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New paths in interventional cardiology: from TAVI to physiology through PCI and pharmacological therapy.

PhD Thesis

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"You cannot discover new oceans

until you have the courage to lose sight of the beach"

Anonymous

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PhD Thesis

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INDEX

CHAPTER 1

General introduction and outline of the thesis pag. 6

CHAPTER 2:

Transcatheter Aortic Valve Replacement pag. 16

1) **A Controlled Trial of Rivaroxaban after Transcatheter Aortic-Valve Replacement**
2) **Transcatheter valve-in-valve implantation in a patient with a degenerative sutureless aortic bioprosthesis: case report and literature review**

CHAPTER 3:

Percutaneous coronary intervention: bifurcations and COVID 19 pag. 39

1) **Population Trends in Rates of Percutaneous Coronary Revascularization for Acute Coronary Syndromes Associated With the COVID-19 Outbreak**
2) **Coronary artery bifurcation lesions**

CHAPTER 4:

Pharmacological therapy in cath lab pag. 85

1) **Other drugs, from vasospasm to hypertensive crisis**
2) **Autologous blood reinfusion during iatrogenic acute hemorrhagic cardiac tamponade: safety and feasibility in a cohort of 30 patients**
3) **Cardiovascular mortality in patients with acute and chronic coronary syndrome: Insights from the clinical evidence on ticagrelor**

CHAPTER 5:

New insights in coronary physiology pag. 131

1) **ADDED Index or percentage diameter of residual coronary stenosis to risk-stratify patients presenting with STEMI**

2) **Impact of the extension of myocardial mass subtended by an intermediate coronary stenosis on diagnostic performance of the non-hyperemic indexes: the need for a gray zone. (submitted)**

CHAPTER 6:

Discussion and conclusions pag. 158

1) **Discussion**

2) **Conclusions**

3) **Bibliography**

4) **Curriculum vitae**

5) **List of pubblications**

6) **Aklowlegements**

GENERAL INTRODUCTION AND OUTLINE OF THE THESIS

Interventional cardiology, in recent years, has greatly expanded its spectrum of action, varying from structural intervention, to pharmacotherapy, to coronary physiology. During the cardiopath PhD, I analyzed these various aspects and here are reported the results of my research.

Accurate estimation of the severity of a coronary stenosis through angiography is essential to decide on the need of revascularization [1]. Despite the fact that coronary angiography still has a lot of pitfalls, in particular the tendency to overestimate the severity of stenoses, it remains the first diagnostic step in the evaluation of a coronary stenosis, on the basis of which the majority of interventional cardiologists take decisions about the patients' treatment [2]. The accuracy in estimating the severity of a coronary stenosis remains rather limited if it is based exclusively on angiography, taking into account the related "oculo-stenotic" reflex, in particular considering that the benefits of revascularization are evident when the treatment is addressed to hemodynamically significant stenoses. In clinical practice, most patients with stable angina are still managed based on angiographic evaluation alone, often in the absence of a preliminary non-invasive test for inducible ischemia. Decision-making strategy can become even more complex in patients with acute coronary syndromes when one or more intermediate stenosis is found in addition to the culprit lesion. Consequently, the study of coronary physiology lies in the ability to identify vaso-related myocardial ischemia and to measure it at the very moment of clinical and interventional decision-making, identifying patients who seek real consequences from PCI [3].

The haemodynamic significance of coronary stenoses is of fundamental importance for the interventional cardiologist, and from this point of view, new diagnostic tools have been introduced for the functional estimation of intermediate grade coronary stenoses. Currently, the fractional flow reserve (FFR) is the reference standard for defining the ischemic potential of stenoses in epicardial coronary vessels. FFR has been well validated in different clinical and anatomical settings, with fundamental prognostic implications [4-5]. In particular, this technique adds important information to the interventional cardiologist, who is able to assess the severity of the stenosis in relation to the

myocardial mass perfused by the target vessel, since it is demonstrated that, as the perfused myocardial tissue increases, the flow gradient through stenosis, and the consequent severity of the same, increases during maximal hyperemia [6-8].

Based on these elements, FFR has gradually become a widely used technique to estimate the hemodynamic severity of a coronary stenosis in the cath lab [9]. This measurement is calculated as the ratio between the average coronary pressure distal to the stenosis (Pd) and the mean coronary pressure proximal to the stenosis (Pa) during the period of maximal hyperemia in which the microvascular resistances are minimal [10]. In practice, FFR = Pd / Pa during maximal hyperemia and it represents the ratio between the maximum blood flow to the myocardium in the territory subtended to the investigated coronary stenosis and the maximum blood flow in the same territory as if the studied coronary artery was free from stenosis. The FFR is measured thanks to a guidewire equipped with a sensor to record the pressure downstream of the target lesion, while simultaneously measuring the proximal coronary pressure through the guide catheter. To obtain a correct measurement of the FFR, it is necessary to administer intracoronary nitroglycerin (100–200 μg), to induce vasodilation of the epicardial compartment and subsequently an hyperemic agent of the coronary microcirculation, such as adenosine, to induce maximal hyperemia and thus minimize the microvascular resistance [11]. Although alternative vasodilators (eg regadenoson, nicorandil, nitroprussiate and dobutamine) have been proposed, adenosine remains the pharmacological agent of choice for the measurement of FFR. The first clinical studies relating to the ability of FFR to detect the haemodynamic significance of a coronary stenosis, have laid important foundations for subsequent studies related to clinical outcome. In particular, having established a single ischemic threshold and having demonstrated the safety in delaying revascularization in patients with FFR> 0.75, they have been found to be of fundamental importance [12].

DEFER Study.

The randomized prospective DEFER trial (Deferral Versus Performance of PTCA in Patients Without Documented Ischemia) was conducted to define the potential role of FFR in multiple clinical contexts [13]. In this study, where the primary endpoint was the absence of adverse cardiovascular events in the 24-month follow-up, 325 patients with stable coronary artery disease, intermediate-grade coronary stenosis and FFR> 0.75 were randomized to medical therapy (deferral group) or PCI (perform group), while patients with a FFR value <0.75, were directly subjected to PCI. The results at 5 [14] and 15 years [15] showed how, in patients with stable coronary artery disease, delaying revascularization in stenosis with FFR> 0.75 is safe, while revascularization of stenosis with FFR> 0.75 does not add any clinical benefit.

FAME Study.

Following the strong evidence that medical therapy was as effective as percutaneous revascularization in non-haemodynamically significant coronary stenoses, the FAME study (Fractional Flow Reserve versus Angiography for Multivessel Evaluation) was presented, whose purpose was to demonstrate the clinical efficacy of FFR-guided revascularization compared to angiography alone in patients with multivessel coronary atherosclerotic disease [16]. In this prospective multicenter trial, 1005 patients with at least a 50% stenosis in two or three epicardial coronary vessels, were randomly assigned to the group performing PCI with drug-eluting stents (DES) implanted by angiography alone or group performing FFR-guided PCI. An important difference beetween FAME and all the other previous studies on FFR [17,18], was the modification of the FFR threshold for the hemodynamic significance of a coronary stenosis from 0.75 (ischemic threshold) to 0.80 (clinical threshold). The rational of this choice was that the threshold value of FFR 0.80 is able to exclude the ischemia of 90% of the cases [19] and, accepting the high limit of the gray zone as a threshold value, the potential number of ischemic lesions untreated is considerably reduced. The primary endpoint of the FAME study was the incidence of death, non-

fatal myocardial infarction and revascularization at one year. If assigned to the angiography-only group, the protocol provided that patients with visually estimated coronary stenoses of 50% were subjected to PCI at the discretion of the operator, while only stenoses with FFR ≤ 0.80 were subjected to PCI if randomized in the FFR group. The most interesting result was a significant reduction in MACE (major adverse cardiac events) to one year of follow-up in the FFR group compared to the angiography-only group (13.2% vs. 18.3%; relative risk 0.72; 95% confidence interval [CI]: 0.54-0.96; p 1⁄4 0.02).

FAME 2 Study.

DEFER and FAME studies have supported the strategy of reserving revascularization only for haemodynamically significant lesions, leaving not critical lesions in medical therapy. Having already underlined the inadequacies of coronary angiography alone in guiding revascularization, the FAME 2 study (Fractional Flow Reserve - Guided PCI versus Medical Therapy in Stable Coronary Disease) tested the hypothesis that the PCI guided by the FFR plus optimal medical therapy (OMT) was superior to the OMT alone [20]. The study population consisted of patients with multivessel coronary artery disease already in OMT who had received indication to PCI. FFR was measured in all target stenoses. If at least one of the stenoses had FFR≤0.80, patients were randomized to receive PCI and OMT or only OMT, while if FFR was> 0.80 patients continued with OMT alone. The primary endpoint was the composite of death, myocardial infarction and urgent revascularization. The study was interrupted prematurely (average follow-up of 7 months) following a significant reduction of the composite primary endpoint in the PCI group compared to the OMT group (Odds ratio [OR]: 0.32; 95% CI: 0.19-0.53; p 0.001), in particular due to the very reduced rate of urgent revascularizations in the PCI group (OR: 0.13; 95% CI: 0.06-0.30; p 0.001). The premature interruption of the study forced the Authors of the FAME 2 to limit their conclusions about the PCI FFR-guided in addition to the OMT to the "only" reduction of the rate of urgent revascularizations

in the PCI group compared to the OMT group [20], with the further limitation of a non-blinded study neither for patients nor for investigators.

Based these data, in 2013 the guidelines for coronary revascularization of the European Society of Cardiology were published, where the FFR received the IA level recommendation in guiding coronary revascularization in patients with stable angina and intermediate coronary stenosis, in the absence of inducible ischemia test [1].

In recent years, the instantaneous wave-free ratio (iFR) has been introduced as an alternative to the FFR, and it should be able to "isolate" the haemodynamic characteristics of a stenosis making them less influenced by the coronary microcirculation [21]. The iFR does not require the use of vasodilators such as adenosine but measures the intracoronary pressure during a very precise phase of the cardiac cycle, in which the microvascular resistances are reduced to a minimum and stable; it is the so-called diastolic "wave-free period" (WFP). Unlike the FFR, which was defined as the ratio between the maximum myocardial flow in the presence of a coronary stenosis and the maximum coronary flow in the absence of this stenosis, the definition of the iFR was initially less clear. It was mostly a technical description of a relationship between distal coronary pressure and aortic pressure during WFP [22]. Once the iFR concept was defined, a series of comparative studies were performed with other myocardial ischemia tests.

The ADVISE study (Adenosine Vasodilator Independent Stenosis Evaluation) and the ADVISE registry were the first studies able to establish the diagnostic accuracy of the iFR compared to FFR as a reference standard [22]. The CLARIFY study (Classification Accuracy of Pressure-Only Ratios Against Indices Using Flow Study) compared iFR and FFR to the hyperemic resistance index of strictures (HSR) [23]. The HSR is a combined pressure and flow rate index that calculates the gradient of the pressure-flow curves [24], as described initially by Gould [25]. In this study, the iFR, FFR and iFR with adenosine had equal diagnostic efficiency when compared to HSR (92% in the absence of statistically significant differences between the two tests and no advantage demonstrated following adenosine administration) [23]. A second, larger study evaluated iFR and

FFR compared to HRS in 120 stenoses, finding a higher concordance rate between the two methods (89% vs. 82%; p 0.01). A further register studied the iFR and FFR with respect to a combined value of ischemia measured by myocardial perfusion scintigraphy and HRS [26], and the results were in line with those of other non-selective cohorts that used perfusional myocardial scintigraphy [27]. Subsequently, iFR and FFR were compared with positron emission tomography (PET), considered the gold standard for quantifying myocardial blood flow [28]. De Waard et al. performed PET imaging (H215O) in 34 patients with 49 intermediate coronary stenoses and subsequently an invasive measurement of the hemodynamic severity of these stenoses. Both the iFR and the FFR had a 76% agreement with PET and had similar areas under the curve for ROC (receiver-operating characteristic) analysis (0.85 for FFR and 0.86 for iFR; p 1⁄4 0.71) [28]. It is interesting to note that both methods showed an identical pattern of agreement and disagreement with myocardial flow measured with PET.

Subsequently, the similar concordance between the iFR, the FFR and the coronary flow reserve (CFR) measured with PET (74% for iFR and 70% for FFR; p 1⁄4 0.36) was confirmed in 115 stenoses of intermediate degree localized at the level of the anterior descending artery [29]. Finally, iFR and FFR were compared with CFR measured invasively in 216 stenoses, with iFR showing better agreement with CFR compared to FFR, and higher AUC in a statistically significant manner (iFR 0.82 vs. FFR 0.72 ; p 0.001). Even considering only the physiological range of iFR (0.60-0.90), this value maintained a greater association with CFR compared to FFR (AUC: 0.78 vs. 0.59; p 0.001) [30]. It is also important to emphasize that iFR has a greater association with hyperemic flow rate and with CFR than FFR.

iFR integration into clinical practice: the hybrid approach.

According to the hybrid strategy, iFR should be measured in all patients; if its value is between 0.86 and 0.93, it is necessary to administer adenosine and calculate the FFR. This method is able to avoid the useless administration of adenosine in 60-70% of patients [31,32]. When proposed for the

first time, the hybrid approach represented a practical solution to rapidly integrate iFR into clinical practice, since clinical outcome data were not yet available in the literature. However, the iFR has been validated in several registers and two large randomized studies; they have shown that the iFR is as valid as the FFR in demonstrating the presence of myocardial ischemia beyond the hybrid strategy.

The iFR and clinical oucome data

Two clinical studies have been published which investigated the safety and feasibility of a uniquely guided iFR approach to coronary revascularization with a single cut-off as an alternative to the FFR. These are the DEFINE-FLAIR studies (functional assessment of the lesion of intermediate stenosis to guide revascularization) [33] and iFR SWEDEHEART (evaluation of the iFR vs FFR in stable angina or acute coronary syndrome) [34].
The ratio for these studies is quite clear: the iFR-guided approach avoids the use of adenosine, potentially improving time and costs of procedures, also avoiding the adverse effects of the drug. Although the primary objective of the studies was to establish the non-inferiority of the iFR with respect to the FFR for the invasive estimation of the severity of intermediate grade stenoses, the final aim was to give a boost to the use of coronary physiology techniques in interventional decision-making strategies. The DEFINE-FLAIR study has a double-blind prospective, multicenter international design [33]. In contrast, the iFR SWEDEHEART study is a randomized trial that used the SCAR open-label registry (the Swedish Coronary Angiography and Angioplasty Registry) for enrollment [34]. In both studies, patients with intermediate grade coronary stenoses were randomized in a 1: 1 ratio to perform coronary revascularization driven by the iFR or FFR. Patients diagnosed with stable coronary artery disease or acute coronary syndrome (ACS) with intermediate grade stenosis on non culprit vessels were enrolled. The primary endpoints of both studies were one-year MACE, defined as a composite of death for each cause, non-fatal MI, or unplanned revascularization. The DEFINE-FLAIR and iFR SWEDEHEART studies were designed to

demonstrate the non-inferiority of the iFR compared to the FFR, with non-inferiority margins of 3.4% and 3.2% respectively. These limits are more conservative than the criteria typically used for the evaluation of medical devices [35].

DEFINE-FLAIR study.

The DEFINE-FLAIR study showed that the iFR-guided coronary revascularization is not inferior to the FFR-guided revascularization regarding to the MACE risk at one year of follow-up. In a population of 2,492 patients, the primary endpoint occurred in 78 of 1,148 patients (6.8%) in the iFR group and in 83 of 1,182 patients (7.0%) in the FFR group (difference in risk 0.2%; 95% CI: 2.3-1.8; p 0.001 for non-inferiority; HR: 0.95; 95% CI: 0.68-1.33; p 1⁄4 0.78). The number of patients who had periprocedural adverse events is significantly lower in the iFR group than in the FFR group (39 patients [3.1%] vs. 385 patients [30.8%]; p 0.001), and the median procedural time is significantly lower in the group iFR (40.5 min vs. 45.0 min; p 1⁄4 0.001).

iFR SWEDEHEART study.

The results of the iFR SWEDEHEART study are in agreement with those of the DEFINE-FLAIR. In particular, in patients with stable angina or ACS, a guided iFR approach was not inferior to the FFR guided revascularization with regard to one-year MACE. Among the 2,037 randomized patients, the primary endpoints were achieved in 68 out of 1.012 patients (6.7%) in the iFR group and in 61 out of 1007 (6.1%) in the FFR group (the difference in events was 0.7%; 95% CI ; ± 1.5-2.8%; p 1⁄4 0.007 for non-inferiority; OR: 1.12; 95% CI: 0.79-1.58; p 1⁄4 0.53). Similar results to the previous study were reported for periprocedural adverse events related to FFR measurement, with anginal symptoms during the procedure in 3.0% of patients in the iFR group and in 68.3% of patients in the FFR group (p 0.001).

Pooled-patients meta-analysis of DEFINE-FLAIR and iFR SWEDEHEART studies.

The combined analysis of the DEFINE-FLAIR and iFR SWEDEHEART studies produced overall outcome data of 4,529 patients with intermediate-grade coronary stenoses managed on the basis of an approach involving the study of coronary physiology [36]. The average value of FFR from the union of the data was 0.83 ± 0.10. This data is in contrast with the study population of the DEFER and FAME studies which were characterized, respectively, by average FFR values of 0.71 and 0.75. Beyond having demonstrated the non-inferiority of the iFR vs FFR guided revascularization, (OR: 1.03; 95% CI: 0.81-1.31; p 1⁄4 0.81), it was particularly important that the additional data, when iFR is used, is refers more often to revascularization than to the FFR. Deferring revascularization occurs in 50% of cases (1,119 of 2,240 patients) in the pooled analysis of the iFR group and in 45% of cases (1.015 of 2,246 patients) of the pooled FFR group (p 0.01). Furthermore, one-year MACE rates are equally low in the two groups regardless of the PCI deferral choice; this indicates that, despite the lower number of revascularizations with the iFR, the outcome of the patients remains substantially the same. The lower rate of PCI deferred with the FFR could, in part, reflect the choice of the clinically accepted threshold of 0.80 compared to the ischemic cut-off of 0.75 or any other value in the gray area. Nevertheless, the uncertainties regarding the more adequate FFR threshold do not explain the physiological differences between iFR and FFR; rather, this explanation would reside in the closer relationship between the coronary flow and the iFR compared to the FFR [30]. In conclusion, the results of the DEFINE-FLAIR and iFR SWEDEHEART studies have made an important contribution in the field of coronary physiology.

These data, free from any potential bias, showed how iFR could be the new standard parameter for the evaluation of intermediate coronary stenoses [35]. Furthermore, the studies also validated the single cut-off of 0.89 for the iFR, eliminating the hybrid approach and the gray zone. In addition to this, the two studies have made available substantial evidence concerning coronary physiology. The iFR, therefore, could represent a low risky, easily calculable and rapid index to measure the

hemodynamic severity of an intermediate grade coronary stenosis with sufficient reliability. Furthermore, previous studies have shown that the measurement of FFR is influenced by the distribution territory subtended to the vessel under study and this relationship can be estimated using an index, called ADDED index [37], which takes into account the Duke Jeopardy Score (DJS) and the Minimal Lumen Diameter (MLD) calculated by quantitative coronary analysis (QCA).

The object of our study was to investigate the relationship between the iFR, RFR and the FFR in relation to the area of distribution of the coronary stenosis studied. We also supposed the presence of a relationship between the DJS and both the iFR and the RFR, able to modify the diagnostic performances of these indexes according to the extent of the myocardial territory studied.

CHAPTER 2: TRANSCATHETER AORTIC VALVE REPLACEMENT

1) A Controlled Trial of Rivaroxaban after Transcatheter Aortic-Valve Replacement

Transcatheter aortic-valve replacement (TAVR) is indicated in symptomatic [43-49] severe aortic stenosis. Thromboembolic complications (stroke, systemic embolism, valve thrombosis, and venous thromboembolism) have been observed after TAVR. Observational data suggest that subclinical leaflet thrombosis may occur with bioprosthetic valves and that this phenomenon may be associated with an increased risk of cerebrovascular events and prevented or reversed by anticoagulation [50-55]. Current practice guidelines recommend the use of dual antiplatelet therapy early after TAVR [56,57] although the recommendation is based mainly on expert consensus. Rivaroxaban directly inhibits factor Xa and has been shown to reduce the risk of thromboembolism in different clinical settings [58-60]. The 10 mg daily dose has been approved for the prevention of venous thromboembolism in several countries. However, there is a dearth of evidence for routine use of anticoagulation after TAVR for the prevention of thromboembolic events. In addition, patients undergoing TAVR are typically elderly, frail, and at increased risk for both ischemic and bleeding complications. In GALILEO (Global Study Comparing a Rivaroxaban-based Antithrombotic Strategy to an Antiplatelet-based Strategy after Transcatheter Aortic Valve Replacement to Optimize Clinical Outcomes), we investigated the role of a treatment strategy including anticoagulation with rivaroxaban at a dose of 10 mg daily as compared with an antiplatelet strategy in patients without established indications for anticoagulation after successful TAVR.

Methods

Trial Design and Oversight

GALILEO was a randomized, open-label, event- driven, multicenter trial [61] The trial was conducted in compliance with the International Conference on Harmonisation and the Declaration of Helsinki. The protocol (available with the full text of this article at NEJM.org) was approved by

the ethics committees and corresponding health authorities for all participating sites. All the patients provided written informed consent to participate.

The trial was supported by the sponsors, Bayer and Janssen Pharmaceuticals. The sponsors and the academic investigators designed and supervised the trial, which was executed with the assistance of the two clinical research organizations, Cardialysis (Rotterdam, the Netherlands) and the Center for Interventional Cardiovascular Research and Clinical Trials (Mount Sinai Hospital, New York). The executive committee included members of the academic leadership and the sponsors. Data analyses were conducted by DATAN (Havix- beck, Germany). An independent data and safety monitoring board provided oversight by periodically reviewing all reported serious adverse events. The first, second, and last authors wrote the first draft of the manuscript and made the decision to submit it for publication. All the authors reviewed and critiqued subsequent drafts and vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. (Additional information about trial organization is provided in the Supplementary Appendix, avail- able at NEJM.org.)

Patient Selection and Randomization

Men and women 18 years of age or older were eligible for participation in the trial if they had undergone successful TAVR for treatment of aortic-valve stenosis. Successful TAVR was defined as correct positioning of any single approved trans- catheter bioprosthetic aortic valve into the proper anatomical location with the intended valve performance and without periprocedural compli- cations [62]. Key exclusion criteria were any established indication for long-term anticoagulation and any absolute indication for dual antiplatelet therapy. (See Supplementary Appendix text and Table S1 for screening procedures and a complete list of the inclusion and exclusion criteria.) After written informed consent had been obtained, eligible patients were randomly assigned (in a 1:1 ratio) through an interactive Web-response system to either the rivaroxaban group or the anti- platelet group 1 to 7 days after TAVR and before hospital discharge.

Trial Treatment and Follow-up

The anticoagulant (experimental) group was assigned to receive rivaroxaban at a dose of 10 mg daily plus aspirin at a dose of 75 to 100 mg daily for 3 months, followed by rivaroxaban monotherapy (10 mg daily). The antiplatelet (control) group was assigned to receive aspirin at a dose of 75 to 100 mg daily plus clopidogrel at a dose of 75 mg daily for 3 months (patients who had not previously received clopidogrel were recommended to receive a single loading dose of ≥300 mg), followed by aspirin monotherapy (75 to 100 mg daily).

Patients in the rivaroxaban group in whom atrial fibrillation developed were to receive rivaroxaban at a dose of 20 mg once daily (or 15 mg for those with an estimated glomerular filtration rate of 30 to 50 ml per minute per 1.73 m2 of body-surface area). In the antiplatelet group, patients in whom new-onset atrial fibrillation developed were to receive vitamin K antagonists (targeting an international normalized ratio of 2 to 3) to replace clopidogrel within 3 months after randomization or to replace aspirin thereafter.

Rivaroxaban was centrally supplied to the sites as trial medication. Clopidogrel, aspirin, and vitamin K antagonists were supplied according to local practice. Patients were followed at 1, 3, and 6 months and every 6 months thereafter. (Details of the follow-up procedures and recom- mendations for concomitant medications are pro- vided in the Supplementary Appendix.)

Outcome Measures

The primary efficacy outcome was the composite of death from any cause or thromboembolic events, including any stroke, myocardial infarction, symptomatic valve thrombosis, systemic embolism (not involving the central nervous system), deep-vein thrombosis, or pulmonary embolism. The primary safety outcome was the composite of life-threatening, disabling, or major bleeding. The secondary efficacy outcome was defined as the primary efficacy outcome with death from cardiovascular causes replacing death from any cause. The net-benefit outcome included all components of the primary efficacy and primary safety outcomes. All the above outcomes and their components were adjudicated in a blinded manner by an independent clinical-events committee

according to Valve Academic Research Consortium definitions [62] (See Table S2 for detailed definitions.)

Statistical Analysis

The primary hypothesis was that the rivaroxaban group would be superior to the antiplatelet group with respect to the time from randomized treatment assignment to the first occurrence of any component of the primary efficacy outcome. The trial was event-driven; we estimated that 440 primary efficacy outcome events would provide the trial with 80% power to detect a 20% lower relative risk in the rivaroxaban group than in the antiplatelet group. (Details on the power calculation and statistical methods are provided in the Supplementary Appendix.)

No formal interim analyses for efficacy or futility were planned. After review by the data and safety monitoring board on August 7, 2018, immediate termination of the trial was recommended because of safety concerns. The trial leadership and the sponsors accepted this recommendation for trial termination on August 13, 2018 (efficacy cutoff date). Because the trial was terminated early, only 183 patients reached the primary efficacy outcome (42% of the planned 440).

The statistical analysis plan originally specified that the primary efficacy outcome was to be analyzed for noninferiority (with a noninferiority margin for the upper boundary of the hazard ratio of 1.20) in the on-treatment data set; a hierarchical testing strategy specified that no tests for superiority would be performed if noninferiority was not shown. However, it was subsequently decided to present conventional two- sided P values to test for the between-group difference for both the primary efficacy outcome and the primary safety outcome; the approach described below and in the Results section is based on that decision.

The main analyses were performed according to the intention-to-treat principle. For time-to- event analyses, hazard ratios and 95% confidence intervals were generated with Cox proportional-hazards models. The confidence intervals were not adjusted for multiple comparisons, and therefore inferences drawn from these intervals may not be reproducible. Kaplan–Meier curves were

used to show the incidence of outcomes over time. The proportionality assumption for the primary efficacy and safety outcomes was not violated.

For the primary efficacy outcome and the primary safety outcome, conventional two-sided log-rank P values were calculated. Prespecified subgroup analyses followed Cox proportional- hazards methods. To describe early and late risks of outcome events, we performed landmark analyses on a post hoc basis with the landmark time point set at 90 days after randomization.

For the on-treatment analyses, trial outcomes were included if they occurred before premature permanent discontinuation of the assigned trial regimen. The time of premature permanent discontinuation was defined as 2 days after the last ingestion of a trial medication. On-treatment Cox regression analyses were performed by imposing additional censoring at the day of premature permanent discontinuation of the trial regimen.

Results

Trial Population

From December 2015 through May 2018, a total of 1644 patients underwent randomization after successful TAVR in 136 centers in 16 countries (Table S3); 826 patients were randomly assigned to the rivaroxaban group and 818 to the antiplatelet group. The median time from TAVR to randomization was 2.0 days (range, 0 to 8). Baseline characteristics are shown in Table 1. The mean (±SD) age was 80.6±6.6 years; 49.5% of the patients were female.

Adherence and Follow-up

Follow-up was complete for 96.8% of the patients, and vital status was available for 98.0% (Fig. 1); the median trial duration was 17 months (interquartile range, 13 to 21). Throughout the trial period, 307 patients in the rivaroxaban group prematurely discontinued the trial regimen, as compared with 194 in the antiplatelet group (Tables S4 and S5 and Fig. S1). In the rivaroxaban group, the median exposure to rivaroxaban was 428 days (interquartile range, 171 to 581), and the median exposure to aspirin was 90 days (interquartile range, 84 to 94). In the antiplatelet group, the median exposure to aspirin was 474 days (interquartile range, 298 to 603), and the median exposure to clopidogrel was

90 days (interquartile range, 85 to 93). New-onset atrial fibrillation developed in 11.0% of the trial population (Table S6).

Primary and Secondary Efficacy Outcomes

In the intention-to-treat analysis, death or first thromboembolic event (the primary efficacy outcome) occurred in 105 patients in the rivaroxaban group and in 78 patients in the antiplatelet group (incidence rates, 9.8 and 7.2 per 100 person-years, respectively; hazard ratio with rivaroxaban, 1.35; 95% confidence interval [CI], 1.01 to 1.81; P=0.04) (Fig. 2A and Table 2). This effect was consistent across prespecified subgroups (Fig. S2).

Death from cardiovascular causes or any thromboembolic event (the key secondary outcome) occurred in 83 patients in the rivaroxaban group and in 68 patients in the antiplatelet group (incidence rates, 7.8 and 6.3 per 100 person-years, respectively; hazard ratio, 1.22; 95% CI, 0.89 to 1.69). Symptomatic valve thrombosis occurred in 3 patients in the rivaroxaban group and in 7 patients in the antiplatelet group (incidence rates, 0.3 and 0.6 per 100 person-years, respectively; hazard ratio, 0.43; 95% CI, 0.11 to 1.66). Rates of stroke and myocardial infarction did not differ significantly between the two groups.

A total of 64 deaths occurred in the rivaroxaban group, and 38 occurred in the antiplatelet group (incidence rates, 5.8 and 3.4 per 100 person- years, respectively; hazard ratio for rivaroxaban, 1.69; 95% CI, 1.13 to 2.53) (Fig. 2B and Table 2). Noncardiovascular mortality rates were 2.6 and 1.0 per 100 person-years, respectively (hazard ratio, 2.67; 95% CI, 1.33 to 5.35). Cardiovascular mortality rates were 3.2 and 2.4 per 100 person- years, respectively (hazard ratio, 1.30; 95% CI, 0.79 to 2.14). Adjudicated causes of death are presented in Tables S7 through S9.

Primary Safety Outcome

In the intention-to-treat analysis, life-threatening, disabling, or major bleeding (the primary safety outcome) occurred in 46 patients in the rivaroxaban group and 31 patients in the anti- platelet group (incidence rates, 4.3 and 2.8 per 100 person-years, respectively; hazard ratio with rivaroxaban, 1.50; 95% CI, 0.95 to 2.37; P = 0.08) (Fig. 2C). There was no significant between- group difference in

the rate of life-threatening or disabling bleeding (1.6 and 1.5 per 100 person- years, respectively; hazard ratio, 1.06; 95% CI, 0.55 to 2.06). Bleeding rates according to other prespecified definitions occurred more frequently in the rivaroxaban group than in the antiplatelet group (Table 2). Subgroup analyses for the primary safety outcome are shown in Figure S3.

Landmark and On-Treatment Analyses

Landmark analyses for the primary efficacy and safety outcomes and for death from any cause are shown in Figures S4 through S6. In the on- treatment analyses, a primary efficacy outcome event occurred in 68 patients during use of rivaroxaban and in 63 patients during use of anti- platelet therapy (incidence rates, 8.1 and 6.6 per 100 person-years, respectively; hazard ratio with rivaroxaban, 1.21; 95% CI, 0.86 to 1.70). A primary safety outcome event occurred in 39 and 28 patients, respectively (incidence rates, 4.6 and 2.9 per 100 person-years; hazard ratio, 1.53; 95% CI, 0.94 to 2.49; P=0.08). There were 26 and 24 deaths during treatment, respectively (incidence rates, 3.0 and 2.5 per 100 person-years; hazard ratio, 1.23; 95% CI, 0.71 to 2.15) (Tables S10 and S11 and Figs. S7 through S9). Kaplan–Meier curves for death from any cause after premature perma- nent trial drug discontinuation are provided in Figure S10.

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Rivaroxaban Group (N=826)	Antiplatelet Group (N=818)
Demographic and clinical characteristics		
Age — yr	80.4±7.1	80.8±6.0
Male sex — no. (%)	426 (51.6)	405 (49.5)
Body-mass index†	28.1±5.5	28.2±5.7
Hypertension — no. (%)	720 (87.2)	697 (85.2)
Diabetes mellitus — no. (%)	236 (28.6)	235 (28.7)
EuroSCORE II‡	4.1±3.9	4.1±3.7
EuroSCORE II risk category — no. (%)‡		
High	50 (6.1)	64 (7.8)
Intermediate	139 (16.8)	140 (17.1)
Low	636 (77.0)	613 (74.9)
Missing	1 (0.1)	1 (0.1)
STS risk score§	4.0±3.2	4.3±3.5
STS risk category — no. (%)§		
High	65 (7.9)	74 (9.0)
Intermediate	383 (46.4)	388 (47.4)
Low	378 (45.8)	356 (43.5)
Congestive heart failure — no. (%)	394 (47.7)	380 (46.5)
NYHA class III or IV — no. (%)	250 (30.3)	222 (27.1)
Coronary artery disease — no. (%)¶	325 (39.3)	305 (37.3)
Previous stroke — no. (%)	51 (6.2)	35 (4.3)
Peripheral artery disease — no. (%)	83 (10.0)	82 (10.0)
Previous venous thromboembolism — no. (%)	18 (2.2)	15 (1.8)
Permanent pacemaker — no. (%)	80 (9.7)	80 (9.8)
Chronic obstructive pulmonary disease — no. (%)	110 (13.3)	88 (10.8)
Glomerular filtration rate — ml/min/1.73 m^2	73.4±23.8	73.2±23.2
Procedural characteristics		
Valve type — no. (%)		
Sapien XT, Edwards Lifesciences	13 (1.6)	13 (1.6)
Sapien 3, Edwards Lifesciences	385 (46.6)	346 (42.3)
CoreValve, Medtronic	33 (4.0)	35 (4.3)
CoreValve Evolut R, Medtronic	206 (24.9)	225 (27.5)
Lotus, Boston Scientific	44 (5.3)	40 (4.9)
Portico, St. Jude Medical	44 (5.3)	40 (4.9)
Acurate Neo, Boston Scientific	82 (9.9)	89 (10.9)
Other	19 (2.3)	30 (3.7)
Valve-in-valve — no. (%)	42 (5.1)	49 (6.0)

Table 1. (Continued.)

Characteristic	Rivaroxaban Group (N=826)	Antiplatelet Group (N=818)
Post-TAVR echocardiographic characteristics		
Aortic valve area — cm^2	1.8±0.6	1.9±0.5
Mean aortic valve gradient — mm Hg	10.0±4.7	10.1±4.6
Left ventricular ejection fraction — %	57.4±10.9	58.2±11.2
Paravalvular aortic regurgitation — no. (%)		
Mild	157 (19.0)	168 (20.5)
Moderate or severe	10 (1.2)	10 (1.2)

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. NYHA denotes New York Heart Association, and TAVR transcatheter aortic-valve replacement.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ Scores on the European System for Cardiac Operative Risk Evaluation II (EuroSCORE II), which measure patient risk at the time of cardiovascular surgery, are calculated by means of logistic-regression equations. A score of greater than 10% indicates high risk, 5 to 10% intermediate risk, and less than 5% low risk.
§ Society of Thoracic Surgeons (STS) risk scores, which measure patient risk at the time of cardiovascular surgery, are calculated by means of logistic-regression equations. A score of greater than 8% indicates high risk, 3 to 8% intermediate risk, and less than 3% low risk.
¶ Coronary artery disease was defined as previous myocardial infarction, percutaneous coronary intervention, or coronary-artery bypass grafting.

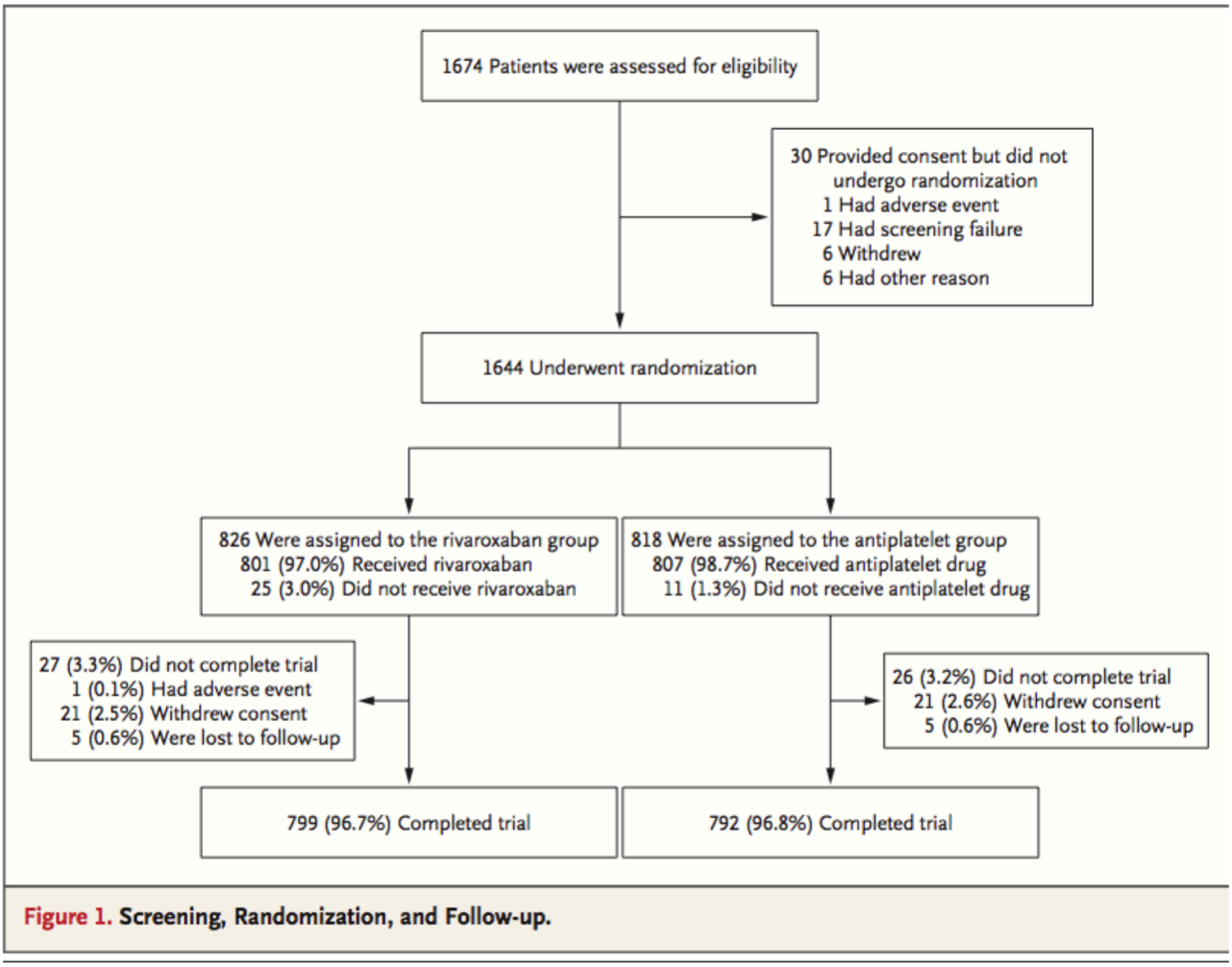


Figure 1. Screening, Randomization, and Follow-up.

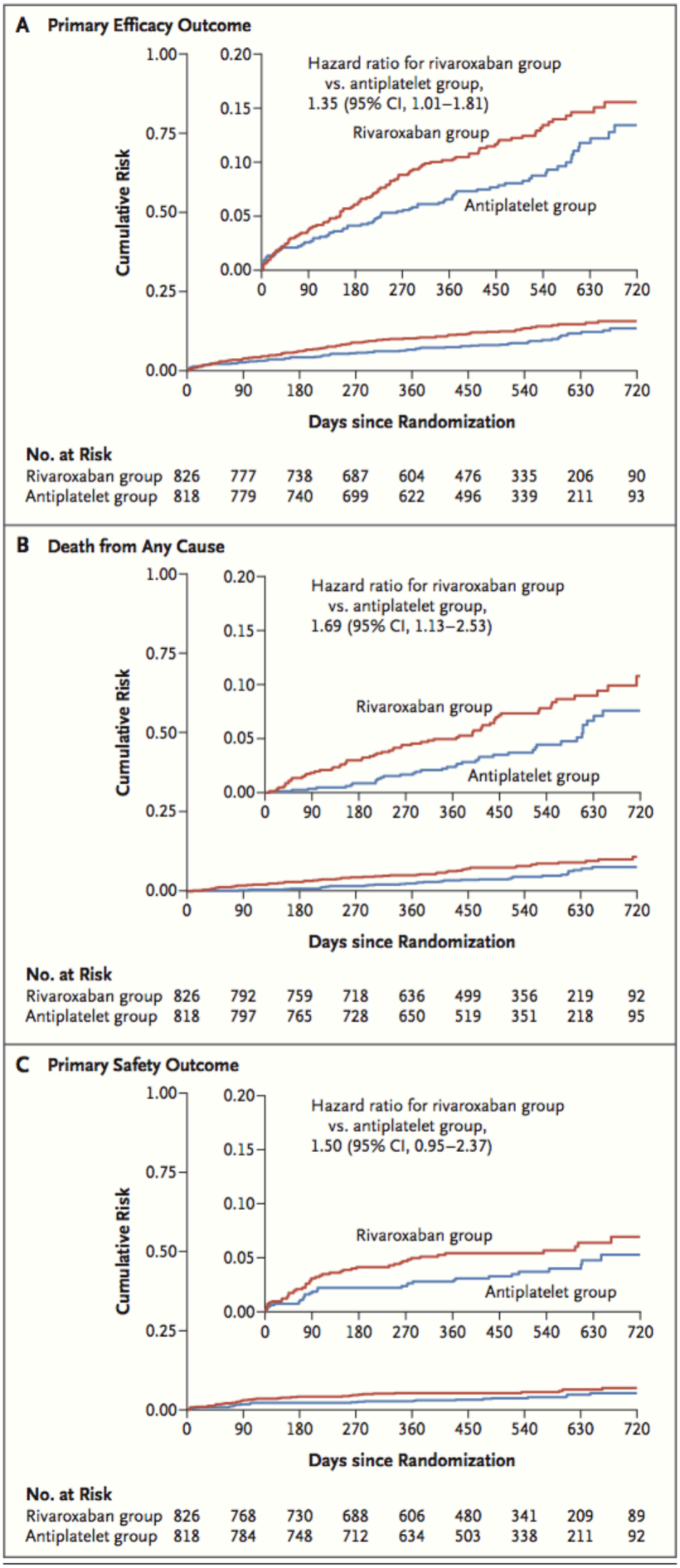


Figure 2. Cumulative Risk of the Primary Efficacy and Primary Safety Outcomes and Death from Any Cause (Intention-to-Treat Analysis).

Shown are time-to-event Kaplan–Meier curves for the primary efficacy outcome, death from any cause, and the primary safety outcome. The primary efficacy outcome was defined as the composite of death, stroke, myocardial infarction, symptomatic valve thrombosis, pulmonary embolism, deep-vein thrombosis, or systemic embolism. The primary safety outcome was defined as the composite of Valve Academic Research Consortium life-threatening, disabling, or major bleeding. The 95% confidence intervals (CIs) presented were not adjusted for multiple comparisons. Insets show the same data on an enlarged y axis.

