective after new-generation DES implantation as compared with bare-metal stents (5,6). By contrast, other randomized clinical trials have shown benefits, even if at greater bleeding risk, of a DAPT regimen longer than 12 months (ranging from 18 to 48 months) as compared with 6- or 12-month therapy (4).

The ITALIC trial adds fuel to this complex panorama, suggesting that 6-month DAPT is noninferior to longer DAPT. The trial was designed and powered to demonstrate the noninferiority of 6- versus 12-month DAPT at 1 year for the primary net composite endpoint of all-cause mortality, myocardial infarction (MI), target vessel revascularization, stroke, or major bleeding, and indeed supported that rates of bleeding and thrombotic events at 1 year were much the same in both treatment groups (7).

SEE PAGE 1202

In this issue of *JACC: Cardiovascular Interventions*, Didier et al. (3) present the 2-year clinical outcomes in aspirin-responsive patients treated with 6- or 24-month DAPT after second-generation DES in the ITALIC trial. Therefore, this study adds new, clinically relevant findings. The investigators report that the composite endpoint, as well as individual rates of MI and stroke, were similar between the groups, though there were nonsignificant trends toward lower ST (0.3% vs. 0.6%; $p = 0.33$) and target vessel revascularization (0.3% vs. 1.0%; $p = 0.10$) at costs of higher mortality (2.2% vs. 1.2%; $p = 0.11$) and major bleeding (0.4% vs. 0%) in the 24-month group.

Importantly, whereas patients were randomly allocated to the 2 DAPT durations at the time of PCI,

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TABLE 1 Trials Testing DAPT Regimens Longer Than 12 Months

Trial Name	N	Treatment Duration, Months	Stent Type	Primary Endpoint
ARCTIC INTERRUPTION	1,259	17 vs. 12	EES, PES, SES, ZES, other DES	Superiority of prolonged DAPT not demonstrated
DAPT	9,961	30 vs. 12	EES, PES, SES, ZES	Superiority of prolonged DAPT demonstrated
DES-LATE	5,045	12 vs. 36	EES, PES, SES, ZES, other DES	Superiority of shorter DAPT not demonstrated
ITALIC	1,850*	6 vs. 24	EES	Noninferiority of shorter DAPT demonstrated, but prematurely stopped
NIPPON	3,307†	6 vs. 18	BES	Noninferiority of shorter DAPT demonstrated (preliminary data), but prematurely stopped
OPTIDUAL	1,385‡	48 vs. 12	EES, PES, SES, ZES, other DES	Superiority of prolonged DAPT not demonstrated, but prematurely stopped
PRODIGY	1,970	24 vs. 6	BMS, EES, PES, ZES	Superiority of prolonged DAPT not demonstrated

*Of the 2,475 patients initially planned. †Of the 4,598 patients initially planned. ‡Of the 1,966 patients initially planned.

ARCTIC INTERRUPTION = Assessment by a double Randomisation of a Conventional antiplatelet strategy versus a monitoring-guided strategy for drug-eluting stent implantation and, of Treatment Interruption versus Continuation 1 year after stenting-Interruption; BES = biolimus A9-eluting stent(s); BMS = bare-metal stent(s); DAPT = dual antiplatelet therapy; DES = drug-eluting stent(s); DES-LATE = Optimal Duration of Clopidogrel Therapy With Drug Eluting Stents to Reduce Late Coronary Arterial Thrombotic Events; EES = everolimus-eluting stent(s); ITALIC = Is There a Life for Drug Eluting Stent (DES) After Discontinuation of Clopidogrel; NIPPON = Nobori Dual Antiplatelet Therapy as Appropriate Duration; OPTIDUAL = Optimal Duration of Dual Antiplatelet Therapy After Drug-Eluting Stent Implantation; PES = paclitaxel-eluting stent(s); PRODIGY = Prolonging Dual Antiplatelet Treatment in Patients With Coronary Artery Disease After Graded Stent-Induced Intimal Hyperplasia Study; SES = sirolimus-eluting stent(s); ZES = zotarolimus-eluting stent(s).

only those event-free at 6 months from PCI entered the study. Although direct randomization at 6 months would have been preferable from a methodological standpoint, this study design excludes the confounding or chance effect eventually observed in the first 6 months, when all patients receive the same antiplatelet regimen.

Overall, the noninferiority of shorter DAPT and absence of benefits with longer DAPT should be interpreted in the context of the study itself.

First, 2-year follow-up was performed in 94% of patients, and there was suboptimal adherence to treatment assignment: in the 6-month DAPT group, 212 patients (23.2%) failed to respect treatment duration (9 stopped before 6 months; 123 were on DAPT after 6 months, but not at 24 months; and 80 remained on DAPT after 24 months), whereas in the 24-month DAPT group, 170 patients (18.7%) discontinued treatment before 24 months.

Second, the findings reported apply to clopidogrel-treated patients, not to patients receiving ticagrelor or prasugrel.

Third, included patients were at low ischemic and bleeding risk, which could have mitigated benefits and risks of longer DAPT. Overall, event rates were low, even more than expected (primary endpoint at 1 year was postulated to occur in 3%, but was 1.6%). The unique study design (selecting aspirin-responders) may have contributed to the low event rates. Although the high-risk acute coronary syndrome (ACS) subgroup did not show particular benefit from prolonged DAPT, there was a significant interaction for the composite endpoint between patients with or without prior MI (patients with prior MI showed a borderline significant benefit from 24-month DAPT) that is in agreement with previous data (8). It should be appreciated that the ACS subgroup analysis is underpowered, especially considering the premature treatment interruption and low event rates. There was a significant interaction in age-based subgroups, showing that elderly patients did benefit from shorter DAPT. On the other hand, patients with diabetes did not benefit from longer DAPT, as previously shown (9).

The present findings support those previously observed in PRODIGY (Prolonging Dual Antiplatelet Treatment in Patients With Coronary Artery Disease After Graded Stent-Induced Intimal Hyperplasia Study), which also compared 6- versus 24-month DAPT but included a population at higher ischemic/bleeding risk (older age, higher rates of patients with prior MI, with ACS, with ST-segment elevation MI, with chronic renal disease) and with higher overall event rates (net composite 11.3% compared with 3.6% in the ITALIC trial) (10).

Notably, the authors report a 45% increase of all-cause death with 24-month DAPT, whereas cardiac death was similar between groups. This finding is obviously underpowered and inconclusive. However, it contributes to the concerning signal previously

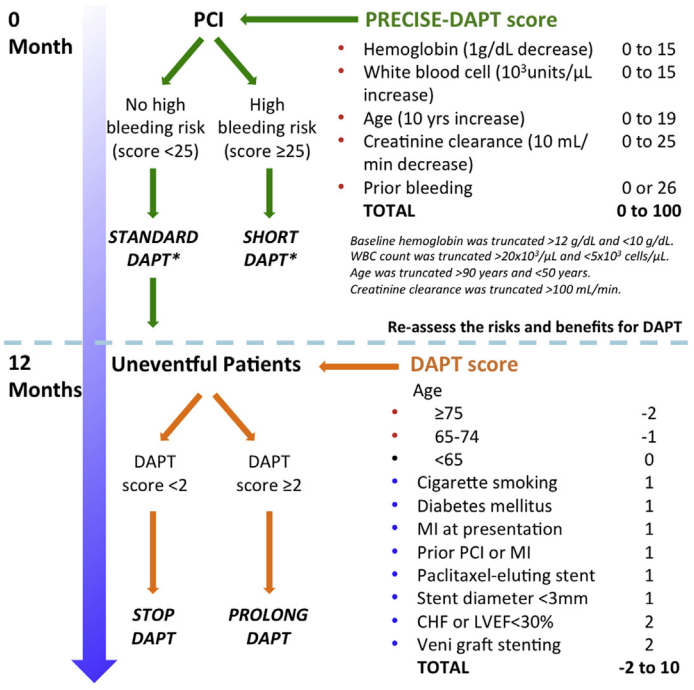
reported for long-term DAPT, which seems to mainly affect noncardiac mortality (11,12).

Altogether, the results of the ITALIC trial fit well with previous evidence and contribute to the current understand of the benefits and risks of prolonged DAPT. New-generation DES are associated with a very low risk of late and very late ST. Therefore, prolonging DAPT because of DES implantation per se does not seem to be justified in an unselected patient population undergoing PCI for stable or unstable coronary artery disease. In this setting, the risk of major bleeding associated with prolonged DAPT roughly equals the benefits in terms of MI prevention, but it largely exceeds the tiny absolute risk reduction in ST.

Consequently, the real question becomes: in which patients to prolong DAPT? For this purpose, 2 scores, the DAPT (13) and PRECISE-DAPT (Predicting Bleeding Complications in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy) (14), have been recently generated and have demonstrated the potential to support clinicians in this delicate decision making. The DAPT score aims at maximizing the benefits over the risks of a prolonged DAPT regimen by integrating predictors of ischemic events (which favor a prolonged DAPT duration) and bleeding (which play against the decision of prolonging DAPT), and should be calculated after 1 year of uneventful DAPT therapy, to decide whether to stop or prolong the treatment. PRECISE-DAPT focuses on bleeding risk only, should be computed soon after PCI, and identifies patients who had, not only bleeding events, but also ischemic recurrences, are lower if treated with a relatively shorter (i.e., 3 to 6 months) DAPT regimen (14). Although both are awaiting large-scale prospective validation, these 2 new decision-making tools should raise awareness in the community on which criteria should influence treatment duration and which characteristics should not (**Figure 1**).

In summary, the 2-year results of the ITALIC study do not generate news on the delicate tradeoff between benefits and risks of prolonging DAPT among DES-treated patients. Because confirmation and replication of study results are a mainstay of science, the absence of news is definitively good news for the interventional community, which is now confronted with the new challenge to tailor DAPT duration to patients' characteristics more than to the implanted coronary devices' characteristics.

FIGURE 1 Use of PRECISE-DAPT and DAPT Scores for Decision-Making of DAPT Duration



Variables included in the scores are associated with increased bleeding risk **(red dots)**, increased ischemic risk **(blue dots)**, or neutral effect **(black dots)**. *In the validation study, short-term DAPT consisted of 3 to 6 months of therapy, and standard DAPT consisted of at least 12-month DAPT duration. CHF = congestive heart failure; DAPT = dual antiplatelet therapy; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PCI = percutaneous coronary intervention; PRECISE-DAPT = Predicting Bleeding Complications in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy.

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KEY WORDS bleeding event(s), drug-eluting stent(s), dual antiplatelet therapy, ischemic event(s), percutaneous coronary intervention

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EDITORIAL COMMENT

To EncourAGE Individualized Dual Antiplatelet Therapy Duration After Drug-Eluting Stent Implantation

A New pAGE of an Intriguing Book*

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Dual antiplatelet therapy (DAPT) is an evidence-based, guideline-recommended, standard-of-care treatment after percutaneous coronary intervention (PCI) (1). Nevertheless, the optimal treatment duration of DAPT remains controversial (1,2). Although DAPT has showed to be highly effective in preventing stent thrombosis (ST) during follow-up, as well as non-stent-related myocardial infarction (MI) and stroke, the increased risk of bleeding is not negligible and has relevant impact on prognosis (1-3). It is now clear that a "one-size-fits-all" approach to balance ischemic and bleeding risks is not applicable; therefore, individualization of DAPT therapy is a key measure and includes the identification of risk factors for ischemic and bleeding events helping to weigh risks against the potential benefits of DAPT prolongation (1,2). Tailored therapy should be based on clinical and procedural considerations, as well as dedicated, clinical risk scores that might better advise the decision making in the context of a comprehensive clinical evaluation. Although some subgroups of patients undergoing drug-eluting stent (DES) implantation have shown to benefit from longer DAPT (i.e., prior MI, acute coronary syndrome [ACS] at presentation, complex PCI, or peripheral arterial disease), others may not (i.e., female, diabetic, chronic kidney disease, elderly, and high-bleeding risk patients) (1,2,4-6).

Elderly individuals represent a growing proportion of patients with coronary artery disease undergoing PCI because of aging of the population with increased life expectancy. Nonetheless, extrapolating findings from randomized trials to elderly patients is challenging because such patients have been underrepresented in these studies and are characterized by peculiar bleeding or ischemic risks.

In PRODIGY (PROlonging Dual-antiplatelet treatment after Grading stent-induced Intimal hyperplasia studY) trial, elderly patients experienced a greater risk of both ischemic and bleeding events, with risk trajectories proceeding similarly with aging (6). In both elderly and nonelderly individuals, DAPT prolongation (24 months) did not reduce the risk of the primary efficacy endpoint of death, MI, or cerebrovascular accidents, and rather increased the risk of Bleeding Academic Research Consortium (BARC) type 2, 3, or 5 (the relative magnitude of treatment effect on bleeding was similar between age subgroups, but the absolute risk difference with prolonged DAPT was greater in elderly compared with nonelderly patients) compared with 6-month DAPT. This suggested that elderly individuals were probably more prone to benefit from a shorter DAPT compared with their younger counterparts. Notably, a treatment by age heterogeneity for the primary endpoint according to age has been observed in ISAR-SAFE (Intracoronary Stenting and Antithrombotic Regimen: Safety And EFficacy of 6 Months Dual Antiplatelet Therapy After Drug-Eluting Stenting) (interaction $p = 0.03$), IVUS-XPL (Impact of Intravascular Ultrasound Guidance on Outcomes of Xience Prime Stents in Long Lesions) (interaction $p = 0.051$), and ITALIC (Is There A LIfe for

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TABLE 1 Age Subgroups in Randomized Clinical Trials Comparing Short (3–6 Months) Versus Long (≥12 Months) DAPT After PCI

Trial	Design	Primary Endpoint	Mean Age (yrs)	Elderly*	Age Subgroups	Interaction p Value
RESET	3 vs. 12	Cardiovascular death, MI, ST, ID-TVR, bleeding	62	46%	<65 yrs of age: 4.4% vs. 4.5% ≥65 yrs of age: 5.1% vs. 4.8%	0.599
OPTIMIZE	3 vs. 12	All-cause death, MI, stroke, major bleeding	62	NA	NA	NA
EXCELLENT	6 vs. 12	Cardiac death, MI, ID-TVR	63	47%	<65 yrs of age: HR 1.61 (95% CI: 0.78–3.31) ≥65 yrs of age: HR 0.83 (95% CI: 0.42–1.65)	0.19
SECURITY	6 vs. 12	Cardiac death, MI, stroke, ST, BARC 2, 3, or 5 bleeding	65	NA	NA ≥75 yrs of age was predictor of the primary endpoint at the multivariable analysis	NA
ISAR-SAFE	6 vs. 12	All-cause death, MI, ST, stroke, major bleeding	67	50%	<67.2 yrs of age: HR 2.02 (95% CI: 0.81–4.99) ≥67.2 yrs of age: HR 0.60 (95% CI: 0.31–1.13)	0.03
I-LOVE-IT 2	6 vs. 12	All-cause death, MI, stroke, major bleeding	60	32%	<65 yrs of age: RR 1.02 (95% CI: 0.66–1.60) ≥65 yrs of age: RR 1.12 (95% CI: 0.71–1.76)	0.79
IVUS-XPL	6 vs. 12	Cardiac death, MI, stroke, major bleeding	64	46%	≤65 yrs of age: HR 6.50 (95% CI: 0.80–52.81) >65 yrs of age: HR 0.67 (95% CI: 0.28–1.62)	0.051
PRODIGY	24 vs. 6	All-cause death, MI, CVA	68	63%/30%	<65 yrs of age: HR 0.57 (95% CI: 0.28–1.16) ≥65 yrs of age: HR 1.12 (95% CI: 0.82–1.51) <75 yrs of age: HR 1.48 (95% CI: 0.95–2.30) ≥75 yrs of age: HR 0.80 (95% CI: 0.55–1.16)	0.09/0.036
ITALIC	6 vs. 24	All-cause death, MI, stroke, urgent TVR, major bleeding	62	14%	<75 yrs of age: NA ≥75 yrs of age: HR 0.35 (95% CI: 0.11–1.09)	0.048
NIPPON	6 vs. 18	All-cause death, MI, stroke, major bleeding	67	21%	≤75 yrs of age: 1.5% vs. 1.5% >75 yrs of age: 3.8% vs. 1.4%	0.15
DAPT-STEMI†	6 vs. 12	All-cause death, MI, stroke, any revascularization, major bleeding	60	NA	Not available	NA
REDUCE†	3 vs. 12	All-cause death, MI, ST, stroke, TVR, major bleeding	61	13%	<75 yrs of age: OR 0.85 (95% CI: 0.56–1.28) ≥75 yrs of age: OR 1.66 (95% CI: 0.71–3.86)	0.16

*Percentage of elderly patients reported is based on the age cutoff used in the study. †Data from TCT 2017 presentations.

BARC = Bleeding Academic Research Consortium; CI = confidence interval; CVA = cerebrovascular accident; DAPT = dual antiplatelet therapy; DAPT-STEMI = Six versus twelve month dual antiplatelet therapy after drug-eluting stent implantation in ST-elevation myocardial infarction; EXCELLENT = Efficacy of Xience/Promus Versus Cypher in rEducing Late Loss After stENTing; HR = hazard ratio; I-LOVE-IT 2 = Evaluate Safety and Effectiveness of the Tivoli DES and the Firebird DES for Treatment of Coronary Revascularization; ID-TVR = ischemia-driven target vessel revascularization; ISAR-SAFE = Intracoronary Stenting and Antithrombotic Regimen: Safety And EFficacy of 6 Months Dual Antiplatelet Therapy After Drug-Eluting Stenting; ITALIC = Is There A LIfe for DES after discontinuation of Clopidogrel; IVUS-XPL = Impact of Intravascular Ultrasound Guidance on Outcomes of Xience Prime Stents in Long Lesions; MI = myocardial infarction; NIPPON = Nobori Dual Antiplatelet Therapy as Appropriate Duration; NA = not available; OPTIMIZE = Optimised Duration of Clopidogrel Therapy Following Treatment with the Endeavor Zotarolimus-Eluting Stent in Real-World Clinical Practice; OR = odds ratio; PCI = percutaneous coronary intervention; PRODIGY = PROlonging Dual-antiplatelet treatment after Grading stent-induced Intimal hyperplasia studY; REDUCE = Randomized Evaluation of Short-term DUal Anti Platelet Therapy in Patients With Acute Coronary Syndrome Treated With the COMBO Dual-therapy stEnt; RESET = REal Safety and Efficacy of 3-month dual antiplatelet Therapy following Endeavor zotarolimus-eluting stent implantation; RR = relative risk; SECURITY = Second-generation Drug-eluting Stent Implantation Followed by 6- versus 12-month dual antiplatelet therapy; ST = stent thrombosis.

DES after discontinuation of Clopidogrel) trials (interaction p = 0.048 at 2 years) favoring the use of short-term DAPT in elderly rather than younger patients (Table 1). It should be noted, however, that the primary endpoint in these latter trials included a composite of ischemic and bleeding events, which makes difficult to completely assess the risk-benefit ratio associated with DAPT in elderly patients. In line with this evidence, age is a predominant risk factor for bleeding in both the PRECISE-DAPT (PREdicting bleeding Complications In patients undergoing Stent implantation and subsEquent Dual Anti Platelet Therapy) score and the DAPT score, supporting that, in the absence of high ischemic risk, a shorter DAPT may be desirable (1).

SEE PAGE 435

In this issue of *JACC: Cardiovascular Interventions*, Lee et al. (7) explored the impact of age in an individual participant data meta-analysis of randomized clinical trials where they compared 3 to 6 month DAPT versus 12-month DAPT after PCI with DES implantation. The authors pooled 6 trials encompassing 11,473 patients of whom 42% presented with ACS and 90% received newer-generation DES. Overall they observed that a 3- to 6-month DAPT regimen was as effective as but safer than 12-month DAPT duration. When exploring age-based subgroups (using 65 years of age as cutoff) they observed that shorter DAPT, as compared with longer DAPT, was noninferior in terms of the ischemic composite of MI, ST, or stroke in elderly patients (n = 5,319, 46.4%), but inferior in younger patients with a significant p value for interaction. A shorter DAPT reduced the risk of bleeding compared with longer DAPT irrespective of age (negative interaction); however, this benefit was statistically significant in elderly but not in younger patients. Thus, the authors concluded that elderly

patients might be those with the highest advantage of shortening DAPT within 1 year of PCI.

The authors should be commended for this interesting study, which adds new relevant insights into the decision making on DAPT duration within 1 year after DES implantation. In the era where DAPT duration is going to be individualized more than generalized, ciphering the impact of specific factors, such as age, in such a large population from randomized trials may help clinical practice.

The definition of elderly individuals is not universal. In LEADERS-FREE (Prospective Randomised Comparison of the BioFreedom Biolimus A9 Drug-Coated Stent Versus the Gazelle Bare-Metal Stent in Patients at High Bleeding Risk) and ongoing MASTER-DAPT (Management of High Bleeding Risk Patients Post Bioresorbable Polymer Coated Stent Implantation With an Abbreviated Versus Prolonged DAPT Regimen) trials, patients are defined at high bleeding risk if ≥75 years of age, and in the ZEUS (Zotarolimus-eluting Endeavor sprint stent in Uncertain DES candidates) trial if >80 years of age, and the age cutoff is heterogeneous also among different DAPT trials (**Table 1**). Regarding the DAPT score, patients with 65 to 74 years of age and ≥75 years of age have -1 and -2 points, respectively (1). With the PRECISE-DAPT score, where age is considered continuously, the greater the age is, and the greater the bleeding risk is. For example, in a patient with no prior bleeding, normal values of hemoglobin and white blood cells and a creatinine clearance of 60 ml/min, 65, 75, 80, 85, and 90 years of age are associated with 17, 22, 24, 27, and 29 points, respectively (1). Here, Lee et al. (7) used the cutoff of 65 years of age that was the prespecified one selected in previous analyses from the same dataset. Interestingly, the authors also analyzed the risk of primary outcome (MI, ST, or stroke) with short-term DAPT according to the quintiles of age, showing that the risk tended to be reduced with increasing age, and that 65 years of age was around a tradeoff point among changes of the risk. They also provided an additional analysis using the cutoff of 75 years of age (elderly n = 1,716, 15%) where the overall tendency regarding the differential effect of DAPT strategy on age remained, but was attenuated and the significant heterogeneity disappeared (interaction p = 0.36). However, this was probably attributable to the mitigation of the effect and power of the main analysis by moving from the elderly to the younger group a large proportion of patients (those of 65 to 75 years of age were roughly 30% of the population) with a different risk of primary endpoint.

One could wonder why the primary endpoint of this analysis is an uncommon composite of MI, ST, or stroke, which did not include cardiac or all-cause death. When looking at numbers, both all-cause and cardiac death were similar between 3- to 6-month and 12-month DAPT groups in elderly patients, but significantly reduced by shorter DAPT in nonelderly patients (being thus in opposition to what observed for ischemic events and leading to different results if included in the primary endpoint). This was assumed to be a chance finding, probably clarifying why composite endpoints with mortality were not analyzed.

The efficacy and safety of shortening DAPT duration after DES implantation in elderly people is in agreement with data from LEADERS-FREE and ZEUS trials (high bleeding risk patients treated with 1-month DAPT), and with the recent SENIOR (Drug-eluting stents in elderly patients with coronary artery disease) trial (elderly: ≥75 years of age; DAPT 1 month or 6 months in stable or ACS patients, respectively) (8).

As for similar studies, the relevance of these findings and their applicability to daily practice should be interpreted with caution and in light of the characteristics of the included patients. First, almost all patients received a clopidogrel-based DAPT, and hence, these results cannot be extended to prasugrel- or ticagrelor-treated patients who represent a large proportion of contemporary PCI patients. Second, the results cannot be extended to all types of DES because zotarolimus- and everolimus-eluting stents were more commonly implanted in this population. Third, this population was characterized by an overall low risk of bleeding at 1 year (1.5% and 0.6% of all and major bleeding, respectively); therefore, the observation that a 12-month DAPT offers more ischemic benefits than bleeding risks in younger patients may not apply to a different population with higher bleeding risk. Fourth, patients presenting with ACS were 42% (n = 2,251 among elderly) the majority of whom (67.0%) had unstable angina, and in a previous analysis of this population a 3-month DAPT was associated with higher risk of ischemic events in ACS but not in stable patients (9); thus, based on the present study only, a shorter DAPT cannot be recommended to all elderly patients irrespective of clinical presentation (particularly if high-risk ACS). Fifth, definition of some clinical endpoints differed slightly across trials, potentially introducing effect modifiers. Last, although the present study includes individual participant data from a very large population, there are some trials missing (**Table 1**) and the findings need to be confirmed.

The optimal duration of DAPT after DES implantation has been extensively investigated but remains debated. To maximize treatment benefits over risks, there is currently agreement that DAPT duration

should be tailored on a patient-by-patient basis taking into account (dynamically) individual risk factors and scores. On this scenario, the present study adds a new step forward, showing that in elderly persons a short-term DAPT may minimize the risk of bleeding without increasing the ischemic risk within 1 year from PCI.

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KEY WORDS age, DAPT, drug-eluting stent(s), elderly, individualized therapy

Part 3

Trade-off for ischemia and bleeding and optimal clinical outcomes during and after transcatheter aortic valve implantation (TAVI):

Optimal antithrombotic therapy during and after TAVI

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Antithrombotic therapy in TAVI patients: changing concepts

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- anticoagulant
- antiplatelet
- antithrombotic therapy
- transcatheter aortic valve implantation (TAVI)

Abstract

The clinical and demographic characteristics of patients undergoing TAVI pose unique challenges for developing and implementing optimal antithrombotic therapy. Ischaemic and bleeding events in the periprocedural period and months after TAVI still remain a relevant concern to be faced with optimised antithrombotic therapy. Moreover, the antiplatelet and anticoagulant pharmacopeia has evolved significantly in recent years with new drugs and multiple possible combinations. Dual antiplatelet therapy (DAPT) is currently recommended after TAVI with oral anticoagulation (OAC) restricted for specific indications. However, atrial fibrillation (which is often clinically silent and unrecognised) is common after the procedure and embolic material often thrombin-rich. Recent evidence has therefore questioned this approach, suggesting that DAPT may be futile compared with aspirin alone and that OAC could be a relevant alternative. Future randomised and appropriately powered trials comparing different regimens of antithrombotic therapy, including new antiplatelet and anticoagulant agents, are warranted to increase the available evidence on this topic and create appropriate recommendations for this frail population. Meanwhile, it remains rational to adhere to current guidelines, with routine DAPT and recourse to OAC when specifically indicated, whilst always tailoring therapy on the basis of individual bleeding and thromboembolic risk.

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Pathophysiology

Calcific aortic stenosis (AS) is the most frequent manifestation of valvular heart disease in the elderly, and its prevalence continues to grow as our population ages. Transcatheter aortic valve implantation (TAVI) has become the therapy of choice for patients with severe AS who are deemed to be inoperable or at high risk for conventional surgical aortic valve replacement (SAVR). The application of TAVI in patients at low to intermediate risk is currently being investigated and it is therefore feasible that the procedure will be offered to an increasing number of patients in the near future.

Like all other vascular interventional or surgical procedures, TAVI carries thrombotic stroke, myocardial infarction or systemic embolism and periprocedural bleeding risks. Importantly, the thrombotic risk also extends during follow-up, particularly in the presence of atrial fibrillation (AF).

The risk of stroke is highest in the periprocedural period owing to the mechanics of valve positioning and implantation[1]. Indeed, stenotic aortic valves, unlike normal aortic valve leaflets, are characterised by large amounts of tissue factor and thrombin that increase inflammation and thrombogenicity. Unlike SAVR, the diseased native valve remains *in situ* during (and after) TAVI and may be mechanically damaged, leading to the exposure and/or embolism of valvular components into the arterial circulation. Additionally, insertion of a prosthesis without removal of the diseased aortic valve creates an irregular zone around the valve frame with modified flow patterns that may predispose to thrombus formation, particularly in the case of small valve sizes with associated patient–prosthesis mismatch. It has been demonstrated that cerebral emboli associated with TAVI can be composed of thrombotic or calcific atherosclerotic material. It remains unclear whether the stroke potential of these two subtypes of embolic material is alike. Importantly, TAVI patients remain at risk of stroke throughout the first months after the procedure. In these patients, mechanisms other than valve manipulation seem to be involved, such as aortic wall injury, post-traumatic surface exposure with consequent activation of the haemostatic system, turbulence or local blood stasis. In addition to the prothrombotic environment related to valve implantation and procedure-related aortic damage, roughly one third of TAVI patients have pre-existing AF and a further variable percentage (ranging from 1-30%) experience new-onset post-procedural AF, which is known to increase the risk of thrombotic complications further[2].

The choice of antithrombotic therapy

Against this background, establishing the optimal antithrombotic therapy for TAVI patients remains a challenge, largely due to the lack of properly powered studies to inform practice. Unfractionated heparin (UFH) is the most common method of anticoagulation during the procedure. In the PARTNER study, UFH was administered as a parenteral bolus of 5,000 IU followed by additional doses to achieve an activated clotting time (ACT) ≥250 s. A subsequent American consensus document recommended a target ACT ≥300 s with reversal of UFH following the procedure with protamine sulphate at a milligram-to-milligram neutralisation dose. The role of bivalirudin instead of UFH remains unclear and is currently being investigated in the ongoing multicentre open-label pilot study BRAVO 2/3 (Effect of Bivalirudin on Aortic Valve Intervention Outcomes 2/3), randomising 870 patients to bivalirudin or UFH (NCT01651780).

Adequately powered studies addressing the optimal antithrombotic therapy after TAVI are non-existent. It may be reasonable to speculate that TAVI patients may benefit from similar antithrombotic treatment as currently used after SAVR with a biological prosthesis. However, it is relevant to emphasise that percutaneous valves have leaflets composed of biological material and a metallic frame similar to vascular stents. Moreover, there is little evidence to demonstrate the ideal antithrombotic regimen after SAVR with biological prostheses and no uniformity amongst guidelines: a) European guidelines support use of aspirin (IIa recommendation) or vitamin K antagonists (VKA, IIb recommendation) for three months; b) AHA/ACC guidelines recommend long-term low-dose aspirin (IIa recommendation; level of evidence [LOE] B) while VKA are considered reasonable for the first three months (IIb recommendation, LOE C); c) ACCP guidelines support low-dose aspirin over VKA (Grade 2C). Therefore, some but not all guidelines recommend VKA in the first 3-6 months after SAVR whereas aspirin may be a preferred long-term treatment.

In TAVI patients, secondary prevention regimes based on antiplatelet therapy have been the most widely accepted treatment option. Given the increased thrombotic risks related to TAVI valve structure, dual antiplatelet therapy (DAPT) with aspirin (indefinitely) and clopidogrel (3-6 months) – in the absence of an indication for anticoagulation – is a widely accepted empirical strategy which has been incorporated into practice guidelines **(Table 1)**. DAPT is also important for the many TAVI patients with concomitant coronary artery disease (CAD) who undergo stenting.

Nevertheless, the benefits of DAPT have been questioned, and recent observations that the addition of clopidogrel to aspirin does not seem to improve efficacy and safety may trigger a paradigm shift in the choice of optimal antithrombotic therapy after TAVI. Pooled analysis of individual patient data from 672 participants comparing aspirin alone versus DAPT after TAVI showed no difference in the rate of 30-day net adverse clinical and cerebral events, but a trend towards less life-threatening and major bleeding was observed in favour of aspirin alone[3]. Conversely, it should be considered that: a) only four studies based on small numbers of patients and events are available and in only two of them was treatment randomly allocated; b) high on-treatment platelet reactivity associated with clopidogrel or aspirin can also occur in TAVI patients[4], although its clinical correlations remain unclear; c) the impact of old versus newer percutaneous valve technologies remains elusive – for example, inclusion of an additional skirt to reduce the frequency of paravalvular leak may potentially increase thrombogenicity.

Forthcoming studies

Further evidence is therefore needed to conclude firmly that DAPT is futile compared with aspirin alone: ongoing trials will help to clarify this debated issue. The Aspirin Versus Aspirin+ClopidogRel Following Transcatheter Aortic Valve Implantation (ARTE) pilot

Table 1. Recommendations for antithrombotic therapy in TAVI patients.

	European guideline and consensus	AHA/ACC guidelines	ACCF/AATS/SCAI/STS consensus	Canadian Society position statement
Aspirin	Low-dose indefinitely	Low-dose (75-100 mg/day) indefinitely	81 mg/day indefinitely	Low-dose indefinitely
Additional antiplatelet therapy	Thienopyridine early after TAVI	Clopidogrel 75 mg/day for 6 months	Clopidogrel 75 mg/day for 3-6 months	Clopidogrel for 1-3 months
Oral anticoagulation	VKA alone in patients with AF but no CAD (VKA+antiplatelet therapy if AF and recent stent implantation, as per CAD guidelines)		VKA if indicated (no clopidogrel)	VKA if indicated (avoid triple therapy unless definite indication)

AF: atrial fibrillation; CAD: coronary artery disease; TAVI: transcatheter aortic valve implantation; triple therapy: dual antiplatelet therapy plus vitamin K antagonist; VKA: vitamin K antagonist

trial (NCT01559298) assesses the efficacy of aspirin alone (80 mg/day for at least six months) versus aspirin (80 mg/day for at least six months)+clopidogrel (75 mg/day for three months) in preventing death, myocardial infarction, ischaemic stroke/transient ischaemic attack (TIA) or life-threatening/major bleeding (primary endpoint) at one year in 200 patients with no indication to OAC. The Dual Antiplatelet Therapy Versus Oral Anticoagulation for a Short Time to Prevent Cerebral Embolism After TAVI (AUREA) trial (NCT01642134) assesses the efficacy of DuoPlavin (aspirin 80 mg/day+clopidogrel 75 mg/day, for three months) compared with acenocumarol in preventing cerebral thromboembolism identified using magnetic resonance (primary endpoint) at three months in 124 patients with no indication to OAC. The Antiplatelet Therapy for Patients Undergoing Transcatheter Aortic Valve Implantation (POPular-TAVI) trial (NCT02247128) hypothesises that omitting clopidogrel in the first three months after TAVI has similar efficacy and greater safety compared with adding clopidogrel to aspirin or OAC. This is a multicentre open-label randomised all-comers trial comparing safety, net clinical benefit and efficacy of clopidogrel omission compared to aspirin (100 mg/day for at least one year)+clopidogrel (75 mg/day for three months) (cohort A) or OAC+clopidogrel (cohort B) in 1,000 patients over one year of follow-up. Future studies will also need to address multiple outstanding issues including the role of clopidogrel monotherapy, the need for a loading dose and the potential role of newer $P2Y_{12}$ antagonists, prasugrel or ticagrelor.

The role of anticoagulation

Whether thrombi produced during and after TAVI have a platelet- or thrombin-based origin remains uncertain. Hence, antiplatelet-based strategies alone may still be suboptimal. Moreover, the need for OAC is also supported by the high burden of pre-existing and new-onset AF in TAVI patients, particularly since the large majority of these patients have a high CHA_2DS_2-VASc score. OAC in this context has great relevance in thrombosis prevention because new-onset and recurrent paroxysmal AF may be silent, clinically unrecognised and high risk unless specifically investigated[2]. Transcatheter valve thrombosis is rare but dangerous and may result in elevated transvalvular gradients requiring OAC. A recent study reviewed a total of 18 published cases (SAPIEN=17, CoreValve=1) and reported four new cases (SAPIEN=1, CoreValve=3)[4], while a larger multicentre retrospective study analysed 4,266 patients, reporting 26 cases of transcatheter valve thrombosis (mean follow-up six months; SAPIEN=20, CoreValve=6)[5]. Clinical presentation was principally with dyspnoea and increased gradients, and anticoagulation therapy was effective in reducing gradients in the majority of patients within two months of treatment. The frequency of transcatheter valve thrombosis may be underestimated, however, since clinical signs and symptoms can be masked by comorbidities, and early follow-up echocardiography is not uniformly performed. Nonetheless, pannus formation or thrombosis should be suspected in patients with sudden elevation in valve gradient, prompting further investigation and therapy with OAC plus single antiplatelet therapy (SAPT) or DAPT. In case of failure, valve-in-valve TAVI or SAVR could be considered.

The concept that OAC could be important in TAVI patients was also discussed at EuroPCR 2015. Neumann presented the results of systematic computed tomography (CT) five days after TAVI (SAPIEN 3 prosthesis), demonstrating clinically silent valve leaflet thickening in 16/156 patients. Full OAC (INR 2.5-3.5) resulted in regression of these findings in 11 patients who underwent follow-up CT (mean 77 days). In the same session, Sondergaard presented data concerning valve leaflet motion assessed with CT approximately three months after TAVI (n=47) or SAVR (n=15), demonstrating that the frequency of reduced leaflet motion was similar with different types of valve (and procedure), and that the phenomenon was not associated with clinical events. Whilst these preliminary underpowered data findings await confirmation and more rigorous evaluation, they may open new perspectives on the post-procedural management of TAVI patients, underlining the need to consider a more liberal approach to the use of OAC after TAVI, even in the absence of known indications (AF, mechanic valves), and the utility of CT imaging during follow-up. Conversely, the necessity of this approach remains the subject of discussion since all patients were asymptomatic and no clinical events were reported or prevented.

Bleeding risks

A crucial aspect to be considered in the management of TAVI patients is the risk of bleeding – a frequent periprocedural complication after TAVI associated with worse prognosis[1]. However, major late bleeding events (>30 days) also significantly increase mortality in this population and have great clinical relevance[6].

The low incidence of transcatheter valve thrombosis and high bleeding risk in most TAVI patients may not justify the routine use of OAC, but recent evidence supports the importance of OAC in some patients and future trials are needed. Accordingly, two multicentre randomised trials have recently been designed **(Figure 1)**. GALILEO (Global multicenter, open-label, randomized, event-driven,

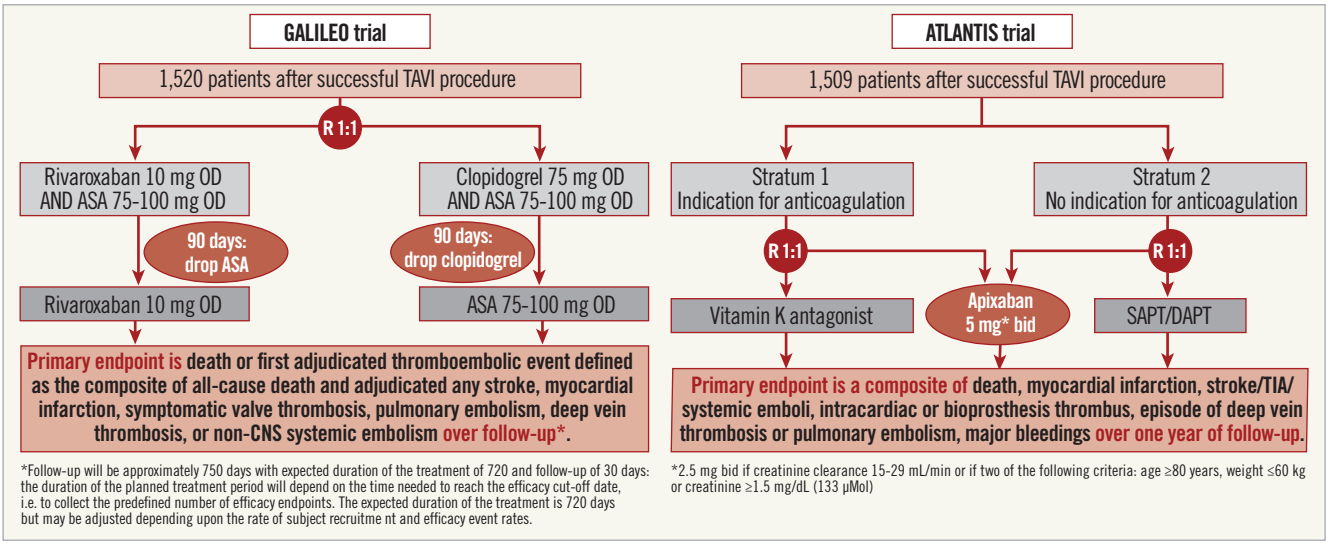

Figure 1. *Flow diagram of the GALILEO and ATLANTIS trials.*

active-controlled study comparing a rivAroxaban-based antithrombotic strategy to an antipLatelet-based strategy after transcatheter aortIc vaLve rEplacement (TAVR) to Optimize clinical outcomes) will compare rivaroxaban-based (rivaroxaban 10 mg/day long-term with aspirin 75-100 mg/day for three months) and antiplatelet-based strategies (aspirin 75-100 mg/day long-term with clopidogrel 75 mg/day for three months) after TAVI in patients without prior indication for anticoagulation. ATLANTIS (Anti-Thrombotic strategy to Lower All cardiovascular and Neurologic ischemic and hemorrhagic events after Trans-aortic valve Implantation for aortic Stenosis) will compare apixaban (5 mg bd or 2.5 mg bd in specific settings) with the standard of care, irrespective of need for oral anticoagulation.

Finally, there is a paucity of data and ongoing controversy concerning the appropriate antithrombotic regimen (and its duration) in AF patients undergoing TAVI. There are only individual reports concerning the use of triple therapy (DAPT+OAC) and no evidence regarding warfarin with one antiplatelet agent or warfarin alone. Indeed, American and Canadian guidelines discourage the use of triple therapy **(Table 1)**. In AF patients undergoing stenting, the combination of OAC with one antiplatelet agent was associated with better safety outcomes (and no excess of ischaemic events) than triple therapy. However, the recent European consensus on AF treatment stated that VKA alone is the preferred option in patients undergoing TAVI with AF but no CAD, since the need for additional antiplatelet therapy remains uncertain. Conversely, patients who have undergone recent PCI should be treated similarly to those receiving stents outwith the context of TAVI, since specific robust data for TAVI are lacking and future trials needed.

In conclusion, the justification for currently recommended regimes of DAPT after TAVI has recently been questioned, while arguments supporting the potential benefits of OAC therapy have now emerged. Well designed and appropriately powered trials are strongly warranted.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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Terapia antitrombotica nei pazienti sottoposti a impianto transcatetere di valvola aortica

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Transcatheter aortic valve implantation (TAVI) has emerged as a valid alternative to surgical replacement in patients with severe aortic stenosis. Bleeding and cerebral ischemic events remain frequent complications of this procedure during the periprocedural period and at follow-up with a severe impact on survival. Therefore, there is growing interest towards the optimal antithrombotic therapy to manage patients undergoing TAVI. International guidelines support the adoption of a dual antiplatelet therapy after TAVI, although there is heterogeneity in the suggested duration and the concomitant association with an oral anticoagulant in patients with specific indications, mainly those with atrial fibrillation. Recent data have questioned the benefits of adding clopidogrel to aspirin, showing a slight increase in bleeding compared with aspirin therapy alone. Importantly, recent studies have also underlined the risks of valve thrombosis and the potential benefits of oral anticoagulant therapy in patients undergoing TAVI. Currently, large randomized trials are ongoing and are expected to provide relevant information to guide recommendations on the most appropriate antithrombotic therapy in these patients. Tailored therapy based on the patient's risk profile remains relevant in daily clinical practice.

Key words. Anticoagulant agents; Antiplatelet agents; Antithrombotic therapy; Bleeding; Stroke; Transcatheter aortic valve implantation.

