



Novel insights in diagnosis, invasive and pharmacological treatment of cardiovascular diseases

PhD thesis

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PhD thesis

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CHAPTER 1

General introduction and outline of the thesis

Cardiovascular disease (CVD) remains one of the leading causes of morbidity and mortality worldwide, driving significant advances in both invasive and pharmacological treatments.(1) Despite substantial progress in understanding and managing these conditions, gaps remain in optimizing treatment strategies and improving patient outcomes.

Thanks to the introduction of new therapies and technologies—both drugs and devices—the treatment of cardiovascular disease has changed dramatically over the past three decades, allowing patients to live longer and with an improved quality of life. Interventional cardiology has played a key role in driving these innovations. Since the introduction of the very first percutaneous coronary angioplasty in September 1977, performed using a handmade balloon catheter to dilate a coronary stenosis, this field has consistently evolved.(2) Percutaneous coronary interventions (PCI) have progressively replaced coronary artery bypass grafting (CABG) as the gold standard approach for treating coronary artery disease (CAD) in many cases.

The field of structural heart interventions, particularly transcatheter techniques, represents the current frontier of innovation. In 2002, the first percutaneous transcatheter aortic valve implantation (TAVI) was performed.(3) Since that groundbreaking procedure, significant advancements have been made, and the field shows no signs of slowing down. The clinical indications for TAVI have expanded progressively due to the safety and efficacy demonstrated by large randomized clinical trials.(4, 5)

In summary, the landscape of cardiovascular diseases treatment has undergone remarkable changes in recent decades, driven by advancements in technology, pharmacology, and our understanding of disease mechanisms. Invasive procedures have significantly improved outcomes for patients with both acute and chronic cardiovascular conditions, while pharmacological treatments have evolved to offer new strategies for managing cardiovascular risk and disease progression.

This thesis aims to provide novel insights into the evolving landscape of diagnosis, as well as invasive and pharmacological interventions for cardiovascular diseases, addressing these gaps and exploring innovative approaches to enhance therapeutic efficacy.

Outline of the thesis

The thesis is divided in seven parts:

Part I. Advances in Coronary Artery Disease Treatment. In the first part of the thesis, we report our research projects published in the field of CAD regarding treatment of in stent restenosis (ISR), the performance of ultrathin drug eluting stent (DES) in challenging lesions, the predictors of PCI from coronary CT angiography (CCTA), and outcomes of PCI for left main lesions when compared with CABG according to age.

Part II. Periprocedural Myocardial Infarction and impact on outcomes. In the second part of the thesis, we report the cluster of research projects that focus on the risk and prognostic relevance of periprocedural myocardial infarction (MI) in patients undergoing elective PCI.

Part III. Evaluation of coronary microvascular function. This part of the thesis is a collection of research projects aimed to evaluate the microvascular function. We investigated the difference in coronary flow reserve (CFR) and microvascular resistance reserve (MRR) with bolus or continuous thermodilution (chapter 10), absolute coronary flow and microvascular resistance before and after TAVI (chapter 11), and different patterns of coronary microvascular dysfunction (CMD) in patients with heart failure (HF) (chapter 12).

Part IV. Aortic stenosis and Transcatheter Aortic Valve Implantation. This section focuses on the topic of aortic stenosis (AS) and TAVI reporting the results of our projects mainly on staging of cardiac damage (CD) in patients with symptomatic aortic stenosis (AS).

Part V. Pharmacological treatment of atherosclerotic disease. This section of the thesis focuses on the latest evidence on pharmacological treatment of atherosclerotic disease, in terms of antithrombotic and Lipid-Lowering Therapy (LLT).

Part VI. Artificial Intelligence application in cardiovascular medicine. In this section we report the results of our study on the application of an Artificial Intelligence (AI) model for the detection of occlusion myocardial infarction (OMI).

Part VII. Discussion and conclusions. The last section of the thesis is discussion of the addressed topics with the conclusions.

Part I

Advances in coronary artery disease treatment

CHAPTER 2

Treatment of in-stent restenosis with ultrathin-strut versus thin strut drug-eluting stents or drug-eluting balloon: a multicenter registry

Background. Limited data exist on ultrathin-struts drug-eluting stents (DES) performance in DES in-stent restenosis (ISR).

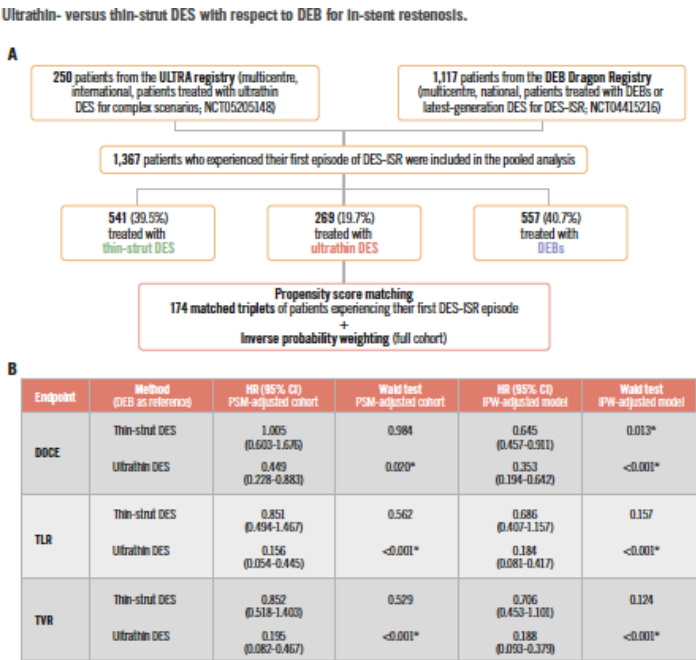
Aims. To assess ultrathin DES efficacy and safety vs thin-strut DES or drug-eluting balloon (DEB) for DES-ISR.

Methods. Patients from DEB-Dragon (NCT04415216) and ULTRA registries (NCT05205148) were divided into ultrathin DES, thin-strut DES, or DEB groups for DES-ISR treatment. Both propensity Score Matching (PSM) and Inverse Propensity Weighting (IPW) were considered to adjust the distribution of patients in each class. Cox regression was applied to the following main endpoints: DOCE (including cardiac death, target-lesion revascularization [TLR] and target vessel myocardial infarction), TLR and target vessel revascularization (TVR).