Table 2. Efficacy and Safety Outcomes (Intention-to-Treat Analysis).*

Outcome	Rivaroxaban Group (N=826)		Antiplatelet Group (N=818)		Difference (95% CI)	Hazard Ratio (95% CI)
	no. (%)	*incidence rate/ 100 person-yr*	*no. (%)*	*incidence rate/ 100 person-yr*	*incidence rate/ 100 person-yr*	
Efficacy outcomes						
Primary efficacy outcome†	105 (12.7)	9.8	78 (9.5)	7.2	2.6 (0.1 to 5.1)	1.35 (1.01 to 1.81)
Death	64 (7.7)	5.8	38 (4.6)	3.4	2.4 (0.6 to 4.1)	1.69 (1.13 to 2.53)
From cardiovascular causes	35 (4.2)	3.2	27 (3.3)	2.4	0.7 (–0.7 to 2.1)	1.30 (0.79 to 2.14)
From noncardiovascular causes	29 (3.5)	2.6	11 (1.3)	1.0	1.6 (0.5 to 2.7)	2.67 (1.33 to 5.35)
Stroke	30 (3.6)	2.8	25 (3.1)	2.3	0.5 (–0.8 to 1.8)	1.20 (0.71 to 2.05)
Ischemic	28 (3.4)	2.6	22 (2.7)	2.0	0.6 (–0.7 to 1.8)	1.28 (0.73 to 2.23)
Hemorrhagic	2 (0.2)	0.2	3 (0.4)	0.3	–0.1 (–0.5 to 0.3)	0.67 (0.11 to 3.98)
Myocardial infarction	23 (2.8)	2.1	17 (2.1)	1.5	0.6 (–0.6 to 1.7)	1.37 (0.73 to 2.56)
Symptomatic valve thrombosis	3 (0.4)	0.3	7 (0.9)	0.6	–0.4 (–0.9 to 0.2)	0.43 (0.11 to 1.66)
Pulmonary embolism	3 (0.4)	0.3	2 (0.2)	0.2	0.1 (–0.3 to 0.5)	1.49 (0.25 to 8.93)
Deep-vein thrombosis	1 (0.1)	0.1	4 (0.5)	0.4	–0.3 (–0.7 to 0.1)	0.25 (0.03 to 2.23)
Systemic embolism	1 (0.1)	0.1	1 (0.1)	0.1	0.0 (–0.3 to 0.3)	0.98 (0.06 to 15.69)
Key secondary efficacy outcome‡	83 (10.0)	7.8	68 (8.3)	6.3	1.5 (–0.8 to 3.7)	1.22 (0.89 to 1.69)
Net clinical benefit§	137 (16.6)	13.2	100 (12.2)	9.4	3.8 (0.9 to 6.7)	1.39 (1.08 to 1.80)
Safety outcomes						
Primary safety outcome¶	46 (5.6)	4.3	31 (3.8)	2.8	1.5 (–0.1 to 3.1)	1.50 (0.95 to 2.37)
VARC life-threatening or disabling bleeding	18 (2.2)	1.6	17 (2.1)	1.5	0.1 (–1.0 to 1.2)	1.06 (0.55 to 2.06)
Fatal bleeding	2 (0.2)	0.2	1 (0.1)	0.1	0.1 (–0.2 to 0.4)	2.01 (0.18 to 22.19)
VARC major bleeding	30 (3.6)	2.8	15 (1.8)	1.4	1.4 (0.2 to 2.6)	2.02 (1.09 to 3.76)
TIMI major or minor bleeding	42 (5.1)	3.9	24 (2.9)	2.2	1.7 (0.3 to 3.2)	1.78 (1.08 to 2.94)
ISTH major bleeding	49 (5.9)	4.6	30 (3.7)	2.7	1.9 (0.2 to 3.5)	1.66 (1.05 to 2.62)
BARC type 2, 3, or 5 bleeding	148 (17.9)	15.4	85 (10.4)	8.2	7.2 (4.2 to 10.3)	1.84 (1.41 to 2.41)

* The 95% confidence intervals (CIs) were not adjusted for multiple comparisons. The proportionality assumption for the primary efficacy and safety outcomes was not violated. BARC denotes Bleeding Academic Research Consortium, ISTH International Society on Thrombosis and Hemostasis, TIMI Thrombolysis in Myocardial Infarction, and VARC Valve Academic Research Consortium.

† The primary efficacy outcome was defined as the composite of death, stroke, myocardial infarction, symptomatic valve thrombosis, pulmonary embolism, deep-vein thrombosis, or systemic embolism.

‡ The key secondary efficacy outcome was defined as the composite of death from cardiovascular causes, stroke, myocardial infarction, symptomatic valve thrombosis, pulmonary embolism, deep-vein thrombosis, or systemic embolism.

§ Net clinical benefit was defined as the composite of the primary efficacy and primary safety outcomes.

¶ The primary safety outcome was defined as the composite of VARC life-threatening, disabling, or major bleeding.

Discussion

GALILEO was a randomized, controlled trial to evaluate the efficacy and safety of rivaroxaban-based antithrombotic therapy as compared with antiplatelet-based therapy after successful TAVR in patients without an established indication for anticoagulation. A dose of rivaroxaban of 10 mg daily (lower than the approved dose for stroke prevention in patients with atrial fibrillation) was selected to provide a level of anticoagulation to prevent valve surface thromboembolism while mitigating bleeding complications.

We observed that the rivaroxaban group had higher rates of death or thromboembolic complications in the intention-to-treat analysis (rates that were attenuated in the on-treatment analysis) and higher rates of bleeding complications. These results underscore the challenge of anti- thrombotic therapy in the TAVR population, which includes patients who are generally elderly, potentially frail, or affected by multiple coexisting conditions associated with an increased risk of both bleeding and thromboembolic events. The lack of a clinical benefit of rivaroxaban in this context occurred despite evidence from an imaging substudy of GALILEO (also now published in the *Journal*) [63] that rivaroxaban was associated with a lower incidence of subclinical valve-leaflet thickening and reduced leaflet motion than antiplatelet therapy.

The overall event rates in this trial were lower than anticipated, probably reflecting the prerequisite of a successfully completed procedure and the overall declining risk profile among patients referred for TAVR (because of expanding indications). However, the rates are in line with those in the pivotal trials involving low-risk and intermediate-risk populations [48,49]. Although the routine use of higher-dose rivaroxaban (15 to 20 mg daily) in this trial population would have been expected to increase bleeding complications, we do not know whether a lower dose (e.g., 2.5 mg twice daily) might have afforded an improved risk–benefit profile as compared with the present results.

The higher number of deaths in the rivaroxaban group than in the antiplatelet group did not appear to be directly attributable to the higher risk of bleeding in the rivaroxaban group. Among patients assigned to rivaroxaban who died, only a minority had a major bleeding event, myocardial

infarction, or stroke within 30 days before death, and most deaths occurred long after discontinuation of the trial drug. Most of the adjudicated causes of death in the rivaroxaban group were sudden or from unknown reasons, as well as due to noncardiovascular causes. Hence, the mechanism underlying the higher mortality in the rivaroxaban group observed in the intention- to-treat analysis in this trial is unclear. The between-group differences in mortality were attenuated in the on-treatment analysis.

Since the inception of TAVR, postprocedural antithrombotic therapy has been based on expert consensus according to regimens used in the pivotal trials [56,57,64-66]. Recent registry results have indicated an association between oral anticoagulation at hospital discharge and an increased risk of death but a decreased risk of bioprosthetic valve dysfunction in comparison to patients undergoing TAVR who did not receive anticoagulation therapy [67]. Whether a short-term course of anticoagulation monotherapy after TAVR is safe and effective warrants further investigation. The 90-day landmark analyses that we conducted did not suggest consistent differential effects over time.

GALILEO was an open-label trial and was potentially subject to reporting and ascertainment bias. However, trial outcomes were prespecified with the use of standardized definitions and adjudicated by a clinical-events committee whose members were unaware of the trial-group assignments. Patients undergoing TAVR with an established indication for anticoagulation were not included in this trial, and treatment strategies for this patient population are being investigated in ongoing studies (ClinicalTrials.gov numbers, NCT02247128, NCT02664649, NCT02943785, and NCT02735902). On-treatment analyses are generally subject to misinterpretation since they effectively subvert the randomization, because patients who continue to receive treatment differ from those who do not, and thus their subsequent risk of an event is no longer comparable between the trial groups. In the present trial, in which there was a substantial imbalance in treatment discontinuation, the on-treatment analysis may be biased as described above. The P values in this article must be read with prudence, because these tests were not prespecified.

Because we report multiple confidence intervals in the context of a trial that was prematurely terminated, all estimated treatment effects and their confidence intervals should be interpreted with caution. Finally, the early trial termination constitutes a limitation in its own right.

Among patients without an established indication for anticoagulation after successful TAVR, a treatment strategy including anticoagulation with rivaroxaban at a dose of 10 mg daily was associated with a higher risk of death or thromboembolic complications and a higher risk of bleeding than an antiplatelet-based strategy.

Supported by Bayer in collaboration with Janssen Pharmaceuticals.

2) Transcatheter valve-in-valve implantation in a patient with a degenerative sutureless aortic bioprosthesis: case report and literature review. (original article in italian)

INTRODUCTION

The use of sutureless aortic bioprostheses (SAB) is continuously increasing due to the reduced aortic clamping times and the shorter duration of cardiopulmonary bypass compared to standard aortic valve replacement techniques [68]. Like other bioprostheses, some may need reoperation due to structural degeneration over time. Transcatheter valve replacement using the valve-in-valve (ViV) technique has proven to be a valid alternative, in terms of efficacy and safety, to surgical aortic valve replacement in most patients with degenerated bioprosthesis and high surgical risk [69,70]. However, the benefits of a ViV in treating a degenerated SAB are not yet defined. A case of transcatheter ViV with a self-expandable valve in a degenerated SAB is presented below, on which technical considerations and a review of the scientific literature on the subject are provided.

CASE REPORT

An 84-year-old female patient with a history of paroxysmal atrial fibrillation, rheumatoid arthritis on chronic steroid therapy and previous (2012) surgical aortic valve replacement was admitted to our Institute in 2017 for worsening exertional dyspnea. During hospitalization, transthoracic and transesophageal echocardiography showed degeneration of the bio-prosthesis (mean transvalvular aortic gradient of 36 mmHg, stroke volume 34 ml, valvular area 0.41 cm2, moderate-severe intra-prosthetic regurgitation, preserved left systolic function and systolic pulmonary hypertension of approximately 65 mmHg) (Figure 1). The angiographic and hemodynamic study confirmed the presence of combined prosthetic degeneration (peak transvalvular gradient of 55 mmHg and grade 3 aortic regurgitation) (Figure 1). The different therapeutic options were discussed by the Heart Team with the decision for a skin ViV procedure compared to a traditional reoperation in consideration of the patient's high surgical risk.

Multidetector computed tomography (MDCT) showed a deformed valve prosthesis with incomplete expansion due to in-folding in the right coronary sinus (Figure 2). By means of a percutaneous

transfemoral approach in slight sedation, the 26 mm Evolut RTM valve (Medtronic, Minneapolis, MN, USA) was implanted without predilatation, with positioning at the level of the lower margin of the SAB. During the initial release phase, a slight push was exerted on the guide to ensure coaxial orientation of the percutaneous prosthesis with the SAB. Subsequently, after the flaring of the prosthesis, a slight push was applied on the release system during the "screwing" of the device to avoid the "pop-up" of the Evolute R and the risk of dragging or displacement of the Perceval (Figure 3). The haemodynamic, echocardiographic and angiographic results are shown in Figures 1 and 3. Arterial haemostasis was obtained using the ProglideTM double vascular closure device (Abbott, Abbott Park, IL, USA). The pre-discharge MDCT showed the correct positioning of the distal ring of the Evolut R about 2 mm above the distal ring of the SAB, with minimal compression of the valve.

DISCUSSION

The catheter ViV procedure is currently an alternative strategy in the treatment of degenerated aortic valve bioprostheses in patients with high surgical risk [69]. With regard to degenerated SABs, the data are very limited due to the relatively recent experience in the implantation of such bioprostheses and the consequent low incidence of degeneration of the same. In a pilot registry by Amabile et al.4, out of 265 implants over a period of 9 years, the degeneration of a SAB occurred in 1.9% of cases. In the series of Baert et al. [72] severe dysfunction of a SAB occurred in 2.9% of the operated patients. In our institute, out of a total of 150 PercevalTM implants over a 5-year period, this is the first reported case of SAB degeneration (0.7%). In the treatment of a sutureless prosthesis two elements should be taken into consideration: a) problems related to the malfunction or degeneration of SAB, b) problems related to the percutaneous ViV procedure in degenerated SAB.

Problems related to the malfunction or degeneration of sutureless aortic bioprosthesis

Malpositioning and inappropriate sizing of the valve are factors associated with the development of paravalvular leak and early degeneration of the prosthesis [72]. In case of malposition, the valve is generally well anchored, but the inflow ring is located below or above the native valve annulus. The

overestimation of the size of the prosthesis can generate premature degeneration of the flaps and recoil of the metal structure with loss of contact between the prosthesis and the aortic wall, and consequent development of paravalvular leak. Even in the absence of recoil, a slight in-folding of the prosthesis can lead to premature degeneration and malfunction of the flaps, with consequent risk of stenosis and / or intraprosthetic regurgitation.

In our case, the inflow ring was correctly positioned with preserved contact at the annulus level, but there was a slight in-folding with intraposthetic regurgitation and degeneration of the flaps, suggesting that the mechanism determining the valvular dysfunction was more probably linked to prosthetic oversizing. As pointed out by some authors [72], in the implantation of the SAB it is necessary to optimize the measurement methods and follow the manufacturer's recommendations, ie choose the smaller prosthesis in case of indecision between two measures. Problems related to the percutaneous valve-in-valve procedure in degenerated sutureless aortic bioprosthesis Only 8 cases of percutaneous ViV in sutureless degenerated bioprostheses have been reported in the literature, of which 5 with self-expandable valves and 3 with balloon-expandable valves [71,73-75]. Percutaneous aortic valve implantation in a SAB requires specific warnings: first of all, the elastic body of the SAB stent and the absence of sutures can theoretically lead to the risk of valve instability and dislocation when an additional (percutaneous) valve is implanted inside the one already present ; second, the optimal positioning of transceter valves inside valves with a metal structure requires detailed knowledge of the structural characteristics of each specific device. The SAB is characterized by two rings (lower and upper), three commissural elements that support the valve and three pairs of sinusoidal elements that guarantee its fixation to the valsalva sinuses. When the SAB is correctly positioned, the upper ring is located at the level of the decalcified annulus, while the lower segment of the valve protrudes into the left ventricular outflow tract for about 5 mm. A ViV with an implant that is too low, in particular with a self-expandable valve, can cause incomplete expansion of the prosthesis with flap malfunction due to the constriction of the nitinol ring at the level of the annulus or the flaps of the SAB. Consequently, the distal edge of the self-

expandable valve should be positioned at the lower edge of the SAB or 2-3 mm higher; third, it is not known which is the best device for a ViV in a SAB. Both self-expandable and balloon-expandable valves have shown good results in the reported cases [71,73-75], but there are still some problems relating to inadequate sealing, with possible residual regurgitation, and to postprocedural transvalvular gradients. Theoretically, a balloon-expandable valve should provide better expansion due to the greater radial force, thus reducing the risk of paravalvular leakage. On the other hand, given the implantation modality of such devices (positioning with the prosthetic valve flaps at the annulus level), higher transprosthetic gradients could be more frequent after an ViV procedure with a ballon expandable valve versus a self-expandable [72]. In our case, the method of positioning of the device and the supra-annular function of the valve flaps of the Evolut R made it possible to obtain transvalvular gradients similar to those of transcatheter implant procedures on native valves, with a trivial paraprosthetic leak.

CONCLUSIONS

As in other previously published reports, the present case demonstrates how transcatheter aortic ViV in a degenerated SAB is feasible and can represent a valid treatment option in selected patients. Further data from multi-center registries are needed to confirm these immediate results and evaluate the long-term outcome.

SUMMARY

Sutureless aortic bioprostheses (SABs) guarantee reduced aortic clamping times and shorter cardiopulmonary bypass duration, when compared with standard aortic valve replacement techniques. As with other bioprostheses, reoperation is sometimes necessary due to long-term structural degeneration of the valve. In patients with degenerated bioprostheses and at high risk for conventional surgical reoperation, transcatheter replacement of the aortic valve using the valve-in-valve (ViV) technique has proven to be an effective and safe alternative to aortic valve replacement. We report a case of transcatheter ViV with self-expandable valve in a degenerate SAB.

Keyword. Sutureless aortic bioprosthesis; Transcatheter implantation of aortic valve; Valve-in-valve procedure.

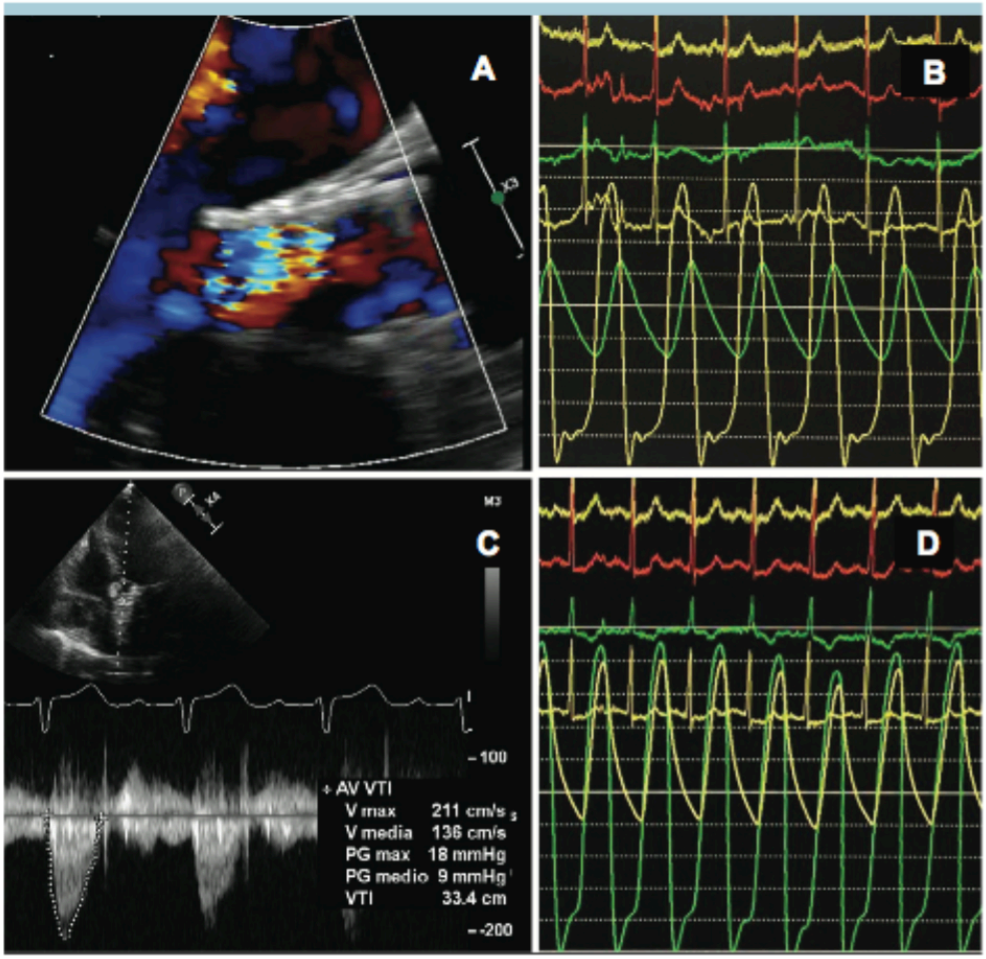


Figura 1. Misurazioni ecocardiografiche ed emodinamiche. *A*: rigurgito intraprotesico all'ecocardiogramma transesofageo. *B*: gradiente transaortico di picco pre-impianto transcatetere di valvola aortica (TAVI). *C*: gradiente transaortico medio post-TAVI. *D*: gradiente transaortico di picco post-TAVI.

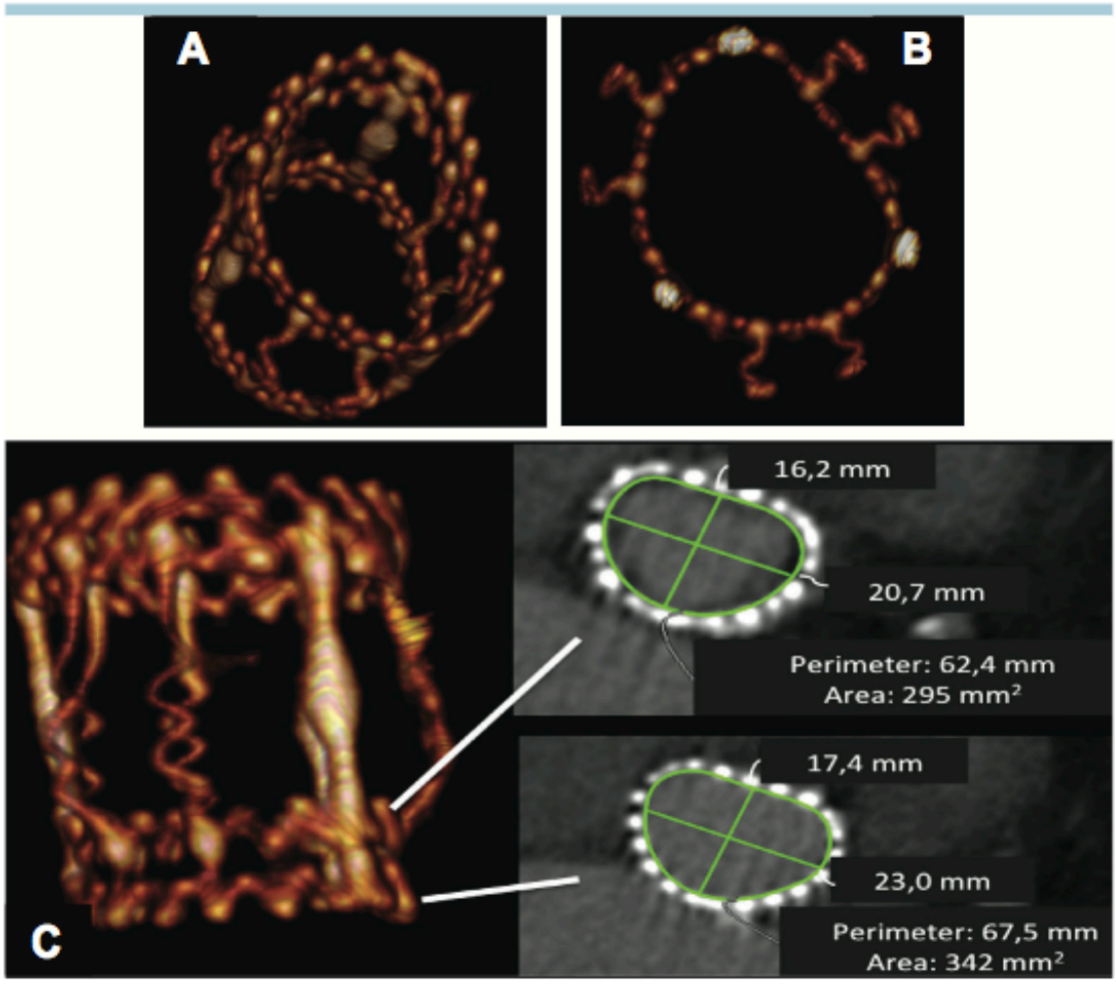


Figura 2. Tomografia computerizzata multidetettore (MDCT). *A* e *B*: ricostruzione MDCT della Perceval M che mostra in-folding della protesi a livello del seno coronarico destro. *C* e *D*: diametri, perimetro ed area a livello degli anelli di inflow e outflow.

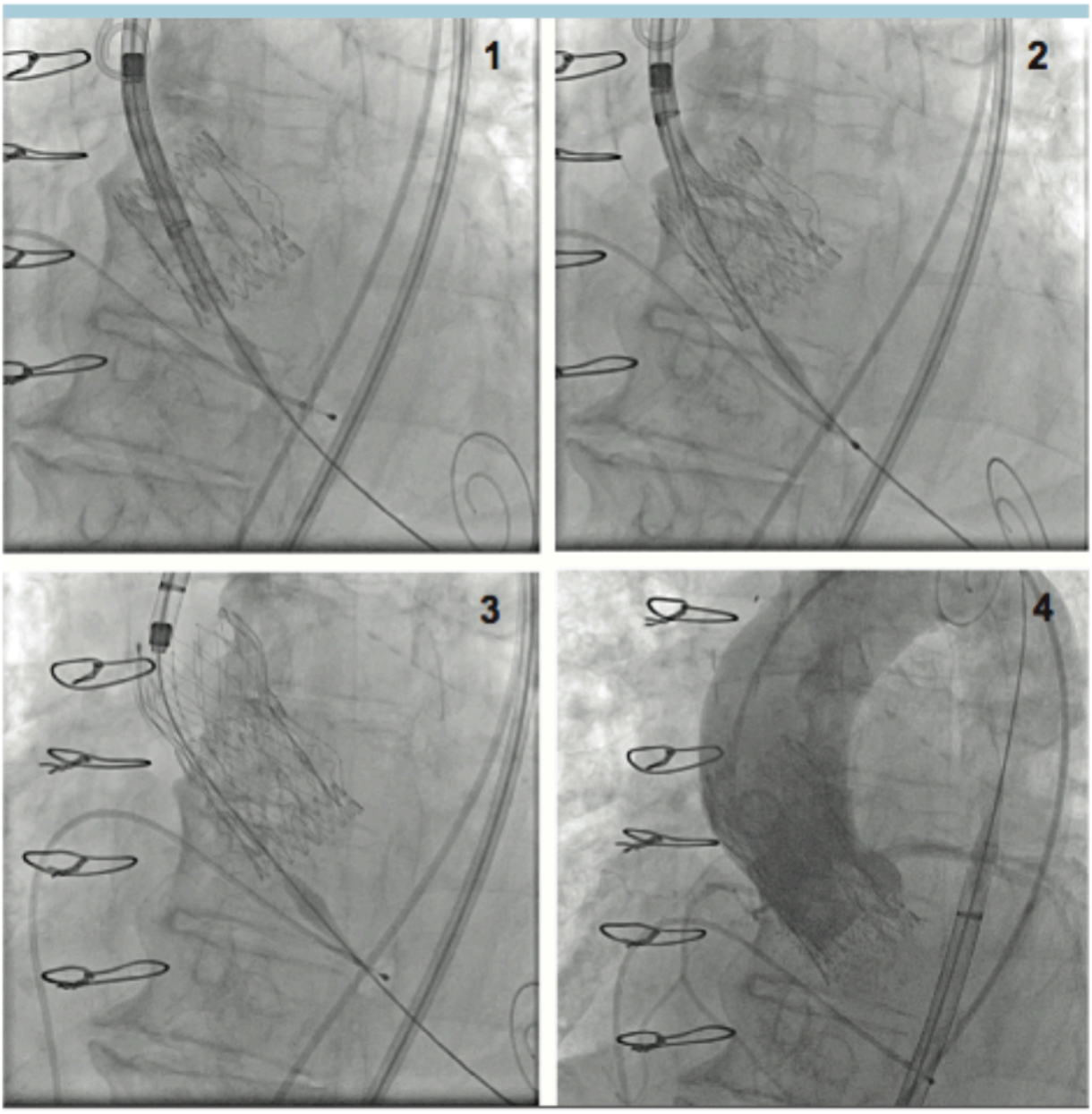


Figura 3. Step fluoroscopici sequenziali del rilascio della valvola Evolut R 26 mm.

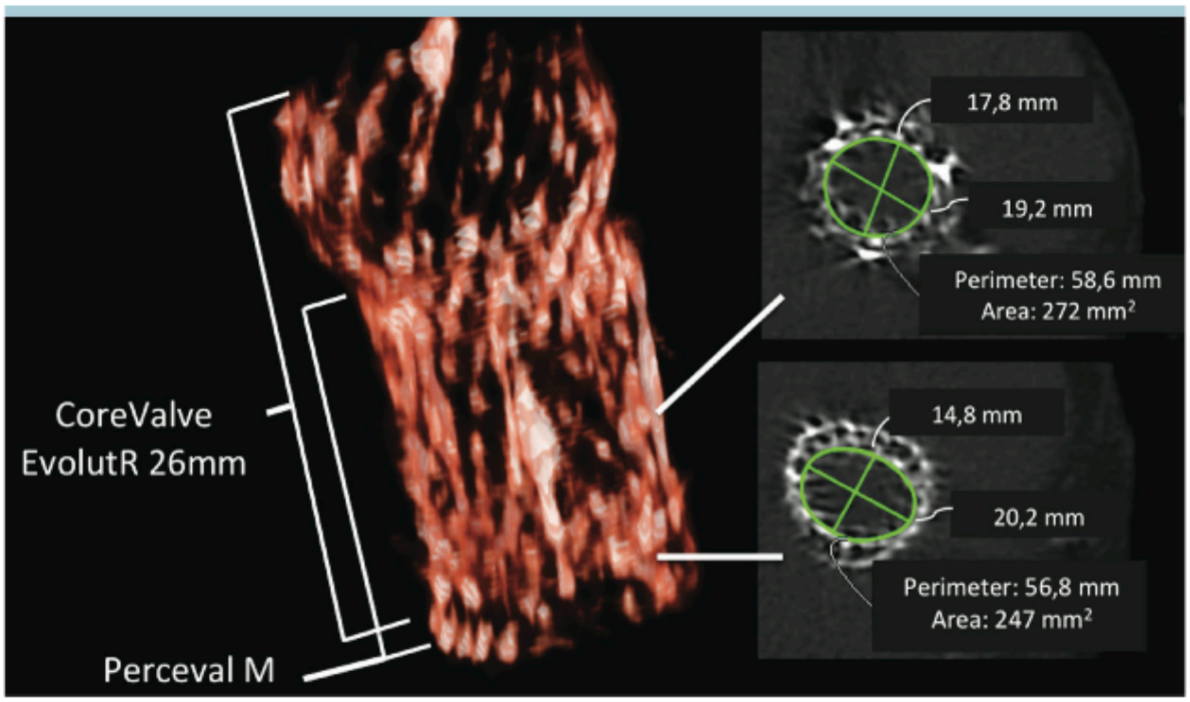


Figura 4. Misurazioni alla tomografia computerizzata multidetettore post-impianto trans-catetere di valvola aortica: diametri, perimetro e area a livello dell'anulus e dei lembi della valvola Evolut R.

CHAPTER 3: Percutaneous coronary intervention: bifurcations and COVID 19.

1) Population Trends in Rates of Percutaneous Coronary Revascularization for Acute Coronary Syndromes Associated With the COVID-19 Outbreak

Areduction in hospital admissions for acute coronary syndromes (ACS) has been observed globally in the aftermath of the pneumonia outbreak caused by coronavirus disease 2019 (COVID-19). [76] Despite the emergence of anecdotal reports, formal evaluation of the variation in percutaneous coronary intervention (PCI) rates during the COVID-19 outbreak has not yet been reported. Italy is one of the countries most heavily affected by the COVID-19 pandemic with 168941 confirmed cases and 22170 deaths as of April 5, 2020.

We investigated the association between the outbreak of COVID-19 and PCI rates for ACS in the Campania region, which, with 5.8 million residents, represents ≈10% of the Italian population. Data were obtained from 20 of 21 PCI centers over an 8-week period, including 4 weeks before and 4 weeks after the COVID-19 outbreak corresponding with the first reported case declared by the Civil Protec- tion Department on February 27, 2020. Incidence rates and their ratios were cal- culated by using Poisson regression analysis, and interactions for sex and age were estimated by adding the interaction term to the regression models.[77] Population denominators, which were used as offset, were obtained from the Italian census. The ratio change in PCI rates for the entire 8-week interval was estimated by adding a linear term to the Poisson regression. The study was approved by the Ethics Committee of the University of Naples Federico II (Naples, Italy).

From January 30, 2020, to March 26, 2020, a total of 1831 PCIs were performed in the Campania region; of them, 738 (40.31%) were elective PCIs (not includ- ed), 604 (32.99%) were PCIs for non–ST-segment–elevation acute ACS, and 489 (26.71%) were PCIs for ST-segment–elevation myocardial infarction (STEMI). Mean age was 65.7 years (SD, 12), and 804 of 1093 PCIs (73.56%) were performed in men. There were no differences in mean age (65.8±11.8 versus 65.6±12.2 years, *P*=0.78) and the proportion of men (72% versus 75%, *P*=0.29) in the 4 weeks before the COVID-19 outbreak in comparison with the subsequent 4 weeks.

The incidence rate of PCI for ACS decreased from 178 to 120 cases per 100 000 residents per year during the 4-week period before in comparison with after the COVID-19 outbreak (Figure). The incidence rate ratio (IRR) was 0.68. The reduction was similar for both non–ST-segment–elevation ACS and STEMI (from 98 to 66 and from 80 to 54 PCI cases per 100 000 residents per year, respectively). The decrease in PCIs for ACS was more evident in women (IRR, 0.60) than in men (IRR, 0.70), resulting in a significant interaction (P<0.001). There was heterogeneity (P-interaction <0.001) in the decline of PCI rates across age categories, with patients <55 years of age less affected by the reduction (IRR, 0.75). Findings were consistent between PCI centers in the metropolitan (IRR, 0.72) versus nonmetropolitan areas (IRR, 0.62). Over the interval from week –4 to week +4, the ratio change in PCI rate was 0.51 (95% CI, 0.50–0.52) for ACS, 0.54 (95% CI, 0.53–0.56) for non–ST-segment–elevation acute ACS, and 0.47 (95% CI, 0.45–0.49) for STEMI (Figure). In comparison with the same period in 2019, PCI rates decreased from 190 to 120, from 107 to 66, and from 84 to 54 cases per 100 000 residents per year for ACS (IRR, 0.63), non–ST-segment–elevation acute ACS (IRR, 0.62), and STEMI (IRR, 0.64), respectively.

In the third most populous region of Italy, we found evidence that the outbreak of COVID-19 was associ- ated with a decline by 32% in the number of PCIs for ACS. In the last 2 weeks of the observational period, PCIs for ACS were reduced by 50%. In comparison with PCI volumes for the same time in 2019, the decline in PCI rates was of a similar magnitude (between 36% and 38%).

Mechanisms underpinning this decrease are unknown, although several explanations might be involved. Chest pain might be underestimated or mises- timated by patients because of the fear of exposure to COVID-19–affected subjects at hospital admission. This

hypothesis might be supported by the stronger decline in PCI rates among women, in whom misdiagnosis and delayed revascularization are more likely to occur in an ACS setting.[78] Other explanations might be related to the unique situation of a country lockdown, potentially leading to less physical activity that might trigger an ACS, coupled with reduced air pollution.

Our data indicate that the COVID-19 outbreak was associated with a remarkable decrease in the rates of PCI across the entire spectrum of ACS. Although we did not measure the hospitalization rates for ACS, PCI represents the most common revascularization modal- ity for patients who have ACS. The Campania region has been less affected than others by the COVID-19 pandemic and, as a result, no changes occurred dur- ing the study period in the regional hub-and-spoke care system and in the management of patients with ACS. Therefore, PCI rates effectively reflect ACS rates. How- ever, we cannot determine to what extent the observed trends reflect changes in patient or physician behavior versus incident ACS.

The findings of this study might have important implications for healthcare systems and suggest that pub- lic campaigns aiming to increase awareness of ischemic symptoms should be reinforced during the COVID-19 pandemic. The lack of appropriate and timely revas- cularization for patients with ACS might have other important clinical consequences, not yet measured, including increased risk for heart failure or sudden cardiac death.

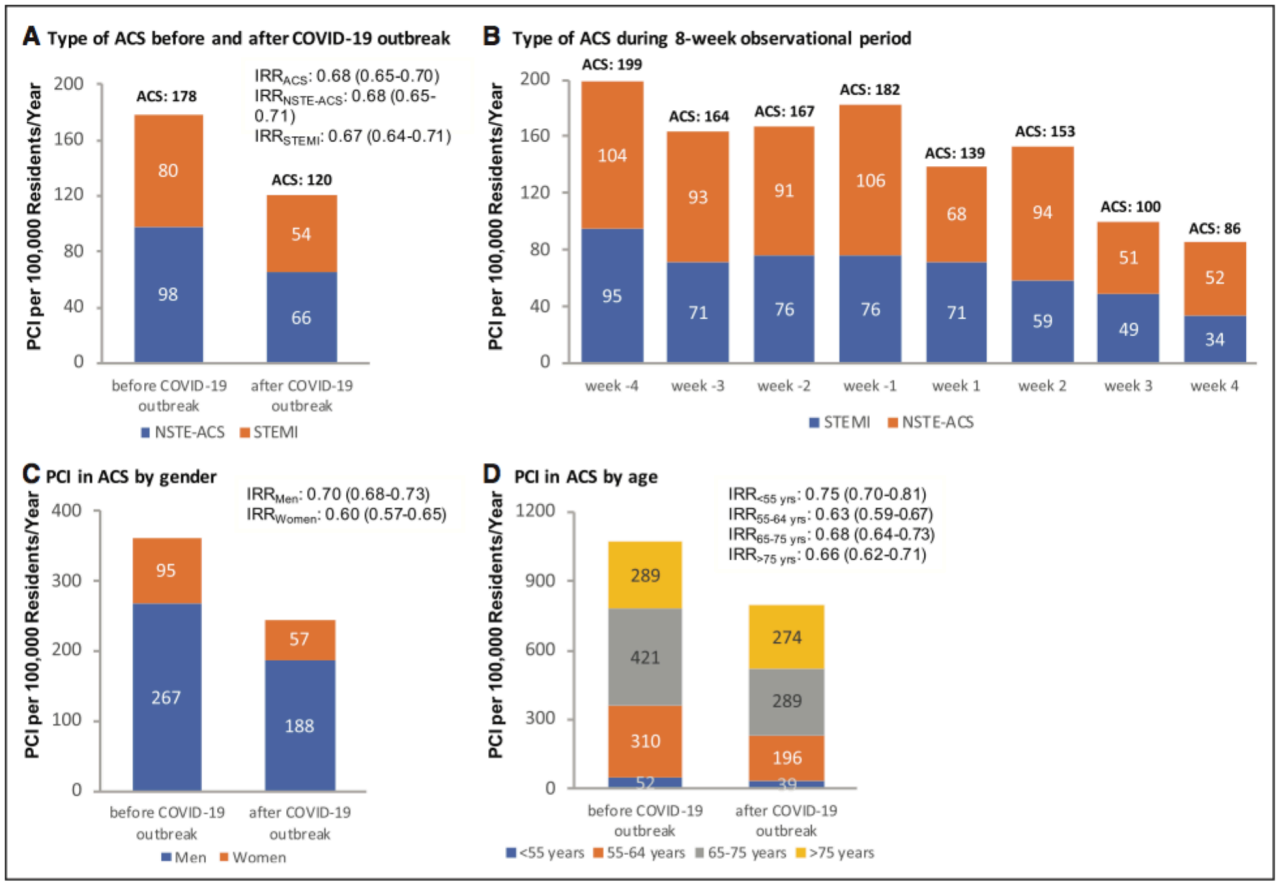


Figure. PCI incidence rates during before and after the COVID-19 outbreak in the Campania region, Italy.
A, Incidence rates before and after the first reported case of COVID-19 according to the type of ACS. Absolute numbers of PCI cases for ACS, NSTE-ACS, and STEMI were 652, 360, 292 and 441, 244, 197 in the 4 weeks before and the 4 weeks after the outbreak of COVID-19, respectively. In 2019, PCI volumes for the corresponding 4-week period after the outbreak of COVID-19 were 699, 392, 307 for ACS, NSTE-ACS, and STEMI, respectively. **B**, Incident rates by week according to the type of ACS. Weeks –4 to –1 represent the 4-week period before the first case of COVID-19 in the Campania region (February 27, 2020) and weeks 1 to 4 represent the 4-week period after the COVID-19 outbreak (data were collected until March 26, 2020). **C**, Incidence rates of PCI for ACS before and after the COVID-19 outbreak according to sex. **D**, Incidence rates of PCI for ACS before and after the COVID-19 outbreak according to age categories. ACS indicates acute coronary syndrome; COVID-19, coronavirus disease 2019; IRR, incidence rate ratio; NSTE-ACS, non–ST-segment–elevation ACS; PCI, percutaneous coronary intervention; and STEMI, ST-segment–elevation myocardial infarction.

2) Coronary artery bifurcation lesions

DEFINITION AND CLASSIFICATION OF CORONARY BIFURCATION

A bifurcation coronary lesion is a lesion occurring at, or adjacent to, a significant division of a major epicardial coronary artery [79]. A "significant" side branch is most often arbitrarily defined and based upon a subjective judgement of the operator. Altough, according to a widespread definition, a significant SB (Side Branch) is >2.25 mm and the plaque involves the bifurcation if the lesion is at least at 5 mm from the ostium. In practice, this implies that a significant side branch is a branch that the operator does not want to lose after evaluating the individual patient in a global context, i.e., patient symptoms, patient comorbidity, diameter and length of side branch, size of the myocardial mass supplied by the side branch, location of ischaemia, viability of the supplied myocardium, collateralizing vessel, left ventricular function, results of functional tests, and so forth. Aim of this chapter is to focus on technical and clinical aspects of non-left main coronary bifurcation lesions providing an in-depth analysis of treatment implications.

Coronary bifurcations account for 15-20% of all percutaneous coronary interventions (PCI) and remain one of the most challenging lesions in interventional cardiology in terms of procedural success rate as well as long-term cardiac events. The optimal management of bifurcation lesions is still, despite a fast growing scientific literature in the field, the subject of considerable debate, where one of the concerns is the potential increased risk of late stent thrombosis associated with treatment complexity [79].

Classifications

To better define bifurcation lesion, a simplified and universal classification, the Medina classification [80], and an accurate definition of the various techniques used in bifurcation stenting combined with a precise classification system to facilitate the description, the MADS classification [81] have been proposed and are now the most used worldwide. (Figure 1: Medina and MADS). The Medina classifications may need some refinements to be more descriptive, but the resulting

increased complexity was feared to hamper the global adoption of the system and was therefore omitted. A more precise lesion description might be attained by taking into consideration the angle between the two branches, the side branch (SB) lesion length, the observed/expected diameter, the TIMI flow, and presence of calcification, plaque distribution, as well as ulcerations.

Also, more objective measures become increasingly available through physiological assessment, quantitative coronary analysis and use of adjunctive imaging, which may aid the description further. [82]

Anatomy

The coronary bifurcation anatomy and physiology as well as the interaction between interventional devices (stents, balloons) and bifurcated vessel walls are promising, evolving fields of research. In recent years, coronary bifurcation anatomy has been the subject of a series of studies, which have helped to characterize the geometric relations linking MVs (main Vessel) and SB. Several mathematical models (Murray's [83], Finet's [84], Huo-Kassab's [85] and "area preservation") have been reported and are based on different assumptions. All together such models, besides some differences in estimated coefficients, confirm that coronary bifurcation anatomy may basically be regarded as a complex vessel/function structure where three different vessel segments (proximal MV, distal MV and SB) are interpolated through the bifurcation core segment where the distinction between MV and SB is merely virtual. (Figure 2: Coronary bifurcation anatomy). Full description of each individual bifurcation should incorporate both vessel diameters and the angles created in the three dimensions of the space by the main axes of the three segments. [86]. Such comprehensive three-dimensional anatomic description is pivotal for future studies on the local coronary flow through bifurcated segments. Furthermore, since coronary circulation is tree-like, the flow reconstructions are expected to be influenced by the eventual presence of different SBs of different sizes [87]. On such bases, a series of investigations based on the flow reconstruction obtained by computer simulations before, during and after PCI in bifurcations has started to provide novel insights in the field. Of note, attempts to understand the clinical impact of bifurcation anatomy by

assessing just a single geometric parameter such as bifurcation angle have so far provided inconclusive results. [88]

DIFFERENCES IN PERCUTANEOUS TREATMENT BEETWEEN CORONARY BIFURCATIONS AND OTHER STENOSES

Although historically bifurcation lesions have been associated with poorer clinical outcomes when compared with non-bifurcation lesions [89], other reports have suggested clinical outcomes to be similar due to advancements in drug-eluting stent (DES) design [90]. Important improvements about the oucomes related to coronary bifurcation PCI have been brought by the LEADERS all-comers trial [91]. This was a prospective, multicenter, randomized, assessor-blind, non-inferiority trial including 1,707 patients with ischemic heart disease at 10 European sites. Patients were randomized in a 1:1 fashion to either the BES or the SES using an interactive voice response system. The primary endpoint was major adverse cardiac events (MACE), defined as the composite of cardiac death, MI (Q-wave and non–Q- wave), or clinically indicated (CI) TVR within 9 months. Secondary endpoints were the individual components of MACE, any TVR, CI TLR, any TLR, and ST according to the definitions of the Academic Research Consortium.

The results of the trial pointed out that PCI of bifurcation lesions was associated with worse long-term clinical outcomes when compared with non-bifurcation lesions, resulting in differences in MACE and DOCE. In conclusion, the use of the BES for the treatment of bifurcation lesions resulted comparable safety and superior efficacy when compared with the SES. The differences in MACE rates between patients with at least one bifurcation lesion versus patients without any bifurcation lesion were observed early and were mainly driven by a numerical difference in MI and CI-TVR rates, while the cardiac death rates were similar. The Kaplan–Meier curve showed an early divergence of the MI endpoint, while beyond 1 year patients with at least one bifurcation lesion were no longer at higher risk of MI. This finding is in-line with the combined 3-year follow-up data from the RESOLUTE all-comers trial and RESOLUTE international registry evaluating a zotarolimus-eluting stent (ZES) second generation DES [92]. In that study, a higher risk for

ischemic events was found in patients treated for at least one bifurcation lesion, although this increased risk was limited to the post- procedural early phase. In terms of efficacy, they found differences between bifurcations and non- bifurcations both in the early phase as well as beyond 30-days up to 3 years, although the absolute differences were quite small. Diletti et al. speculated that the differences between patients with and without bifurcation lesions were smaller because of the introduction of second generation DES, thereby improving outcomes after bifurcation PCI.

This, however, must be regarded as hypothesis generating given the absence of a control arm of a first generation DES. Costopoulos et al compared in a non- randomized fashion first generation DES (either SES or Taxus paclitaxel-eluting stent, total n1⁄4289) with second generation DES (either EES, EES, or ZES, total n1⁄4199) and conclude that the use of these second generation DES were associated with improved clinical outcomes for the treatment of bifurcation lesions [93]. The only available randomized data comparing first and second generation DES in bifurcation lesions is from the SEAside and CORPAL randomized trials, comparing EES with SES [94-95]. The individual trials were small and therefore under- powered to be able to demonstrate any clinical benefit of second generation DES over the first generation DES at 1 year follow-up [96]. However, by pooling data from both studies and extending follow-up until 3 years, a statistical significant difference in TVR between 1 and 3 years was demonstrated in favor of EES [95].