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INTRODUZIONE

La stenosi aortica (SA) è la più frequente valvulopatia cardiaca in Europa e Nord America e si presenta principalmente come SA calcifica nei soggetti adulti. La prevalenza della patologia aumenta all'aumentare dell'età. La SA è una patologia cronica e progressiva che può rimanere asintomatica per anni. La morte improvvisa è una frequente causa di morte, sebbene sia rara nei pazienti asintomatici. È ben noto che dall'insorgenza dei sintomi della patologia, la prognosi è infausta. La terapia medica non è in grado di modificare la prognosi di questi pazienti, dunque l'unica terapia efficace consiste nella sostituzione della valvola aortica stenotica.

Per molti anni, la sostituzione valvolare chirurgica (*surgical aortic valve replacement*, SAVR) è stata l'unica opzione per i pazienti sintomatici con SA severa. Tuttavia, questo intervento è gravato da un significativo rischio di complicanze e mortalità ed inoltre non può essere offerto a tutti in considerazione del fatto che spesso i pazienti con SA sono molto anziani e hanno comorbilità tali da renderli a rischio chirurgico molto elevato o inoperabili. Nel 2002, il Professor Alain Cribier impiantò per la prima volta una valvola aortica per via percutanea, procedura oggi nota come TAVI o TAVR (*transcatheter aortic valve implantation or replacement*). Da allora, crescenti evidenze hanno dimostrato che la TAVI potesse diventare una valida alternativa alla procedura chirurgica. La TAVI ha innanzitutto permesso di modificare la prognosi infausta e prolungare la sopravvivenza ai pazienti giudicati inoperabili. Inoltre la TAVI è oggi diffusamente considerata una strategia efficace e sicura nei pazienti con SA ad alto rischio chirurgico, come anche raccomandato dalle linee guida internazionali.

La TAVI, similmente ad altre procedure interventistiche o chirurgiche, presenta rischi trombotici (ictus, infarto miocardico o embolismo sistemico) e di sanguinamento, soprattutto nella fase periprocedurale[1-3]. Tali rischi tuttavia sono anche presenti durante il follow-up, soprattutto nei pazienti con fibrillazione atriale (FA). Nonostante i progressi nella tecnologia e nell'esperienza con questa procedura, le complicanze ischemiche ed emorragiche sono ancora frequenti e hanno un impatto prognostico negativo in questa categoria di pazienti anziani e con frequenti comorbilità. Per tale ragione, l'identificazione della terapia antitrombotica ottimale che possa bilanciare appropriatamente il rischio ischemico ed emorragico è un obiettivo di diffuso interesse.

RISCHIO DI ICTUS E SANGUINAMENTI

Il rischio di ictus è particolarmente elevato nel periodo periprocedurale in relazione al posizionamento ed impianto del nuovo dispositivo[1-3]. Infatti, la valvola aortica stenotica presenta una grande quota di fattore tissutale e di trombina che contribuiscono all'infiammazione e alla trombogenicità. Durante la TAVI, a differenza dell'intervento chirurgico, la valvola nativa malata resta *in situ* e viene manipolata durante la fase di impianto della nuova valvola potendo comportare esposizione e/o embolizzazione dei suoi componenti nel circolo arterioso. Inoltre, la sovrapposizione del nuovo dispositivo

Gli autori dichiarano nessun conflitto di interessi.
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alla valvola nativa può creare zone di turbolenza che possono predisporre alla generazione di trombi, soprattutto in caso di valvole piccole che possono determinare un "mismatch" valvola-paziente. Gli emboli cerebrali durante TAVI si sono dimostrati composti da materiale trombotico o calcifico. Durante i mesi successivi alla TAVI i pazienti presentano comunque un aumentato rischio di ictus, probabilmente correlato a diversi meccanismi (danno della parete aortica, attivazione del sistema emostatico, turbolenze e stasi ematica locale, ecc.). Inoltre la FA contribuisce in modo rilevante a questo rischio. Una recente metanalisi ha infatti dimostrato che circa il 33% dei pazienti che vengono sottoposti a TAVI presenta una FA preesistente all'intervento, e che un altro 17% può sviluppare una nuova FA post-procedurale (il dato può essere sottostimato a causa della mancata documentazione di eventuali episodi di FA parossistica in pazienti non sottoposti a monitoraggio continuo)[4].

I sanguinamenti sono complicanze frequenti e rilevanti nei pazienti sottoposti a TAVI[1-3]. In particolare, nella fase periprocedurale il 15-30% dei pazienti può avere un sanguinamento maggiore e nel 5-15% l'emorragia è rischiosa per la vita. Questi eventi sono spesso, ma non esclusivamente, correlati a complicanze vascolari e dell'accesso utilizzato per la procedura. Tuttavia, anche sanguinamenti in altre sedi (per esempio genitourinari o gastrointestinali) possono presentarsi dopo la procedura o durante il follow-up e certamente la terapia antitrombotica può avere un ruolo importante in questi eventi. Inoltre, molti pazienti sottoposti a TAVI hanno un variabile grado di anemia che può predisporre alla necessità di trasfusione in caso di emorragia.

TERAPIA ANTITROMBOTICA DURANTE E DOPO IMPIANTO TRANSCATETERE DI VALVOLA AORTICA: ATTUALI EVIDENZE

La terapia antitrombotica ottimale per i pazienti sottoposti a TAVI è un argomento molto dibattuto, soprattutto perché esistono pochi dati forniti da studi clinici dedicati.

Durante la procedura, la strategia più utilizzata prevede la somministrazione di eparina non frazionata (*unfractionated heparin*, UFH). Il protocollo previsto dagli studi PARTNER prevede la somministrazione di un bolo di 5000 UI seguito da eventuali boli addizionali con l'obiettivo di mantenere il tempo di coagulazione attivato (*activated clotting time*, ACT) ≥250 s. Un documento di consenso raccomandava come obiettivo il mantenimento di un ACT ≥300 s. Entrambi i protocolli prevedevano l'eventuale uso del solfato di protamina per antagonizzare l'UFH. In considerazione della riduzione dei sanguinamenti maggiori ottenuta con l'uso di bivalirudina rispetto ad UFH in pazienti trattati con angioplastica coronarica, anche nei pazienti TAVI si sta valutando questa opzione. Tuttavia, nonostante la bivalirudina abbia una breve emivita e la sua azione termini rapidamente dopo la sospensione dell'infusione, bisogna anche considerare che l'UFH offre il vantaggio di poter essere antagonizzata immediatamente con solfato di protamina, cosa che può essere necessaria in caso di complicanze emorragiche potenzialmente fatali che avvengono durante la procedura come il tamponamento cardiaco, la rottura dell'anulus aortico o di vasi periferici. Recentemente, sono stati pubblicati i risultati dello studio randomizzato BRAVO-3 (Bivalirudin versus Heparin Anticoagulation in Transcatheter Aortic Valve Replacement) che ha confrontato UFH e bivalirudina nei pazienti sottoposti a TAVI e ha dimostrato che la bivalirudina si associa a simile incidenza di eventi clinici maggiori rispetto ad UFH senza essere superiore[5]. Complessivamente 802 pazienti (bivalirudina = 404 e UFH = 398) sono stati randomizzati con due principali obiettivi: 1) sanguinamenti maggiori entro 48h dalla procedura o prima della dimissione (a seconda di quale si è verificato per primo); 2) incidenza a 30 giorni di eventi clinici avversi netti (*net adverse clinical events*, NACE) definiti dalla combinazione dei sanguinamenti maggiori con gli eventi cardiovascolari avversi maggiori (morte per tutte le cause, infarto miocardico o ictus). L'ipotesi principale era che la bivalirudina potesse dimostrarsi superiore in termini di sanguinamenti maggiori, ma la superiorità non è stata dimostrata sebbene gli eventi fossero numericamente ridotti nel gruppo bivalirudina (sanguinamenti BARC [Bleeding Academic Research Consortium] ≥3b: 6.9 vs 9.0% nei gruppi bivalirudina vs UFH; p=0.27). L'ipotesi di non inferiorità in termini di NACE a 30 giorni invece è stata dimostrata, ma anche in questo caso non si è osservata superiorità (14.8 vs 15.9%; p per non inferiorità <0.01; p per superiorità =0.66).

Le evidenze sulla terapia antitrombotica ottimale dopo TAVI sono scarse. Alcuni sostengono che i pazienti TAVI possono essere paragonati ai pazienti che ricevono intervento chirurgico con impianto di protesi biologica. Tuttavia, le protesi impiantate per via percutanea sono diverse da quelle chirurgiche perché sono costituite da materiale biologico montato su una struttura metallica, simile agli stent coronarici. Inoltre, anche nel caso della terapia antitrombotica dopo intervento chirurgico di impianto di valvola biologica non c'è uniformità tra le varie linee guida internazionali. Infatti: a) le linee guida europee raccomandano preferenzialmente la somministrazione di aspirina per 3 mesi (classe di raccomandazione IIa) rispetto all'anticoagulante orale (IIb); b) le linee guida americane AHA/ACC (American Heart Association/American College of Cardiology) raccomandano l'uso di aspirina a lungo termine (IIa) e l'anticoagulante orale è considerato ragionevole nei primi 3 mesi (IIb); c) le linee guida americane ACCP (American College of Chest Physicians) supportano preferenzialmente l'aspirina rispetto all'anticoagulante orale (grado di raccomandazione 2C).

Nei pazienti sottoposti a TAVI la strategia più diffusa nel corso degli anni è stata quella basata sull'impiego della terapia antipiastrinica piuttosto che anticoagulante orale. In particolare, in considerazione della struttura della protesi e dell'uniformità con i dati ottenuti nei pazienti che ricevono impianto di stent coronarico, empiricamente la doppia antiaggregazione (*dual antiplatelet therapy*, DAPT) è divenuta la strategia condivisa (Tabella 1). In pazienti senza indicazione a terapia anticoagulante orale (TAO), generalmente si raccomanda la somministrazione di aspirina a lungo termine e di clopidogrel per 3-6 mesi. Tuttavia questa raccomandazione empirica è stata messa in dubbio da recenti evidenze, le quali suggeriscono che l'aggiunta di clopidogrel non determina vantaggi clinici. Quattro studi hanno confrontato il regime di sola aspirina a quello di aspirina + clopidogrel (Tabella 2)[6-9] e la metanalisi di questi (2 randomizzati e 2 osservazionali) ha incluso 672 pazienti e ha dimostrato che non ci sono differenze di NACE a 30 giorni tra i due gruppi di terapia, ma l'aspirina da sola si associava ad un numero inferiore di sanguinamenti maggiori, seppur statisticamente non significativo[10]. Tuttavia bisogna considerare che: a) gli studi sono solo 4, con pochi pazienti totali e di questi

Tabella 1. Raccomandazioni per la terapia antitrombotica nei pazienti sottoposti a impianto transcatetere di valvola aortica.

	Linee guida e consensus ESC	Linee guida AHA/ACC	Consensus ACCF/AATS/SCAI/STS	Linee guida canadesi
Aspirina	Bassa dose indefinitamente	Bassa dose (75-100 mg/die) indefinitamente	81 mg/die indefinitamente	Bassa dose indefinitamente
Antipiastrinico aggiuntivo	Tienopiridina precoce dopo TAVI	Clopidogrel 75 mg/die per 6 mesi	Clopidogrel 75 mg/die per 3-6 mesi	Clopidogrel per 1-3 mesi
Anticoagulante orale	AVK in monoterapia nei pazienti con FA e senza CAD AVK + antipiastrinici se FA e recente impianto di stent (come da linee guida sulla rivascolarizzazione miocardica)		AVK se indicato (senza clopidogrel)	AVK se indicato (clopidogrel). Evitare tripla terapia in assenza di specifica indicazione

AATS, American Association for Thoracic Surgery; ACC, American College of Cardiology; ACCF, American College of Cardiology Foundation; AHA, America Heart Association; AVK, antagonista della vitamina K; CAD, malattia coronarica; FA, fibrillazione atriale; SCAI, Society for Cardiovascular Angiography and Interventions; STS, Society of Thoracic Surgeons; TAVI, impianto transcatetere di valvola aortica.

Tabella 2. Caratteristiche degli studi che hanno confrontato aspirina e duplice terapia antiaggregante dopo impianto transcatetere di valvola aortica.

	Studi randomizzati				Studi osservazionali senza matching			
	Ussia et al.[6]		Stabile et al.[7]		Poliacikova et al.[8]		Durand et al.[9]	
	Aspirina	DAPT	Aspirina	DAPT	Aspirina	DAPT	Aspirina	DAPT
N. pazienti	39	40	60	60	91	58	164	128
Procedura (%)								
TF	100	95	NR	NR	NR	NR	84	77
TA	0	0	NR	NR	NR	NR	15	23
Altro	0	5	NR	NR	NR	NR	1	0
CoreValve	100	100	0	0	0	0	33	0
Edwards Sapien	0	0	100	100	100	100	67	100
Terapia pre-TAVI								
Aspirina (mg)	100	100	75-160	75-160	300	300	75	75
Clopidogrel carico (mg)	–	300	NR	NR	–	300	300	300
INR	NR	NR	NR	NR	NR	NR	<1.5	<1.5
ACT (s)	200-250	200-250	>250	>250	NR	NR	NR	NR
Terapia post-TAVI								
Aspirina (mg)	100	100	75-160	75-160	75	75	75	75
Clopidogrel (mg/mesi)	–	75/3	–	75/6[a]	–	75/6	–[b]	75/1
Eventi clinici								
Morte a 30 giorni (%)	10.0	10.0	3.3	1.7	3.3	6.9	7.9	9.4
Morte a 6 mesi (%)	13.0	10.0	5.0	5.0	NR	NR	NR	NR
IM a 30 giorni (%)	0	0	0	0	NR	NR	1.2	0.8
Ictus a 30 giorni (%)	5.0	3.0	3.3	1.7	2.2	3.4	1.2	4.7
Complicanze vascolari a 30 giorni (%)	NR	NR	0	5.0	3.3	5.2	5.5	10.2
Sanguinamenti minori a 30 giorni (%)	10.0	8.0	1.7	5.0	NR	NR	2.4	5.5
Sanguinamenti maggiori a 30 giorni (%)	30.0	5.0	3.3	3.3	NR	NR	2.4	13.3
Sanguinamenti pericolosi per la vita a 30 giorni (%)	5.0	5.0	5.0	6.6	NR	NR	3.7	12.5
Tutti i sanguinamenti a 30 giorni (%)	18.0	18.0	10.0	15.0	8.8	19.0	8.5	31.3

ACT, tempo di coagulazione attivato; DAPT, duplice terapia antiaggregante; IM, infarto miocardico; INR, international normalized ratio; NR, non riportato; TA, transapicale; TAVI, impianto transcatetere di valvola aortica; TF, transfemorale.
[a]in alternativa: ticlopidina 500 mg bid.
[b]in alternativa monoterapia con clopidogrel 75 mg/die.

solo 2 sono randomizzati; b) anche pazienti trattati con TAVI possono avere un'elevata reattività piastrinica durante terapia con clopidogrel o aspirina[11]; c) il profilo di sicurezza dei nuovi dispositivi resta sconosciuto. Infatti, le nuove protesi valvolari presentano un diverso disegno e non è noto se per esempio il tessuto aggiuntivo disegnato per ridurre il leak paravalvolare possa aumentare il potenziale trombogenico della protesi. Dunque, sulla base di queste considerazioni, è chiaro che sono necessarie ulteriori evidenze per chiarire se la monoterapia con aspirina sia sufficiente rispetto alla DAPT.

STUDI CLINICI IN CORSO

Sono in corso alcuni studi che potranno contribuire a chiarire questo aspetto:

- studio ARTE (Aspirin vs Aspirin + Clopidogrel Following TAVI Pilot Trial; NCT01559298) che valuta l'efficacia della monoterapia con aspirina (80 mg/die per 6 mesi) rispetto ad aspirina (80 mg/die per 6 mesi) e clopidogrel (75 mg/die per 3 mesi). L'endpoint primario sarà valutato in 200 pazienti (senza indicazione a TAO) ed è costituito dall'incidenza di morte, infarto, ictus/attacco ischemico transitorio o sanguinamenti maggiori ad 1 anno di follow-up;
- studio AUREA (Dual Antiplatelet Therapy Versus Oral Anticoagulation for a Short-Time to Prevent Cerebral Embolism After TAVI; NCT01642134) che valuta l'efficacia di aspirina 80 mg/die + clopidogrel 75 mg/die per 3 mesi rispetto ad acecumarolo nel prevenire eventi tromboembolici cerebrali valutati a 3 mesi con risonanza magnetica (endpoint primario) in 124 pazienti senza indicazione a TAO;
- studio POPULAR-TAVI (Antiplatelet Therapy for Patients Undergoing TAVI; NCT02247128) che ipotizza di dimostrare simile efficacia ma migliore sicurezza del non aggiungere clopidogrel rispetto ad aggiungere clopidogrel (75 mg/die per 3 mesi) ad aspirina (100 mg/die per 1 anno) o TAO sulla base dell'indicazione (coorte A: assenza di FA; coorte B: presenza di FA) in circa 1000 pazienti durante un follow-up di 1 anno.

Studi futuri dovranno esplorare anche il ruolo di altre strategie, per esempio la monoterapia con clopidogrel, la necessità o meno di una dose di carico post-procedurale e l'uso di nuovi antipiastrinici (prasugrel o ticagrelor).

TERAPIA ANTICOAGULANTE: RAZIONALE ED EVIDENZE SCIENTIFICHE

Recentemente diverse evidenze hanno suggerito che la TAO dopo TAVI potrebbe essere una strategia giustificata per la prevenzione di eventi trombotici in questi pazienti. Poiché resta ancora da chiarire se gli eventi trombotici durante e dopo TAVI siano di origine piastrinica o trombinica, la sola terapia antipiastrinica potrebbe non essere una strategia preventiva sufficiente. Inoltre, l'uso della TAO potrebbe anche essere supportato dal fatto che molti pazienti TAVI, come precedentemente sottolineato, presentano FA al basale o la sviluppano dopo la procedura o nel follow-up, anche considerato che l'età avanzata e la frequente comorbilità in questa popolazione li rende spesso ad alto rischio con elevato CHA_2DS_2-VASc score.

La TAO potrebbe avere un ruolo importante nel prevenire eventi trombotici valvolari. La trombosi della protesi valvolare aortica è una complicanza rara ma pericolosa. Uno studio recente ha analizzato i casi descritti in letteratura (n=18 di cui 17 coinvolgevano valvole Sapien e 1 caso era su valvola CoreValve) e riportato 4 nuovi casi (1 in Sapien e 3 in CoreValve)[11]. Un altro studio ha effettuato un'analisi multicentrica retrospettiva di 4266 pazienti e ha riportato 26 casi di trombosi di protesi percutanea valvolare aortica ad un follow-up medio di 6 mesi (Sapien = 20; CoreValve = 6)[12]. Questi casi clinicamente si presentavano principalmente con dispnea ed aumento dei gradienti. La maggior parte dei casi mostrava riduzione dei gradienti nell'arco di 2 mesi di TAO.

Tuttavia, l'incidenza di trombosi della protesi valvolare può essere un evento sottostimato perché i segni e sintomi possono essere sfumati o mascherati dalla presenza di comorbilità in questi pazienti e perché l'ecocardiografia precoce non viene eseguita in modo uniforme. Inoltre, un recente studio pubblicato sul *New England Journal of Medicine* ha ulteriormente sottolineato la rilevanza della trombosi delle bioprotesi aortiche e la sua sottostima clinica supportando la necessità della TAO in questi pazienti[13]. L'ispessimento e la ridotta motilità dei lembi protesici sono emersi quali segni subclinici di trombosi bioprotesica[13]. Lo studio PORTICO-IDE (Portico Re-sheathable Transcatheter Aortic Valve System US Investigational Device Exemption), attualmente in corso, sta valutando l'efficacia e la sicurezza della nuova protesi Portico e nel protocollo è previsto l'uso della tomografia computerizzata (TC) in un sottogruppo di pazienti per valutare la struttura metallica della protesi. Durante lo studio, si è riscontrato alla TC una riduzione della motilità dei lembi bioprotesici in un paziente che aveva avuto un ictus e in alcuni altri pazienti asintomatici. Da quel momento tutte le immagini TC furono rivalutate e si decise di iniziare due registri dedicati a questo aspetto, il RESOLVE (Assessment of Transcatheter and Surgical Aortic Bioprosthetic Valve Thrombosis and Its Treatment with Anticoagulation) e il SAVORY (Subclinical Aortic Valve Bioprosthesis Thrombosis Assessed with Four-Dimensional Computed Tomography). Il manoscritto citato riporta appunto i risultati dell'analisi di 55 pazienti dello studio PROTICO-IDE e di 132 pazienti trattati con TAVI o SAVR nei due registri[13]. La riduzione della motilità dei lembi bioprotesici è stata riscontrata in 22 dei 55 pazienti (40%) e in 17 dei 132 (13%) nei registri. La terapia anticoagulante con warfarin si associava a una ridotta incidenza di questo evento rispetto alla doppia antiaggregazione (0 vs 55%, p=0.01 nel trial; 0 vs 29%, p=0.04 nei registri uniti in un singolo database). La ripetizione della TC al follow-up dimostrava che la TAO si associava al ripristino del normale movimento dei lembi bioprotesici (11/11 pazienti) a differenza di chi non riceveva la TAO (risoluzione solo in 1/10 pazienti) con differenza significativa (p<0.001). L'impatto clinico di questa alterazione necessita di un'ulteriore valutazione perché l'incidenza di ictus/attacco ischemico transitorio non differiva tra coloro che avevano o non avevano la riduzione della motilità nel trial (2/22 vs 0/33; p=0.16) ma differiva significativamente nei pazienti dei registri (3/17 vs 1/115; p=0.007). Uno studio della Mayo Clinic ha dimostrato che la trombosi valvolare non è rara anche dopo anni dall'intervento chirurgico e che alcune caratteristiche cliniche ed ecocardiografiche possono essere utili nel predire e diagnosticare l'evento[14]. Gli autori hanno esplorato il problema della trombosi delle bioprotesi valvolari impiantate chirurgicamente analizzando i referti istopatologici di 397 casi di valvole espiantate e valutando le caratteristiche cliniche dei pazienti con trombosi rispetto a quelli senza tale complicanza[14]. La trombosi era presente in 46 casi (11.6%) di cui 29 erano aortiche. La maggior parte dei casi di trombosi si era presentata dopo 2 anni dall'impianto (65%) e i predittori di evento erano: a) aumento del gradiente medio eco-Doppler >50% rispetto al basale; b) FA parossistica; c) INR sub-terapeutico; d) aumento dello spessore delle cuspidi; e) anomala motilità delle cuspidi. La contemporanea presenza dei 5 fattori prediceva la trombosi bioprotesica con alta sensibilità e specificità[14].

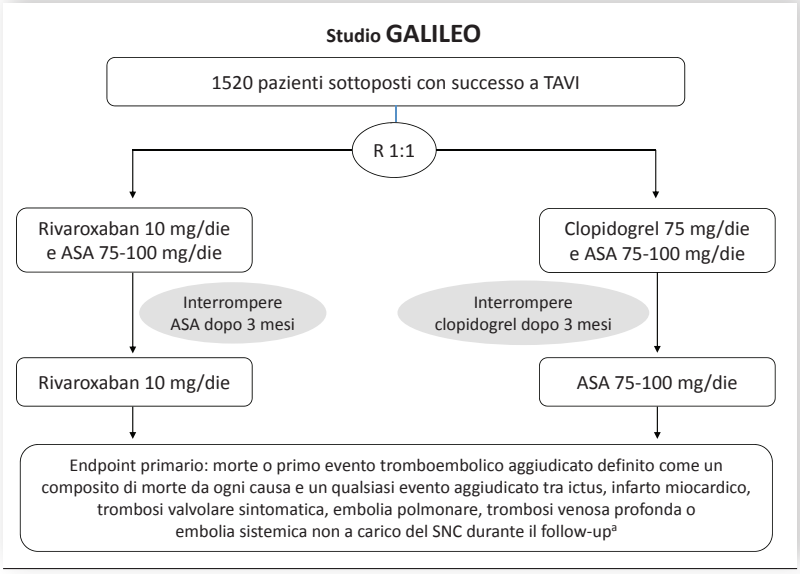

Figura 1. Disegno dello studio GALILEO.
ASA, aspirina; SNC, sistema nervoso centrale; TAVI, impianto transcatetere di valvola aortica.
[a]il follow-up sarà di circa 750 giorni con una durata prevista del trattamento di 720 giorni e monitoraggio di 30 giorni; la durata del trattamento previsto dipenderà dal tempo necessario per raggiungere il cut-off di efficacia, vale a dire il numero predefinito di endpoint di efficacia. La durata prevista del trattamento di 720 giorni potrebbe variare in funzione del numero di pazienti arruolati e dell'incidenza degli eventi di efficacia.

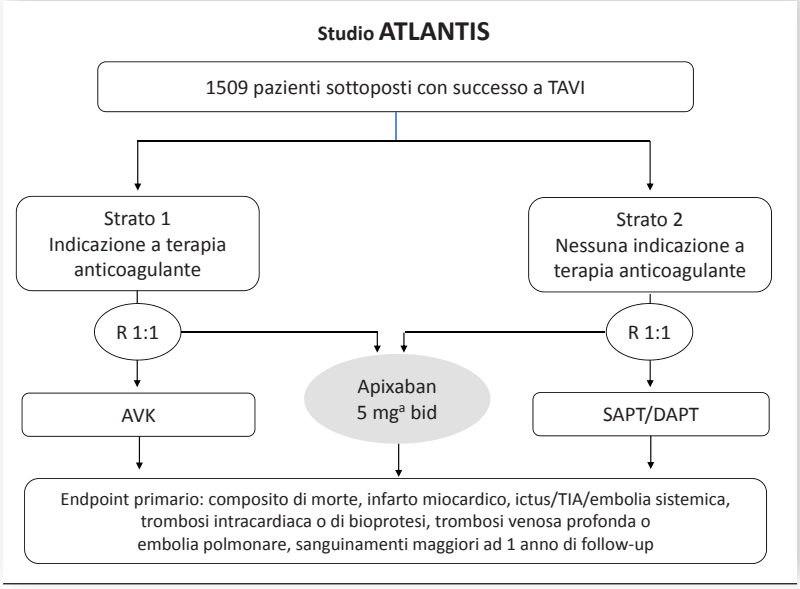

Figura 2. Disegno dello studio ATLANTIS.
AVK, antagonista della vitamina K; DAPT, duplice terapia antiaggregante; TIA, attacco ischemico transitorio; SAPT, monoterapia antiaggregante.
[a]2.5 mg bid in caso di clearance della creatinina 15-29 ml/min o in presenza di due dei seguenti criteri: età ≥80 anni, peso ≤60 kg o creatinina ≥1.5 mg/dl (133 µmol).

Un aspetto cruciale tuttavia da prendere in considerazione nel valutare l'uso della TAO in pazienti TAVI riguarda il rischio di sanguinamento. Come precedentemente descritto, il sanguinamento post-procedurale dopo TAVI è una complicanza frequente e rilevante con un impatto negativo sulla sopravvivenza[1-3]. Inoltre, anche episodi di sanguinamento maggiore durante follow-up (oltre 30 giorni dopo la procedura) non sono rari e aumentano la mortalità[15].

Dunque, due aspetti complessivamente (l'alto rischio di sanguinamento e la bassa frequenza degli eventi tromboti-

ci) non permettono ad oggi di considerare la TAO come la terapia da raccomandare in tutti i pazienti TAVI in assenza di nuove evidenze a supporto di questa strategia. In quest'ottica, un importante trial randomizzato è stato disegnato recentemente (Figura 1). Lo studio GALILEO (Global multicenter, open-label, randomized, event-driven, active-controlled study comparing a rivAroxaban-based antithrombotic strategy to an antipLatelet-based strategy after transcatheter aortIc vaLve rEplacement to Optimize clinical outcomes) sarà condotto in oltre 100 centri in Europa e Stati Uniti e confronterà una strategia anticoagulante con rivaroxaban (10 mg/die a lungo termine e aspirina 75-100 mg/die nei primi 3 mesi) ad una strategia antipiastrinica (aspirina 75-100 mg/die a lungo termine e clopidogrel nei primi 3 mesi) in pazienti senza una precedente indicazione a TAO.

Similmente, lo studio multicentrico francese ATLANTIS (Anti-Thrombotic Strategy to Lower All Cardiovascular and Neurologic Ischemic and Hemorrhagic Events after Trans-Aortic Valve Implantation for Aortic Stenosis) confronterà apixaban (5 mg bid oppure 2.5 mg in specifici contesti clinici) con la terapia standard (Figura 2).

PAZIENTI CON FIBRILLAZIONE ATRIALE

Nei pazienti con FA sottoposti a TAVI ci sono ad oggi pochi dati in merito a quale possa essere la più appropriata strategia antitrombotica e la sua durata. Le linee guida americane e canadesi scoraggiano l'uso della triplice terapia con TAO più aspirina e clopidogrel (Tabella 1). Nei pazienti con FA e con malattia aterosclerotica coronarica che ricevono impianto di stent coronarico, la combinazione di TAO con un singolo antipiastrinico ha dimostrato migliore sicurezza in termini di sanguinamento senza aumento di eventi ischemici rispetto all'uso di una triplice terapia. Tuttavia, un recente documento di consenso europeo sulla gestione dei pazienti con FA raccomanda di preferire la singola terapia con warfarin in pazienti sottoposti a TAVI senza concomitante coronaropatia significativa piuttosto che aggiungere anche un antipiastrinico che aumenterebbe il rischio emorragico con dubbio beneficio ischemico. Viceversa, nei pazienti con FA e recente impianto di stent coronarico che sono sottoposti a TAVI si raccomanda la stessa strategia di coloro che non ricevono TAVI poiché ad oggi non ci sono specifici e convincenti dati in questa tipologia di pazienti[16]. Studi futuri sono necessari per offrire evidenze scientifiche specifiche per questi pazienti così da confermare o suggerire eventuali modifiche delle attuali raccomandazioni.

CONCLUSIONI

La terapia antitrombotica ottimale nei pazienti con SA severa trattati mediante TAVI resta ancora dibattuta. Le evidenze recenti suggeriscono di rivalutare l'attuale raccomandazione di trattare questi pazienti con DAPT per 3-6 mesi (in assenza di indicazione specifica ad anticoagulazione). In particolare, nuovi dati mostrano i potenziali effetti benefici della TAO in questi pazienti. I risultati di nuovi studi contribuiranno a chiarire come stabilire la terapia antitrombotica ottimale in pazienti sottoposti a TAVI. Nella pratica clinica quotidiana è quindi sempre fondamentale avere un approccio individualizzato che tenga conto delle caratteristiche cliniche e procedurali di ogni paziente.

RIASSUNTO

L'impianto transcatetere di protesi valvolare aortica è una procedura molto diffusa ed alternativa all'intervento chirurgico per il trattamento della stenosi aortica severa. Gli eventi ischemici cerebrali e i sanguinamenti nel periodo periprocedurale e durante follow-up rappresentano complicanze frequenti e gravi per la prognosi dei pazienti, pertanto, vi è grande interesse nello stabilire la terapia antitrombotica ottimale per questi pazienti. La maggior parte delle linee guida internazionali supporta l'utilizzo di una doppia terapia antipiastrinica dopo la procedura, seppure con alcune differenze nella durata e nell'eventuale associazione ad anticoagulante orale nel caso di pazienti con specifica indicazione, principalmente coloro con fibrillazione atriale. Recenti evidenze indicano però che la doppia antiaggregazione non offre vantaggi, anzi aumenta i rischi di sanguinamento, rispetto alla monoterapia con aspirina. Alcuni studi recenti hanno mostrato però che la terapia anticoagulante potrebbe avere un ruolo molto importante in questi pazienti nel prevenire e trattare la trombosi della protesi valvolare aortica, che sembra essere spesso subclinica e sottostimata, ma frequente. Diversi studi clinici in corso forniranno un importante supporto per le future raccomandazioni sulla gestione terapeutica di questi pazienti. Nella pratica clinica quotidiana, la considerazione del profilo di rischio di ciascun paziente è fondamentale nella personalizzazione della terapia.

Parole chiave. Anticoagulanti; Antiaggreganti; Ictus; Impianto transcatetere di valvola aortica; Sanguinamento; Terapia antitrombotica.

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Editorial

Antithrombotic therapy after transcatheter aortic valve implantation: a new piece of the still unresolved puzzle

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The 2017 marks the 40th anniversary of percutaneous coronary intervention (PCI), but also the 15th anniversary for transcatheter aortic valve implantation (TAVI) (1). For more than 50 years, surgical aortic valve replacement (SAVR) has been the standard of care for patients with severe symptomatic aortic stenosis, improving outcomes and prolonging the lives of these patients. In 1990s the transcatheter delivery of a bioprosthetic aortic valve was conceptualized and largely tested in animals. The first human implantation of a percutaneous implantable prosthetic heart valve composed of 3 bovine pericardial leaflets mounted within a balloon-expandable stent was performed in Rouen on 16 April 2002 in a 57-year-old desperately ill man in cardiogenic shock, with critical aortic stenosis, subacute leg ischemia deemed inoperable due to multiple comorbidities (valve replacement had been declined for this patient, and balloon valvuloplasty had been performed with nonsustained results) (2).

Since then, TAVI has dramatically evolved, devices and procedural techniques have rapidly improved and results of randomized clinical trials have revolutionized the current treatment of severe aortic stenosis leading today to more than 300,000 procedures performed worldwide in more than 1,000 centers and 65 countries (1). Fifteen years after the first-in-man case, we can consider TAVI, with its explosive potential, as one of the major medical breakthroughs of the past decade in cardiology. Technological improvements and favorable clinical outcomes allowed to clearly establish the role of TAVI as the recommended strategy compared with medical therapy for inoperable patients, and alternative to surgery for high-risk patients, reaching more recently also the appropriate scientific evidence to recommend this procedure in patients at intermediate-risk (3-7). Furthermore, trials among low-risk patients are ongoing and evidence on feasibility and safety of TAVI in other clinical settings (treatment of patients with bicuspid aortic valve, pure native aortic regurgitation, degenerated surgical bioprosthetic valves or those with symptomatic moderate aortic stenosis or asymptomatic severe aortic stenosis) is being accumulated (3-7). However, ischemic and bleeding events soon after or at long-term after TAVI remain high, advocating dedicated investigations on optimal antithrombotic therapy (*Figure 1*) (8).

The prevention of ischemic complications during TAVI most likely requires full-dose anticoagulation. The most frequently used anticoagulant is unfractionated heparin, and the only trial comparing this latter with bivalirudin, the BRAVO 3 (Effect of Bivalirudin on Aortic Valve Intervention Outcomes 3), showed that bivalirudin did not reduce rates of major bleeding at 48 hours or net adverse cardiovascular events within 30 days compared with heparin (even if the non-inferiority hypothesis was reached for

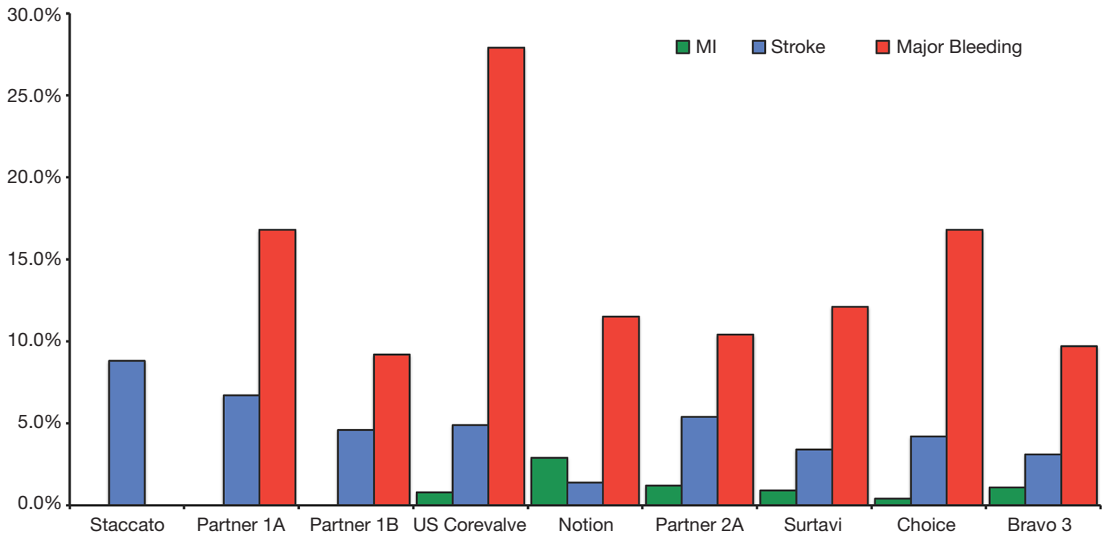

Figure 1 Rates of myocardial infarction, stroke and major bleeding 30 days after TAVI in main randomized clinical trials. Data on major bleeding were not available for STACCATO trial. The rate of myocardial infarction was 0% in STACCATO, PARTNER 1A and 1B. MI, myocardial infarction.

this endpoint) supporting the concept that heparin should remain the standard of care in TAVI patients (9). Regarding the post-procedural antithrombotic therapy, based on the increased thrombotic risks related to TAVI valve structure, dual antiplatelet therapy (DAPT) with aspirin (indefinitely) and clopidogrel (1 to 6 months)—in the absence of an indication for anticoagulation—has been a widely accepted empirical treatment, which was incorporated into practice guidelines. Differently from surgical interventions, the diseased native valve is not removed in TAVI procedures and may be mechanically damaged, leading to the exposure and/or embolism of valvular components into the arterial circulation. Moreover, the insertion of the prosthesis into the diseased native valve creates an irregular zone around the valve frame with modified flow patterns that may predispose to thrombus formation, particularly in the case of small valve sizes with associated patient–prosthesis mismatch. Notably, TAVI patients remain at risk for stroke throughout the first months after the procedure and mechanisms other than valve manipulation seem to be involved (i.e., aortic wall injury, posttraumatic surface exposure with consequent activation of the hemostatic system, turbulence or local blood stasis, atrial fibrillation). For all these reasons, although empirical, the recommendation to adopt DAPT has reached widespread clinical practice. DAPT is a mainstay therapy for patients undergoing PCI compared with aspirin monotherapy, but the higher risks of bleeding and the well-known impact of bleeding on mortality represent a crucial aspect to be taken into account when deciding on its duration (10-16). In TAVI patients, two important considerations should be done: (I) TAVI patients are often old, frail and with multiple comorbidities leading to high risk of bleeding. Hence the balance between preventing ischemic complications at acceptable costs for bleeding remains a challenge in this population; (II) the benefits of DAPT over aspirin monotherapy have been questioned by recent evidence (17). Indeed, the evidence from 2 small randomized trials, some small observational studies and meta-analyses does not support the use of DAPT compared with aspirin alone due to increased risk of bleeding in the absence of sizable beneficial effects on ischemic endpoints (17).

Recently, a third randomized clinical trial has been published (18). This is a prospective, randomized, open-label multicenter clinical trial including 222 patients undergoing TAVI with a balloon-expandable Edwards SAPIEN XT (92.3%) or SAPIEN 3 (7.7%) valves, with no indication to oral anticoagulation (OAC), who have been randomized to aspirin or DAPT. Overall, the patient population was old (mean age was 79 years) and the mean Society of Thoracic Surgeons score was 6.3. The investigators observed a significantly higher rate of major or life-threatening bleeding events in the DAPT group (10.8% *vs.* 3.6%; P=0.038). Notably, the excess of

bleeding events occurred within 30 days, the majority of which was post-procedurally and mainly included vascular or access-site complications or gastrointestinal bleeding. This increased risk of bleeding was the major driver for the higher (despite statistically borderline: 15.3% *vs.* 7.2%; P=0.065) rate of the primary endpoint, consisting of death, myocardial infarction, transient ischemic attack/ischemic stroke, or major/life-threatening bleeding 3 months after TAVI. Individual ischemic endpoints and mortality did not different between the 2 regimens, although numerically higher in the DAPT group. These findings represent an important step forward in the field.

The study was prematurely stopped due to slow recruitment and lack of financial support. Overall 222 patients of the 300 planned were included. However, it is important to note that even the requirement of 300 patients only was established for exploratory purposes without a formal sample size assumption. Therefore, ARTE, as all previous studies, lacks sufficient study power and its findings should be interpreted with caution and considered hypothesis-generating only.

Even when pooling together the three available randomized trials available, DAPT does not offer ischemic benefits rather bleeding harms (19). Yet, the overall number of patients remains limited and uncertainty around the point estimates for ischemic endpoints remain considerable and do entail the possibility that DAPT may offer greater protection than aspirin monotherapy. Additionally, no data is currently available in patients receiving more contemporary TAVI devices (e.g., it is unknown if the additional skirt aimed at reducing post-implantation paravalvular leak may potentially increase thrombogenicity). The impact of the high on-treatment platelet reactivity associated with clopidogrel or aspirin (which seems more frequent in TAVI patients) is yet to be understood.

Five of the 16 severe bleeds observed in the ARTE trial were gastro-intestinal. Despite the claim of the investigators that proton-pump inhibitors (PPI) were not specifically recommended in patients included in the trial, one wonders if and how much the preventive use of PPI would have impacted that risk. The use of PPI is currently recommended in all DAPT patients, even if the risk of GI complications a prior is not high (20,21).

Stroke mainly occurs in the acute phase after TAVI and cerebral protection devices have been proposed to integrate pharmacologic therapy to prevent such complications. Recent studies support benefits of embolic protection during TAVI, indirectly providing further evidence for the importance of embolic debris in periprocedural stroke events (22,23).

While ARTE and the two prior trials investigated the concomitant use of clopidogrel in TAVI patients (18), there are arguments supporting the preferential use of OAC therapy instead of antiplatelet agents. First, there is still uncertainties regarding the exact mechanisms causing thrombotic events after TAVI and currently we cannot exclude that thrombin is the major driver or a co-driver of such complications. Second, the rates of pre-existing atrial fibrillation and new-onset atrial fibrillation are relevant in TAVI population and significantly impact on stroke and mortality (24,25). Third, there is evidence that leaflet thrombosis of transcatheter heart valves could be a relatively novel and important mechanism of transcatheter heart valve-related thrombotic events or even valve failure. Data from two registries, the SAVORY (Subclinical Aortic Valve Bioprosthesis Thrombosis Assessed with Four-Dimensional Computed Tomography) and the RESOLVE (Assessment of Transcatheter and Surgical Aortic Bioprosthetic Valve Thrombosis and Its Treatment with Anticoagulation), suggest that subclinical leaflet thrombosis, represented by leaflet thickening on computed tomography, is more common with transcatheter valves compared with bioprosthetic surgical valves, and is associated with increased rates of stroke or TIA (26). Importantly, anticoagulation (both novel OACs and warfarin), but not DAPT, was effective in the prevention or treatment of subclinical leaflet thrombosis (26), providing the rationale for investigating OAC use in TAVI patients (27). However, the natural history and clinical significance of asymptomatic leaflet thrombosis remains unclear. Assuming OAC therapy to be the solution, does starting it earlier rather than later make any difference and for how long should it be prescribed? Considering the OAC-related bleeding risks, it seems logical for the time being, in the absence of compelling evidence that the decision on which antithrombotic therapy should be individualized, after with careful consideration of the risk/benefit profile.

Currently, the complex puzzle of the optimal antithrombotic therapy after TAVI remains intriguing but unsolved. Clinical trials are ongoing (*Table 1*) and their results will hopefully add the missing pieces in this complex puzzle of optimal antithrombotic therapy after TAVI.

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None.