Results. 269, 541, and 557 patients received ultrathin DES, thin-strut DES, and DEB respectively. After 3 years of follow-up, in the overall cohort, at IPW ultrathin DES were associated with a significantly reduced risk of DOCE compared to DEB (Hazard Ratio 0.353, 95% confidence intervals 0.194-0.642, $p<0.001$), as well as thin-strut DES (0.645, 0.457-0.911, $p=0.013$). Compared to DEB, ultrathin DES also reduced risk of both TLR (0.184, 0.081-0.417, $p<0.001$) and TVR (0.188, 0.093-0.379-0, $p<0.001$), while thin-strut DES did not (TLR: 0.686, 0.407-1.157, $p=0.157$; TVR: 0.706, 0.453-1.101, $p=0.124$). For *diffuse ISR patients*, ultrathin DES reduced risk of DOCE (0.364, 0.188-0.705, $p=0.003$), as thin-strut DES (0.602, 0.367-0.987, $p=0.044$), while reduction of TLR (0.220,

0.091-0.531, $p<0.001$) and TVR (0.241, 0.113-0.513, $p<0.001$) was achieved only by ultrathin DES (Figure 1).

Conclusions. Ultrathin DES were associated with a reduced DOCE, TLR and TVR risk in diffuse ISR compared to DEB.



Ovidio De Filippo et al. • EuroIntervention 2024;20:e1-e15 • DOI: 10.4244/EIJ-D-24-00491

A) Study flowchart; (B) summary of the key results. *Statistical significance, i.e., p -value<0.05. In patients being treated for a first episode of DES-ISR, ultrathin-strut DES are associated with a reduced risk of DOCE, TVR and TLR compared to thin-strut DES and DEBs. Such a difference is mainly observed in the context of diffuse ISR. CI: confidence interval; DEB: drug-eluting balloon; DES: drug-eluting stent; DOCE: device-oriented composite endpoint; HR: hazard ratio; IPW: inverse probability weighting; ISR: in-stent restenosis; PSM: propensity score matching; TLR: target lesion revascularisation; TVR: target vessel revascularisation; ultrathin DES: ultrathin-strut DES

Figure 1. Ultrathin vs thin strut DES with respect to DEB for in stent restenosis

CHAPTER 3

Predictors of percutaneous coronary intervention derived from CCTA in patients with chronic coronary syndrome

Background. To identify anatomical and morphological plaque features predictors of PCI and create a multiparametric score to increase the predictive yield. Moreover, we assessed the incremental predictive value of FFRCT (Fractional Flow Reserve derived from CCTA) trans-lesion gradient (Δ FFRCT) when integrated into the score.

Methods. Observational cohort study including patients undergoing CCTA for suspected coronary artery disease, with FFRCT available, referred to invasive coronary angiogram and assessment of fractional flow reserve. Plaque analysis was performed using validated semi-automated software. Logistic regression was performed to identify anatomical and morphological plaque features predictive of PCI. Optimal thresholds were defined by area under the receiver-operating characteristics curve (AUC) analysis. A scoring system was developed in a derivation cohort (70 % of the study population) and tested in a validation cohort (30 % of patients).

Results. The overall study population included 340 patients (455 vessels), among which 238 patients (320 vessels) were included in the derivation cohort. At multivariate logistic regression analysis, absence of left main disease, diameter stenosis (DS), non-calcified plaque (NCP) volume, and percent atheroma volume (PAV) were independent predictors of PCI. Optimal thresholds were: DS $\leq$ 50 %, volume of NCP > 113 mm³ and PAV > 17 %. A weighted score (CT-PCI Score) ranging from 0 to 11 was obtained. The AUC of the score was 0.80 (95%CI 0.74–0.86). The integration of Δ FFRCT in the CT-PCI score led to a mild albeit not significant increase in the AUC (0.82, 95%CI 0.77–0.87, $p = 0.328$).

Conclusions. Plaque anatomy and morphology derived from CCTA could aid in identifying patients amenable to PCI.

CHAPTER 4

Predictors of target lesion failure after treatment of left main, bifurcation, or chronic total occlusion lesions with ultrathin strut drug-eluting coronary stents in the ULTRA registry

Background. Data about the long-term performance of new-generation ultrathin strut drug-eluting stents (DES) in challenging coronary lesions, such as left main (LM), bifurcation, and chronic total occlusion (CTO) lesions are scant.

Methods. The international multicenter retrospective observational ULTRA study included consecutive patients treated from September 2016 to August 2021 with ultrathin-strut ($<70\text{ }\mu\text{m}$) DES in challenging de novo lesions. Primary endpoint was target lesion failure (TLF): composite of cardiac death, target-lesion revascularization (TLR), target-vessel myocardial infarction (TVMI), or definite stent thrombosis (ST). Secondary endpoints included all-cause death, acute myocardial infarction (AMI), target vessel revascularization, and TLF components. TLF predictors were assessed with Cox multivariable analysis.

Results. Of 1801 patients (age: 66.6 ± 11.2 years; male: 1410 [78.3%]), 170 (9.4%) experienced TLF during follow-up of 3.1 ± 1.4 years. In patients with LM, CTO, and bifurcation lesions, TLF rates were 13.5%, 9.9%, and 8.9%, respectively. Overall, 160 (8.9%) patients died (74 [4.1%] from cardiac causes). AMI and TVMI rates were 6.0% and 3.2%, respectively. ST occurred in 11 (1.1%) patients while 77 (4.3%) underwent TLR. Multivariable analysis identified the following predictors of TLF: age, STEMI with cardiogenic shock, impaired left ventricular ejection fraction, diabetes, and renal dysfunction. Among the procedural variables, total stent length increased TLF risk (HR: 1.01, 95% CI: 1–1.02 per mm increase), while intracoronary imaging reduced the risk substantially (HR: 0.35, 95% CI: 0.12–0.82).

Conclusions. Ultrathin-strut DES showed high efficacy and satisfactory safety, even in patients with challenging coronary lesions. Yet, despite using contemporary goldstandard DES, the association persisted between established patient- and procedure-related features of risk and impaired 3-year clinical outcome.