A report from the TWENTE trial also showed higher periprocedural MI rates in bifurcation lesions when using EES and ZES newest generation DES [97]. It is noteworthy that at 5-year follow-up, there was no longer a statistical significant difference in MI between BES and SES due to a late "catch-up" in MI events related to the higher incidence of very late ST in Cypher. Importantly, there were no differences in cardiac death rate between BES and SES, both in the early as in the long-term phase [98]. It seems that improvements in DES stent design indeed do improve clinical outcomes after PCI of bifurcation lesions. Besides improvements in DES design, gained knowledge on bifurcation stenting and the introduction of specific bifurcation techniques, including stent sizing according to the distal diameter to prevent carina shift [99-100], the proximal optimization

technique [101], the importance of distal cell recrossing during side branch rewiring after main branch stenting [102], final kissing balloon dilatation [103-104], and the need to use non-compliant balloons, have improved clinical outcomes after PCI of bifurcation lesions even further [105]. Therefore, it seems justified to conclude that with the current knowledge and the contemporary armamentarium of interventionalists, not all bifurcation lesions should longer be considered as high risk lesions. Even Medina 1,1,1, lesion are not necessarily "complex" if the side branch lesion is short with an intermediate stenosis severity. The current challenge is to adequately identify bifurcation lesions which are at high risk for procedural complications and worse clinical outcomes. The so called "DEFINITION" criteria have been associated with adverse clinical outcomes and seem to be able to objectively assess the complexity of bifurcation lesions [106].

In the LEADERS all-comers study, "complex" bifurcations lesions were defined as Medina 1,1,1/0,1,1, bifurcation lesions with side branch diameter greater than 2.5 mm, side branch stenosis severity greater than 90%, and side branch lesion length greater than 10 mm with an additional high-risk criterion [106]. It seems worthwhile to focus future research on such high-risk sub groups to further improve outcomes after treatment of bifurcation lesions [106].

PERCUTANEOUS TREATMENT OF CORONARY BIFURCATIONS

Bifurcation treatment techniques should be considered when SB patency might affect prognosis or a side branch stenosis may cause symptoms. A quantitative relation between SB diameter and length and the size of supplied myocardium has been established in swine [107-108]. According to the 10 years EBC consensus, SB diameter and length can both be used visually as surrogates for volume of muscle at risk; wiring of the SB before MV stenting is recommended when the SB is deemed important by the operator or at least >2.25 mm [109].

The Medina classification [110] and an accurate definition of the various techniques used in bifurcation stenting combined with the MADS classification [111] have provided the valuable opportunity to standardize reports, to allow comparisons between studies and to facilitate interpretation of published results. For all these reasons, systematic use of these classifications is

still strongly recommended by the EBC. Based on multiple randomised trials and registries of one versus two- stent techniques in coronary bifurcation lesions, and based on the KISSS principle (Keep it simple, swift and safe)[112-116], the EBC recommends the provisional stenting technique as the preferred technique for the majority of bifurcation lesions. In this technique the main vessel (MV) is stented first and the side branch (SB) is only stented in case of severe restenosis or flow limitations to the side branch (provisional SB stenting) after MV stenting. Most of the available literature comparing one versus two-stent techniques is burdened with a design dilemma.

The populations in most of the published studies favour the provisional technique, because of inclusion of non-true bifurcations, and inclusion of bifurcations with SB diameter below 2.5 mm. The randomised Nordic-Baltic IV trial (TCT 2013) showed a trend towards improved midterm outcome when using a two-stent technique compared to provisional stenting in bifurcations with large SBs (≥2.75 mm) having more than 50% diameter stenosis in the SB. A similar signal was supported by the DKCRUSH II trial [117] and by a subgroup analysis of the Tryton IDE study (EuroPCR 2014).

The EBC II trial on provisional T-stenting technique vs. culotte two-stent technique in bifurcation lesions (SBs ≥2.50 mm and more than 50% SB diameter stenosis) reported that, when treating complex coronary bifurcation lesions with large stenosed SBs, there is no difference between a provisional T-stent strategy and a systematic 2-stent culotte strategy in a composite end point of death, myocardial infarction, and target vessel revascularization at 12 months[118]. Therefore, two-stent technique may be considered up-front for bifurcations with large SB (ref. diameter ≥2.75 mm) and significant disease extending into the SB. Another design dilemma was the inclusion of non-prognostic periprocedural biomarker release in composite primary endpoints favouring provisional stenting. Periprocedural myocardial infarctions may be prognostic when baseline markers are normal and CK-MB is increased at least to 8-10 times the upper limit of the 99% confidence interval or ECG indicates Q-wave infarction [119]. From a technical point of view, it is important to decide beforehand whether to use two stents. When using the provisional T strategy, the operator is

restricted in all cases to using a technique where the SB is stented through the MV stent. This technique has an inborn risk of missing coverage of the SB or protruding into the MV. This problem can only be solved by using a provisional culotte technique, which, however, is more technically demanding. The technical result might be better in a two-stent technique if the SB is stented first, resulting in a satisfying result in the MV, but also in a more complex procedure than a provisional approach where SB stenting is not needed. The problem of choosing between a one and a two-stent technique before the start of the procedure is that it is difficult to predict the need for SB stenting before the main branch stent is placed. If the SB needs to be secured with a stent first (because of difficult wiring or because it supplies a large territory), the procedure will most likely end with a two-stent technique. If the risk of SB closure is low, it is possible to choose a simpler strategy (provisional approach), with lower periprocedural risk and lower long- term event rates. This technique carries an inborn risk of losing the SB if, despite the pre-treatment risk evaluation, it closes during the procedure [120]. As a consequence, the optimal management of bifurcation lesions is still, despite a fast growing body of scientific literature in the field, the subject of considerable debate. The way forward calls for more long-term follow-up data in the already finalised studies to gain more knowledge of the long-term effects of the different techniques and devices. Furthermore, studies on stent techniques with the new-generation DES as well as with dedicated devices should be encouraged to define their role in the treatment of coronary bifurcations.

PROVISIONAL STENT STRATEGY

The provisional SB stent implantation strategy should be considered the standard approach for treatment of bifurcation lesions. In particular, it represents the first choice when the side branch size is <2.5 mm, or the bifurcation is not a “true” bifurcation (Medina 1-0-0, 0-1-0, 1-1-0) or when the disease on the side branch is very focal, localized whitin 3 mm from the ostium [121]. The EBC recommends the KISSS principle; it is really important, when approaching a bifurcation lesion to keep this principle in mind, avoiding too long and ineffective procedures. The main postulates of

the provisional single-stent strategy are optimal MB stenting and a possibility of subsequent SB stenting only in case of significant flow impairment and/or severe stenosis with haemodynamic relevance for a clinically important myocardial territory [122]. When performing bifurcation PCI in general, and in the provisional single-stent strategy in particular, it is imperative to keep in mind that long-term clinical outcomes are mainly dependent on the success of MB stenting. Therefore, optimization of results in the MB should take priority over "pre-eminence" of the angiographic result in the SB.

Given the tridimensional structure of bifurcations, it is impossible to avoid a foreshortening effect when trying to obtain a plane image of the three bifurcation segments. Consequently, it is necessary to record several views from various angles to obtain a comprehensive picture of the lesion characteristics, in order to carry out the technical procedure appropriately and assess the procedural outcome. [123] The SB take-off is the crucial point, which is rarely visualized adequately from two orthogonal views and may be explored from a single angle called "the working view". This view allows the visualization of branch division as well as the measurement of angles and assessment of the degree of ostial SB stenosis.

This is generally an anterior-posterior projection with marked cranial angulation for left anterior descending coronary artery (LAD)-diagonal bifurcations, a slight RAO or LAO projection with caudal angulation for circumflex-proximal marginal bifurcations or cranial angulation for dominant distal circumflex (Cx) coronary arteries, and an anteroposterior projection with cranial angulation for distal right coronary arteries. Intravascular imaging can provide additional important information in these situations. (Figure 3, optimal angiographic views for coronary bifurcation PCI).

The type of wire chosen for a bifurcation PCI and the branch which has to be wired first, depend on the lesion anatomy [121]. The wire could be "jailed" in the side branch during main branch PCI (predilation and stent implantation), so consideration of specific wire properties including use of hydrophilic wires and special bends including the "reverse wire technique" may be useful.

Hydrophilic wires might pass more easily but also increase the risk of dissection. Wiring the SB could be considered the standard approach, because it represents more frequently the most difficult branch to wire due to its tortuosity and angulation. In some cases, the SB is so small that, in the operator's opinion, its loss would be irrelevant, so the decides not to wire it. As this decision can be difficult to make when flow may be compromised by stenosis, an attempt to wire the SB should always be actively considered [123]. A narrow angle bifurcation, inferior to 70°, bifurcations with ostial SB disease, and bifurcations with smaller SB reference diameters are most likely to occlude after MB stenting. Factors increasing complexity in SB wiring include severe proximal MV stenosis, ostial SB stenosis, steep angulation and <TIMI 3 flow. Specific tools and techniques have been devised for wiring difficult SBs. Single lumen and especially dual lumen microcatheters can be useful to facilitate SB wiring in difficult cases. When initial wiring of the SB is impossible, plaque modification with balloon or rotablation may facilitate wire passage.

Predilation of the MB prior to stenting is the usual approach. It facilitates MB sizing and post-stenting treatment of the proximal MB segment, which may influence the long-term results of bifurcation stenting. Oversizing of the balloon should be avoided but it is important to observe optimal balloon expansion of the MB before stenting. When this does not occur, further lesion preparation and/or debulking is required before stent deployment. Predilation of the SB remains a subject of controversy. [123] It is generally preferable not to predilate the SB ostium, given that the occurrence of dissection inherent in the enlargement of the lumen of the SB ostium could increase the likelihood of unintended access to the SB through a proximal strut. This is based on the fact that plaque is most often distributed opposite the flow divider in the SB ostium, thus increasing the chance that the stent cell covering the small opening is actually a distal cell. Routine SB dilation is unnecessary but in the presence of severe ostial stenosis of the SB it should be considered.

Potential advantages of SB predilation may include increased ostial SB lumen, facilitated rewiring of the SB after stenting and avoiding rewiring and post-dilatation of the SB after implantation of the MV stent. Disadvantages of SB predilation include the risk of dissection with a potential increase in

the requirement for SB stenting [124]. Also, if the dilated SB ostium is not scaffolded by the MV stent, the risk of restenosis may be increased. Factors favouring SB predilation include suboptimal SB flow after wiring, extensive calcification and extensive SB disease extending beyond the ostium. Access through a distal strut is the only possibility for projecting struts in the SB in order to treat both the MB and the SB ostium with only one stent. Song et al [125] assessed the effect of SB predilation on outcomes for true bifurcation lesions using a provisional approach. After propensity score-matched population analysis, they observed that SB predilation could be associated with an increased risk of repeat revascularisation. However, Pan et al [126] reported that, after randomisation to either SB predilation or no SB predilation, the rate of SB rewiring failure, the time of rewiring, the number of wires used, and the incidence of major events were similar in both groups of patients. The only difference was a higher TIMI flow rate in the SB after MB stenting in the SB predilation group, but final SB TIMI flow and clinical outcomes were similar in both groups at the end of the procedure. When carrying out SB predilation, it is very important to assess the angiographic result carefully before MB stenting and to be ready to switch to another strategy (reverse provisional stenting strategy or DK-crush) in cases of dissection or difficult SB access.

Second-generation drug-eluting stents (DES) are recommended for bifurcation treatment. Selection of the most appropriate stent platform is essential and should be made according to the maximal expansion ability of the stent, in order to allow stent apposition both on the MB wall and on the SB ostium [127]. The maximal opening diameter of the MB stent at the SB ostium is also an important criterion for the most proximal bifurcations. The choice of stent diameter for MB stenting is crucial [128]: when too large (stent diameter selected according to the proximal MB reference diameter), it may significantly increase the risk of SB occlusion caused by carina shifting, or create a dissection in the distal segment. Stent diameter should be selected according to the reference diameter of the MB distal segment in accordance with the fractal law, the potential drawback being inadequate apposition of the stent on the proximal MB segment. However, this can be easily corrected by proximal optimization technique (POT) and/or kissing balloon inflation (KBI).

Another important criterion which has to be considered for MB stent choice, is the cell design, because, after MB stent deployment, we need to cross into the SB through the MB stent struts [121]. In the open cell design, the struts are stretched and displaced with SB balloon dilation, so that the opening becomes larger as the balloon size increases. In the closed cell design, on the opposite, there is not a progressive opening of all the stent cells with SB balloon dilation. This consideration has to be kept in mind in case of large SB ostium, because the maximal strut opening into the SB should not be too much smaller than the SB ostium diameter.

Proximal optimization technique (POT) is performed with the aim of achieving the correction of malapposition in the proximal MB; facilitation of the SB rewiring by modifying the orientation of the SB ostium and preventing the guidewire from entering the space between the stent and the vessel wall; facilitation of SB ostium scaffolding and restoration of the circularity of the proximal vessel. POT should be performed routinely after MB stenting to correct for stent undersizing in the proximal MB. A short NC balloon, 0.5-1.0 mm larger than the MB stent diameter (depending on the "step-down" diameter of the distal MB), is recommended for performing POT, by positioning the distal marker of the balloon in front of the carina and the proximal marker inside the proximal stented segment [122]. This parameter needs to be taken into account before choosing the MB stent length, in order to leave at least 6 to 8 mm of stent length proximal to the carina (the smallest length of commonly available balloons) [129]. Careful positioning of the balloon for POT is crucial and may influence the final result: if too distal, it increases the risk of SB occlusion; if too proximal, it has no effect on the stent strut towards the SB. Ideally, the distal shoulder of the balloon should be positioned just proximal to the carina while the proximal part is still in the stent in order to avoid geographical miss. [123] The main problem is that the positioning of the distal marker compared to the distal shoulder varies among the different balloons currently available. If the balloon does not span the entire stented proximal MB stent segment, it should be repositioned and re-inflated to ensure that the most proximal part of the stent is also sufficiently expanded. The diameter ratio between the balloon and the proximal MB reference segment should be 1/1. Thus, compliant or

non-compliant balloons can be used, depending on the diameter the operator wants to achieve. Inflation is performed at nominal pressure or higher in order to reach the appropriate diameter. As a result, the original anatomical configuration of the bifurcation is restored in compliance with the branching law.

Computer simulations and in vivo application have shown the other advantages of using POT in bifurcation lesion treatment [130]. First, by apposing the stent strut to the proximal MB wall, POT prevents the guidewire from recrossing into the SB between the arterial wall and the stent. Second, POT induces a constant increase in cell size area and modifies the orientation of the SB ostium. This phenomenon facilitates access towards the SB, and may also facilitate the distal recrossing (close to the carina). Consequently, POT is particularly helpful in instances of crossing failure with the wire. This also facilitates the recrossing of the balloon and sometimes the stent by reducing the friction towards the enlarged strut.

The fundamental advantage of the provisional SB stenting approach is that SB treatment remains an open option throughout the procedure. When the SB is small, a “keep it open strategy” is probably the best approach, starting by wiring both branches and stenting the MB. The same strategy can be applied when the SB needs attention regardless of the possibility that the operator may decide not to open the struts towards the SB, based on the POT results. If the operator considers that the MB stent struts should be opened, then the MB wire (or a third wire) can be used to enter the SB through the most distal strut and perform subsequent SB ostium dilatation followed by KBI and a final POT. If SB stenting is necessary, it should be followed by KBI, and the procedure should be finalised with a second POT [123]. After stenting the MB, rewiring may be necessary if there is impaired SB flow. Difficult SB rewiring may be facilitated by modifying the distal guidewire tip, using a guidewire with different characteristics or performing a new POT with higher pressure or a larger balloon if the first POT was inadequate [124]. If SB rewiring is not possible, a bailout technique is performed by leaving an uninflated balloon in the MB and advancing a low-profile 1.0 to 1.5 mm balloon catheter on the jailed wire. A “tunnel” can then be created to allow passage of an SB balloon. It is

essential to ensure final re-expansion of the proximal MB stent. Re-crossing into the SB in the distal portion of the stent promotes better ostial SB stent coverage and apposition. This can be achieved by "pullback rewiring" by advancing the guidewire with a bent tip into the distal MV and then carefully retracting the wire while turning and directing it towards the SB. Opening the distal strut (close to the carina) of the MB stent towards the SB improves SB ostium scaffolding and decreases the need for SB stenting. The wire position can be verified by optical coherence tomography (OCT). Reports have shown that using a non-compliant (NC) balloon is associated with a lower risk of SB dissection and better clinical outcomes.

After opening the SB ostium, it is strongly recommended that final POT or KBI should be performed, preferably with two short NC balloons sized according to the actual reference size of the vessels or 0.5 mm below. In order to avoid proximal MB stent distortion, it is recommended that the balloons should not be positioned proximal to the bifurcation core segment. A NC balloon is recommended for SB dilatation and should be sized according to the SB reference diameter to reduce the risk of dissection, after rewiring through the distal stent cell, as close to the carina as possible.

Isolated dilation of the SB after MB stenting may cause partial or complete jailing of the MB and is inadvisable [124]. Historically, a routine double balloon kissing strategy in single-stent treatment was considered. However, it is now clear that this routine approach has no clinical advantage despite the theoretical improvements in the restoration of bifurcation anatomy, expansion of the proximal MB, apposition of jailing struts and balloon dilation of ostial SB lesions [124]. This lack of evidence of benefit of routine kissing balloon inflation probably reflects the increased procedural complexity, the risk of SB dissection and the potential for accidental stent crush by proximal abluminal rewiring distortion. According to randomised data [131], routine KBI in provisional bifurcation PCI does not improve clinical outcome. However, in case of a severe stenosis of the SB ostium (>75%) or SB flow impairment (TIMI <3), reopening of the SB and KBI may restore normal flow to the myocardium subtended by the SB. By performing KBI, we correct strut

malapposition in the proximal MB and achieve a central position of the carina. When the flow in the SB is normal, discrete ostial SB pinching may not require further intervention and, prior to deployment of a further stent, use of a pressure wire can be considered. When SB pinching is discrete with normal flow, FFR measurement will usually reassure the operator that an SB stent is unnecessary. Often the acute ostial SB pinching will be caused by transient obstruction, speculated to be thrombus, plaque debris or vessel wall oedema, that may disappear over time. Distortion of the MB stent after kissing inflations is common and might result in a suboptimal outcome. An optimised sequence including a final POT (rePOT) has shown favourable results compared to finalising with kissing balloon only in bench testing and modelling. (Figure 4, Provisional stenting technique)

T STENTING TECHNIQUE

In case of a bifurcation lesion with a SB at a 90° angle, the T-stenting technique is commonly recommended because it provides complete coverage of the SB ostium [132]. A wire is placed in both the MB and the SB and a stent is deployed in the SB, with its proximal edge at the ostium being careful of not protruding it into the lumen of the MB. The SB wire is then removed, and a stent is deployed in the MB across the origin of the SB. Finally, a wire is re-advanced into the SB across the stent in the MB aiming for a distal cell crossing, and final Kissing Balloon inflation with two, ideally noncompliant, balloons sized appropriately for the SB and distal MV, is performed. MV preparation is at the operator's discretion. SB predilatation is discouraged unless considered essential. Stent diameter should be chosen according to the diameter of the distal MV segment. Proximal optimization treatment of the MV stent with a balloon size according to the proximal MV diameter is encouraged but not mandatory. After these steps, if one of the following conditions occurred:

- <thrombolysis in myocardial infarction 3 flow in the SB
- >90% ostial pinching of the SB
- threatened SB vessel closure

- SB vessel dissection >type A The operator is free to implant a second stent in the SB as a T-stent, with no, or minimal, stent strut overhanging into the MV.[133]. After placement of the stent in the main branch, rewiring and pre-dilatation of the side branch, the operator advances the second stent in the side branch and places a balloon in the main branch at the orifice of the side branch. Then, the stent in the side branch is meticulously positioned, taking care that the marker band and about the first half millimetre of the stent is within the main branch stent. When the optimal position of the side-branch stent is achieved, the operator can deploy the side-branch stent by a kissing balloon manoeuvre, first inflating the side-branch balloon with the stent and immediately afterwards the main branch balloon. Among the many approaches to bifurcation stenting, the T-stenting has the intention to avoid non-stented gaps at the orifice of the side branch with minimal stent distortion or stent overlap in the carina region. In the provisional T-stenting technique, the main branch is stented and final kissing-balloon dilatation with a balloon matching the size of the vessel is performed in all patients, even if there was no relevant side-branch stenosis. This is done to adapt the main branch stent to the orifice of the side branch and to facilitate access to the side branch, in case it will be needed in the future. Thus, final 'kissing-balloon' dilatation is performed irrespective of whether a routine or provisional T-stenting is performed [134].
  Figure 5: T stenting technique

T AND PROTRUSION (TAP) TECHNIQUE

The TAP stenting technique is a modification of the T-stenting technique aimed at optimizing "bail-out" SB stent implantation in bifurcation lesions treated with the "provisional" approach. Thus, according to the standard practice of TAP stenting, it is applied after the MV stent has been implanted and kissing balloon inflation has been performed[135]. The TAP technique is a modification of the T- stenting technique and is based on an intentional minimal protrusion of the SB stent inside the MV stent. The SB stent is deployed with a non-inflated balloon positioned in the MV across the SB take-off. After SB stent deployment, the SB stent balloon should be pulled back

a few mm inside the MV and inflated to flare the protruded part of the SB stent in the MV prior to KBI. KBI is performed with the stent delivery balloon and the balloon already positioned in the MV. The advantages of the TAP technique are compatibility with 6 Fr guiding catheters, full coverage of the side branch ostium and facilitation of KBI. This technique therefore ensures performance of KBI in all cases. The main drawback is related to the creation of a "metallic neocarina" of variable length, depending on the SB angle. T-stenting and TAP are recommended in bifurcations with wide angles (>70°). In TAP, the operator should try to limit the protrusion of the SB stent inside the MV and reduce the length of the neocarina. When final POT is performed in TAP, precise balloon positioning is crucial to avoid crushing the metallic neocarina. An anticipated pitfall of this technique is that a single layer "neocarina" is created by the SB stent struts protruding inside the MV at the level of the coronary bifurcation flow divider. Conversely, in the rest of the bifurcation area, TAP allows full stent coverage. A bench testing study comparing TAP with crush and culotte techniques showed that stent strut malapposition in the proximal vessel and the maximal wall-malapposed strut distance are significantly reduced by the TAP technique [136]. During TAP stenting, the operator should pay attention to and try to limit as much as possible the protrusion inside the MV, which influences the length of the neocarina. Nevertheless, two main determinants of neocarina length should be recognized: the SB take-off angle and the "quality" of pre-TAP kissing inflation. The impact of the SB take-off angle is quite intuitive: when the SB has a "T" shape take-off, small or absent SB stent protrusion inside the MV is needed to cover the SB ostium successfully. On the other hand, acute SB angles (Y-shapes) are associated with longer, oval-shaped SB.

The "quality" of pre-TAP kissing balloon inflation is probably less recognized but may theoretically have similar relevance.

Indeed, the site of the MV stent's side cells recrossing with the guidewire is known to influence the SB ostium scaffolding after kissing [137-138]. In particular, wider MV stent strut scaffolding at the SB ostium site is obtained when kissing ballooning follows distal rewiring. As a consequence, when

implanting a SB stent according to TAP (especially in acute angled bifurcations), a limited need of protrusion inside the MV is achieved with distal rewiring followed by kissing balloon inflation.

Moreover, when further MV and/or SB ballooning at the bifurcation site is needed, final kissing is recommended to ensure the "central" seating of the neocarina at procedure end. In contrast to other techniques, such as crush or kissing stenting, the TAP technique has been designed to optimize SB stenting in the setting of provisional procedures. However, due to its effectiveness, TAP stenting has also started to be considered by some operators as a valuable technique to treat bifurcation lesions, with the anticipated high probability of requiring double stenting. When planning a TAP stenting procedure in such high- risk anatomies (extensive disease, large SBs), the operator should aim to optimize the procedure course by carefully selecting the "operative" MV axis. As, by definition, it is necessary first to implant a stent across a major branch, it is mandatory to consider carefully the risk of "parent" branch closure after crossover stenting and to anticipate the easiness of "jailed" branch rewiring, dilation and stenting. In other words, TAP and so-called "inverted TAP" [139] are selected on a case by case basis. As a consequence, the first stent is usually implanted from the proximal MV towards the vessel which is more diseased, larger and/or more difficult to wire, regardless of its nomenclature (either distal MV or SB).

The main difficulty of a "perfect" TAP stenting procedure is the selection of an appropriate site for SB stenting. An intravascular ultrasound study clearly documented the variability of neocarina length obtained in clinical practice with a mean length of 2.7±1.4 mm [140]. In the case of a stent deployment site being unintentionally too distal, the failure to cover the ostium may be noticed. In such a circumstance, the operator may either accept the result or consider attempting another stent implantation according to TAP. The other main pitfall which may be encountered during TAP stenting is a protrusion inside the MV being accidentally too long; in this case, part of the SB stent protruding inside the proximal MV should be ballooned with an appropriately sized balloon (to try to adapt it to the proximal MV size). Then, the distal MV should be rewired in order to finish with a kissing balloon inflation.

Being relatively young, TAP stenting has not been selected as a technique to be investigated in any study design in the large prospective trials on coronary bifurcation lesions which have been conducted in recent years.

However, some data regarding the outcome of patients treated by TAP have been published recently by independent groups and, despite the overall high-risk pattern of the study populations enrolled, the reported clinical results look very promising [141-145].

Of note, intravascular ultrasound data showed that an optimal SB ostium dilation constitutes a critical issue with the TAP technique, since the SB ostium is the most frequent site of both post-procedural minimal stent area and largest neointimal formation [144]. Figure 6: TAP technique

DOUBLE KISSING CRUSH TECHNIQUE

The crush technique was firstly introduced by Colombo et al [146] and it has achieved multiple modifications during years, due to its potential limitations such as stent thrombosis and delayed endothelization. The mini-crush technique is recommended over classic crush to avoid the large area of three strut layers in the proximal MB [147]. The location of recrossing may affect the acute results of crush stenting, with potential gap formation at the SB ostium if recrossing is too proximal or too distal. Rates of successful kissing balloon inflation in crush stenting are 75-90% [148], thus lower than for culotte stenting. The double kissing modification (DK-crush) may aid recrossing into the SB after MV stenting. DK- crush also increases the expanded stent cell area in front of the SB detectable at follow-up[149].

Firstly, two wires are positioned distal in both the main and the side branch. The stent in the SB is positioned with its proximal end protruding 1-2 mm into the MB. Then, a balloon is positioned in the MB and the stent in the SB is deployed. Immediately after SB stent deployment, guidewire and stenting balloon have to be removed from the SB simultaneously.

Then, the balloon positioned previously in MV is inflated so that it is able to crush the stent at the ostial SB. The balloon in the MV is then pushed distally, the SB is re-wired through proximal struts and a balloon is advanced in it. So the first Kissing balloon angioplasty is performed, aimed to

expand the orifice of the side branch. The wire and the balloon from SB are withdrawn again. Then, the stent in the MV is positioned and inflated to further crush the side branch stent. Finally, a second kissing angioplasty is than repeated after second “proximal” rewiring and re-ballooning of the side branch [150]. The DK crush technique requires a 6 Fr guide, so it is simply used with work-horse setting for a routine PCI. The two kissing balloon inflations are easily performed because of the presence of only one layer of stent struts across the SB ostium. Moreover, DK crush is associated with a larger SB ostium opening thanks to the first KBI which is able to repair the distorted proximal segment of the SB stent. The re-wiring of the side branch is also more simple than in other bifurcation techniques because of the fewer metal struts present in the neo-carina. [151] Figure 7: Double Kissing Crush Technique

CULOTTE TECHNIQUE

The culotte technique consists of stenting one of two branches of the bifurcation lesion first, and after balloon dilatation of the stent meshes, stenting the uncovered branch through the first stent and leaving the proximal main vessel covered with two overlapped stents. Ideally, the procedure is terminated by kissing balloon dilatation of both branches [153]. In narrow angle bifurcations, if SB stenting is needed, either culotte or DK-crush techniques may be utilized. The culotte technique is better suited for bifurcations with similar diameters of the SB and the distal MB.

Two wires are inserted in the distal bed of the 2 branches and PTCA is conducted by sequential inflation of a semicompliant balloon in each branch using a balloon: artery ratio between 1 and 1.1. After balloon removal, the first stent is introduced in the MV and deployed using regular pressure. Stent length has to be chosen in order to cover the proximal part before the bifurcation, the ostium level, and the distal part after the bifurcation. A third wire is then used to recross the struts of the first stent towards the side branch using the first side branch wire as a marker. Afterward, the first side branch wire is removed between the wall and the stent. A balloon is used in the side branch in order to open the struts and prepare the way for the second stent. Sometimes it could be necessary to use a new balloon to cross the struts. A second stent of the same type as the first (but of different

length if lesion length is different) is then inserted crossing the struts of the first. This second stent is placed in order to cover the distal part and the ostium of the side branch, but also to widely overlap the first stent in the proximal part of the bifurcation. After deployment of this stent, a wire is replaced in the main branch and a simultaneous kissing balloon inflation is performed. [154]

Culotte can also be performed as an extension of a provisional single-stent strategy; after the SB is rewired, preferably re-crossing through the distal struts, the MB stent cell is opened by balloon inflation. Then, a second stent is deployed into the SB with minimal overlap with the proximal MV stent and followed by a POT. The procedure is finished with KBI. Culotte can also be performed starting with the SB stenting ("classic" culotte), with the advantage of deploying the first stent in the most angulated vessel first. [154] Figure 8: Culotte Technique

SIMULTANEOUS KISSING STENT

The simultaneous kissing stent technique (SKS) is a modified V stent technique proposed by Sharma et al [155,156]; it involves two stents, one in the distal main vessel (DMV) and one in the SB, with overlapping stents in the proximal main vessel (PMV) creating a new carina. This technique allows complete coverage of the SB ostium, relatively maintains the geometry of the bifurcation and avoids excessive deformation of the stents, but can be proposed only in large- size vessel bifurcations with a PMV that can accommodate two stents with a size at least two- thirds of the aggregate diameter of the 2 stents. To avoid retrograde dissection or rupture of the PMV, SKS implies, however, low-pressure simultaneous final inflation of the balloons, which may not ensure optimal final stent apposition. In addition, the long-term results and restenosis rate of SKS, which creates a new metal carina, have not been fully investigated.

A 7 or 8 Fr guiding catheter has to be used so that the two stents can be advanced simultaneously [156]. A first guidewire is advanced in the MV and a second guidewire is advanced in the SB. In patients with tight stenosis, predilation needs to be performed prior to stent positioning in the MV and in the SB. Two stents are then advanced, one in the MV and one in the SB. Stent lengths is selected in order to cover the lesions completely as well as creating a new carina inside the

proximal protective stent. The proximal markers of both stents has to be overlapped at the same level. After confirmation of stent positions, the two stents are dilated sequentially at 10 to 12 atm and then at 10 to 12 atm simultaneously. After these 2 first low-pressure inflations, the 2 balloons are then sequentially inflated at high pressure (15 to 20 atm) and finally inflated simultaneously also at the same level of high pressure (15 to 20 atm). In cases of non-satisfactory results, additional simultaneous kissing inflations can be performed with 2 noncompliant balloons at high atm. A modified SKS technique is used in cases with a long lesion in the proximal part of MV, before bifurcation. In such cases, a large stent is first deployed proximally over the guidewire in the MV. Then, wiring the side branch is performed via proximal stent and then advancing the two stents through the MV stent to distal MV and the SB and deployed in trouser-and-seat pattern.

Figure 9: Simultaneous kissing stent technique

DEDICATED DEVICES FOR CORONARY BIFURCATIONS

Many devices dedicated to bifurcation lesion PCI have been developed during last years, although most of them have never entered routine clinical practice. Yet, several devices raised the interest of some operators. The interest of interventional cardiologists for dedicated bifurcation devices has been hampered during the years by the practical difficulty to use them. Most of these devices have complex and asymmetrical design, implicating a more difficult placement that require high operator-skill, some have been specifically designed for SB treatment at first step, include balloon and self-expandable devices, require different size introducers and have different torsion and rigidity properties, implicating a limited use specially for treatment of bifurcations occurred during acute coronary syndrome [157].

The Tryton bifurcation device (Tryton Medical, Inc., Durham, North Carolina) was a bare-metal stent designed with different proximal and distal diameters designed for a “culotte technique” and first side-branch stenting. After preliminary satisfactory safety results from registries [158, 159], the randomized Tryton Pivotal Trial comparing the device vs provisional stenting/side branch balloon

strategy failed to show its non-inferiority in stable lesions, mainly related to higher peri-procedural myocardial infarction rate in the Tryton stent group [160].

However, its post hoc analysis restricted to lesions involving side-branch stenting with a reference vessel diameter ≥ 2.25 mm [161] supported the efficacy of the Tryton stent for treatment of stable bifurcation lesions involving large side-branches. Data on the use of Tryton stent in coronary artery bifurcation lesions occurred during ACS mainly have to be extrapolated from few international non-randomized experiences. A single-centre registry from the Academic Medical Center in Amsterdam reported one and two-year clinical follow-up data after Tryton stent implantation in 91 patients, of which almost a half (42%) had an acute coronary syndrome, but even in this experience the reported target-vessel failure rates were high [162]. Based on data available, Tryton stent may be considered in complex bifurcation anatomies with extensive disease in large side branches, but specific data are necessary in acute coronary syndrome patients specially when the device will be further improved by a drug-coating.

The sirolimus-eluting BIOSSR LIM stent (Balton, Warsaw, Poland) has a structure similar to the Tryton but it is designed to treat the main branch first; the device consists of two parts, the proximal larger than distal, joined with two connecting struts at the middle zone. In the randomized open-label multicenter POLBOS II trial, when compared with standard bifurcation treatment with DES, the BIOSSR LIM stent showed a similar cumulative MACE incidence (11.8% vs. 15%), and TLR rate (9.8% vs. 9%) at 12 months [163] in stable and NSTE-ACS coronary lesions; moreover, from an international registry its use resulted safe and feasible also in 74 patients with left-main stenosis including 20% NSTE-ACS patients [164]. However, due to its design the BIOSS LIM often requires side-branch rewiring and leaves the side-branch ostium uncovered, with absolute need of a second side-branch stenting which may represent a further difficulty in ACS setting.

The Axxess stent is a self-expanding biolimus-A9 eluting stent specifically designed to treat easily the complex anatomy of bifurcation lesions, with a rapid exchange catheter running over a single wire. This stent meets the idea to have available one dedicated bifurcation device that “might fit” all

or almost all bifurcation lesions. It can be used for many bifurcation types, with the only limitation being a bifurcation angle of 70° or less. After the early safety and intravascular imaging results [165,166], the 3-year clinical results reported from the Diverge trial were encouraging [167]. The MACE rate was 9.3% at one year, 14.0% at two years and 16.1% at three years. Individual events at three years were 10.1% for ischemia-driven TLR, 2.0% for cardiac death, and 7.4% for MI. ST rate was low, with 2.0% definite ST and 0.7% probable ST. Verheye et al. reported the five-year clinical impact of side branch stenting with a drug-eluting stent following Axxess stent implantation in 400 pooled patients treated with the Axxess stent. There were no significant differences in terms of MACE and its individual components of death, MI and ischemia-driven TLR at five-year follow-up between patients treated with side branch stenting following Axxess stent implantation and patients treated with a provisional strategy without stent. Moreover, there were no differences in definite ST after side branch stenting for Axxess plus side branch stent compared to Axxess only.

In the italian Carinax registry [168], a two-center study designed to evaluate the safety and efficacy of the Axxess stent in de novo bifurcation lesions compared to a propensity-matched population, 163 patients were enrolled, including 25% ACS, with angiographic success in all patients and no differences in intra-hospital and 12-month MACE between groups. IVUS analysis performed in only 21 patients showed inaccurate Axxess position in moderate-to-severe calcified lesions and in more distal lesions, suggesting to avoid its use in those cases. The randomized COBRA trial was designed to investigate the healing response of true coronary bifurcations after Axxess implantation in stable patients: limited from small sample size, it compared n = 20 patients receiving Axxess in the main vessel/Biomatrix stent in the side-branch vs n = 20 patients receiving conventional culotte technique, reporting no differences in malapposition or uncovered segments between the two strategies at 9-months OCT evaluation [169].

Therefore, most of experience with dedicated bifurcation devices embraces elective patients with stable coronary artery disease.

The STENTYS coronary stent is a self-apposing, nitinol, sirolimus-eluting stent (1.4 μg/mm² of stent) with a nominal strut width of 68 μm (0.0027") incorporated in a proprietary coating ProTeqtor®(Hemoteq AG, Würselen, Germany), a durable polymer matrix of polysulphone and a soluble polyvinylpyrrolidone that acts as an excipient [170]. The stent is compatible with a 6 Fr guide catheter and is delivered using a rapid exchange delivery system over a conventional 0.014" guidewire. The device is deployed by withdrawal of a retractable sheath and is available in three lengths (17, 22 and 27 mm) with diameters suitable for vessels ranging from 2.5-3.0 mm (small), 3.0-3.5 mm (medium), and 3.5-4.5 mm (large).

The APPOSITION IV trial [170] supports the use of the self-expandable sirolimus-eluting STENTYS for treatment of bifurcations in STEMI patients. Compared with the balloon-expandable zotarolimus-eluting stent, STENTYS resulted in significantly less malapposition and uncovered struts at four months after implantation with similar rates of apposition and coverage segments between groups at nine months, as assessed by OCT.

Luminal dimensions were significantly larger in the STENTYS group, with late loss being equivalent between groups, both at four and at nine months. Whether the use of the STENTYS can improve clinical outcomes in STEMI patients undergoing primary PCI compared to balloon-expandable stents needs to be proven.

By the way, it has to be taken in account that the impressive safety and efficacy reached by provisional stenting with latest-generation DES make the role of dedicated stents for non-LM lesions quite limited. Based on this, the EBC consensus was in favour of highlighting the treatment of LM bifurcation, due to its specific anatomic complexity, as the main field, which may theoreticcally benefit from technical improvements of dedicated devices. [171]

IMAGING IN CORONARY BIFURCATIONS

Due to the complex three-dimensional structure of bifurcations causing overlapping and foreshortening, conventional angiography has an inherent limitation in the quantitative assessment of bifurcation lesions. Intravascular optical coherence tomography (OCT) is an important

adjunctive tool for guiding coronary bifurcations with its unrivalled high resolution. Compared to angiography, intravascular OCT has a clear advantage in that it depicts ostial lesion(s) in bifurcation without the misleading two-dimensional appearance of conventional angiography such as overlap and foreshortening. In addition, OCT has the ability to reconstruct a bifurcation in three dimensions and to assess the side branch (SB) ostium from a three-dimensional (3D) reconstruction of the main vessel (MV) pullback. Although all the potential benefits of adequately using the OCT information are highly appealing, its clinical value remains to be established. The currently available clinical data regarding its use in the coronary bifurcartion lesions setting are based mainly on observational studies with a small number of patients [172].

Current OCT catheters are used with a standard 0.014-inch steerable guidewire with a monorail system. During image acquisition, typically, contrast medium is injected at a speed of 3-5 ml/s. With a pullback speed of 10-40 mm/s, image acquisition usually finishes in 5-10 seconds. Recent consoles enable an automatic detection of luminal border as well as online 3D reconstruction, which could foster the understanding of the complex anatomy of bifurcations [173,174]. In bifurcations, special attention is needed to acquire an optimal OCT image. Due to the difference in diameter of distal and proximal vessels, the scan range should be adjusted according to the size of the proximal vessel. The evaluation of a side branch ostium is often of interest; however, the guidewire shadow can hide the ostium partially or entirely. In such a case, repeat pullback after manipulation of the guidewire may be required. The nature of the bifurcation should be taken into account, including the tapering of the vessel according to conservation of flow and plaque distribution, especially on the opposite side of the carina. Predilatation of the SB is often necessary for successful OCT acquisition in the SB. The recent OCT consoles can co-register optical cross-section images with cineangiography acquired during a pullback, by automatic detection of the radiopaque marker of the optical lens on cineangiography. Practically, it is essential to acquire the cineangiography during the whole pullback, starting angiographic acquisition just before the start of pullback. In a complex bifurcation lesion, it is often challenging to co-register OCT and angiography accurately due to the

overlap and foreshortening of bifurcation anatomy on angiography [175]. It is important to select the angiographic view with the best visualisation of the bifurcation with minimal overlap and foreshortening. The online co-registration could help the operator to position a stent in a precise landing zone according to the OCT finding, and potentially reduce the risk of geographic miss as well as subsequent adverse outcomes. With two-dimensional (2D) imaging it is difficult and not always feasible to visualise the complex anatomy of the bifurcation and the effects of intervention. With 3D OCT it is easier to recognise the anatomical changes after intervention than with 2D OCT. For example, in the endoscopic 3D view of the coronary artery, it is possible to demonstrate the carina shift towards the SB after MV stenting, creating a stenosis at the SB ostium [176]. Preprocedural assessment of lumen and plaque distribution in coronary bifurcations with OCT may provide essential information on treatment indication and planning of PCI. Although the functional assessment of stenosis is a standard of care for angiographically intermediate lesions, interpretation of fractional flow reserve (FFR) results may be challenging, for example, in bifurcation lesions with proximal stenosis, or downstream stenosis due to the so-called “branch-steal” phenomenon [177]. There are several cut-off criteria of OCT-derived minimum lumen area (MLA) to predict significant FFR; however, such a threshold should be used considering the distal myocardial mass beyond each branch of the bifurcation lesion. In other words, there is no single threshold to be used [178]. Conversely, functional assessment without anatomical information cannot predict the anatomical changes after stenting (e.g., carina shift), which is essential for bifurcation PCI planning. Lipid accumulation tends to develop in the zone opposite the side branch. In a multi-modality assessment of bifurcation with IVUS virtual histology and OCT, the proximal rim of the ostium of the side branch was identified as a region more likely to contain thin fibrous cap and a greater proportion of necrotic core [179-180]. However, it remains to be demonstrated how we can integrate this information to guide bifurcation intervention.

Assessment of calcification by OCT could indicate which lesion preparation should be performed. Since calcification does not scatter light, OCT could evaluate the circumferential extension and the

depth of calcification. In general, extensive calcification on OCT is associated with suboptimal stent expansion, stent malapposition, and failure of device delivery. OCT assessment of the preprocedural bifurcation angle could be derived from OCT pullback in the MV. The carina tip angle is measured in a longitudinal view of OCT of the MV pullback as an angulation of the proximity of the carina. It has been demonstrated that the OCT-derived bifurcation angle has a good agreement with the computed tomography-derived bifurcation angle [181]. The preprocedural carina tip angle as assessed on OCT has an impact on side branch complication and strut coverage after stenting. The OCT study by Watanabe et al demonstrated that a carina tip angle less than 50° and a branching point-carina tip length less than 1.70 mm were independent predictors of side branch complication after MV stent implantation [182] (Figure 10: OCT in coronary bifurcations). In the side branch ostium region, a significant negative correlation was found between the uncovered strut percentage and OCT-derived branching angle.

It remains controversial whether lumen area (LA)-based measurement or external elastic membrane (EEM)-based measurement should be used as a sizing parameter. Due to the limited penetration depth of OCT, visualization of the external elastic lamina (EEL) is often not possible, especially in a large coronary vessel with significant plaque burden, or in a vessel with a lipidic plaque. In the randomized trials comparing IVUS and OCT (OPINION and ILUMIEN III), lumen-based and EEM-based algorithms were developed. In the OPINION trial [183], the reference site was set at a cross-section adjacent to the target lesion that was most normal looking and free of lipid plaque (defined as a signal-poor region with a diffuse border). Then, the stent diameter was decided by measuring the lumen diameter at the proximal and distal reference sites, and stent length was decided by measuring the distance from the distal to proximal reference sites. In ILUMIEN III [184], the mean of EEL diameters at the proximal and distal references was measured and the smallest of these diameters was rounded down to the nearest 0.25 mm to determine the stent diameter. When the EEL could not be visualized, the proximal and distal reference lumen diameters were used. It should be noted that both the ILUMIEN III and OPINION trials were not studies

dedicated to bifurcation. In the absence of sufficient clinical data dedicated to bifurcation, both methods (EEM and lumen area-based) could be used for sizing of a bifurcation lesion. It is important to avoid as a landing zone a segment with a large plaque burden or with a lipidic plaque. Whenever the vessel, especially the proximal vessel, is too large to measure the vessel area despite the maximal scan range, the lumen area-based algorithm is recommended. In a bifurcation lesion, it is important to select a stent size according to the tapering of the bifurcation, in order to restore fractal geometry with the law of flow conservation [185]. The choice of stent size should therefore be based on measurement of the reference site(s) in the proximal MV, the distal MV and/or the distal SB according to the stenting strategy. The MV stent should be sized according to the distal MV reference diameter, whereas the MV stent should allow for expansion to the reference diameter of the proximal MV [186]. In terms of stent length evaluation on OCT, the operator should aim to cover the bifurcation stenosis segment at least 6-8 mm from the proximal stent edge to the bifurcation carina, to enable the appropriate proximal optimization technique (POT) with the shortest available balloon when indicated. POT is currently recommended just after implanting the stent with the distal MV diameter, whatever complementary technique may be used.