Table 1 Ongoing trials on the antithrombotic treatment after TAVI

Trials	ATLANTIS	AUREA	AVATAR	ENVISAGE-TAVI	GALILEO	POPULAR-TAVI	CLOE
ClinicalTrials.gov ID	NCT02664649	NCT01642134	NCT02735902	NCT02943785	NCT02556203	NCT02247128	Announced
Patients	1,510	124	170	1,400	1,520	1,000	NA
Indication to OAC	Yes	No	Yes	Yes	No	Yes (cohort B)	Yes
Comparison	Apixaban *vs*. SAPT/DAPT (no OAC indication) or VKA (OAC indication)	DAPT *vs*. VKA	VKA *vs*. ASA + VKA	Edoxaban *vs*. VKA. APT per local practice	Rivaroxaban + ASA *vs*. DAPT for 3 m then rivaroxaban vs. ASA	ASA *vs*. DAPT (cohort A) or Clop + VKA vs. VKA (cohort B)	ASA *vs*. DAPT or clop + VKA *vs*. VKA
Follow-up (months)	Up to 13	3	12	36	Up to 25	12	NA
Primary endpoint	Composite of death, MI, stroke, SEE, intracardiac or bioprosthesis thrombus, any DVT or PE, life-threatening or disabling or major VARC-2 bleeding	Prevention of cerebral thromboembolism by the detection of new areas of cerebral infarction by MRI at 3 months	Composite of all-cause death, MI, stroke all causes, valve thrombosis and hemorrhage ≥2 as defined by the VARC-2	Composite of all-cause death, MI, ischemic stroke, SEE, valve thrombosis, and ISTH major bleeding	Composite of all-cause death and adjudicated any stroke, MI, symptomatic valve thrombosis, PE, DVT, or non-CNS-SE	Freedom of all BARC bleeding at 1 y. The co-primary outcome is freedom of non-procedure related BARC bleeding at 1 y	NA

ATLANTIS, Anti-Thrombotic Strategy After Trans-Aortic Valve Implantation for Aortic Stenosis; APT, antiplatelet therapy; ASA, aspirin; AUREA, Dual Antiplatelet Therapy Versus Oral Anticoagulation for a Short Time to Prevent Cerebral Embolism After TAVI; AVATAR, Anticoagulation Alone Versus Anticoagulation and Aspirin Following Transcatheter Aortic Valve Interventions; BARC, Bleeding Academic Research Consortium; non-CNS-SE, Non-central nervous system-systemic embolism; DAPT, dual antiplatelet therapy; DVT, deep vein thrombosis; ENVISAGE TAVI, Edoxaban Compared to Standard Care After Heart Valve Replacement Using a Catheter in Patients With Atrial Fibrillation; GALILEO, Global Study Comparing a rivaroxaban-based Antithrombotic Strategy to an antiplatelet-based Strategy After Transcatheter aortic valve replacement to Optimize Clinical Outcomes; ISTH, International Society on Thrombosis and Haemostasis; MI, myocardial infarction; MRI, Magnetic Resonance Imaging; NA, not available; OAC, oral anticoagulation; PE, pulmonary embolism; Popular-TAVI, Antiplatelet Therapy for Patients Undergoing Transcatheter Aortic Valve Implantation; SEE, systemic embolic events; VARC, Valve Academic Research Consortium; VKA, vitamin K antagonist.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Part 3

Trade-off for ischemia and bleeding and optimal clinical outcomes during and after transcatheter aortic valve implantation (TAVI):

Risk stratification and optimization of clinical outcomes in patients undergoing TAVI

Annals of Internal Medicine

REVIEW

Transcatheter Aortic Valve Implantation Versus Surgical Aortic Valve Replacement

A Systematic Review and Meta-analysis

Giuseppe Gargiulo, MD; Anna Sannino, MD; Davide Capodanno, MD, PhD; Marco Barbanti, MD; Sergio Buccheri, MD; Cinzia Perrino, MD, PhD; Piera Capranzano, MD; Ciro Indolfi, MD, PhD; Bruno Trimarco, MD; Corrado Tamburino, MD, PhD; and Giovanni Esposito, MD, PhD

Purpose: To compare clinical outcomes, including early (≤30-day) and midterm (≤1-year) mortality, in adults with severe aortic stenosis undergoing either transapical aortic valve implantation (TAVI) or surgical aortic valve replacement (SAVR).

Data Sources: MEDLINE, Cochrane, and Scopus databases (without language restrictions) from April 2002 to 5 April 2016; multiple registries and Web sites; scientific meeting presentations.

Study Selection: Five randomized trials and 31 observational matched studies comparing mortality outcomes after TAVI or SAVR.

Data Extraction: Two investigators independently extracted study data and rated risk of bias.

Data Synthesis: A total of 16 638 patients were analyzed. Overall, there was no statistically significant difference between TAVI and SAVR in early (odds ratio [OR], 1.01 [95% CI, 0.81 to 1.26]) or midterm (OR, 0.96 [CI, 0.81 to 1.14]) all-cause mortality. Analyses restricted to trials (early: OR, 0.80 [CI, 0.51 to 1.25]; midterm: OR, 0.90 [CI, 0.64 to 1.26]) were inconclusive, with wide CIs, whereas analyses of matched studies were similar to the overall results. Transfemoral TAVI provided mortality benefits over SAVR in trials. Analyses restricted to studies of patients at low to intermediate risk showed statistically nonsignificant reductions in early (OR, 0.67 [CI, 0.42 to 1.07]) and midterm (OR, 0.91 [CI, 0.67 to 1.23]) mortality with TAVI. Incidence of periprocedural myocardial infarction, major bleeding, acute kidney injury, and new-onset atrial fibrillation was lower with TAVI, but risk for pacemaker implantation, vascular complications, and paravalvular leak increased. Overall, there was a statistically nonsignificant increased risk in long-term (2- to 5-year) all-cause mortality with TAVI (OR, 1.28 [CI, 0.97 to 1.69]), whereas long-term mortality outcomes in patients at low to intermediate risk were inconclusive, with wide CIs (OR, 1.06 [CI, 0.59 to 1.91]).

Limitation: The number of trials was limited, and study designs and patient characteristics were heterogeneous.

Conclusion: Compared with SAVR, TAVI may have similar or better early and midterm outcomes for adults with aortic stenosis, including those at low to intermediate risk.

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*Drs. Gargiulo and Sannino contributed equally to this work.

For decades, surgical aortic valve replacement (SAVR) was the standard of care to alleviate symptoms and improve survival in patients with severe aortic stenosis (1). Recently, transcatheter aortic valve implantation (TAVI) emerged as a better option than either medical therapy or balloon aortic valvuloplasty for adult patients who cannot undergo SAVR and as a reasonable alternative to SAVR for those considered at high surgical risk (1–4).

Similar clinical outcomes at 5 years between TAVI with the Sapien balloon-expandable prosthesis (Edwards Lifesciences) and SAVR have been reported in high-risk surgical candidates from the PARTNER (Placement of Aortic Transcatheter Valves) trial (5). Compared with SAVR, TAVI with the CoreValve self-expanding prosthesis (Medtronic) showed benefits at 3 years in the U.S. CoreValve High Risk Study (6–8). As evidence supporting TAVI in patients at high risk consolidates, interest is increasing in comparative studies of TAVI and SAVR in patients at low or intermediate surgical risk (9–17). In the all-comers NOTION (Nordic Aortic Valve Intervention) trial, in which approximately 80% of patients were considered low risk, TAVI was not found to be superior to SAVR for the composite outcome of death from any cause, stroke, or myocardial infarction at 1 year (13.1% vs. 16.3%; *P* for superiority = 0.43) (9, 10). PARTNER 2A, a recent trial in intermediate-risk patients, also showed no statistically significant differences between TAVI and SAVR for the primary end point of death or disabling stroke at 2 years (11).

Given several recent studies, extended follow-up of previous studies, and some conflicting results, we conducted an updated meta-analysis comparing clinical outcomes, including short- and midterm mortality, of adult patients with severe aortic stenosis undergoing either TAVI or SAVR.

METHODS

Protocol

We developed and followed a protocol (**Supplement 1**, available at www.annals.org) and followed PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) reporting guidelines (18).

See also:

Web-Only
Supplement

Data Sources and Searches

MEDLINE, Cochrane, and Scopus databases were searched, without language restrictions, for articles published from April 2002 (first-in-human TAVI date) until 5 April 2016. The search strategy used a combination of terms, such as "transcatheter aortic valve implantation" or "transcatheter aortic valve replacement" or "TAVI" or "TAVR" and "versus" and "surgical aortic valve replacement" or "SAVR" (**Supplement 2**, available at www.annals.org). Additional sources searched from January 2015 to 5 April 2016 included www.clinicaltrials.gov, www.clinicaltrialresults.org, www.tctmd.com, www.cardiosource.org, www.theheart.org, www.escardio.org, Google Scholar, and abstracts/presentations from major cardiovascular meetings. Reference lists of relevant studies, reviews, editorials, and letters also were scrutinized.

Study Selection

Citations were screened at the title and abstract level by 2 independent reviewers, and full text was retrieved for those reporting outcome data. Discrepancies, if any, were resolved by consensus. Randomized or observational matched studies were included if they reported mortality data of adult patients with severe aortic stenosis treated with TAVI versus SAVR. Matched studies had to have TAVI and SAVR groups matched for propensity score or preoperative variables to minimize the effect of baseline confounding factors. A study was excluded if any of the following criteria applied: It reported observational unmatched data (no type of matching was used to account for differences in preoperative characteristics); it was a duplicate publication; or the mortality outcome was not reported or could not be derived from the published results.

Data Extraction and Study Quality

The most up-to-date or inclusive data for a given study were chosen for abstraction. Two investigators independently identified studies, extracted data, and rated the risk of bias at the study level. The quality of randomized and observational matched studies included in the meta-analysis was appraised, respectively, by using Cochrane methods (selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias) and Newcastle–Ottawa Scale (selection, comparability, and outcome) criteria as previously described (19–21).

Study Outcomes

Main outcomes of interest in this study were early (≤30-day) and midterm (≤1-year) all-cause mortality. Secondary outcomes of interest included long-term (>1-year) all-cause mortality; 30-day and midterm stroke; and an array of periprocedural complications, including 30-day cardiovascular mortality, myocardial infarction, permanent pacemaker implantation, major bleeding, vascular complication, acute kidney injury, new-onset atrial fibrillation, and moderate to severe paravalvular leak.

Data Synthesis and Analysis

Effect sizes were calculated with the Knapp–Hartung random-effects estimator and expressed as odds ratios (ORs) and 95% CIs, as previously reported (22). Heterogeneity was assessed by I^2 tests, with substantial heterogeneity defined as I^2 greater than 50%. Mortality outcomes were stratified by study design (randomized or matched) and TAVI access. Multiple sensitivity analyses were performed to investigate potential sources of inconsistency, including removal of the following: individual studies at each time, non–propensity-matched studies, studies including fewer than 100 patients, studies recruiting patients at low to intermediate risk, studies performing TAVI by transapical approach only, studies that did not use standardized definitions (Valve Academic Research Consortium [VARC]/VARC2 and VARC/VARC2-like criteria), and studies with moderate to high risk of bias. A subgroup analysis restricted to patients at lower (low to intermediate) surgical risk also was performed that included only studies that prespecified inclusion of patients at lower risk. Mortality data from post hoc analyses of the U.S. CoreValve (patients with Society of Thoracic Surgery [STS] score <7%) and PARTNER (patients with STS score <11%) trials did not contribute to this subanalysis because the entry criterion of these trials was "high risk" as defined by clinicians on the basis of STS score and other clinical variables not included in the STS score algorithm. Exploratory metaregressions also were done to investigate the influence of baseline characteristics as potential effect modifiers. Publication bias was assessed by using funnel plots, Begg tests, Egger tests, and the trim-and-fill method. Data were analyzed by using the metafor package for R (R Foundation for Statistical Computing), Reviewer Manager (RevMan, version 5.2; Cochrane), and ProMeta (version 2; Internovi) software (22–25).

Role of the Funding Source

No external funding was received.

RESULTS

Search Results and Study Details

Of 444 articles initially identified, 80 were retrieved for detailed evaluation and 36 met inclusion criteria (**Supplement Figure 1**, available at www.annals.org). Five studies were randomized trials (5, 6, 9, 11, 26), and 31 were observational matched designs (12–17, 27–51). Propensity score matching was used in 25 studies, whereas 6 were matched on the basis of selected clinical characteristics. All studies provided data on short- or midterm all-cause mortality, whereas long-term mortality data (ranging from 2 to 5 years; mean, 33 months) were available for 4 randomized (5, 8, 10, 11) and 6 matched (15, 37, 42, 44, 45, 51) studies. The risk of bias in studies mostly was low, although the interventions were unavoidably unblinded (**Supplement Tables 1** and **2**, available at www.annals.org). Among randomized trials, STACCATO (A Prospective, Randomised

Table. Characteristics of the Randomized Trials*

Characteristic	NOTION (9, 10)	PARTNER (3–5)	PARTNER 2A (11)	STACCATO (26)	U.S. CoreValve (6–8)
End of enrollment	2013	2009	2013	2011	2012
Year of publication	2015	2011	2016	2012	2014
Patients randomly assigned, *n*	280	699	2031	72	795
Country	Denmark (2 sites), Sweden (1 site)	United States (22 sites), Canada (2 sites), Germany (1 site)	United States (55 sites), Canada (2 sites)	Denmark (2 sites)	United States (45 sites)
Randomization	TAVI vs. SAVR	Transfemoral TAVI vs. SAVR Transapical TAVI vs. SAVR	Transfemoral TAVI vs. SAVR Transapical/transaortic TAVI vs. SAVR	Transapical TAVI vs. SAVR	TAVI vs. SAVR
Valve type	CoreValve (Medtronic)	Sapien (Edwards)	Sapien XT	Sapien	CoreValve
Design	Superiority	Noninferiority	Noninferiority	Superiority	Noninferiority and superiority
Primary end point	Death from any cause, stroke, or myocardial infarction at 1 y	Death from any cause at 1 y	Death from any cause or disabling stroke at 2 y	Death from any cause or cerebral stroke and/or renal failure requiring hemodialysis at 30 d	Death from any cause at 1 y
Result	Superiority not shown	Noninferiority shown	Noninferiority shown	Inconclusive due to premature termination	Noninferiority and superiority shown

NOTION = Nordic Aortic Valve Intervention; PARTNER = Placement of Aortic Transcatheter Valves; SAVR = surgical aortic valve replacement; STACCATO = A Prospective, Randomised Trial of Transapical Transcatheter Aortic Valve Implantation Versus Surgical Aortic Valve Replacement in Operable Elderly Patients with Aortic Stenosis; TAVI = transcatheter aortic valve implantation.
* Values in parentheses in column headings are reference numbers.

Trial of Transapical Transcatheter Aortic Valve Implantation Versus Surgical Aortic Valve Replacement in Operable Elderly Patients With Aortic Stenosis) had a high risk of bias because of underpowered results and was terminated prematurely after accruing only 70 of the 200 planned patients.

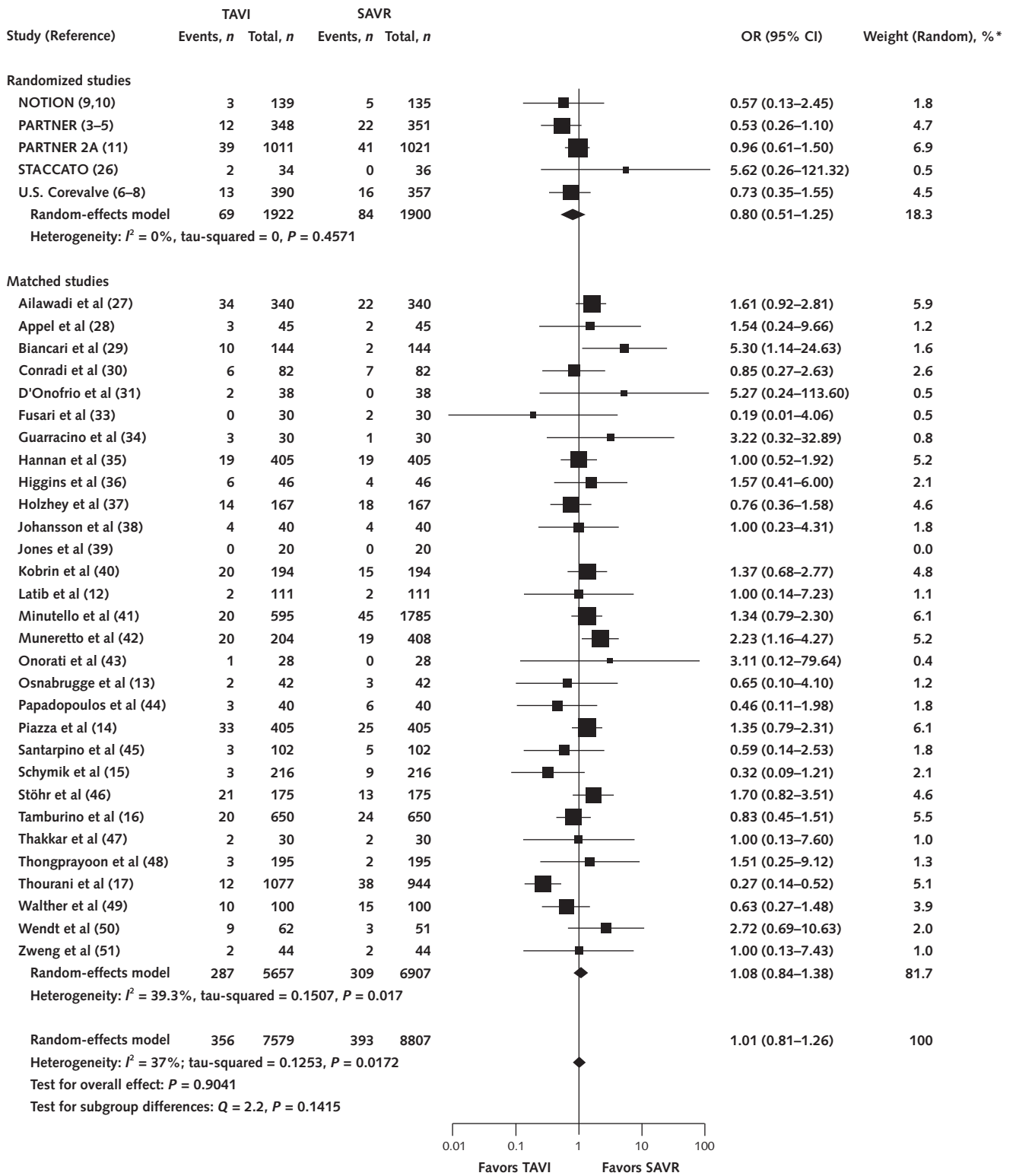
Patient Characteristics

A total of 16 638 patients undergoing TAVI (n = 7732) or SAVR (n = 8906) were analyzed. Although most studies involved patients at high surgical risk, 2 randomized trials (9, 11) and 6 matched studies (12–17) included patients at low to intermediate risk. The NOTION trial included patients across the full spectrum of risk, with most considered low risk (mean STS score, 3.0%) (9), whereas the PARTNER 2A trial involved intermediate-risk patients (mean STS score, 5.8%) (11). The mean age of patients enrolled in all the included studies ranged from 70 to 84 years. Most patients were in New York Heart Association functional class III or IV. Comorbid conditions varied across studies, and some studies focused on selected scenarios or patients. Four focused on redo procedures; of these, 1 included patients with prior coronary artery bypass grafting and 3 included those with prior cardiac surgery (39, 43, 44, 50). One study analyzed only patients with liver disease (47) and another only those on dialysis (40). In most cases, TAVI patients received a first-generation valve, except those in 1 study that used the latest-generation balloon-expandable Sapien 3 valve (17). Transfemoral access was the predominant approach, although 7 studies focused exclusively on transapical procedures (26, 31, 36, 37, 43, 44, 49). In most studies, SAVR was done conventionally, with 4 studies using a sutureless approach (29, 31, 42, 45). Detailed characteristics of the studies are reported in the **Table** and in **Supplement Tables 3** to **6** (available at www.annals.org).

Main Outcomes: Early and Midterm All-Cause Mortality

There was no statistically significant difference in early all-cause mortality between TAVI and SAVR (35 studies, 16 386 patients; OR, 1.01 [95% CI, 0.81 to 1.26]) (**Figure 1**). The lack of statistically significant differences was consistent across multiple sensitivity analyses (**Supplement Tables 7** and **8**, available at www.annals.org). The stratified analysis showed a statistically nonsignificant 20% risk reduction with TAVI compared with SAVR (5 studies, 3822 patients; OR, 0.80 [CI, 0.51 to 1.25]) in randomized trials and no apparent difference in matched studies (30 studies, 6372 patients; OR, 1.08 [CI, 0.84 to 1.38]) without significant subgroup interaction (interaction P = 0.14) (**Figure 1**). In exploratory metaregression analyses, statistically significant treatment modifiers were age, coronary artery disease, previous percutaneous coronary intervention, and valve type. Older age, greater prevalence of coronary artery disease, previous percutaneous coronary intervention, and use of the Sapien valve were associated with an improved 30-day treatment effect of TAVI, whereas use of the CoreValve was associated with worse 30-day outcomes (**Supplement Figure 2** and **Supplement Table 9**, available at www.annals.org). Funnel plots, the Begg test (P = 0.56), the Egger test (P = 0.76), and the trim-and-fill method (1 study trimmed; OR, 1.00 [CI, 0.81 to 1.25]) did not highlight any significant publication bias.

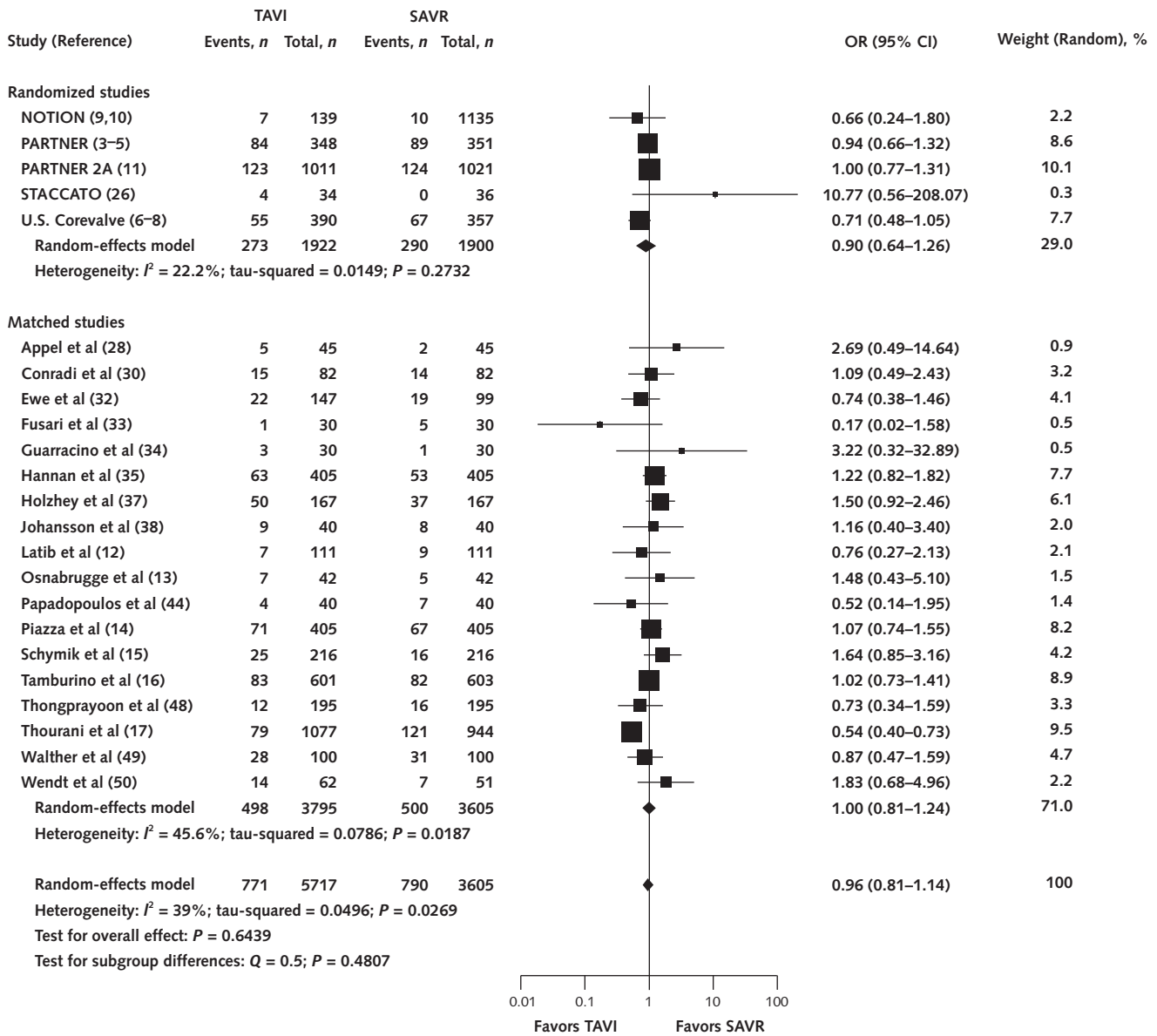
Figure 1. Forest plot for early all-cause mortality in the overall population.



Knapp–Hartung random-effects OR and 95% CI for 30-day all-cause mortality stratified by study design. NOTION = Nordic Aortic Valve Intervention; OR = odds ratio; PARTNER = Placement of Aortic Transcatheter Valves; SAVR = surgical aortic valve replacement; STACCATO = A Prospective, Randomised Trial of Transapical Transcatheter Aortic Valve Implantation Versus Surgical Aortic Valve Replacement in Operable Elderly Patients With Aortic Stenosis; TAVI = transcatheter aortic valve implantation.

* Percentages do not sum to 18.3% and 81.7% for randomized and matched studies, respectively, because of rounding.

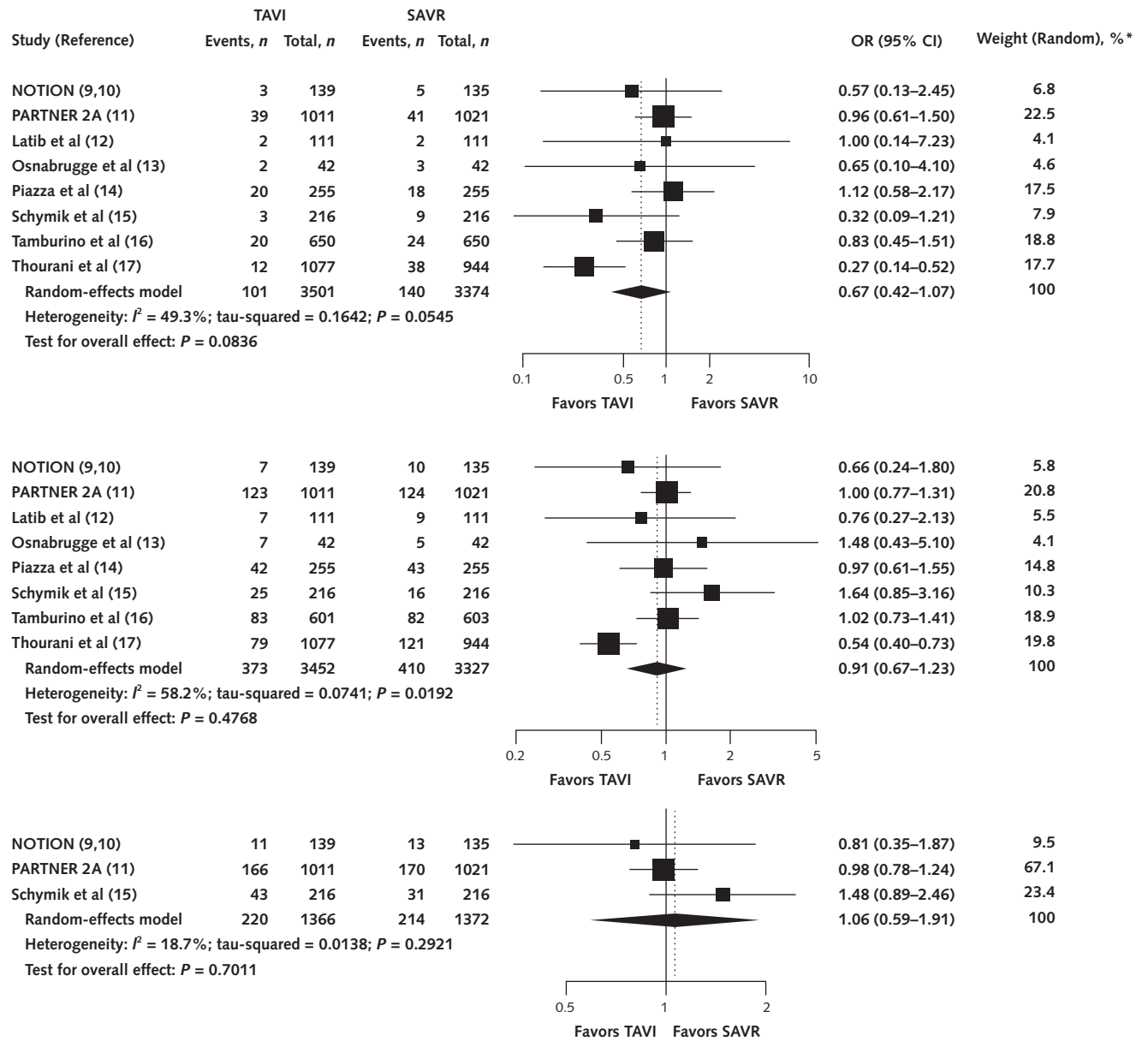
Figure 2. Forest plot for midterm all-cause mortality in the overall population.



Knapp–Hartung random-effects OR and 95% CI for midterm all-cause mortality stratified by study design. NOTION = Nordic Aortic Valve Intervention; OR = odds ratio; PARTNER = Placement of Aortic Transcatheter Valves; SAVR = surgical aortic valve replacement; STACCATO = A Prospective, Randomised Trial of Transapical Transcatheter Aortic Valve Implantation Versus Surgical Aortic Valve Replacement in Operable Elderly Patients With Aortic Stenosis; TAVI = transcatheter aortic valve implantation.

Midterm all-cause mortality did not differ between TAVI and SAVR (23 studies, 11 222 patients; OR, 0.96 [CI, 0.81 to 1.14]) (**Figure 2**). The lack of statistically significant differences was consistent in multiple sensitivity analyses (**Supplement Tables 7** and **8**) and in the subgroups of randomized trials (5 studies, 3822 patients; OR, 0.90 [CI, 0.64 to 1.26]) (**Figure 2**) and matched studies (18 studies, 7400 patients; OR, 1.00 [CI, 0.81 to 1.24]; interaction P = 0.48) (**Figure 2**). In exploratory metaregression analyses, statistically significant treatment modifiers were age, male sex, and coronary artery disease; older age and a higher percentage of men or patients with coronary artery disease were associated with an improved treatment effect of TAVI at 1 year (**Supplement Figure 3** and **Supplement Table 9**, available at www.annals.org). No other factors modified the treatment effect of TAVI, including the type of prosthesis implanted (Sapien or CoreValve). Funnel plots, the Begg test (P = 0.75), the Egger test (P = 0.27), and the trim-and-fill method (2 studies trimmed; OR, 0.95 [CI, 0.81 to 1.12]) did not suggest significant publication bias.

Figure 3. Forest plots for all-cause mortality in the low- to intermediate-risk population.



Knapp–Hartung random-effects OR and 95% CI for 30-day (*top*), midterm (*middle*), and long-term (*bottom*) all-cause mortality in patients at low to intermediate risk. NOTION = Nordic Aortic Valve Intervention; OR = odds ratio; PARTNER = Placement of Aortic Transcatheter Valves; SAVR = surgical aortic valve replacement; TAVI = transcatheter aortic valve implantation.
* Percentages do not sum to 100% for early all-cause mortality because of rounding.

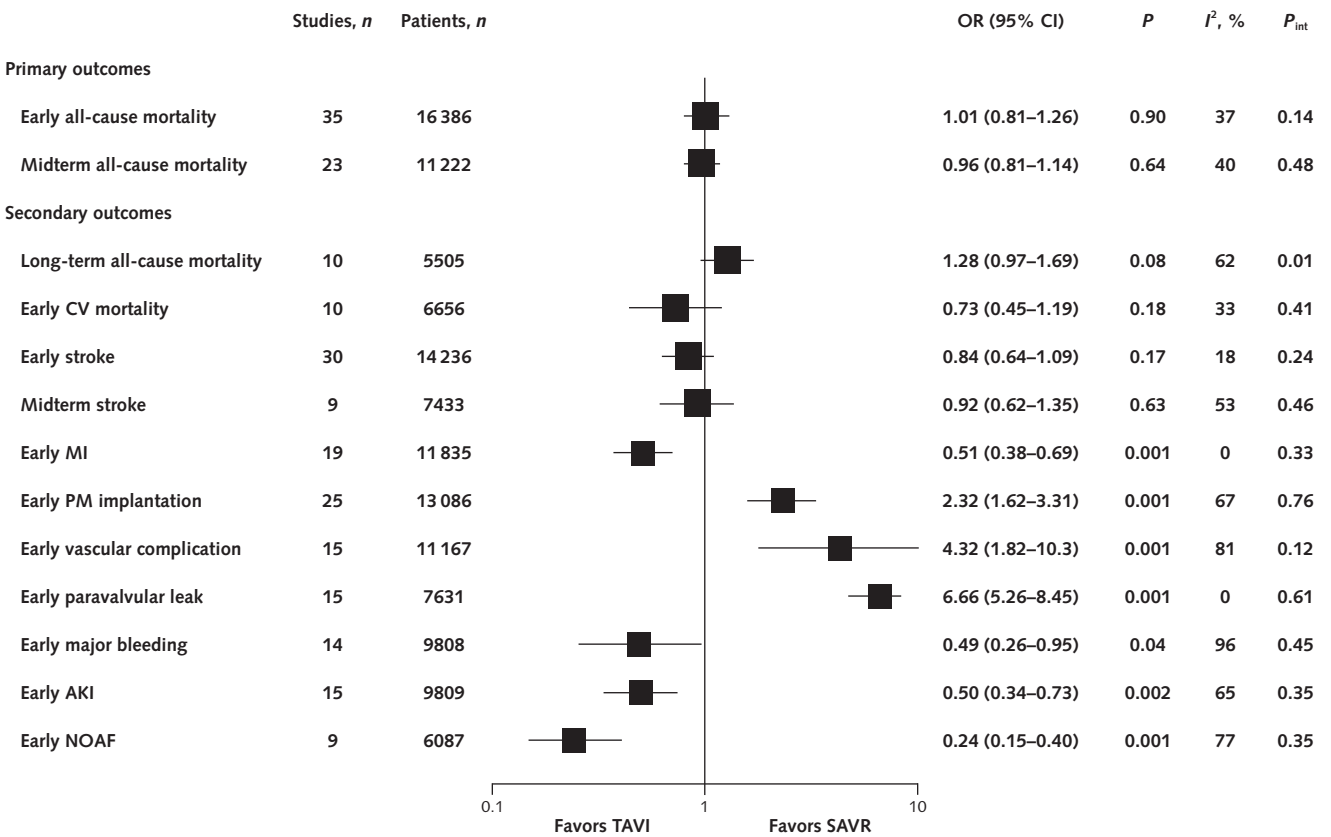
Effect of TAVI Approach

When early all-cause mortality in randomized trials was stratified by TAVI approach, lower mortality was observed in patients who received transfemoral TAVI than in those who underwent SAVR (4 studies, 3063 patients; OR, 0.68 [CI, 0.53 to 0.87]) (**Supplement Figure 4**, available at www.annals.org) but was not seen in those who had transapical TAVI (3 studies, 759 patients; OR, 1.27 [CI, 0.15 to 10.9]) (**Supplement Figure 4**). This finding also was observed for midterm mortality (transfemoral: 4 studies, 3063 patients; OR, 0.80 [CI, 0.68 to 0.93]; transapical: 3 studies, 759 patients; OR, 1.41 [CI 0.51 to 3.86]; test for interaction $P = 0.02$) (**Supplement Figure 5**, available at www.annals.org).

Patients at Low to Intermediate Risk

Analyses of the subgroup of studies with patients at low to intermediate risk showed a statistically nonsignificant reduction in early (8 studies, 6875 patients; OR, 0.67 [CI, 0.42 to 1.07]) and midterm (8 studies, 6779 patients; OR, 0.91 [CI, 0.67 to 1.23]) mortality with TAVI compared with SAVR (**Figure 3**).

Figure 4. Forest plot for all outcomes of the meta-analysis.



Summary of Knapp–Hartung random-effects OR and 95% CI for all end points, including forest plots and details of studies and participants. AKI = acute kidney injury; CV = cardiovascular; MI = myocardial infarction; NOAF = new-onset atrial fibrillation; OR = odds ratio; P_{int} = interaction *P*; PM = pacemaker; SAVR = surgical aortic valve replacement; TAVI = transcatheter aortic valve implantation.

Secondary Outcomes

There was a statistically nonsignificant increased risk in long-term all-cause mortality between TAVI and SAVR overall (10 studies, 5505 patients; OR, 1.28 [CI, 0.97 to 1.69]) (**Supplement Figure 6**, available at www.annals.org). In the analysis stratified by study design, no statistically significant differences were noted in the randomized studies, whereas SAVR was better than TAVI in matched studies, with significant interaction between these subgroups (interaction $P = 0.008$) (**Supplement Figure 6**). Long-term mortality stratified by the TAVI approach in randomized trials showed that TAVI was better than SAVR in the transfemoral subgroup, with the opposite result in the transapical subgroup and significant interaction between subgroups (interaction $P < 0.001$) (**Supplement Figure 7**, available at www.annals.org). Long-term mortality was similar for TAVI and SAVR in patients at low to intermediate risk (3 studies, 2738 patients; OR, 1.06 [CI, 0.59 to 1.91]) (**Figure 3**).

Other secondary outcomes are displayed in **Figure 4** and the **Supplemental Material** (available at www.annals.org). No statistically significant differences were apparent between TAVI and SAVR in early cardiovascular death (10 studies, 6656 patients; OR, 0.73 [CI, 0.45 to 1.19]) (**Supplement Figure 8**, available at www.annals.org) or stroke (early: 30 studies, 14 236 patients; OR, 0.84 [CI, 0.64 to 1.09]; midterm: 9 studies, 7433 patients; OR, 0.92 [CI, 0.62 to 1.35]) (**Supplement Figures 9** and **10**, available at www.annals.org). Myocardial infarction was reduced by 49% in patients undergoing TAVI (19 studies, 11 835 patients; OR, 0.51 [CI, 0.38 to 0.69]) (**Supplement Figure 11**, available at www.annals.org), with consistency in randomized and matched studies (interaction $P = 0.33$). Permanent pacemaker implantation (**Supplement Figure 12**, available at www.annals.org), vascular complications (**Supplement Figure 13**, available at www.annals.org), and moderate to severe paravalvular leak (**Supplement Figure 14**, available at www.annals.org) were more frequent after TAVI, whereas major bleeding (**Supplement Figure 15**, available at www.annals.org), acute kidney injury (**Supplement Figure 16**, available at www.annals.org), and new-onset atrial fibrillation (**Supplement Figure 17**, available at www.annals.org) were more frequent after SAVR (**Figure 4**).

DISCUSSION

This meta-analysis highlights several key points. Compared with SAVR, TAVI may have similar or reduced early and midterm all-cause mortality outcomes in patients with high and low to intermediate risk. Transfemoral TAVI provides mortality benefits over SAVR. Compared with SAVR, TAVI reduces early myocardial infarction, but its benefits on early cardiovascular death and stroke remain unclear. Acute kidney injury, major bleeding, and new-onset atrial fibrillation occur less often after TAVI than after SAVR. Pacemaker implantation, vascular complications, and paravalvular leak occur more often after TAVI than after SAVR. Effects of TAVI on long-term mortality are unclear but may depend on the patient's underlying risk level and the TAVI approach used.

These findings, which apply to adults with severe aortic stenosis, consolidate the role of TAVI as an alternative to SAVR. Since the first percutaneous aortic valve implantation in a human in 2002, TAVI has attracted growing interest. Patients undergoing TAVI typically are older adults who have clinically relevant comorbid conditions that preclude SAVR (1, 2). It originally emerged as a treatment option for patients who were judged inoperable due to prohibitive surgical risk and referred to medical therapy. During the past decade, clinical practice guideline committees have reviewed accumulating evidence and have recognized TAVI as a reasonable alternative to SAVR for patients at high surgical risk (1, 2). As experience with TAVI increased and the outcomes improved, 2 important clinical questions arose: First, is TAVI similar to or better than SAVR in patients at high risk? Second, is the adoption of TAVI justified for patients at lower surgical risk?

We tried to address these questions by summarizing the available comparisons of TAVI and SAVR in the literature. We elected all-cause mortality as the most relevant outcome for many reasons, including its clinical implications, frequent reporting, and indisputable definition. In our analysis of the 5 available randomized trials, early and midterm all-cause mortality was nonsignificantly reduced with TAVI, but the treatment effect of TAVI was greater (although it did not reach formal statistical significance) when we excluded the STACCATO trial, a study with well-known limitations that did not replicate contemporary practice or outcomes of TAVI (26), and became statistically significant when we restricted the analysis to studies in which TAVI was done transfemorally, in line with the most recent evidence (11, 52). Among the observational matched studies, there also was no difference between TAVI and SAVR, resulting in no significant interaction across subgroups defined by study design, although randomized studies remain the best evidence to guide inference and interpretation. Other studies (with increased available total information size) are needed to provide definitive results regarding long-term mortality, which was found to be nonsignificantly increased in TAVI patients (a secondary end point in our study because of the limited number of studies), although this result was driven mainly by matched studies. Long-term follow-up information currently is being provided by 4 randomized trials (PARTNER, U.S. CoreValve, PARTNER 2A, and NOTION, with 5, 3, 2, and 2 years of follow-up, respectively) and so far has shown no significant difference between TAVI and SAVR (**Supplement Figure 6**). However, the matched studies showed lower long-term mortality for SAVR, and a significant interaction by study design was observed. In the aggregate, long-term results were available from 10 studies with a mean follow-up of 33 months; thus, more evidence is warranted in this regard, particularly concerning the sustained durability of TAVI prostheses. However, increasing expertise, new-generation TAVI devices, and the transfemoral approach might lead to better long-term comparative results from TAVI in the near future, as suggested by the most recent studies (11, 17). Indeed, TAVI techniques continue to improve, newer valves address the issue of paravalvular leak, the percentage of persons with pacemakers is decreasing, and the rate of vascular complications is expected to decline as the result of smaller sheaths and improved procedural techniques. Future mortality studies will assess the net effects of emerging technical improvements and potential long-term clinical gains versus a possible increase in the late adverse consequences of paravalvular leak and pacemaker implantation.

Interestingly, exploratory metaregressions suggest that TAVI may be more beneficial than SAVR in elderly patients and those with coronary artery disease, probably because these groups might represent markers of heightened risk favoring less invasive approaches. Notably, TAVI showed greater benefit regarding early mortality when the Sapien valve rather than the CoreValve was implanted, but this finding is guided mainly by the large study by Thourani and colleagues (17) (showing superiority of TAVI with the new Sapien 3 valve) and did not emerge at midterm follow-up. Future studies directly comparing these valves, as well as new devices, would overcome the limitations of this analysis.