CHAPTER 5

Percutaneous coronary intervention versus coronary artery bypass grafting for left main disease according to age: a meta-analysis

Objectives. The aim of this meta-analysis was to investigate outcomes after percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) for unprotected left main (ULM) disease according to age of presentation.

Methods. Randomized controlled trials (RCTs) and adjusted observational studies comparing PCI vs CABG in patients with ULM disease and reporting outcomes according to a prespecified patients' age cutoff were included. All-cause death was the primary endpoint. Major adverse cardiovascular events (MACE), myocardial infarction and repeated revascularization were the secondary endpoints. Sensitivity analysis including only RCTs was performed for the main outcome.

Results. Fourteen studies (4 RCTs, 10 adjusted observational), encompassing 24767 patients (7952 and 16779 treated with PCI or CABG, respectively) were included. Median follow up was 4.6 years and median age cut-off was 72.5 years old. Among nonelderly patients, PCI was associated with an increased risk of all-cause death (HR 1.51, 95%CI:1.17-1.97) and repeat revascularization (HR 4.31, 95%CI:1.08-15.84) compared with CABG, with no significant difference for any other secondary endpoint. Among elderly patients, PCI was associated with a higher risk of MACE compared with CABG (HR 1.25, 95%CI 1.05-1.48), a difference driven by studies using a lower age cutoff (65-75 years old) to define "elderly" patients. Conversely, among elderly patients, PCI and CABG were associated with a similar risk of all-cause death, MI, and repeat revascularization (Figure 2)

Conclusions. Among non-elderly patients with ULM disease, PCI is associated with a higher risk of all-cause death and repeat revascularization compared with CABG. Among elderly patients, CABG and PCI are associated with similar outcomes, with the exception of MACE, for which a lower risk with CABG, driven by studies using a lower age threshold, was observed.

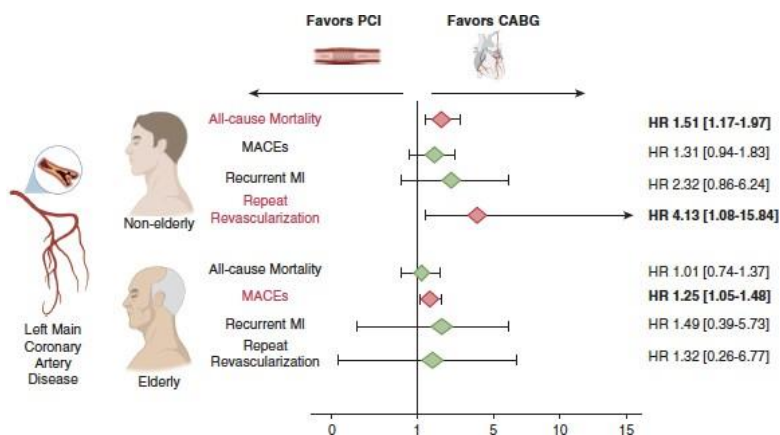


Figure 2. Comparative outcomes between PCI and CABG for ULM according to age of presentation.

Diamonds represent HRs. Green diamonds: nonstatistically significant differences; red diamonds: statistically significant results. On the right side, HRs in bold represent statistically significant results. PCI, Percutaneous coronary intervention; CABG, coronary artery bypass grafting; ULM, unprotected left main; HR, hazard ratio; MACE, major adverse cardiovascular events; MI, myocardial infarction

CHAPTER 6

Ultrathin Struts Drug-Eluting Stents: A State-of-the-Art Review

New-generation drug-eluting stents (DESs) represent the standard of care for patients undergoing percutaneous coronary intervention (PCI). Recent iterations in DES technology have led to the development of newer stent platforms with a further reduction in strut thickness. This new DES class, known as ultrathin struts DESs, has struts thinner than 70 μm . The evidence base for these devices consists of observational data, large-scale meta-analyses, and randomized trials with long-term follow-up, which have been conducted to investigate the difference between ultrathin struts DESs and conventional new-generation DESs in a variety of clinical settings and lesion subsets.

Ultrathin struts DESs may further improve the efficacy and safety profile of PCI by reducing the risk of target-lesion and target-vessel failures in comparison to new-generation DESs. In this article, we reviewed device characteristics and clinical data of the Orsiro (Biotronik, Bülach, Switzerland), Coroflex ISAR (B. Braun Melsungen, Germany), BioMime (Meril Life Sciences Pvt. Ltd., Gujarat, India), MiStent (MiCell Technologies, USA), and Supraflex (Sahajanand Medical Technologies, Surat, India) sirolimus-eluting stents. **(Figure 3)**

	Oraino	CoroFlex IsarNeo	Biomime	Biomime Morph	Evermine 50	MiStent	Supraflex Cruz
							
Company	Biotronik	B. Braun	Meril	Meril	Meril	Stentys	Sahajjand Medical Technologies (SMT)
Platform material and Strut thickness (µm)	2.5 to 3 mm 90	3.5 to 4 mm 55, 65	3.5 to 4 mm 65	3.5 to 4 mm 65	3.5 to 4 mm 60	3.5 to 4 mm 64	3.5 to 4 mm 60
Crossing Profile	0.95 mm	0.79 to 0.95 mm	0.83 to 1.19 mm	0.93 to 1.03	0.83 to 1.19	n.a.	0.95 mm
Available diameters (mm)	2.25, 2.5, 2.75, 3.0, 3.5, 4.0	2.0, 2.25, 2.5, 2.75, 3.0, 3.5, 4.0	2.0, 2.25, 2.75, 3.0, 3.5, 4.0, 4.5	2.75-2.25, 3.0-2.5, 3.5-3.0	2.0, 2.25, 2.50, 2.75, 3.0, 3.5, 4.0, 4.5	n.a.	2.0, 2.25, 2.5, 2.75, 3.0, 3.5, 4.0, 4.5
Lengths available (mm)	9 to 40	9 to 38	8 to 48	30 to 60	8 to 48	n.a.	8 to 48 mm
Polymer type	Biodegradable (proBIO®)	Polymer free	Biodegradable Biocompatible	Biodegradable Biocompatible	Biodegradable Biocompatible	Biodegradable	Biodegradable
Coating distribution	Circumferential	-	Circumferential	Circumferential	Circumferential	Circumferential	Circumferential
Polymer material and thickness	3.5 µm polyimide, 7.5 µm tantum	-	2 µm	2 µm	2 µm	5 µm/15 µm	4-5 µm
Polymer absorption	15 months	-	60 days	60 days	60 days	3 months	9-12 months
Eluted drug	Sirolimus	Sirolimus and Probucol	Sirolimus	Sirolimus	Everolimus	Sirolimus (microcrystals)	Sirolimus
Drug dose	1.4 µg/mm ²	1.2 µg/mm ²	1.25 µg/mm ²	1.25 µg/mm ²	1.25 µg/mm ²	2.4 µg/mm ²	1.4 µg/mm ²
Drug release	50% by 1 month 80% by 3 months	80% by 28 days 100% by 90 days	30-40 days	30-40 days	30-40 days	9 months	70% by 1 week 100% by 3-4 months
	 Cobalt-Chromium PLLA PLLA and PLGA PLLA + PCL + PVP						