In bench testing it was demonstrated that POT significantly reduced SB ostium strut obstruction, from 34.0% to 26.0%, concomitantly increasing the distal cell area ratio from 22.1% to 28.7% [187]. Following this recommendation, OCT from the SB could be used to evaluate the distribution of the calcified lesion in the side branch. In the presence of a severe ostial lesion in the SB, blood clearance is sometimes incomplete for obtaining clear OCT images in the SB. Therefore, predilatation with a small balloon may be required. After placing the stent in the bifurcation using either a one-stent or two-stent technique, kissing balloon inflations are used in order to form the stent in bifurcation fractal geometry [186]. To minimize the risk of struts being pushed inside the MV by kissing balloon inflation by creating a so-called de novo “metal carina” in the MV, it is important to rewire in the most distal cell of the jailed side branch ostium. The feasibility of OCT guidance in selecting the recrossing point and its potential benefit have been assessed in a few

studies. Alegria-Barrero et al [188] reported that, in 52 patients undergoing elective treatment of bifurcation lesions using provisional stenting as the default strategy, lesions that were recrossed with OCT guidance had a significantly lower number of malapposed stent struts, especially in the quadrants towards the SB ostium. In a prospective registry with 3D OCT acquisition in bifurcation, Okamura et al demonstrated that the feasibility of assessment of the guidewire recrossing point after MV stenting was 89.9% [189,190]. However, the evidence stemming from these two studies is limited to mechanistic observation. By the way, it is recommended that 3D OCT imaging on the recrossing position after main vessel stenting is performed before final kissing balloon, to ensure the optimal position of the wire. The repeated 3D OCT imaging should be performed cautiously taking into account the cumulative amount of contrast agent.

After PCI in a bifurcation, OCT is used to evaluate stent underexpansion, malapposition, tissue protrusion, dissection, geographic miss and thrombus [191]. Stent expansion is evaluated either as an absolute measurement of the minimum stent cross-sectional area or as a relative expansion compared with the predefined reference area. In a bifurcation, considering its fractal anatomy, stent expansion should be evaluated separately in the proximal MV, distal MV and SB, with respect to each reference area [192]. Larger stent expansion is generally associated with better clinical outcomes. It has been demonstrated that stent malapposition is more common at the proximal MV and tissue prolapse or dissection at the distal MV segment. In addition, previous studies have demonstrated the feasibility of 3D OCT for correction of eccentricity in the ostium area of the side branch [193-194].

In patients with complex bifurcation stenosis undergoing PCI with a dedicated bifurcation system, FKBI is associated with improved anatomical and functional results at the SB ostium, without compromising the result at the MB. In general, a small edge dissection found on OCT which is undetected on angiography most likely does not have a clinical impact [195-196]. However, the following factors need to be considered: the longitudinal (≥3 mm) and circumferential extension (≥60 degrees) of the dissection, the distance between the flap and the vessel wall (>200 μm), the

intra-dissection lumen area respective to the reference (<90%) and the depth of the dissection (media or even adventitia). With recent technical and technological advances, it is feasible to use OCT in guiding complex procedures in bifurcations. Although the recent clinical evidence starts to support OCT guidance, dedicated evidence for bifurcation treatment is still lacking.

CLINICAL OUTCOMES

Despite the major progress in stent technologies and adjunctive pharmacotherapies, the treatment of bifurcations is still challenging. Although the single stent strategy is associated with a reduced risk of untoward events [197] and is currently recommended, the double stent strategy may be required to guarantee the patency of both the main vessel (MV) and side branch (SB) [198]. In addition, it is unclear whether the clinical outcomes of PCI in bifurcations can be modulated by the choice of adjunctive P2Y12 inhibitor, the optimal duration of dual antiplatelet therapy (DAPT), as well as the selection of the stent platform.

The largest registry enrolling subjects who underwent PCI for a coronary bifurcation lesion reported the following findings:

- Clinical variables, as age, diabetes, ACS at presentation and reduced LVEF are independent predictors of outcomes.
- Among angiographic variables, beyond multivessel CAD, the length of SB lesion is independently associated with MACE, being more relevant than the sole SB involvement, as reflected by the Medina classification.
- Treatment strategy must be carefully selected, as a “bail-out” placement of a stent beyond planning is an independent predictor of adverse events.
- Adherence to medical treatment after complex PCI is of utmost relevance, as premature discontinuation of DAPT before 6 months in patients with SCAD and 12 months in patients with ACS is independently associated with MACE.

Among patients with coronary bifurcation, an ACS at admission identifies a subgroup with a high atherothrombotic burden, accruing a risk for adverse events far more relevant than angiographic

complexity as identified by the Medina classification [199]. COBIS II registry findings documented that ACS was significantly associated with SB occlusion after MV stenting [200]. Low LVEF is a ubiquitous risk marker associated with death both in patients with and without CAD [201]. Diabetes is a strong predictor of recurrences after DES-PCI, mostly in complex (type B2/C) lesions [202]; a patient-level analysis of the Korean bifurcation pooled cohorts [203] recently documented that diabetes was an independent predictor of target vessel failure, mainly TVR, in the treatment of bifurcations with double stenting. The presence of a coronary bifurcation is one of the main causes for lacking the accomplishment of a complete coronary revascularization in patients with multivessel CAD [204]. In the past, several "adjunctive" technique has been proposed for effective treatment of ostial and bifurcating lesions [205]. The core of the controversy for the treatment of coronary bifurcations has focused mostly during the last decade on the issue whether a single or a double stenting would be the appropriate treatment.

The consensus document of the EuroBifurcation Club [206] recommends the provisional single stent technique as the preferred strategy for the majority of bifurcation lesions and recommend stenting of the SB only for the presence of significant SB flow limitation or poor angiographic results in an SB supplying a significant myocardial territory; large SBs with significant extensive disease are likely to require a two-stent strategy. Double stenting is associated with an increased risk of MACE as compared with single stenting, but the true condition responsible for a heightened risk is the deployment of a stent beyond the planned strategy.

The use of "newer" P2Y12 inhibitors clearly documented a risk reduction of adverse events as compared with clopidogrel among patients with ACS [207,208]. Discontinuation of DAPT before the period recommended by current guidelines [209] was independently associated with adverse events in a real-world registry of coronary bifurcation PCI and it is associated with a thrombotic propensity of the target segment. In such complex procedures, the benefit/risk ratio of an extended DAPT has already been documented as favorable, with a magnitude of benefit that is progressively greater per increase in procedural complexity.

In patients undergoing PCI of a coronary bifurcation with currently available drug and stent technology, clinical variables, such as older age, diabetes, clinical presentation with an ACS and reduced LVEF are independent predictors of mid- term adverse events. Among procedural and treatment variables, multivessel CAD, length of the SB lesion, “bail-out” stenting beyond planning and premature discontinuation of DAPT before 6 months in patients with SCAD and 12 months in patients with ACS are independent predictors of untoward outcome.

These findings highlight the importance of a carefully planned PCI strategy in coronary bifurcations and advocate a strict adherence to medications with a close clinical follow-up [210]. Many clinical trials have compared a single-stent strategy (MV only with a provisional approach to SB stenting) with an up-front 2-stent strategy. At short- term follow-up, randomized controlled trials (RCTs) show overall similar efficacy between the 2 approaches; however, a provisional single-stent strategy (with bailout use of a second stent) demonstrates improved safety and lower costs [211]. Data emerging from Asia support the double-kissing (DK) crush 2-stent technique over provisional stenting, refueling the debate about the optimal treatment of these lesions. [212] A short-term focus on these patients did not find out important late complications (>1 year) including death, myocardial infarction (MI), stent thrombosis (ST), and target lesion revascularization (TLR). These important events may accrue particularly as the protective effect of dual antiplatelet therapy (DAPT) is withdrawn, unmasking sequelae of underexpanded stents and malapposed struts. The frequency of these outcomes may vary in the longer term, according to treatment strategy [213]. In a large meta-analysis, the use of a single- stent strategy was associated with shorter procedural time and less volume of contrast used. Crossover to 2 stents in the single-stent group occurred in 17.9% of lesions treated. Crossover to a single stent in the 2-stent group occurred in 7.6% of lesions. Compared with 2-stent techniques, the provisional single-stent approach was associated with lower all-cause mortality. The absolute risk difference in mortality was 1.29% lower with a provisional single-stent technique. There was no difference in MACE or MI between the allocated treatment

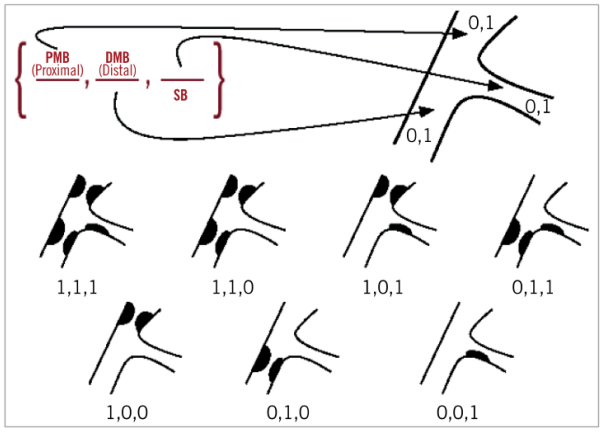
groups. These secondary end points at ≥12 months of follow-up were reported for 8 of the 9 RCTs in the analysis. There was no difference in TLR or ST.

In the aforementioned meta-analysis of randomized trials comparing treatment strategies for coronary bifurcation lesions, [213] there was a reduction in all-cause mortality at medium- to long-term follow-up in patients randomly assigned to an initial strategy of MV stenting only compared with up-front stenting of both the MV and SB. There was a 31% relative risk reduction in death at mean weighted follow-up of 3.1 years, extending to an overall 37% relative risk reduction at mean 4.7 years of follow-up. The provisional single-stent "less is more" approach is attractive and clinically impactful because of simplicity without compromising long-term outcomes. Overall, long-term all-cause mortality is low throughout the studies. Notably, there wasn't a difference in MACE, MI, TLR, or ST; therefore, the reason for the increased death rate is not immediately apparent. There are several reasons why this might be seen. One limiting assumption is that the differential mortality rates most likely reflect increased cardiac death from STs. Another potentially relevant mode of all-cause death in the 2-stent group relates to bleeding episodes, which would vary according to the duration of DAPT. Physicians choose to preferentially keep the 2-stent group on prolonged DAPT with inherent risks of bleeding related morbidity, and mortality in the long term. Indeed, a large meta-analysis of RCTs showed increased all-cause mortality in patients randomized to extended DAPT [214]. Bleeding events and duration of DAPT were not uniformly reported, so the precise cause of mortality is unclear. Data from non-randomized trials also support the more conservative approach of MV stenting only [215]. The provisional stent strategy still appears to be associated with a reduced mortality at medium- to long-term follow-up.

On the other hand, after 5 years of follow-up in the DK Crush II trial [212], patients treated with the 2-stent strategy had improved outcomes compared with MV-only stenting. This effect was largely driven by reduced TLR. Importantly, the DK crush studies may account for an important heterogeneity. Differences between these and other studies include more patients with acute coronary syndrome and left main coronary disease, as well as more frequent stenting of the SB in

the provisional stent group. Furthermore, there was increased use of final kissing balloons in the single-stent arm. The high crossover to 2 stents in the patients randomized to single stent may reflect an increased complexity of bifurcation disease in the DK crush trials and may explain the surprisingly high rate of ST in the provisional arm of DK Crush V [216]. Despite recent studies supporting a default 2-stent strategy for treatment of coronary bifurcation lesions, no one size fits all. All the studies and the meta-analysis so far supports the provisional single-stent strategy as the default approach for treatment of coronary bifurcation lesions. [213]

1.1



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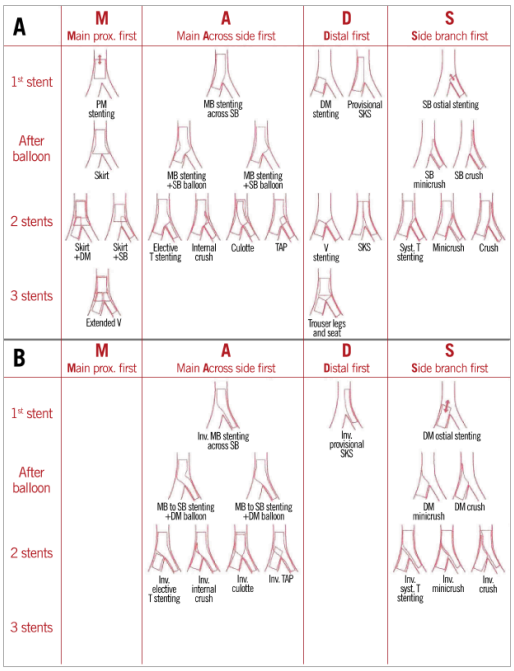


Figure 1: Medina and MADS

1.1 Medina Classification: the ciphers describe, the PMV, the DMV and the SB.
If the segment has a stenosis >50%,it is termed “1”, otherwise “0”

1.2 MADS Classification: it is grouped in families according to the number of stents implanted and the implantation order. “M” begins with a MV stent implantation; “A” begins with a MV stent implantation across the SB; “D” is for double stent implantation, simultaneously or not, “S” is for SB stent implantation first. In the box A there are “classic” techniques, the box B the “inverted” techniques.

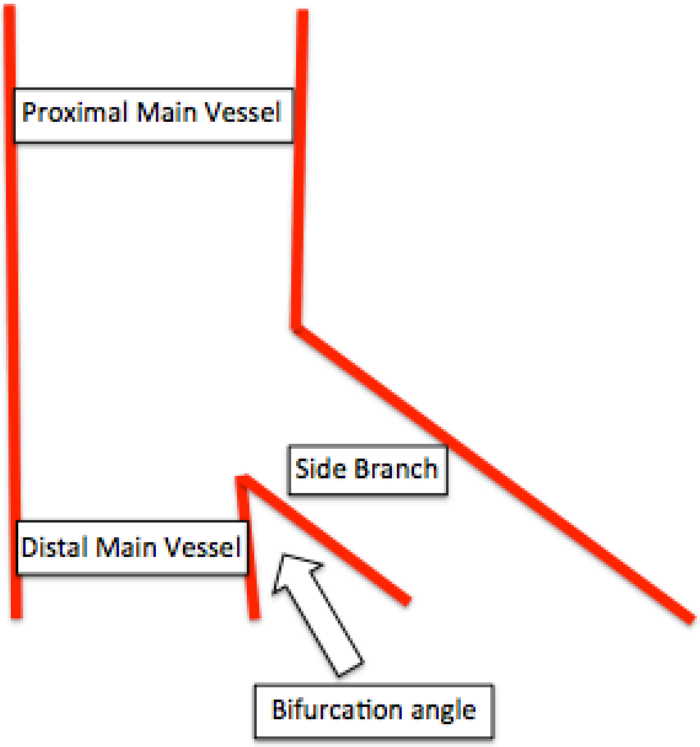


Figure 2: Coronary bifurcation anatomy
Schematic representation of a coronary bifurcation which is composed by : Proximal Main Vessel, Distal Main Vessel, Side Branch and bifurcation angle

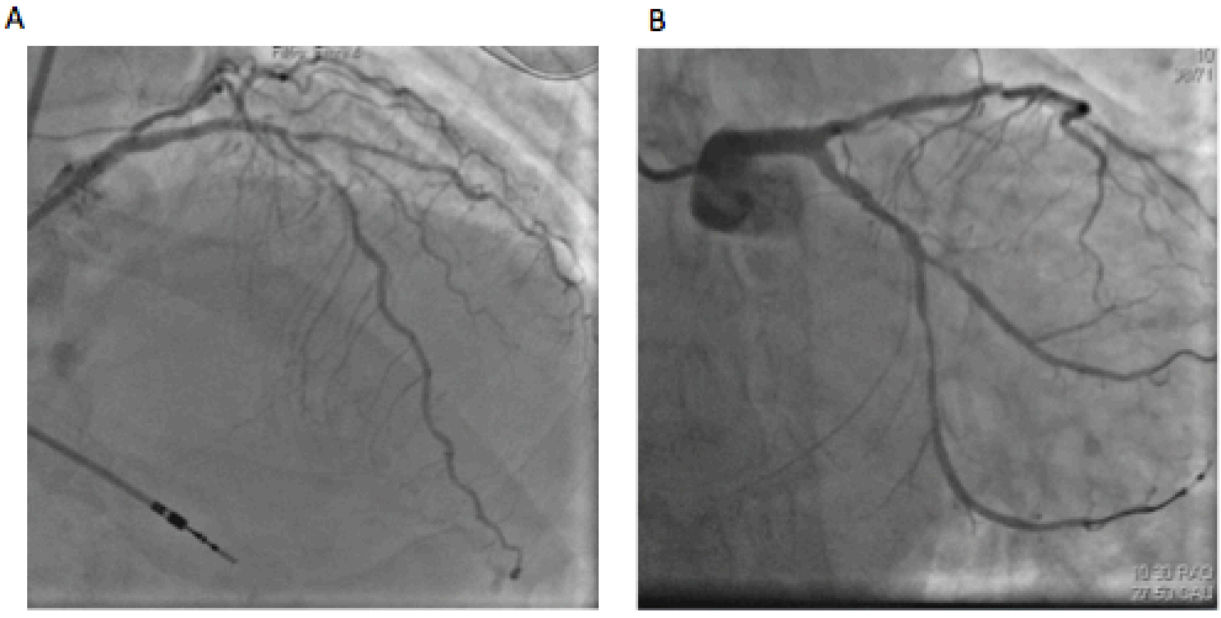


Figure 3: Optimal angiographic views for coronary bifurcations PCI.
A: Antero-posterior cranial is usually the best view for LAD-diagonal bifurcations
B: Antero-posterior caudal or RAO-caudal are the most used views for CX-OM bifurcations

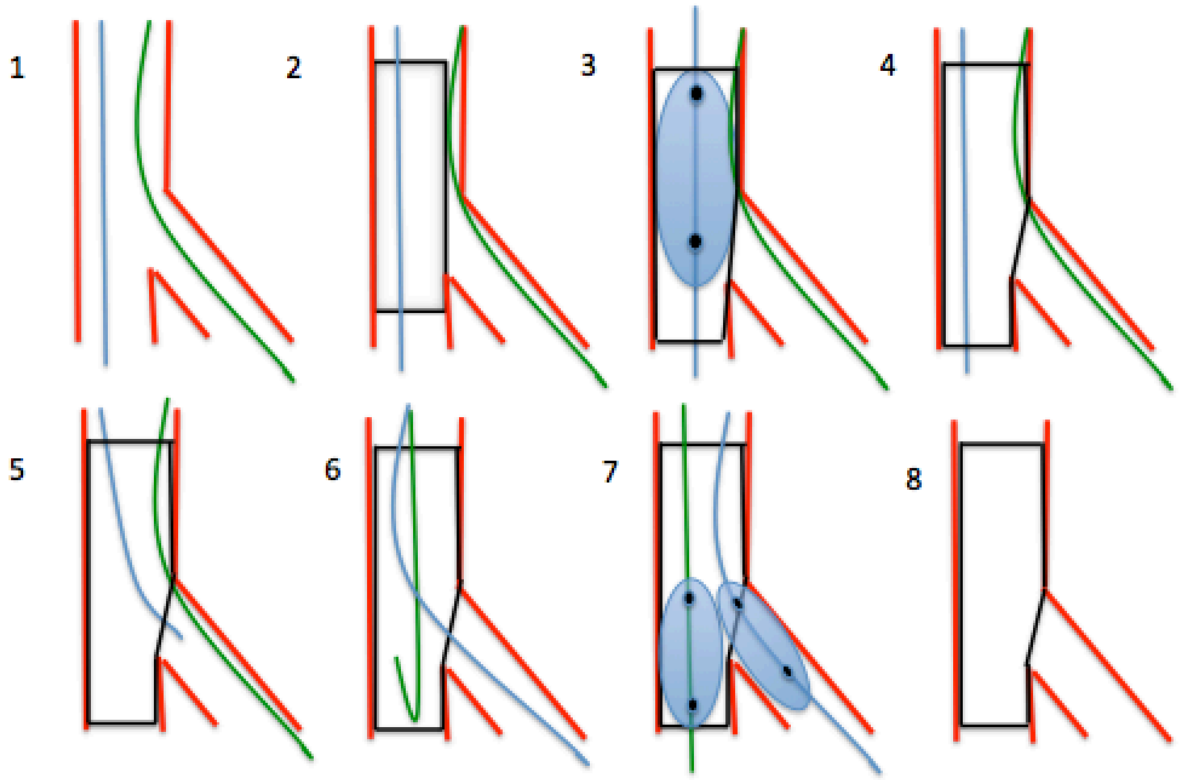


Figure 4: Provisional stenting technique
1: two wires placed in the MV and in the SB; 2: MV stenting sized according to distal diameter; 3-4: Proximal optimization technique (POT); 5: access in the SB towards the distal strut; 6: wire exchange; 7: final kissing balloon inflation; 8: Final result

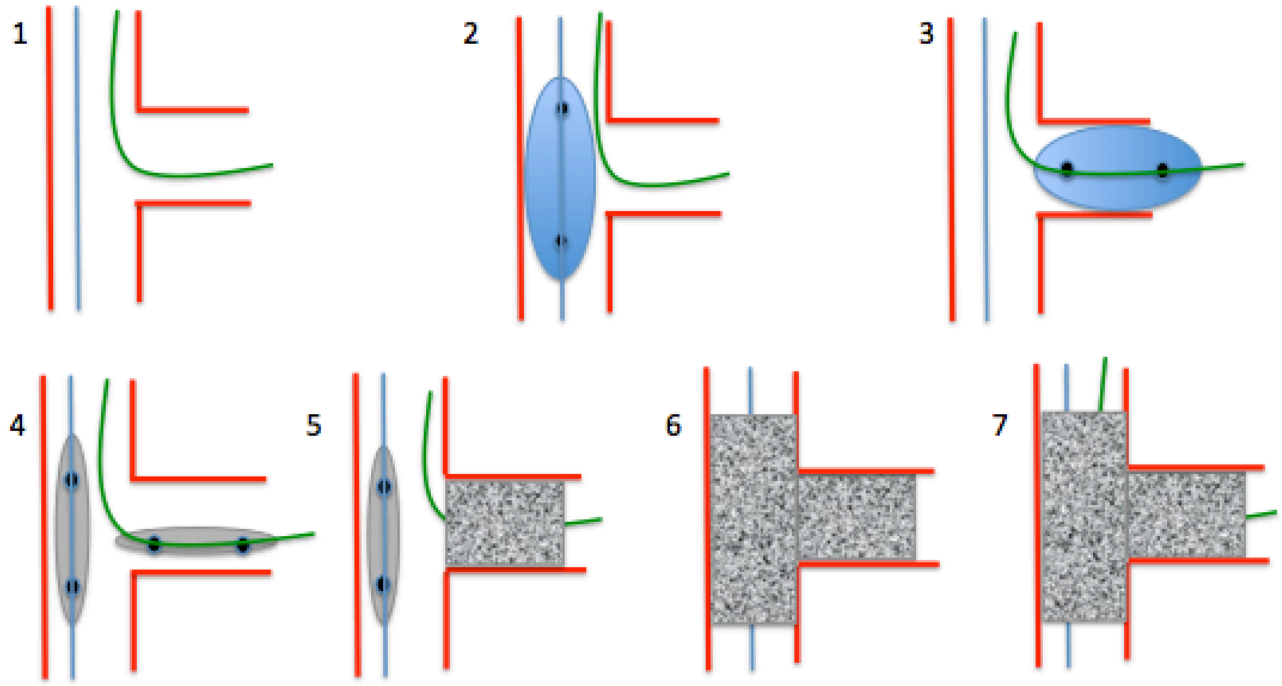


Figure 5: T stenting technique
1: two wires are placed in MV and SB; 2: predilation of MV; 3: predilation of SB; 4: positioning of both unexpanded stents; 5: deployment of the stent in the SB; 6: deployment of the stent in the MV after the removement of the wire in the SB; 7: recrossing of the wire in a distal strut of the MV stent and optional final KBI

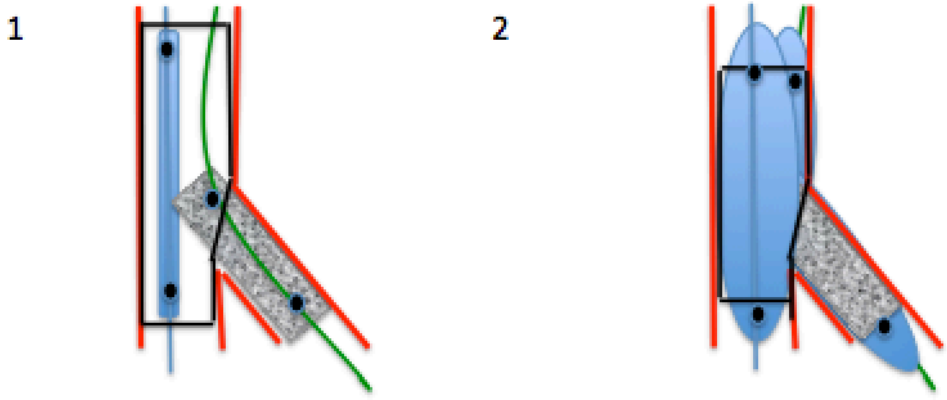


Figure 6: TAP technique.
After the placement of the stent in the MV with provisional strategy, a stent in the SB may be necessary in "bail-out" situations.
1: Deployment of the stent in the SB with minimal protrusion; a balloon is placed uninflated in the MV;
2: Final Kissing Balloon inflation.

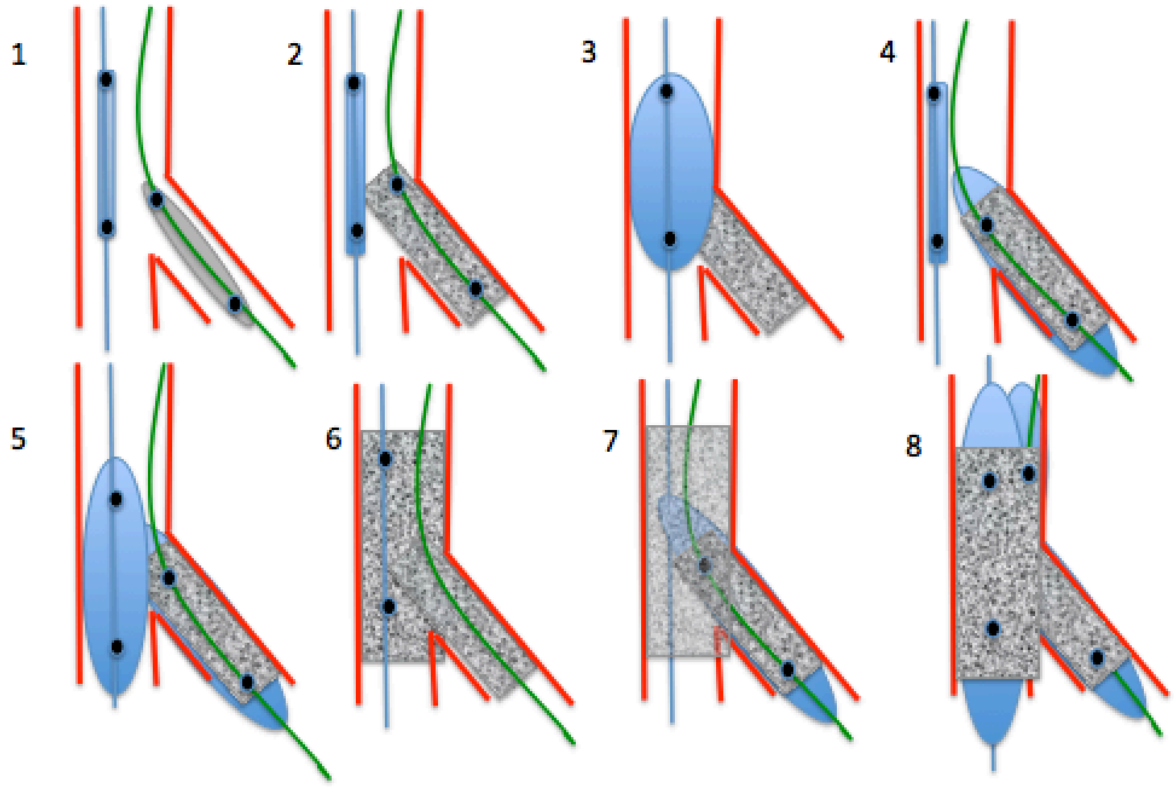


Figure 7: Double Kissing Crush Technique.
1: A balloon and a stent are positioned uninflated respectively in the MV and in the SB, 2: the stent is deployed in the SB with a small protrusion and the wire is removed; 3: the balloon in the MV is inflated to crush the stent in the SB;
4: rewiring in the SB and postdilation of the stent; 5: first Kissing balloon inflation and removal of the wire in the SB ;
6: Deployment of the stent in the MV; 7: rewiring in the SB towards the MV stent struts and postdilation in the SB stent;
8: Final Kissing Balloon inflation

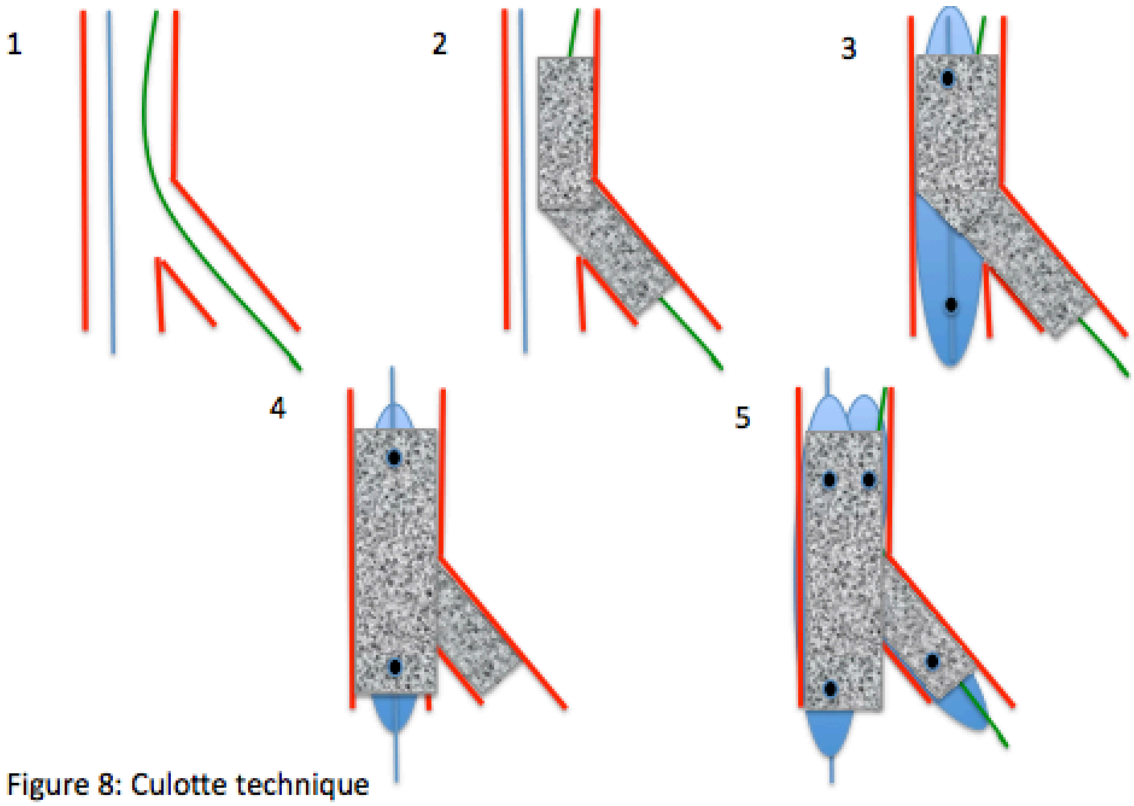


Figure 8: Culotte technique
1: Two wires are placed in the MV and in the SB; 2: A stent is implanted in the SB across the PMV; 3: Rewiring in the MV and postdilation of the proximal part of the stent;
4: Deployment of the stent in the MV with some proximal overlap; 5: Rewiring in the SB and final Kissing Balloon Inflation

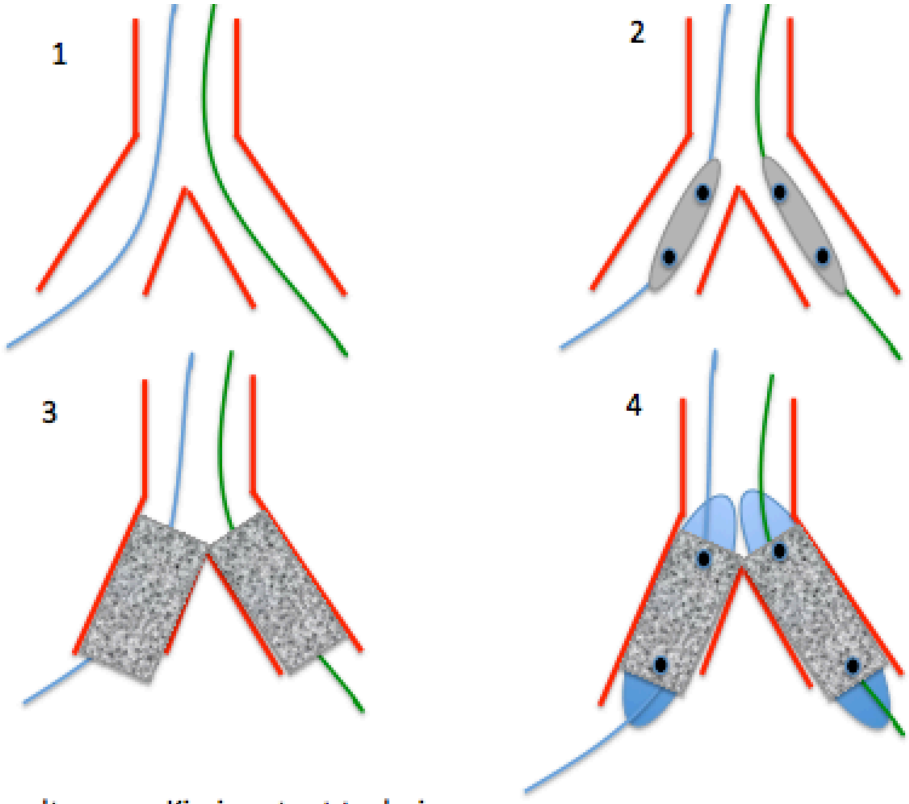


Figure 9: Simultaneous Kissing stent technique
1: two wires are placed in the MV and in the SB; 2: two stent are placed in the MV and SB; 3: the two stents are deployes simultaneously; 4: final Kissing balloon inflation is performed

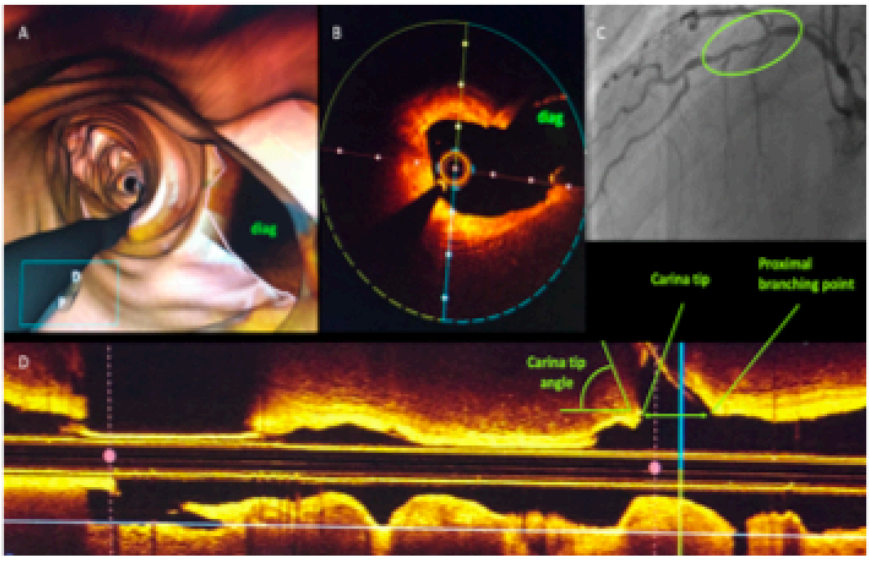


Figure 10: OCT in coronary bifurcations.
LAD long lesion with bifurcation involvement (I diagonal) seen with 3D reconstruction OCT (A), short axis OCT view (B) and angiography (C).
In the bottom panel (D) an OCT long view is shown with the main reference points for bifurcation assessment highligthed (carina tip, proximal branching point, carina tip angle).

Bifurcation device	Design	Clinical data (ACS data available in bold)	Advantages in ACS	Disadvantages in ACS
BiOSS LIM (Balton, Poland)	Balloon-expandable paclitaxel eluting stent; new-available Sirolimus-stent; biodegradable polymer, similar to Tryton but designed for main-branch stenting at first step; central thin part connecting the proximal and distal device structure;	In the POLBOS II randomised trial, the sirolimus eluting device showed similar MACE (11.8%vs15%) and TLR (9.8%vs9%) rate at 12 months compared to DES implantation, **included stable and NSTE-ACS pts.; One international registry reported the safety and feasibility in 74 patients with left-main stenosis including 20% NSTE-ACS patients.**	Developed for MV stenting at first	Complex structure; Requires SB rewiring; risk of wire twist; Suboptimal SB ostium coverage; requires SB stenting for optimal treatment
Tryton™ (Tryton Medical, Inc., NC, USA)	Balloon-expandable stent; cobalt-chromium thin strut; designed for culotte technique and side- branch stenting at first step. Radio-opaque markers.	Despite excellent FIM study results, (6 months late loss 0.17 mm, TVR rate 3%), randomized Tryton Privotal Study failed to show non inferiority results vs provisional stenting with mandatory SB dilatation (TVF was 17.4% in Tryton group vs 12.8% in the provisional group; IVUS substudy showed favourable results with no differences in MV and SB luminal area at 9 months between two groups. **One long-term single-centre experience enrolling 91 pts. with 42% ACS, reported high TVR rate at 1 and 2 year follow-up.**	6-French introducer required; Radio-opaque markers.	Developed for side-branch stenting at first; balloon expandable not adapting to carena; precludes the use of a provisional strategy as by design the Tryton requires a double stenting technique with DES in the MV.
Axxess™ (Devax Inc., CA, USA)	Self expandable stent; conical shape; biolimus A9-eluting stent; designed for MV stenting ending into the carena-proximal SB; Radio-opaque markers.	Studied in 302 pts. with de novo bifurcation stable lesions in the DIVERGE trial; SB was stented with DES Cypher in 64.7% pts.; restenosis rate at 9 months was 6.4% and late loss 0.17 ± 0.34 mm in the SB. MACE rate was 7.7% including 4.4% TLR at 9 months. **The Carinax registry** evaluated the safety and efficacy of the Axxess stent in **163 pts. with de novo bifurcation lesions including 25% ACS**, with angiographic success in all patients, **but no data are reported regarding the ACS patients treated in this registry.**	Developed for MV stenting at first; fast deployment; adapts its conical shape to carena; rapid exchange catheter over a single wire; SB recrossing and kissing balloon not required; proximal and distal radio-opaque markers; provisional stenting not precluded	7-French introducer required
Stentys ™ (Stentys SAS, Paris, Frances)	Self expandable syrolimus eluting stent; designed for MV stenting; The design allows for strut disconnection after balloon redilatation, requires SB rewiring	OPEN I trial enrolled 40 pts. with de novo stable coronary artery lesions, MACE rate at 30 days was 5.1%. OPEN II study in >200 patients confirmed excellent 4-year clinical data. **Apposition IV trial comparing Stentys SES with DES Resolute in STEMI patients showed favourable results**, with minimum late loss 0.24 mm and excellent stent apposition at 9 months evaluated by OCT.	Developed for MV stenting at first; provisional stenting not precluded. Favourable results in STEMI patients compared to Resolute stent.	Requires SB rewiring;

TABLE 1: Bifurcation dedicated devices: design, major clinical data available and advantages /disadvantages if used in true bifurcation lesions during acute coronary syndrome.

CHAPTER 4: PHARMACOLOGICAL THERAPY IN CATH-LAB

1) Other drugs, from vasospasm to hypertensive crisis.

1. Introduction

Technological development allows continuous important improvements in cardiovascular procedures outcomes in the catheterization laboratory. However, adjunctive pharmacotherapy remains a cornerstone for the management of complications in emergency clinical scenarios and the number of safe and effective drugs is constantly increasing [217].

Indeed, drugs remain essential in preventing potential complications during both diagnostic and interventional procedures and in optimizing the mechanical reperfusion therapy. Furthermore, the interventionalist must be prepared and able to medically manage an unparalleled range of conditions, ranging from diabetes and chronic kidney disease to complications such as hypotension, arrhythmias, and anaphylaxis which take place in the catheterization laboratory.

Thus, pharmacologic agents represent one of the most important explanations for the constantly improving procedural success rates and the purpose of the present chapter is to review these agents [218].

2. Conscious sedation

Subjects undergoing percutaneous interventions usually experience anxiety and psychomotor agitation which represent a limit common to all procedures not using general anesthesia. In such patients, it may be useful to perform sedation before and during the procedure. Also, sedation helps to relief anxiety and the associated sympathetic response possibly reducing vasospasm. The most used drug is the short- acting benzodiazepine midazolam. The recommended dose is 1-2.5 mg every 2'-3 ', avoiding exceeding the 5 mg dose [219].

3. Management of radial artery approach

The benefits of the transradial approach for percutaneous coronary intervention have been well documented in the past several years [220-230]. Technological advances in the field of interventional cardiology, as well as extensive experience with the transradial technique have

resulted in success rates that now approach that of femoral procedures [230]. In Figure 1 there is a full description of the radial artery puncture technique.

Adequate local anesthesia is essential for a successful catheterization. Inadequate anesthesia leads indeed to poor patient cooperation and makes the time in the Cath-Lab unpleasant for both patients and operators [217]. Local anesthesia is provided with subcutaneous lidocaine. Only small dosage is usually administered to get radial access (1–2 cc). Fentanyl in 25 mg increments can be administered intravenously to control any other patient discomfort during the procedure.

The radial artery is a muscular vessel with a rich supply of alpha-1 adrenoreceptors [231]. Smooth muscles cells within the vessel wall contract in response to stimulation of these adrenoreceptors, resulting in a significant reduction in lumen diameter. The radial artery has been classified as a type III vessel, reflecting the high rates of spasm found with this vessel as compared to others [232]. Circulating catecholamines and mechanical stimulation result in significant vasospasm, which can prevent arterial access and interfere with catheter manipulation causing significant patient arm discomfort. Thus, prevention of vasospasm is mandatory for successful transradial procedures [218].

During the puncture on the radial artery and throughout the procedure, a variety of stimuli may result in artery spasm. He and Yang demonstrated rapid, prolonged in vitro relaxation of radial artery segments collected from patients undergoing coronary bypass surgery after a combination of verapamil plus nitroglycerin [233-234]. Subsequent in-vivo studies have confirmed that this combination substantially reduces the incidence of vasospasm in patients undergoing transradial procedures and is more effective than other agents [235-236]. For this reason, prophylactic use of such pharmaceutical agents (Verapamil 2.5 mg and/or Nitroglycerin 0.1–0.4 mg) are routinely used and are best given directly in the radial artery immediately after vascular access. One other possible radial cocktail administered includes 2 mg of Verapamil (0.8 ml of a 5 mg in 2 ml preparation), 200 mcg of nitrate, 1 ml of 1% lidocaine and 1 ml of bicarbonate [217]. This solution may cause burning and is thus administered incrementally with further dilution using blood withdrawn from

the arterial sheath. Vasodilation occurs immediately as seen using radial artery intravascular ultrasound [237]. In one study, radial artery area increased of 44% after the administration of verapamil plus sublingual nitroglycerin with only a moderate reduction in mean arterial pressure and no significant change in heart rate [237]. Without the use of the spasmolytic cocktail, vasospasm will cause arm pain in a significant number of patients [235-236]. Particular caution in using spasmolytic cocktails should be used in patients prone to hypotension related to these agents, such as those with severe aortic stenosis. Although there is no strong evidence demonstrating superiority of any pharmacologic regimen, it has been demonstrated that lack of pretreatment is associated with symptomatic spasm in up to 30% of cases [238].

As previously mentioned, mechanical stimulation may evoke radial artery spasm. This particularly may occur after initial unsuccessful attempts to cannulate the vessel. In a recent study, the local subcutaneous administration of 400 mcg nitroglycerin resulted in a rapid return of pulse and facilitated cannulation [239]. The use of hydrophilic arterial sheath also reduced patient arm discomfort [240,241]. Presumably, the increased lubricity of the sheath resulted in less mechanically induced vasospasm.

Magnesium sulfate has been evaluated as a spasmolytic agent with potential additional advantages in terms of analgesia and neutral hemodynamic impact [242-243]. Magnesium sulfate, administered as a 150 mg intra-arterial bolus over 1 min, resulted in a 36% increase in radial artery diameter with a reduced hemodynamic effect compared to verapamil. Phentolamine 2.5 mg administered intravenously has been used by some physicians as a radial vasodilator [244]. Unfractionated heparin (2500-5000 international units) is also usually given even during diagnostic procedures (dose, timing and route of administration determined by operator) to reduce the risk of radial occlusion [217].

4. Coronary vasodilators

Nitrates acts as coronary arterial vasodilator and venodilator, dilating both normal and stenotic vessels with diameter > 100 μm with multiple uses in the cath lab. They redistribute the flow

through the collateral circulation and from the epicardial to the endocardial region. Among other, Nitroglycerin can be administered via the intra-arterial route to relieve coronary spasm and prevent spasm from intracoronary tools such as intravascular ultrasound catheters or coronary wires. Nitroglycerin relieves angina and mitigates heart failure by causing coronary dilation and reducing preload and afterload. Effects occur within 2 minutes and resolve within 5 minutes by discontinuation.