Although the potential benefits of TAVI versus SAVR in terms of early cardiovascular mortality and stroke remain unclear, TAVI was associated with significantly less risk for myocardial infarction than SAVR; however, a sound mechanistic explanation cannot be drawn from our data. That the observed reduction in myocardial infarction might be responsible for the nonsignificant lower cardiac death rate is intriguing and warrants further investigation. TAVI was also associated with significant reductions in major bleeding, acute kidney injury, and new-onset atrial fibrillation compared with SAVR, but the need for pacemaker implantation, vascular complications (related mainly to the access site), and paravalvular leak were significantly less with SAVR (**Figure 4**).

To our knowledge, this is the largest meta-analysis of TAVI versus SAVR that includes randomized trials and explores the effect of the TAVI approach (transfemoral or transapical) (53–57). Unlike the authors of a recent study, we investigated the risk for death in the

subgroup of patients at low to intermediate risk, extending our observation to mid- and long-term mortality and not considering the U.S. CoreValve or STACCATO trials in this subgroup because, regardless of the mean STS score, they enrolled high-risk patients in accordance with their inclusion criteria (58). To improve the power and reliability of our results while minimizing the risk of bias, we also included observational studies but applied a restriction to those with matched populations. Indeed, we excluded many available observational studies that compared the 2 procedures in unbalanced populations, namely TAVI in inoperable or high-risk patients (according to evidence and guidelines) and SAVR in lower-risk cohorts.

Ongoing trials comparing TAVI and SAVR will provide additional data (**Supplement Tables 10** and **11**, available at www.annals.org). The results of the SURTAVI (Surgical Replacement and Transcatheter Aortic Valve Implantation) trial (NCT01586910) will shed light on patients at intermediate risk, whereas 2 recently announced trials will explore the safety and effectiveness of TAVI in low-risk patients: PARTNER 3 (NCT02675114), using the Sapien 3 device, and a Medtronic study (NCT02701283) using the CoreValve/Evolut R system.

Several limitations of this review and of the underlying evidence merit careful consideration. There were few trials and, in some instances, few events. Confidence bounds around some of the summary estimates of effect were too wide to rule out potentially important benefits or harms from TAVI versus SAVR. Definitions of clinical outcomes, other than mortality, varied across studies (**Supplement Table 5**). Because baseline characteristics were not reported uniformly, results of metaregression analyses were mainly exploratory (**Supplement Tables 3**, **4**, and **9**). Long-term data were limited, which is a particularly critical limitation because valve durability is a major unknown of TAVI and an important issue when the procedure is being considered for younger or lower-risk patients. Mean age of patients in the included studies ranged from 70 to 84 years, and findings cannot be extended to younger or older patients. It was not possible to analyze mortality after excluding patients with paravalvular leak. A post hoc analysis from the PARTNER trial demonstrated that the mortality of patients with postprocedural paravalvular leak was greater than that of patients without this complication (4). If patients with paravalvular leak are removed from the mortality analyses (a plausible scenario in the future, considering the very low rate of paravalvular regurgitation with new-generation TAVI devices) (59, 60), the results might turn in favor of TAVI, but this has to be demonstrated. The definition of "low" or "intermediate" risk is based on the definition used in the original studies, which is not standardized. Some studies were based on STS score and others on EuroSCORE; however, surgical risk scores alone do not account for the clinical characteristics and comorbid conditions that may have increased the level of patient risk perceived by the local heart teams.

Compared with SAVR, TAVI may lead to similar or lower early and midterm mortality rates in adults with aortic stenosis, including those at low to intermediate risk. There was a significant interaction between TAVI approach and mortality, with transfemoral TAVI being more beneficial than SAVR. At long-term follow-up, the effects on mortality remain unclear but may depend on the underlying risk level of the patient or procedural approach.

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Reproducible Research Statement: *Study protocol:* See **Supplement 1**. *Statistical code and data set:* Available from Dr. Gargiulo (e-mail, peppegar83@libero.it or giuseppe.gargiulo1@unina.it).

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A meta-analysis of the impact of pre-existing and new-onset atrial fibrillation on clinical outcomes in patients undergoing transcatheter aortic valve implantation

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KEYWORDS

- mortality
- new-onset atrial fibrillation
- pre-existing atrial fibrillation
- severe aortic stenosis
- transcatheter aortic valve implantation

Abstract

Aims: Little is known about the prognostic role of pre-existing atrial fibrillation (AF) and new-onset AF (NOAF) in transcatheter aortic valve implantation (TAVI). Therefore, the aim of this meta-analysis was to compare the short- and long-term clinical outcomes of patients undergoing TAVI with and without pre-existing and new-onset AF.

Methods and results: Twenty-six studies, enrolling 14,078 patients undergoing TAVI, of whom 33.4% had pre-existing AF and 17.5% had NOAF, were analysed for early and long-term all-cause mortality, cardiovascular mortality and cerebrovascular events (CVE). In patients with pre-existing AF, 30-day all-cause mortality was similar to patients in sinus rhythm (SR). Conversely, long-term all-cause and cardiovascular mortality were significantly greater in pre-existing AF patients than in patients with SR (20 studies; 8,743 patients; HR: 1.68; p<0.00001, and three studies; 1,138 patients; HR: 2.07; p=0.01, respectively). Pre-existing AF was not a predictor of CVE at long-term follow-up. NOAF patients showed similar short- and long-term all-cause mortality when compared to patients in SR, whereas they experienced a significantly higher incidence of CVE at short-term follow-up (six studies; 2,025 patients; HR: 2.86; p<0.00001). A non-significant increase in the incidence of CVE was observed at long-term follow-up.

Conclusions: Pre-existing AF is a predictor of all-cause mortality in patients undergoing TAVI. NOAF is related to the occurrence of CVE at short-term follow-up. Similarly to surgical aortic valve replacement (SAVR), the optimal management and risk stratification of these patients should be further investigated.

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Abbreviations

AF	atrial fibrillation
AS	aortic stenosis
CI	confidence interval
CVE	cerebrovascular events
HR	hazard ratio
NOAF	new-onset atrial fibrillation
SAVR	surgical aortic valve replacement
SR	sinus rhythm
TAVI	transcatheter aortic valve implantation

Introduction

Atrial fibrillation (AF) is the most common arrhythmia in the general population, with a higher prevalence in the elderly as well as in patients with severe aortic stenosis (AS)[1]. AF and AS coexist in almost 30% of patients, with a prevalence that varies from 16% to 40%[2]. New-onset AF (NOAF) post transcatheter aortic valve implantation (TAVI), however, occurs in approximately 13% of patients, ranging from 0.7% to 31.9%[3].

Pre-existing AF and NOAF significantly affect cardiovascular physiology, due to loss of atrioventricular synchrony and irregularity of ventricular contraction resulting in reduced cardiac output and increased filling pressures, which may be further accentuated by the presence of severe AS and myocardial hypertrophy[4]. Additionally, the left ventricular outflow obstruction provoked by AS results in left ventricular hypertrophy and diastolic dysfunction, which may itself precipitate AF due to increased left atrial pressures[4].

AF has an important impact on cardiovascular morbidity and mortality[5]. Population-based studies have indicated an increased risk of stroke and systemic embolism as well as impaired long-term survival of individuals with AF compared to those with normal sinus rhythm (SR)[6]. In the general population, AF is estimated to increase the risk of death 1.5-fold among men and 1.9-fold among women[5]. Moreover, it has been shown previously that, after surgical aortic valve replacement (SAVR), AF represents an independent predictor of late adverse cardiac and cerebrovascular events (CVE), including congestive heart failure, stroke, and mortality[7,8]. Similarly, NOAF is associated with overall and late mortality after coronary artery bypass graft surgery and perioperative complications, and 30-day mortality and CVE in post-myocardial infarction patients[9].

In the last decade, TAVI has become the treatment of choice for inoperable or high-risk patients with severe, symptomatic AS, but the indication might be expanded in the near future. In the subset of patients with indications for TAVI, sparse and partly contrasting evidence exists regarding the impact of AF on morbidity and mortality. Some studies have indicated the absence of any significant impact of AF on prognosis[10-18], whilst others have shown increased mortality among patients with AF undergoing TAVI[19-30]. Moreover, a recent meta-analysis did not mention AF among predictors of all-cause mortality in patients undergoing TAVI[31].

Therefore, the aim of this meta-analysis was to compare the short- and long-term clinical outcomes of patients undergoing TAVI with and without pre-existing and new-onset AF.

Methods

The study was designed according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) requirements[32,33]. MEDLINE, Cochrane, ISI Web of Science and SCOPUS databases were searched for articles published from April 2002[34] (first-in-human TAVI date) until January 2015. Studies were identified using the major medical subject heading "transcatheter aortic valve implantation OR transcatheter aortic valve replacement OR TAVI OR TAVR" combined with "clinical outcome or mortality" and "atrial fibrillation". Citations were screened at the title and abstract level by two independent reviewers and retrieved as a full report if they reported data on outcomes after TAVI, based on the presence/absence of AF and/or if AF was considered as a predictor of mortality in their regression models. No language limitations were applied. The full texts and bibliographies of all potential articles were also retrieved in detail to seek additional relevant studies.

Studies were included if: 1) TAVI was performed in high surgical risk or inoperable patients (as defined by a logistic EuroSCORE >20 or by the presence of contraindications to surgery such as porcelain aorta, severe respiratory failure, unfavourable anatomy for sternotomy) with symptomatic, severe AS (defined as an aortic valve area <1 cm^2, or an indexed aortic valve area <0.6 cm^2/m^2); 2) they reported data of mortality outcomes according to the presence of pre-existing AF or NOAF.

Studies were excluded if any of the following criteria applied: 1) duplicate publication; 2) lack of data on pre-existing AF before TAVI or NOAF after the procedure; 3) the outcome of interest was not clearly reported or was impossible to extract or calculate from the published results.

Two reviewers independently screened articles for fulfilment of inclusion criteria. Reviewers compared selected trials and discrepancies were resolved by consensus. Baseline characteristics, AF at baseline and outcomes, including mortality outcomes, were abstracted.

The primary endpoint evaluated was the incidence of early and long-term all-cause mortality in patients with baseline or new-onset AF undergoing TAVI. Secondary endpoints of interest were the cardiovascular mortality and the incidence of CVE in the same population. Long-term follow-up included a time frame ranging from six months to five years from the procedure. Short-term follow-up corresponded to 30-day follow-up.

Of 1,424 articles identified by the initial search, 45 were retrieved for more detailed evaluation and 26 trials were included in the study **(Appendix Figure 1)**.

The number of events, participants, hazard ratios (HR) and confidence intervals (CI) were abstracted. Pooled measures were calculated assuming a random effects model using inverse variance weighting, and used the adjusted HR. The results were also confirmed with a fixed effects model; however, the random effects model was prioritised in case of significant heterogeneity. Statistical significance was set at $p \leq 0.05$ (two-tailed). Heterogeneity was assessed by a Q-statistic and I^2 test. Significant heterogeneity was considered present for p-values <0.10 or an I^2 >50%.

Meta-regressions were performed to test the influence of baseline characteristics included in **Table 1** as potential effect modifiers (significance at p≤0.05).

Publication bias was assessed using funnel plots and Egger's test, consisting of a linear regression of the intervention effect estimates on their standard errors, weighting by 1/(variance of the intervention effect estimate)[35]. If there was some evidence of publication bias, the trim and fill method, which estimates the number and results of potential missing studies resulting from publication bias, was applied[36].

All data analyses were performed using Prometa Software, Version 2 (Internovi, Cesena, Italy), and Review Manager (RevMan), Version 5.2 (The Cochrane Collaboration, London, United Kingdom)[37-41].

Results

Of the 1,424 articles identified in the initial search, 45 were retrieved for more detailed evaluation. Nineteen studies were subsequently excluded. Therefore, 26 studies, enrolling 14,078 patients, were finally included in the analyses **(Table 1, Appendix Table 1, Appendix Figure 1)**[10-30,42-46].

Pre-existing AF is common among patients with symptomatic severe aortic stenosis undergoing TAVI, with an average prevalence of 33.4±9.6% in our meta-population (23 studies; 13,241 patients; 3,824 pre-existing AF). NOAF incidence after TAVI was, on the other hand, 17.5±8.7% (nine studies; 4,749 patients; 831 NOAF).

In patients with pre-existing AF, the overall mortality risk post TAVI was not significantly increased at 30-day follow-up (eight studies, 3,329 patients, HR: 1.12, 95% confidence interval [CI]: 0.95 to 1.33; p=0.19, I^2=25%) **(Figure 1A, Appendix Table 2, Appendix Table 3)**. Conversely, it was significantly increased at long-term follow-up (20 studies, 8,743 patients, HR: 1.68, 95% CI: 1.45 to 1.96; p<0.00001, I^2=54%) **(Figure 1B, Appendix Table 2, Appendix Table 3)**.

Cardiovascular mortality at long-term follow-up was significantly increased in patients with pre-existing AF when compared to patients with baseline SR (three studies, 1,138 patients, HR: 2.07, 95% CI: 1.17 to 3.65; p=0.01, I^2=53%) **(Figure 2A, Appendix Table 2, Appendix Table 3)**.

Additionally, the presence of pre-existing AF in patients undergoing TAVI did not predict CVE at long-term follow-up (five studies, 4,604 patients, HR: 1.68, 95% CI: 0.86 to 3.30; p=0.13, I^2=75%) **(Figure 2B, Appendix Table 2-Appendix Table 4)**. All these results were confirmed with fixed effect models (**Appendix Figure 2** and **Appendix Figure 3**).

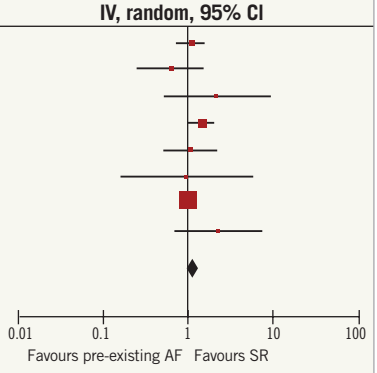
Table 1. Studies included in the meta-analysis.

	Publication year	Number of patients	FU (months)	Type of study
Alassar et al[29]	2013	119	16	Observational prospective, single-centre
Allende et al[24]	2014	619	12	Observational prospective, multicentre (9 centres)
Amat-Santos et al[44]	2012	138	12	Observational prospective, single-centre
Auffret et al[14]	2014	163	6	Observational prospective, single-centre
Barbash et al[30]	2015	371	1 12	Observational prospective, single-centre
Elhmidi et al[27]	2013	373	12	Observational prospective, single-centre
Gotzmann et al[26]	2013	202	18	Observational prospective, single-centre
Lange et al[12]	2012	420	1 6	Observational prospective, single-centre
LeVen et al[21]	2013	639	12	Observational retrospective, multicentre (2 centres)
Maan et al [46]	2014	137	12	Observational prospective, single-centre
Nombela-Franco et al[22]	2012	1,061	12	Observational prospective, multicentre (5 centres)
Nuis et al[28]	2012	995	1 12	Observational prospective, multicentre (7 centres)
Nuis et al[42]	2012	214	13	Observational prospective, single-centre
Ribeiro et al[13]	2014	333	20	Observational prospective, single-centre
Rodés-Cabau et al[20]	2010	339	1 42	Observational prospective, multicentre (6 centres)
Sabaté et al[25]	2014	1,416	12	Observational prospective, single-centre
Salinas et al[11]	2012	34	1 10.4	Observational prospective, single-centre
Seiffert et al[43]	2013	326	12	Observational prospective, single-centre
Stortecky et al[19]	2014	389	12	Observational prospective, single-centre
Tamburino et al[16]	2011	663	12	Observational prospective, multicentre (14 centres)
Tay et al [10]	2011	253	12	Observational prospective, single-centre
Tchetche et al[17]	2014	3,191	6	Observational prospective, multicentre (34 centres)
Toggweiler et al[15]	2013	88	60	Observational prospective, single-centre
Unbehaun et al[23]	2014	730	12	Observational prospective, single-centre
Urena et al[45]	2015	485	1	Observational prospective, multicentre (6 centres)
Yankelson et al[18]	2014	380	1 12	Observational retrospective, single-centre

A PRE-EXISTING AF: EARLY ALL-CAUSE MORTALITY

Study or subgroup	log [hazard ratio]	SE	Pre-AF total	SR total	Weight	Hazard ratio IV, random, 95% CI
Barbash et al 2014	0.104	0.195	143	182	0.3%	1.11 [0.76, 1.63]
Lange et al 2012	–0.462	0.45	97	323	0.0%	0.63 [0.26, 1.52]
Maan et al 2014	0.788	0.727	67	70	0.0%	2.20 [0.53, 9.14]
Nuis et al 2012	0.378	0.161	265	730	0.4%	1.46 [1.06, 2.00]
Rodés-Cabau et al 2010	0.104	0.369	115	224	0.1%	1.11 [0.54, 2.29]
Salinas et al 2012	0	0.916	17	17	0.0%	1.00 [0.17, 6.02]
Unbehaun et al 2014	0.02	0.01	217	513	99.2%	1.02 [1.00, 1.04]
Yankelson et al 2014	0.829	0.588	118	231	0.0%	2.29 [0.72, 7.25]
Total [95% CI]			**1,039**	**2,290**	**100.0%**	**1.02 [1.00, 1.04]**

Heterogeneity: Tau^2=0.01; Chi^2=9.31, df=7 (p=0.23); I^2=25%
Test for overall effect: Z=1.32 (p=0.19)



B PRE-EXISTING AF: LONG-TERM ALL-CAUSE MORTALITY

Study or subgroup	log [hazard ratio]	SE	Pre-AF total	SR total	Weight	Hazard ratio IV, random, 95% CI
Alassar et al 2013	–0.598	0.777	19	100	0.3%	0.55 [0.12, 2.52]
Allende et al 2014	0.489	0.086	217	513	27.9%	1.63 [1.38, 1.93]
Auffret et al 2014	0.871	0.627	71	92	0.5%	2.39 [0.70, 8.17]
Barbash et al 2014	0.993	0.34	143	182	1.8%	2.70 [1.39, 5.26]
Elhmidi et al 2014	1.144	0.517	83	290	0.8%	3.14 [1.14, 8.65]
Gotzmann et al 2013	0.732	0.324	69	133	2.0%	2.08 [1.10, 3.92]
Lange et al 2012	0.457	0.274	97	323	2.8%	1.58 [0.92, 2.70]
LeVen et al 2013	0.412	0.147	236	40	39.6%	1.51 [1.13, 2.01]
Maan et al 2014	0.626	0.458	67	70	1.0%	1.87 [0.76, 4.59]
Nuis et al 2012	0.336	0.151	265	730	9.1%	1.40 [1.04, 1.88]
Ribeiro et al 2014	0.451	0.214	101	232	4.5%	1.57 [1.03, 2.39]
Rodés-Cabau et al 2010	0.554	0.268	115	224	2.9%	1.74 [1.03, 2.94]
Sabaté et al 2014	0.577	0.147	402	1,014	9.6%	1.78 [1.33, 2.38]
Salinas et al 2012	–0.301	0.78	17	17	0.3%	0.74 [0.16, 3.41]
Seiffert et al 2013	0.131	0.232	106	220	3.8%	1.14 [0.72, 1.80]
Stortecky et al 2012	0.896	0.247	104	258	3.4%	2.45 [1.51, 3.98]
Tamburino et al 2011	0.166	0.268	109	554	2.9%	1.18 [0.70, 2.00]
Toggweiler et al 2013	–0.083	0.25	45	43	3.3%	0.92 [0.56, 1.50]
Unbehaun et al 2014	0.507	0.135	217	513	11.3%	1.66 [1.27, 2.16]
Yankelson et al 2014	1.81	0.299	118	231	2.3%	6.11 [3.40, 10.98]
Total [95% CI]			**2,601**	**6,142**	**100.0%**	**1.64 [1.50, 1.79]**

Heterogeneity: Tau^2= 0.05; Chi^2=40.87, df=19 (p=0.003); I^2=54%
Test for overall effect: Z=6.70 (p<0.00001)

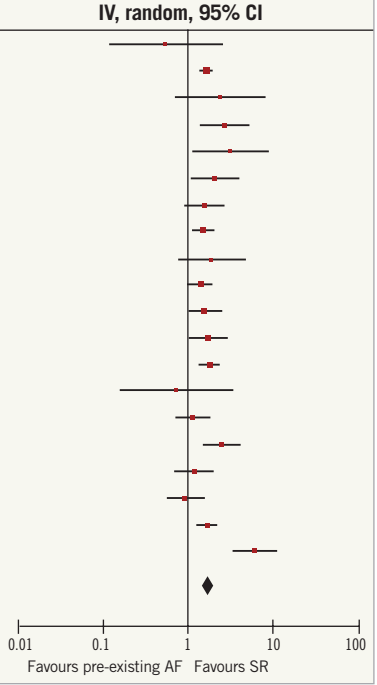


Figure 1. *Impact of pre-existing AF on early and long-term all-cause mortality. Random effects hazard ratio and 95% confidence interval for early (A) and long-term (B) all-cause mortality.*

Patients with and without NOAF did not show significant differences of 30-day (four studies, 971 patients, HR: 1.41, 95% CI: 0.85 to 2.34; p=0.18, I^2=0%) **(Figure 3A, Appendix Table 2, Appendix Table 3)** or long-term all-cause mortality (four studies, 971 patients, HR: 1.43, 95% CI: 0.96 to 2.14; p=0.08, I^2=0%) **(Figure 3B, Appendix Table 2, Appendix Table 3)**.

On the other hand, NOAF proved to be a significant predictor of CVE at short-term follow-up (six studies, 2,025 patients, HR: 2.86, 95% CI: 1.88 to 4.34; p<0.00001, I^2=0%) **(Figure 4A, Appendix Table 2-Appendix Table 4)**, while there was a non-significant increase in the incidence of CVE at long-term follow-up (five studies, 3,997 patients, HR: 1.44, 95% CI: 0.50 to 4.10; p=0.50, I^2=79%) **(Figure 4B, Appendix Table 2-Appendix Table 4)**.

Meta-regression analysis showed no relationship between all the analysed effect modifiers and the outcomes of interest (all p-values >0.05) **(Appendix Table 5, Appendix Table 6)**.

The funnel plots **(Appendix Figure 4-Appendix Figure 7)**, Egger's test **(Appendix Table 2)** and the trim and fill method did not show any publication bias, in all the analyses performed.

Discussion

The present meta-analysis demonstrated that AF is common among high-risk elderly patients undergoing TAVI, with a prevalence of 33.4% in this patient population, and that AF is associated with a significantly increased risk of all-cause mortality at long-term follow-up. However, the presence of AF at baseline does not

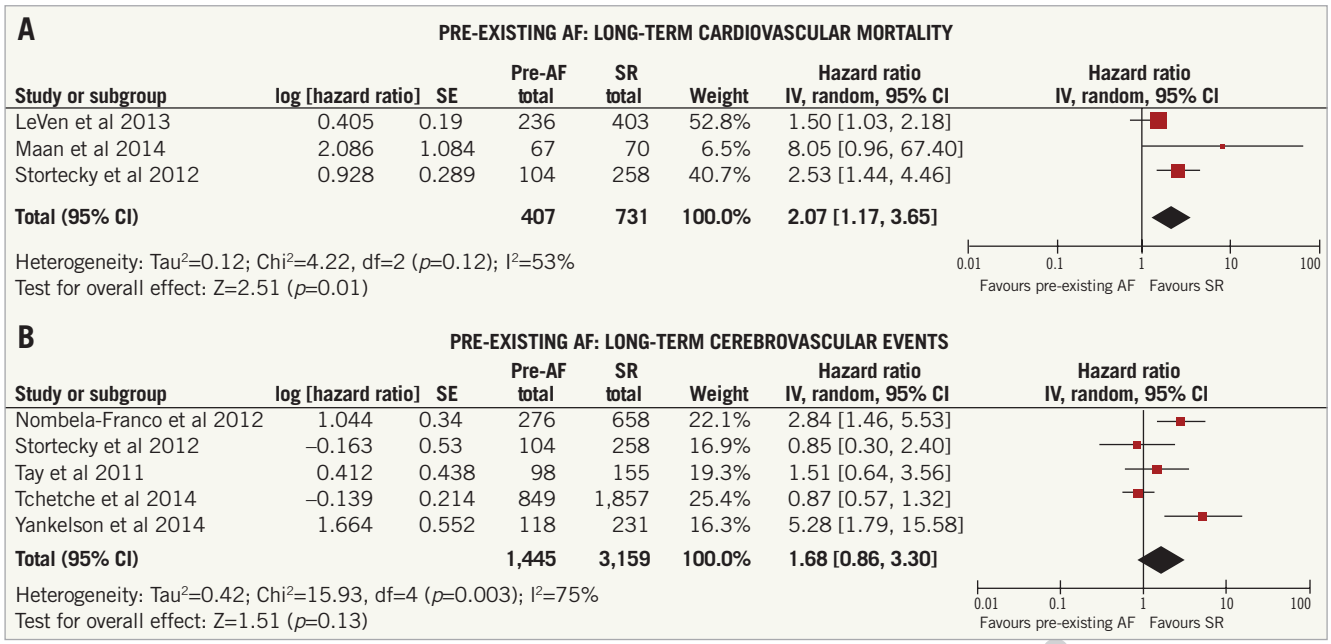


Figure 2. *Impact of pre-existing AF on long-term cardiovascular mortality and cerebrovascular events. Random effects hazard ratio and 95% confidence interval for long-term cardiovascular mortality (A) and long-term cerebrovascular events (B).*

seem to represent a risk factor for 30-day all-cause mortality or for CVE in the long term following TAVI. On the other hand, NOAF occurred in 17.5% of patients after TAVI and was not associated with increased mortality, but with an increased risk of CVE.

AF is the most common cardiac arrhythmia, and is associated with structural heart disease, in particular hypertensive heart disease, coronary artery disease and valvular heart disease. Due to the high prevalence of AF in the elderly population and to the similarity of risk factors for both AF and severe degenerative AS, both conditions coexist in almost 50% of patients. Similar to the general population, in whom AF is estimated to carry a 1.5-fold increased risk of death among men and 1.9-fold among women[5],

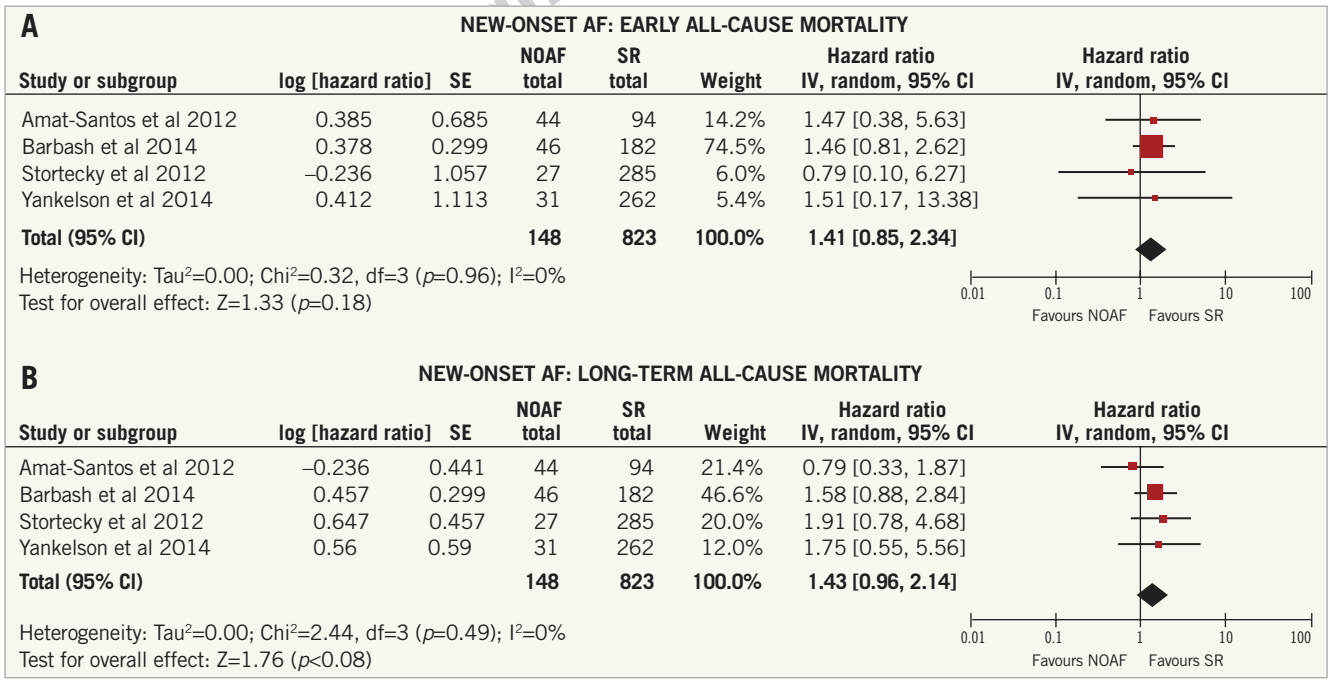


Figure 3. *Impact of NOAF on early and long-term all-cause mortality. Figure showing random effects hazard ratio and 95% confidence interval for early (A) and long-term (B) all-cause mortality. Note: fixed effects estimates for early (four studies, 971 patients, HR: 1.41, 95% CI: 0.85 to 2.34; p=0.18, I^2=0%) and long-term all-cause mortality (four studies, 971 patients, HR: 1.43, 95% CI: 0.96 to 2.14; p=0.08, I^2=0%).*

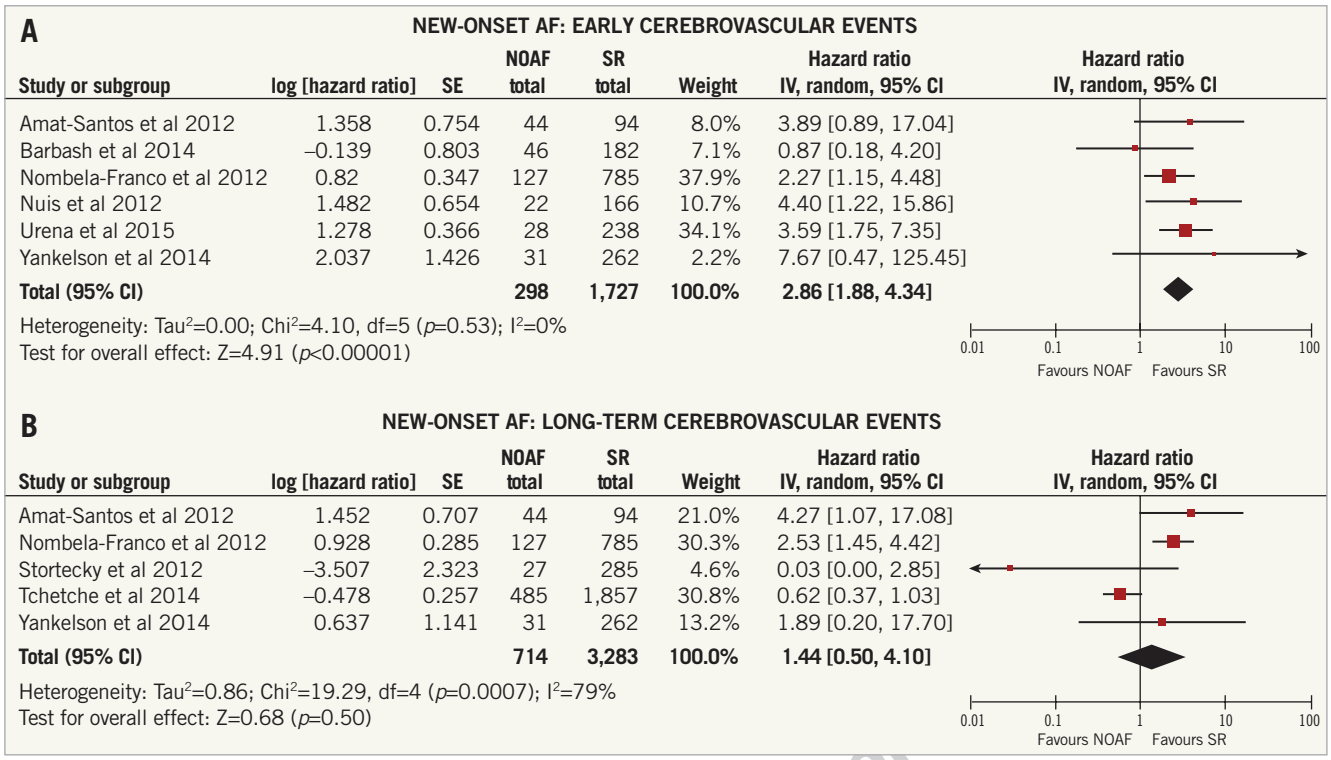


Figure 4. *Impact of NOAF on early and long-term cerebrovascular events. Figure showing random effects hazard ratio and 95% confidence interval for early (A) and long-term cerebrovascular events (B). Note: fixed effects estimates for early (six studies, 2,025 patients, HR: 2.86, 95% CI: 1.88 to 4.34, p<0.00001, I²=0%) and long-term cerebrovascular events (five studies; 971 patients, HR: 0.26, 95% CI: 0.88 to 1.79; p=0.21, I²=79%).*

our meta-regression analysis confirms these data also for patients undergoing TAVI, with a higher HR for all-cause mortality.

The observed differences in outcome among patients in SR and patients with baseline AF are not surprising and may be attributable to a worsening in heart failure from decreased ventricular filling secondary to loss of atrial systolic contraction, tachycardia-induced cardiomyopathy and/or complications associated with systemic embolisation, all conditions also contributing to all-cause mortality[37,47]. Indeed, heart failure might be precipitated in hypertrophied left ventricles with a lower ejection fraction because of the sudden loss of the Frank-Starling mechanism in cardiac reserve compensating in part for the reduced left ventricle contractility. This is particularly relevant in pressure-overload left ventricular hypertrophy, when geometry is often concentric and myocardial mechanics are substantially depressed due to structural modifications. As far as NOAF is concerned, although inflammatory components have been shown to be responsible for its occurrence after cardiac surgery[48], the mechanisms leading to the arrhythmia after TAVI have still to be clarified. No hypothetical differences between different types of valve or procedure have emerged up to now. Indeed, the results of our meta-regression analysis did not evidence any significant difference between the CoreValve® (Medtronic, Minneapolis, MN, USA) and the Edwards SAPIEN (Edwards Lifesciences, Irvine, CA, USA) valve, or between transfemoral and transapical implantation in terms of the incidence of NOAF.

The results of this meta-analysis demonstrate that pre-existing AF is a predictor of all-cause mortality in the long term following TAVI. This provides clarification to the current literature, since, even in recent publications, AF was not identified as a predictor of all-cause mortality[31].

It is important to underline that patients undergoing TAVI exhibit an incidence of stroke which is not negligible[49]: this is principally due to manipulation of large catheters in atherosclerotic and calcified aortas and to embolisation after valvuloplasty or valve implantation. On the other hand, AF itself represents a risk factor for stroke. Interestingly, the result of this meta-analysis, although coming from a pooled analysis of only five studies with a limited number of patients (4,604), clarifies that patients with pre-existing AF did not experience a higher incidence of new CVE when compared to patients in SR. These data, probably corroborating what has been previously shown, might support the concept that the main causes of stroke following TAVI are technical. However, in the subset analysed in this meta-analysis, we were not able to reach a statistical significance on this outcome. This might be due to a variety of issues. First, the total number of CVE is generally low and the number of studies/patients for this analysis is relatively low to draw consistent and final conclusions. Second, it has to be taken into account that, both in patients with pre-existing AF and in those with NOAF, drug therapy was administered. Unfortunately, we were not able to consider the effects of drugs on CVE because often these data were not reported in the primary studies. Conversely, the occurrence of

NOAF seemed to be linked to a higher incidence of CVE, particularly at short-term follow-up.

However, while pre-existing AF analysis demonstrating increased mortality was obtained in up to 8,000 patients, the results in NOAF were observed in fewer than 1,000 patients. Therefore, we cannot exclude an impact of NOAF on mortality, and future studies in larger populations of NOAF are needed.

Certainly, these results might have been induced by the different therapeutic strategies adopted in AF patients when compared to patients in SR. Unfortunately, the absence of the use of a standardised therapy in the available trials made it impossible to analyse, in this meta-analysis, the effect of different antithrombotic regimens on outcome after TAVI, in particular in AF patients. Therefore, future randomised studies are needed to determine the most appropriate antithrombotic therapy in arrhythmic TAVI patients. In addition, this meta-analysis is limited by the inclusion of observational studies not directly comparing AF and non-AF patients, except in one case. The limitations of this study are mainly related to differences in the studies included, as is the case for all meta-analyses. All the studies were observational and the data reported were not sufficient to analyse the role of AF subtypes or AF clinical management. Due to incomplete/unequal reporting of data, not all studies were analysed for all outcomes.

Long-term CVE for both pre-existing AF and NOAF showed a high heterogeneity (>70%) not explained by analysis of potential modifiers or publication bias. Therefore, the results should be considered with caution. However, this heterogeneity reflects the contrasting results among the studies included on this issue, supporting the need for a meta-analysis and future larger studies.

Finally, among the studies included there were no overlapping populations (duplicates were excluded in the eligibility screening). However, given that many studies are multicentre, a small number of overlapping patients cannot be excluded.

Conclusions

In conclusion, pre-existing AF, but not NOAF, is a predictor of long-term mortality. NOAF, on the contrary, predicts new CVE in the short term after TAVI. Screening patients' rhythm may help to identify a subgroup at higher risk of future major events, while preventing NOAF may help to reduce CVE in patients undergoing TAVI. Thus, similar to the results with SAVR, AF should be taken into account when referring a patient for a TAVI procedure.

Impact on daily practice

Despite the clinical safety of TAVI, mortality and cerebral events still occur. New prognostic predictors could be useful for future risk scores and for decision making in daily practice for patients with moderate-to-severe aortic stenosis. These findings should be taken into account not only when selecting patients for TAVI, but also after treatment in order to reach an appropriate diagnosis, to decide on clinical management and to reduce clinical events, optimising prognosis after TAVI.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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Supplementary data

Appendix Table 1. Baseline characteristics of the studies included in the meta-analysis.

Appendix Table 2. Outcome summary information in pre-existing AF and NOAF.

Appendix Table 3. Adjustment of data included in the meta-analysis.

Appendix Table 4. Cerebrovascular event definitions in the included studies.

Appendix Table 5. Meta-regression analysis in pre-existing AF.

Appendix Table 6. Meta-regression analysis in NOAF.

Appendix Figure 1. Meta-analysis flow chart.

Appendix Figure 2. Early and long-term all-cause mortality in pre-existing AF. Fixed effects model.

Appendix Figure 3. Long-term cardiovascular mortality and cerebrovascular events in pre-existing AF. Fixed effects model.

Appendix Figure 4. Pre-existing AF: funnel plots of outcome.

Appendix Figure 5. Pre-existing AF: funnel plots of outcome.

Appendix Figure 6. New-onset AF: funnel plots of outcome.

Appendix Figure 7. New-onset AF: funnel plots of outcome.

International Journal of Cardiology 203 (2016) 264–266

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New-onset atrial fibrillation and increased mortality after transcatheter aortic valve implantation: A causal or spurious association?

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Dear Editor,

Newly-onset atrial fibrillation (NOAF) has emerged in the last few years as a potential prognostic factor in patients undergoing transcatheter aortic valve implantation (TAVI). NOAF after TAVI could be detrimental due to atrio-ventricular dissynchrony resulting in reduced cardiac output and increased filling pressures. In addition, NOAF could be responsible for fatal cerebrovascular events (CVE). In the last few years some studies explored the incidence and the prognostic impact of NOAF after TAVI [1–5], and recently new large series have added to our knowledge [6–8]. However, the incidence of NOAF varies significantly across registries (around 6–32%), with controversial findings on its prognostic significance, hence the rationale for a meta-analysis.

We searched MEDLINE, Scopus and Cochrane databases until September 20, 2015 using Internet-based engines, with no language restrictions using various keywords including "new-onset atrial fibrillation" or "NOAF" and "transcatheter aortic valve implantation" or "TAVI" or "TAVR". The reference lists of relevant studies and reviews, editorials and letters were searched. The analysis was restricted to studies reporting data on mortality and CVE after TAVI stratified by the occurrence of NOAF. The most updated or inclusive data for a given study were selected. All studies were observational and the highest-quality estimate available was picked for the overall meta-analysis, with the following ranking: adjusted with propensity score > adjusted with multivariable analysis > unadjusted. The number of events, participants, hazard ratios (HR) and confidence intervals (CI) for all-cause death and CVE at 30-day and 1-year were abstracted. The results of all studies were combined using a random-effects model to minimize heterogeneity among groups. Statistical heterogeneity was quantified with the I^2 test. Systematic bias was explored with funnel plots. A 2-tailed alpha of 5% was used for hypothesis testing. Statistical analysis was performed with Review Manager (Version 5.2 Copenhagen).

A total of 8 studies encompassing 4959 patients were included [1–8]. Overall, the mean incidence of NOAF was 10.1% (499 patients with NOAF and 4460 patients in sinus rhythm after TAVI). Patients with NOAF showed a borderline increase of 30-day and a significant increase in 1-year all-cause death compared with those in sinus rhythm (Fig. 1). Conversely, CVE were significantly increased at 30-day but non-significantly albeit numerically increased at 1-year follow-up in NOAF patients (Fig. 2). The main limitation of this meta-analysis is related to the differences in NOAF definition across the included studies. We excluded the study by Tchetche et al. [9] because most recent data from the FRANCE-2 registry were available [8].

In conclusion, this updated meta-analysis on the role of NOAF on outcomes after TAVI supports the understanding that NOAF is associated with clinical events after TAVI. Whether this is a causal or spurious association demands further research in this field.

Disclosures

None.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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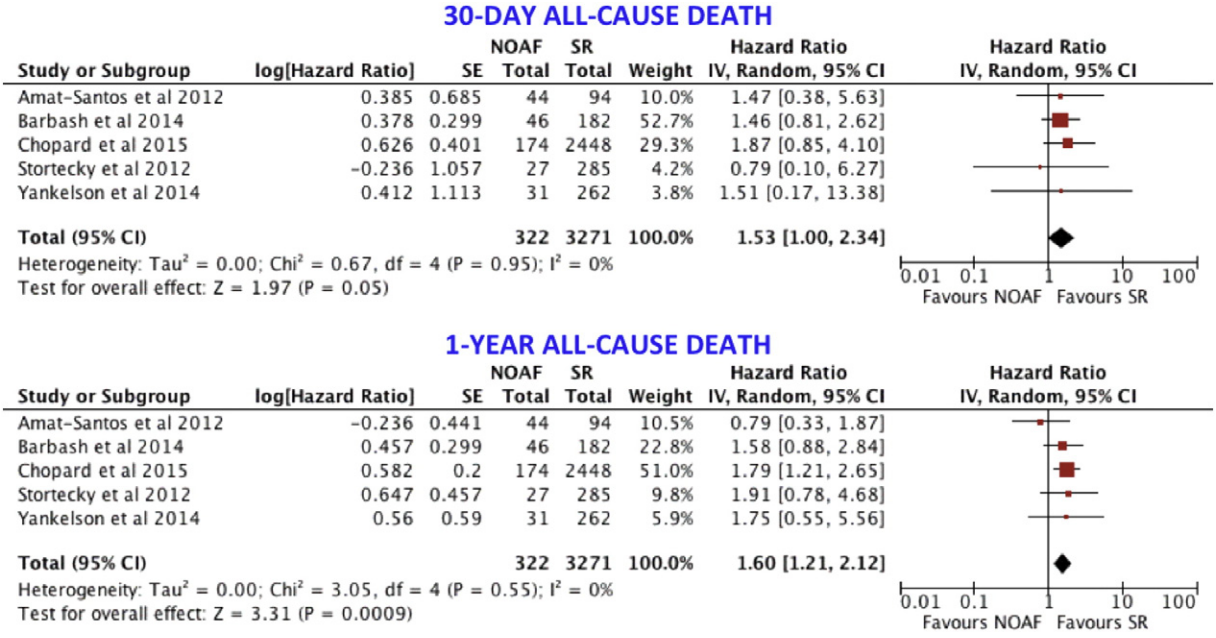

Fig. 1. Early and 1-year mortality after TAVI according to the occurrence of NOAF. Early and 1-year random-effects hazard ratios and 95% confidence interval for all-cause mortality after TAVI.