Figure 3. Comparison of currently available ultrathin drug-eluting stents (DESS).

CoCr: cobalt chrome; n.a.: not available, PCL: poly-caprolactone; PLGA: poly-D,L-lactide-co-glycolide; PLLA: poly-L-lactic acid; proBIO: amorphous hydrogen-rich silicon carbide; PVP: poly vinyl pyrrolidone.

Part II

Periprocedural myocardial infarction and impact on outcomes

CHAPTER 7

Periprocedural myocardial infarction in patients undergoing complex versus noncomplex percutaneous coronary intervention

Background. Limited data are available on the risk of periprocedural myocardial infarction (MI) in patients undergoing complex versus noncomplex percutaneous coronary intervention (PCI).

Methods. We assessed the risk of periprocedural MI according to the fourth Universal definition of myocardial infarction (UDMI) and several other criteria among patients undergoing elective PCI in a prospective, single-center registry. Complex PCI included at least one of the following: 3 coronary vessels treated, ≥ 3 stents implanted, ≥ 3 lesions treated, bifurcation with 2 stents implanted, total stent length >60 mm, treatment of chronic total occlusion, and use of rotational atherectomy.

Results. Between 2017 and 2021, we included 1010 patients with chronic coronary syndrome, of whom 226 underwent complex PCI (22.4%). The rate of periprocedural MI according to the fourth UDMI was significantly higher in complex compared to noncomplex PCI patients (26.5% vs. 14.5%, $p < 0.001$). Additionally, periprocedural MI was higher in the complex PCI group using SCAI (4% vs. 1.1%, $p = 0.009$), ARC-2 (13.7% vs. 8.0%, $p = 0.013$), ISCHEMIA (5.8% vs. 1.7%, $p = 0.002$), and EXCEL criteria (4.9% vs. 2.0%, $p = 0.032$). SYNTAX periprocedural MI occurred at low rates in both groups (0.9% vs. 0.6%, $p = 0.657$) (**Figure 4**). Complex PCI was an independent predictor of the fourth UDMI periprocedural MI (odds ratio [OR] 1.54, 95% confidence interval [CI]: 1.04–2.27, $p = 0.031$).

Conclusions. In patients with chronic coronary syndrome undergoing elective PCI, complex PCI is associated with a significantly higher risk of periprocedural

MI using multiple definitions. These findings highlight the importance of considering upfront this risk in the planning of complex PCI procedure.

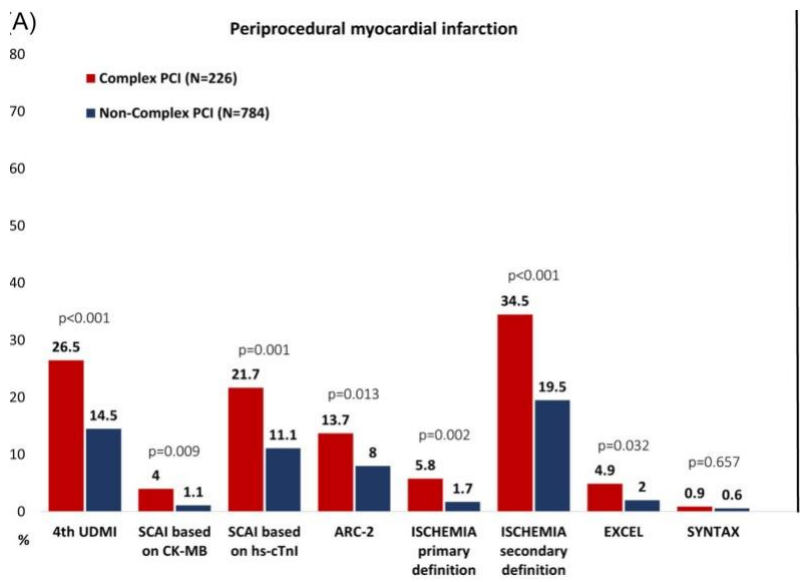


Figure 4. Frequency of periprocedural myocardial infarction.

ARC-2, Academic Research Consortium-2; EXCEL, XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization; ISCHEMIA, International Study of Comparative Health Effectiveness with Medical and Invasive Approaches; PCI, percutaneous coronary intervention; SCAI, Society for Cardiovascular Angiography and Intervention; SYNTAX, Synergy between PCI with Taxus and Cardiac Surgery; UDMI, Universal Definition of Myocardial Infarction

3.

CHAPTER 8

Impact of biomarker type on periprocedural myocardial infarction in patients undergoing elective PCI

Background. Periprocedural myocardial infarction (MI) according to the Society for Cardiovascular Angiography and Interventions (SCAI) criteria has prognostic relevance among patients undergoing percutaneous coronary intervention (PCI). However, it is unclear whether the type of cardiac biomarker used for the diagnosis of periprocedural MI plays a role in terms of event frequency and outcomes.

Objectives. To compare the characteristics of SCAI periprocedural MI based on creatine kinase-myocardial band fraction (CK-MB) vs. high-sensitivity cardiac troponin (hs-cTn) in patients undergoing elective PCI.