Nitroglycerin can be administered via the intracoronary (IC), intravenous (IV), transdermal, and sublingual routes. Typical doses range from 50 to 300 mcg IC, 20–200 mcg/min IV, and 0.3 to 0.4 mg sublingual. Doses can be repeated until the desired effect is generated or hypotension develops. Intracoronary administration of nitrate should be routinely made during coronary angiography prior to cine acquisition [245]. A dosage of 10-50 mcg is associated with a selective coronary vasodilation; with an IC dosage of 100-200 mcg there is a mild systemic hypotension and for dosages > 250 mcg there is an increased risk of hypotension without coronary flow augmentation. Of note, nitroglycerin is not effective in vessels of less than 200 microns in diameter. Nitroglycerin therefore should not be used to treat no-reflow phenomenon unless there is superimposed epicardial vasospasm.

Contraindications to the use of nitrates are obstructive hypertrophic cardiomyopathy, severe aortic stenosis, right ventricular infarction, hypotension, constrictive pericarditis, tamponade and severe anemia. Adenosine is the drug of choice to obtain microcirculation maximal hyperemia. It can be used for both diagnostic purposes, during Fractional Flow Reserve (FFR), or for therapeutic purposes, as for prevention and treatment of the no-reflow phenomenon. It is a degradation product of ATP or cAMP and is synthesized in physiological or pathological conditions that require an increase in metabolic

demands due to its powerful vasodilatory properties on the microcirculation. Of note, when an epicardial coronary stenosis occurs (50-90%), there is a proportional reduction in the vascular resistances downstream aimed to maintain a steady blood flow at rest. Adenosine administration, in

this condition, leads to a global vasodilation in myocardial arterioles, but the effect will be much lower or completely null in the arterioles downstream of the stenosis because these are already dilated in rest conditions. This determines a diversion of the flow towards the healthy vessels at the expense of the tributary microcirculation of the conductance vessels presenting an epicardial stenosis. This phenomenon determines a kind of "theft" in the region of myocardium subtended to the stenotic vessels and possibly generates ischemia.

As said, intravenous adenosine (at the dosage of 140 mcg/kg/min) is ideal to obtain maximal hyperemia during functional evaluation of coronary stenoses with FFR because it is able to induce stable and relatively fast hyperemia (60-90 sec from the beginning of the infusion) which is persistent during the infusion. Adenosine's side effects are chest discomfort, dyspnoea and heating. From a haemodynamic point of view, there is a 10-20% drop in blood pressure with a consensual reflex increase in heart rate (unless the direct bradycardia effect of the drug itself prevails). The effectiveness of the drug can be hindered by the administration, in the previous 24 hours, of methylxanthine (caffeine) or aminophylline (theophylline) by possible competitive block of A2A receptors. Intra-coronary adenosine reaches the peak within 10 sec from the administration but its effect lasts for less than 20 sec. It represents a more rapid and cheap approach for hyperemia induction, without the systemic side effects caused by iv administration; on the other hand, there is a high risk of transient AV block (especially when the drug is administered in the right coronary artery).

Optimal dosage of ic adenosine for prevention or treatment of no-reflow has not been established yet; an advisable approach is to test progressively increasing doses (ie from 60 to 600 mcg), switching to iv administration if AV block occurs. The most frequent adenosine dosages are 100 mcg for right coronary artery and 200 mcg for left coronary artery.

5. **Prevention of contrast-induced acute kidney injury** Contrast-induced Acute Kidney Injury (CI-AKI) represents a possible complication in patients undergoing diagnostic and interventional procedures with use of contrast media. Efforts to stratify the risk of each patient to develop CI-AKI

should be performed [246]. Factors associated with higher incidence of CI-AKI are a low estimated glomerular filtration rate (eGFR <60 mL/min per 1.73 m2), diabetes mellitus and contrast media dose. Further, dehydration secondary to inadequate fluid intake or diuretic agents increase the risk. Thus, adequate hydration and withdrawal of any potentially nephrotoxic medication should be performed prior to the procedure. Conversely, hydration with isotonic saline has been demonstrated to reduce the rate of CI-AKI. A common hydration protocol employed by several Cath Labs to prevent CI-AKI consists in the intravenous (IV) administration of 1.0–1.5 ml/kg/h of isotonic saline for 3–12 hours before and up to 6–12 hours after contrast media exposure. According to the randomized POSEIDON trial, a hydration protocol based on measured haemodynamic demonstrated to improve clinical outcomes up to 6 months. Hydration with normal saline personalized on the basis of left ventricular end-diastolic pressure resulted in a significantly lower rate of death, myocardial infarction (MI), or dialysis at 6 months compared with standard hydration (3.1% versus 9.5%; RR 0.32, 95% CI 0.13 to 0.79) [247]. The use of a bicarbonate-based hydration (NaHCO3 3 ml/kg/h for 1 h before and 1 ml/kg/h for 6 h after procedure) also demonstrated some reduction of CI-AKI incidence but its use did not result in significant benefit in terms of death or dialysis incidence [248].

6. Premedication for patients at high risk for anaphylactoid reaction to contrast media

Steroids and histaminic receptor 1 antagonists (H1 blockers) are the basic components of most premedication regimens for patients at high risk for an anaphylactoid reaction to contrast media. Prednisone 50 mg per os should be administered 13, 7 and 1 hour before procedure together with diphenhydramine 50 mg per os 1 hr before procedure. This is effective in the reduction of recurrent anaphylactoid reactions to standard contrast agents [249].

7. Acute Heart Failure/Cardiogenic Shock

Patients presenting with acute heart failure can be essentially classified in 2 groups: patients with acute pulmonary edema and those with cardiogenic shock. Vasodilators and inotropic agents represent the main therapeutic drugs to treat patients with acute heart failure. Nitrates work by

increasing vascular cyclic GMP and NO. Their major effect is venous rather than arteriolar dilation, thus being most suited to patients with raised pulmonary wedge pressure and clinical features of pulmonary congestion, acute pulmonary edema. Nitroglycerin can be administered IV with a starting dose of 0.3 to 0.5 μg/kg body weight per min.

Intravenous sodium nitroprusside remains the reference vasodilator for severe acute low-output left-sided heart failure caused by mitral or aortic regurgitation, because it acts rapidly and has a balanced effect on the afterload and preload, dilating both arterioles and veins. Indications include the following situations: (1) severe acute-on-chronic heart failure, especially with regurgitant valve disease; (2) hypertensive crisis; (3) dissecting aneurysm. Contraindications include preexisting hypotension (systolic < 90 mm Hg, diastolic < 60 mm Hg). Sodium nitroprusside need careful continuous monitoring for its light sensitivity, and for the severe risk of cyanide toxicity [250]. Sodium nitropusside can be administered IV with a starting dose of 1 to 10 μg/kg body weight per min, which has to be adapted according to the hemodynamic response.

In cardiogenic shock with acute pulmonary edema, an important drug is morphine. It is an opioid agonist with analgesic effect. It induces sedation and reduces preload. The initial dose is 2-5 mg e.v or i.m. (1/3 fl, 1/2 fl) repeatable every 5', not exceeding the dose of 30 mg. The contraindications are severe hypotension and asthmatic crisis. The antidote is naloxone (0.4-2 mg every 2 min untill max 10 mg in 30') [219]. Other therapeutic options for cardiogenic shock with pulmonary edema are high flow oxygen therapy and high doses of intra-venous diuretics, like furosemide. Drugs used for the acute treatment of shock are amines. Sympathomimetic agents act on the acutely failing heart stimulating several receptors. The β1-stimulation has an inotropic effect, β2-stimulation has afterload reduction (peripheral arterial vasodilation), while the α-stimulation restores the pressure. However, these agents may be associated with some side effects. For example, the β1-effect may precipitate arrhythmias and tachycardia, which can potentially increase ischemia, which is very important in MI patients. Excessive α-effects increase the afterload as the BP rises beyond what is required for adequate perfusion, thus increasing myocardial work. Although β2-activation achieves

beneficial vasodilation and also mediates some inotropic effect, such stimulation also causes hypokalemia with enhanced risk of arrhythmias. These are the reasons why sympathomimetics are used only in short-term treatment of acute heart failure [251].

Epinephrine is used when combined inotropic/chronotropic stimulation is urgently needed, as in cardiac arrest and in refractory cardiogenic shock. Side effects include tachycardia, arrhythmias, anxiety, headaches, cold extremities, cerebral hemorrhage, and pulmonary edema. Contraindications include late pregnancy because of risk of inducing uterine contractions. Acute dose is 0.5 mg subcutaneously or intramuscularly (0.5 ml of 1:1000), or 0.5 to 1.0 mg into the central veins, 0.1 to 0.2 mg intracardiac. Infusion dose: 0.01– 0.5 mcg/kg/min (In 70-kg adult, 7–35 mcg/ min) [217]. Norepinephrine stimulates α-receptors in the periphery (with more marked α-effects than epinephrine) and β-receptors in the heart; therefore it is typically used when a shock-like state is accompanied by peripheral vasodilation ("warm shock"). The recommended dosage is 0.1–0.5 mcg/kg/min (In 70 kg adult, 7– 35 mcg/min).

Dopamine is a catecholamine-like that stimulates the heart by both β-and α-adrenergic receptors and causes vasodilation through dopamine receptors. Theoretically, dopamine has the valuable property in severe HF or shock of specifically increasing blood flow to the renal, mesenteric, coronary, and cerebral beds by activating the specific postjunctional dopamine DA1 receptors. At high doses dopamine increase the risk of tachycardia, arrhythmias, renal vasoconstriction. Dopamine has different effects depending on the dosage used; at low dosage (2-5 mcg/kg/min) it acts on renal dopaminergic receptors leading to vasodilation also in brain circulation; at intermediate and high dosage (5-20 mcg/kg/min) it acts on alfa-adrenergic and B1 receptors, leading to positive inotropic effect and vasoconstriction.

Dobutamine is a synthetic analogue of dopamine characterized by a potent inotropic effect. However, its β2-stimulatory effect may lead to hypotension and sometimes to a fall in diastolic pressure with reflex tachycardia. The ideal candidate for dobutamine therapy is the patient who has severely depressed left ventricular (LV) function with a low cardiac index and elevated LV filling

pressure, but in whom extreme hypotension is not present (mean arterial BP < 70 mm Hg but no clinical shock). A combination of dopamine with dobutamine is typically used [217]. Reccomended dose for dobutamine is 5–10 mcg/kg/min. In Table 1 a review about the dosages and the main effects of the aforementioned drugs.

8. **Management of Arrhythmias in Cath Lab** Tachyarrhythmia management depends strictly on the patient's clinical status. If hemodynamic instability or signs of shock is present, immediate electrical cardioversion should be performed. In contrast, several antiarrhythmic drugs can be used intravenously. Lidocaine is the drug of first choice for the interruption of arrhythmias that occur during AMI. It is an antiarrhythmic drug with properties of local anesthetic, (IB class of Vaughan-Williams). It acts mainly on ischemic tissue, where it promotes blocking of conduction, thus interrupting the re-entry circuits; increases the ventricular fibrillation threshold and does not have the side effect of increasing QT. To obtain maximum efficacy, there must be high levels of extracellular potassium, so any hypokalemia should be corrected. It is contraindicated in the presence of sinoatrial, atrioventricular and intraventricular blocks. The initial dose is 1.0-1.5 mg / kg in 1-2 minutes repeatable after 5'-10 '; do not exceed 3 mg / kg; the maintenance dose is 2-4 mg / min for 24-30 h.[219] Metoprolol is a beta-1-selective beta-1 blocker with no intrinsic sympathomimetic activity. it is indicated in supraventricular and ventricular arrhythmias; the initial dose is 5 mg i.v. in 5 ', giving a total of 15 mg repeatable at intervals of 5'-10'. Maintenance must be done per os: 15 'after 25-50 mg, 6- 12-18h after 25-50 mg. Verapamil is a non-dihydropyridine calcium antagonist (Vaughan-Williams class IV) which slows down conduction through the AV node and prolongs its effective refractory period. It decreases the request of O2 from the myocardium. It is indicated during supraventricular tachycardias due to nodal re-entry. It is contraindicated in case of atrioventricular blocks of II or III, ventricular tachycardia and hypotension. The bolus: dilute 1 fl in 13 ml of physiological solution to be infused slowly in 5 ', repeatable after 15'-30'. Esmolol is a cardioselective beta-blocker, with a rapid onset of action and short duration. It has negative inotropic and chronotropic effects and slows down the A-V

conduction. It is contraindicated in case of atrioventricular blocks of II or III, important bradycardia, cardiogenic shock. The loading dose is 3-40 mg, generally it starts with 3-6 mg i.v. in bolus in 1 '. The maintenance i.v. It is 50 ug/kg/ min.

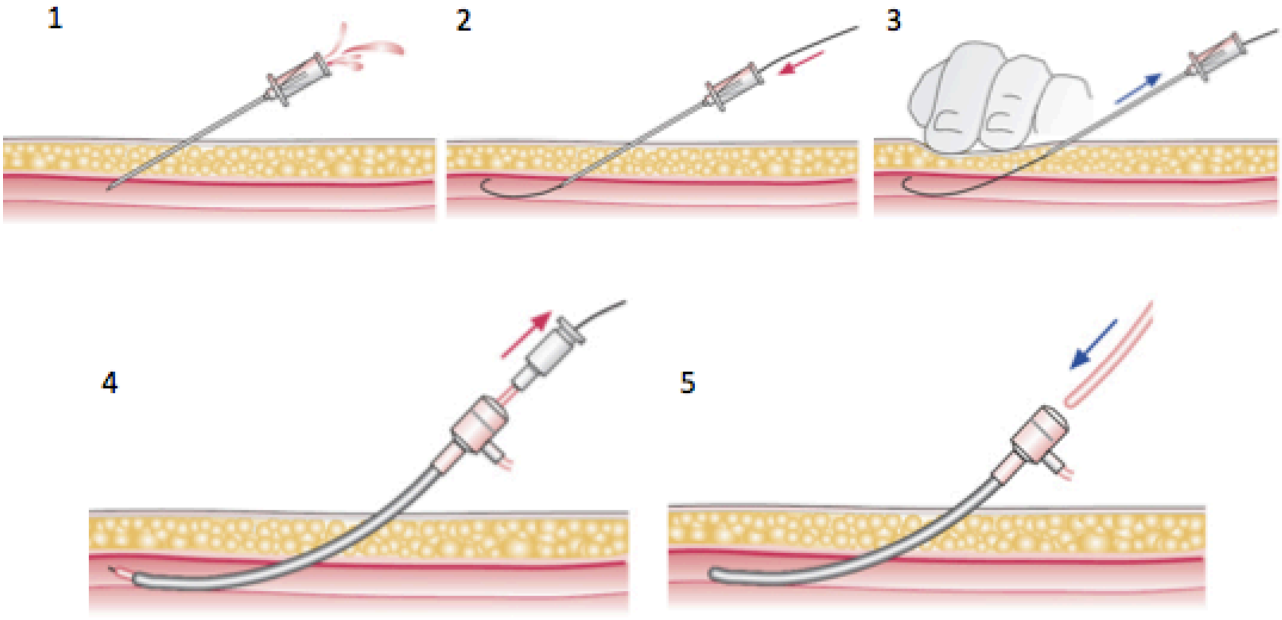
9. Conclusions

Pharmacological management is of paramount importance in patients undergoing diagnostic and interventional procedures in the Cath Lab. Several developments in this field during last decades have drastically reduced the rate of complications and improved procedural outcomes of such patients. Continuous information and training of interventional cardiologists is crucial for correct drug management in the difficult scenario of the Cath-Lab.

Table 1.

Drug	Dose	Indications
Epinephrine	Acute dose is 0.5 mg subcutaneously or intramuscularly, or 0.5 to 1.0 mg into the central veins, 0.1 to 0.2 mg intracardiac. Infusion dose: 0.01– 0.5 mcg/kg/min (In 70-kg adult, 7–35 mcg/ min). A low physiologic infusion rate (<0.01 µg/kg per minute) decreases BP (vasodilator effect), whereas more than 0.2 µg/kg per minute increases peripheral resistance and BP (combined inotropic and vasoconstrictor effects). The α-stimulatory effect of high-dose epinephrine helps to maintain the blood pressure and overcomes the peripheral vasodilation achieved by β2-receptor stimulation.	•Cardiac arrest (asystole, PEA, VF),[anaphylactoidrxn,anaphylaxis] •Shock: IV 2-10 mcg/min; CPR: 1 mg q 3 min. •To treat severe hypotension (eg, systolic blood pressure70 mm Hg) •For symptomatic bradycardia if atropine and transcutaneous pacing fail or if pacing is not available. •For anaphylaxis associated with hemodynamic instability or respiratory distress.
Norepinephrine	0.1–0.5 mcg/kg/min (In 70 kg adult, 7– 35 mcg/min)	•Shock refractory to other sympathomimetics-low systemic vascular resistance states. •Used to treat severe hypotension (eg, systolic blood pressure70 mm Hg) and a low total peripheral resistance. •Relatively contraindicated in patients with hypovolemia. It may increase myocardial oxygen requirements, mandating cautious use in patients with ischemic heart disease. •Usually induces renal and mesenteric vasoconstriction; in sepsis, however, norepinephrine improves renal blood flow and urine output.
Dopamine	Dose dependent effects: • 2-5 mcg/kg/min DA1 (renal) and DA2 (peripheral) vasodilation (including cerebral). . 5-10 mcg/kg/min B1 agonist-contractility (less HR or BP). . 10-20 mcg/kg/min alfa adrenergic effect.	• Hypotension, poor tissue perfusion (oliguria, anuria, altered level of consciousness), especially if it is associated with symptomatic bradycardia.
Dobutamine	5–10 mcg/kg/min •The (+) isomer is a potent beta-adrenergic agonist, whereas the (–) isomer is a potent alpha-1-agonist •The vasodilating beta2-adrenergic effects of the (+) isomer counterbalance the vasoconstricting alpha-adrenergic effects, often leading to little change or a reduction in systemic vascular resistance.	• Hypotension, poor tissue perfusion (oliguria, anuria, altered level of consciousness). • Severely depressed left ventricular (LV) function with a low cardiac index and elevated LV filling pressure, but in whom extreme hypotension is not present (mean arterial BP < 70 mm Hg but no clinical shock).

Adapted from Bernelli C. 2015 [1]



Radial artery puncture technique.
1:The puncture cannula is advanced into the artery until pulsating blood exits.
2: The guidewire is then advanced into the artery via the cannula.
3:The cannula is removed under compression of the puncture site.
4: The sheath is advanced with the dilator inserted.
5:After removal of the dilator, a catheter can be inserted into the artery

2)Autologous blood reinfusion during iatrogenic acute hemorrhagic cardiac tamponade: safety and feasibility in a cohort of 30 patients

INTRODUCTION

Iatrogenic hemorrhagic pericardial tamponade (IHPT) represents a life- threating condition requiring emergency pericardiocentesis. Recent evidence indicates that the incidence of pericardial effusions following percutaneous catheter-based procedures are increasing.[252-255] As reported in literature, the incidence of cardiac perforation with conse- quent pericardial effusion is 1.5–4.7% for valvuloplasty,[256] 0.2–1% for radiofrequency ablation,[257-258] 0.1–0.2% for electrophysiological study,[259] 0.03% for coronary angioplasty (PCI),[260] 0.5% for cardiac biopsy,[261] and 0.01% for diagnostic catheterization.[262] Notably, during transcatheter aortic valve implantation, emergent surgery is mainly due to left ventricular perforation by the guide wire (28.3%), whereas pericardial tamponade is the cause of surgery in 6.6 to 13.6% of the cases.[263-264] Moreover, in the ACCESS-EU MitraClip registry pericardial tampo- nade resulted in 0.9% of cases and in 3.5% after left atrial appendage (LAA) closure.[265-266]. Additionally, approximately half of the catheter- based pericardial tamponade occur in the catheterization laboratory, while the remaining half develop later with a median delayed presentation time of 5 hr.[267-269]. Despite pericardiocentesis represents a life-saving maneuver in these cases, active bleeding is associated with progressive shock until the underlying mechanism of hemorrhagic tamponade is resolved. In such critical circumstances, the immediate reinfusion of blood removed from the pericardial space in a central vein, can contribute to temporally stabilize the patient and sustain hemodynamic conditions. However, this technique is not routinely adopted, due to the reluctance to reinfuse whole, non-filtered blood, and the lack of consensus about the safety. Potential risks are the development of coagulation abnormalities, with hemorrhage and disseminated intravascular coagu- lation, which, in the setting of PCI, could theoretically lead to stent thrombosis (ST). Another drawback of the autotransfusion could be the potential risk of infective events and hyperkalemia due to hemolysis.

In our institution, we routinely reinfuse unprocessed blood drained from pericardium, in case of IHPT. However, no data are available about the systematic utilization of the pericardium-central vein closed circuit, in the cases of acute iatro- genic hemopericardium.This study aims to assess the feasibility and safety of urgent auto- transfusion from the pericardium to a femoral vein in case of IHPT, caused by percutaneous interventional procedures.

METHODS

We retrospectively reviewed all the cases of iatrogenic tamponade occurred in our institution from January 2007 to January 2017 treated with blood reinfusion. All clinical and procedural data have been collected from archive medical folders. Thirty days and 1-year follow- up were carried out. Description of the technique: after a fast-echocardiographic eval- uation, in case of IHPT an emergency pericardiocentesis is performed through subxiphoid approach under fluoroscopic guidance. A 6 French pig-tail catheter is positioned in the pericardial space, and a 6Fr sheath is inserted in a femoral vein and connected with a plastic tube and a luer stopcock with the pig-tail catheter. With a 20 ml luer lock syringe the blood is gently aspirated from the pericardium and directly rein- fused in the femoral vein through the closed circuit (Figure 1A,B). The decision to perform the pericardial puncture before or after obtaining the femoral venous access, was at the operator discretion. When two interventionalists were present, the two maneuvers were generally performed at the same time. In case of a single operator, we usually puncture the femoral vein first, in order to reinfuse all the blood that is successively removed from the pericardium. When the circuit is ready, blood aspiration and reinfusion are performed by the second operator while the first operator tries to stop the bleeding. Aspiration and reinfusion continue until the hemorrhagic problem and cardio- genic shock is solved. In the majority of cases, the pig-tail catheter is left in situ and connected to a vacuum bowl for 24 hr to assess a pos- sible bleeding recurrence. If the pericardial drain was kept in place, antibiotics covering was administered, patients were monitored and ultrasound evaluation were performed

every 4–6 hr. In this report, we assessed the technical feasibility of this proce- dure and the potential adverse events. Major and minor bleeding were defined according to BARC classification19 and thrombotic complica- tions according to the ARC consortium definition.20

STATISTICAL METHODS

Continuous variables are reported as mean ± standard deviation (SD). Categorical data are reported as counts and proportions. Comparisons between groups were based on unpaired Student t test for continuous variables and chi-square or Fisher's exact tests for categorical vari- ables. Statistical data were considered significant with a P-value<0.05. All analyses were performed with SPSS (Statistical Package for Social Science, IBM) version 24.

RESULTS

Over 10 years, in our institution, 30 patients with IHPT have been treated with autologous blood reinfusion through a closed circuit. Demographics and clinical characteristics are listed in Table 1. Patients had a mean age of 73, female accounted for 60% of the population. Six patients (20%) had an ejection fraction lower than 40%. Hematological parameters were within the normal range for an elderly population. As concerns antithrombotic therapy, most of the patients were on aspirin treatment and only 9 (30%) on dual antiplatelet therapy. Four patients (13.3%) were treated with oral anticoagulants for atrial fibrillation. Most of the patients had a normal renal function defined by a GFR > 60 ml/min (27, 90%). As reported in Table 2, the vast majority of cases were secondary to coronary artery perforations during PCI (21, 70%), Six cases of IHPT (20%) were related to a structural heart intervention (4 TAVI, 1 mitral valvuloplasty and 1 PFO closure). Interestingly, in 16 cases (53.3%) IHPT occurred in the cath- lab during the intervention, while in the remaining 14 cases (46.6%) IHPT was delayed with a median time of 4.0 hr after the procedure (Table 3). All patients developed hemodynamic collapse with an invasive systolic pressure of 59 ± 17 mmHg. In 10 cases (30%), systolic

pressure was lower than 60 mmHg. All patients required fluid administration and inotropic support; 43% of patients underwent endotracheal intubation. Intra-aortic balloon pump (IABP) was used in only 4 patients. Notably, periprocedural hemotransfusion was required in only 6 (20%) patients with a mean of <2 blood units per patient. The pericardial bleeding was attempted to be managed percutaneously in all the PCI related IHPT, but in 6 out of 21 cases (28.6%) it was not effective. In three cases, surgery was needed for an intractable bleeding with ventricular tear-like rupture, and in other three cases cardiac arrest occurred during the procedure. In 7 patients, the pericardial bleeding stopped spontaneously (management flow-chart, Figure 2). Protamine was administered in five cases of acute presentation IHPT, in structural procedures, after pericardiocentesis, during blood reinfu- sion. An emergent surgical procedure was required in 5 out of 30 patients (16.7%), for unceasing bleeding. Two intractable pericardial tamponade were related to TAVI procedures, with a right tear-like ventricular rupture due to the temporal pacing and a tear-like left ventricular rupture due to the extra-stiff wire. The remaining three cases were PCI related with a left ventricular tear evident in two cases, while in the third the source of bleeding remained unknown. Minor complications occurred during the postprocedural period in 23% of cases. We observed only two cases of minor hemorrhage (mild hematuria and rectorrhagia), managed conservatively. Infective com-plications developed in only three patients: one patient suffered from pneumonia in the postoperative period, two patients had a gram- positive sepsis efficaciously treated with a course of endovenous anti- biotic therapy. Finally, we observed two procedure-unrelated throm- botic complications: an apical thrombus in a severely dysfunctional left ventricle and a pulmonary embolism in a patient confined to bed. No ST was observed during hospitalization and 1-year follow-up (Table 4). Finally, no cases of hyperkalemia due to hemolysis were detected. There were no statistical differences between acute and delayed pericardial tamponade presentation in terms of infective complications and thrombotic events. Patients with delayed presentation required more often cardiac surgery (28.6 vs. 6.2%, P value 0.04). Regarding the mortality rate,

four patients had a negative out- come, three died in the cath-lab (mortality rate of 10%) and one died three days later from chronic pulmonary disease exacerbation. The overall in-hospital mortality in our case series was 13.3%. Conversely, the other 26 patients were alive after one year. All intraoperative fatal cases were PCI-related IHPT and developed a cardiac arrest due to pulseless electrical activity in the Cath-lab. Autopsy was performed in two out of four deceased patients. In one patient, the cause of pericardial bleeding remains unknown, in the other one, autopsy revealed a small coronary leak after stenting.

DISCUSSION

IHPT is an unpredictable fatal complication requiring emergency pericardiocentesis, advanced care support and occasionally emergent cardiac surgery. In our experience, the systematic blood autotransfusion from the pericardial space to a femoral vein resulted a safe and effec- tive treatment. The mortality rate was acceptable (10%) if we consider that the occurrence of pericardial tamponade is itself a life-threating complication. Only a few patients required IABP to stabilized their poor hemodynamic condition. Furthermore, allogenic blood transfu- sion was performed in only six cases (20%) during hospitalization. Despite its hemodynamic utility in case of IHPT, the blood auto- transfusion from the pericardial space to a femoral vein is not routinely performed for the potential risk of thrombotic and infective events. However, we did not observe, in our experience, any major bleeding or thrombotic events directly related to the autotransfusion itself. Prompt recognition of pericardial bleeding is essential, so that prevention from effusion to tamponade can be attempted and the "downward spiral" of this fatal complication can be averted and treated. Urgent pericardiocentesis requires great expertise. The number of major complications of echo and fluoro-guided pericardiocentesis are around 1–2%. [272-274] The major complications include, mortality, cardiac arrest, cardiac perforation, right coronary perforation, pericardial/epicardial thrombus, injury to an intercostal vessel, pneumothorax, ventricular tachycardia, pulmonary edema, and local/systemic infection. [275-

278]. In cases of IHTP, until the source of bleeding is stopped, a pericardial hemorrhagic loss can add insult to injury, without the possibility to stabilized the patient. With blood autotransfusion from pericardium to a femoral vein through a closed sterile circuit, we obtain two impor- tant goals: first of all, we “detamponade” the patient and secondary, we avoid sudden volume and hematocrit fall deriving from continuous bleeding in the pericardium. [279] Furthermore, autotransfusion of blood aspirated from pericardium can limit the amount and risk of allogenic blood transfusion adverse reaction and in selective cases, may also permit the completion of the interventional procedure or it can be used as “a bridge to a definitive treatment such percutaneous or surgical treatment” or “a bridge to a recovery”. Despite several case reports having anecdotally [279-280] highlighted the importance of this potential life-saving technique and cell-savage instrument to autotransfuse have been proposed, scientific evidence on this topic is lacking. The data available for autologous blood reinfusion, concern various conditions like orthopedic, cardiac, and abdominal surgery. [281] Some authors describe several methods to filter the blood and eventually separate red-blood cells before the reinfu- sion. These filtering systems should limit the complications hypotheti- cally deriving from direct reinfusion of whole blood. In these opened surgical conditions with blood contamination, direct blood reinfusion, without cleaning techniques, is questionable, due to the concrete pos- sibility of thrombotic and infective events. Venkatachalam et al. [282] assessed the feasibility of urgent use of an autologous blood recovery system in the electrophysiology laboratory to autotransfuse blood aspirated from the pericardium. The authors present nine cases of ablation procedure-related pericardial effusions requiring emergency pericardial drainage, in which a cell-salvage system has been successfully used. [283-284] All the cases available, to our knowledge, in the literature have been briefly reported in Table 5. Interventional cardiologists are reluctant to use autotransfusion of whole blood on a routine basis, although it may be a life-saving technique, as demonstrated in our study. However, blood filtering systems are not always available in the cath-lab, and would increase the costs and time of the procedure.

This study is, to our knowledge, the widest case series available of IHPT treated with direct whole blood autotransfusion. Our results encourage the spreading of this technique that should, in our opinion, be adopted routinely in case of IHPT. This approach led us to bridge five patients to surgery, four of them for a tear-like ventricular rupture. Furthermore, this tech- nique stabilized patients to perform safely percutaneous management of coronary perforation. No significant adverse events were reported in the acute period. Moreover, the late thrombotic and infective complications observed in the postoperative period cannot be directly related to the autologous pericardial blood reinfusion. As concerns thrombotic event, one apex cardiac thrombus was due to left ventricular dysfunction and a case of pulmonary embolism occurred in a bed-ridden patient. In our study, three cases of infection have been reported; however, the link between pericardial autotransfusion and infection cannot be proven in the presence of so many confounding factors (pericardiocentesis puncture, central vein access, anesthesiologist manoeuvres and cardiac surgery). Finally, this technique should be taken in consideration to manage patients suffering from cardiac tamponade with stronger antiplatelet therapy after PCI, or in patients anticoagulated with VKA and NOACs, especially in sites without on-site cardiac surgery.

LIMITATIONS OF THE STUDY

This study is monocentric and it is a retrospective cohort study with a time span of 10 years. The lack of a control group and any form of randomization limits our assumption.

CONCLUSION

Autologous blood reinfusion from pericardial space to a femoral vein can be a life-saving procedure. In our clinical experience of 30 patients with hemorrhagic cardiac tamponade, this technique was successful to limit blood transfusions, to prevent further clinical worsening and bridge patients with intractable bleeding, to cardiac surgery, to percutaneous management or to

a definite recovery. No major adverse reactions related to blood autotransfusion were observed. In the complex clinical scenario of acute tamponade occurring during catheter- based procedures, autotransfusion of blood from pericardial to femoral vein, can be a useful trick up the sleeve of the interventional cardiologists.

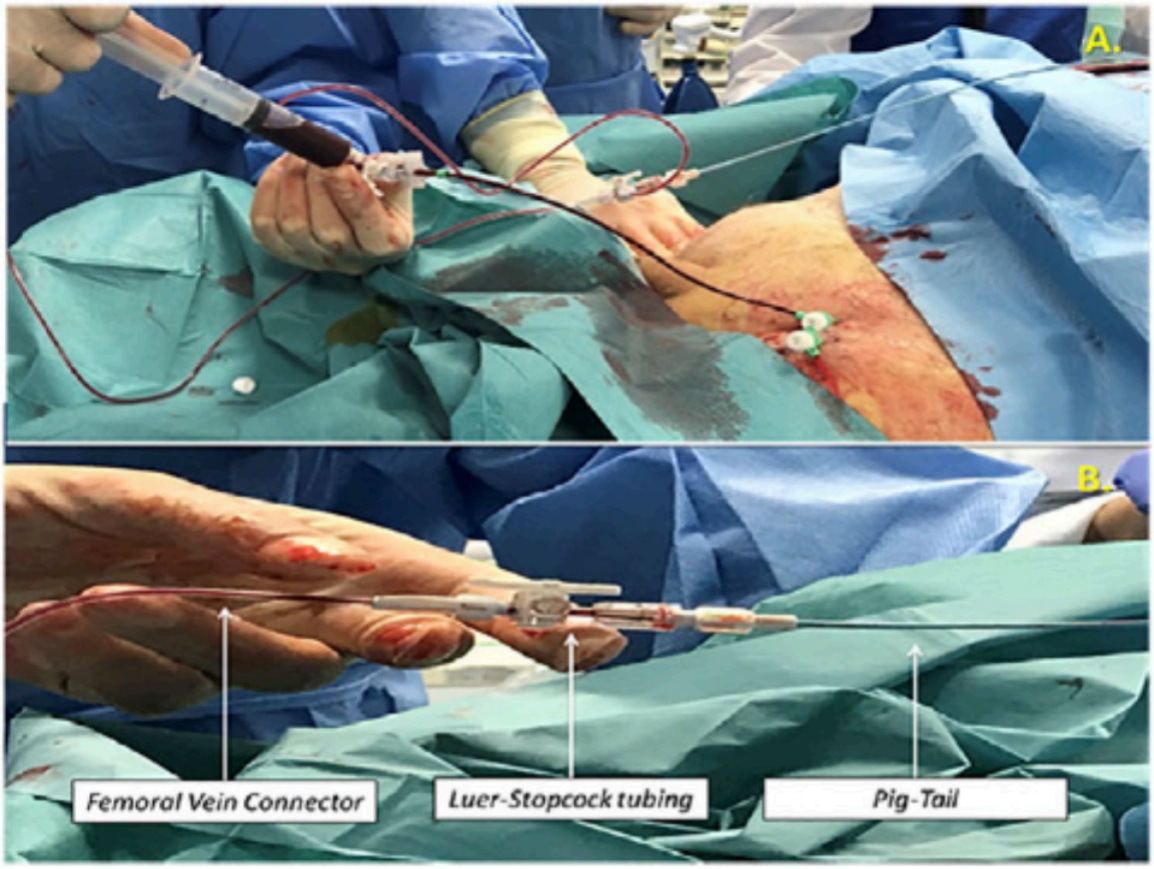


FIGURE 1 A, A detail of the circuit with a Luer-stopcock tubing connecting the pig-tail in the pericardial space with the femoral vein. B, Gentle reinfusion of the drained pericardial blood into the venous femoral sheath through the circuit with a Luer-Stopcock tubing [Color figure can be viewed at wileyonlinelibrary.com]

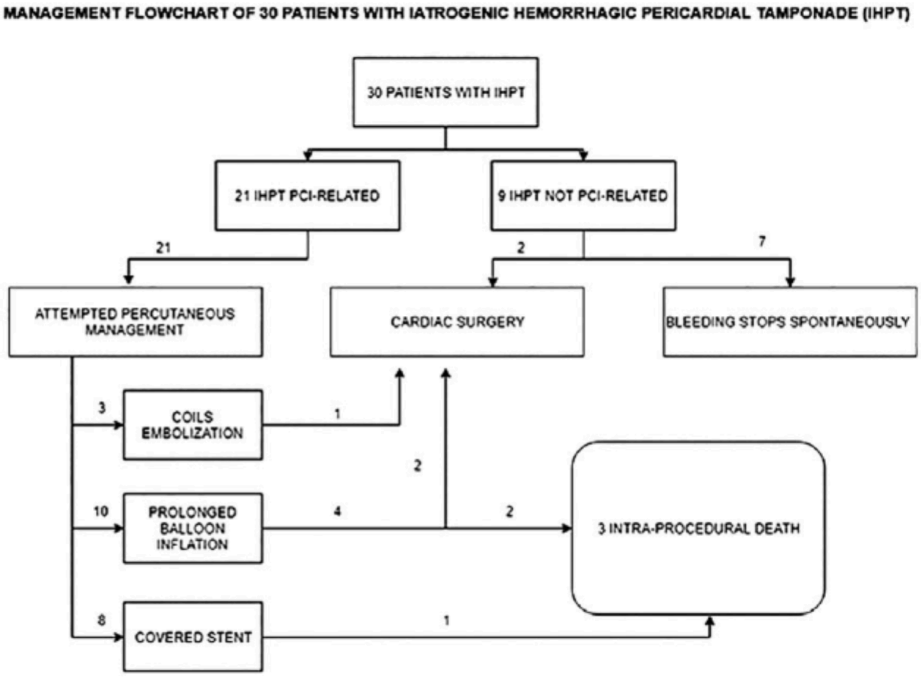


TABLE 1 Clinical characteristics of the patient population

Preoperative demographics and risk factors	
Age (years ± SD)	72.9 ± 10
Female	18/30 (60%)
BMI (kg/m^2 ± SD)	25.1 ± 4.4
Hypertension, *n* (%)	25 (83.3)
Dyslipidemia, *n* (%)	14 (46.7)
Chronic kidney disease, *n* (%)	3 (10)
Smoker status, *n* (%)	12 (40)
Diabetes, *n* (%)	5 (10)
Known coronary artery disease[a], *n* (%)	14 (46.7)
Previous stroke, *n* (%)	3 (10)
History of heart failure, *n* (%)	4 (13.3)
Atrial fibrillation, *n* (%)	4 (13.3)
Ejection fraction <40%, *n* (%)	6 (20)
Mean ejection fraction, % ± SD	51 ± 10
Baseline laboratory test	
Hemoglobin (g/dl ± SD)	12.7 ± 1.6
Hematocrit (% ± SD)	37.8 ± 4
Platelets (Unit/10^9/l ± SD)	227 ± 73
Total white counts (Unit/mcL ± SD)	7.8 ± 2.4
Creatinine (mg/dl ± SD)	1 ± 0.38
INR ratio (*n* ± SD)	1.1 ± 0.14
Preoperative antithrombotic therapy	
ASA, *n* (%)	18 (60)
Clopidogrel, *n* (%)	10 (33.3)
DAPT (ASA + Clopidogrel), *n* (%)	9 (30)
Warfarin, *n* (%)	3 (10)
NOAC, *n* (%)	1 (3.3)

[a] Chronic kidney disease was defined on the basis of an estimated GFR < 60 ml/min.

TABLE 2 Etiology of IHPT

Ventricular tachycardia ablation, *n* (%)	1 (3.3)
Percutaneous PFO closure, *n* (%)	1 (3.3)
Balloon mitral valvuloplasty, *n* (%)	1 (3.3)
Right ventricle biopsy, *n* (%)	2 (6.6)
Transcatheter aortic valve implantation, *n* (%)	4 (13.3)
Coronary perforation during PCI in ACS, *n* (%)	4 (13.3)
Coronary perforation during PCI in stable CAD, *n* (%)	17 (56.6)

Abbreviations: PFO, patent foramen ovale; ACS, acute coronary syndrome;

TABLE 3 Clinical presentation and management of IHPT

Clinical presentation	
Acute presentation	16/30
Delayed presentation	14/30
Median delayed presentation time (hr)	4
Max pericardial effusion diameter (mm ± SD)	9.4 ± 4.9
Mean systolic blood pressure (mmHg ± SD)	59 ± 17
Volume of pericardial blood drained (ml ± SD)	427 ± 245
Volume of pericardial blood reinfused (ml ± SD)	407 ± 210
Drained blood reinfused (% ± SD)	95 ± 16
Right femoral site reinfusion, *n* (%)	24 (80)
Left femoral site reinfusion, *n* (%)	6 (20)
Shock management	
Fluid administration, *n* (%)	28 (93.3)
Eterologous blood transfusion, *n* (%)	6 (20)
Volume of blood transfused (ml ± SD)	330 ± 260
Inotropic support, *n* (%)	25 (83.3)
Orotracheal intubation, *n* (%)	13 (43)
IABP, *n* (%)	4 (13.3)
Attempted Management of Coronary Perforation	
Prolonged balloon inflation, *n* (%)	10 (47.6)
Covered stents, *n* (%)	8 (38.1)
Coils, *n* (%)	3 (14.3)
Successful percutaneous management, *n* (%)	15 (71.4)
Failed percutaneous management, *n* (%)	6 (28.6)
Failure with bailout surgery, *n* (%)	3 (14.3)
Failure due to cardiac arrest, *n* (%)	3 (14.3)
Emergent cardiac surgery	
Cardiac surgery for intractable pericardial bleeding	5 (16.6)
Cardiac surgery for intractable bleeding of unknown origin	1 (3.3)
Cardiac surgery for tear-like ventricular rupture, *n* (%)	4 (13.3)

TABLE 4 Complications

Major complications	
Cardiac arrest, *n* (%)	4 (13.3)
Intraprocedural death, *n* (%)	3
Postprocedural death, *n* (%)	1
Minor in hospital complications	
Fever, *n* (%)	3 (10)
Infections, *n* (%)	3 (10)
Minor bleeding (BARC Type 1), *n* (%)	2
ST (acute, early, and late), *n* (%)	0 (–)
Thrombotic events, *n* (%)	2 (6.6)

Bleeding complications according BARC definitions were hematuria and rectorrhagia conservatively managed.
Infective complications: one patient developed pneumonia in the postoperative period, two patients had a gram+ sepsis (MRSA and a streptococcus) efficaciously treated with a course of endovenous antibiotic therapy.
Thrombotic complications: One thrombotic event was due to an apical thrombus with severe left dysfunction, another was a pulmonary embolism in a patient confined to bed by sickness.

TABLE 5 Autoblood Reinfusion during pericardial tamponade cases report in literature

Authors	Year of publication	Number of cases	Characteristics	Management	Outcomes
Morton et al. [29]	2006	1	Coronary Perforation during PCI	Autotrasfusion from the pericardial space to a femoral venous sheath	Patient survived
O'Neill et al. [34]	2008	1	Atrial fibrillation (AF) ablation	Autotrasfusion from the pericardial space to a femoral venous sheath, directly and with the CellSaver (Haemonetics, MA)	Patient survived
Venkatachalam et al. [31]	2009	9 ablations (AF 5, Accessory pathway-mediated tachycardia 1, Atrial tachycardia 1 Ventricular tachycardia 2)	Ablation procedures	The autologous blood from pericardium was hemoconcentrated and washed using a cell salvage instrument (ELMD 500; Medtronic Electromedics, Inc., Parker, CO). Processed blood was transfused via a peripheral intravenous line	Only one patient required surgical intervention because of ongoing pericardial bleeding. Five patients required additional allogeneic blood transfusion because of severe pericardial effusions
W ter Woerds et al. [35]	2011	1	Complication of pericardiocentesis performed for pericardial effusion with left ventricular perforation	Autotrasfusion from the pericardial space to a femoral venous sheath	Patient survived
Khaledi et al. [28]	2012	1	Spontaneous post MI Ventricular rupture	Autotrasfusion from the pericardial space to a femoral venous sheath	Patient survived
Muth et al. [36]	2012	1	Ablation AF in a Jehovah's Witness	Autotrasfusion from the pericardial space to a femoral venous sheath	Patient survived
Gianni et al. [37]	2016	2	Ablation AF	Autotrasfusion from the pericardial space to a femoral venous sheath	Patient survived
Ali et al. [38]	2017	1	LAA closure	Autotrasfusion from the pericardial space to a femoral venous sheath	Patient survived
Gosling et al. [39]	2018	1	Coronary perforation during PCI of CTO	Autotrasfusion from the pericardial space to an intravenous cannula	Patient survived

3) Cardiovascular mortality in patients with acute and chronic coronary syndrome: Insights from the clinical evidence on ticagrelor (submitted)

INTRODUCTION

Coronary artery disease (CAD) poses a significant public health burden as it contributes to significant morbidity and mortality with approximately 7.5 million deaths worldwide [291]. Death occurs in approximately 35% of the subjects experiencing a coronary event in each year and in almost one in six having an MI [292]. Therefore, one of the goals physicians caring for CAD patients are currently pursuing is to lower as much as possible their risk of acute events and death [293]. Greater knowledge of the natural history of CAD [294] as well as the evolution in current CAD management practice including the use of functional tests of ischemia and imaging modalities paved the way towards the recognition that CAD is a chronic multi-faceted disease in which phases of stability and instability [e.g., occurrence of acute atherothrombotic event such as unstable angina (UA), myocardial infarction (MI) with or without ST Segment Elevation] are closely intertwined [295]. To this end, the latest European Society of Cardiology (ESC) guidelines introduced the term "chronic coronary syndrome' to label the disease over its entire course, thus acknowledging that CAD clinical presentations can be categorized as either acute coronary syndrome (ACS) or chronic coronary syndrome (CCS) as commonly encountered in real world clinical practice [295]. Viewing CAD as a dynamic process of atherosclerotic plaque accumulation and functional alterations of coronary circulation, that can be modulated by lifestyle and pharmacological and surgical procedures, supports the concept that, even during stable phases, the disease demands integrated efforts to prevent progression, to reduce incidence of acute thrombotic events and development of ventricular dysfunction [295].