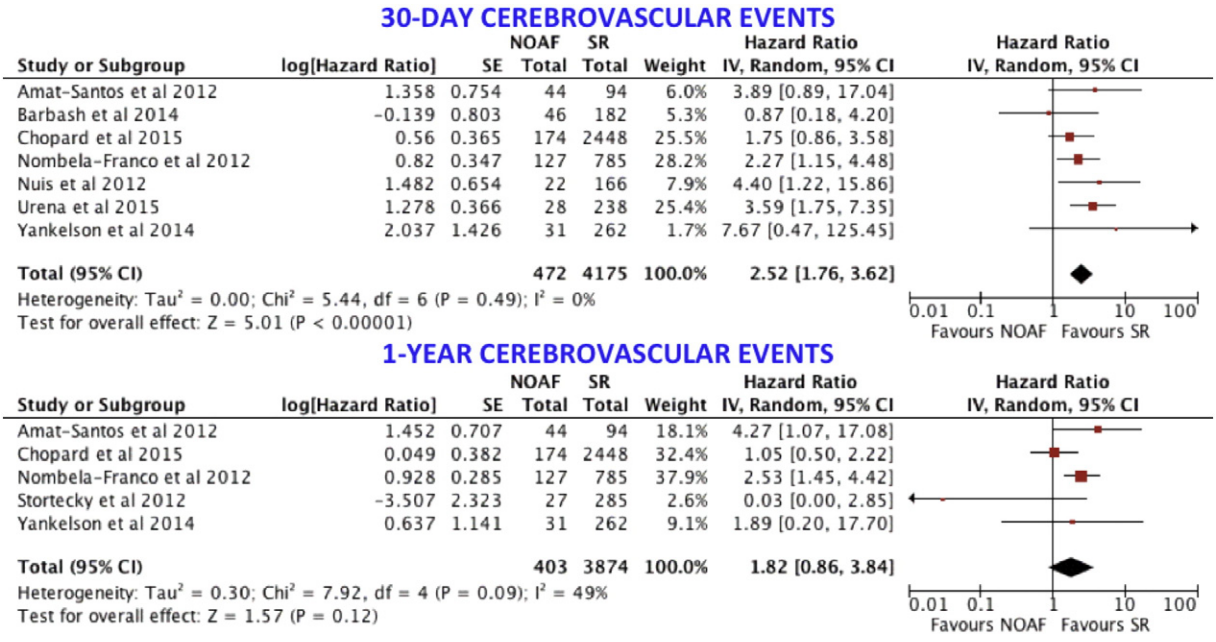

Fig. 2. Early and 1-year cerebrovascular events after TAVI according to the occurrence of NOAF. Early and 1-year random-effects hazard ratios and 95% confidence interval for cerebrovascular events after TAVI.

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Meta-Analysis of Effect of Body Mass Index on Outcomes After Transcatheter Aortic Valve Implantation

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Controversial data exist regarding the impact of body mass index (BMI) on TAVI outcomes. Thirteen TAVI studies were included and analyzed for the incidence of procedural complications, 30-day, and long-term all-cause mortality. Three comparisons were executed: (1) underweight versus normal weight, (2) overweight versus normal weight, and (3) obese versus normal weight patients. Underweight patients (BMI <20 kg/m^2) had similar 30-day all-cause mortality compared with the normal, although they displayed a significant worse survival at long-term follow-up (hazard ratio 1.68, 95% confidence interval (CI) 1.09 to 2.59, p = 0.02). Underweight patients showed a higher incidence of major and life-threatening bleedings (2,566 patients, odds ratio 1.64, 95% CI 1.10 to 2.45, p = 0.02) and of major vascular complications (2,566 patients, odds ratio 1.86, 95% CI 1.16 to 2.98, p = 0.01), compared with normal weight patients. Overweight patients (BMI ≥25 and <30 kg/m^2) display similar 30-day and long-term all-cause mortality, as well as similar procedural complication rate compared with normal weight patients. Obese patients (BMI >30 kg/m^2) had similar 30-day all-cause mortality rates compared with the normal weight category, whereas they displayed a significant better survival at long-term (hazard ratio 0.79, 95% CI 0.67 to 0.93, p = 0.004). Procedural complications did not differ between obese and normal body weight patients. In conclusion, a low BMI is linked to a significantly worse prognosis after TAVI. Therefore, BMI represents an important and handily tool that might be used in the risk prediction of patients to be addressed for TAVI. **(Am J Cardiol 2017;119:308−316)**

Obesity is a major modifiable risk factor for cardiovascular morbidity and mortality.[1] Nevertheless, a considerable number of studies showed better outcomes for overweight and obese patients after percutaneous and surgical cardiovascular interventions in general and after surgical aortic valve replacement in particular.[2] This phenomenon was termed the "obesity paradox," given its contrast with the classical U-shape or U-shape−like survival hazard curve attributed to body mass index (BMI) when treated as continuous variable. Possible mechanisms for this protective effect include production of the soluble tumor necrosis factor-α receptor in adipose tissue and subsequent neutralization of the adverse effects of tumor necrosis factor-α on mortality in patients with chronic inflammation diseases such as cardiovascular diseases.[3] Noteworthy, the relation between BMI and transcatheter aortic valve implantation (TAVI) outcome is to date controversial. Some authors reported a protective role of obesity, as opposed to a significant higher 30-day and 1-year mortality in patients with low body weight.[4,5] The FRANCE-2 registry data showed better outcomes in overweight and obese patients than normal weight ones.[6] Others did not confirm the existence of this obesity paradox, arguing that the obese population is younger, seeks medical care earlier, is treated medically more aggressively, and therefore benefits more from medical and interventional treatment.[7,8] However, the real impact of body weight on survival after TAVI still remains highly debated. Given these observations, in the present meta-analysis, we investigated the effect of different BMI categories on short- and long-term outcomes of elderly high-risk patients with severe symptomatic aortic valve stenosis undergoing TAVI.

Methods

The study was designed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses requirements.[9] MEDLINE, Cochrane, ISI Web of Science, and SCOPUS database were searched for studies published from April 2002 (first-in-human TAVI date) until April 2016. Additional sources included *www.clinicaltrials.gov*, *www.clinicaltrialresults.org*, *www.tctmd.com*, *www.cardiosource.com*, and abstracts/presentations from major cardiovascular meetings. The reference lists of relevant studies, reviews,

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See page 315 for disclosure information.

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editorials, and letters were scrutinized to identify further citations. Studies were identified using the major medical subject heading "transcatheter aortic valve implantation or transcatheter aortic valve replacement or TAVI or TAVR" combined with "body mass index or body weight or BMI." Citations were screened at the title and abstract level by 2 independent reviewers and retrieved as a full report if they reported data on outcomes after TAVI, when BMI was considered as a predictor of mortality in their regression models as a categorical and/or continuous variable. No language limitations were applied. The most updated or inclusive data for a given study were chosen for abstraction.

Studies were included if: (1) TAVI was performed in patients with symptomatic, severe aortic stenosis (defined as an aortic valve area <1 cm^2 or an indexed aortic valve area <0.6 cm^2/m^2); (2) outcomes data were reported according to the BMI values (reported as either categorical or continuous variable); (3) BMI categories were identified following the World Health Organization[10] or Valve Academic Research Consortium-2 (VARC-2) definitions.[11] Studies were excluded if any of the following criteria applied: (1) duplicate publication date; (2) lack of data on BMI values and their impact on TAVI outcomes; (3) the outcome of interest was not clearly reported or was impossible to extract or calculate from the published results; (4) number of patients <100. Two reviewers independently screened studies for fulfillment of inclusion criteria. Reviewers compared selected trials and discrepancies were resolved by consensus. Baseline characteristics, outcomes, including mortality and procedural complications, were abstracted.

The primary outcomes evaluated were the incidence of 30-day and long-term all-cause mortality in obese, overweight, and underweight patients compared with normal weight patients undergoing TAVI. Secondary outcomes of interest were the incidence procedural complications in the same populations (defined as: device success rate, major vascular complications, major and life-threatening bleedings, cerebrovascular events, myocardial infarction, and acute kidney injury). A separate analysis on long-term all-cause mortality was performed including studies reporting BMI as a continuous variable.

Weight categories were defined according to accepted criteria[10,11] and specifically: underweight was defined as BMI <20 kg/m^2, normal weight category included BMI ≥ 20 kg/m^2 and <25 kg/m^2, overweight category included BMI ≥ 25 kg/m^2 and <30 kg/m^2, and obese was defined as BMI ≥ 30 kg/m^2.

The number of events, participants, and percentages as well as adjusted hazard ratios (HRs) and CIs were abstracted when available. Highest quality data were prioritized (adjusted HR >number of events). Estimates of effect were calculated with a random-effects model and confirmed by a fixed-effects model and expressed as odds ratio (OR) or HR. Statistical significance was set at $p \leq 0.05$ (2 tailed). Heterogeneity was assessed by a Q-statistic and I^2 test. Significant heterogeneity was considered present for p values <0.10 or an $I^2 > 50\%$. In case of significant heterogeneity, the random-effects model was prioritized over the fixed-effects model, and subgroup and sensitivity analyses were performed to explore sources of inconsistency. Meta-regressions were performed to test the influence of baseline characteristics included in Table 1 as potential effect modifiers (significance at $p \leq 0.05$).

Publication bias was assessed using funnel plots and Egger's test, consisting in a linear regression of the intervention effect estimates on their standard errors, weighting by 1/(variance of the intervention effect estimate).[12] If there was some evidence of publication bias, the trim and fill method, which estimates the number and results of potential missing studies resulting from publication bias, was applied.

All data analyses were performed using Prometa Software (Version 2, Internovi, Cesena FC, Italy), and Reviewer Manager (RevMan, version 5.2, Copenhagen, Denmark).[13–16]

Results

Of the 224 studies identified in the initial search, 36 were retrieved for more detailed evaluation. Twenty-three studies were subsequently excluded, and therefore, 13 studies were finally included in the analyses[4–8,17–24](Figure 1, Table 1, and Supplementary Table 1). Studies design and follow-up definitions are reported in Supplementary Table 2.

Underweight patients (BMI <20 kg/m^2) had similar 30-day all-cause mortality compared with the normal weight category (3 studies; 2,883 patients, HR 1.61, 95% CI 0.57 to 4.53, $p = 0.37$, $I^2 = 71\%$, Figure 2, Table 2), although they displayed a significant worsening in survival at long-term follow-up (5 studies; HR 1.68, 95% CI 1.09 to 2.59, $p = 0.02$, $I^2 = 60\%$, Figure 2, Table 2). As far as procedural complications regard, underweight patients showed a higher incidence of major and life-threatening bleedings (5 studies; 2,566 patients, OR 1.64, 95% CI 1.10 to 2.45, $p = 0.02$, $I^2 = 0\%$, Figure 3, Table 2) and of major vascular complications, as well (5 studies; 2,566 patients, OR 1.86, 95% CI 1.16 to 2.98, $p = 0.01$, $I^2 = 19\%$, Figure 3, Table 2). Conversely, device success rate (4 studies; 2,428 patients, OR 0.94, 95% CI 0.51 to 1.72, $p = 0.84$, $I^2 = 0\%$, Figure 3, Table 2), incidence of cerebrovascular events (5 studies; 2,565 patients, OR 1.11, 95% CI 0.58 to 2.14, $p = 0.75$, $I^2 = 0\%$, Figure 3, Table 2), myocardial infarction (3 studies; 2,237 patients, OR 1.31, 95% CI 0.34 to 4.98, $p = 0.69$, $I^2 = 0\%$, Figure 3, Table 2) and acute kidney injury (5 studies; 2,566 patients, OR 0.93, 95% CI 0.51 to 1.69, $p = 0.80$, $I^2 = 0\%$, Figure 3, Table 2) did not differ significantly between the 2 groups.

Overweight patients (BMI ≥ 25 and <30 kg/m^2) display similar mortality rates both at 30-day (3 studies, 3,769 patients, OR 0.78, 95% CI 0.54 to 1.13, $I^2 = 37\%$, Supplementary Figure 1, Table 3) and at long-term follow-up (4 studies, HR 0.94, 95% CI 0.77 to 1.16, $I^2 = 18\%$, Supplementary Figure 1, Table 3), compared with normal weight patients. The 30-day mortality turned significantly lower for the overweight patients, when the fixed-effect model was used; however, this is a pooled analysis of only 3 studies and should therefore be considered with caution. Similarly, major and life-threatening bleedings (5 studies; 4,380 patients, OR 1.11, 95% CI 0.89 to 1.39, $p = 0.34$, $I^2 = 0\%$, Supplementary Figure 1, Table 3), of major vascular complications (5 studies; 4,380 patients, OR 1.09, 95% CI 0.84 to 1.41, $p = 0.52$, $I^2 = 0\%$, Supplementary Figure 1, Table 3), device success rate (4 studies; 4,079 patients, OR 1.03,

Table 1
Baseline characteristics of selected studies included in meta-analysis

First Author (Ref.#)	Year	n	Age (years)	AF	Balloon expandable	BMI (kg/m^2)	CAD	CKD	COPD	Diabetes	Dyslipidemia	EF	Women	Hypertension	Logistic EURO score
Abramowitz[8]	2016	805	82	33.5%	91.5%	26.8	64.6%	N/A	37.5%	31.8%	N/A	56.8%	39.9%	91.3%	N/A
Kodali[17]	2012	348	83.6	40.7%	100%	N/A	74.7%	10.8%	43.7%	N/A	N/A	52.5%	42.2%	N/A	29.3%
Koifman(A)[19]	2015	476	83.5	39.7%	N/A	27.5	N/A	N/A	30.2%	33.2%	N/A	N/A	27.1%	89.9%	N/A
Koifman(B)[5]	2016	491	82.9	42.8%	67.4%	27.8	N/A	N/A	33.2%	33.4%	N/A	N/A	49.9%	93.5%	N/A
Konigstein[18]	2015	409	82	30%	25%	N/A	59%	N/A	19%	34.5%	78%	55.8%	58%	88%	24%
Leon[20]	2016	1011	81.5	31%	100%	28.6	69.2%	5.0%	31.8%	37.7%	N/A	56.2%	45.8%	N/A	N/A
Mok[21]	2013	319	80	30.7%	98.7%	26.8	63.9%	60.2%	29.5%	37.3%	N/A	54%	53.9%	89%	N/A
Seiffert[22]	2013	326	80.6	33.2%	86.2%	N/A	61.6%	8.9%	26.7%	N/A	N/A	N/A	55.5%	N/A	22.7%
Seiffert[23]	2014	845	80.9	33.9%	N/A	26.5	44%	N/A	28.5%	28.4%	N/A	N/A	51.1%	N/A	20.4%
van der Boon[4]	2013	940	81	N/A	46.3%	26.2	45%	63%	34%	29%	N/A	N/A	46%	70%	20.9%
Wenaweser[24]	2011	200	82.9	26%	35%	25.6	62.5%	N/A	N/A	25%	58%	51%	80%	77%	24.6%
Yamamoto[6]	2013	3072	82.8	N/A	66.8%	26	47.8%	10.3%	25.4%	25.5%	48.1%	53.2%	49%	69%	22%
Yamamoto[7]	2015	777	83.4	N/A	60%	25.8	N/A	63.4%	26.4%	23%	50.8%	50.8%	51.5%	71.4%	22.3%

AF = atrial fibrillation; BMI = body mass index; CAD = coronary arterial disease; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; EF = ejection fraction; MI = myocardial infarction; N/A = not applicable (data not shown in the primary study or not obtainable; otherwise, the analysis was conducted only in a subgroup of the entire study population); NYHA = New York Heart Association; PAD = peripheral arterial disease; PCI = percutaneous coronary interventions; PM = pacemaker; STS = Society of Thoracic Surgeons.

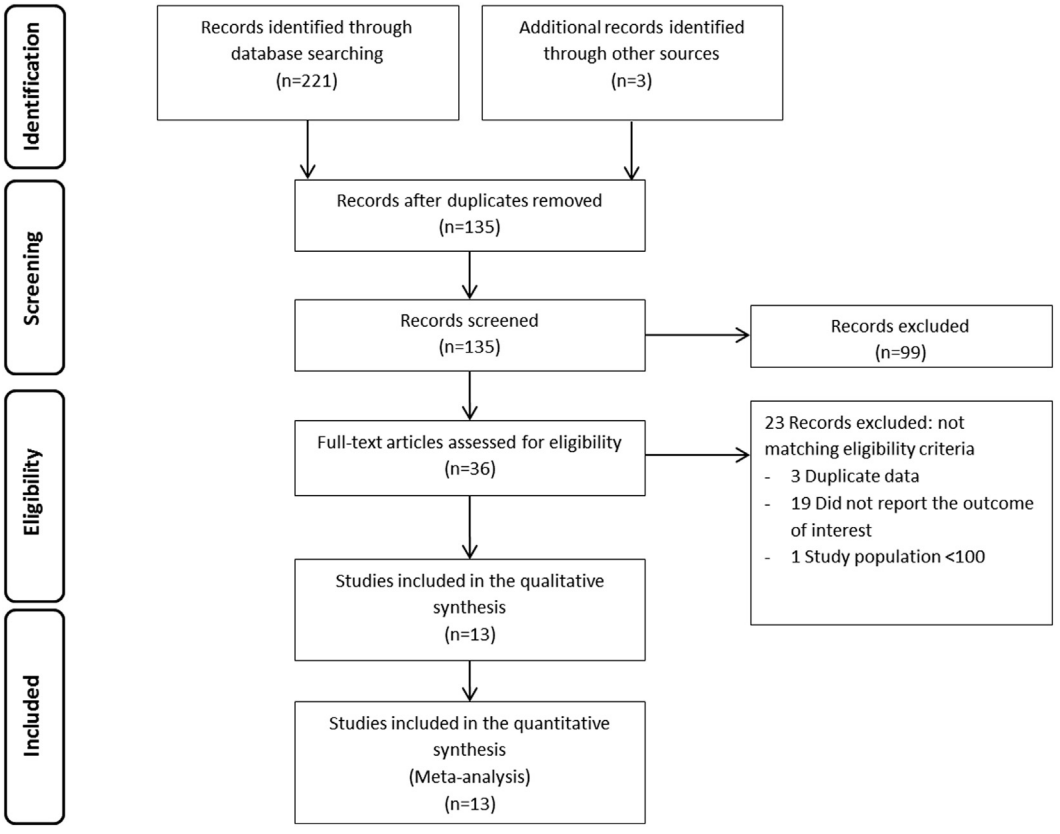

Figure 1. Meta-analysis flow chart. Flow chart showing study search and selection.

95% CI 0.76 to 1.40, p = 0.86, I^2 = 0%, Supplementary Figure 1), incidence of cerebrovascular events (5 studies; 4,373 patients, OR 1.11, 95% CI 0.58 to 2.14, p = 0.75, I^2 = 0%, Supplementary Figure 1, Table 3), myocardial infarction (3 studies; 3,769 patients, OR 1.31, 95% CI 0.34 to 4.98, p = 0.69, I^2 = 0%, Supplementary Figure 1, Table 3), and acute kidney injury (5 studies; 4,380 patients, OR 1.29, 95% CI 0.92 to 1.79, p = 0.80, I^2 = 0%, Supplementary Figure 1, Table 3) did not differ significantly between the 2 groups.

Obese patients (BMI ≥30 kg/m^2) had similar 30-day all-cause mortality ratios compared with the normal weight category (6 studies; 3,367 patients, HR 0.87, 95% CI 0.65 to 1.16, p = 0.35, I^2 = 58%, Figure 4, Table 4),

Table 1
(continued)

NYHA class III/IV	Obese	PAD	Prev Cardiac Surgery	Prior MI	Prior PCI	Prior PM	Prior Stroke	Self expandable	Smoke	STS score	Subclavian	Transaortic	Transapical	Transfemoral	Under weight
N/A	23.1%	35.3%	26.3%	16.3%	N/A	20.9%	21%	8.5%	N/A	8.1%	2%	7.4%	4.8%	85.2%	33.3%
94.3%	N/A	43.2%	42.5%	26.5%	33.5%	19.8%	N/A	0%	N/A	11.8%	0%	0%	29.9%	70.1%	N/A
89.1%	N/A	33.4%	32.1%	N/A	28.1%	16.8%	15.3%	N/A	N/A	10%	0%	0%	25.4%	74.6%	N/A
85.7%	28.1%	29.1%	33.4%	N/A	29.9%	16.3%	12.2%	24%	N/A	11%	0%	0%	0%	100%	8.8%
67%	25%	7%	17%	17%	43%	N/A	10%	75%	26%	N/A	0%	0%	0%	100%	1%
77.3%	N/A	27.9%	23.6%	18.3%	27.1%	11.7%	N/A	0%	N/A	5.8%	0%	0%	23.3%	76.7%	N/A
80.3%	N/A	34.8%	38.6%	35.1%	N/A	N/A	19.1%	1.3%	4.7%	6.3%	0%	N/A	N/A	39.2%	N/A
81.6%	61.7%	N/A	19.9%	19.9%	35.3%	N/A	19.3%	13.8%	N/A	8.3%	0.9%	0%	54.3%	44.8%	5.6%
N/A	N/A	36.9%	18.9%	19.3%	36.6%	11.3%	N/A	N/A	N/A	6.4%	0%	0.1%	0%	99.9%	N/A
81%	16.9%	25%	22%	17%	30%	11%	16%	53.7%	N/A	N/A	6%	0.4%	10%	84%	2.7%
N/A	N/A	23.5%	20%	20%	22%	11%	9%	65%	N/A	6.4%	1.5%	0%	21.5%	77%	N/A
65.7%	18.6%	20.6%	20.1%	16%	N/A	14%	9.8%	33.2%	N/A	N/A	6.6%	1.8%	17.8%	74.5%	3.1%
80.4%	51.3%	28.4%	16%	14.4%	N/A	15.2%	9.8%	40%	N/A	10.9%	N/A	N/A	N/A	65.4%	7.2%

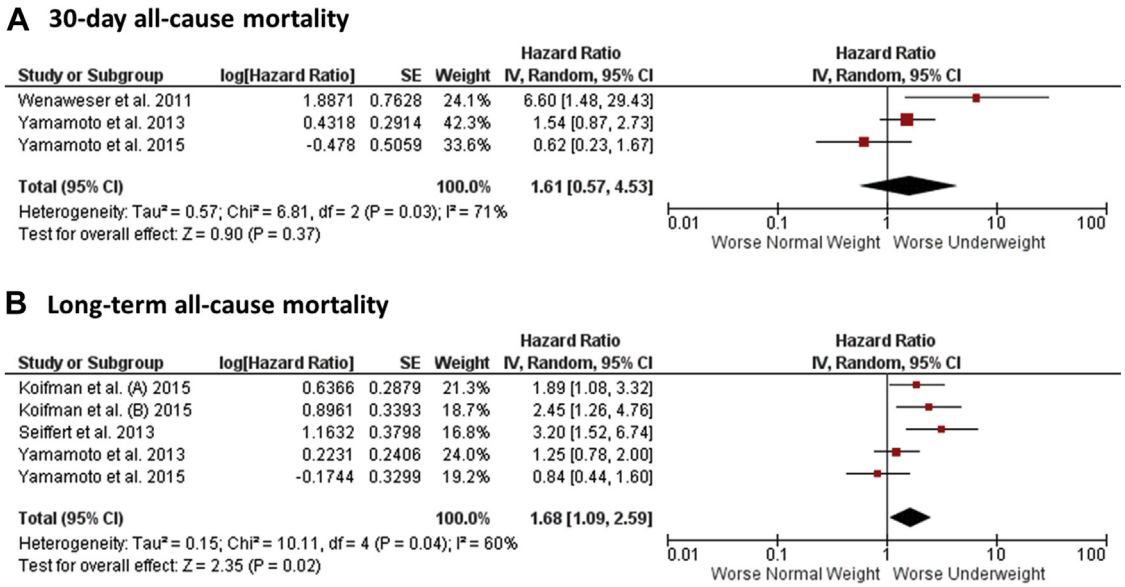

Figure 2. Impact of BMI <20 kg/m^{2}on 30-day and long-term all-cause mortality. Random-effects HR and 95% CI for 30-day *(A)* and long-term *(B)* all-cause mortality.

whereas they displayed a significant improvement in survival at 1-year follow-up (7 studies; 4,709 patients, HR 0.79, 95% CI 0.67 to 0.93, p = 0.004, I^2 = 0%, Figure 4, Table 4). As far as procedural complications regard, no differences were found between obese and normal body weight patients (major and life-threatening bleedings, 5 studies, 4,237 patients, OR 1.05, 95% CI 0.75 to 1.46, p = 0.79, I^2 = 49%, Figure 5, Table 4; major vascular complications, 6 studies, 4,237 patients, OR 1.14, 95% CI 0.85 to 1.52, p = 0.38, I^2 = 11%, Figure 5, Table 4; device success, 5 studies, 4,003 patients, OR 1.07, 95% CI 0.75 to 1.54, p = 0.70, I^2 = 29%, Figure 5, Table 4; cerebrovascular events, 6 studies, 4,237 patients, OR 1.10, 95% CI 0.63 to 1.94, p = 0.74, I^2 = 56%, Figure 5, Table 4; myocardial infarction, 4 studies, 3,717 patients, OR 0.67, 95% CI 0.33 to 1.39, p = 0.28, I^2 = 0%, Figure 5, Table 4; acute kidney injury, 6 studies, 4,237 patients, OR 1.02, 95% CI 0.77 to 1.36, p = 0.88, I^2 = 0%, Figure 5, Table 4).

In addition, when BMI was analyzed as a continuous variable, each increase in 1 unit of kg/m^2 was associated with a significant reduction in long-term all-cause mortality (7 studies; 4,677 patients, HR 0.96, 95% CI 0.93 to 1.00, p = 0.03, I^2 = 73%, Supplementary Figure 2, Table 4).

Meta-regression analysis showed no relation between all the analyzed effect modifiers and the outcomes of interest, except for diabetes, previous myocardial infarction, and self-expandable valves in the analysis of long-term all-cause mortality for the comparison of underweight versus normal weight patients (Supplementary Figure 3). In the overweight versus normal weight comparison, coronary arterial disease, and a transaortic approach were significantly associated with higher 30-day all-cause mortality (Supplementary Figure 4).

Table 2
Outcomes after TAVI in underweight versus normal weight patients

Outcome	Studies	Patients	RE HR/OR [95% CI]	*P* Value	χ^2	FE HR/OR [95% CI]	*P* Value	χ^2	I^2%	Egger Test	Trim and Fill HR
All-cause mortality											
30-day	3	2883	1.61[0.57-4.53]	0.37	6.81	1.45[0.91-2.32]	0.12	6.81	71	0.793	1.61[0.57-4.52]
Long-term	5	N/A	1.68[1.09-2.59]	0.02	10.11	1.61[1.23-2.10]	0.0005	10.11	60	0.394	1.68[1.09-2.59]
Major and life-threatening bleeding	5	2566	1.64[1.10-2.45]	0.02	2.31	1.61[1.07-2.40]	0.02	2.31	0	0.607	1.53[1.04-2.24]
Major Vascular complication	5	2566	1.86[1.16-2.98]	0.01	4.94	1.78[1.20-2.65]	0.004	4.94	19	0.907	1.86[1.16-2.98]
Device Success	4	2428	0.94[0.51-1.72]	0.84	1.51	0.99[0.54-1.81]	0.98	1.51	0	0.497	0.94[0.51-1.72]
Cerebrovascular events	5	2565	1.11[0.58-2.14]	0.75	0.53	1.08[0.56-2.08]	0.81	0.53	0	0.993	1.11[0.58-2.14]
Myocardial Infarction	3	2237	1.31[0.34-4.98]	0.69	1.06	1.10[0.30-4.05]	0.89	1.06	0	0.746	1.31[0.34-4.98]
Acute Kidney Injury	5	2566	0.93[0.51-1.69]	0.80	2.70	0.86[0.47-1.57]	0.62	2.70	0	0.199	0.75[0.43-1.29]

Mortality data are reported as HR; procedural outcomes are reported as OR according to the availability of crude events in the primary studies.

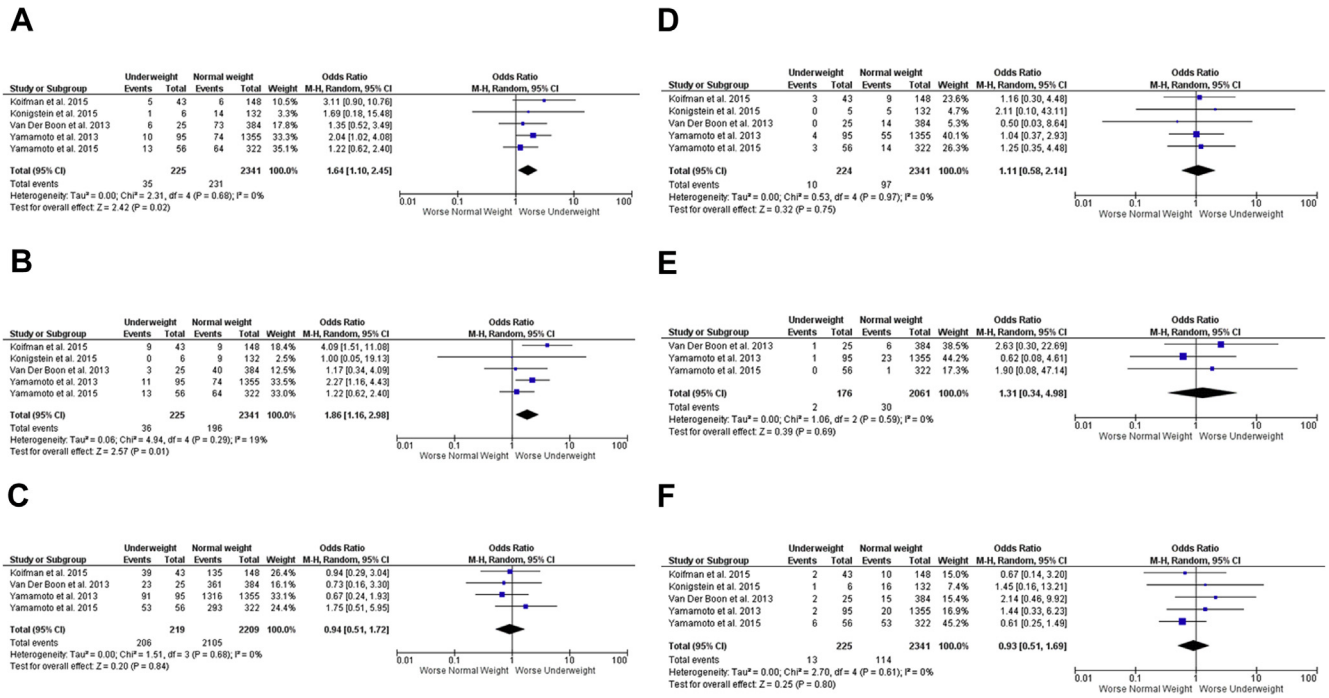

Figure 3. Impact of BMI <20 kg/m^{2}on procedural complications. Random-effects OR and 95% CI for major and life-threatening bleedings *(A)* major vascular complications, *(B)* device success, *(C)* cerebrovascular events, *(D)* myocardial infarction, and *(E)* acute kidney injury *(F)*.

For the obese versus normal weight comparison, there was an association between chronic obstructive pulmonary disease and higher long-term all-cause mortality (Supplementary Figure 5).

The long-term all-cause mortality in the comparison between underweight and normal weight patients lost the statistical significance removing the study from Koifman et al[19] (HR 1.64, 95% CI 0.94 to 2.88), Koifman et al[5] (HR 1.54, 95% CI 0.94 to 2.53) and Seiffert et al (HR 1.47, 95% CI 0.97 to 2.25). Similarly, the significant reduction in long-term all-cause mortality was confirmed for obese patients when meta-analyses were repeated removing 1 study at the time; however, when removing Seiffert et al (HR 0.78, 95% CI 0.66 to 1.93) and Yamamoto et al, 2013 (HR 0.82, 95% CI 0.67 to 1.01), this result lost its statistical significance. Additional sensitivity analyses are reported in Supplementary Tables 6 to 9.

The funnel plots and Egger's test did not suggest any significant publication bias for all the analyses performed, except for the long-term all-cause mortality in the overweight versus normal weight comparison (HR 0.87, 95% CI 0.70 to 1.07, p = 0.003), although not changing the final result.

Discussion

This meta-analysis of 13 TAVI studies adds to the current knowledge with the following considerations: (1) underweight patients (BMI <20 kg/m^2) experience a higher mortality at long term after TAVI, as well as increased rates of major vascular complications and major and life-threatening bleedings (VARC-2 definitions) during the procedure, compared with normal body weight patients; (2) overweight patients (BMI ≥25 and <30 kg/m^2) display similar 30-day and long-term all-cause mortality, as well as

Table 3
Outcomes after TAVI in overweight versus normal weight patients

Outcome	Studies	Patients	RE HR/OR [95% CI]	*P* Value	χ^2	FE HR/OR [95% CI]	*P* Value	χ^2	I^2%	Egger Test	Trim and Fill HR
All-cause mortality											
30-day	3	3769	0.78[0.54-1.13]	0.19	3.18	0.76[0.60-0.96]	0.02	3.18	37	0.584	0.78[0.54-1.13]
Long-term	4	N/A	0.94[0.77-1.16]	0.58	3.66	0.91[0.77-1.07]	0.25	3.66	18	0.003	0.87[0.70-1.07]
Major and life-threatening bleeding	5	4380	1.11[0.89-1.39]	0.34	2.98	1.11[0.89-1.39]	0.34	2.98	0	0.932	1.08[0.87-1.35]
Major Vascular complication	5	4380	1.09[0.84-1.41]	0.52	3.97	1.09[0.84-1.41]	0.53	3.97	0	0.692	1.09[0.84-1.41]
Device Success	4	4079	1.03[0.76-1.40]	0.86	0.22	1.03[0.76-1.40]	0.86	0.22	0	0.289	1.03[0.76-1.40]
Cerebrovascular events	5	4373	0.90[0.66-1.24]	0.52	2.80	0.90[0.66-1.23]	0.52	2.80	0	0.948	0.90[0.66-1.24]
Myocardial Infarction	3	3769	0.57[0.30-1.08]	0.09	1.48	0.56[0.30-1.05]	0.07	1.48	0	0.891	0.57[0.30-1.08]
Acute Kidney Injury	5	4380	1.29[0.92-1.79]	0.14	0.88	1.29[0.92-1.80]	0.14	0.88	0	0.981	1.25[0.92-1.70]

Long-term mortality is reported as HR; 30-day mortality and procedural outcomes are reported as OR according to the availability of crude events in the primary studies.

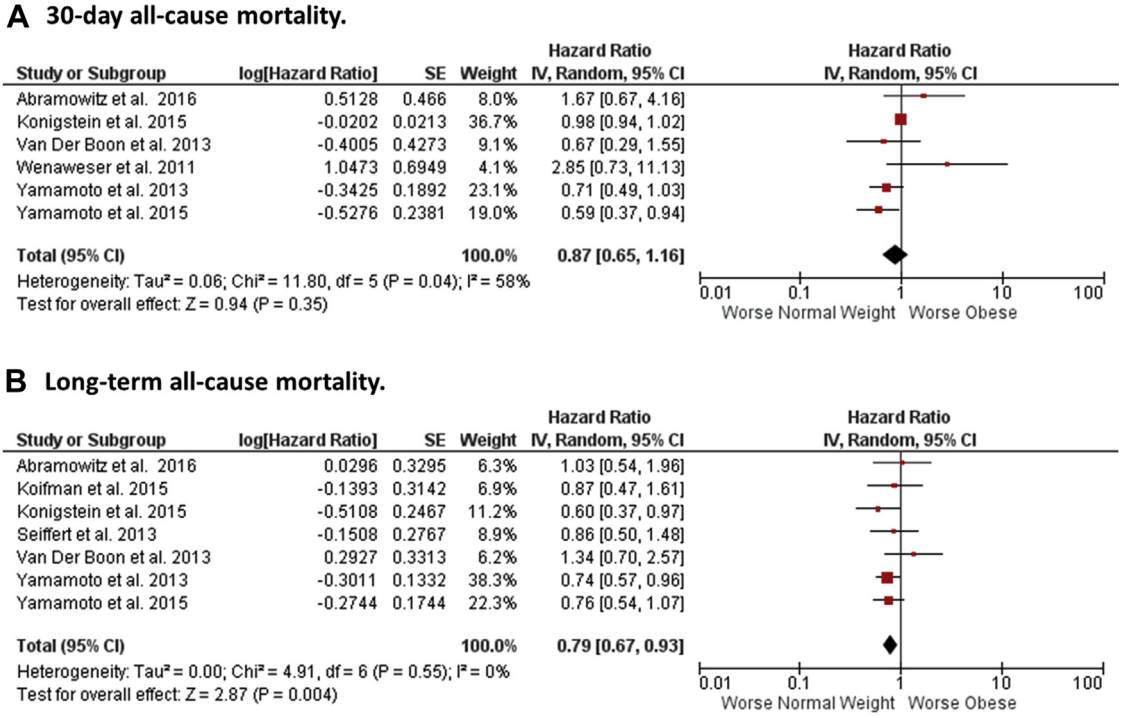

Figure 4. Impact of BMI $\geq$30 kg/m^2 on 30-day and long-term all-cause mortality. Random-effects HR and 95% CI for 30-day *(A)* and long-term *(B)* all-cause mortality.

similar procedural complication rates compared with normal weight patients; (3) obese patients (BMI $\geq$30 kg/m^2) showed lower long-term all-cause mortality and similar rates of procedural complications compared with normal body weight patients. These data in aggregate suggest that low body weight patients are exposed to worse outcomes after TAVI.

Although not statistically significant, the early, slightly higher, mortality of the underweight patients could be attributed to the higher rate of vascular complications and major and life-threatening bleedings in this population, which may result from similar sized sheath in a smaller peripheral access site in a smaller patient.[25] Late mortality could be explained by frailty of the low-BMI patients, as suggested in the VARC-2 criteria, in which a BMI <20 kg/m^2 and/or weight loss 5 kg/year have been included. Previous studies in TAVI cohorts have actually demonstrated the importance of frailty as an independent predictor of mortality, yet its assessment incorporated different methods, including questionnaires, various gait-speed and strength tests, and physicians' subjective assessments, which can have substantial variance according to method and observer interpretation.[26] Our meta-regression analysis suggested that in underweight patients, the presence of diabetes and previous myocardial infarction led to an increased risk of long-term all-cause mortality. Interestingly, for the same comparison, the lower long-term mortality was reported in those studies with a higher usage of self-expandable valves. However, this result came from a pooled analysis of only 4

Table 4
Outcomes after TAVI in obese versus normal weight patients

Outcome	Studies	Patients	RE HR/OR [95% CI]	*P* Value	χ^2	FE HR/OR [95% CI]	*P* Value	χ^2	I^2%	Egger Test	Trim and Fill HR
All-cause mortality											
30-day	6	3367	0.87[0.65-1.16]	0.35	11.80	0.97[0.93-1.01]	0.20	11.80	58	0.662	0.82[0.60-1.13]
Long-term	7	4709	0.79[0.67-0.93]	0.004	4.91	0.79[0.67-0.93]	0.004	4.91	0	0.151	0.75[0.63-0.89]
Long-term *(for each 1 kg/m^2 increase)*	7	4677	0.96[0.93-1.00]	0.03	22.54	0.96[0.95-0.98]	<0.00001	22.54	73	0.528	0.96[0.93-1.00]
Major and life-threatening bleeding	6	4237	1.05[0.75-1.46]	0.79	9.79	0.99[0.79-1.23]	0.90	9.79	49	0.377	1.05[0.75-1.46]
Major Vascular complication	6	4237	1.14[0.85-1.52]	0.38	5.59	1.14[0.87-1.48]	0.34	5.59	11	0.771	1.14[0.85-1.52]
Device Success	5	4003	1.07[0.75-1.54]	0.70	5.61	1.06[0.79-1.42]	0.70	5.61	29	0.305	0.86[0.58-1.27]
Cerebrovascular events	6	4237	1.10[0.63-1.94]	0.74	11.43	0.98[0.70-1.37]	0.91	11.43	56	0.347	1.10[0.63-1.94]
Myocardial Infarction	4	3717	0.67[0.33-1.39]	0.28	1.00	0.66[0.32-1.34]	0.25	1.00	0	0.868	0.67[0.33-1.39]
Acute Kidney Injury	6	4237	1.29[0.92-1.79]	0.14	0.88	1.29[0.92-1.80]	0.14	0.88	0	0.407	1.29[0.92-1.79]

Mortality data are reported as HR; procedural outcomes are reported as OR according to the availability of crude events in the primary studies.