Methods and results. Between 2017 and 2021, periprocedural MI was assessed in a prospective study. The primary clinical outcome of interest was all-cause death at 1-year follow-up. A total of 1010 patients undergoing elective PCI were included. SCAI periprocedural MI based on CK-MB vs. hs-cTnI occurred in 1.8 and 13.5% of patients, respectively. hs-cTnI periprocedural MI in the absence of concomitant CK-MB criteria was associated with lower rates of ancillary criteria, including angiographic, ECG, and cardiac imaging criteria. At 1-year follow-up, periprocedural MI defined by CK-MB (adjusted hazard ratio, HR, 4.27, 95% confidence intervals, CI, 1.23–14.8; $P = 0.022$) but not hs-cTnI (adjusted HR 2.04, 95% CI 0.94–4.45; $P = 0.072$) was associated with a higher risk of all-cause death. Hs-cTnI periprocedural MI was not predictive of death unless accompanied by CK-MB criteria (adjusted HR 4.64, 95% CI 1.32–16.31; $P = 0.017$) (**Figure 5**).

Conclusion. In the setting of elective PCI, using hs-cTn instead of CK-MB resulted in a substantial increase in SCAI periprocedural MI events, which were not prognostically relevant in the absence of concurrent CK-MB elevations.

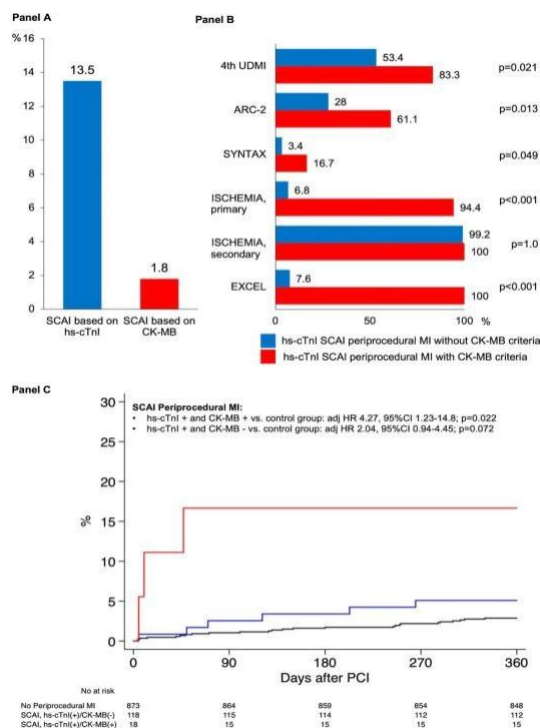


Figure 5.

Panel A. Rates of periprocedural myocardial infarction (MI) defined by high sensitivity cardiac troponin I (hs-cTnI) and creatine kinase myocardial band fraction (CK-MB). Panel B. Rates of periprocedural MI according to other definitions in patients with hs-cTnI SCAI periprocedural MI with or without creatine kinase-myocardial band fraction criteria. Panel C. Kaplan-Meier curves in patients without SCAI periprocedural MI defined by hs-cTnI (black line), patients with hs-cTnI SCAI periprocedural MI without CK-MB criteria (blue line), and patients with hs-cTnI SCAI periprocedural MI with CK-MB criteria (red line). ARC-2, Academic Research Consortium-2; EXCEL, Evaluation of XIENCE vs. Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization; ISCHEMIA, International Study of Comparative Health Effectiveness with Medical and Invasive Approaches; SCAI, the Society for Cardiovascular Angiography and Interventions; SYNTAX, Synergy between PCI with Taxus and Cardiac Surgery; UDMI, Universal Definition of Myocardial Infarction.

CHAPTER 9

Evidence Supporting Criteria for Periprocedural Myocardial Infarction in Patients Undergoing Elective Percutaneous Coronary Intervention

Percutaneous coronary intervention (PCI) represents an established treatment for patients with chronic coronary syndrome due to the improvement in symptoms and the reduction of ischemic events in comparison to medical therapy. Periprocedural myocardial infarction (MI) after PCI occurs in a wide range with this variability primarily resulting from the definition used. The fourth universal definition of myocardial infarction (UDMI) is distinguished by a higher incidence of periprocedural MI, along with a diminished prognostic impact in comparison with other criteria. At variance with the definitions purely based on increased cardiac troponin levels after PCI, periprocedural MI using the fourth UDMI requires the additional presence of 1 of the following criteria: electrocardiographic (ECG) ischemic changes, cardiac imaging abnormalities, or angiographic complications. To date, the prognostic significance of these criteria remains unexplored. We included 1,010 patients undergoing elective PCI between 2017 and 2021 at the Federico II University of Naples in a prospective registry (NCT05248165). The study conformed to the Declaration of Helsinki on human research and was approved by the local ethics committee. All patients provided the informed consent. Adjudication of periprocedural MI was performed by 2 reviewers with potential events triggered by biomarker increases after PCI. ECGs and angiograms were adjudicated by reviewers, whereas adjudication of cardiac imaging abnormalities was based on source documents, if available. Periprocedural MI defined by the fourth UDMI occurred in 174 patients (17.2%); of these, 124 (71.3%) and 50 (28.7%) patients met 1 and 2 or 3 criteria, respectively. The criteria leading to periprocedural MI were, in

descending order, ECG (n . 105 [60%]), angiographic (n . 79 [45%]), and imaging (n . 51 [29%]) criteria. Patients with periprocedural MI had an increased risk of all-cause death at the 1-year follow-up as compared with patients without periprocedural MI in a multivariable Cox regression analysis (12 of 174 [6.9%] vs 22 of 836 [2.6%], respectively; adjusted HR: 2.47; 95% CI: 1.19-5.12; P . 0.015). ECG criteria (adjusted HR: 3.22; 95% CI: 1.48-6.97; P . 0.003), imaging criteria (adjusted HR: 3.45; 95% CI: 1.26-9.46; P . 0.016) and angiographic criteria (adjusted HR: 3.21; 95% CI: 1.27-8.09; P . 0.013) were all associated with an increased risk of all-cause death. However, periprocedural MI with only 1 criterion did not increase the risk of death (5 of 124 [4.0%]; adjusted HR: 1.39; 95% CI: 0.52-3.75; P . 0.514). Conversely, periprocedural MI with 2 or 3 criteria was associated with an increased risk of all-cause death at 1 year (7 of 50 [14.3%]; adjusted HR: 5.38; 95% CI: 2.24-12.9; P . 0.001) (**Figure 6**). The role of elective PCI in stable patients remains controversial and periprocedural MI plays a critical role in the risk-benefit ratio between medical therapy and myocardial revascularization. Indeed, although elective PCI decreases the risk of spontaneous MI, it concurrently increases the risk of periprocedural ischemic events, resulting in a net neutral effect on the overall MI risk. The optimal definition of periprocedural MI is far more contentious due to prognostic heterogeneity across existing definitions. Yet, the fourth UDMI is the most frequent but carries the least prognostic significance. This study is the first to investigate the prognostic significance of evidence-supporting criteria used for the diagnosis of periprocedural MI as defined by the fourth UDMI. Our data suggest that this definition holds prognostic significance predominantly when 2 or 3 criteria are fulfilled. This study should be interpreted in view of the following limitations. The adjudication of periprocedural MI was based on the availability