Despite adjusted mortality rates after acute MI have declined steadily over the last decade following advances in therapeutic options, improved cardiovascular (CV) risk factors control [296] and widespread implementation of guideline-directed medical therapy, the residual risk of recurrent ischemic events remains high even beyond one year [297] and despite adequate and complete

revascularization [298-300]. Predictive factors for higher risk of recurrent events or cardiovascular death include age > 65 years, diabetes mellitus (DM), prior MI, stroke, unstable angina, heart failure (HF), chronic kidney disease (CKD), multivessel coronary artery disease (CAD) [295-301] as well as biomarkers such as high-sensitivity troponins, C-reactive protein, NT-proBNP [302-303]. To date, the underlying atherosclerotic condition may drive recurrent events as recently reported in a large observational study carried out in patients after MI [299]; a risk of recurrent MI not originating from a previously untreated lesion was found to be 2-fold higher than that of lesions originating from a previously stented lesion. Importantly, multivessel disease was one of the strongest predictors of future non-culprit lesion recurrent MI [299]. In line with this, in a recent real-world study, in patients with established atherosclerosis or at high risk for atherosclerotic complications, the proportion of patients experiencing major adverse cardiovascular event (MACE) increased by nearly 5-fold from year 1 to 4 of follow-up, particularly in patients with atherosclerotic disease in single or multiple vascular beds [304]. Finally, also in patients well medically treated, as those included in the international ProspeCtive observational LongitudinAl RegIstry oF patients with stable coronary arterY disease (CLARIFY) registry [305], there was a substantial residual risk for MACE with a rate of cardiovascular death, non-fatal MI, or non-fatal stroke equal to 9.5%. Notably, similar findings emerged from the The COROnariens stables en régionNORd-pas-de-Calais (CORONOR) registry with an estimated 5-year cardiovascular mortality rates varying from less than 2% to more than 50% with 40% of cardiovascular origin [293]. Overall, in routine practice it is paramount to carefully target major predictors of cardiovascular death or non-fatal MI thus identifying patients with prior MI and angina as candidates for intensive treatment. For such high-risk patients, one of the key goals should be to reduce the residual risk and consecutively subsequent events [306].

Platelet activation and aggregation underlies the symptomatic coronary thrombosis and stand as a key element in the pathobiology of cardiovascular ischemic events; thus, it provides the rationale of targeting platelet function in patients with ACS and CCS as ischemic event prevention strategy

[307-308]. Dual antiplatelet therapy (DAPT) with aspirin and an oral $P2Y_{12}$ inhibitor is the cornerstone of antithrombotic therapy after MI and/or PCI [295] and it is recommended for long-term secondary prevention in patients with both highly or at least moderately increased risk of ischemic events and without high bleeding risk (HBR) [295]. To date, DAPT can influence the residual thrombotic risk [306], reduce ischemic recurrences in patients with ACS [309-310], in clinically stable patients undergoing PCI [311] or those who have had coronary stenting [312], as well as lower ischemic relapse in those with a history of MI [313-314]. Among oral $P2Y_{12}$ inhibitors, significant differences are emerging with regard to mortality benefit with ticagrelor showing significantly reduced cardiovascular mortality [HR: 0.82, 95% confidence interval(CI), 0.72-0.92] and all-cause mortality [HR, 0.83 (95% CI, 0.75-0.92)] compared to clopidogrel as well as reduced ischemic outcomes in high-risk patients [315]. Ticagrelor has been acknowledged as a drug with more rapid onset as well as more significant platelet inhibition function in ACS patients [316], an alternative strategy in treating patients with clopidogrel intolerance or resistance[26] and a valuable option in CCS patients with a history of MI [313].

In this narrative review, we discuss the relevance of cardiovascular mortality as clinical outcome in both ACS and CCS settings with a focus on the broad clinical evidence supporting ticagrelor mortality benefit across multiple subpopulations, including those at moderate-to-high risk of ischemic event.

Selection of Evidence

Papers considered for the present review were retrieved by a PubMed search, using different combinations of keywords (e.g., mortality AND coronary syndrome AND dual antiplatelet therapy AND ticagrelor), without limitations in terms of publication date and language. Papers were selected for inclusion according to their relevance for the topic, as judged by the Authors.

RELEVANCE OF MORTALITY RISK AND OUTCOME IN ACUTE AND CHRONIC CORONARY SYNDROMES

Preventing ischemic events and death is of outmost relevance in both ACS and CCS patients, given the high rate of recurrence of such events and fatalities. In the ACS setting, PCI is the dominant modality for myocardial revascularization and its short and long-term outcomes are associated with different rates of mortality [317]. To date, within the first 30 days, stent thrombosis accounts for MI or death in 50-70% of cases with patients with ACS displaying a higher risk than those with stable CAD [317]. Over 12 months, late adverse events can increasingly occur and result from the failure of the original inserted coronary device(s) or the progression of underlying CAD [317].

The risk of a recurrent CV event or death is the highest in the first year following an ACS event [298,318] and continues to increase for at least 5 years [319]. Of note, even in the absence of a recurrent event within the first 12 months post-MI, there is a 36% risk of MI, stroke, or death during the following 3-year period [319] with one in five individuals experiencing an event in the aforementioned time period [297]. To date, recent epidemiological data from Italy show that 30-day mortality rate post MI is about 9% with a stable trend in post-discharge mortality and an increased one-year fatal readmissions (5.28% vs 4.75; p=0.0019) from 2001 to 2011 [320]. Therefore, it is paramount to better identify the subpopulations at risk and manage them accordingly. Among ACS patients, subtle differences emerged in terms of mortality risk with greater all-cause mortality in STEMI vs UA/NSTEMI over the first 2-3 months after the event; however, over long-term follow-up, higher mortality has been reported among UA/NSTEMI vs STEMI [321]. Similar findings have been observed in the IMPROVE-IT study with higher mortality rates in STEMI vs UA/NSTEMI during the first month after which the mortality (both cardiovascular and non-cardiovascular) was greater in UA/STEMI vs STEMI [322]. It has been suggested that the long-term higher CV and non-CV mortality among UA/ NSTEMI patients could be attributed to a higher baseline prevalence of multiple comorbidities, including multivessel CAD, HF, DM, CKD [320,321]. A recent analysis

of IMPROVE-IT has shown that the relative incidence of CV and non-CV death differed based on ACS type with STEMI patients reporting predominantly higher CV death for four years following the index event and afterwards only non-CV death. In contrast, UA/NSTEMI patients remain at higher risk for CV death than non-CV death over long-term follow-up (despite advancements in pharmacotherapy and invasive management) [321].

Less is known regarding the long-term prognosis and survival outcomes in current CCS patients for whom the risk of annual cardiac mortality is used to describe the event risk. Such limited information is mostly related to the evolving nature of CCS patients who were previously defined largely via their angina symptoms but now display a broad spectrum of clinical presentations and prior medical history. Thus, previous evidence stemming from the Euro Heart survey and the REACH registry was mostly based on CCS patient subpopulations, who do not encompass the full spectrum of CCS and potentially receiving less contemporary treatment than the current CCS patients [323-324]. The international CLARIFY registry involving over 30,000 patients with CCS has recently provided useful insights on CV mortality as assessed as CV death or non-fatal MI as well as triple composite of cardiovascular death [305]. The 5-year crude rate of CV death or non-fatal MI was 8.0% while the CV death rate was 5.5% with 20% of CV deaths were due to MI and 10% were due to stroke. To date, higher rates of CV death and of non-fatal MI were reported among patients with prior MI vs those without; in addition, patients with prior MI and angina symptoms had worse prognosis (5-year rate of CV death: 11.8%) compared with non-angina patients (8.2%) ($P<0.001$) [305]. Overall, history of prior MI and angina symptoms stand as major determinants of adverse CV outcomes thus placing patients with history of MI and angina symptoms at highest risk for CV mortality. Therefore, the CV mortality risk of this subgroup, which represents about 14% of CCS patients, needs to be addressed appropriately via intensive monitoring and treatment.

THE ROLE OF $P2Y_{12}$ INHIBITORS IN DAPT: ARE ALL EQUALLY EFFECTIVE IN PREVENTING CARDIOVASCULAR MORTALITY?

DAPT is the cornerstone of antithrombotic interventions aimed at lowering the rate of hard clinical outcomes (namely, prevention of ischemic events and death) in patients treated both conservatively or invasively after ACS, as well as at improving prognosis in patients with CCS. DAPT is recommended in both STEMI [325], whose in-hospital mortality rates vary between 4 and 12%, and in NSTE-ACS [326] patients whose cumulative incidence of CV death is approximately 2.67% after one year from the event [327]. DAPT benefit on long-term outcomes can result from both prevention of MACCE (a composite of death from any cause, stroke, MI, or repeat revascularization after 12months) and of stent thrombosis, which in turn impacts cardiovascular mortality [317]. Importantly, DAPT benefit relies on an accurate clinical assessment of the relative weight of ischemic and bleeding events on mortality as well as of the optimal (or minimal necessary) timing of duration which in turn are heavily linked to baseline patient's risk profile and CAD underlying condition [307]. While clinical guidelines recommended 12-month (or longer) duration of DAPT following PCI in STEMI [325] and NSTE-ACS [326] unless there is excessive risk of bleeding, there is a mounting need to better identify subgroups that may benefit from long-term DAPT with no or acceptable bleeding risk as well as to better address those who may be candidates for prolonged DAPT such as DM and CKD [307,327]. Recent data from the Coronary Bifurcation Stenting Registry II [328] and RENAMI registry [329] have shed further light on the effects of prolonged DAPT duration on long term outcomes in both patients receiving drug-eluting stents for bifurcation lesions [328] and real-life ACS patients undergoing PCI and stent implantation [329]. Compared with <12-month DAPT group, prolonged DAPT duration after PCI for coronary bifurcation lesion is associated with reduced risk of all-cause death or MI with no difference in CV death. In contrast, in unselected ACS patients treated with prasugrel or ticagrelor for longer than 12 months a marked reduction in fatal and non-fatal ischemic events was observed, included CV death (1.2 vs. 5.1 risk of death) compared with those treated for less than 12 months

[329]. Nevertheless, a recent meta-analysis suggested that a significant net benefit of prolonged DAPT could be documented for ACS patients but not in those with stable CAD [330] thus reinforcing the notion that DAPT duration should be defined for each patient on an individual basis [307].

Beyond DAPT duration, $P2Y_{12}$ inhibitors differently impact long-term outcomes, particularly mortality, as documented by contrasting results from studies in ACS [309,310,331] or in patients with CCS [312,313,332][2] In ACS patients, combining aspirin with clopidogrel or prasugrel proved to lower MACE [310,333] but did not provide any survival benefit. In contrast, adding ticagrelor to aspirin provided a significant reduction in both rate of all-cause death (5.9% vs. 4.5%; $p < 0.001$) and death from vascular causes (5.1% vs. 4.0%; $p = 0.001$), along with an improvement in MACE incidence when compared with clopidogrel [309]. In CCS patients (e.g., with a history of MI), clopidogrel proved to be effective in reducing MACE without any effects on CV and all-cause death [334] while ticagrelor reduced the 3-year combined incidence of MI, stroke, or CV death compared with placebo in stable aspirin-treated patients with a history of MI 1-3 years previously [313]. Of note, the treatment with 60 mg ticagrelor in post-MI setting, when initiated according to EU approved label, was associated with a relative risk reduction of 20% in CV death, MI, or stroke [335].

Whether subtle pharmacological differences within the $P2Y_{12}$ inhibitor family may contribute to the different mortality outcomes is currently unknown. However, it has been proposed that some features of the newer $P2Y_{12}$ antagonists prasugrel and ticagrelor, including fast onset of action, rapid offset of effect, less variable on-treatment platelet reactivity and reversibility, may laid the foundation for the greater efficacy of newer $P2Y_{12}$ vs clopidogrel [307,336,337] in terms of survival post ACS.[25] Furthermore, pleiotropic effects have also been documented for ticagrelor that, unlike clopidogrel and prasugrel, is able to inhibit cellular uptake of adenosine by targeting its equilibrative nucleoside transporter 1 (ENT1) [338-341]. As a result, ticagrelor enhances the biological effects of endogenous adenosine by prolonging adenosine half-life and increasing its

concentration as documented in animal models [342]. Of note, the clinical relevance of ticagrelor pleiotropic effect has been evaluated in post-ACS patients with contrasting results [343-344].

In the following paragraphs we discuss in more detail the clinical evidence supporting ticagrelor CV mortality benefit as documented in both acute and chronic setting across a broad spectrum of patient subgroups from high to very high risk of experiencing future CV events.

TICAGRELOR MORTALITY BENEFIT IN ACS: INSIGHTS FROM THE LANDMARK PLATO STUDY

The primary goal in the management of ACS patients is to stabilize coronary blood flow, evaluate overall CV disease burden and initiate appropriate antithrombotic treatment to minimize subsequent ischemic events including MI and related mortality. Current guidelines recommend $P2Y_{12}$ in addition to aspirin for 12 months after PCI and maintained over 12 months unless there are contraindications or an excessive risk of bleeding in STEMI and NSTE-ACS patients (indication IA) [325-326]. Of note, ticagrelor, but not prasugrel, can be used irrespective of the planned treatment strategy (invasive or conservative) [180 mg loading dose (LD), 90 mg twice daily] [326]. The evidence-base for the aforementioned recommendations mostly stems from the findings of the landmark PLATelet inhibition and patient Outcomes PLATO study [309] as well as of the TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet InhibitioN with Prasugrel-Thrombolysis In Myocardial Infarction 38 (TRITON-TIMI 38) trials [310].

The PLATO trial was designed to test the hypothesis that ticagrelor (180 mg LD, 90 mg twice daily) would be superior to the available standard of care (e.g., clopidogrel, 300-600 LD, 75 mg once daily) at preventing CV events and death in a very broad population (n=18,624) of patients presenting with an ACS (both STEMI and NSTE-ACS within 24 hours of symptoms' onset) who were followed up for a minimum of 6 months to a maximum of 12 months [309]. To date, PLATO population encompassed ACS patients who were either initially managed medically or with PCI or with coronary artery bypass graft (CABG). The primary endpoint, a composite of death from

vascular causes, MI, or stroke, was found to occurr less frequently among ticagrelor-treated patients than among those receiving clopidogrel [9.8% vs 11.7%; HR:0.84; p<0.001] on top of daily aspirin. Such outcome appeared mainly driven by the reduction of both MI [5.8% vs 6.9%, HR:0.84, p<0.005] and death from vascular causes [4.0% vs 5.1%, HR:0.79, p<0.001], it has been documented as early as 30 days of therapy and was sustained up to 12 months with an overall relative risk reduction (RRR) of 16% [345]. It has been estimated that such mortality benefit translates in one CV death prevented every 91 patients treated with ticagrelor [345].

Patients with ACS who are intended for invasive management (e.g., PCI or CABG) may experience a wide range of short- and long-term outcomes such as stent thrombosis or target lesion revascularization (TRL), which are associated with MI or death. Therefore, one of the pre-specified objectives of the PLATO trial was to compare the incidence of stent thrombosis in ticagrelor and clopidogrel recipients. In patients who underwent stenting, ticagrelor reduced the incidence of definite (e.g., angiographically documented) stent thrombosis (1.3 vs. 1.9 %; HR 0.67, p=0.0091) and such reduction was consistent across NSTE-ACS, STEMI and regardless of stent characteristics [346]. Furthermore, in 13,408 PLATO patients for whom an invasive strategy was planned, ticagrelor benefit over clopidogrel on primary endpoint [9% vs 10.7%, HR: 0.84, p=0.0025] rates of MI [5.3% vs 6.6%, HR: 0.80, p=0.0023], CV death [3.4 vs 4.3, HR: 0.82, p=0.0250] and all-cause death [3.9 vs 5.0, HR: 0.81, p= 0.0103] was in line with the results of the overall population [308-347].

Patients with ACS may also be treated conservatively with 30-60% of NSTE-ACS patients not undergoing cardiac catheterization or even not revascularized; overall, such patients display a high prevalence of comorbidities and experiences increased morbidity and mortality compared with those undergoing invasive strategies [317]. Ticagrelor significantly lowered the incidence of primary endpoint [12% vs 14.3%, HR: 0.85, p=0.045] as well as CV death [5.5.% vs 7.2%, HR:0.76, p= 0.019] and all-cause death [6.1% vs 8.2%, HR:0.75, p=0.010] thus confirming that the benefits apply across diversified intervention strategies [348].

In the PLATO overall population, about 59% of patients (n=11,080) were categorized as NSTE-ACS at randomization. NSTE-ACS patients are characterized by a lower short-term mortality rates and higher rates of long-term mortality than STEMI, with an overall 10-year survival rate after NSTE-ACS being approximately 50% [349-350]. Thus, the risk-benefit assessment and the clinical decision making in such subgroup appear challenging and demand clear evidence to support treatment choices. In a sub-study of the PLATO trial conducted in NSTEMI patients, ticagrelor provided lower rates of primary endpoint [10% vs 12.3%, HR: 0.83, p=0.0013], CV death [3.7% vs 4.9%, HR:0.77, p= 0.0070] and all-cause death [4.3% vs 5.8%, HR: 0.76, p=0.0020] consistently with the overall PLATO trial and regardless of performed revascularization during the initial ten days [351].

Following an ACS event, age stands as both a strong predictor of adverse events, including impaired healing process and greater recurrence of ischemic events and/or complications, and a risk factor for bleeding. Thus, in the elderly population, the well-documented DAPT net clinical benefit may be reduced thereby warranting caution when choosing a $P2Y_{12}$ inhibitor [352]. Accordingly, a pre-specified objective of the PLATO trial was to evaluate the clinical efficacy of ticagrelor in elderly (≥75 years of age) vs younger (< 75 years of age) ACS patients. Importantly, the clinical benefit of ticagrelor over clopidogrel was not different between elderly and younger ACS patients regarding the primary composite endpoint in line with the main PLATO cohort [17.2% vs 18.3% (HR: 0.89) in the elderly; 8.6% vs 10.4% (HR: 0.84) in younger patients] [352]. Of note, similar reduction has been reported in ticagrelor-treated elderly compared to those receiving clopidogrel with respect to CV death, MI and all-cause mortality, with interaction p=0.56, p=0.47 and p=0.76 for primary endpoint, CV death and all -cause mortality, respectively [352].

A recent large observational study [353] from the SWEDEHEART registry (Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies), questioned the benefits of ticagrelor in ≥80-year-old patients because observed that the superiority of ticagrelor over clopidogrel in terms of composite endpoint, as well

as death and MI was significant in patients <80-year-old but not in older patients. It has been suggested that elderly may have a different benefit-risk ratio when treated with ticagrelor compared with clopidogrel when discharged after a MI. Despite real-world data are very important, it cannot undermine the solid and consistent findings from the PLATO randomized trial given its limitations: it was an observational study, with unmeasured confounders despite adjustments, without data on eventual cross-over or interruption (only intention-to-treat data available), and without causes of death collected. Yet, a different cutoff for defining age, a variable ischemic and bleeding risk in this populations, and evolution of techniques and concomitant therapies compared with PLATO's patients might contribute to explain the different results. Therefore, only a future adequately powered randomized study in the elderly population would provide definitive conclusions.

Increased recurrence of CV events and bleeding complications, including intracranial bleeding, are well documented in ACS patients with a history of stroke or transient ischemic attack (TIA), thus highlighting the relevance of balancing the antithrombotic efficacy with the bleeding risk in this high-risk and frail population. Although a very small proportion of PLATO overall population presented with a history of stroke or TIA at randomization, in this high-risk subgroup ticagrelor proved its benefit over clopidogrel with respect to primary endpoint [19% vs 20.8%, HR: 0.87 (95% CI:0.66-1.13)] along with a low risk of intracranial hemorrhage or fatal stroke with an overall 13% reduction in the rate of primary endpoint which is comparable to that achieved in patients without a history of stroke or TIA (e.g., 16%) [354]. Therefore, in contrast with prasugrel, this delicate subset of patients does not represent a contraindication to ticagrelor use.

Patients with diabetes are more prone to recurrent ischemic events following an ACS (including 80% higher mortality risk compared to those without diabetes) and have been reported to display a higher on-treatment platelet reactivity and worse clinical outcomes when receiving aspirin and clopidogrel [355-357]. Therefore, it is of relevance evaluating whether the potent $P2Y_{12}$ inhibitor ticagrelor would be able to offer this patient population additional benefit compared to clopidogrel. In the diabetic cohort of the PLATO trial (n=4,662) ticagrelor provided consistent reduction in the

occurrence of the primary composite endpoint [14.1% vs 16.2%, HR:0.88 (95% CI: 0.76-1.03)] but without nominal statistical significance [358]. Moreover, ticagrelor cardioprotective effects were observed in patients with levels of HbA_{1c} ≥6% or poor glycemic control on admission with 22% reduction in all-cause death vs clopidogrel [HR: 0.78 (95% CI: 0.65-0.93)]. To date, while no differences in major bleeding rates were reported, ticagrelor-treated patients experienced more frequent non-CABG-related bleeding than those receiving clopidogrel [358].

Higher risk of bleeding complications has been reported in ACS patients following interventional procedures such as CABG; therefore, in these patients a rapid offset of $P2Y_{12}$ inhibition, in contrast to the longer offset observed with clopidogrel and/or prasugrel, can be of help. In PLATO overall population about 1,261 patients underwent CABG post-randomization and received DAPT last intake within seven days before surgery. These patients experienced a reduction in total mortality from 9.7% (58 of 629) to 4.7% (29 of 629; HR: 0.49; 95% CI: 0.32 to 0.77; $p < 0.01$), in CV death from 7.9% (47 of 629) to 4.1% (25 of 629; HR: 0.52; 95% CI: 0.32 to0.85; $p < 0.01$) at no expenses of higher risk in CABG-related bleeding [359]. Importantly, despite the shorter treatment-free interval before CABG achieved with ticagrelor therapy, no significant differences vs clopidogrel have been observed in terms of major bleeding, fatal bleeding at surgery or reoperation occurrence. Finally, ticagrelor benefit on mortality over clopidogrel has also been reported in additional high-risk subpopulations who often exhibit a worse prognosis in ACS setting including patients with CKD [360], with peripheral artery disease (PAD)[361] and STEMI [362]. Overall, the beneficial effects on mortality of ticagrelor over clopidogrel were achieved across a broad spectrum of ACS settings (**Figure 1**) without a significant increase in the rate of major bleeding but with an increase in the rate of non–procedure-related bleeding. To aid in clinicians' evaluation of the extent and long-term impact of such adverse event a comprehensive analysis of bleeding complications reported in the PLATO trial has been performed by using three different scales according to the PLATO, TIMI and GUSTO (Global Use of Streptokinase and Tissue plasminogen activator to Open occluded coronary arteries)-based definitions [363]. The higher rate of non-CABG related

major bleeding in ticagrelor-treated patients was significant not before the first 30 days on treatment and was independently associated with several predictive factors such as increasing age, reduced creatinine clearance, female sex or prior gastrointestinal bleeding. In addition, fatal bleeding and transfusion rates were similar (0.3% vs 0.3%, p=0.66 and 8.5% vs. 8.3%, p=0.81, respectively). Collectively, in the ACS setting ticagrelor prevents the first occurrence of the composite endpoint of MI, stroke, or CV death more effectively than clopidogrel, with the treatment effect driven by reductions in the rate of MI and CV death; in addition, ticagrelor benefit was seen within 30 days of treatment, maintained up to one year and well documented in both ACS patients managed invasively and noninvasively as well as those deemed to be at high risk of bleeding complications.

In line with this, in NSTE-ACS patients planned for conservative management earlier guidelines recommended $P2Y_{12}$ inhibition (preferably with ticagrelor) in the absence of contraindications as soon as the diagnosis is confirmed [364].

In last few years, new evidence on head-to-head comparison of ticagrelor and prasugrel has been generated. The PRAGUE-18 trial [365], compared their efficacy and safety in 1,230 patients with acute MI treated with primary or immediate PCI. Overall, there were no significant differences between the two compounds and the study did not support the hypothesis that one could be more effective or safer than the other. However, the study was open-label, underpowered, with lower than expected even rates, with a change of the primary outcome and prematurely terminated for futility, thus remaining inconclusive.

A more recent head-to-head comparison of prasugrel and ticagrelor has been performed in the ISAREACT 5 trial [331,366]. ACS patients (n=4,018, of whom 41.1% STEMI) planned for invasive management were randomly assigned to a prasugrel-based or to ticagrelor-based strategy. Finally, the former was superior in reducing the incidence of death, MI, or stroke at 1 year (6.9% vs. 9.3%, p = 0.006), and this result was driven by a significant reduction of 1.8 percentage points in the incidence of recurrent MI, with no significant difference in major bleeding. However, some relevant limitations should be considered: a) open-label design, b) unexpected results (in the

opposite direction of the primary hypothesis), c) lower than expected event rate in prasugrel arm (6.9% vs 12.9%), d) events mainly ascertained through telephone contact, with limited site-based follow-up (10%), e) not negligible lost-to-follow-up patients (19 vs 18, which were higher than the 17 corresponding to the difference in all-cause death), f) high discontinuation rate (30-35%) of which 19% before discharge, g) differential exclusion from safety analysis (23 ticagrelor vs 233 prasugrel) and h) some confounding effect related to different treatment strategies between randomized therapies (loading dose of ticagrelor started as soon as possible after randomization, while timing of loading dose of prasugrel was based on clinical presentation, being as soon as possible in STEMI and after coronary angiography in NSTE-ACS). To date, in NSTE-ACS patients undergoing PCI, the time from randomization to the loading dose was 6 minutes in the ticagrelor arm and 61 minutes in the prasugrel arm. Moreover, since the trial design mandated routine pretreatment with ticagrelor in all patients but no pretreatment with prasugrel in

NSTE-ACS patients, the loading dose was given to more patients in the ticagrelor arm (98.7%) compared with prasugrel arm (86.1%). The ISAR-REACT 5 had relevant impact on most recent ESC-NSTE-ACS guidelines in which a preference to prasugrel over ticagrelor was acknowledged for the first time (prasugrel should be considered in preference to ticagrelor for NSTE-ACS patients who proceed to PCI, IIa, B) [326]. However, it does not mean that all NSTE-ACS will be treated with prasugrel. Indeed, the same guidelines introduced another important practice-changing recommendation: "it is not recommended to administer routine pre-treatment with a $P2Y_{12}$ receptor inhibitor in patients in whom coronary anatomy is not known and an early invasive management is planned (III, A)"[326]. Additional evidence against the utility of $P2Y_{12}$ inhibitor pre-treatment in NSTE-ACS has also been provided by the recent DUBIUS trial [367]. Overall, this recommendation will determine that the majority of NSTE-ACS undergoing PCI will be $P2Y_{12}$ inhibitor naïve, thus opening the door to a wider use of cangrelor in this setting. Given that ticagrelor, but not prasugrel or clopidogrel, can be given immediately after cangrelor start, one could argue that, when cangrelor is used, ticagrelor might be the preferred oral $P2Y_{12}$ inhibitor to

limit drug-drug interactions and potential risks of a variable time-window with inadequate platelet inhibition at the end of cangrelor infusion [368-371].

TICAGRELOR MORTALITY BENEFIT IN SECONDARY PREVENTION: INSIGHTS FROM THE PEGASUS TRIAL

The optimal duration of antithrombotic therapy for secondary prevention, and strategies for tailoring this based on patient profile, in patients at high risk of ischemic events is a matter of debate mostly owing to the conflicting results of several randomized trials [312,334,372,373] and depending on the relative contribution of ischemic and bleeding events on mortality [374]. Therefore, while some alternative approaches have been focus of recent research (i.e. short DAPT, monotherapy, de-escalation), in clinical practice establishing whether continuation of DAPT beyond one year offers a substantial reduction in important cardiovascular outcomes as well as to identify patients who may derive benefit from shortened or extended DAPT courses for secondary prevention of CAD remains challenging [307,375,376]. This assessment is particularly difficult when considering that a variable but not negligible proportion of patients are at HBR [377-381]. In addition, such considerations are particularly relevant in high-risk populations such as MI survivors who exhibit a 30% higher risk of all-cause death and cardiovascular outcomes (including cardiovascular death) than general population at both 1–3 years and 3–5 years after MI thus remaining at heightened risk for recurrent events [382,383].

The role of DAPT with aspirin and ticagrelor (tested at two dose intensities: 60 and 90 mg) in stable patients with a history of MI between 1 and 3 years previously and at least one additional atherothrombotic risk factor [e.g., diabetes, evidence of multivessel disease (MVD) or PAD], as effective option to promote secondary prevention, has been defined by the Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared with Placebo on a Background of Aspirin-Thrombolysis in Myocardial Infarction 54 (PEGASUS-TIMI 54) trial [313,384]. The primary endpoint, a composite of cardiovascular death, MI, or stroke at three years,

was found occurring less frequently in patients treated with ticagrelor [Kaplan-Meier (KM) event rates at 3 years of 7.77% (60 mg) or 7.85% (90 mg)] compared with placebo (KM: 9.04%) [313]. Overall, both dose regimens provided a mortality benefit with a consistent treatment effect over the entire study period, yielding a 16% RRR and 1.27% ARR for ticagrelor 60 mg and a 15% RRR and 1.19% ARR for ticagrelor 90 mg [345]. Notably, the rates of TIMI major bleeding were reported to be greater with both ticagrelor dose regimens compared to placebo with no significant differences in either fatal or intracranial bleeding [313].

While the two dose regimens displayed a similar extent of efficacy in the intention-to-treat analysis, patients receiving the lower dose intensity presented with lower rates of bleeding, dyspnea and treatment discontinuation thus unveiling a better tolerability profile with the 60 mg dose. Notably, the 60 mg dose is currently approved in many countries for the prevention of atherothrombotic events in patients with a history of MI and a high risk of developing an atherothrombotic event; to this end, we will mostly discuss the results of the 60 mg treatment group [313]. Therefore, a subsequent analysis focusing on the effects of extended treatment with ticagrelor 60mg in patients treated according to the approved label was performed and showed, compared with placebo, a 20% reduction in composite primary endpoint (HR:0.80) as well as 28% and 29% reduction in coronary heart and cardiovascular death, respectively [335]. The aforementioned findings were found to be translated in a net clinical benefit equal to 10 prevented CV deaths every 1,000 patients treated with ticagrelor for three years [335]. Furthermore, when yearly long-term effects of ticagrelor were also analyzed, a sustained benefit without late waning in efficacy was observed [385]. Of note, such mortality benefit occurs only in high-risk patients as being not reported in either clinically stable patients >2 years from the MI or more than 1-year after stopping previous ADP receptor inhibitor treatment [345]. An earlier study highlighted a three-fold gradient in cumulative risk of cardiovascular death, MI or stroke within a large set of patients at various stages along the atherosclerotic continuum ranging from 7% in nondiabetic patients with other risk factors for atherothrombosis to 25% in patients with poly-vascular disease and prior ischemic event [386].

Therefore, there are additional risk factors that identify patients deemed to undergo a more intensive treatment and follow-up and for whom an established mortality benefit is highly desirable. The PEGASUS overall population (n=21,162) comprised 6,806 diabetic patients who experienced 17% reduction in primary composite endpoint, 26% reduction in cardiovascular death and 36% reduction in coronary heart disease death following treatment with ticagrelor 60 mg. Among patients at high-risk for recurrent ischemic events and mortality, namely at least 2-fold higher MACE risk, individuals with PAD were found experiencing a ARR of 5.2% at three years following ticagrelor 60 mg treatment along with a significant 31% reduction in primary composite endpoint (p=0.045) and 53% reduction in cardiovascular death (p=0.014) vs placebo [386]. This observation is relevant if one considers that PAD is often accompanied by further markers of atherothrombotic risk including renal dysfunction, diabetes and smoking.

It has been suggested that the association between DAPT duration (short- versus prolonged) and clinical outcomes would be influenced by patients' underlying disease and, in presence of angiographic MVD, shorter duration DAPT was associated with increased risk of MACE thus hypothesizing that prolonged therapy could be favored in such subset of patients [387]. Almost 60% (59.4%) of PEGASUS overall population had a history of MVD and displayed a greater risk of coronary events compared to those without MVD. In this high-risk patient subgroup, ticagrelor treatment provided a 19% reduction in composite primary endpoint [HR.0.81 (95% CI: 0.7-0.95), $p_{interaction}$=0.55] and a 36% reduction in event rate for coronary death compared with placebo [HR: 0.64, (95% CI: 0.45-0.89) $p_{interaction}$=0.045] [388]. Therefore, these data support first evidence that ticagrelor can be offered to patients with MVD for long-term therapy. Overall, the PEGASUS trial provided a clear evidence of a favorable benefit-risk balance for long-term ticagrelor 60 mg in patients with prior MI and additional risk factors that make such subgroup more prone to recurrent events and death, particularly in terms of CV mortality (**Figure 2**).

While current guidelines [295] also recommend the combination of low-dose rivaroxaban and aspirin for event prevention based on the findings of the COMPASS trial [389], the pre-specified

significance thresholds for cardiovascular mortality and all-cause mortality were not met thus leaving unanswered the question whether the COMPASS-like regimen may stand as an alternative option to PEGASUS-TIMI-like regimen in conferring cardio-protection in patients at high-risk of ischemic events without a high bleeding risk. Pending further research on comparative studies between long-term DAPT with ticagrelor or treatment with low-dose factor Xa inhibitors on top of aspirin, evidence stemming from real world studies and/or registries may provide guidance on the generalizability of PEGASUS-TIMI and COMPASS trials to routine clinical practice [390,392].

DISCUSSION

Prevention of coronary thrombosis and its acute and chronic sequelae is of paramount clinical relevance when managing patients with ACS and CCS [295] with recurrent ischemic events and mortality being primary treatment goals. Owing to the evolving nature of CCS patients, characterized by a broad spectrum of clinical presentation and prior medical history, as well as the advances in therapeutic and surgical management of ACS, a greater attention towards the rate of hard clinical outcomes, the improvement of long-term prognosis and the reduction of residual risk of recurrent events is increasingly reported among cardiologists. To this end, the seminal findings from the PLATO [309] and PEGASUS-TIMI 54 [313] trials and their related subgroup analyses provided evidence that accomplishing clinically meaningful reduction in cardiovascular mortality is feasible in both ACS and CCS setting across a broad range of high-risk patient populations and is associated with increased major but not fatal or intracranial bleeding. Definition of benefits and risks to be expected in real life is of great relevance and holds great potential in confirming the generalizability of randomized trials' evidence to clinical practice. With respect to ticagrelor, the evidence stemming from national registries and observational studies may translate the earlier findings in PLATO and PEGASUS-TIMI 54 populations, whose strict eligibility criteria and risk definition assessment do not fully acknowledge the current knowledge of the natural history of CAD, into contemporary practice. In line with this, a prospective study performed in over 45,000

patients enrolled in the SWEDHEART registry showed a 15% reduction in the risk of the primary outcome [11.7 vs 22.3%, adjusted HR: 0.85 (95% confidence interval: 0.78-0.93)] and a 17% reduction in the risk of death [5.8 vs 12.9% (adjusted HR: 0.83 (0.75-0.92)] in ticagrelor treated patients compared with those receiving clopidogrel [393]. Further evidence of ticagrelor benefit on mortality was also reported in a real-world STEMI population in a case-control study examining all patients with STEMI included in the Cardio-STEMI SANREMO registry [394]. Of note, a significant lower rates of unadjusted cardiac hospital death occurred in the ticagrelor group (0.7% vs 5.4%; p = 0.024) compared with clopidogrel group as well as a greater unadjusted survival at 1 year after STEMI was reported in ticagrelor- vs clopidogrel-treated patients (97.8% vs 87.8%; p = 0.024) [394]. There was no difference in Bleeding Academic Research Consortium bleeding and in unadjusted incidence of hospital major adverse cardiovascular events (MACE; cardiac death, myocardial infarction, or stroke) [394].

Furthermore, by taking advantage of the Cardio-STEMI SANREMO registry, a recent study also clarified how many real-world patients meet the PEGASUS-TIMI54 criteria and the extent to which these criteria predict a patient's risk and prognosis [395]. To date, about 70% of the patients hospitalized for STEMI met the PEGASUS-TIMI 54 criteria and were identified by having a significantly lower 4-year survival and being at increased risk of mortality; importantly, in such patients ticagrelor treatment proved to be effective at improving 4-year survival and lowering mortality rates compared to other antiplatelet agents [395]. Further evidence of ticagrelor 60 mg use in real-life post-MI patients has been also provided in a recent Italian prospective observational study [391]. In the majority of cases, patients with more than 2 risk factors were deemed eligible for receiving ticagrelor 60 mg bid and almost seven patients in ten (66.7%) were patients with recurrent events; importantly, PEGASUS criteria for eligibility to prolonged DAPT as per PEGASUS study design such as MVD, age >65 years and diabetes were also found to be the eligibility criteria for prescribing prolonged DAPT with ticagrelor [380]. Finally, the applicability in real-life of PEGASUS-TIMI54 trial was explored in the analysis of the EYESHOT (EmploYEd antithrombotic

therapies in patients with acute coronary Syndromes HOspitalized in iTaly) registry that provided meaningful insights on current management and treatment of patients with prior MI referring to cardiologists [390]. Overall, it has been suggested that, by virtue of their ease of use, the PEGASUS-TIMI 54 inclusion criteria, along with the DAPT score and the PRECISE-DAPT score, may stand as useful tool to support clinical decision-making about the duration of DAPT [396]. While deaths averted provide a measure of health gain and improved prognosis, cost-effectiveness studies are useful to monitor the feasibility of the evidence gathered in randomized trials in the current practice routine where reimbursement-related issues may impact treatment selection. Interestingly, ticagrelor was found to be cost-effective compared with clopidogrel in preventing downstream morbidity and mortality associated with ACS [396] and to yield a cost-effectiveness ratio providing higher value for high- risk patients including those with >1 prior MI, MVD, diabetes, renal dysfunction, and PAD [397].

CONCLUSION

Ticagrelor is an effective and well tolerated option to attain a meaningful and clinically relevant reduction in cardiovascular mortality upon both acute and chronic setting (**Figure 3**) across a broad range of high-risk patient subpopulations with an acceptable payoff in terms of bleeding risk.

Figure 1

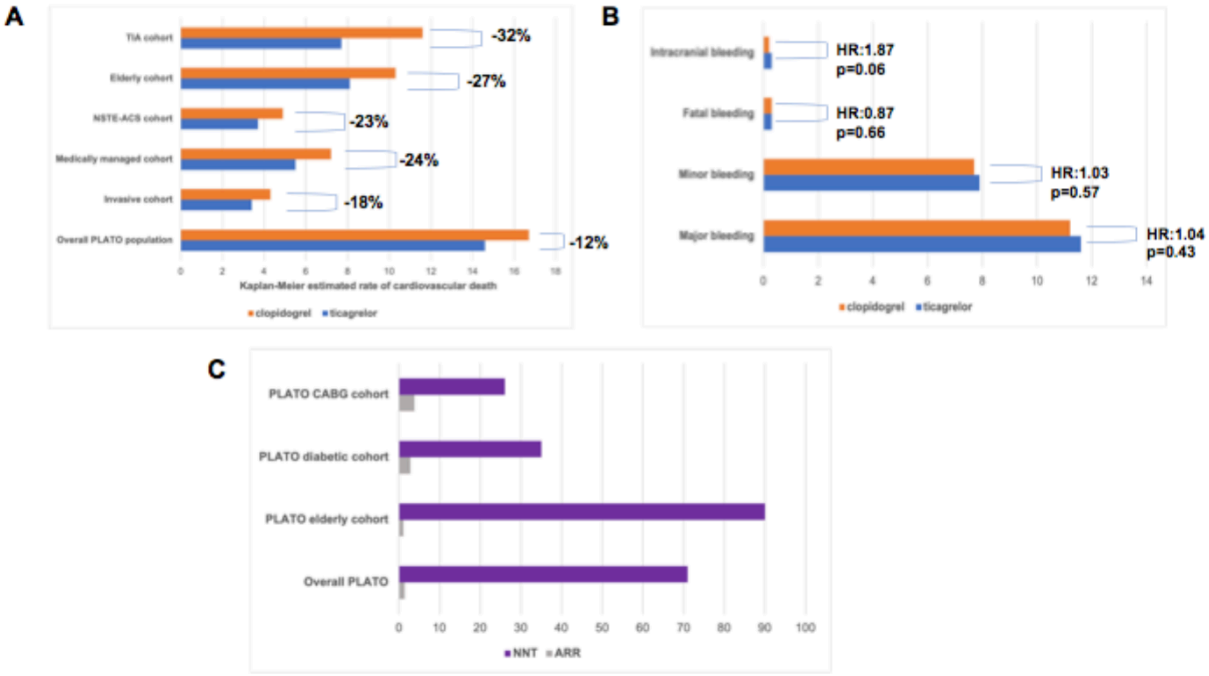


Figure 2

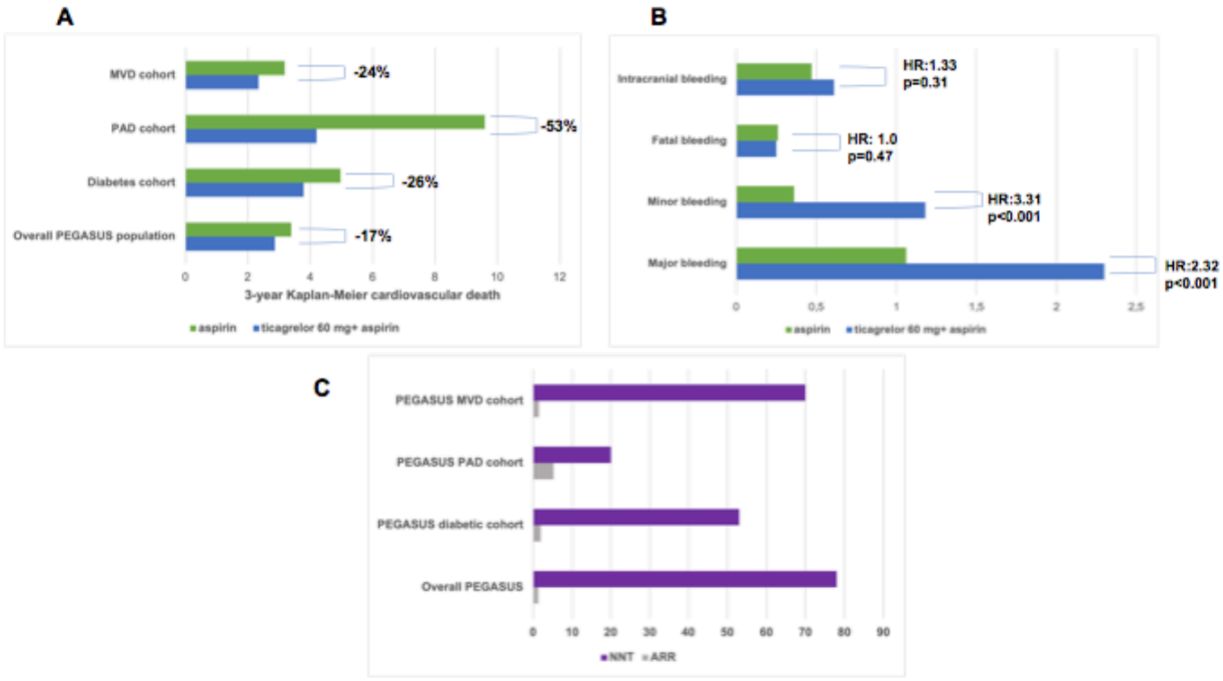


Figure 3

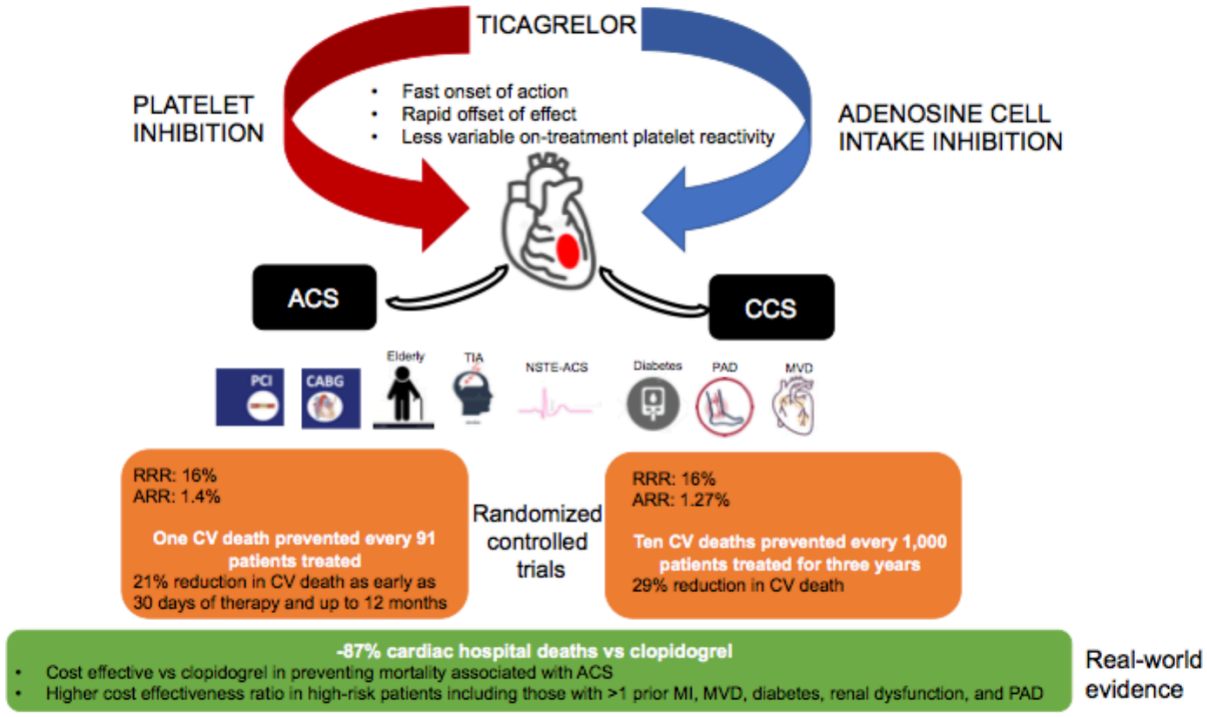


FIGURE LEGEND

Figure 1. Cardiovascular protective benefit of ticagrelor over clopidogrel in ACS patients. Mortality benefit (panel A) and bleeding risk (panel B). Graphical elaboration of data in [309,347,348,351,352,354,358,359].