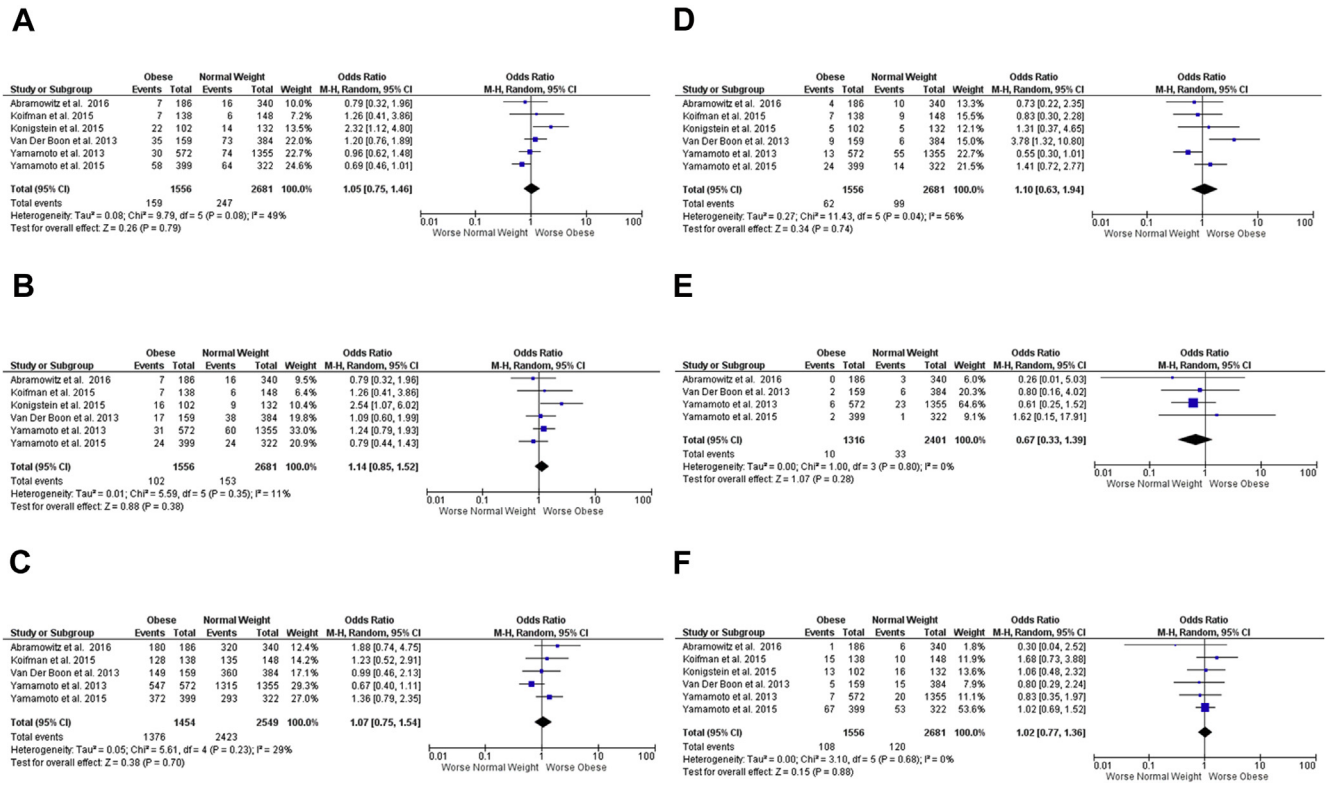

Figure 5. Impact of BMI ≥30 kg/m^2 on procedural complications. Random-effects OR and 95% CI for major and life-threatening bleedings *(A)* major vascular complications, *(B)* device success, *(C)* cerebrovascular events, *(D)* myocardial infarction, *(E)* acute kidney injury *(F)*.

studies, not sufficient to draw effective conclusions. As far as procedural complication regards, the higher incidence of major and life-threatening bleedings as well as of major vascular complications might suggest that in underweight patients with very small peripheral vessels, new devices with progressively smaller introduction and delivery system should be used to reduce the risk of vascular complications and bleeding issues. Indeed, this issue has been previously reported also in small body sized patients undergoing TAVI.[27]

Our meta-analysis shows a lower mortality in obese patients thus corroborating pervious studies demonstrating the "obesity paradox" in TAVI patients. Actually, even when BMI was analyzed a continuous variable, each increase in 1 unit of kg/m^2 was linked to a significantly lower rate in long-term mortality. Obesity was shown to result in a worse prognosis in general population cohorts, with BMI conferring a U-shaped curve in relation to mortality, as both obesity and underweight have been found to have detrimental effects on overall survival.[1] However, in severe aortic stenosis patients undergoing surgical aortic valve replacement[2] or TAVI,[6,18,28] BMI was found to have a protecting effect, with obese patients having a better outcome than normal weight patients. Some possible explanations can be suggested for the obesity paradox. First, the obese group often consists of younger subjects, although age did not emerge as a significant modifier in our analysis.

Second, it is possible that obese patients are treated more aggressively with cardioprotective drugs that may contribute to better outcomes.

As of today, BMI is not part of the risk scores ordinarily used to screen and to predict mortality after TAVI. The currently used scores (logistic EuroSCORE, Society of Thoracic Surgeons score, EuroSCORE II, Age, Creatinine, and Ejection Fraction [ACEF] score, Ambler's risk score, OBSERVANT, SURgical replacement and Transcatheter Aortic Valve Implantation [SURTAVI] model, and survival post TAVI [STT] score) provide important prognostic information but still lack calibration and discriminatory power.[29] This is probably because they do not consider a number of factors that have subsequently emerged in recent series, as significantly affecting outcome of patients undergoing TAVI. Among those, BMI has not been considered so far in the risk prediction for patients undergoing TAVI; however, given the results of this meta-analysis BMI should definitely be included in new TAVI-oriented risk score models.

The results of this meta-analysis are affected by limitations and differences of the original included studies themselves. All meta-analyses share limitations related to differences in study design, end point definitions, and publication bias. Importantly, we found a substantial variation in the categorization of BMI in the included studies, which might have led to differences in the reported outcomes and contributed to the heterogeneity observed.[30] The analysis of 30-day all-cause mortality in the comparison underweight versus normal weight patients and the analysis of long-term mortality when BMI was used as a continuous variable showed a high heterogeneity (>70%) not explained by analysis of potential modifiers or publication bias. Therefore, the results should be considered with caution. However, this heterogeneity reflects the contrasting results among the studies included on this issue, supporting the need for a meta-analysis and future larger studies. Although mortality analyses are based on the highest quality of data (adjusted HR), patient-level data from TAVI studies prospectively reporting on BMI could be of added value to confirm our findings and further elucidate this topic. Moreover, although it might be supposed that people with a BMI of 45 have a different risk profile compared with people with a BMI of 31, we were not able to investigate the differences in outcome, if any, among different grades of obesity. Actually, the vast majority of obese patients laid in the grade 1 category and data about morbid obese patients are usually included (and therefore lost) in a one categorization group. Another limitation is that all the analyses about the procedural complications were performed on unadjusted data, which might suffer the weight of other covariables (Table 2).

Disclosures

Dr. Grayburn has received research grants from Abbott Vascular, Medtronic, Boston-Scientific, Edwards, Tendyne, ValTech Cardio, NeoChord and is a consultant for Abbott Vascular, NeoChord, ValTech Cardio. Dr. Gargiulo has received research grant from European Association for Percutaneous Coronary Interventions (EAPCI) and Cardiopath PhD program (Federico II University of Naples).

Supplementary Data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.amjcard.2016.09.031.

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REVIEW

Renal dysfunction and transcatheter aortic valve implantation outcomes

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ABSTRACT

Introduction: Transcatheter aortic valve implantation (TAVI) underwent progressive improvements until it became the default therapy for inoperable patients, and a recommended therapy in high-risk operable patients with symptomatic severe aortic stenosis. Recent evidence will further support TAVI as treatment for a growing number of patients.

Areas covered: This review will discuss on the current knowledge about the role of both pre-procedural chronic kidney disease (CKD) and post-procedural acute kidney injury (AKI) in adult patients with severe aortic stenosis undergoing TAVI.

Expert commentary: Pre-procedural CKD is one of the most frequent comorbidities of TAVI patients and has been found to significantly worsen patients' prognosis at short and long-term follow-up. Similarly, post-procedural AKI is a frequent and relevant complication associated with increased mortality. The risk stratification of the patient, the prevention of complications and the appropriate post-procedural management are the main focus of the future research aimed at further improving clinical outcomes of TAVI patients.

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TAVI; renal dysfunction; chronic kidney disease; acute kidney injury; mortality

1. Introduction

Transcatheter aortic valve implantation (TAVI) has accumulated growing evidence in the last year supporting the concept that it should now be considered a valid alternative to surgical aortic valve replacement (SAVR) [1]. Patients undergoing TAVI are commonly very old and have a high prevalence of comorbidities. Renal dysfunction is a relevant medical issue for elderly patients with severe aortic stenosis (AS) being both a baseline risk factor for increased mortality and complications after treatment as well as a post-procedural adverse event impacting on the prognosis of patients undergoing TAVI.

This review will discuss on the current knowledge about the role of both pre-procedural chronic kidney disease (CKD) and post-procedural acute kidney injury (AKI) in adult patients with severe AS undergoing TAVI.

2. Pre-procedural CKD

2.1. Definition and prevalence of baseline CKD

CKD is a growing worldwide public health problem with relevant economic and social repercussions and is a well recognized modifier of the natural history of cardiovascular diseases being associated with a poorer prognosis in these patients [2]. According to KDIGO (Kidney Disease: Improving Global Outcomes), CKD is generally classified into five stages: Stage 1 = kidney damage (albuminuria, proteinuria, hematuria) with normal or higher estimated glomerular filtration rate (eGFR) (≥90 mL/min/1.73 m^2; normal CKD); Stage 2 = kidney damage (albuminuria, proteinuria, hematuria) with mild eGFR reduction (60–89 mL/min/1.73 m^2; mild CKD); Stage 3 = moderate eGFR reduction (30–59 mL/min/1.73 m^2; moderate CKD, chronic renal insufficiency, early renal insufficiency); Stage 4 = severe eGFR reduction (15–29 mL/min/1.73 m2, severe CKD, chronic renal insufficiency, late renal insufficiency); Stage 5 = renal failure with eGFR<15 mL/min/1.73 m^2 or dialysis (kidney failure, uremia, end-stage renal disease [ESRD]) [3].

Patients with AS are generally elderly and their renal function is often reduced. In currently available clinical trials of TAVI versus SAVR, CKD was not uniformly defined and the prevalence of preoperative CKD was not so high as in other trials or registries (Figure 1). In the PARTNER trial, patients with creatinine levels >2 mg/dL (>177 micromol/L) were 9.0% (TAVI 38/343, SAVR 24/344); in the PARTNER 2 trial, patients with creatinine levels >2 mg/dL were 5.1% (TAVI 51/1011, SAVR 53/1021); in the STACCATO trial, patients with creatinine levels >2.2 mg/dL (200 micromol/L) were 1.4% (TAVI 1/34, SAVR 0/36); in the US CoreValve trial, patients with CKD 4–5 were 12.7% (TAVI 48/390, SAVR 52/396); in the NOTION trial, patients with creatinine levels >2 mg/dL were 1.1% (TAVI 2/145, SAVR 1/135). On the other hand, CKD was present in 24.7% and 54.6% of TAVI patients included in the DEFLECT III (CKD definition not reported) and BRAVO 3 (CKD defined as eGFR<60 mL/min) trials, respectively [4,5] and was ranging from 20% to more than 60% in many real-world registries [1,6–10].

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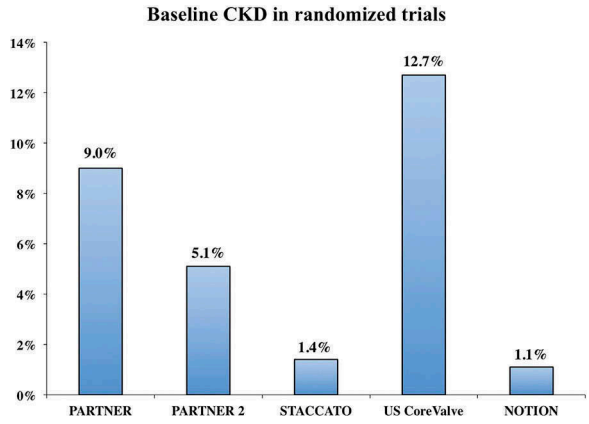

Figure 1. Prevalence of pre-operative CKD in randomized trials comparing TAVI vs SAVR.

2.2. Impact of CKD on outcomes after TAVI

It is well known that baseline CKD increases early and late mortality in patients undergoing cardiac surgery, particularly for those with ESRD [11]. On the contrary, this was a debated issue in patients undergoing TAVI with some contrasting evidence, indeed, some studies found that CKD predicted mortality [6,7,10,12,13], while a large national registry did not confirm this finding [14]. Moreover, two studies had showed that only CKD stages 4 and 5 but not stage 3 were associated with significant increase of mortality [15,16]. On this background, our group conducted a meta-analysis to explore this issue including 9 studies with a total of 4992 patients [17]. As first step, we assessed the impact of overall renal dysfunction comparing outcomes of patients categorized as CKD stages 3–5 with those in the stages CKD 1 and 2 (Figure 2); then we looked for a potential different impact on prognosis related to the severity of CKD analyzing separately the role of moderate CKD (stage 3) and severe CKD (stages 4 and 5). We found that overall CKD (stages 3–5) was associated with significant increase of early and 1-year all-cause and cardiovascular mortality, early stroke, AKI, AKI 2 to 3, need for dialysis, and length of stay in the absence of differences in contrast medium administration, but also that compared with lower degree of CKD, worse renal impairment (i.e. CKD 4–5 versus CKD 1–2; CKD 4–5 versus CKD 3; CKD 3 versus 1–2) was associated with increased all-cause and cardiovascular mortality, stroke, AKI, AKI 2–3, need for dialysis and bleeding. More importantly, moderate CKD alone emerged for the first time to significantly impact on all-cause mortality, stroke, and AKI (Figure 3). Altogether, these findings support the concept that not only patients with severe CKD may experience worse prognosis after TAVI but also those with a moderate degree of renal dysfunction [17].

After this meta-analysis, a new study exploring the role of CKD on outcomes according to its severity was published by the FRANCE2 registry investigators [8]. This study analyzed a total of 2929 patients of whom 1386, 711, 547, 189, and 96, respectively, belonged to CKD 1–2, CKD 3a, CKD 3b, CKD 4, and CKD 5 stages. They confirmed that both 30-day and 1-year mortality rates were significantly increased and positively correlated with CKD severity in all groups [8].

Even after pooling these data with our prior analyses, we found that CKD (stages 3–5) as well as moderate CKD (only stage 3) worsened mortality after TAVI [18]. Notably, in the study by Oguri et al., moderate CKD was further divided into stage 3a (45–59 mL/min/1.73 m^2) and 3b (30–44 mL/min/

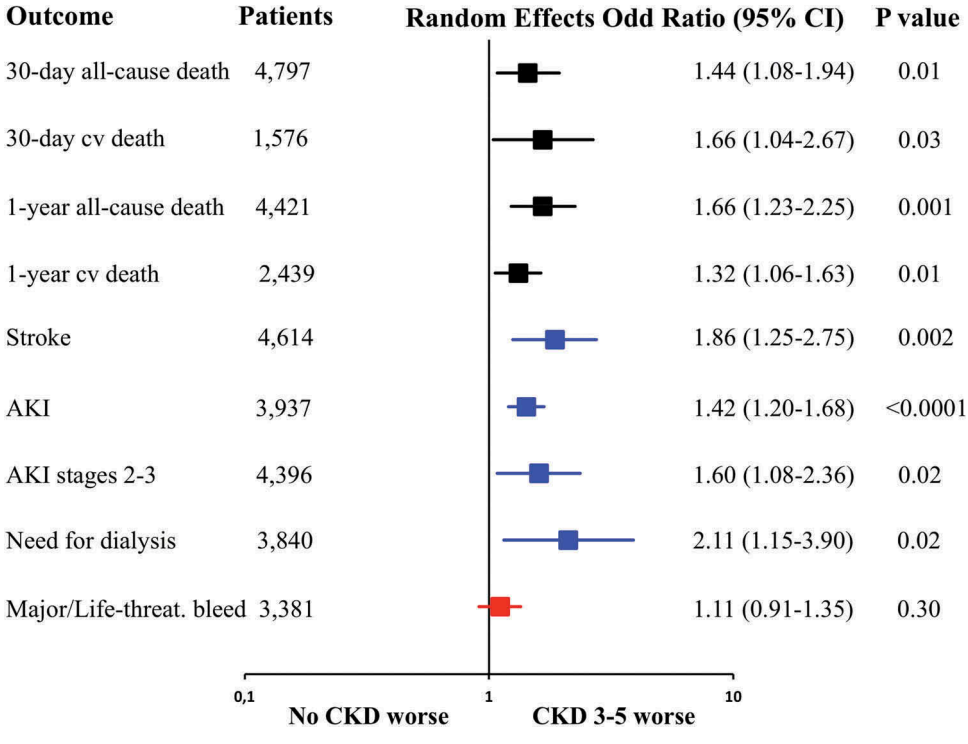

Figure 2. Prognostic impact of CKD stages 3 to 5 on clinical outcomes [17].

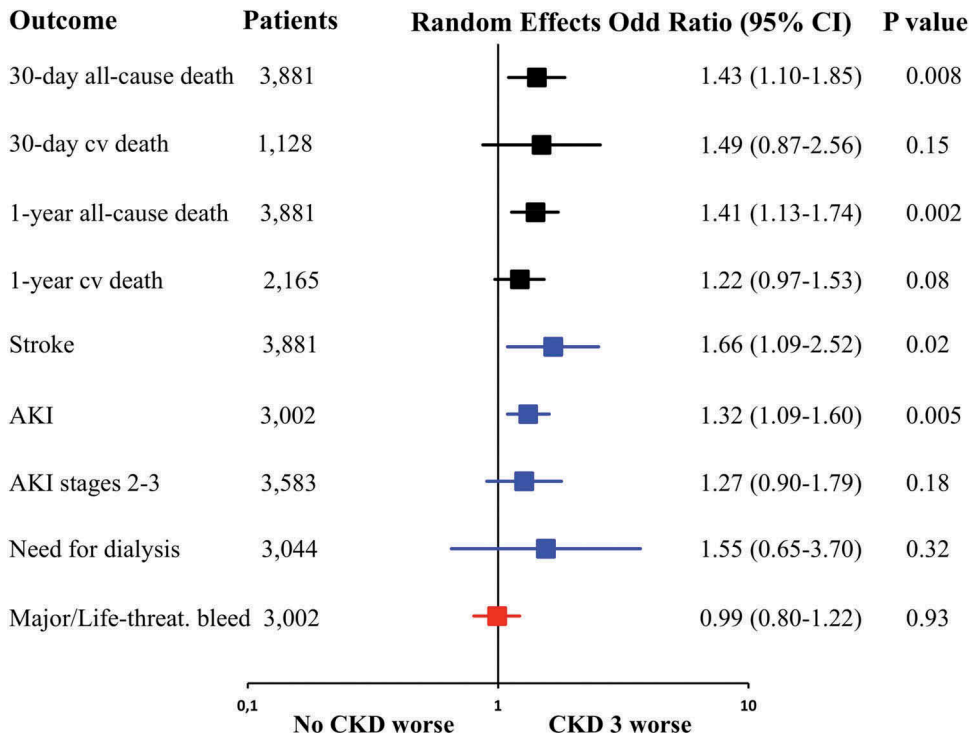

Figure 3. Prognostic impact of moderate CKD (stages 3) on clinical outcomes [17].

1.73 m^2) and the authors observed that both CKD 3a and 3b did not emerge as independent predictor of 30-day mortality, while at one year, stage 3b (p = 0.045) but not stage 3a (p = 0.59) significantly predicted mortality [8]. However, this finding of differential impact between stage 3a and 3b needs to be further confirmed in larger studies to exclude that it was driven by underpowered analyses, particularly due to the observation that the prognostic impact is related to the degree of renal dysfunction (CKD stages 4–5 worse prognosis than stage 3). This would be clinically relevant because patients with CKD 3a represent a large cohort (in the FRANCE2 24% compared with 19%, 7%, and 3% of stages 3b, 4, and 5, respectively) and because a further stratification of patient's risk with significant association to prognosis might help in decision-making.

Further studies have confirmed the detrimental impact of CKD on prognosis of patients undergoing TAVI. Ferro et al. analyzed 3980 patients from the UK TAVI registry and found that eGFR <45 mL/min/1.73 m^2 was significantly associated with increased mortality, even after adjustment for risk factors and that for every 10 mL/min/1.73 m^2 decrease in eGFR, cumulative mortality increased by 4.4% at a median follow-up of 543 days [19]. Interestingly, this study confirmed that the worse the renal function, the worse is prognosis. Another meta-analysis explored the role of the pre-procedural renal dysfunction and confirmed that CKD was associated with increased mid-term mortality after TAVI with CKD stage 4 being associated with a significantly higher rate of peri-procedural complications and a poorer prognosis [20].

Notably, a study by Dvir et al. has been recently presented at the international EuroPCR 2016 meeting [21]. The authors analyzed 378 patients treated with TAVI and with follow-up longer than 5 years (5-14 years) from St. Paul's Hospital in Vancouver, Canada and Hôpital Charles Nicolle in Rouen, France in order to explore long-term durability of TAVI valves. Valve degeneration was defined as at least moderate regurgitation and/or mean gradient ≥20 mmHg, which did not appear within 30 days of the procedure and was not related to endocarditis. This study found that baseline renal failure (defined as eGFR<60 mL/min) was present in 46.3% of patients and emerged as the strongest correlate for valve degeneration (HR = 3.22, CI 1.45–7.15, p = 0.004) in a multivariable model including age, gender, baseline orifice area, baseline left ventricular ejection fraction, body mass index, renal failure, valve type, valve size, anticoagulation treatment (i.e. warfarin) after TAVI [21].

2.3. Outcomes of patients on dialysis

TAVI is emerging as an alternative to SAVR also for patients with ESRD, even if it is known that the worse is the renal function the worse is the patient prognosis after TAVI. AS is common in patients with ESRD and the rate of progression is faster than in patients without end-stage renal disease. However, these patients have also a high risk for SAVR with poor short- and long-term outcomes [22]. A large European cohort reported that 6.9% of patients undergoing TAVI were on dialysis [23]. TAVI might be therefore a promising alternative to SAVR in this setting of patients but they are often excluded by trials and few data are currently available on their outcomes. In the large multicenter Italian OBservational Study of Effectiveness of AVR—TAVI procedures for severe Aortic steNosis Treatment (OBSERVANT) Registry, 44 of the

1911 consecutive patients (2.3%) enrolled between 2010 and 2012 were on dialysis [24]. They were more commonly men (74%), severely symptomatic (NYHA III/IV 70%) and mean age was 78 years. The majority underwent transfemoral TAVI (77%) and 64% received the third-generation self-expanding transcatheter heart valve (CoreValve ReValving System) while 36% the balloon-expandable valve (Edwards Sapien XT) [24]. Regarding procedural outcomes, moderate-to-severe paravalvular regurgitation and new permanent pacemaker implantation were reported in 12% and 20% of the patients, respectively. Mortality rates were 4.5% in-hospital, 9.1% at 30 day and 34.1% at 1 year whereas the composite of major adverse cardiac and cerebrovascular events was 36.4% at 1 year and rehospitalization was reported in 47.7% of patients.

In the multicenter study by Allende et al. [16], 67 of 2075 patients (3.2%) were defined as stage 5 CKD (eGFR <15 or on dialysis). In this study, dialysis was an independent predictor of mortality as was atrial fibrillation as in other studies [25,26]. The 30-day pacemaker implantation and moderate-to-severe aortic regurgitation were observed in 12.1% and 11.9%, respectively. AKI occurred in 30% of those not on dialysis and major or life-threatening bleeding events were reported in 10.4% of patients while no cerebrovascular events occurred. Mortality was 11.9% at 30-day and 50.7% at mid-term follow-up (median follow-up of 15 months).

In the 4-center collaborative analysis by Dumonteil et al. (PRAGMATIC-Plus), 33 of 942 patients (3.5%) were on dialysis and showed the following outcomes at 30 day after TAVI: death 15.2%, myocardial infarction 6.2%, stroke 6.1%, major bleeding 24.2%, AKI stage III 31.2%, and new permanent pacemaker implantation 12.5%. At 1 year, mortality was approximately 45% [27].

In the study by Goebel et al., 15 of 270 patients (5.6%) were on dialysis of whom 20% needed pacemaker implantation after TAVI, and mortality was 20% at 30 day [28].

Although further data are needed for this complex setting of patients, these preliminary findings suggest favorable safety and efficacy at short- and mid-term follow-up of TAVI in patients with severe symptomatic AS and chronic dialysis. However, many efforts should be provided to optimize their outcomes, indeed the subtle equilibrium between thrombotic and hemorrhagic events and the implications for antithrombotic treatment have been well recognized in TAVI patients [29,30]. Severe CKD patients are particularly challenging and should be carefully managed avoiding antithrombotic overtreatment to reduce risks of complications after TAVI.

3. Post-procedural AKI

3.1. Definition

AKI has a great clinical relevance due to several reasons: (i) AKI is common; (ii) it is associated with a heavy burden of illness (morbidity and mortality); (iii) it is associated with high cost of managing; (iv) it is amenable to early detection and potential prevention; (v) there is considerable variability in practice to prevent, diagnose, treat, and achieve outcomes of AKI.

The Acute Dialysis Quality Initiative (ADQI) group developed a system for diagnosis and classification of a broad range of acute impairment of kidney function through a broad consensus of experts (Table 1) [31]. The acronym RIFLE stands for the increasing severity classes Risk, Injury, and Failure; and the two outcome classes, Loss and ESRD. The three severity grades are defined on the basis of the changes in serum creatinine (sCr) or urine output where the worst of each criterion is used, while the two outcome criteria, Loss and ESRD, are defined by the duration of loss of kidney function.

To define AKI and its stages after TAVI, the first document by VARC proposed to adopt serum creatinine criteria from the 'modified' RIFLE classification [32]. Two important changes were applied to modify the original RIFLE classification including (i) smaller changes in serum creatinine (0.3 mg/dL) are included in stage 1 (Risk); (ii) the 'Loss' and 'ESRD' categories have been removed due to a lack of uniform indications and timing of renal replacement therapy (RRT) and variability in RRT resources in different countries. A timing of 72 h from the index procedure was selected for diagnosing AKI based on evidence that adverse outcomes were observed when the elevation occurred within 24 -48 h of the procedure and to ensure that the process was both acute and related to the procedure itself rather than as a consequence of post-procedure multiorgan system failure. RIFLE classification also underlined the predictive value of urine output criteria in defining AKI, but first VARC criteria did not include this measure in the definition of AKI since urine outputs may not be measured accurately or routinely in all cases. VARC proposed to adopt the modified RIFLE classification to (i) capture even the earliest stages of AKI (stage 1) on case report forms, (ii) define AKI as

Table 1. RIFLE and AKIN diagnostic criteria for acute kidney injury.

Class output	Criteria: GFR/sCr	Criteria: urine
RIFLE criteria (7days)		
R-*Risk*	Increase sCr × 1.5 or GFR decrease >25%	<0.5 mL/kg/h for >6 h but <12 h
I-*Injury*	Increase sCr × 2 or GFR decrease >25%	<0.5 mL/kg/h for >12 h but <24 h
F-*Failure*	Increase sCr × 3 or GFR decrease >75% or sCr ≥4 mg/dL, Acute rise 0.5 mg/dL	<0.3 mL/kg/h for ≥24 h or anuria for ≥12 h
L-*Loss*	Persistent kidney failure >4 weeks	
E-*ESKD*	Terminal kidney injury >3 months	
Stage output		
AKIN criteria (48 h)		
Stage 1	Increase of sCr × 1.5 or ≥0.3 mg/dL	<0.5 mL/kg/h for >6 h but <12 h
Stage 2	Increase of sCr × 2	<0.5 mL/kg/h for >12 h but <24 h
Stage 3*	Increase of sCr × 3 or ≥4 mg/dL	<0.3 mL/kg/h for ≥24 h or anuria for ≥12 h

AKIN: acute kidney injury; ESKD: end-stage kidney disease; GFR: glomerular filtration rate; sCr: serum creatinine.
*Patients receiving renal replacement therapy are considered to meet stage 3 criteria irrespective of other criteria.

either stage 2 or 3, and (iii) report any case of RRT (hemodialysis, peritoneal dialysis, or hemofiltration) occurring during the index hospitalization or within 30 days after the index procedure. In addition, based on the well-recognized damaging impact of contrast media on renal function, VARC also recommended reporting the volume and type of contrast medium used during the index procedure [32]. The subsequent VARC-2 document [33] recommended using the AKIN system (Table 1) [34], which is a modified version of RIFLE that has been adopted by many in the nephrology community, including the KDIGO initiative [33]. Consequently, AKI was to be diagnosed also according to urine output measures (Table 1). Furthermore, the timing for the diagnosis of AKI was extended from 72 h to 7 days and it was recommended that patients who experience AKI should have follow-up renal function assessments after 7 days until stabilization [33].

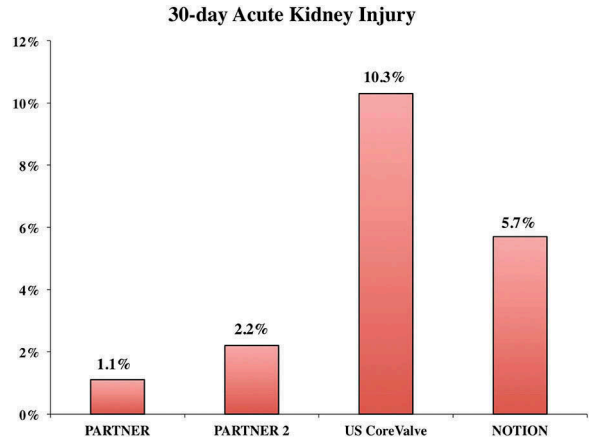

Figure 4. Incidence of AKI in randomized trials comparing TAVI vs SAVR.

3.2. Pathophysiology of AKI

Renal dysfunction in patients undergoing TAVI is usually multifactorial: the commonest cause is acute tubular necrosis as a result of hypoxic damage to nephrons in the medullary region of the kidney secondary to hypotension, hypovolemia, and/or dehydration, that can occur fairly often during and after the procedure [31]. The contrast media increases intra-renal vasoconstriction and osmotic load, decreasing medullary blood supply and leading to an increased oxygen requirement in the presence of an already low tissue oxygen tension. In addition, the hypovolemia plays a key role in the development of AKI, by activating series of vasoconstrictor, salt-retaining neurohumoral systems (these include the sympathoadrenal system, angiotensin, aldosterone, and antidiuretic hormone). The initial response to a contracted extracellular fluid volume is a decrease in both the GFR and the filtered solute load.

3.3. AKI incidence and impact on outcomes after TAVI

Differently from percutaneous coronary intervention in which AKI is mainly related to contrast-induced damage, TAVI patients might develop kidney injury after the procedure for several factors including contrast agent administration, concomitant drugs, need for rapid pacing with resulting hypotension, and renal hypoperfusion, blood loss, embolization during the implantation due to patient's age and frequent coexistence of atherosclerosis, and postoperative severe inflammatory response syndrome [35].

The incidence of AKI after TAVI is widely ranging. In the currently available randomized trials of TAVI versus SAVR, the AKI incidence is quite low compared to registries (Figure 4). In the PARTNER trial, all patients with AKI were 1.1% (TAVI 4/348, SAVR 4/351); in the PARTNER 2 trial, patients with AKI were 2.2% (TAVI 13/1011, SAVR 31/1021); in the US CoreValve trial, patients with AKI were 10.3% (TAVI 23/390, SAVR 54/357); in the NOTION trial, patients with AKI were 5.7% (TAVI 1/139, SAVR 9/135); in the STACCATO trial, AKI was not assessed, but 1 patient in the TAVI group required permanent hemodialysis after the procedure. Conversely, data from real-world registries reported that AKI might occur also in higher than 40% of patients. A recent meta-analysis has explored the impact of AKI on outcomes in 24 studies including 5,971 and found that the mean incidence of AKI in this population was 22.1%±11.2 (Table 2) [35]. More importantly, this meta-analysis contributed to clarify the prognostic role of AKI after TAVI. Whereas it was clear that AKI worsened outcomes after SAVR [36,37], there was still conflicting and debated evidence for TAVI patients with some studies showing no significant impact of AKI on mortality [38–41] compared with other studies [42–45]. As compared with no-AKI, AKI was found to significantly increase early and 1-year all-cause and cardiovascular mortality as well as early myocardial infarction, life-threatening bleeding, need for transfusion, need for dialysis (Figure 5) with a nonsignificant increase of stroke, length of hospitalization (mean difference [MD] 1.73; 95% CI, 20.31 to 3.77), and contrast medium received (MD 4.74; 95% CI, 22.33 to 11.81) [35]. Furthermore, meta-regression analyses showed that the presence of coronary artery disease and a lower ejection fraction at baseline were significantly associated with worse 1-year all-cause mortality in accordance with prior studies [46–48].

Table 2. AKI incidence in observational studies included in the meta-analysis by Gargiulo et al. [35].

Authors	Year	Age (years)	All patients	AKI patients	AKI incidence (%)
Aregger et al.	2009	83.0	58	15	25.9
Bagur et al.	2010	82.0	213	25	11.7
Barbanti et al.	2014	82.0	1157	231	20.0
Barbash et al.	2012	85.0	165	24	14.5
Elhmidi et al.	2011	81.0	234	46	19.7
Garcìa-Lara et al.	2014	80.8	131	17	13.0
Gebauer et al.	2012	82.0	140	28	20.0
Généreux et al.	2013	85.4	218	18	8.3
Goebel et al.	2013	81.6	270	41	15.2
Johansson et al.	2013	80.0	64	21	32.8
Keles et al.	2013	77.6	70	5	7.1
Khawaja et al.	2012	82.2	248	89	35.9
Kong et al.	2012	84.0	52	15	28.8
Konigstein et al.	2013	83.2	251	42	16.7
Nuis et al.	2011	82.0	118	22	18.6
Nuis et al.	2012	82.0	995	206	20.7
Pilgrim et al.	2013	82.5	389	64	16.5
Saia et al.	2013	83.7	102	42	41.2
Sinning et al.	2010	80.8	77	20	26.0
Sinning et al.	2014	80.9	132	30	22.7
Strauch et al.	2010	82.1	28	16	57.1
Van Linden et al.	2011	82.0	261	42	16.1
Wessely et al.	2012	81.1	183	49	26.8
Yamamoto et al.	2013	83.6	415	63	15.2

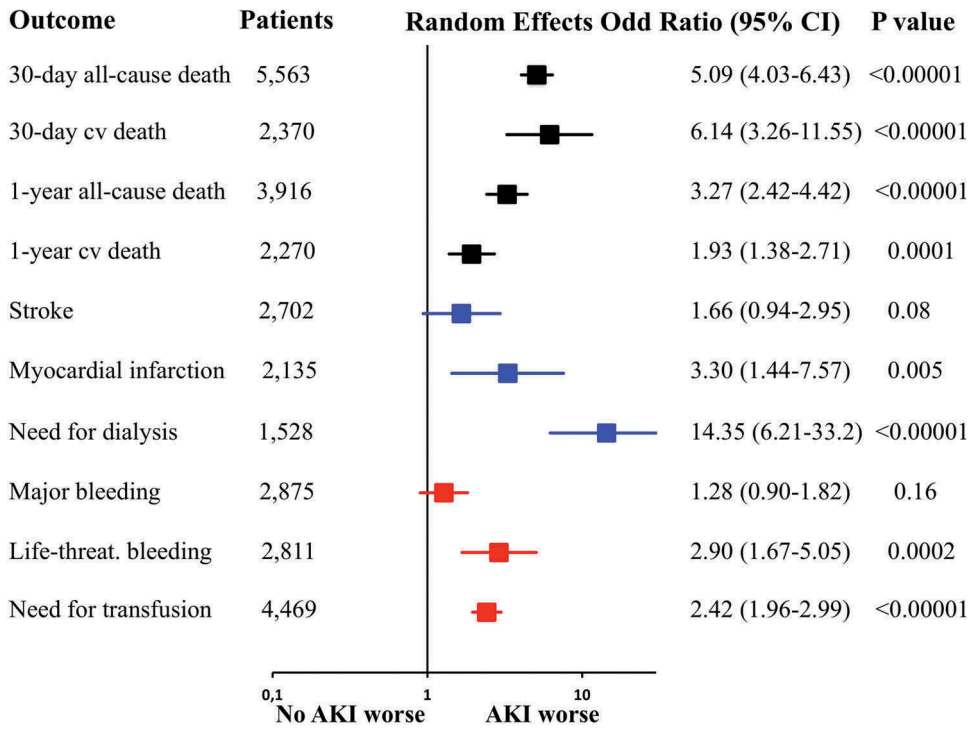

Figure 5. Prognostic impact of post-procedural AKI on clinical outcomes [33].

Anyway, this complication and its impact should not limit indication to TAVI procedure, indeed, even if frequent, AKI is significantly reduced with TAVI compared with SAVR [1].

These findings support the clinical relevance of AKI and the need for future studies to address the preoperative risk evaluation, strategies for AKI prevention and the postoperative patient management of these patients to improve their outcomes. However, future studies should also take into account the current management of TAVI patients; indeed, the improvement of assistance and outcomes has led to reduction in length of hospitalization and this might be a potential issue to be considered for the timing required for AKI diagnosis [49–51].

3.4. AKI prevention

AKI prevention is a relevant aim for the future research because AKI has detrimental effects on prognosis as previously discussed, but also because we do not have yet large scientific evidence regarding risk factors and the role of preventive strategies in this setting of patients compared with patients undergoing coronary angiography or intervention. As for these latter patients, the contrast amount received is a relevant risk factor for AKI [45], but we also recognized above that the pathophysiology of AKI after TAVI is not exclusively related to contrast administration. Therefore, the identification of specific risk factors for TAVI patients is fundamental. As underlined before, pre-operative CKD, particularly if more severe, is a critical factor increasing the risk of AKI after TAVI [16,17,42,52], but also other factors were found to independently predict AKI including female gender, general anesthesia, heart failure, transfusion (≥3 red blood cell units), major bleeding, peripheral vascular disease, maximum leukocyte count (within 72 h), and logistic EuroSCORE [42,45,53,54].

Many trials have explored several prevention strategies with conflicting results for patients undergoing coronary angiography or intervention, but few data are available for TAVI patients. Even if hydration is fundamental for all patients, it should be considered that in patients with impaired left ventricular function and left side valvular heart diseases, hydration is usually suboptimal due to the perceived risk of overhydration and pulmonary edema. In line with this, hydration has been combined with diuretic agents in order to increase urine output and prevent overhydration. Indeed, the RenalGuard System is a device delivering intravenous fluids matched to the urine output that emerged as an alternative strategy for AKI prevention.

The recent PROphylactic effecT of furosEmide-induCed diuresis with matched isotonic intravenous hydraTion in Transcatheter Aortic Valve Implantation (PROTECT-TAVI) has evaluated for the first time in a randomized trial the role of RenalGuard System in the prevention of AKI in patients undergoing TAVI [55]. The PROTECT-TAVI was a single-center, prospective, open-label, registry-based randomized study that used the TAVI institutional registry of the Ferrarotto Hospital in Catania, Italy, as the platform for randomization, data collection, and follow-up assessment. Overall, 112 consecutive TAVI patients were randomized to hydration with normal saline solution controlled by the RenalGuard System and furosemide (RenalGuard group = 56) or normal saline solution (Control group = 56). The primary end point was the incidence of AKI in the first 72 h after the procedure according to the VARC definition [55]. Three patients (5.4%) developed AKI stage I in the RenalGuard group while no AKI stages II–III were observed. In the control group, AKI stage I and stage III

occurred in 13 (23.2%) and 1 (1.8%), respectively. Therefore, AKI overall was significantly lower in RenalGuard group compared with control (5.4% vs. 25.0%, $p = 0.014$). No patient required in-hospital dialysis due to renal failure and no significant differences were reported at 30 days in terms of mortality, cerebrovascular events, bleeding, and hospitalization for heart failure [55].

A further experience on the role of RenalGuard System has recently added to this study [56]. This prospective nonrandomized study included 48 patients with CKD that were assigned to: (1) hydration with sodium bicarbonate solution (154 mEq/L of sodium bicarbonate in dextrose and H2O plus N-acetylcysteine at a high dose) (control group = 26), or (2) hydration with RenalGuard System in order to achieve an optimal urine flow of ≥300 mL/h (RenalGuard group = 22). Criteria for treating the patients with the RenalGuard System were: (a) eGFR ≤30 mL/min/1.73 m^2, or (b) a predicted risk for AKI ≥50%. All patients received CoreValve System by transfemoral approach. The primary end point was the occurrence of AKI defined as an increase of ≥0.3 mg/dL in the serum creatinine concentration at 7 days. AKI occurred in 10/26 (38.5%) patients in the control group and in 1/22 (4.5%) patients in the RenalGuard group ($p = 0.005$). RenalGuard demonstrated to protect against AKI (OR 0.71, 95% CI: 0.07–0.775, $p = 0.026$), while post-procedural hypotension defined as peri-procedural mean blood pressure <55 mmHg (OR 3.88, 95% CI: 1.06–14.24, $p = 0.040$), and contrast media volume (OR 3.65, 95% CI: 1.15–5.75, $p = 0.043$) were found to significantly increase the risk of AKI [56].

4. Expert commentary

We believe that the evidence discussed here should serve as basis to plan future research and offer the better quality in daily assistance to patients in order to improve their quality of life and prognosis. The advances in our current knowledge will translate into advances in patients' care.

TAVI patients with baseline CKD have a higher risk of experiencing further deterioration of renal function as well as other negative outcomes including mortality and long-term valve deterioration during follow-up. Due to the high prevalence of these patients among those undergoing TAVI and to this poor prognosis, it will be pivotal to focus clinical and research efforts to appropriately manage these patients and their complications.

Even if risky, TAVI is an important alternative for such patients, particularly those with ESRD, and a close follow-up as well accurate and specific pharmacological management is required to optimize the risk/benefit ratio of TAVI in these patients.

It is also important to underline that patients with severe CKD should not be deprived a priori of the opportunity to receive TAVI, indeed, some data show that TAVI may also be beneficial for renal function in some patients due to improvement in functional status (New York Heart Association class) and absence of valve hemodynamic anomalies [16,57].

AKI remains one of the most frequent complications after TAVI, and its prevention still needs to be adequately addressed. Therapeutic efforts not to exceed the threshold value of contrast medium administration may reduce the risk of AKI after TAVI. Similarly, prevention of bleeding and need for transfusion would be also important to decrease AKI incidence. The trends in shortening of hospitalization length should carefully consider the AKI definition and occurrence in the days after the procedure. All patients developing AKI should receive careful monitoring to prevent further complications and improve their prognosis.

5. Five-year view

TAVI has dramatically changed the clinical practice offering a life-saving therapy for inoperable patients as well as a valid alternative for high-risk patients [1]. Pre-procedural CKD and post-procedural AKI are frequently observed in patients undergoing TAVI and need to be further addressed due to their detrimental impact on prognosis, particularly because in the near future TAVI is going to be extended worldwide to intermediate- and low-risk patients in whom all efforts should be provided in order to achieve optimal outcomes [1].