of source documents. In a small subset of patients (n=77), post-PCI echocardiographic evaluations were not available and, consequently, for these patients, imaging criteria were considered absent. Despite the inclusion of several covariates in our adjusted models, we must consider the possibility that our study may not be adequately powered to yield fully adjusted risk estimates. Based on these findings, we suggest a reevaluation of the fourth UDMI periprocedural MI criteria to improve their clinical usefulness. Adopting a 2- or 3-criteria approach could harmonize UDMI criteria, which encompass biomarkers and clinical features, with purely biomarker-based definitions. This approach might also decrease the incidence of periprocedural MI by focusing on clinically significant events.

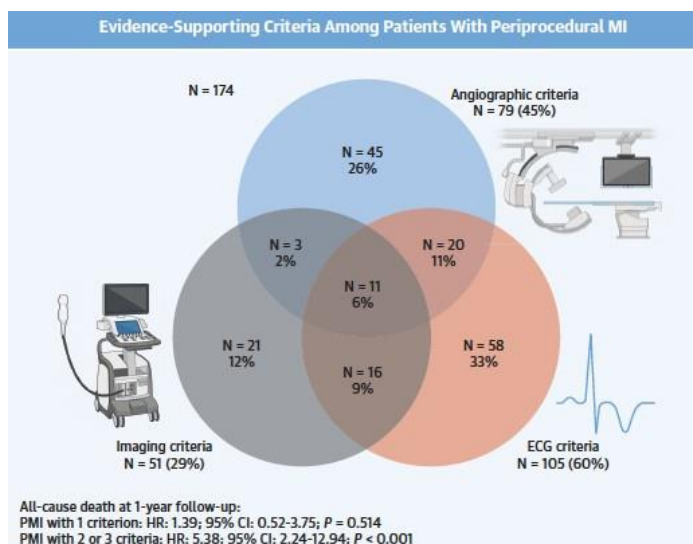


Figure 6. Distribution of evidence-supporting criteria and Cox regression analysis for all-cause death at the 1-year follow-up among patients with periprocedural MI based in the fourth UDMI. ECG, electrocardiograph; MI, myocardial infarction; PCI, percutaneous coronary intervention; UDMI, universal definition of myocardial infarction.

Part III

Evaluation of coronary microvascular function

CHAPTER 10

Continuous vs Bolus Thermodilution to Assess Microvascular Resistance Reserve

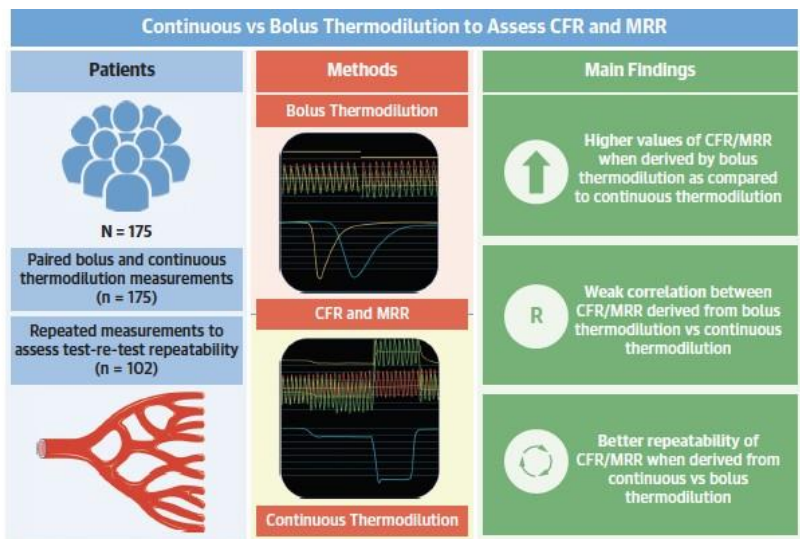
Background. Coronary flow reserve (CFR) and microvascular resistance reserve (MRR) can, in principle, be derived by any method assessing coronary flow.

Objectives. The aim of this study was to compare CFR and MRR as derived by continuous (CFR_{cont} and MRR_{cont}) and bolus thermodilution (CFR_{bolus} and MRR_{bolus}).

Methods. A total of 175 patients with chest pain and nonobstructive coronary artery disease were studied. Bolus and continuous thermodilution measurements were performed in the left anterior descending coronary artery. MRR was calculated as the ratio of CFR to fractional flow reserve and corrected for changes in systemic pressure. In 102 patients, bolus and continuous thermodilution measurements were performed in duplicate to assess test-retest reliability.

Results. Mean CFR_{bolus} was higher than CFR_{cont} (3.47 ± 1.42 and 2.67 ± 0.81 [P < 0.001], mean difference 0.80, upper limit of agreement 3.92, lower limit of agreement 2.32). Mean MRR_{bolus} was also higher than MRR_{cont} (4.40 ± 1.99 and 3.22 ± 1.02 [P < 0.001], mean difference 1.2, upper limit of agreement 5.08, lower limit of agreement 2.71). The correlation between CFR and MRR values obtained using both methods was significant but weak (CFR, r = 0.28 [95% CI: 0.14-0.41]; MRR, r = 0.26 [95% CI: 0.16-0.39]; P < 0.001 for both). The precision of both CFR and MRR was higher when assessed using continuous thermodilution compared with bolus thermodilution (repeatability coefficients of 0.89 and 2.79 for CFR_{cont} and CFR_{bolus}, respectively, and 1.01 and 3.05 for MRR_{cont} and MRR_{bolus}, respectively) (**Figure 7**).