Figure 2. Cardiovascular protective benefit of ticagrelor in patients with prior MI (1 to 3 years) and at least one of the following additional high-risk features: age of 65 years or older, diabetes mellitus requiring medication, a second prior spontaneous MI, multivessel coronary artery disease, or chronic renal dysfunction. Mortality benefit (panel A) and bleeding risk (panel B). Graphical elaboration of data in [313,335,386,388].

Figure 3. Ticagrelor benefit in ACS and CCS patients. ACS, acute coronary syndrome; CABG, coronary artery bypass graft; CCS, chronic coronary syndrome; MI, myocardial infarction; MVD, multivessel disease, NSTE-ACS, acute coronary syndromes without ST-segment elevation; PCI, percutaneous coronary intervention; PAD, peripheral artery disease; TIA, transient ischemic attack.

CHAPTER 5: New insights in coronary physiology

1) ADDED Index or percentage diameter of residual coronary stenosis to risk-stratify patients presenting with STEMI

1. Introduction

Multivessel coronary artery disease (MVD) is commonly observed in patients presenting with STEMI, occurring in about half of the patients undergoing PCI with significant impact on in-hospital and long-term clinical outcomes [398,399]. While it is recommended to treat the "culprit" stenosis, evidence supporting revascularization of residual "significant" coronary artery stenosis is conflicting [400]. Recent randomized trials showed improved clinical outcomes in patients undergoing complete revascularization as compared with patients in whom culprit-only PCI was performed [401–404]. Although a FFR-guided complete coronary revascularization was associated with a significant advantage in terms of car- diovascular events, in daily practice the vast majority of decisions about revascularization are based on the visually estimated diameter stenosis (DS) assessed at the angiography, being a DS ≥50% historically used as cut-off to justify revascularization [403,405–408]. However, FFR measurement of non-culprit coronary artery stenosis remains largely underused. A new recently validated Angiography-DeriveD hEmoDynamic index (ADDED index), taking into account both the minimal lumen diameter of a coronary artery stenosis and the amount of jeopardized myocar- dium subtended, was able to predict the functional significance of a cer- tain intermediate coronary artery stenosis, due to its high correlation with the FFR [409]. The aim of the present retrospective study was to compare the prognostic value of the ADDED Index with DS of residual coronary stenosis (RS) in patients presenting with STEMI and MVD, after successful PCI of the culprit lesion.

2. Materials and methods

All consecutive patients presenting with STEMI who referred to our department for primary, rescue or elective (after successful thrombolysis) PCI between January 2013 and December 2015 were included. Diagnosis of STEMI and clinical/interventional management was made according to the

current guidelines [400]. PCI was performed according to the conventional strategies and operators' routine practice. Patients with previous CABG, CTO, diffusely diseased main vessels, undergoing not successful PCI of the culprit stenosis, or patients who did not survive after the acute procedure were excluded. In patients with MVD, the de- cision to perform non-culprit vessel PCI, either during the index proce- dure or in a staged session, was left to the operator choice. Staged PCI was defined as revascularization of at least one non-culprit lesion dur- ing the index hospital admission or planned in the following 30 days. Digitally archived angiograms were reviewed by two interventional car- diologists blinded to clinical outcomes. Intermediate coronary artery stenosis was defined on the basis of visual estimation as those deter- mining a reduction of vessel diameter comprised between 30% and 75% [410]. Two-dimensional QCA was performed offline using the cardio- vascular angiography analysis system (Pie Medical Imaging, Maastricht, the Netherlands) and reference vessel diameter (RVD), lesion length (LL) and minimal lumen diameter (MLD) were calculated. The amount of perfused myocardium subtended by the target stenosis was assessed using the Duke Jeopardy Score (DJS) as previously reported [409,411,412]. The ADDED index for a single vessel was defined as the ratio between the DJS and the MLD [409].

After completion of eventually staged procedures, patients were grouped as following:

a) According to the ADDED Index of the RS: 1. Patients with at least one RS with an ADDED Index value ≥ 2.23

(ADDED Positive group) 2. Patients with one or more RS with an ADDED Index value < 2.23 and no RS with an ADDED index ≥ 2.23 (ADDED Negative group) b) According to the visually estimated DS of the RS:

1. Patients with at least one RS with a DS ≥ 50% (RS Positive group)

2. Patients with one or more RS with a DS<50% and no RS with a DS ≥ 50% (RS Negative group)

Patients without any RS served as control (Control group).

The study conformed to the Declaration of Helsinki on human research, and all patients gave informed consent.

Demographic, clinical, echocardiographic, angiographic and laboratory data at admission were collected and recorded in a computerized database, in accordance with our department's protocol for patients with STEMI undergoing PCI. Clinical follow-up was performed using hospital records and telephone interviews.

Primary endpoints were: 1) Major Adverse Cardiac Events (MACE), defined as the composite of all-cause death, myocardial infarction (MI), clinically driven revascularization; 2) deferred non-culprit Vessel-Oriented Clinical Events (VOCE), defined as composite of all- cause death, deferred non-culprit vessel related MI and clinically driven revascularizations. Staged procedures were not considered as events. All events were classified and adjudicated by a physician who was un- aware of the study group and of the angiographic details of the lesions.

Continuous variables are presented as mean ± standard deviation (SD) or median with interquartile range (IQR) as appropriate. Normal distribution was assessed by the Kolmogorov-Smirnov test. Categorical variables are reported as frequencies and percentages. Comparisons be- tween categorical variables were evaluated using the Pearson $\chi 2$ test. Continuous variables were compared using one-way ANOVA. A propen- sity score was built with a non-parsimonious method to account for po- tential differences in treatment allocation and then entered into a logistic regression model, considering complete revascularization as the dependent variable. In particular, all variables listed in Tables 1A, 1B, 2A and 2B with a p value <0.05 were incorporated into the model, and the score was then used in the proportional hazards analyses as a covariate. The three groups have been analyzed pairwise. Clinical end points were evaluated by Kaplan-Meier method and Cox proportional hazard analysis. Data were analyzed with SPSS, version 25.0, software

3. Results

A total of 596 patients were included and 314 (53%) underwent complete coronary revascularization (Control group) because present- ing with one single vessel disease or undergoing PCI of non-culprit stenosis (29%), mainly in a staged procedure, on the basis of the operator's choice. Patients with at least one RS were grouped either according to the ADDED Index value

(153 patients in the ADDED Negative group and 129 in the ADDED Positive group) or to the DS of the RS (177 patients in the RS Negative group and 105 patients in the RS Positive group). Among these patients, the ADDED Index provided an important reclassification; in fact, as shown in the Supplementary Table 1S, 41% of patients with a RS deemed to be significant (≥50%) at the visual estima- tion (RS Positive) have been reclassified as Negative according to the ADDED Index (ADDED Index Negative), while 38% of patients with a non-significant RS (<50%) at the visual estimation (RS Negative) have been reclassified as Positive on the basis of the ADDED Index (ADDED Index Positive).

When the ADDED Index was used to classify patients with a RS, those included in the ADDED Positive group were significantly older, with higher prevalence of diabetes mellitus, hypertension, hyperlipid- emia and peripheral artery disease (Table 1A). A similar proportion of patients among groups underwent primary PCI. Left Anterior Descend- ing Artery (LAD) was more often the culprit vessel of patients included in both the Control and the ADDED Negative groups as compared with the ADDED Positive group (Table 2A). No significant difference was found between the three groups in terms of proportion of DES im- planted for the treatment of the culprit stenosis. PCI of non-culprit ste- nosis was performed, at operator's discretion, in 92 (29%), 30 (20%) and 31 (24%) patients respectively included in the Control, ADDED Neg- ative and ADDED Positive groups. Of note, among patients included in the ADDED Positive group, as compared with the ADDED Negative group, the LAD was more often left untreated despite the presence of a RS with a comparable DS at visual estimation. The Left Circumflex (LCX) was equally left untreated in half of the patients included in the two groups while the right coronary artery (RCA) was more often left untreated in the ADDED Negative group.

When visually estimated DS was used to classify patients with a RS, those included in the RS Positive group (DS ≥ 50%) were significantly older, with higher prevalence of hypertension and peripheral artery dis- ease (Table 1B). A similar proportion of patients among groups underwent primary PCI and the LAD was more often the culprit vessel.

(DS: Diameter Stenosis, LAD: Left Anterior Descending Artery, LCX: Left Circumflex, MLD: Minimal Lumen Diameter, PCI: Percutaneous Coronary Intervention, RCA: Right Coronary Artery, TV: Target Vessel, *: $p < 0.05$ RS Positive vs RS Negative group).

No significant difference was found between the three groups in terms of proportion of DES implanted for the treatment of the culprit stenosis (Table 2B). Distribution of the residual vessels was similar among the two groups excepted for the LCX which was more often left untreated in the RS Positive group.

Clinical follow-up was obtained in 589 (99%) of 596 patients at a me- dian of 24 months (14–40 month). At the Kaplan-Meier analysis, both MACE-free and VOCE-free survival were significantly lower in the ADDED Positive group as compared with both the ADDED Negative and the Control groups (p for trend <0.001). In addition, no significant difference was found between the ADDED Negative and Control groups (MACE: $p = 0.81$ and VOCE: $p = 0.42$) (Fig. 1, panels A and B). At the Propensity Score adjusted Cox's analysis, (Table 3A), MACE rate was sig- nificantly higher in the ADDED Positive group (28%) as compared with both the ADDED Negative (6%, hazard ratio [HR] 4.96, 95% confidence interval [CI] 2.38–10.32, $p < 0.001$) and the Control groups (7%, HR: 3.27 [1.54–6.93], $p < 0.001$). This difference was mainly driven by the higher rate of overall clinically driven revascularizations and the higher incidence of MI. Similarly, the rate of VOCE was significantly higher in patients included in the ADDED Positive group (25%) as compared with both the ADDED Negative (5%, HR: 5.63 [2.46–12.79], $p < 0.001$) and the Control groups (3%, HR: 10.09 [3.33–30.56], $p < 0.001$). This dif- ference was mainly driven by the higher rate of deferred non-culprit vessel related MI and clinically driven revascularizations. When patients were classified according to the visually estimated DS of the RS (Table 3B), at the Kaplan-Meier analysis, both MACE-free and VOCE-free survival were significantly lower in the RS Positive group as compared with both the RS Negative and the Control groups (p for trend <0.001). In addition, no significant difference was found between the RS Negative and the RS Positive groups (MACE: $p = 0.13$ and VOCE: $p = 0.11$) while a significant difference was also found between the

RS Negative and Control groups (MACE: p = 0.01 and VOCE: p < 0.001) (Fig. 2, panels A and B). At the Propensity Score adjusted Cox's analysis, (Table 3B), patients included in the RS Positive group showed only a trend towards higher MACE rate (19%) as compared with Control group (7%, HR: 2.24 [0.98–5.12], p = 0.06). In addition, the rate of MACE did not significantly differ between the RS Positive and the RS Negative groups (14%, HR: 1.53 [0.84–2.77], p = 0.16). Furthermore, the rate of VOCE was significantly higher in patients included in the RS Positive group (17%) as compared with Control group (3%, HR: 6.64 [2.01–21.86], p < 0.001). Conversely, the rate of VOCE did not signifi- cantly differ between the RS Positive and the RS Negative groups (11%, HR: 1.63 [0.86–3.10], p = 0.13).

4. Discussion

In the present study we showed the usefulness of the ADDED Index to identify those patients presenting with STEMI and multivessel disease who would benefit the most of complete myocardial revascularizа- tion. In fact, after PCI of the culprit stenosis, deferring treatment of RS with an ADDED Index ≥2.23 is associated with a significant higher risk of cardiovascular events. In the ADDED Positive group indeed, the higher incidence of both MACE and VOCE was mainly driven by the higher rate of both myocardial infarctions and clinically driven revascu- larizations. Of note, clinical outcome of patients included in the ADDED Negative group, namely those with one or more RS with a negative ADDED Index value, did not differ significantly as compared with the Control group. Differently, when patients were grouped on the basis of visually estimated DS, although those with a positive (DS ≥ 50%) RS showed the highest incidence of both MACE and VOCE, patients' clinical outcome did not differ significantly from patients with a negative (DS < 50%) RS, being these latter patients at higher risk of clinical events as compared with Control group, suggesting that visual estimation of RS should not be used to safely defer revascularization because of the higher risk to underestimate the ischemic potential of RS, particularly those subtending large myocardial mass.

Taken together, these results suggest that the ADDED Index might help to decide whether or not to treat intermediate coronary artery ste- nosis after PCI of the culprit stenosis in STEMI patients with MVD. On the contrary, a decision based on the visual estimation of the RS should not be adopted to defer a complete coronary revascularization, particularly in this clinical setting.

Routine revascularization of "significant" non-culprit stenosis should be considered in STEMI patients with MVD before hospital dis- charge, preferably during a staged procedure [400]. In this setting, a com- plete coronary revascularization was associated with a significant reduction of cardiovascular events, as compared with patients in whom the culprit lesion was only treated [400,404]. However, the decision of performing or not the PCI of the non-culprit stenosis may be challeng- ing when facing with intermediate coronary artery stenosis. Angio- graphic assessment of lesion severity conveys a significant risk to overestimate or underestimate the functional significance of intermedi- ate coronary artery stenosis, particularly those supplying respectively small and large myocardial territories [401,413]. The usefulness of FFR in the setting of the acute coronary syndromes has been well established as well as for stable coronary artery disease [403,414]. In particular, a FFR- guided complete revascularization of non-culprit stenosis, after primary PCI, showed to be safe and associated with a reduction in cardiovascular hard endpoints. However, FFR is still underused particularly in ACS pa- tients, probably because of concerns on procedural time duration, aden- osine administration and pressure-wire manipulation [414–416]. Hence, planning a staged procedure to perform a PCI of an intermediate coro- nary artery stenosis on the basis of the visual estimation of diameter ste- nosis would increase the risk of performing PCI for "non-functionally" significant coronary artery stenosis, thereby increasing both the risks and costs for procedures that are not really necessary from a clinical standpoint. Moreover, in a not negligible percentage of cases, staged measurement of FFR finds not-functionally significant coronary stenosis while exposing the patient to all the potential risk of an invasive proce- dure. At this regard, indeed, the percentage of significant (DS $\geq$ 50%) non–culprit coronary artery stenosis with a negative FFR Value (>0.80) was 31% in the DANAMI-3–PRIMULTI trial and 50% in the

Com- pare Acute trial [6,16]. To further extend the available evidence, in our patients' population, 41% of stenosis stated “significant” at visual esti- mation (DS ≥ 50%) had a negative ADDED Index value (<2.23), thereby with a high risk to find a negative FFR value if this latter would have been measured. On the contrary, 38% of the stenosis stated “not significant” at visual estimation (DS < 50%) had a positive ADDED Index value (≥2.23) at high risk, indeed, to be functionally significant. Therefore, to overcome these limitations, the assessment of non-culprit intermediate coronary artery stenosis is generally postponed to a later stage by performing non-invasive imaging tests, bearing in mind all the potential limitations associated with such non-invasive procedures [417].

Thereby, an angiographic-based tool able to predict the FFR value, drug- and wire-free, would limit staged procedures to functionally sig- nificant coronary artery stenosis only, thereby reducing the risk of performing clinically unnecessary coronary interventions.

The ADDED Index complies with this function, allowing to safely defer, better than the visual estimation, the treatment of non- functionally significant coronary artery stenosis without increasing the risk of major cardiovascular events at long term follow up. In addition, such index might be used to plan staged procedures for patients who would benefit the most from functionally complete coronary revascu- larization. Finally, the ADDED Index might decrease the need for further non-invasive testing or repeated unnecessary catheterizations and therefore shorten diagnostic work-up after an acute MI.

This study might be affected by the limitations inherent to all retro- spective registries: that is, events underreporting, low event rate, espe- cially for death, bias related to the operator's decision as to the revascularization strategy to be adopted, and many other potential con- founding factors. In particular, the decision to perform a complete coro- nary revascularization might have been influenced by several clinical and procedural features; these limitations remain, although we tried to minimize their impact by performing a propensity score adjusted Cox regression analysis to assess the clinical outcome. FFR was not ap- plied to guide revascularization of non-culprit intermediate

coronary artery stenosis and non-invasive functional testing was available only in a few patients but we are unable to evaluate whether they have been used for PCI guidance. Even though most of the staged procedures (95%) were performed during the index hospitalization, we cannot ex- clude that some deferred non-culprit PCI, particularly those occurred within 6 months (n = 7) from discharge, might have been originally planned later than 30 days for several reasons that we cannot account due to the retrospective nature of the present study. Both MLD and visu- ally estimated DS was derived by the angiography performed during the acute phase and, in such adrenergic context, this might have leaded to an overestimation of the stenosis severity.

5. Conclusions

Among patients presenting with STEMI and MVD, calculation of the ADDED Index, rather than the visually estimated diameter, of the resid- ual coronary artery stenosis, allows to identify those patients who would benefit the most from a complete coronary revascularization while avoiding unnecessary PCI or adjunctive invasive or non-invasive procedures to assess the functional significance of non-culprit coronary stenosis.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.carrev.2021.01.030.

Table 1A
Clinical characteristics.

	No residual stenosis	Residual stenosis		*p* value
	Control group	ADDED Index Negative	ADDED Index Positive	
n	314	153	129	
Age	59 ± 12	63 ± 12	64 ± 12	<0.001
Male gender	244(78)	116(76)	100(77)	0.90
LVEF (%)	44 ± 8	44 ± 7	42 ± 8	0.12
Diabetes	58(18)	28(18)	38(29)*	0.02
Hypertension	169(54)	90(59)	89(69)	0.01
Hyperlipidaemia	112(36)	58(38)	64(50)	0.02
Smoker	131(42)	53(35)	49(38)	0.32
Previous MI	23(7)	12(8)	16(12)	0.21
Previous PCI	19(6)	12(8)	10(8)	0.70
PAD	1(0)	3(2)	6(5)	0.01
CKD	7(2)	2(1)	7(5)	0.08
Atrial fibrillation	2(1)	1(1)	4(3)	0.08

(CKD: Chronic Kidney Disease, LVEF: Left Ventricle Ejection Fraction, MI: Myocardial Infarction, PAD: Peripheral Artery Disease, PCI: Percutaneous Coronary Intervention, *: $p < 0.05$ vs ADDED Negative group).

Table 1B
Clinical characteristics.

	No residual stenosis	Residual stenosis		*p* value
	Control group	RS Negative	RS Positive	
n	314	177	105	
Age	59 ± 12	63 ± 12	65 ± 13	<0.001
Male gender	244(78)	140(79)	76(72)	0.41
LVEF (%)	44 ± 8	43 ± 8	43 ± 7	0.41
Diabetes	58(18)	40(23)	26(25)	0.29
Hypertension	169(54)	110(62)	69(66)	0.04
Hyperlipidaemia	112(36)	77(43)	45(43)	0.16
Smoker	131(42)	66(37)	36(34)	0.34
Previous MI	23(7)	19(11)	9(9)	0.44
Previous PCI	19(6)	14(8)	8(8)	0.70
PAD	1(0)	5(3)	4(4)	0.02
CKD	7(2)	6(3)	3(3)	0.75
Atrial fibrillation	2(1)	3(2)	2(2)	0.43

(CKD: Chronic Kidney Disease, LVEF: Left Ventricle Ejection Fraction, MI: Myocardial Infarction, PAD: Peripheral Artery Disease, PCI: Percutaneous Coronary Intervention).

Table 2A
Angiographic and procedural characteristics.

	No residual stenosis	Residual stenosis		*p* value
	Control group	ADDED Index Negative	ADDED Index Positive	
n	314	153	129	
Revascularization strategy				0.51
Elective PCI	61(19)	26(17)	23(18)	
Rescue PCI	58(18)	20(13)	20(15)	
Primary PCI	195(62)	107(70)	86(67)	
Number of diseased vessels				<0.001*
1	222(71)	0(0)	0(0)	
2	82(26)	107(70)	61(47)	
3	10(3)	46(30)	68(53)	
MVD	92(29)	153(100)	129(100)	<0.001
Target vessel PCI				<0.001*
LAD	173(55)	87(57)	47(36)	
LCX	32(10)	23(15)	23(18)	
RCA	109(35)	43(28)	59(46)	
Stent diameter	3.1 ± 0.4	3.0 ± 0.4	3.0 ± 0.4	<0.001
Stent length	26 ± 14	29 ± 16	28 ± 15	0.07
Stent type				0.10
Bare metal stent	28(9)	8(5)	15(12)	
Drug eluting stent	286(91)	145(95)	114(88)	
Non-culprit PCI	92(29)	30(20)	31(24)	0.07
Mutivessel PCI	33(36)	9(30)	8(26)	0.55
Residual vessel				
LAD		39(25)	79(61)	<0.001
DS(%)		46(37–50)	45(40–56)	0.21
ADDED Index		1.54 (1.18–1.82)	3.08 (2.61–3.62)	<0.001
LCX		74(48)	68(53)	0.48
DS(%)		45(37–53)	57(49–70)	<0.001
ADDED Index		1.43 (1.20–1.67)	2.39 (1.56–3.32)	<0.001
RCA		67(44)	38(29)	<0.001
DS(%)		43(38–50)	48(40–61)	0.07
ADDED Index		1.11 (0.92–1.41)	1.54 (1.02–2.50)	0.02

(DS: Diameter Stenosis, LAD: Left Anterior Descending Artery, LCX: Left Circumflex, MLD: Minimal Lumen Diameter, PCI: Percutaneous Coronary Intervention, RCA: Right Coronary Artery, TV: Target Vessel, *: $p < 0.05$ ADDED Positive vs ADDED Negative group).

Table 2B
Angiographic and procedural characteristics.

	No residual stenosis	Residual stenosis		*p* value
	Control group	RS Negative	RS Positive	
n	314	177	105	
Revascularization strategy				0.34
Elective PCI	61(19)	28(16)	21(20)	
Rescue PCI	58(18)	23(13)	17(16)	
Primary PCI	195(62)	126(71)	67(64)	
Number of diseased vessels				<0.001*
1	222(71)	0(0)	0(0)	
2	82(26)	125(71)	43(41)	
3	10(3)	52(29)	62(59)	
MVD	92(29)	177(100)	105(100)	<0.001
Target vessel PCI				0.19
LAD	173(55)	85(48)	49(47)	
LCX	32(10)	28(16)	18(17)	
RCA	109(35)	64(36)	38(36)	
Stent diameter	3.1 ± 0.4	3.0 ± 0.4	3.0 ± 0.4	0.005
Stent length	26 ± 14	27 ± 13	32 ± 19	0.005
Stent type				0.35
Bare metal stent	28(9)	14(8)	9(9)	
Drug eluting stent	286(91)	163(92)	96(91)	
Non-culprit PCI	92(29)	34(19)	27(26)	0.049*
Mutivessel PCI	33(36)	10(29)	7(26)	0.56
Residual vessel				
LAD		68(38)	50(48)	0.14
DS(%)		40(36–46)	55(44–60)	<0.001
ADDED Index		2.27 (1.54–3.09)	2.86 (1.82–3.61)	0.03
LCX		72(41)	72(69)	<0.001
DS(%)		41(35–45)	59(52–70)	<0.001
ADDED Index		1.43 (1.16–1.82)	1.82 (1.43–2.62)	<0.001
RCA		64(36)	41(39)	0.70
DS(%)		40(35–47)	54(45–65)	<0.001
ADDED Index		1.05 (0.90–1.20)	1.43 (1.00–1.96)	0.01

(DS: Diameter Stenosis, LAD: Left Anterior Descending Artery, LCX: Left Circumflex, MLD: Minimal Lumen Diameter, PCI: Percutaneous Coronary Intervention, RCA: Right Coronary Artery, TV: Target Vessel, *: $p < 0.05$ RS Positive vs RS Negative group).

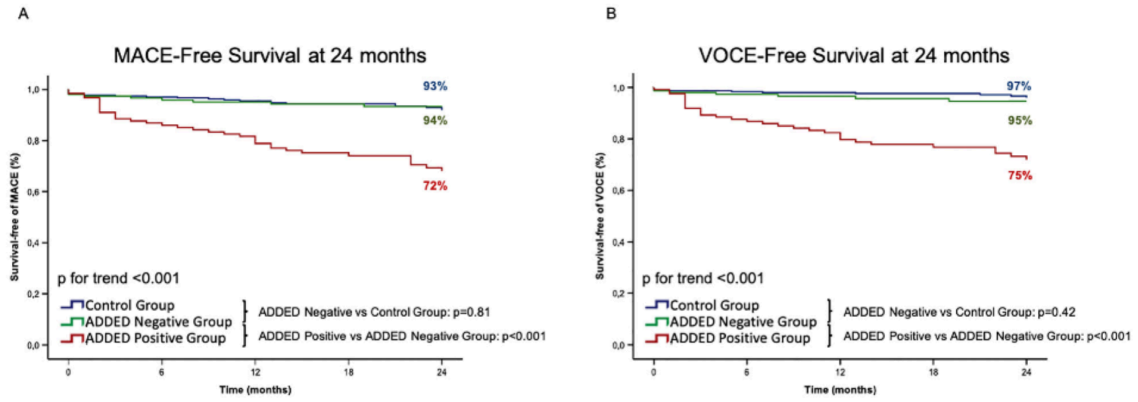


Fig. 1. Kaplan-Meier analysis of the two-primary endpoints at 2-years follow-up in patients grouped according to the ADDED Index of RS. Panel A. MACE-free survival was significantly lower in the ADDED Positive group as compared with both the ADDED Negative and the Control groups. Of note, no significant difference was found between the Control Group and the ADDED Negative group. Panel B. VOCE-free survival was significantly lower in the ADDED Positive group as compared with both the ADDED Negative and the Control groups. Of note, no significant difference was found between the Control Group and the ADDED Negative group.

Table 3A
Clinical events at 24 months follow up.

	Control group	ADDED Index Negative	PS adjusted HR (95%CI)	*p* value	ADDED Index Positive	PS adjusted HR (95%CI)	*p* value
n	311	152			126		
Overall death	10 (3)	5 (3)			7 (6)		
	Reference		2.09 (0.33–13.08)	0.43		3.14 (0.59–16.73)	0.18
		Reference				1.44 (0.45–4.63)	0.54
Non-fatal MI	8 (3)	3 (2)			10 (8)		
	Reference		0.51 (0.11–2.42)	0.40		2.19 (0.63–7.62)	0.41
		Reference				4.06 (1.12–14.76)	0.03
Deferred non-culprit vessel related non-fatal MI	–	1 (1)			6 (5)		
	Reference		–	–		–	–
		Reference				6.84 (0.82–57.30)	0.08
Overall revascularization	10 (3)	3 (2)			27 (21)		
	Reference		0.40 (0.09–1.76)	0.23		6.30 (2.07–19.19)	0.001
		Reference				11.33 (3.43–37.38)	<0.001
Deferred non-culprit vessel related revascularization	–	2 (1)			24 (19)		
	Reference		–	–		–	–
		Reference				15.14 (3.57–64.11)	<0.001
VOCE	10 (3)	7 (5)			31 (25)		
	Reference		2.19 (0.30–15.79)	0.44		10.09 (3.33–30.56)	<0.001
		Reference				5.63 (2.46–12.79)	<0.001
MACE	21 (7)	9 (6)			35 (28)		
	Reference		0.46 (0.06–3.48)	0.45		3.27 (1.54–6.93)	<0.001
		Reference				4.96 (2.38–10.32)	<0.001

Table 3B
Clinical events at 24 months follow up.

	Control group	RS < 50%	PS adjusted HR (95%CI)	*p* value	RS ≥ 50%	PS adjusted HR (95%CI)	*p* value
n	311	175			103		
Overall death	10 (3)	7 (4)			5 (5)		
	Reference		2.48 (0.43–14.28)	0.31		2.83 (0.49–16.24)	0.24
		Reference				1.01 (0.32–3.22)	0.98
Non-fatal MI	8 (3)	9 (5)			4 (4)		
	Reference		1.27 (0.38–4.26)	0.70		0.95 (0.23–3.96)	0.94
		Reference				0.81 (0.25–2.66)	0.73
Deferred non-culprit vessel related non-fatal MI	–	5 (3)			2 (2)		
	Reference		–	–		–	–
		Reference				0.76 (0.15–3.98)	0.75
Overall revascularization	10 (3)	14 (8)			16 (15)		
	Reference		1.59 (0.55–4.54)	0.39		3.64 (1.23–10.77)	0.02
		Reference				2.25 (1.09–4.63)	0.03
Deferred non-culprit vessel related revascularization	–	13 (7)			13 (13)		
	Reference		–	–		–	–
		Reference				2.01 (0.93–4.36)	0.08
VOCE	10 (3)	20 (11)			18 (17)		
	Reference		9.17 (2.72–30.86)	<0.001		6.64 (2.01–21.86)	<0.001
		Reference				1.63 (0.86–3.10)	0.13
MACE	21 (7)	24 (14)			20 (19)		
	Reference		3.08 (0.98–9.67)	0.05		2.24 (0.98–5.12)	0.06
		Reference				1.53 (0.84–2.77)	0.16

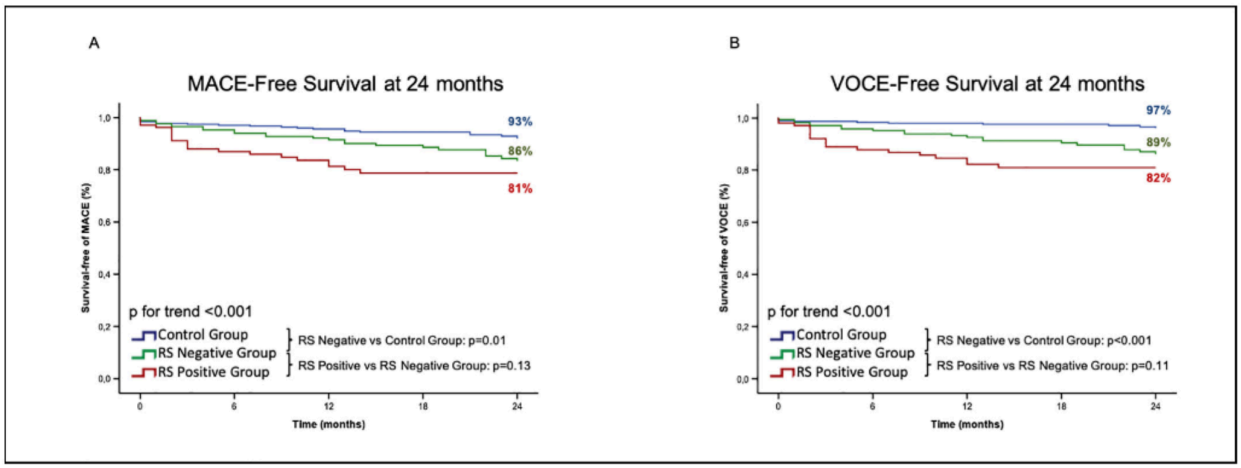


Fig. 2. Kaplan-Meier analysis of the two-primary endpoints at 2-years follow-up in patients grouped according to the visually estimated diameter of RS. Panel A. MACE-free survival was significantly lower in the RS Positive group. Of note, a significant difference was also found between the Control group and the RS Negative group, while no significant difference was found between this latter group and the RS Positive group. Panel B. VOCE-free survival was significantly lower in the RS Positive group. Of note, a significant difference was also found between the Control group and the RS Negative group, while no significant difference was found between this latter group and the RS Positive group.

2) Impact of the extension of myocardial mass subtended by an intermediate coronary stenosis on diagnostic performance of the non-hyperemic indexes: the need for a gray zone (submitted)

Introduction

The Fractional Flow Reserve (FFR) represents the gold standard for invasively assessing the ischemic potential of an equivocal coronary artery stenosis.[416] It has been well validated in several clinical and anatomic context and it has been shown to guide coronary revascularization better than angiography [417-426]. Non Hyperemic pressure-derived Indexes (NHI) have been recently introduced, and the instantaneous wave-free ratio (iFR) has been earlier described as alternative to the FFR; it does not require hyperemic drugs since it samples intracoronary pressure during the "diastolic wave-free" period, where microvascular resistance are supposed to be lower and stable [427]. However, it has been shown that microvascular resistance during the wave-free period can be lowered even further after adenosine administration, suggesting that calculating the iFR during adenosine administration (iFRADO) may improve its accuracy [428]. Furthermore, the hybrid approach, requiring FFR measurement when the iFR values are comprised between 0.86 and 0.93, has been shown to increase its diagnostic performance [429]. However, two large-scale randomized trials showed the iFR to be clinically non-inferior to the FFR [430,431]. Starting from these results, several newer NHI have been developed and validated showing a good correlation with both the FFR and iFR. The Resting Full-cycle Ratio identifies the lowest distal coronary pressure to the aortic pressure ratio (Pd/Pa) during the entire cardiac cycle, while the diastolic Pressure Ratio (dPR) measures the Pd/Pa during the flat period of the dP/dt of the aortic pressure [432,433]. Notably, the FFR specifically relate the severity of a stenosis to the mass of myocardial tissue subtended [434]. However, it remains unclear whether the extension of the perfused myocardial mass might affect the accuracy of NHI [428,435,436]. Thus, we aimed this study at evaluating the diagnostic performance of the NHI on the basis of the extension of myocardial tissue subtended by the equivocal coronary artery stenosis assessed.

Methods

From January 2018 to August 2019, all consecutive patients undergoing physiological assessment of an equivocal coronary artery stenosis using both the FFR and RFR measurement were screened. The study conformed to the Declaration of Helsinki on human research, and all patients gave informed consent. Patients with chronic total occlusions (CTO) or previously undergone to CABG as well as clinically unstable patients were excluded. Intermediate coronary artery stenoses were defined on the basis of visual estimation as those determining a reduction of vessel diameter comprised between 40% and 70% [437]. Serial lesions or supplying an infarcted area of myocardium, were also excluded.

Diagnostic coronary angiography was performed through radial or femoral percutaneous approach. Coronary stenoses were visually assessed by the operator. After heparin (70–100 IU/kg IV) administration, nitrates were injected to get maximum coronary vasodilatation (nitroprusside 0.6 μg/kg IC bolus) and, as soon as the calibration was performed, a 0.014-inch pressure-wire (Pressure Wire X, ABBOTT Vascular) was finally introduced and advanced into the guiding catheter and, after "equalization", it was advanced through the coronary artery, distally to the target stenosis. FFR was calculated as the lowest ratio of distal coronary pressure divided by the aortic pressure after achievement of maximal hyperemia at the steady-state, obtained using IV adenosine administration (140μg/kg/min) through a femoral vein [438]. For each coronary stenosis, both the RFR and FFR were recorded. In addition, during i.v. adenosine induced maximal hyperemia, a second measurement of the RFR was obtained (RFRADO). All the pressure waveform tracings were reviewed and anonymized and both the iFR, iFRADO, dPR and dPRADO were calculated from each individual waveform using a fully automated off-line software algorithm (CoroLab; Coroventis Research AB, Uppsala, Sweden). The relative difference, in percentage, between each NHI and its hyperemic counterpart (NHIADO) was also calculated (DNHI: DiFR, DdPR and DRFR). Localization on the coronary tree and quantitative assessment of stenosis severity at coronary angiography was performed, offline, independently by 2 expert interventional

cardiologists, blinded to clinical and hemodynamic data. Two-dimensional QCA was performed offline using the cardiovascular angiography analysis system (Centricity Cardiology CA1000, GE Healthcare, Barrington USA). Automated distance calibration was used to determine pixel size. All analyses were performed during the ECG- gated end-diastolic frame. Reference vessel diameter (RVD), lesion length (LL), minimal lumen diameter (MLD), and percentage diameter stenosis (DS) were calculated. The amount of perfused myocardium subtended by the target stenosis was assessed using the Duke Jeopardy Score (DJS) as previously described [439-443].

Continuous variables are presented as mean ± standard deviation (SD). The normal distribution was tested with the D'Agostino and Pearson test. The continuous variables were compared using the ANOVA test or the Kruskal-Wallis test as appropriate. Post-hoc analysis was performed using the Dunnet's Test. Categorical variables are reported as numbers and percentages. The comparison between categorical variables was performed using Pearson's $\chi 2$. Correlation was studied using Pearson's *r* test and linear regression. Receiver operator characteristics curves were compared as described by Hanley and McNeil [444]. Sensitivity, specificity, positive predictive value, negative predictive value and accuracy were calculated using the Mc Nemar's test. The diagnostic performance was assessed by using the Youden's index, calculated as [(sensitivity + specificity) – 1]. All statistical analyzes were performed using SPSS (version 26.0, Armonk, New York) and Prism 9.0 (GraphPad Software Inc., La Jolla, CA) software. The value of $p < 0.05$ was considered statistically significant.

Results

One-hundred-seventy coronary artery stenosis from 151 patients were grouped according to the extension of the subtended myocardial territory as assessed by the DJS: A) Small extension (DJS=2, n=82); B) Moderate extension (DJS=4, n=53); C) Large extension (DJS>4, n=35). Clinical and angiographic features are showed in Table 1 and Table 2, respectively. No significant difference in terms of age or left ventricle ejection fraction (LVEF) was found between the three groups. Patients were referred to coronary angiography mostly because of a chronic coronary

syndrome (66%) with no significant difference among the three groups. In patients presenting with an acute coronary syndrome (34%) the non-culprit intermediate coronary artery stenosis was functionally interrogated few days after PCI or rarely during the same acute procedure. The left anterior descending coronary artery (LAD) was more often measured (55%). In addition, patients included in the DJS=2 group presented more often with an intermediate stenosis of the right coronary artery (RCA) or the left circumflex (LCX) rather than the distal LAD, while patients included in the DJS=4 presented more often with an intermediate stenosis of the mid-LAD rather than the proximal LCX and rarely the large dominant RCA. On note, all the intermediate stenosis measured in patients included in the DJS>4 group mostly involved the proximal LAD and the left main (LM). When visually estimated, percentage diameter stenosis did not differ between the three groups; conversely, at QCA evaluation DS significantly decreased with the increasing of the extension of the subtended myocardial territory. Both the FFR, the NHI and the NHIADO significantly decreased across the three groups and functionally significant stenoses were more often found for larger subtended territories.

Diagnostic performance of NHI as compared with FFR.

With the FFR as reference, the Receiver Operating Characteristic (ROC) curves (Figure 1A) showed a good discrimination power for both the iFR (AUC:0.88 (0.83-0.93),

p<0.001), the dPR (AUC:0.88 (0.83-0.93), p<0.001) and the RFR (AUC:0.87 (0.82-0.92), p<0.001). In addition, a significant correlation was found between FFR and both iFR (r2: 0.57, p<0.001), dPR (r2: 0.57, p<0.001) and RFR (r2: 0.58, p<0.001), regardless of the extension of the subtended myocardial territory (Figures S1 and S2). As reported in Table 3, with the FFR as reference, diagnostic performance significantly changed across the three groups. With the increasing of the subtended myocardial territory, both the sensitivity and the positive predictive value (PPV) significantly increased while both specificity and negative predicting value (NPV) significantly decreased. Of note, mean Youden's index significantly changed with the increasing of the extension of jeopardized myocardium (DJS=2: 0,39±0.05, DJS=4: 0,68±0.06, DJS>4:

0,28±0.06, p<0.001) as it was lower for intermediate stenosis subtending small (DJS=2) and large (DJS>4) myocardial territories (Figure 2A).

Diagnostic performance of NHIADO as compared with FFR.

With the FFR as reference, the Receiver Operating Characteristic (ROC) curves (Figure 1B) showed a very good discrimination power for both the iFRADO (AUC: 0.96 (0.93- 0.98), p<0.001), the dPRADO (AUC: 0.96 (0.94-0.99), p<0.001) and the RFRADO (AUC: 0.97 (0.95-0.99), p<0.001). A significant correlation between FFR and both the iFRADO (r2: 0.88, p<0.001), dPRADO (r2: 0.89, p<0.001) and the RFRADO (0.89, p<0.001) was found, regardless to the extension of the subtended myocardial territory (Figures S3 and S4). As reported in Table 4, with the FFR as reference, diagnostic performance did not change significantly according to the extension of the jeopardized myocardium, excepted for dPR sensitivity and iFR negative predictive value. Of note, mean Youden's index (Figure 2B) did not significantly change according to the extension of the subtended myocardial territory (DJS=2: 0,76±0.02, DJS=4: 0,88±0.02, DJS>4: 0,82±0.02, p<0.72).

Diagnostic performance of the Hybrid Approach as compared with FFR.

The Receiver Operating Characteristic curves (Figure 1C) showed a good discrimination power for both the iFRHA (AUC: 0.93 (0.89-0.97), p<0.001), the dPRHA (AUC: 0.90 (0.85-0.94), p<0.001) and the RFRHA (AUC: 0.92 (0.88-0.97), p<0.001). With FFR as reference, the hybrid approach allowed for a good diagnostic performance, which did not significantly change according to the extension of myocardial territory, excepted for dPR sensitivity (Table 5). Similarly, the Youden's index (Figure 2C) did not significantly change with the extension of the subtended myocardial mass (DJS=2: 0,82±0.07, DJS=4: 0,84±0.02, DJS>4: 0,88±0.02, p<0.70).

Comparison between NHI, NHIADO and NHIHA

At the ROC analysis, NHIADO showed a significantly higher discrimination power as compared with the regular NHI for both the iFR (DAUC: 0.08 ± 0.03, p=0.03), the dPR (DAUC: 0.08 ± 0.03, p=0.03) and RFR (DAUC: 0.10 ± 0.03, p=0.002). Of note, no significant difference was found in

terms of discrimination power between NHIHA and NHIADO (DAUC for iFR: 0.05 ± 0.04, p=0.07; DAUC for dPR: 0.02 ± 0.04, p=0.64; DAUC for RFR: 0.05 ± 0.04, p=0.17). Furthermore, as compared with NHI (0.45±0.18), Youden's index was significantly higher for both NHIADO (0.82±0.05, p<0.001) and NHIHA (0.84±0.04, p<0.001), while it was similar between NHIADO and NHIHA (p=0.51, Figure 3).

Interestingly, DNHI significantly increased with the extension of the subtended myocardial territory (Figure 4).

Diagnostic performance of dPR and RFR as compared with iFR.

A good correlation between iFR and both dPR and RFR was found (respectively, r2: 0.96 and 0.95, p<0.001, Figure S5) regardless of the extension of the subtended myocardial territory (Figure S6). Furthermore, a very high correlation was also found between the RFR and the dPR (r2: 0.96, p<0.001). The Receiver Operating Characteristic curves (Figure S7)

showed a very good discrimination power for both the dPR (0.99 [0.99-1.00], p<0.001) and the RFR (0.99 [0.97-1.00], p<0.001). As reported in the supplemental Table S1, with the iFR as reference, both the accuracy, sensitivity and specificity were high regardless of the extension of the subtended myocardial area.

Discussion

With the present study we provided the readers with the following informations:

1. Diagnostic performance of NHI is significantly influenced by the extension of the myocardial mass subtended by the functionally assessed stenosis; in particular, NHI might overestimate or underestimate the ischemic potential of intermediate stenosis subtending respectively large or small myocardial mass;
2. Either adenosine administration or the hybrid approach allows for a better diagnostic performance of the NHI regardless of the extension of the subtended myocardial territory;
3. Finally, newer NHI, such as the dPR and the RFR are equivalent to the iFR;

Influence of myocardial mass on diagnostic performance of NHI.