Key issues

- CKD is frequent in patients undergoing TAVI and is a relevant factor increasing pre-procedural risk
- Baseline CKD predicts short- and long-term mortality, as well as other relevant outcomes, including long-term valve deterioration
- In addition to severe pre-procedural CKD, also moderate CKD was found to significantly reduce survival of TAVI patients
- The presence of CKD at baseline also increases the risk of 30-day stroke, AKI, need for dialysis, and length of hospitalization
- AKI remains a frequent complication after TAVI and has a significant negative impact on the prognosis increasing mortality, myocardial infarction, need for dialysis, and life-threatening bleeding
- Furosemide-induced diuresis with matched isotonic intravenous hydration using the RenalGuard system is an effective therapeutic tool to reduce the occurrence of AKI in patients undergoing TAVI
- There is the need for studies on risk stratification, prevention strategies and postoperative management of transcatheter aortic valve implantation patients with baseline CKD or developing AKI

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Impact of Renal Dysfunction on Results of Transcatheter Aortic Valve Replacement Outcomes in a Large Multicenter Cohort

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Patients with advanced chronic renal dysfunction were excluded from randomized trials of transcatheter aortic valve replacement (TAVR). The potential impact of chronic renal disease on TAVR prognosis is not fully understood. We aim to evaluate outcomes within a large cohort of patients who underwent TAVR distinguished by renal function. Baseline characteristics, procedural data, and clinical follow-up findings were collected from 10 high-volume TAVR centers in Europe, Israel, and Japan. Data were analyzed according to renal function. Patients (n = 1,204) were divided into 4 groups according to pre-TAVR-estimated glomerular filtration rate (eGFR): group I (eGFR >60), n = 288 (female 45%), group II (eGFR 31 to 60), n = 452 (female 61%), group III (eGFR ≤30), n = 398 (female 61%), and group IV (dialysis), n = 66 (female 31%). Mean Society of Thoracic Surgeons score was higher in patients with lower preprocedural eGFR. All-cause mortality at 1 year was higher in patients with lower eGFR (9.0%, 12.1%, 24.3%, and 24.2% for group I, II, III, and IV, respectively, p <0.001). Multivariate analysis demonstrated that eGFR ≤30, but not eGFR 31 to 60, was associated with increased risk of death (odds ratio 3), bleeding (odds ratio 5.2), and device implantation failure (hazard ratio 2.28). For each 10 ml/min decrease in eGFR, there was an associated relative increase in the risk of death (35%; p <0.001), cardiovascular death (14%; p = 0.018), major bleeding 35% (p <0.001), and transcatheter valve failure (16%; p = 0.007). Renal dysfunction was not associated with stroke or need for pacemaker implantation. In conclusion, among patients who underwent TAVR, baseline renal dysfunction is an important independent predictor of morbidity and mortality. **(Am J Cardiol 2016;118:1888–1896)**

Transcatheter aortic valve replacement (TAVR) has been consolidated as the treatment of choice for inoperable patients with severe symptomatic aortic stenosis (AS) and as an alternative for those at high surgical risk.[1–4] Patients who underwent TAVR are, thus, commonly very old and have a high prevalence of co-morbidities.[5,6] Population aging, hypertension, and the diabetes mellitus pandemic account for the increased prevalence of chronic kidney disease (CKD).[7,8] Renal insufficiency modifies the natural history of cardiovascular diseases, and the presence of CKD has been associated with poor prognosis in patients diagnosed with heart failure, coronary artery or valvular heart disease, and in those who underwent cardiac interventions.[9,10] The association between AS and renal dysfunction has been established.[11,12] Furthermore, patients with renal dysfunction who underwent surgical aortic valve replacement have higher rates of bleeding, postsurgical infections, and higher mortality rates.[13] Advanced and end-stage CKD has been found to be an independent predictor for all-cause and cardiovascular mortality post-TAVR.[14] However, controversy exists as to whether milder CKD is a predictor of worse outcomes as well. This multicenter international collaboration study sought to assess the implications of baseline estimated glomerular filtration rate (eGFR) and dialysis therapy on the periprocedural and 1-year clinical outcomes from a large cohort of patients with severe symptomatic AS who underwent TAVR.

Methods

A total of 1,204 consecutive patients with severe symptomatic AS who underwent TAVR from 2006 to 2015 with

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and without CKD were enrolled from 10 centers in Europe (Ferrarotto Hospital, Catania, Italy; Inselspital University Hospital, Bern, Switzerland; Institute Cardiovasculaire Paris Sud, Massy, France; Galway University Hospital, Galway Ireland; CHRU, Lille, France; University Hospital, Antwerp, Belgium; Bonn University Hospital, Bonn, Germany), Japan (Keio University Hospital, Keio), and Israel (Rabin Medical Center, Petach Tikva and Sheba Medical Center, Ramat Gan). Treatment assignments, device selection, and access approach were determined by each center according to local practice. All treated patients were evaluated by their local heart team and found suitable for TAVR because of high or prohibitive surgical risk. Each center submitted a dedicated database detailing patient baseline demographic and clinical characteristics, echocardiographic and/or multislice computed tomographic data, procedural information, and follow-up data. Prospective data collection was performed in all centers. Outcomes and events were adjudicated according to Valvular academic research consortium 2 (VARC-2) criteria.[15] Baseline creatinine values were available for all patients. The eGFR rate was calculated using the modified diet on renal disease formula.[16] Patients were divided into 4 groups according to their preprocedural eGFR: >60 ml/min/1.73 m^2 (normal-mild CKD, group I), 31 to 60 ml/min/1.73 m^2 (moderate CKD, group II), ≤30 ml/min/1.73 m^2 (advanced CKD, group III), and dialysis (group IV).[17] Data for all eGFR groups were obtained from 3 centers, whereas the 7 remaining centers submitted data for patients with eGFR ≤30. Acute kidney injury (AKI) after TAVR was adjudicated using the modified Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (RIFLE) classification criteria using the highest post-TAVR in hospital creatinine value.[18] Categorical data are presented as frequencies and percentages and continuous variables are presented as mean ± SD or median (interquartile range), according to distribution. Baseline characteristics of study patients were compared using the Kruskal-Wallis test, chi-square, or Fisher's exact tests, as appropriate. The probabilities of all-cause mortality and cardiovascular mortality by eGFR and dialysis groups were graphically displayed using Kaplan-Meier curves, which were compared by the log-rank test. Univariate logistic regression analysis was used to evaluate the association between eGFR (assessed both as a categorical and as a continuous variable) and mortality. The best subsets regression procedure was used to identify significant variables to be included in the multivariable regression models. Multivariable logistic regression analysis was used to evaluate the association between eGFR and dialysis groups and mortality adjusting for the following variables: gender, device implanted, New York Heart Association functional class, median Society of Thoracic Surgeons (STS) score, peak gradient across the valve, and left ventricular ejection fraction. An eGFR (continuous)-by-eGFR group interaction term was used to estimate the mortality risk associated with eGFR decrease in patients with eGFR <30 versus eGFR >30 ml/min. Separate multivariable models were constructed using logistic regression analysis for the following end points: major bleeding, major vascular complications, device failure, new permanent pacemaker implantation, and inhospital cerebrovascular accident. An additional sensitivity analysis was performed to examine the consistency of results in the 3 centers that provided eGFR data on all patients who underwent TAVR (Rabin Medical Center, Ferrarotto Hospital, and Sheba Medical Center). All statistical tests were 2 sided, and a p value of <0.05 was considered statistically significant. All analyses were conducted using the SAS Statistical Package, version 9.4 (SAS Institute, Inc., Cary, North Carolina).

Results

Of the 1,204 patients, 288 were included in group I (eGFR >60 ml/min), 458 in group II (eGFR 31 to 60 ml/min), 452 in group III (eGFR ≤30 ml/min), and 66 in group IV (dialysis). Baseline characteristics of the study population according to CKD severity are listed in Table 1. Mean age increased with decreasing eGFR in patients who did not undergo dialysis, whereas patients in the dialysis group were the youngest ($p<0.001$). Mean STS score increased with decreasing eGFR ($p<0.001$). Baseline echocardiography demonstrated lower ejection fraction, lower mean, and peak transvalvular gradients and larger aortic valve area in patients with lower baseline eGFR. Procedural characteristics are described in Table 2.

At 12 months of follow-up, Kaplan-Meier survival analyses demonstrated a direct relation between poor renal function and all-cause mortality and cardiovascular mortality (Figure 1, $p<0.001$). Rates of all-cause mortality, cardiovascular mortality, major bleeding events, and vascular complications at 1-year follow-up were higher for patients with lower preprocedural eGFR, with 1-year all-cause death reaching almost a quarter of the patients in groups III and IV (Figure 2). Clinical status pre- and post-TAVR was assessed using the New York Heart Association functional class classification (Figure 3). The echocardiographic transaortic valve gradients at follow-up are presented in Figure 4.

The results of the multivariable analyses evaluating the predictors of adverse events are listed in Table 3. In comparison with group I (eGFR >60 ml/min), group III (eGFR ≤30) was associated with a threefold increase (odds ratio [OR] 3.01, 95% confidence interval [CI] 1.72 to 5.26; $p<0.001$) of 1-year all-cause mortality, a twofold increase of 1-year cardiovascular mortality (OR 2.22, 95% CI 1.95 to 4.14; $p=0.12$), a fivefold increase (OR 5.19, 95% CI 2.43 to 11.1; $p<0.001$) of inhospital major/life-threatening bleeding, and more than twofold increase in unsuccessful valve implantation (OR 2.28, 95% CI 1.22 to 4.25; $p=0.01$). Strikingly, dialysis was associated with eightfold increase (OR 7.9, 95% CI 2.76 to 22.59; $p<0.001$) in 30-day major/life-threatening bleeding. When analyzing eGFR as a continuous variable, multivariable analysis demonstrated that every 10 ml/min decrease in eGFR was associated with a respective 19% ($p<0.001$), 14% ($p=0.018$), 35% ($p<0.001$), and 16% ($p=0.007$) increase in the risk of death, cardiovascular death, major bleeding, and valve failure, respectively. It should be noted that the association between low eGFR and increased mortality risk was mainly driven by eGFR <30. Consequently, in patients with an eGFR <30 every 10 ml/min decrease in eGFR was associated with a twofold increase in 1-year mortality (OR 2.24, 95% CI 1.22 to 4.12; $p=0.010$), whereas in patients with eGFR ≥30 every 10 ml/min decrease

Table 1
Baseline and echocardiographic characteristics of the study population

	Dialysis (n = 66)	GFR ≤30 ml/min/1.72 m^2 (n = 398)	GFR 31-60 ml/min/1.72 m^2 (n = 452)	GFR >60 ml/min/1.72 m^2 (n = 288)	p-Value
Age (years)	76.1 ±7.5	83.8 ±5.1	82.3 ±4.9	78.5 ±7.5	<0.001
Men	70%	39%	39%	55%	<0.001
Smoker	17%	19%	15%	16%	0.541
Chronic obstructive lung disease	15%	25%	28%	26%	0.153
Diabetes Mellitus	38%	29%	31%	35%	0.163
Hypertension	85%	86%	97%	93%	<0.001
Previous myocardial infarction	20%	15%	14%	13%	0.451
Previous coronary artery bypass graft surgery	23%	14%	15%	22%	0.01
Atrial fibrillation	28%	24%	9%	9%	<0.001
"Porcelain" aorta	15%	7%	6%	6%	0.117
Baseline Pacemaker	17%	13%	8%	10%	0.035
Pre/Periprocedural Coronary Angiography	79%	85%	98%	98%	<0.001
Transesophageal Echocardiogram	83%	74%	89%	90%	<0.001
Gated Cardiac Computed tomography	56%	38%	34%	39%	0.007
Society of thoracic surgeons score	10.1 (7.7-16)	8.8 (6.0-12.6)	6 (4.3-9)	5.4 (3.7-7.1)	<0.001
Hemoglobin (gr/dl)	11 (10.1- 12.1)	11.3 (10.1-12.3)	11.7 (10.5-12.7)	12.2 (11-13.5)	<0.001
Echocardiographic variables					
Left ventricular ejection fraction (%)	49.2±13.6	51.2±13.8	51.7±10.6	53.7±10.6	0.013
Peak gradient (mmHg)	72.2±26.1	77.7±26.2	82.5±23.6	78.3±23.2	<0.001
Mean gradient (mmHg)	42.0±15.5	47.2±17.6	51.4±16.1	48.8±15.3	<0.001
Aortic valve area (cm^2)	0.7 (0.6-0.8)	0.6 (0.5-0.7)	0.6 (0.5-0.7)	0.6 (0.5-0.8)	<0.001

Variables are expressed as n (%), mean ± standard deviation or median (interquartile).
GFR = Glomerular filtration rate.

Table 2
Procedural characteristics

	N	Dialysis (n = 66)	GFR ≤30 ml/min/1.72 m^2 (n = 398)	GFR 31-60 ml/min/1.72 m^2 (n = 452)	GFR >60 ml/min/1.72 m^2 (n = 288)	p-Value
Device type						
Corevalve	790	39 (59%)	236 (60%)	317 (71%)	198 (69%)	0.073
Edward XT	376	24 (36%)	144 (36%)	126 (28%)	82 (28%)	
Edwards Sapien 3	12	2 (3%)	7 (2%)	1 (0.2%)	2 (0.7%)	
Lotus Valve	11	0	3 (1%)	4 (0.9%)	4 (1%)	
Corevalve Evolut R	4	0	0	2 (0.4%)	2 (0.7%)	
Other	11	1	8 (2%)	2 (0.4%)	0	
Access						
Transfemoral	1092	53 (80%)	367 (92%)	417 (93%)	255 (89%)	0.002
Trans-apical	70	9 (14%)	25 (6%)	18 (4%)	18 (6%)	
Trans-axillary	36	3 (5%)	8 (2%)	13 (3%)	12 (4%)	
Other	6	1 (1%)	0	3 (0.7%)	2 (0.7 %)	
Hospitalization length (in days)	1204	7 (IQR 5.5 − 11)	7 (IQR 5-9)	5 (IQR 4-7)	5 (IQR 4-6)	<0.001

Variables are expressed as n (%) or median (Interquartile).
GFR = glomerular filtration rate.

in eGFR was not associated with a significant increase in 1-year mortality. The p value for interaction (GFR decrease by GFR group) was 0.022. Renal dysfunction was not associated with an increased risk of stroke or requirement for new pacemaker implantation. A sensitivity analysis including only patients enrolled in the centers that provided eGFR data for all patients who underwent TAVR showed consistent results in which every 10 ml/min decrease in eGFR was associated with

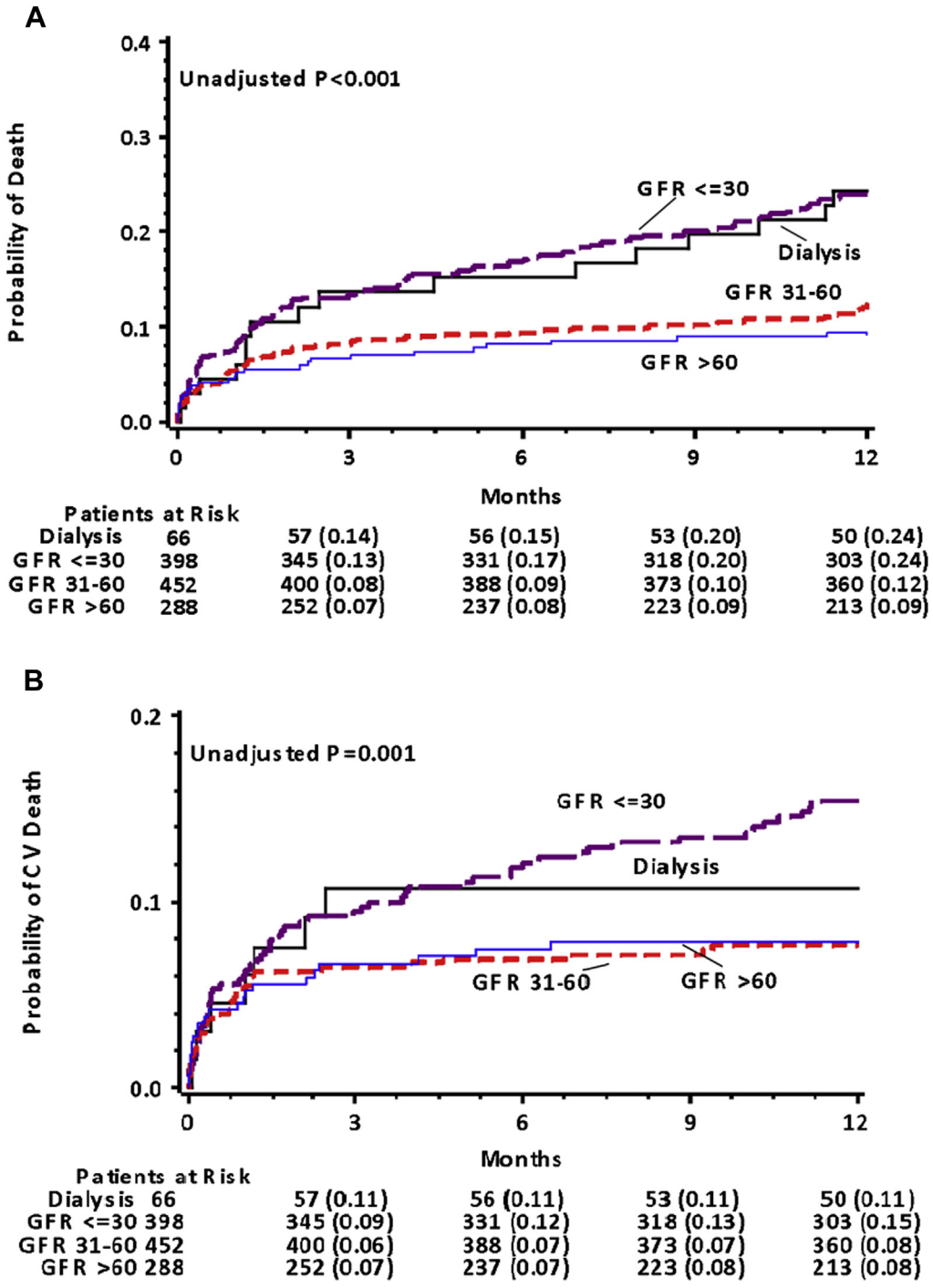

Figure 1. Kaplan-Meier curve for all cause death *(A)* and cardiovascular death *(B)* with respect to the eGFR group.

a 13% increase in 1-year mortality (OR 1.13, 95% CI 1.02 to 2.26; p = 0.019).

AKI and need for dialysis after TAVR are presented in Table 4. AKI occurred in 378 patients (33%) after TAVR and was classified as stage 1 in 305 patients (26.8%), stage 2 in 33 patients (2.9%), and stage 3 in 40 patients (3.5%). Although 1 patient with baseline advanced CKD deteriorated to end-stage renal disease requiring permanent dialysis therapy, 28 patients (2.5%) required a single dialysis and 7 patients (0.6%) required temporary dialysis. The occurrence of AKI and the need for dialysis were significantly related to lower baseline eGFR (p <0.001 for both). The association between AKI and all-cause mortality at 1-year follow-up is presented in Table 5.

Discussion

In this large multicenter analysis of patients who underwent TAVR for the treatment of severe symptomatic AS, renal dysfunction was associated with poor clinical outcomes.

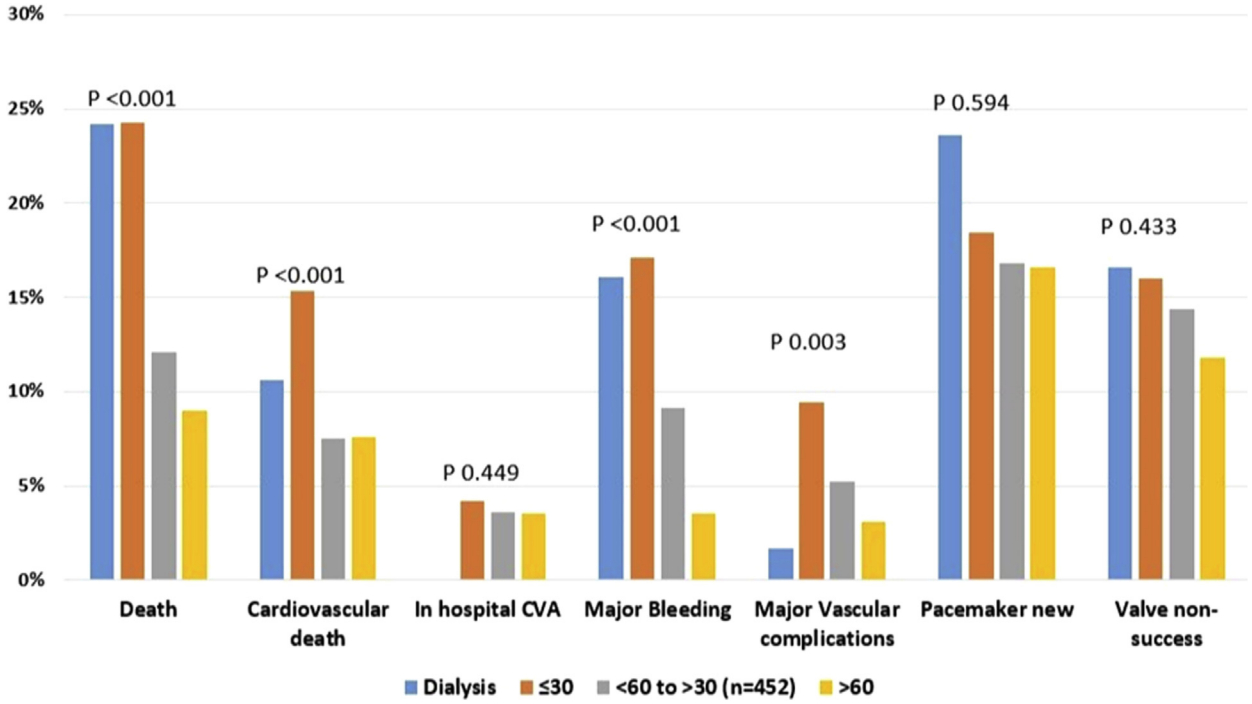

Figure 2. Outcomes with respect to the eGFR group.

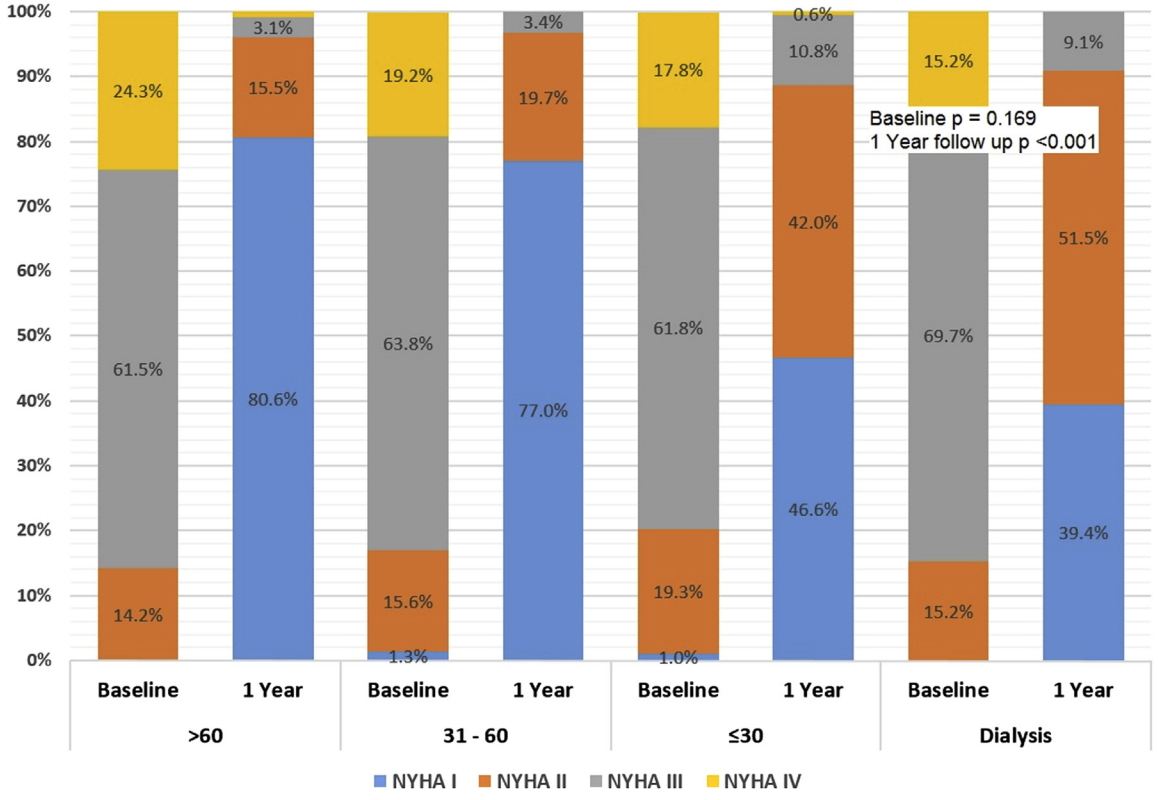

Figure 3. The distribution of baseline and 1-year New York Heart Association functional class with respect to the eGFR group.

All-cause and cardiovascular mortality rates during the follow-up period increased with decreasing renal function. Importantly, a eGFR ≤30 ml/min was identified as an independent predictor for all-cause and cardiovascular mortality.

There is a broad agreement that TAVR outcomes are negatively influenced by advanced and end-stage renal dysfunction (stage 4/5 CKD).[19] However, the effect of moderate renal dysfunction (stage 3 CKD) on TAVR

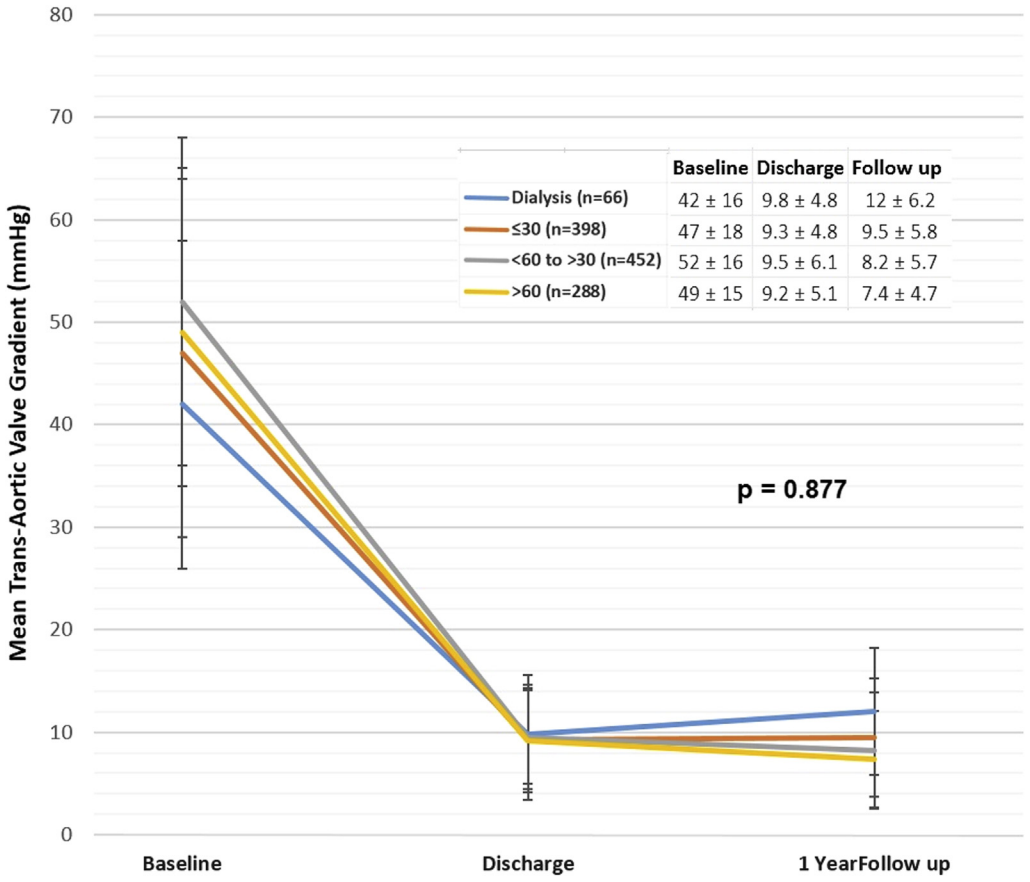

Figure 4. Mean transaortic valve gradient (mm Hg) at baseline, discharge, and at 1-year follow-up with respect to the eGFR group.

outcomes is still debatable. Although several trials showed that stage 3 CKD was not predictive of all-cause and cardiovascular mortality after TAVR,[20] other data are contradictory.[21,22] In the present study, moderate renal dysfunction was not an independent predictor for adverse events in the current trial. Moreover, when analyzed as a continuous variable, eGFR decrease was associated with an increase in 1-year mortality in patients with eGFR <30 but not in those with eGFR ≥ 30. The precise reasons for increased morbidity and mortality after TAVR in patients with renal dysfunction are unclear but are likely to be multifactorial and complex and related to higher baseline risk profile. Median STS score increased with decreasing eGFR, reflecting the impact of renal function on STS score calculation. Patients with an STS score $>10\%$ for perioperative mortality are considered very high-risk surgical candidates in most TAVR trials and registries.[1,4–6] In our experience, only the group of patients on dialysis fits this definition (median STS score of 10.1 [7.7 to 16]), whereas patients with advanced moderate and mild CKD were at high to intermediate risk (8.8 [6.0 to 12.6, 6 [4.3 to 9], and 5.4 [3.7 to 7.1], respectively). This finding is consistent with contemporary TAVR practice, where most treated patients belong to the category of moderate risk.[23,24]

Atrial fibrillation was pointed out as a strong predictor of mortality in patients with advanced kidney disease who underwent TAVR.[25,26] In the present study, patients with advanced and end-stage renal disease had a higher prevalence of atrial fibrillation possibly contributing to the increased mortality and morbidity in this group.

Renal dysfunction also carries a higher risk of bleeding. Bleeding diathesis in patients with CKD is because of impaired platelet activation and aggregation, anemia, frequent need for antiplatelet drugs, anticoagulants, and invasive procedures.[27] Major bleeding was fivefold and eightfold more common in patients with advanced and end-stage renal disease, respectively, in comparison with those with a GFR >60. Moreover, the increased risk for vascular complications with eGFR decrease poses these patients at an exceedingly higher risk for extended hospital stay, morbidity, and overall mortality.

Finally, patients with decreased renal function are at an increased risk for AKI and CKD after TAVR.[28,29] Contrast media administration, sudden hemodynamic changes during the procedure (rapid pacing, balloon valvuloplasty, valve deployment, and postdilation), and manipulation of large catheters in the aorta are all considered contributing factors. AKI has an important prognostic significance after TAVR as it is associated with higher rates of mortality, major bleeding, and vascular complications after TAVR.[30] In our experience, patients with moderate and advanced CKD showed higher rates of moderate and severe post-TAVR AKI according to the RIFLE classification and greater requirements for temporary and permanent renal replacement therapy, respectively.

Our data have several limitations. First, this is a registry-based study with the inherent limitations of an observational

Table 3
Multivariate logistic regression analysis

Outcome	Odds Ratio	95% Confidence Interval	p Value
All cause death			
eGFR 31-60	1.66	0.95 − 2.9	0.075
eGFR ≤ 30	3.01	1.72 − 5.26	<0.001
Dialysis	2.25	0.93 − 5.44	0.072
eGFR Continuous per 10 ml/min/1.72m^2 decline	1.35	1.18 − 1.54	<0.001
Cardiovascular Death			
eGFR 31-60	1.12	0.59 − 2.11	0.734
eGFR ≤ 30	2.22	1.95 − 4.13	0.012
Dialysis	1.01	0.31 − 3.31	0.980
eGFR Continuous per 10 ml/min/1.72m^2 decline	1.14	1.02 -1.27	0.018
Bleeding			
eGFR 31-60	1.66	0.75 − 3.7	0.21
eGFR ≤ 30	5.19	2.43 − 11.1	<0.001
Dialysis	7.9	2.76 − 22.59	<0.001
eGFR Continuous per 10 ml/min/1.72m^2 decline	1.35	1.18 − 1.54	<0.001
Major Vascular complications			
eGFR 31-60	1.15	0.51 − 2.58	0.750
eGFR ≤ 30	2.14	0.95 − 4.82	0.065
Dialysis	0.76	0.091 − 6.36	0.802
eGFR Continuous per 10 ml/min/1.72m^2 decline	1.18	1.02 − 1.37	0.026
Device failure			
eGFR 31-60	1.29	0.74-2.25	0.368
eGFR ≤ 30	2.28	1.22− 4.25	0.010
Dialysis	2.49	0.90 − 9.96	0.080
eGFR Continuous per 10 ml/min/1.72m^2 decline	1.16	1.04 − 1.29	0.007
Pacemaker implantation			
eGFR 31-60	1.05	0.65 − 1.70	0.856
eGFR ≤ 30	1.47	0.86− 2.52	0.156
Dialysis	1.72	0.59 − 5.03	0.320
eGFR Continuous per 10 ml/min/1.72m^2 decline	1.07	0.97 − 1.1	0.088
In hospital CVA			
eGFR 31-60	1.12	0.50 − 2.54	0.783
eGFR ≤ 30	1.09	0.45 − 2.65	0.839
Dialysis	NA	NA	NA
eGFR Continuous per 10 ml/min/1.72m^2 decline	1.08	0.94− 1.24	0.272

CVA = cerebrovascular accident; eGFR =estimated glomerular filtration rate in ml/min/1.72 m^2.

Table 4
Acute kidney injury according to the RIFLE criteria and the need for renal replacement therapy after transcatheter aortic valve replacement in respect to glomerular filtration rate groups (for all patients not on dialysis at baseline)

RIFLE Acute Kidney Injury Class	Baseline Estimated Glomerular Filtration Rate (ml/min/1.72m^2)			p-Value
	≤30 (n = 398)	31 -60 (n = 452)	>60 (n = 288)	
0	255 (64%)	326 (72%)	178 (62%)	<0.001
1	105 (26%)	113 (25%)	87 (30%)	
2	13 (3.3%)	11 (2%)	9 (3%)	
3	24 (6%)	2 (0.4%)	14 (5%)	
4	1 (0.2%)	0	0	
Renal replacement therapy				
Not needed	373 (94%)	449 (99%)	280 (97%)	<0.001
Preformed once	18 (4%)	3 (0.6%)	7 (2%)	
Preformed temporarily	6 (1%)	0	1 (0.3%)	
Permanent	1 (0.2%)	0	0 (0%)	

study design. Indications to proceed to a TAVR procedure rather than surgical aortic valve replacement or conservative treatment were established by each local institutional heart team. Outcomes and adverse events were adjudicated individually by each center without external validation from a core laboratory. There was a small number of patients in the dialysis group, which may have accounted for the lack of statistical significance for all-cause mortality and

Table 5
Acute kidney injury according to the RIFLE criteria and the risk for all-cause mortality after one year of follow-up (for all patients not on dialysis at baseline)

RIFLE Acute Kidney Injury Class	1 year All Cause Death	p-Value
0	91 (12%)	<0.001
1	62 (20%)	
2	12 (36%)	
3	11 (27%)	
4	1 (100%)	

cardiovascular mortality in this group. Finally, the data for patients with eGFR >30 were only collected only from 3 centers. The current cohort should, therefore, not be interpreted as representative of the entire TAVR population but rather as a platform for comparison between patients in different CKD groups. A sensitivity analysis including only patients enrolled in the centers that provided eGFR data for all patients was preformed to mitigate concerns of a possible selection bias, yielding consistent results.

In conclusion, among patients who underwent TAVR, advanced CKD and dialysis are associated with increased rates of all-cause and cardiovascular mortality, major and life-threatening bleeding, and vascular complications. CKD should, therefore, be considered as an important factor during preprocedural risk stratification.

Disclosures

The authors have no conflicts of interest to disclose.

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Predictors of 1-Year Mortality After Transcatheter Aortic Valve Implantation in Patients With and Without Advanced Chronic Kidney Disease

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Advanced chronic kidney disease (CKD) is an independent predictor of mortality in patients undergoing transcatheter aortic valve implantation (TAVI). We aimed to identify predictors of 1-year mortality in patients after TAVI stratified by the presence or absence of advanced CKD (defined as estimated glomerular filtration rate ≤30 ml/min/1.73 m^2 or permanent renal replacement therapy). Patients (n = 1204) from 10 centers in Europe, Japan, and Israel were included: 464 with and 740 without advanced CKD. Advanced CKD was associated with a 2-fold increase in the adjusted risk of 1-year all-cause death (p <0.001), and a 1.9-fold increase in cardiovascular death (p = 0.016). Interaction-term analysis was used to identify and compare independent predictors of 1-year mortality in both groups. Impaired left ventricular ejection fraction and poor functional class were predictive of death in the advanced CKD group (odds ratio [OR] 2.27, p = 0.002 and OR 3.87, p = 0.003, respectively) but not in patients without advanced CKD (p for interaction = 0.035 and 0.039, respectively), whereas bleeding was a predictor of mortality in the nonadvanced CKD group (OR 3.2, p = 0.005) but not in advanced CKD (p for interaction = 0.006). Atrial fibrillation was associated with a 2.2-fold increase (p = 0.032) in the risk of cardiovascular death in the advanced CKD group but not in the absence of advanced CKD (p for interaction = 0.022). In conclusion, the coexistence of advanced CKD and either reduced left ventricular ejection fraction or poor functional class has an incremental effect on the risk of death after TAVI. In contrast, bleeding had a greater effect on risk of death in patients without advanced CKD. **(Am J Cardiol 2017;120:2025–2030)**

Transcatheter aortic valve implantation (TAVI) has emerged as the treatment of choice for patients with severe symptomatic aortic stenosis (AS) at prohibitive risk for surgical aortic valve replacement and is an established alternative to surgery for patients at high and intermediate risk.[1–4] Chronic kidney disease (CKD) frequently accompanies severe AS and is known to have a negative prognostic effect on the course of valvular heart disease and on the outcomes of cardiovascular interventions.[5,6] In a study recently published by our group, we analyzed the outcomes of 1,204 patients with TAVI distinguished by renal function. In our experience, advanced CKD (defined as estimated glomerular filtration rate [eGFR] ≤ 30 ml/min/1.73 m^2 or permanent renal replacement therapy), emerged as a potent independent predictor of peri- and postprocedural morbidity and mortality.[7] However, little is known about the comparative performance of predictors of death after TAVI in patients with advanced CKD and patients without advanced CKD. We therefore aimed to estimate the interaction between advanced CKD and known risk factors of death 1 year after TAVI.

Methods

Most of our methods have been previously described in detail.[7] Briefly, 1,204 patients with severe symptomatic AS undergoing TAVI in 10 high-volume centers in Europe, Japan, and Israel were included. Three centers provided data of all consecutive patients with TAVI, whereas the remaining 7 centers submitted data of patients with eGRF ≤ 30 ml/min/1.73 m^2. Our dedicated database included patients' demographic, clinical, and preprocedural

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characteristics. eGFR was calculated for each patient using the modified diet on renal disease formula.[8] Based on previous studies that identified CKD stages 4 and 5 as a potent independent predictor of adverse outcomes, patients were distinguished by the presence or absence of advanced CKD, defined as eGFR ≤30 ml/min/1.73 m^2 or permanent renal replacement therapy.[7,9] Outcomes were adjudicated according to the Valvular Academic Research Consortium 2 criteria definitions,[10] and reported for 1-year follow-up period. Categorical data are presented as frequencies and percentages, and continuous variables are presented as mean ± standard deviation or median (interquartile range), according to distribution. Baseline characteristics of the study patients were compared using the Student *t*, Mann-Whitney *U*, chi-square, or Fisher's exact tests, as appropriate.

The following method was applied to examine and compare predictors of 1-year mortality and cardiovascular mortality in patients with and without advanced CKD. First, potential variables were selected based on clinical and statistical significance and evaluated by univariate analysis. The cumulative probability of death in the CKD groups distinguished by bleeding (major or life-threatening), Society of Thoracic Surgeons (STS) score, atrial fibrillation, age, left ventricular ejection fraction (LVEF), and New York Heart Association (NYHA) FC were graphically displayed using Kaplan-Meier (KM) curves and compared by the log-rank test. Categorical cutoff values for STS score, Hb, and age were chosen to be 7%, 12 md/dl, and 82 years, respectively, based on median values of these variables in our dataset.

To compare predictors of 1-year all-cause and cardiovascular mortality in the 2 groups, a multivariable logistic regression model was constructed for each dichotomous risk factor adjusting for gender, age (≥82 vs <82), NYHA functional class (I or II vs III/ or IV), previous myocardial infarction, STS score (≤7 vs >7), peak Doppler wave velocity across the stenotic valve (≤4 m/s vs >4 m/s), LVEF (<50% vs ≥50%), bleeding (severe or life-threatening), chronic obstructive pulmonary disease, and atrial fibrillation with the addition of a "risk factor"-by-"renal function group" interaction term. A significant interaction implies that the adjusted odds ratio (OR) for high risk versus low risk (e.g., LVEF <50% vs ≥50%) in the advanced CKD group is significantly different from the adjusted OR of high risk versus low risk in the patients without advanced CKD.

Data collection was approved in each of the 10 centers individually by the institutional human research committee. All statistical tests were 2-sided, a p value of <0.05 was considered statistically significant. All analyses were conducted using the SAS statistical package version 9.4 (SAS Institute, Inc., Cary, NC).

Results

Baseline demographic and clinical characteristics are presented in Table 1. Patients with advanced CKD were older, had higher rates of peripheral vascular disease, higher STS score, and lower gradients across the aortic valve compared with their counterparts without advanced CKD (p <0.001 for all). Procedural characteristics and short-term clinical outcomes are presented in the *supplementary material*. Although no significant difference in 30-day all-cause death, 30-day cardiovascular death, or in-hospital stroke rate was observed between the groups, bleeding and vascular complications occurred more often in patients with advanced CKD (22.2% vs 10.2% p <0.001, and 17.3% vs 15.9% p = 0.03, respectively).

Table 1
Baseline demographic, clinical, and echocardiographic characteristics

Variable	Advanced Kidney Disease		p-value
	Yes (n = 464)	No (n = 740)	
Age (years)	82.8 ± 6.1	80.8 ± 6.4	<0.001
Men	56.9%	54.5%	0.42
Smoker	14.7%	15.6%	0.18
Chronic lung disease	23.8%	27.3%	0.16
Diabetes mellitus	29.4%	32.8%	0.31
Dyslipidemia	58.8%	69.6%	<0.001
Hypertension	86.1%	95.4%	<0.001
Body mass index (Kg/m2)	24.8 ± 4.1	27.4 ± 4.8	<0.001
Previous myocardial infarction	16.0%	13.4%	0.21
Previous coronary bypass surgery	15.3%	17.9%	0.334
Previous stroke	12.3%	14.6%	0.26
Peripheral vascular disease	20.9%	10.7%	<0.001
Atrial fibrillation	13.3%	25.3%	0.01
"Porcelain" aorta	7.1%	6.1%	0.23
Baseline Pacemaker	13.4%	8.6%	0.013
Society of thoracic surgeons score	11 ± 7.6	7.2 ± 5.2	<0.001
New York heart association FC III-IV	80.4%	84.1%	0.11
Log Euro Score	26.7 ± 16.8	18.3 ± 12.7	<0.001
Hemoglobin (gr/dL)	11.2 ± 1.6	11.8 ± 1.7	0.04
Preprocedural assessment			
Coronary angiography	93.5%	98.9%	<0.001
Gated cardiac computerized tomography	40.8%	36.4%	0.14
Echocardiographic variables			
Left ventricular ejection fraction (%)	50.9 ± 13.7	52.5 ± 10.7	0.03
Peak gradient (mmHg)	77 ± 26.1	80.9 ± 23.5	0.009
Mean gradient (mmHg)	46.5 ± 17.2	50.4 ± 15.9	<0.001
Aortic valve area (cm2)	0.64 ± 0.19	0.64 ± 0.18	0.65

Variables are expressed as n (%), mean ± standard deviation, or median (interquartile).

Compared with patients without advanced CKD, patients with advanced CKD had a higher 1-year mortality and cardiovascular mortality (24% vs 11% and 15% vs 8%, respectively; Figure 1, log-rank p <0.001). After adjusting for multiple risk factors, patients with advanced CKD exhibited a 2-fold increase in the risk of 1-year all-cause mortality (p = 0.001), and 1.9-fold (p = 0.016) increase in the risk of cardiovascular mortality, compared with their counterparts without advanced CKD.