Conclusions. Compared with bolus thermodilution, continuous thermodilution yields lower values of CFR and MRR accompanied by an almost 3-fold reduction of the variability in the measured results.



Gallinoro E, et al. J Am Coll Cardiol Intv. 2023;16(22):2767-2777.

CFR – coronary flow reserve; MRR – microvascular resistance reserve.

Figure 7. Study design and main results.

CHAPTER 11

Absolute coronary flow and microvascular resistance before and after transcatheter aortic valve implantation

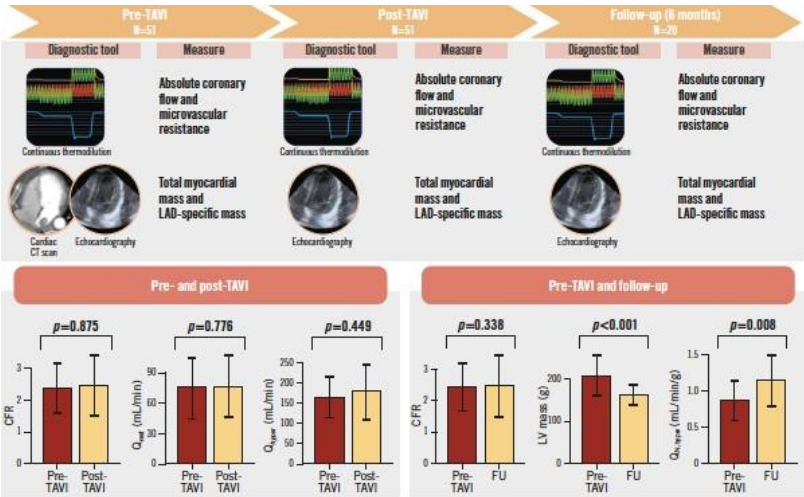
Background. Severe aortic stenosis (AS) is associated with left ventricular (LV) remodelling, likely causing alterations in coronary blood flow and microvascular resistance.

Aims. We aimed to evaluate changes in absolute coronary flow and microvascular resistance in patients with AS undergoing transcatheter aortic valve implantation (TAVI).

Methods. Consecutive patients with AS undergoing TAVI with non-obstructive coronary artery disease in the left anterior descending artery (LAD) were included. Absolute coronary flow (Q) and microvascular resistance (R_{μ}) were measured in the LAD using continuous intracoronary thermodilution at rest and during hyperaemia before and after TAVI, and at 6-month follow-up. Total myocardial mass and LAD-specific mass were quantified by echocardiography and cardiac computed tomography. Regional myocardial perfusion (QN) was calculated by dividing absolute flow by the subtended myocardial mass.

Results. In 51 patients, Q and R were measured at rest and during hyperaemia before and after TAVI; in 20 (39%) patients, measurements were also obtained 6 months after TAVI. No changes occurred in resting and hyperaemic flow and resistance before and after TAVI nor after 6 months. However, at 6-month follow-up, a notable reverse LV remodelling resulted in a significant increase in hyperaemic perfusion (QN,hyper: 0.86 [interquartile range {IQR} 0.69-1.06] vs 1.20 [IQR 0.99-1.32] mL/min/g; $p=0.008$; pre-TAVI and follow-up, respectively) but not in resting perfusion (QN,rest: 0.34 [IQR 0.30-0.48] vs 0.47 [IQR 0.36-0.67] mL/min/g; $p=0.06$) (**Figure 8**).

Conclusions. Immediately after TAVI, no changes occurred in absolute coronary flow or coronary flow reserve. Over time, the remodelling of the left ventricle is associated with increased hyperaemic perfusion.



Emanuele Gallinoro et al. • *EuroIntervention* 2024;20:e1-e11 • DOI: 10.4244/EIJ-D-24-00075

CFR: coronary flow reserve; CT: computed tomography; FU: follow-up; LAD: left anterior descending artery; LV: left ventricular; Q_{hyp} : hyperaemic absolute coronary flow; Q_{rest} : myocardial perfusion during hyperaemia; Q_{rest} : resting absolute coronary flow; TAVI: transcatheter aortic valve implantation

Figure 8. Summary and main results of the study

CHAPTER 12

Coronary Microvascular Dysfunction in Patients With Heart Failure: Characterization of Patterns in HFrEF Versus HFpEF

Background. Coronary microvascular dysfunction (CMD) is involved in heart failure (HF) onset and progression, independently of HF phenotype and obstructive coronary artery disease. Invasive assessment of CMD might provide insights into phenotyping and prognosis of patients with HF. We aimed to assess absolute coronary flow, absolute microvascular resistance, myocardial perfusion, coronary flow reserve, and microvascular resistance reserve in patients with HF with preserved ejection fraction and HF with reduced ejection fraction (HFrEF).

Methods. Single-center, prospective study of 56 consecutive patients with de novo HF with nonobstructive coronary artery disease divided into HF with preserved ejection fraction (n=21) and HFrEF (n=35). CMD was invasively assessed by continuous intracoronary thermodilution and defined as coronary flow reserve <2.5. Left ventricular and left anterior descending artery–related myocardial mass was quantified by echocardiography and coronary computed tomography angiography. Myocardial perfusion (mL/min per g) was calculated as the ratio between absolute coronary flow and left anterior descending artery–related mass.

Results. Patients with HFrEF showed a higher left ventricular and left anterior descending artery–related myocardial mass compared with HF with preserved ejection fraction ($P<0.010$). Overall, 52% of the study population had CMD, with a similar prevalence between the 2 groups. In HFrEF, CMD was characterized by lower absolute microvascular resistance and higher absolute coronary flow at rest (functional CMD; $P=0.002$). CMD was an independent predictor of a lower

rate of left ventricular reverse remodeling at follow-up. In patients with HF with preserved ejection fraction, CMD was mainly due to higher absolute microvascular resistance and lower absolute coronary flow during hyperemia (structural CMD; $P \leq 0.030$) (**Figure 9**).