It has been already shown that iFR diagnostic accuracy might be influenced by the extension of myocardial mass subtended by the investigated stenosis. Kobayashi and colleagues have indeed previously showed that iFR specificity is significantly lower for intermediate stenosis of the left anterior descending artery and left main stem, thereby subtending a large myocardial mass. Our results are in line with this observation, being both the specificity and the sensitivity a function of the myocardial mass. In fact, along with the increasing of the subtended myocardial mass the sensibility increases while the specificity decreases. The Youden's Index, indeed, is particularly low either when the subtended myocardial mass is small (DJS=2) or very large (DJS>4) (Figure 3A). This result is not limited to the iFR, but it is also evident for both the dPR and the RFR. Of note, when adenosine is given and NHIADO measured, the influence of myocardial mass extension disappears. In fact, the Youden's Index did not significantly differ between the three groups of stenosis (Figure 3B) and it was significantly higher as compared with the regular "resting" one (Figure 4). This result is in agreement with previous studies demonstrating a significantly higher accuracy for hyperemic iFR values to correctly identify FFR positive stenoses [428]. Of note, NHI diagnostic accuracy significantly increases also when the hybrid approach is considered and the "gray zone" for NHI is allowed. In fact, in this case, the Youden's Index was significantly higher regardless of the extension of the jeopardized myocardium (Figure 3C and 4). The "hybrid approach" has been previously proposed by Petraco and colleagues [429]. It requires a "gray zone" for the iFR values (comprised between 0.86 and 0.93) where adenosine administration is allowed and FFR measured, providing a better accuracy to predict FFR positive stenoses. Our data further support this approach, since the influence of myocardial mass on NHI appears to be significantly reduced and the diagnostic performance significantly improved.

DNHI as measure of the subtended myocardial mass. When vessels supply a greater amount of myocardium the change in coronary flow, from rest to maximal hyperemia, is greater; thereby, the higher peak flow results in a larger pressure gradient across a given stenosis and a lower FFR

value.(20) Because NHI have been considered “resting” measures, performed by definition during submaximal hyperemia, and their values can be lowered even further with adenosine administration, the relative difference between each “resting” NHI and its “hyperemic” counterpart (DNHI) might be considered as the empiric measure of the extension of the subtended and stimulated myocardial mass [428,445]. For these reasons, one may predict a greater discordance between NHI and FFR with the increasing of the DNHI value, thereby for stenoses
subtending a larger amount of myocardium. In our study, indeed, we showed that DNHI increases along with the extension of the subtened myocardial mass.

A “class-effect” of Non-Hyperemic pressure-derived Indexes (NHI).

In our study we further extend the available evidence supporting the equivalence with iFR of newer NHI for functionally assess intermediate coronary artery stenosis. In fact, although the NHI differ from each other from a conceptual point of view, they are equivalent in clinical practice, providing a similar diagnostic performance to predict the FFR. A “class effect” can be proposed for such indexes since, in our patient’s population we confirm they work the same way.

In conclusion, our results suggest that diagnostic accuracy of NHI is significantly affected by the extension of the subtended myocardial mass, particularly underestimating the ischemic potential of intermediate stenosis subtending small territories. The hybrid approach, allowing the combined use of NHI and FFR, might be useful to overcome this limitation.

Table 1. Clinical characteristics

	All Patients (n=151)	DJS=2 (n=67)	DJS=4 (n=50)	DJS>4 (n=34)	p value
Age	63 ± 9	63 ± 8	62 ± 8	63 ± 10	0.62
BMI (kg/m^2)	26.9 ± 3.9	27.1 ± 3.8	26.5 ± 4.4	27.1 ± 3.3	0.67
Male Gender, n (%)	133 (88)	60 (90)	39 (78)	34 (100)	0.01
Smoking habit, n (%)	56 (37)	24 (36)	21 (42)	11 (32)	0.64
Hypertension, n (%)	102 (67)	44 (66)	37 (74)	21 (62)	0.45
Diabetes, n (%)	39 (26)	15 (22)	15 (30)	9 (26)	0.64
Hyperlipidemia, n (%)	75 (50)	32 (48)	27 (54)	16 (47)	0.75
Previous MI, n (%)	43 (28)	18 (27)	14 (28)	11 (32)	0.84
Stable Angina, n (%)	100 (66)	43 (64)	32 (64)	25 (73)	0.59
STEMI, n (%)	22 (15)	10 (15)	9 (18)	3 (9)	0.50
NSTEMI, n (%)	29 (19)	14 (21)	9 (18)	6 (18)	0.89
LVEF	50 ± 10	51 ± 10	51 ± 9	48 ± 13	0.58

(BMI: Body mass index; LVEF: Left ventricle ejection fraction; NSTEMI: non-ST elevation myocardial infarction; STEMI: ST elevation myocardial infarction).

Table 2. Angiographic characteristics

	All Stenosis (n=170)	DJS =2 (n=82)	DJS =4 (n=53)	DJS>4 (n=35)	p value
Target Vessel					<0.001
LM, n (%)	3 (2)	0 (0)	0 (0)	3 (9)	
LAD, n (%)	94 (55)	20 (24)	43 (81)	32 (91)	
LCX, n (%)	39 (23)	31 (38)	8 (15)	0 (0)	
RCA, n (%)	34 (20)	31 (38)	2 (4)	0 (0)	
$DS_{(visually\ estimated)}$, (%)	52 ± 14	52 ± 15	53 ± 13	52 ± 11	0.82
$DS_{(QCA)}$, (%)	47 ± 10	48 ± 10	47 ± 11	43 ± 8*	0.04
MLD (mm)	1.5 ± 0.5	1.4 ± 0.5	1.5 ± 0.5	1.8 ± 0.5*^	<0.001
RD (mm)	2.9 ± 0.7	2.7 ± 0.6	2.9 ± 0.7	3.1 ± 0.7*	0.03
Lesion lenght (mm)	17 ± 8	16 ± 7	19 ± 8	17 ± 10	0.23
FFR	0.82 ± 0.08	0.86 ± 0.07	0.80 ± 0.08*	0.76 ± 0.07*^	<0.001
FFR +, n (%)	71 (42)	19 (23)	26 (49)	26 (74)	<0.001
iFR	0.88 ± 0.08	0.92 ± 0.06	0.86 ± 0.09*	0.83 ± 0.09*	<0.001
iFR +, n (%)	84 (49)	22 (27)	32 (60)	30 (86)	<0.001
iFR_ADO	0.75 ± 0.12	0.80 ± 0.09	0.72 ± 0.13*	0.67 ± 0.11*	<0.001
ΔiFR, (%)	16 ± 9	14 ± 7	17 ± 10	20 ± 9*	0.003
dPR	0.89 ± 0.09	0.92 ± 0.06	0.86 ± 0.09*	0.83 ± 0.09*	<0.001
dPR +, n (%)	81 (48)	22 (27)	31 (58)	28 (80)	<0.001
dPR_{ADO}	0.75 ± 0.12	0.80 ± 0.10	0.72 ± 0.13*	0.67 ± 0.11*	<0.001
ΔdPR, (%)	16 ± 9	14 ± 7	17 ± 10	19 ± 8*	0.006
RFR	0.88 ± 0.08	0.92 ± 0.06	0.86 ± 0.08*	0.83 ± 0.09*	<0.001
RFR +, n (%)	85 (50)	24 (29)	32 (60)	29 (83)	<0.001

RFR_{ADO}	0.74 ± 0.12	0.79 ± 0.10	0.72 ± 0.13*	0.66 ± 0.11*	<0.00´
ΔRFR, (%)	16 ± 9	14 ± 7	17 ± 10	20 ± 10*	0.004

(DS: Diameter stenosis; LAD: Left anterior descending coronary artery; LCX: Left circumflex; LM: Left main coronary artery; MLD: Minimal lumen diameter; QCA: Quantitative coronary angiography; RCA: Right coronary artery; RD: Reference diameter; *:p<0.05 vs DJS=2; ^: p<0.05 vs DJS=4).

Table 3. Diagnostic performance of NHI as compared with FFR

dPR vs FFR	**Overall**	DJS=2	DJS=4	DJS>4	p value
Accuracy	80%	77%	87%	77%	0.33
Sensitivity	83%	58%	96%	88%	<0.01
Specificity	78%	83%	78%	44%	0.04
PPV	73%	50%	81%	82%	0.02
NPV	87%	87%	95%	57%	0.03
Difference with FFR	0.06±0.06	0.07±0.05	0.06±0.06	0.07±0.06	0.69
RFR vs FFR					
Accuracy	78%	77%	81%	74%	0.73
Sensitivity	83%	63%	92%	88%	0.02
Specificity	74%	81%	70%	33%	0.01
PPV	69%	50%	75%	79%	0.048
NPV	86%	88%	90%	50%	0.03
Difference with FFR	0.06±0.06	0.06±0.05	0.06±0.06	0.07±0.06	0.86
iFR vs FFR					
Accuracy	78%	74%	85%	77%	0.59
Sensitivity	83%	53%	96%	92%	0.03
Specificity	75%	81%	74%	33%	0.01
PPV	70%	45%	78%	80%	0.01
NPV	86%	85%	95%	60%	0.11
Difference with FFR	0.06±0.06	0.06±0.05	0.06±0.06	0.07±0.06	0.78

(NPV: Negative predictive value; PPV: Positive predictive value).

Table 4. Diagnostic performance of NHI_{ADO} as compared with FFR

dPR_{ADO} vs FFR	Overall	DJS=2	DJS=4	DJS>4	p value
Accuracy	91%	90%	94%	89%	0.59
Sensitivity	86%	68%	96%	88%	0.03
Specificity	95%	97%	93%	89%	0.48
PPV	92%	87%	93%	96%	0.57
NPV	90%	91%	96%	73%	0.08
Difference with FFR	0.07±0.05	0.06±0.04	0.08±0.06*	0.09±0.05*	0.04
Difference with dPR	0.14±0.07	0.13±0.06	0.14±0.08	0.16±0.08	0.06
RFR_{ADO} vs FFR					
Accuracy	91%	89%	93%	91%	0.45
Sensitivity	89%	74%	86%	92%	0.05
Specificity	92%	94%	89%	89%	0.70
PPV	89%	78%	89%	96%	0.17
NPV	92%	92%	96%	80%	0.29
Difference with FFR	0.08±0.05	0.07±0.04	0.08±0.05	0.10±0.05*	0.003
Difference with RFR	0.14±0.08	0.13±0.06	0.14±0.08	0.17±0.09*	0.04
iFR_{ADO} vs FFR					
Accuracy	91%	91%	92%	89%	0.81
Sensitivity	90%	84%	96%	88%	0.39
Specificity	92%	94%	89%	89%	0.70
PPV	89%	80%	89%	96%	0.25
NPV	93%	95%	96%	73%	0.02
Difference with FFR	0.07±0.05	0.06±0.04	0.08±0.05	0.10±0.05*	0.001
Difference with iFR	0.14±0.07	0.12±0.06	0.14±0.08	0.16±0.08*	0.04

Table 5. Diagnostic performance of Hybrid Approach as compared with FFR

dPR vs FFR	**Overall**	DJS=2	DJS=4	DJS>4	p value
Accuracy	93%	91%	92%	97%	0.54
Sensitivity	93%	79%	96%	100%	0.02
Specificity	93%	95%	89%	89%	0.49
PPV	90%	83%	89%	96%	0.34
NPV	95%	94%	96%	100%	0.72
RFR vs FFR					
Accuracy	94%	95%	91%	97%	0.38
Sensitivity	94%	89%	92%	100%	0.27
Specificity	94%	97%	89%	89%	0.28
PPV	92%	89%	89%	96%	0.56
NPV	96%	97%	92%	100%	0.52
iFR vs FFR					
Accuracy	94%	94%	92%	94%	0.93
Sensitivity	94%	89%	96%	96%	0.56
Specificity	93%	95%	89%	89%	0.49
PPV	91%	85%	89%	96%	0.42
NPV	96%	97%	96%	89%	0.54

Figure 1. Receiver Operating Characteristic curves. Panel A. With the FFR as reference, ROC curves showed a good discrimination power for both the iFR (0.88 (0.83-0.93), p<0.001), the dPR (0.88 (0.83-0.93), p<0.001) and the RFR (0.87 (0.82-0.92), p<0.001). Panel B. With the FFR as reference, ROC curves showed a significantly higher discrimination power for both the iFR_{ADO} (0.96 (0.93-0.98), p<0.001, ΔAUC vs iFR: 0.08 ± 0.03, p=0.03), the dPR_{ADO} (0.96 (0.94-0.99), p<0.001, ΔAUC vs dPR:: 0.08 ± 0.03, p=0.03) and the RFR_{ADO} (0.97 (0.95-0.99), p<0.001, ΔAUC vs RFR: 0.10 ± 0.03, p=0.002). Panel C. With the FFR as reference, ROC curves showed a good discrimination power for both the iFR_{HA} (0.93 (0.89-0.97), p<0.001), the dPR_{HA} (0.90 (0.85-0.94), p<0.001) and the RFR_{HA} (0.92 (0.88-0.97), p<0.001). No significant difference was found between NHI_{HA} and NHI_{ADO} (ΔAUC for iFR: 0.05 ± 0.04, p=0.07; ΔAUC for dPR: 0.02 ± 0.04, p=0.64; ΔAUC for RFR: 0.05 ± 0.04, p=0.17).

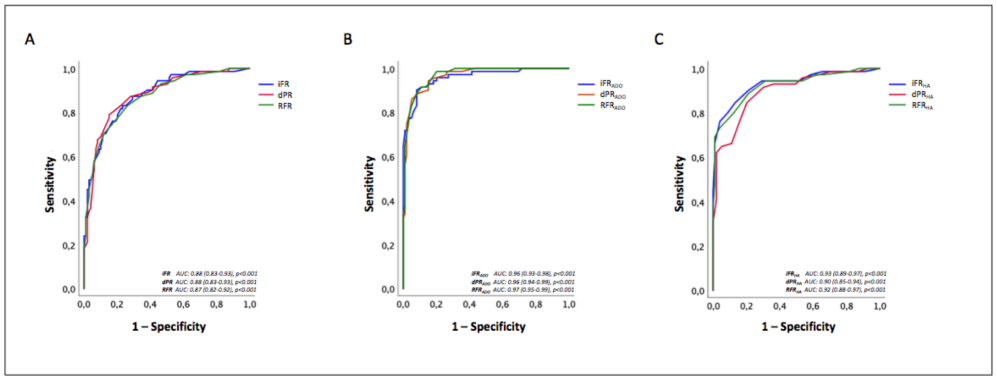


Figure 2. Youden's Index variation according to the Duke Jeopardy Score. Panel A. The Youden's index for both the iFR, dPR and the RFR significantly changes with the extension of the myocardial territory. Panel B describes the diagnostic performance of the hyperemic NHI (NHI_{ADO}). The Youden's index for both the iFR_{ADO}, dPR_{ADO} and the RFR_{ADO} is particularly high regardless of the extension of the myocardial territory. Panel C describes the diagnostic performance of NHI in case the hybrid approach would have been used. The Youden's index for both the iFR, dPR and the RFR is particularly high, and it does not change with the extension of the myocardial territory.

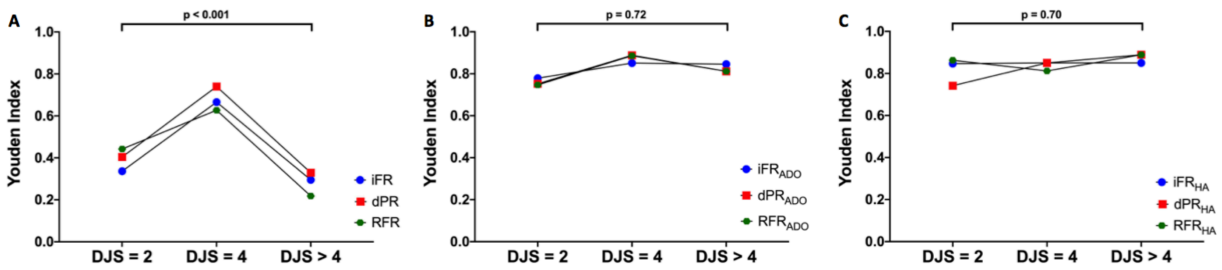


Figure 3. Youden's Index of NHI. With the FFR as standard of reference, a significant increase of the Youden's index was observed when using the hybrid approach (NHI_{HA}) or adenosine administration (NHI_{ADO}) as compared with standard NHI. In this latter case, Youden's index was lower for stenoses subtending small (DJS=2) or large myocardial mass (DJS>4).

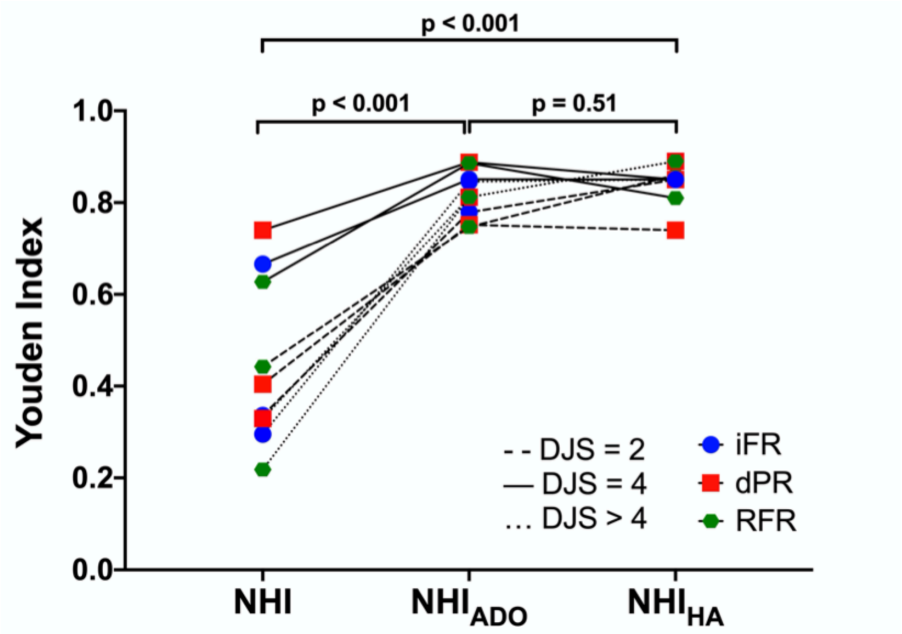
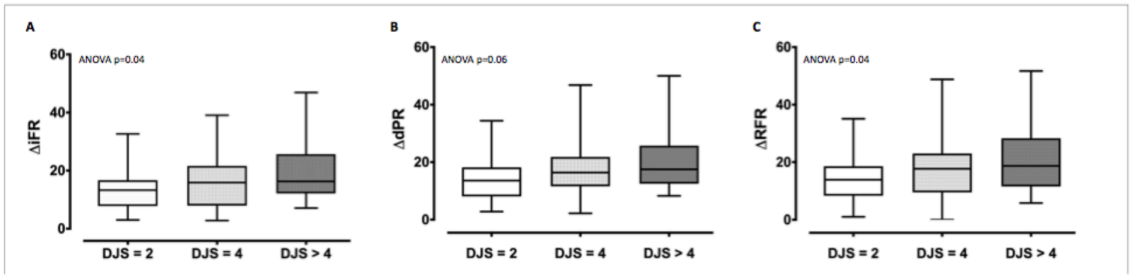


Figure 4. ΔNHI variation according to myocardial mass extension. Panel A. The relative difference between the iFR value and its hyperemic counterpart (ΔiFR) significantly increases with the extension of the subtended myocardium. Panel B. The relative difference between the dPR value and its hyperemic counterpart (ΔdPR) numerically increases along with the extension of the subtended myocardial mass. Panel C. The relative difference between the RFR value and its hyperemic counterpart (ΔRFR) is significantly associated with the extension of myocardial mass subtended by the assessed stenosis.



CHAPTER 6: DISCUSSION AND CONCLUSIONS

1) Discussion

In the field of coronary physiology, in recent years the search for an alternative parameter to FFR has spread, which is able to predict the hemodynamic significance of an intermediate degree stenosis, reducing its risks and costs. The iFR is considered by many authors to be a risk-free alternative to FFR, capable of avoiding the adverse events associated with the administration of adenosine. [33,34] This, however, is only partially true, since it is still an invasive measurement and the majority of complications are not related to the administration of adenosine, but rather occur in the initial period of the procedure, ranging from inserting the guide catheter to advancing the pressure wire [37]. Furthermore, it is not always possible to predict the FFR value from the iFR value, as demonstrated by some studies that detect areas of discrepancy between the two indices [42,446]. In this study, important answers were provided to questions related to the iFR and its relationship to the FFR. First of all, we have shown, as also known in some previous studies [42,446], that in our sample of patients there is a statistically significant correlation between the values of FFR and iFR. However, in our sample, there is a share of intermediate lesions in which there is a not insignificant discrepancy between the two values. Furthermore, it has been shown that, like FFR, iFR also has a statistically significant correlation with the Duke Jeopardy Score. This means that the iFR is also affected by the distribution territory downstream of the coronary stenosis studied. According to Lee et al., The discordance between iFR and FFR occurs more frequently when the lesion under study is on the anterior descending branch of the left coronary artery; otherwise, if the lesion is on the circumflex branch or on the right coronary artery, the two values show a good correlation. Furthermore, the same authors show that the clinical and angiographic characteristics of patients with discordance between iFR and FFR differ significantly.

Patients with negative FFR and positive iFR are more frequently female, older and with multiple comorbidities, and stenoses are more severe, longer and with greater atherosclerotic burden. Conversely, in the group with positive FFR and negative iFR there are more men, younger and

patients have fewer comorbidities, stenoses are less severe, shorter and with less atherosclerotic burden. These results are absolutely consistent with the results of our study; where, while maintaining the relationship between iFR and FFR for the different DJS values, the share of false positives and false negatives increases with low and high DJS. More specifically, in the group with DJS = 2, there is a greater number of false positives and, consequently, a lower sensitivity of the iFR compared to the FFR. In the group with DJS> 4, on the other hand, there is a higher number of false negatives and, consequently, a low specificity. These results indicate that the iFR is able to correctly estimate the FFR, and consequently the hemodynamic significance, of an intermediate grade coronary stenosis, when the myocardial territory underlying the stenosis is of intermediate size.

Conversely, when the DJS is low, therefore in distal vessels with reduced myocardial territory downstream, the iFR tends to overestimate the severity of the stenosis compared to the FFR. Consequently, referring only to the iFR value, it would tend to treat stenosis that are not hemodynamically significant more frequently, moreover in distal areas where technically angioplasty is usually more difficult to perform. Finally, in proximal areas, with large areas of myocardial tissue downstream and consequently with DJS> 4, the iFR tends to underestimate the severity of the stenosis compared to the FFR. Consequently, this would lead to a lower rate of PCI on hemodynamically significant stenosis, if we were based on the iFR value alone. This data is particularly risky, because stenosis on proximal and large-caliber vessels (such as the proximal anterior descending branch) would be untreated, even if they are hemodynamically significant and prognostically very significant. These results are consistent with data already present in the literature, [448] which indicate lower diagnostic accuracy of the iFR when the stenoses under study are located at the level of the common trunk or the proximal anterior descending branch. It is important to underline that the sample object of our study has clinical characteristics uniformly distributed among the various groups of DJS and that most of the angiographic characteristics do not differ significantly except for a difference in the minimum luminal diameter, in the localization

of the stenosis within the coronary tree and in the mean values of FFR, iFR and iFR after adenosine administration. The echocardiographic study of myocardial contractility was particularly relevant in our study. We have in fact evaluated the WMSI and the WMSI TV. As evident in table 1, there were no statistically significant differences within the groups, and the average value of WMSI TV was comparable to that of WMSI. This indicates that the myocardial territory underlying the stenosis studied showed good contractility, not being the site of previous ischemic insults.

After highlighting the diagnostic performance of the iFR compared to the FFR in relation to the DJS, we wondered if administring adenosine could modify the characteristics of the iFR and its relationship with the FFR. We then calculated the difference between iFR and iFR after administration of adenosine (iFRADO) and reported the percentage value: ΔiFR-iFRADO%. The difference between the groups was statistically significant, with $p = 0.032$ calculated by Kruskal-Wallis test, since the variables were not normally distributed. In the post-hoc analysis, only the difference between group 1 and group 3 was statistically significant with $p = 0.025$. These data show that as the DJS increases (and therefore the myocardial territory underlying the stenosis), the percentage difference between iFR and iFRADO increases. This shows that the cause of the difference in reliability between iFR and FFR, as well as the method of calculating the two values, is due to the incorrect assumption that WFP is comparable to the maximal hyperemia obtainable by administering Adenosine. This difference increases with the increase in the extension of the distribution area. Finally, we searched for the presence of a correlation between the ΔiFR-iFRADO% value and the DJS classes. We therefore found a statistically significant correlation between the aforementioned values: $R2 = 0.06$ $p < 0.001$, which indicates that as the DJS increases, there is an increase in ΔiFR-iFRADO%. For this reason iFR, despite being less expensive economically and less risky, not providing for the administration of adenosine, is less accurate than FFR. The low diagnostic performance of the iFR for high and low DJS values clearly indicate that this value cannot guide coronary revascularization in either very proximal or very distal stenosis, significantly reducing its field of action. Although numerous studies have shown the correlation

between iFR value and patient prognosis [33,34], exactly as was previously demonstrated for FFR [13,16], our data indisputably indicate that iFR, compared to at FFR, it has reduced diagnostic performance.

LIMITATIONS OF THE STUDY

It is necessary to point out some limitations related to the presented study. First of all, it is a retrospective, monocentric study, with a relative limited sample size, so it would be necessary to integrate this study with data from other centers, in order to expand the sample and eliminate potential selection bias. Although data from invasive evaluations carried out by several interventional cardiologists have been considered, in fact, there may be bias in the data collection, coming from the standardized technique with which we usually record the FFR in our laboratory or with the manual measurement of the iFR. Furthermore, we used QCA to estimate the angiographic characteristics of intermediate stenoses; although QCA may underestimate the severity of coronary artery stenosis, we considered the minimum luminal diameter (MLD) as a reference indicator [45] and its reliability is demonstrated by the fact that the calculated mean value differs significantly between the three DJS groups. Furthermore, we still considered the visual estimate to calculate the severity of the stenosis, reporting the percentage value together with the value measured by the QCA. It is important to consider that many of the enrolled patients had not previously performed a non-invasive test for myocardial ischemia: this finding is consistent with the fact that they were also patients with acute coronary syndrome. It would have been interesting to evaluate the extension of the ischemic myocardium using non-invasive techniques to establish a comparison with the FFR and iFR values. In addition, 39% of the patients enrolled in this study underwent coronary angiography following a diagnosis of acute coronary syndrome. In this setting, the use of FFR and iFR is controversial, especially due to the scarce evidence relating to the measurement of FFR and iFR in culprit vessels.

The use, instead, of this measurement in non-culprit vessels, is well validated in the literature and the FFR, as well as the iFR, can be used to study non culprit vessels even in the course of primary

PCI following the diagnosis of STEMI. Finally, regarding myocardial contractility, it is important to underline that in our patients WMSI TV was substantially comparable to WMSI; this data clearly indicates that the coronary stenosis studied underlie a healthy myocardial tissue and not the site of previous necrosis or ischemic insults. It would therefore be interesting to calculate the same data on vessels with previous necrosis to integrate them with those of our study to evaluate whether the relationships we found can also be extended to myocardial territories with previous ischemic insults.

2) CONCLUSIONS

In this study we demonstrated how the functional assessment of intermediate grade coronary stenosis, through the FFR and iFR, is influenced by the distribution territory downstream, measured through the DJS. In fact, as previously demonstrated for the FFR, the IFR is also influenced by the distribution area. In addition, although the IFR has a good diagnostic accuracy in all distribution territories, compared to the FFR, for less extensive territories (DJS = 2), the IFR tends to overestimate the severity of the stenosis compared to the FFR; vice versa, for larger territories (DJS> 4), and therefore with a higher prognostic impact, the iFR tends to underestimate the severity of the stenosis. As a demonstration, the difference between iFR and iFR after administration of adenosine (ΔiFR-iFRADO%) significantly increases as the extension of the distribution area increases. These data indicate that the use of relatively "safer" and "less expensive" functional methods, such as the iFR, can only be used in association with the gold-standard (FFR), according to a hybrid approach, in order to avoid under- treatment of significant stenoses and overtreatment of non-haemodynamically significant stenoses. Further studies are therefore needed to improve the use of these new methods in association with the FFR.

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4) CURRICULUM VITAE

FORMATO EUROPEO PER IL CURRICULUM VITAE

PERSONAL INFORMATIONS

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Telephone	**3890281475**
E-mail	**fed.serino@gmail.com**
Nationality	Italiana
Date of birth	06/05/1988

WORKING EXPERIENCE

• Date	*From 01/12/2020 to today*
• Institute	*AORN Cardarelli, Napoli*
• Activity	*Interventional cardiologist in Catheterization Laboratory and UCC*
• Date	*From 01/09/2019 to 30/11/2020*
• Institute	*ASL SALERNO, PO Maria SS Addolorata di Eboli*
• Activity	*Interventional cardiologist in Catheterization Laboratory and UCC*

EDUCATION AND TRAINING

• Date	*From 01/11/2018 to today*
• Institute	*"Federico II" University - Napoli*
• Activity	Ph.D "Cardiovascular Pathophysiology and Therapeutics"
• Date	*From 08/08/2013 al 25/07/2018.*
• Institute	*University "Federico II" - Napoli*
• Qualification	Medical specialization in Cardiovascular diseases Specialization thesis: ***IMPACT OF MYOCARDIAL SIZE ON INSTANTANEOUS WAVE-FREE RATIO (iFR) VERSUS FRACTIONAL FLOW RESERVE (FFR) IN INTERMEDIATE CORONARY STENOSIS***
• Date	*From 01/02/2017 to 31/07/2017*
• Institute	Cardiology and Catheterizaion Laboratory at "Carlo Poma" Hospital - Mantova (Director Dr. Corrado Lettieri),
• Activity	Specialist training, experienced as first and second operator in Catheterization Laboratory
• Date	*From 01/07/2016 to 31/01/2017*
• Institute	Catheterization Laboratory at "Papa Giovanni XXIII" Hospital - Bergamo (Dr. Giuseppe Musumeci)
• Activity	Specialist training, experienced as first and second operator in Catheterization Laboratory

• Date	From 01/06/2015 to 30/06/2016 and from 01/08/2017 to 31/10/2018
• Institute	Catheterization Laboratory at "Federico II" Unoversity - Napoli (Director Prof. Giovanni Esposito)
• Activity	Specialist training, experienced as first and second operator in Catheterization Laboratory
• Date	06/03/2013
• Activity	Enrollement in the register of medicatl doctors of Napoli n. 34080
• Date	Second session, 2013
• Qualification	Professional qualification as phsician
• Date	20/07/2012
• Qualification	Medicin degree at "Federico II" University –Napoli- 110/110, cum laude and special mention Graduation thesis: ***"Seven In Absentia Homolog 2 (SIAH2 E3) ubiquitin-ligase deletion, improves mytocondrial function and prevents post-myocardial infarction heart failure onset"***
NATIVE LANGUAGE	Italian
OTHER LANGUAGES	English, Spanish
• Reading ability	Excellent
• Writing ability	Excellent
• Speaking ability	Excellent
	First Certificate in English (FCE)

EXPERIENCE

First and second operator in more than 2000 interventional cardiovascular procedures (coronary angiography, PCI, lower limb PTA, carotid artery PTA, temporary PMK implantazion, IABP positioning, PFO occlusion, left atrial appendage occlusion, TAVI) of which 450 coronary angiography, 300 PCI and 110 primary PCI as first operator

SCIENTIFIC ACTIVITY

PUBBLICATIONS

- Fiocca L, Cereda AF, Bernelli C, Canova PA, **Serino F**, Niglio T, Musumeci G, Guagliumi G, Vassileva A, Senni M, Valsecchi O. Catheter Cardiovasc Interv. 2018 Sep 23

- Lettieri C, Romano M, Camurri N, Niglio T, **Serino F**, Cionini F, Baccaglioni N, Buffoli F, Rosiello R, Rambaldini M. *Impianto transcatetere di valvola aortica in paziente con bioprotesi aortica sutureless degenerata: descrizione di un caso e revisione della letteratura*. G Ital Cardiol 2017;18 (12 Suppl 1):18S-21S.

- Esposito G, Schiattarella GG, Perrino C, Cattaneo F, Pironti G, Franzone A, Gargiulo G, Magliulo F, **Serino F**, Carotenuto G, Sannino A, Ilardi F, Scudiero F, Brevetti L, Oliveti M, Giugliano G, Del Giudice C, Ciccarelli M, Renzone G, Scaloni A, Zambrano N, Trimarco B. *Dermcidin: a skeletal muscle myokine modulating cardiomyocyte survival and infarct size after coronary artery ligation.* Cardiovasc Res. 2015 Sep 1;107(4):431-41.

- Trimarco V, Izzo R, Stabile E, Rozza F, Santoro M, Manzi MV, **Serino F**, Schiattarella GG, Esposito G, Trimarco B. *Effects of a new combination of nutraceuticals with Morus alba on lipid profile, insulin sensitivity and endotelial function in dyslipidemic subjects. A cross-over, randomized, double-blind trial.*

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- Perrino C, Schiattarella GG, Sannino A, Pironti G, Petretta MP, Cannavo A, Gargiulo G, Ilardi F, Magliulo F, Franzone A, Carotenuto G, **Serino F**, Altobelli GG, Cimini V, Cuocolo A, Lombardi A, Goglia F, Indolfi C, Trimarco B, Esposito G. *Genetic deletion of uncoupling protein 3 exaggerates apoptotic cell death in the ischemic heart leading to heart failure.* J Am Heart Assoc. 2013 May 20;2(3):e000086

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- Giugliano G, Sannino A, Brevetti L, Perrino C, Schiattarella GG, Franzone A, **Serino F**, Ferrone M, Scudiero F, Carbone A, De Paulis M, Izzo R, Amato B, Trimarco B, Esposito G. *Ankle/brachial index to everyone*. BMC Surg. 2012;12 Suppl 1:S18

- Giugliano G, Laurenzano E, Rengo C, De Rosa G, Brevetti L, Sannino A, Perrino C, Chiariotti L, Schiattarella GG, **Serino F**, Ferrone M, Scudiero F, Carbone A, Sorropago A, Amato B, Trimarco B, Esposito G. *Abdominal aortic aneurysm in patients affected by intermittent claudication: prevalence and clinical predictors.*BMC Surg. 2012;12 Suppl 1:S17

- Gargiulo G, Giugliano G, Brevetti L, Sannino A, Schiattarella GG, **Serino F**, Carbone A, Scudiero F, Ferrone M, Corrado R, Izzo R, Chiariotti L, Perrino C, Amato B, Trimarco B, Esposito G. *Use of statins in lower extremity artery disease: a review.* BMC Surg. 2012;12 Suppl 1:S15.

- Franzone A, Ferrone M, Carotenuto G, Carbone A, Scudiero L, **Serino F**, Scudiero F, Izzo R, Piccolo R, Saviano S, Amato B, Perrino C, Trimarco B, Esposito G *The role of atherectomy in the treatment of lower extremity peripheral artery disease.* BMC Surg. 2012;12 Suppl 1:S13

- Schiattarella GG, Perrino C, Magliulo F, Ilardi F, **Serino F**, Trimarco V, Izzo R, Amato B, Terranova C, Cardin F, Militello C, Leosco D, Trimarco B, Esposito G. *Statins and the elderly: recent evidence and current indications.* Aging Clin Exp Res. 2012 Jun;24(3 Suppl):47-55

- Ilardi F, Magliulo F, Gargiulo G, Schiattarella GG, Carotenuto G, **Serino F**, Ferrone M, Visco E, Scudiero F, Carbone A, Perrino C, Trimarco B, Esposito G. *Endovascular treatment of carotid artery stenosis: evidences from randomized controlled trials and actual indications.* Monaldi Arch Chest Dis. 2011 Dec;76(4):183-91

- Perrino C, Schiattarella GG, Magliulo F, Ilardi F, Carotenuto G, Gargiulo G, **Serino F**, Ferrone M, Scudiero F, Carbone A, Trimarco B, Esposito G. *Cardiac side effects of chemotherapy: state of art and strategies for a correct management.* Curr Vasc Pharmacol. 2014 Jan;12(1):106-16

CONVENTIONS

Moderator at "40° National Congress of GISE", from 15 to 18/10/2019, in the session "Clinical Cases", at MiCo Congress Centre, Milano.

Speaker at Campus Cuore Congress in the session "Gestione pratica della DAPT a lungo termine dopo sindrome coronarica acuta" 20-21/04/2018 at Hotel Excelsior, Napoli

***Speaker*,** at "38th national congress Italian Society of Interventional Cardiology/PCR

	Peripheral Course", in the section Clinical Cases (Transcatheter valve implantation in degenerative sutureless aortic bioprostheses: case report and overview) 10-13/10/2017 at MiCo Congress Centre, Milano. ***Speaker,*** at 37° National Congress of GISE 2016, in the section Clinical Cases (CAD e stenosi aortica severa in paziente anziano), 11-14/10/2016 at Porto Antico-Centro Congressi, Genova ***Speaker***, at 76°National Congress of SIC, in the section "Meccanismi fisiopatologici della disfunzione endoteliale" (Psoriasi e rischio cardiovascolare: effetto degli inibitori del TNF-alfa sulla funzione endoteliale) 11-14/12/2015 at Hotel Cavalieri, Roma.
COMPUTER SKILLS	Excellent knowledge of Office and SPSS
DRIVING LICENCE	B

5) LIST OF PUBBLICATIONS

1) Cardiovascular mortality in patients with acute and chronic coronary syndrome: insights from the clinical evidence on ticagrelor. Gargiulo G, **Serino F**, Esposito G. Eur Rev Med Pharmacol Sci. 2022 Apr. PMID: 35442468. DOI: 10.26355/eurrev_202204_28490
2) ADDED Index or percentage diameter of residual coronary stenosis to risk-stratify patients presenting with STEMI.Di Serafino L, Magliulo F, Barbato E, Cirillo P, Esposito M, **Serino F**, Ziviello F, Stabile E, Franzone A, Piccolo R, Borgia F, Morisco C, Rapacciuolo A, Esposito G.Cardiovasc Revasc Med. 2021 Jan 29:S1553-8389(21)00081-6. doi: 10.1016/j.carrev.2021.01.030. Online ahead of print.PMID: 33547023
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4) A Controlled Trial of Rivaroxaban after Transcatheter Aortic-Valve Replacement. Dangas GD, Tijssen JGP, Wöhrle J, Søndergaard L, Gilard M, Möllmann H, Makkar RR, Herrmann HC, Giustino G, Baldus S, De Backer O, Guimarães AHC, Gullestad L, Kini A, von Lewinski D, Mack M, Moreno R, Schäfer U, Seeger J, Tchétché D, Thomitzek K, Valgimigli M, Vranckx P, Welsh RC, Wildgoose P, Volkl AA, Zazula A, van Amsterdam RGM, Mehran R, Windecker S; **GALILEO Investigators**.N Engl J Med. 2020 Jan 9;382(2):120-129. doi: 10.1056/NEJMoa1911425. Epub 2019 Nov 16.PMID: 31733180
5) Autologous blood reinfusion during iatrogenic acute hemorrhagic cardiac tamponade: Safety and feasibility in a cohort of 30 patients. Fiocca L, Cereda AF, Bernelli C, Canova PA, **Serino F**, Niglio T, Musumeci G, Guagliumi G, Vassileva A, Senni M, Valsecchi O.Catheter Cardiovasc Interv. 2019 Jan 1;93(1):E56-E62. doi: 10.1002/ccd.27784. Epub 2018 Sep 23.PMID: 30244510
6) Transcatheter valve-in-valve implantation in a patient with a degenerative sutureless aortic bioprosthesis: case report and literature review. Lettieri C, Romano M, Camurri N, Niglio T, **Serino F**, Cionini F, Baccaglioni N, Buffoli F, Rosiello R, Rambaldini M.G Ital Cardiol (Rome). 2017 Dec;18(12 Suppl 1):18S-21S. doi: 10.1714/2835.28628.PMID: 29297908

7) Dermcidin: a skeletal muscle myokine modulating cardiomyocyte survival and infarct size after coronary artery ligation. Esposito G, Schiattarella GG, Perrino C, Cattaneo F, Pironti G, Franzone A, Gargiulo G, Magliulo F, **Serino F**, Carotenuto G, Sannino A, Ilardi F, Scudiero F, Brevetti L, Oliveti M, Giugliano G, Del Giudice C, Ciccarelli M, Renzone G, Scaloni A, Zambrano N, Trimarco B.Cardiovasc Res. 2015 Sep 1;107(4):431-41. doi: 10.1093/cvr/cvv173. Epub 2015 Jun 22.PMID: 26101262
8) Effects of a new combination of nutraceuticals with Morus alba on lipid profile, insulin sensitivity and endotelial function in dyslipidemic subjects. A cross-over, randomized, double-blind trial. Trimarco V, Izzo R, Stabile E, Rozza F, Santoro M, Manzi MV, **Serino F**, Schiattarella GG, Esposito G, Trimarco B.High Blood Press Cardiovasc Prev. 2015 Jun;22(2):149-54. doi: 10.1007/s40292-015-0087-2. Epub 2015 Apr 14.PMID: 25870124
9) Cardiac side effects of chemotherapy: state of art and strategies for a correct management.Perrino C, Schiattarella GG, Magliulo F, Ilardi F, Carotenuto G, Gargiulo G, **Serino F**, Ferrone M, Scudiero F, Carbone A, Trimarco B, Esposito G.Curr Vasc Pharmacol. 2014 Jan;12(1):106-16. doi: 10.2174/15701611120114032716330 2.PMID: 22563720
10) Genetic deletion of uncoupling protein 3 exaggerates apoptotic cell death in the ischemic heart leading to heart failure. Perrino C, Schiattarella GG, Sannino A, Pironti G, Petretta MP, Cannavo A, Gargiulo G, Ilardi F, Magliulo F, Franzone A, Carotenuto G, **Serino F**, Altobelli GG, Cimini V, Cuocolo A, Lombardi A, Goglia F, Indolfi C, Trimarco B, Esposito G.J Am Heart Assoc. 2013 May 20;2(3):e000086. doi: 10.1161/JAHA.113.000086.PMID: 23688674
11) Statins and the elderly: recent evidence and current indications. Schiattarella GG, Perrino C, Magliulo F, Ilardi F, **Serino F**, Trimarco V, Izzo R, Amato B, Terranova C, Cardin F, Militello C, Leosco D, Trimarco B, Esposito G.Aging Clin Exp Res. 2012 Jun;24(3 Suppl):47-55.PMID: 23160507
12) Endovascular treatment of lower extremity arteries is associated with an improved outcome in diabetic patients affected by intermittent claudication. Giugliano G, Perrino C, Schiano V, Brevetti L, Sannino A, Schiattarella GG, Gargiulo G, **Serino F**, Ferrone M, Scudiero F, Carbone A, Bruno A, Amato B, Trimarco B, Esposito G.BMC Surg. 2012;12 Suppl 1(Suppl 1):S19. doi: 10.1186/1471-2482-12-S1-S19. Epub 2012 Nov 15.PMID: 23174008
13) Ankle/brachial index to everyone. Giugliano G, Sannino A, Brevetti L, Perrino C, Schiattarella GG, Franzone A, **Serino F**, Ferrone M, Scudiero F, Carbone A, De Paulis M,

Izzo R, Amato B, Trimarco B, Esposito G.BMC Surg. 2012;12 Suppl 1(Suppl 1):S18. doi: 10.1186/1471-2482-12-S1-S18. Epub 2012 Nov 15.PMID: 23173985

14) Abdominal aortic aneurysm in patients affected by intermittent claudication: prevalence and clinical predictors. Giugliano G, Laurenzano E, Rengo C, De Rosa G, Brevetti L, Sannino A, Perrino C, Chiariotti L, Schiattarella GG, **Serino F**, Ferrone M, Scudiero F, Carbone A, Sorropago A, Amato B, Trimarco B, Esposito G.BMC Surg. 2012;12 Suppl 1(Suppl 1):S17. doi: 10.1186/1471-2482-12-S1-S17. Epub 2012 Nov 15.PMID: 23173942
15) Use of statins in lower extremity artery disease: a review.Gargiulo G, Giugliano G, Brevetti L, Sannino A, Schiattarella GG, **Serino F**, Carbone A, Scudiero F, Ferrone M, Corrado R, Izzo R, Chiariotti L, Perrino C, Amato B, Trimarco B, Esposito G.BMC Surg. 2012;12 Suppl 1(Suppl 1):S15. doi: 10.1186/1471-2482-12-S1-S15. Epub 2012 Nov 15.PMID: 23173874
16) The role of atherectomy in the treatment of lower extremity peripheral artery disease.Franzone A, Ferrone M, Carotenuto G, Carbone A, Scudiero L, **Serino F**, Scudiero F, Izzo R, Piccolo R, Saviano S, Amato B, Perrino C, Trimarco B, Esposito G.BMC Surg. 2012;12 Suppl 1(Suppl 1):S13. doi: 10.1186/1471-2482-12-S1-S13. Epub 2012 Nov 15.PMID: 23173800
17) Endovascular treatment of carotid artery stenosis: evidences from randomized controlled trials and actual indications.
Ilardi F, Magliulo F, Gargiulo G, Schiattarella GG, Carotenuto G, **Serino F**, Ferrone M, Visco E, Scudiero F, Carbone A, Perrino C, Trimarco B, Esposito G.Monaldi Arch Chest Dis. 2011 Dec;76(4):183-91. doi: 10.4081/monaldi.2011.175

6) AKNOWLEGEMENTS

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Thanks to my family, which never left me alone: my mother, with her sweetness and otpimism, my father, with his seriousness and stubborness (which is also mine), my beautiful sister, who is my safe port whenever I need an help.
Last but not least, thanks to my husband Tullio, who is always by my side, helping me at work, in home life, understanding and always supporting me; I would never have become who I am if he had not been next to me.