One-year KM estimates of death in patients with and without advanced CKD in selected subgroups are presented in the *supplementary material*, and the KM plots for bleeding, LVEF, and FC are presented in Figure 2. Severe or life-threatening bleeding was associated with comparable death rate to no or mild bleeding in patients with advanced CKD (24% vs 23%, respectively, p = 0.68), but with a considerably higher death rate (22% vs 10%, respectively, p = 0.001) in patients without advanced CKD. Although patients with LVEF <50%, STS score ≥7%, and NYHA FC III or IV had

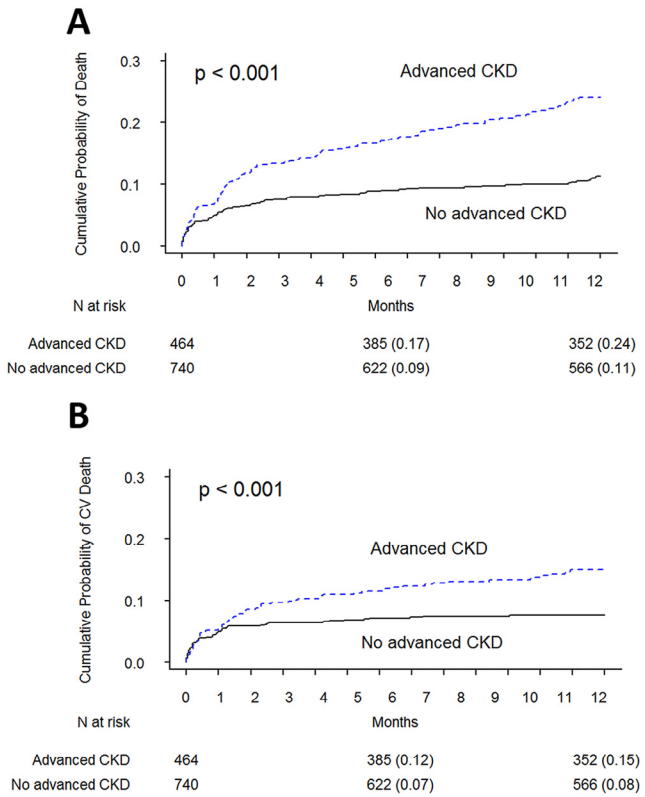

Figure 1. Kaplan-Meier curves depicting the cumulative probability of 1-year all-cause death (*A*) and cardiovascular death (*B*) in the advanced chronic kidney disease (CKD) group versus the nonadvanced CKD group.

an increased rate of 1-year demise compared with their lower risk counterparts in the advanced CKD group (p <0.05 for all), there was no such association in patients without CKD.

Independent predictors of 1-year all-cause mortality distinguished by CKD groups and interaction analysis are presented in Table 2. Severe or life-threatening bleeding during hospitalization was predictive of a 3-fold (95% CI 1.42 to 7.34, p = 0.005) and 0.78-fold (95% CI 0.36 to 1.67, p = 0.53) increase in the OR of death in the nonadvanced and advanced CKD groups, respectively (p for interaction = 0.014). Impaired baseline LVEF was predictive of 2.27-fold (95% CI 1.23 to 4.19, p = 0.002) and 1.05-fold (95% CI 0.61 to 1.80, p = 0.614) increase in the OR of death in the advanced and nonadvanced CKD groups respectively (p for interaction = 0.035). The OR for death in the poor versus mildly impaired FC was 3.87 (95% CI 1.52 to 9.83, p = 0.004) and 1.10 (95% CI 0.51 to 2.38, p = 0.316) in the advanced and nonadvanced CKD groups, respectively (p for interaction = 0.039). Predictors of 1-year cardiovascular mortality (presented in the *supplementary material*) demonstrated a similar trend as in all-cause mortality and included bleeding in the nonadvanced CKD group (OR 3.85, 95% CI 1.44 to 9.19, p = 0.004) and poor FC (OR 3.06, 95% CI 1.14 to 10.8, p = 0.045) coupled by impaired LVEF (OR 2.02, 95% CI 1 to 4.1, p = 0.05) in the advanced CKD group. Additionally, preexisting atrial fibrillation emerged as an independent predictor of cardiovascular death in the advanced CKD group (OR 2.21, 95% CI 1.05 to 4.54, p = 0.032), but not in the nonadvanced CKD group (p for interaction = 0.022).

Table 2
Predictors of 1-year mortality (multivariate analyses)

Risk subsets	Adjusted odds ratio (95% CI)	p for interaction
Bleeding yes vs. no		
Advanced kidney disease	0.78 (0.36–1.67)	0.014
Non-advanced kidney disease	3.2 (1.42–7.34)	
Age ≥82 vs. <82 years		
Advanced kidney disease	0.52 (0.28–0.95)	0.128
Non-advanced kidney disease	0.97 (0.56–1.66)	
Female vs. male gender		
Advanced kidney disease	0.69 (0.37–1.25)	0.686
Non-advanced kidney disease	0.58 (0.33–1.01)	
LV ejection fraction <50% vs. ≥50%		
Advanced kidney disease	2.27 (1.23–4.19)	0.035
Non-advanced kidney disease	1.05 (0.61–1.80)	
Functional class III/IV vs. I/II		
Advanced kidney disease	3.87 (1.52–9.83)	0.039
Non-advanced kidney disease	1.10 (0.51–2.38)	
Chronic lung disease yes vs. no		
Advanced kidney disease	1.06 (0.55–1.97)	0.894
Non-advanced kidney disease	1 (0.5–1.75)	
Atrial fibrillation yes vs. no		
Advanced kidney disease	1.32 (0.76–2.53)	0.067
Non-advanced kidney disease	0.44 (0.15–1.1)	
STS score ≥7% vs. < 7%		
Advanced kidney disease	2.09 (1.07–4.07)	0.437
Non-advanced kidney disease	1.48 (0.75–2.90)	
Hemoglobin <12 vs. ≥12 g/dL		
Advanced kidney disease	1.07 (0.54–2.11)	0.493
Non-advanced kidney disease	1.46 (0.83–2.56)	
Peak velocity ≥ m/s vs. < 4 m/s		
Advanced kidney disease	0.58 (0.30–1.11)	0.479
Non-advanced kidney disease	0.79 (0.45–1.36)	
Post-procedural pacemaker		
Advanced kidney disease	0.53 (0.22–1.26)	0.150
Non-advanced kidney disease	1.19 (0.59–2.39)	

Odds ratio (95% confidence interval) for every risk subset was calculated after adjustment to multiple clinical, laboratory, and echocardiographic variables (see Methods section).

CI = confidence interval; LV = left ventricular; STS = Society of Thoracic Surgeons.

Discussion

In the current analysis, we compared predictors of 1-year mortality in patients after TAVI distinguished by the presence or absence of advanced CKD. Our major findings are as follows: (1) the presence of advanced CKD was independently associated with 2-fold increase in the risk of 1-year death compared with the absence of advanced CKD; (2) poor FC and impaired LVEF were independently associated with an increased risk of death in the presence of advanced CKD but not in its absence; (3) the presence of preexisting atrial fibrillation was predictive of increased risk of cardiovascular death in the advanced CKD group; and (4) periprocedural severe or life-threatening bleeding was more common in patients with advanced CKD, but had a greater negative effect on survival in the absence of advanced CKD.

Even though previous trials have identified impaired LVEF,[11,12] poor FC,[13] atrial fibrillation,[14] and advanced CKD[7,9,13,15–17] as independent predictors of death after TAVI,

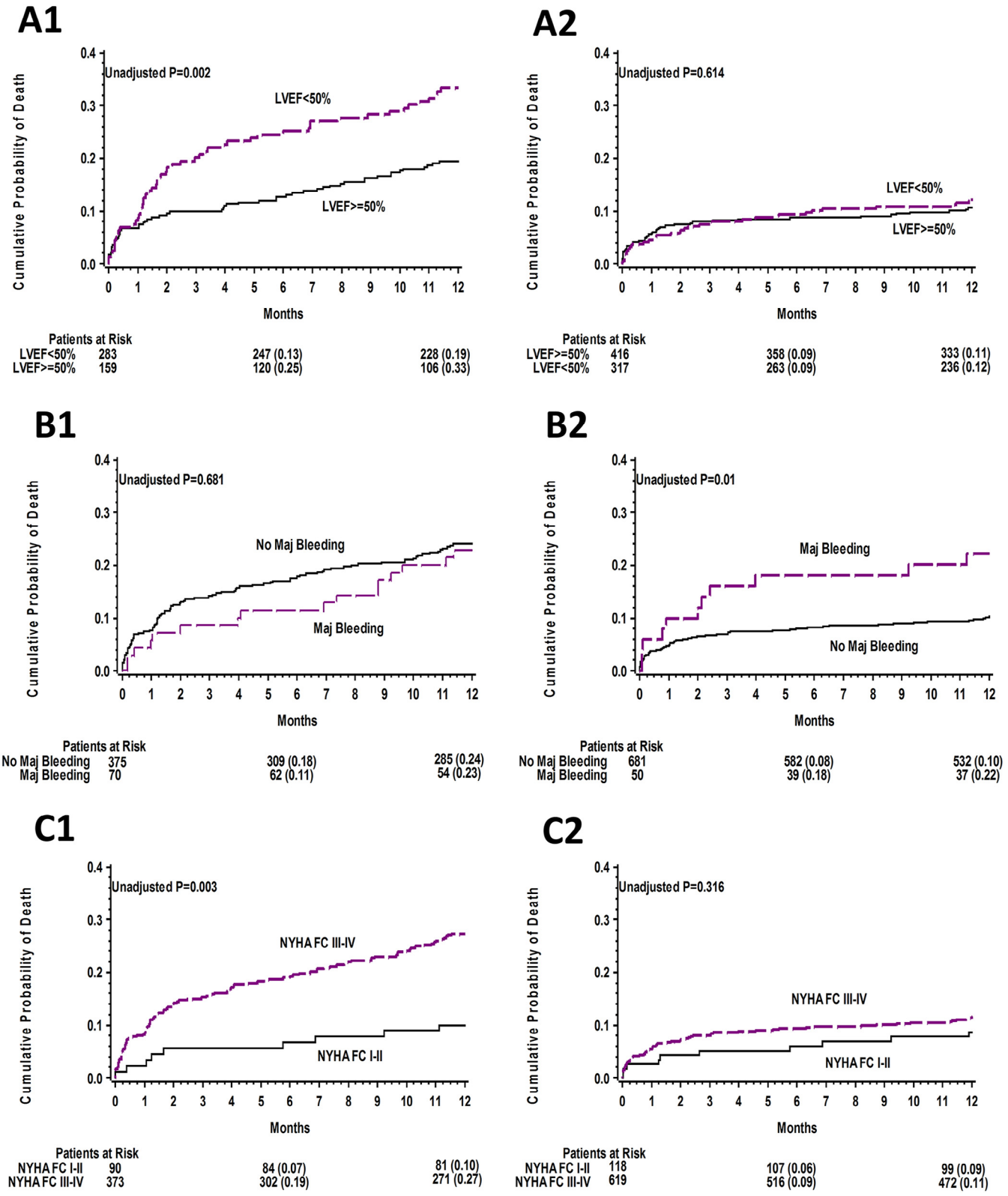

Figure 2. Kaplan-Meier curves depicting the cumulative probability of 1-year all-cause death in the advanced chronic kidney disease (CKD) group (*left column*), and in the nonadvanced CKD group (*right column*) of patients with high versus low left ventricular ejection fraction (LVEF ≥50% and <50%, A1 and A2), major periprocedural bleeding versus no bleeding (B1 and B2), and at functional class I or II versus III or IV (C1 and C2).

data regarding the predictors of mortality in patients with TAVI distinguished by renal function is lacking. In our experience, poor FC was predictive of 3.87-fold increase and impaired LVEF of 2.27-fold increase in 1-year mortality in patients with advanced CKD, but not in patients without advanced CKD. KM curves for poor versus normal or mildly decreased FC in the advanced CKD group separated early and continued to diverge during the first year after TAVI, suggesting that differences between the groups were related both to periprocedural and late death. Indeed, patients with advanced CKD and poor FC represent a high-risk subgroup and are prone to periprocedural complications including mechanical ventilation, longer hospitalization intervals, higher rates of acute kidney injury and dialysis, and nosocomial infections, and are therefore at higher risk of periprocedural death. Additional research is required to further characterize this subgroup and to ascertain whether intervention is warranted earlier in the clinical course of patients with severe AS with concomitant advanced CKD.

Our observation of increased mortality in patients with baseline CKD and impaired LVEF reinforces the well-established correlation between impaired renal function and risk of death and cardiac decompensation in patients with heart failure.[18] Previous studies have shown that patients with severe LV dysfunction enjoy significant improvement in LVEF after TAVI both in the immediate postprocedural period because of acute decrease of afterload,[19] and in the intermediate and late period, mediated by regression of LV hypertrophy,[20,21] causing an improvement in FC[22] and possibly prolonging survival.[23] However, patients with advanced CKD are at risk of ventricular dysfunction and dilatation,[24] and may not gain a similar improvement in LVEF, functional capacity, and survival.

Severe or life-threatening bleeding events were more frequent in the advanced CKD group (15.1% vs 6.8%, p <0.001), but were a stronger predictor of mortality in the patients without advanced CKD. Several explanations may apply: (1) bleeding was more common in patients with advanced CKD, but more often classified life-threatening in the nonadvanced CKD group (38% vs 50% respectively), probably reflecting bleeding diathesis and higher rate of "trivial" nonprocedural bleeding (i.e., gastrointestinal bleeding, genitourinary bleeding, or no obvious source) in contrast to higher rate of catastrophic procedural-related bleeding, associated with greater morbidity, when occurring in patients without advanced CKD; (2) because patients with advanced CKD were at an increased risk of death compared with patients without advanced CKD even in absence of bleeding (1-year unadjusted death risk 24% vs 10%), the addition of a fixed absolute risk inflicted by bleeding would translate to a lower relative risk increase than in patients without advanced CKD; (3) as per the Valvular Academic Research Consortium 2 definition, Hg drop of ≥3 gr/dl and the administration of >1 units of packed blood cells define major bleeding or life-threatening bleeding. Patients with advanced CKD were more often anemic (mean baseline hemoglobin 11.8 vs 11.2 gr/dl, p = 0.04), and at greater risk of receiving >1 blood transfusions (8.4% vs 2.9%, p <0.001), thus at higher risk of complying with the definition of major or life-threatening bleeding even if effectively having a minor bleeding.

In our experience, the presence of a preexisting atrial fibrillation doubled the risk of cardiovascular death after TAVI in patients with advanced CKD but did not affect risk in patients without advanced CKD. This observation is in line with a previous trial reporting the predictors of death in a small cohort of patients with advanced CKD,[15] but in disagreement with a previous publication from the France 2 registry reporting an increased risk of death in patients with preexisting atrial fibrillation regardless of kidney function.[25]

Our study has several limitations. First, it was a multicenter international collaboration, based on institutional registries without a central core laboratory or data validation system. Data of patients with eGFR >30 ml/min were available only from 3 centers. However, a sensitivity analysis that included only patients enrolled in the centers that provided data for all unselected patients with TAVI showed consistent results with regard to mortality and cardiovascular mortality by eGFR.[7] Second, data on paravalvular leak were not available. Finally, this was a subgroup analysis study, with its well-known inherent limitations. Nevertheless, the importance of the current study lies in the preliminarity of our findings and our big multicenter cohort of large-volume centers.

In conclusion, patients with and without severe CKD have different predictors of mortality, which call for different considerations in the patient selection and management. Although poor FC, impaired LVEF, and atrial fibrillation were stronger predictors of mortality in patients with advanced CKD, major or life-threatening bleeding was a harbinger of death regardless of renal function.

Disclosures

The authors have no conflicts of interest to disclose.

Supplementary Data

Supplementary data associated with this article can be found, in the online version, https://doi.org/10.1016/j.amjcard.2017.08.020.

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Summary and Conclusions

- *In medio stat virtus ("virtue stands in the middle"), scholastic philosophers of the Middle ages*
- *"Virtue is the balance point between a deficiency in a trait and an excess of a trait; virtue must vary and reflect the intermediate and best condition at the right times, about the right things, towards the right people, for the right end, and in the right way", Aristotle's Nicomachean Ethics*
- *Est modus in rebus ("there is an optimal condition in all things: everything in proportion"), Horace's Satires*
- *Medio tutissimus ibis ("you will go most safely by the middle course"), Ovid's Metamorphoses*

In the last years there was a radical change in the perception of the ischemia/bleeding balance in patients undergoing PCI, which was reflected in both guidelines and the community. Although more potent and prolonged treatments to reduce ischemic recurrences have been traditionally the main focus of clinical research, recent data pointed the attention towards the risk of increasing bleeding events, which in turn even negatively affect patient prognosis. In patients managed with antithrombotics after an ACS, the impact of major bleeding as compared to recurrent myocardial infarction appeared similar or even greater in particular cases. This data reinforces the concept that clinicians should prevent both ischemia and bleeding and should perform a careful assessment of the ischemia/bleeding risk when deciding the treatment management of a single patient.

Many pharmacological and mechanical strategies have been proposed to reduce bleeding and ischemia during PCI as well as early and late after the procedure.
During PCI, unfractionated heparin (UFH) has the main advantages of being cheap and antagonizable by means of intravenous protamine sulfate, thus it remains the most widely used anticoagulant agent during PCI. However, UFH has a poorly predictable effect on the coagulation cascade and a relatively narrow therapeutic window. Additionally, despite the measurement of activated clotting time (ACT) at the time of PCI has been advocated to mitigate both ischemic and bleeding events during or soon after intervention, there is limited evidence from prospective studies, there is no full agreement on cut-offs to be used and ACT is not routinely used to adjust UFH dosing in many centres (Chapter 1.6). Bivalirudin has emerged to be a valid alternative to UFH (Chapters 1.1 to 1.8). Despite most recent trials, including MATRIX trial, failed to demonstrate the superiority of bivalirudin over UFH in terms of composite ischemic/bleeding endpoints and most recent guidelines have slightly downgraded their recommendations on its use in ACS patients, there is large evidence from single trials and pooled analyses that bivalirudin use is associated with reduction of bleeding complications (Chapter 1.1 and 1.5). While the bleeding benefit observed in previous studies was probably attributable to the fact that the comparator group was UFH plus GPI, which notoriously increase the risk of bleeding, in the MATRIX trial, bivalirudin significantly reduced bleeding complications, mainly those not related to access site, irrespective of planned use of GPI (Chapter 1.5). Yet, the optimal regimen of bivalirudin after PCI and whether this differs across ACS with or without ST-segment elevation is unknown, but after adjustment, the full post-PCI bivalirudin dose was associated to improved efficacy and safety outcomes when compared to the low post-PCI bivalirudin regimen, no post-PCI infusion or unfractionated heparin groups (Chapter 1.8).

The use of the radial artery rather than femoral artery reduces access site bleeding and mortality in ACS patients undergoing invasive management (Chapters 1.9 to 1.11). These advantages that led to recommend radial approach in European guidelines have been observed in studies in which operators were properly trained and must have sufficient expertise in both radial and femoral access (Chapter 1.9). Interestingly, women are generally characterized by higher risk of severe bleeding and access site complications, and have smaller radial arteries that are more prone to spasm as well as shorter aortic roots than men, which adds to the operative difficulty and may undermine the efficacy of radial access in this population. However radial access demonstrated to be an effective method to reduce these complications as well as composite ischemic and ischemic or bleeding endpoints (Chapter 1.10). More importantly, the benefit of radial over femoral access in ACS patients undergoing invasive management has been found to be also related to prevention of acute kidney

injury (AKI), indeed, radial access was associated with a reduced risk of AKI compared with FA (Chapter 1.11). Additionally, AKI is a relevant complication of PCI still today due to both its frequency and negative impact on prognosis, and several pharmacologic strategies have been proposed to be used to prevent such important complication but there is great debate on the real effectiveness of all of them. Statin administration was found to be associated with a marked and consistent reduction in the risk of AKI compared with saline, while for other strategies, including xanthine, N-acetylcysteine (NAC), sodium bicarbonate (NaHCO3), NAC+NaHCO3, ischemic preconditioning, and natriuretic peptide, although some nephroprotective effects have been described, data are not consistent and conclusive to support their use (Chapter 1.17).

In more than 40 years from its birth, PCI has evolved significantly and procedural aspects have played an important role in the optimization of outcomes related to this treatment (Chapters 1.12 to 1.16). In-stent restenosis has been for years one of the weakness of PCI and the use of more recent strategies, including drug-coated balloons (DCB) and new generation drug-eluting stents (DES) have been found to provide better efficacy compared to older strategies (i.e. plain balloons, bare-metal stents (BMS), brachytherapy, rotational atherectomy, and cutting balloons) (Chapter 1.12). DES in particular, have demonstrated to be superior to BMS in several settings, also leading PCI to become a valid alternative to CABG characterized by equivalent rates of hard endpoints for patients with left main coronary artery disease (Chapter 1.14). Coronary stent selection has been traditionally considered a major determinant of post-procedural antithrombotic treatment duration, hence impacting bleeding/ischemia balance. Based on preliminary evidence coming from first-generation DES, DES have traditionally been considered more thrombogenic leading to the common practice to provide longer DAPT treatments to patients treated with DES as compared to BMS. Consequently, patients deemed at high bleeding risk, which would not tolerate prolonged DAPT courses, have been more commonly selected for BMS implantation, however, current evidence suggests that DES is superior and recommended over BMS in all clinical settings irrespective of coronary complexity, operator experience or patient bleeding risk and that a short DAPT is plausible and safe with new-generation DES (Chapters 1.15 and 1.16).

In order to optimize PCI outcomes, an adequate platelet inhibition should be obtained and even the optimization of the concomitant therapy (i.e. use of proton pump inhibitors in all patients undergoing DAPT to reduce the bleeding risk; use of beta-blockers, ACE-inhibitors and ARB in patients with acute myocardial infarction to reduce ischemic complications and mortality) has a crucial role (Chapters 2.1 to 2.4).
Despite the fact that adverse event rate is relatively higher during the first month after the procedure, the vast majority of ischemic and bleeding complications occur late after revascularization, and might be modulated by adjusting DAPT duration. Therefore, the selection of optimal DAPT duration after PCI has a central role in the balance of ischemic/bleeding risk (Chapters 2.5 to 2.17). Longer DAPT duration has been associated with a consistent reduction of major adverse cardiovascular events (MACE) and stent thrombosis, but also with an increase in major bleeding and a worrisome increase in mortality (Chapter 2.5), which raised concern in the community. The large and sometimes contrasting evidence accumulated in the last 25 years in the field of DAPT type and duration has generated great debate on the optimal regimen of DAPT to adopt after PCI. What we have learned from this huge discussion is that probably we cannot apply a “one-size fits all” approach, rather we should shift to a new paradigm of “personalized medicine” able to select the optimal treatment in the individual patient.

In last 10-15 years, the optimization of ischemic and bleeding outcomes has been a focus of great interest even for patient undergoing TAVI. In few years TAVI has dramatically evolved, devices and procedural techniques have rapidly improved and results of randomized clinical trials have revolutionized the current treatment of severe aortic stenosis. A large body of evidence has demonstrated that TAVI is non-inferior to SAVR, or even superior when performed transfemorally (rather than through transthoracic access) in terms of all-cause mortality in high-risk patients as well as patients deemed at low-to-intermediate risk (Chapter 3.4). Yet, compared with SAVR, TAVI is associated with similar rates of early stroke, reduces early myocardial infarction, AKI, major bleeding, and new-onset atrial fibrillation, while is associated with higher rates of

pacemaker implantation, vascular complications, and paravalvular leak (Chapter 3.4). Effects of TAVI on long-term mortality and device durability over long time are still unclear and remain the focus of current and future studies. Although there are risk scores used in daily practice to help guiding the Heart-Team clinicians in the decision-making in patients with severe AS, these scores have important limitations, were mainly generated in outdated studies of surgery and cannot account for all risk factors. Many studies have assessed specific risk factors trying to identify patients at higher risk of complications and death after TAVI. For example, in large TAVI populations a low BMI was linked to a significantly worse prognosis after TAVI, thus suggesting that BMI could represent an important and handily tool in the risk prediction of patients to be addressed for TAVI (Chapter 3.7). Similarly, pre-procedural renal dysfunction (even moderate CKD) has been found to be one of the most frequent comorbidities of TAVI patients and to significantly worsen patients' prognosis at short and long-term follow-up (Chapters 3.8 to 3.10). Another important comorbidity that significantly impacts on TAVI patients' prognosis in atrial fibrillation (AF). Both pre-existing and new onset AF are very frequent and are associated with worse prognosis (Chapters 3.5 and 3.6). The presence of this comorbidity or its occurrence, often silent, after the procedure also contribute to make complex the decision regarding the optimal antithrombotic therapy in patients undergoing TAVI. From one side TAVI patients are exposed to ischemic/thrombotic risks (i.e. stroke, transient ischemic attack, myocardial infarction related to possible comorbidities such as CAD or leaflet thrombosis), while on the other side they have bleeding risks related to the procedure and to the antithrombotic therapy (Chapters 3.1 to 3.3). A DAPT regimen is often recommend, but compared with single antiplatelet therapy it has been found to increase bleeding risks without significantly prevent thrombotic complications. The use of oral anticoagulation, particularly of novel and safer non-vitamin K antagonists, in all patients, irrespective of AF, has been advocated to prevent thrombotic complications of the implanted devise, however, to date we have no sufficient evidence for such an approach. Consequently, the complex puzzle of the optimal antithrombotic therapy after TAVI remains intriguing but still unsolved. Clinical trials are ongoing and their results will hopefully add the missing pieces in this complex puzzle. Thus, as for PCI patients, even in TAVI patients the careful risk evaluation and selection of antithrombotic regimen during and after the procedure should be individualized based on the factors influencing ischemic and bleeding risks and aiming at balancing these risks.

More than 2,400 years ago, Hippocrates, the father of western medicine, recognized the individuality of each patient and the importance of adapting treatment accordingly saying that "It is more important to know what sort of person has a disease than to know what sort of disease a person has." Since than, clinicians struggled understanding patients' characteristics that predict a different response to treatment. Adjusting treatment based on baseline characteristics, biohumoral or genomic markers is the premise of Precision Medicine, which aims to the construction of an evidence-based medical model for customized decision-making based on single patient characteristics. In conclusion, choosing between 2 evils (ischemia or bleeding) occurring at similar frequencies and carrying comparable prognostic implications is still evil. Personalized treatment algorithms maximizing benefits over risks represent the only sensible way forward.

Curriculum vitae

NAME: Giuseppe Gargiulo

BIRTH DATE: September 6, 1983, Sorrento (Naples, Italy)

NATIONALITY: Italian

LANGUAGES: Italian (Native proficiency), English (Full professional proficiency), French (Basic proficiency), German (Limited working proficiency)

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Giuseppe Gargiulo was born on September 6th 1983 in Sorrento (Naples), Italy. He obtained his medical degree in 2009 with Summa cum Laude at the University of Naples Federico II, Italy. He completed his training in cardiology with Summa cum Laude at University of Naples Federico II in 2015. During this period, he was part of the research group in molecular cardiology lead by Prof. C. Perrino and G. Esposito. In 2014 he started a research fellowship in interventional cardiology at the Department of Cardiology of University of Catania (Italy) under the supervision of Prof. D. Capodanno and C. Tamburino. In 2015 he started a research fellowship in interventional cardiology at the Bern University Hospital (Bern Switzerland) under the supervision of Prof. M. Valgimigli and S. Windecker.

CLINICAL EXPERIENCES:

- 2007-2015: Clinical cardiology (clinical visits, intensive care unit, echocardiography, non-invasive stress tests, non-invasive diagnostic tests, etc.) at University Federico II of Naples.
- 2012-2015: Interventional procedures performed as first or second operator (elective/urgent coronary angiography and intervention; peripheral angiography/interventions) at University Federico II of Naples.

GRANTS/AWARDS:

- 2015-2016: Research Grant from EAPCI for 1-year Research Fellowship at Bern University with the project: "Endothelial function effects of antiplatelet agents in patients with acute coronary syndrome treated with percutaneous coronary interventions – HI-TECH study" under the supervision of Prof. M. Valgimigli
- 2016-2017: Research Grant from Italian Society of Cardiology-MSD Italia for 1-year Research Fellowship at Bern University with the project: "Sex based differences and transradial impact on outcomes of patients with acute coronary syndromes treated with percutaneous coronary interventions: post hoc analysis of the MATRIX Trial", under the supervision of Prof. M. Valgimigli
- 2017: Research Grant from Fondazione Umberto Veronesi for 6-month Research Fellowship at Bern University with the project: "Clinical and molecular evaluation of endothelial function in patients with acute coronary syndromes treated with dual antiplatelet therapy", under the supervision of Prof. M. Valgimigli
- 2018-2024: Italian scientific qualification to Associate Professorship reached on Oct 31 2018 up to Oct 31 2024.

EDITORIAL ACTIVITY:

- International Associate Editor of Eurointervention, Official Journal of EuroPCR and the European Association of Percutaneous Cardiovascular Interventions (2017 Impact Factor 4.417) from February 2018: https://www.pcronline.com/eurointervention/pages/information/editorial-team/
- Member of the Editorial Board of Journal of Cardiovascular Translational Research (2017 Impact Factor 2.337) from January 2018: http://www.springer.com/medicine/cardiology/journal/12265?detailsPage=editorialBoard
- Reviewer invited for the following journals: European Heart Journal, Journal of American College of Cardiology Cardiovascular Interventions, Circulation Cardiovascular Interventions, Eurointervention, Annals of Internal Medicine, International Journal of Cardiology, Thrombosis and Haemostasis, Medicine, American Journal of Cardiology, Europace, Plos Medicine, Plos One, British Journal of Clinical Pharmacology, Journal of Cardiovascular Translational Research, Journal of Cardiovascular Medicine, Internal and Emergency Medicine, Journal of the Saudi Heart Association

SCIENTIFIC SOCIETIES MEMBERSHIP:

- Member of the Italian Society of Cardiology (SIC)
- Member of the Italian Society of Interventional Cardiology (SICI-GISE)
- Member of the American Heart Association (AHA)
- Member of the European Society of Cardiology (ESC)
- Member of the European Association of Percutaneous Cardiovascular Interventions (EAPCI)
- Member of the ESC working group on Cellular Biology

CLINICAL STUDIES PARTECIPATIONS:

- 2018: Member of the committee for the classification of reasons of non-adherence for the multicentre randomized clinical trial GLOBAL LEADERS, ClinicalTrials.gov Identifier NCT01813435 (Ticagrelor plus aspirin for 1 month, followed by ticagrelor monotherapy for 23 months vs aspirin plus clopidogrel or ticagrelor for 12 months, followed by aspirin monotherapy for 12 months after implantation of a drug-eluting stent: a multicentre, open-label, randomised superiority trial. Vranckx P, et al. Lancet. 2018 Aug 24. pii: S0140-6736(18)31858-0).
- 2018: Sub-Investigator for the centre in Bern of the multicentre study ID-076A202 from IDORSIA entitled "A multicentre open-label randomized study to assess the onset of platelet aggregation inhibition after a single subcutaneous injection of ACT-246475 in adults with acute myocardial infarction", ClinicalTrials.gov Identifier NCT03487445.

- 2017-today: Coordinator and investigator for the centre in Bern of the platelet function substudy of the multicentre randomized clinical trial PACMAN-AMI (Sponsor Bern University Hospital): "Effects of the PCSK9 Antibody AliroCuMab on Coronary Atherosclerosis in PatieNts With Acute Myocardial Infarction: A Serial, Multivessel, Intravascular Ultrasound, Near-Infrared Spectroscopy And Optical Coherence Tomography Imaging Study"; ClinicalTrials.gov Identifier NCT03067844.
- 2016-today: Coordinator and investigator of the multicentre randomized clinical trial FABOLUS-FASTER (Sponsor Bern University Hospital): "Facilitation Through Aggrastat or Cangrelor Bolus and Infusion Over prasugreL: a mUlticenter Randomized Open-label Trial in patientS With ST-elevation Myocardial inFarction Referred for primAry percutaneous inTERvention.FABOLUS FASTER Trial"; ClinicalTrials.gov Identifier NCT02978040.
- 2016-today: Support Member of Executive Committee e local sub-investigator (centre of Bern) of the multicentre randomized clinical trial GALILEO (Sponsor Bayer in collaboration with Janssen Research & Development, LLC) "Global Multicenter, Open-label, Randomized, Event-driven, Active-controlled Study Comparing a rivAroxaban-based Antithrombotic Strategy to an antipLatelet-based Strategy After Transcatheter aortIc vaLve rEplacement (TAVR) to Optimize Clinical Outcomes"; NCT02556203.
- 2015-oggi: Coordinator of data collection and analysis for multiple substudies of the multicentre randomized clinical trial MATRIX "Minimizing Adverse Haemorrhagic Events by TRansradial Access Site and Systemic Implementation of AngioX" (Sponsor: Società Italiana di Cardiologia Interventistica (SICI-GISE) and support from The Medicines Company and Terumo); ClinicalTrials.gov Identifier NCT01433627.
- 2010-2015: Local Study Coordinator/Sub-Investigator for the following studies:
  1. The STabilisation of Atherosclerotic plaque By Initiation of darapLadIb TheraphY (Stability)
  2. The Stabilisation Of pLaques usIng Darapladib-Thrombolysis In Myocardial Infarction 52 (SOLID-TIMI52)
  3. Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events (TRA 2P-TIMI 50) Trial
  4. Study of RO4607381 in Stable Coronary Heart Disease Patients With Recent Acute Coronary Syndrome (dal-OUTCOMES)
  5. Determination of EFfectiveness of the SilverHawk®PerIpheral Plaque ExcisioN System (SIlverHawk Device) for the Treatment of Infrainguinal VEssels / Lower Extremities (DEFINITIVE LE)
  6. Safety and Efficacy of TCD-10023 drug-eluting stent in management of patients with Acute ST-Elevation Myocardial Infarction (MASTER)

NATIONAL AND INTERNATIONAL CONGRESS PARTECIPATIONS:

- Faculty and Member of the Scientific Committee for the National Congress of Società Italiana di Cardiologia Invasiva (SICI-GISE) GISE 2018, Milano 16-19 October 2018: Chairperson for the session: Oral Communications-Physiology; and Invited Speaker for the Expert Debate presentations entitled: "NSTEMI patient with diffuse coronary aneurysm/ectasia - DAPT with ASA and ticagrelor" and "Timing for oral P2Y12 administration in NSTEMI: the (almost) neverending story - Pretreatment remains the best strategy in NSTEMI patients".
- Faculty Member and Moderator, Congress of the European Association of Percutaneous Cardiovascular Interventions, EAPCI, EuroPCR 2018, Paris, 22-25 May 2018.
- Speaker, Congress of the European Association of Percutaneous Cardiovascular Interventions, EAPCI, EuroPCR 2018, Paris, 22-25 May 2018, title: "Impact of the SYNTAX score in uncertain DES candidates receiving zotarolimus-eluting or bare-metal stents: insights from the ZEUS trial".
- Speaker, Congress of the Società Italiana di Cardiologia (SIC) 2017, Rome 15-18 December 2017, title: "Short term versus long term DAPT after implantation of DES in patients with or without diabetes: systematic review and meta-analysis of individual participant data from randomised trials".
- Speaker invited, Congress of the Società Italiana di Cardiologia Invasiva (SICI-GISE) GISE 2017, Milano 10-13 October 2017; title: "TAVI in a patient at intermediate risk: My tips & tricks".
- Speaker invited, Congress GISE TOLOVE 2017, Napoli 8-9 September 2017; title: "Inibitori del recettore P2Y12 e glicoproteina IIb/IIIa: manuale per l'uso 2017".
- Speaker invited, Congress GISE POST-MI 2017, Napoli 8-9 June 2017; session "terapia antiaggregante a 12 mesi", title: "Rivalutazione del rischio ischemico/emorragico e della terapia a 12 mesi".
- Speaker, Congress of the European Association of Percutaneous Cardiovascular Interventions, EAPCI, EuroPCR 2016, Paris 16-19 May 2016, title: "Gender-related impact on 2-year clinical outcomes in patients treated with 6 or 24-month DAPT duration: insights from the PRODIGY trial".
- Speaker, Congress of the European Association of Percutaneous Cardiovascular Interventions, EAPCI, EuroPCR 2016, Paris, 16-19 May 2016, title: "Impact of diabetes on contrast-based FFR performance".
- Coordinator and Tutor/Speaker of the course for cardiologists at Federico II University of Napoli entitled "Stenosi Aortica: Attualità e Prospettive Future", Napoli 21 December 2015, title: "TAVI e SAVR: update e nuove prospettive".
- Speaker, Congress of the Società Italiana di Cardiologia (SIC) 2015, Rome 11-14 December 2015, title: "Moderate and severe preoperative chronic kidney disease worsen clinical outcomes after TAVI: meta-analysis of 4992 patients".
- Speaker, Congress of the Società Italiana di Cardiologia (SIC) 2014, Rome 13-15 December 2014, title: "Low-dose quinacrine reduces vascular restenosis without affecting re-endothelialization".
- Speaker, Congress of the Società Italiana di Cardiologia (SIC) 2012, Rome 15-17 December 2012, title: "Cardiovascular effects of treadmill exercise in physiological and pathological preclinical settings".
- Poster presentation, Congress of the Società Italiana di Cardiologia (SIC) 2012, Rome 15-17 December 2012, title: "Preserved brain perfusion imaging despite severe and diffuse atherosclerosis of supra-aortic trunks".
- Speaker, Congress of the Società Italiana di Cardiologia (SIC) 2011, Rome 10-12 December 2011, title: "Quinacrine as a novel drug in the prevention of in-stent restenosis and thrombosis".
- Speaker, Congress of the American Heart Association (AHA) 2011, Orlando (Florida, USA) 12-16 November 2011, title: "The Role of Quinacrine in the Prevention of In-stent Restenosis and Thrombosis".
- Speaker, Congress of the Società Italiana di Cardiologia Interventistica (SICI-GISE) 2011, Genova 11-14 October 2011, title: "Quinacrine as a novel drug in the prevention of in-stent restenosis and thrombosis".

List of publications

Total Impact Factor 625,709; h-index:19; citations: 954 (source SCOPUS on 19 December 2018);

A) Peer Reviewed-Refereed Papers

1. Esposito G, Perrino C, Schiattarella GG, Belardo L, di Pietro E, Franzone A, Capretti G, **Gargiulo G**, Pironti G, Cannavo A, Sannino A, Izzo R, Chiariello M. Induction of mitogen-activated protein kinases is proportional to the amount of pressure overload. Hypertension. 2010 Jan;55(1):137-43. doi: 10.1161/HYPERTENSIONAHA.109.135467. PMID:19901160
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B) Peer Reviewed-Refereed National Papers

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C) Book Chapters

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6. Valgimigli M and **Gargiulo G.** Post-Procedural Management and Antithrombotic therapy. Chapter 4 "Post-Procedural Care: Post-Procedural Management and Antithrombotic Therapy" of the CathSAP 5 (fifth edition of the self-assessment program covering cardiac catheterization and interventional cardiology) from the American College of Cardiology, 2017, and subsequent update in 2019. Editors: Sunil Rao, David Kandzari. Sunil V. Rao (Editor in Chief), Ajay J. Kirtane (Chair, Question Writing Group), Subhash Banerjee, Aloke V. Finn, Allen Jeremias, David E. Kandzari, Matthew J. Price, Arnold H. Seto, Mehdi H. Shishehbor.
7. **Gargiulo G** and Valgimigli M**.** Chapter 20 "Stents and Stent Thrombosis" of the 3rd Edition of "1003 Questions: An Interventional Cardiology Board Review" 2017. Editors: Debabrata Mukherjee, Richard Lange, Leslie Cho, Saurav Chatterjee, and David J. Moliterno.

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When looking back on my career, I think I should write another book like this to tell the complete story and properly thank all the people who personally enriched my life and played such an important role in helping me reach key steps, which include this PhD. However, anyone who knows me, can confirm that I don't like speaking so much, so, to keep the long story short:

I would start by thanking Prof M. Chiariello, the first to highlight me the importance of research when I was at the 3rd year of Medicine School. I asked him to attend the Cardiology Department of this University. He recommended I should start with molecular cardiology and introduced me to Prof Cinzia Perrino, at that time a young researcher coming back from USA. I became Cinzia's first internal student, and to me, she became a guide and role model. Together with Prof Giovanni Esposito, Cinzia allowed me to work in the laboratory of molecular cardiology to learn basic (and rigorous) principles of research, to participate in many projects, and most of all, to start developing my passion for research. I was really glad to be part of their research team that had begun to build up during those years, the "lab-13 team". I sincerely want to thank them and all my friends and colleagues in that wonderful group. Subsequently, during my residency in Cardiology, Giovanni allowed me to enter into the daily life of the cath-lab, and constantly pushed me to continue my research activities. He has always believed in me and urged me to do more. His positive pressure was probably the most important input and factor that influenced me in deciding to follow this career path. During my 3rd year of residency, at the end of one of his many long days at the hospital, we both agreed I should dedicate myself to clinical research, with a focus to Interventional Cardiology. From this moment on, we began to plan which steps would be optimal to proceed along this line. We agreed I should study biostatistics and learn the principles of clinical studies. We planned that the ideal course of my future research training could be to obtain a fellowship in Italy with Professors Tamburino and Capodanno, and then abroad with Prof Valgimigli. He worked tirelessly to enable me to reach the needed steps to make concrete the ideal plan…so what initially only seemed like a dream, then soon became a reality! I will always be thankful (probably never enough!) to both Cinzia and Giovanni for their human and professional support, and their precious example as mentors throughout all the years of my professional training as a cardiologist and researcher. I can doubtlessly say they were and still are, the best promoters I could ever have hoped to have had.

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At the end of this PhD, and in line with my thinking that this is hopefully just one step further along a lengthy journey, I would conclude to again thank my mentors who taught me that research is possibility, novelty, passion, curiosity, perseverance, improvement, innovation, originality, advance, perspective...future…but it always requires criticism, questioning mind, scientific rigor, appropriateness, reproducibility, diligence, systematicity, and quality!

CardioPaTh
Cardiovascular Pathophysiology & Therapeutics

In the Greek mythology, the Chimera was a monstrous fire-breathing hybrid creature of Lycia in Asia Minor, composed of the parts of more than one animal (usually depicted as a lion, with the head of a goat arising from its back, and a tail of snake). Homer's brief description in the Iliad is the earliest surviving literary reference. The term Chimera has come to describe any mythical or fictional animal with parts taken from various animals, or to describe anything composed of very disparate parts, or perceived as wildly imaginative, implausible, difficult to realize or utopian.

Bellerophon was the hero who fought and killed the Chimera. When he arrived in Lycia, the Chimera was truly ferocious, and he could not harm the monster even while riding on Pegasus. He felt the heat of the breath the Chimera expelled, and was struck with an idea. He got a large block of lead and mounted it on his spear. Then he flew head-on towards the Chimera, holding out the spear as far as he could. Before he broke off his attack, he managed to lodge the block of lead inside the Chimera's throat. The beast's firebreath melted the lead, and blocked its air passage. The Chimera suffocated, and Bellerophon returned victorious to King Iobates.

Percutaneous cardiovascular interventions are the cornerstone treatment of cardiovascular diseases. Antithrombotic therapy during and after these interventions is fundamental to prevent ischemic recurrences, but has the risk to increase bleeding complications. To find the optimal strategy to prevent ischemia without affecting bleeding in all patients is matter of ongoing discussion and research, and probably remains a chimera. Like Bellerophon searching for and fighting with the Chimera, clinicians should be aware of the trade-off of both bleeding and ischemia and their impact on patients' health, thus searching for the optimal therapy which has not to face with a single animal (ischemia or bleeding), rather must account and balance for the effects on both these entities. In such a context, personalized medicine characterized by individualization of therapies patient-by-patient based on the individual risk/benefit profile appears to be a promising approach that clinicians might adopt to kill this nightmare.

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