Conclusions. Continuous intracoronary thermodilution allows the definition and characterization of patterns with distinct CMD in patients with HF and could identify patients with HFrEF with a higher rate of left ventricular reverse remodeling at follow-up.

Part IV

Aortic stenosis and Transcatheter Aortic Valve Implantation

CHAPTER 13

Combined Cardiac Damage Staging by Echocardiography and Cardiac Catheterization in Patients with Clinically Significant Aortic Stenosis

Background. Cardiac damage (CD) staging enhances risk stratification in patients with clinically significant aortic stenosis (AS). We aimed to assess the prognostic value and reclassification rate of right heart catheterization (RHC) compared with transthoracic echocardiography (TTE) in characterising CD staging at 3-year follow-up in patients with clinically significant AS, to identify patients that would benefit from RHC for prognostic stratification, and to test the prognostic value of combined CD staging.

Methods. An observational cohort study of 432 AS patients undergoing TTE and RHC were divided into moderate or asymptomatic severe (m/asAS) and symptomatic severe (ssAS) AS. Kaplan-Meier curves were used to compare survival. The accuracy in prognostic stratification was tested by area under the receiver operating characteristic curve analysis and Delong test.

Results. In both cohorts, TTE- and RHC-derived staging systems had prognostic value, although the agreement between them appeared moderate. A higher proportion of patients were assigned to stage 2 by TTE than by RHC. Patients in TTE-derived stage 2 had a high reclassification rate, with 40%-50% presenting with right chamber involvement (stages 3-4) according to RHC. Discordant cases were significantly older, with higher prevalence of atrial fibrillation, markedly elevated N-terminal pro-B-type natriuretic peptide, and higher indexed left atrial volume, E/e₀, and systolic pulmonary artery pressure vs concordant cases ($P < 0.05$). The combined CD staging, integrating TTE and RHC, was more accurate in predicting mortality than the TTE-derived system ($P < 0.05$) (**Figure 10**).

Conclusions. In patients with m/asAS and ssAS, the combined CD staging, derived from TTE and RHC, was more accurate in predicting mortality than TTE alone. In a subset of AS patients, the integration of RHC may significantly improve prognostic stratification.

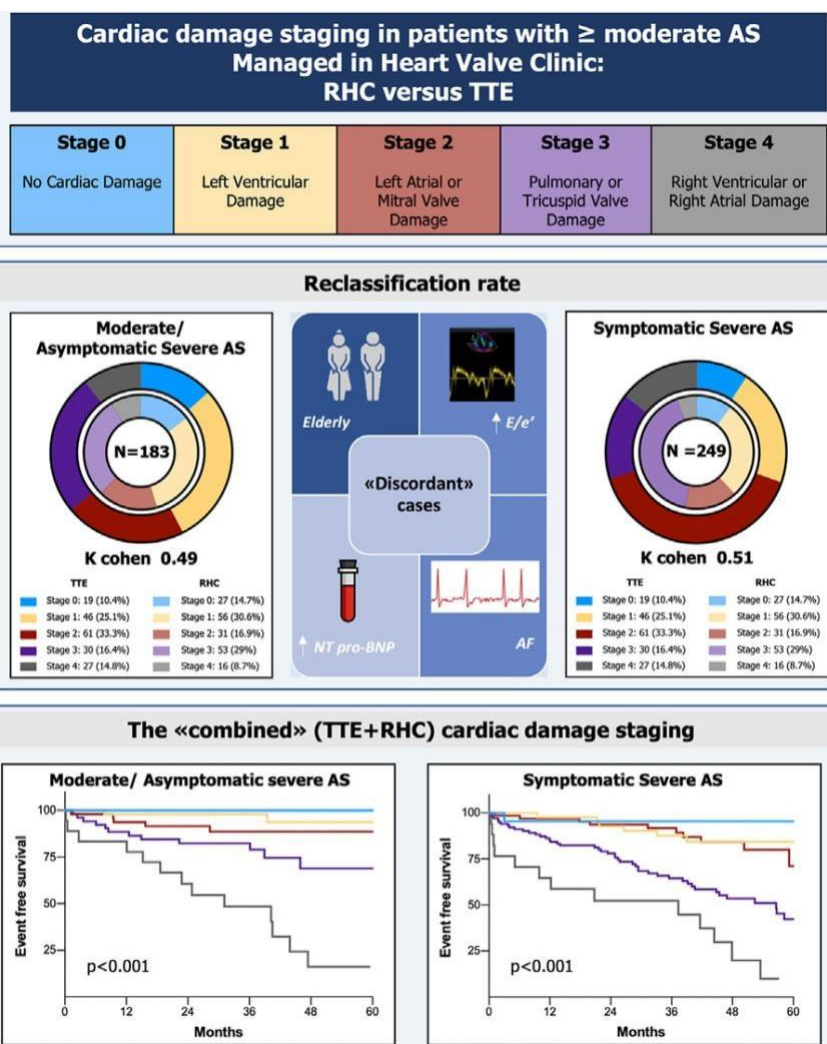


Figure 10. Study design and main results

CHAPTER 14

Extent of Cardiac Damage and Mortality in Patients Undergoing Transcatheter Aortic Valve Implantation

Aims. We sought to assess the impact of the extent of cardiac damage on survival among real-world patients with severe aortic stenosis (AS) undergoing transcatheter aortic valve implantation (TAVI).

Methods. A staging classification was applied to 262 patients from the EffecTAVI Registry at baseline and re-assessed within 30-days after TAVI. The primary endpoint of the study was all-cause mortality at 1-year. Secondary endpoints included cerebrovascular accident, myocardial infarction, permanent pacemaker implantation, endocarditis, and re-hospitalization for all causes.

Results. At baseline, 23 (8.7%) patients were in Stage 0/1 (no cardiac damage/left ventricular damage), 106 (40.4%) in Stage 2 (left atrial or mitral valve damage), 59 (22.5%) in Stage 3 (pulmonary vasculature or tricuspid valve damage) and 74 (28.3%) in Stage 4 (right ventricular damage). At 30-days after TAVI, a lower prevalence of advanced stages of cardiac damage than baseline, mainly driven by a significant improvement in left ventricular diastolic parameters and right ventricular function, was reported. At 1-year, a stepwise increase in mortality rates was observed according to staging at baseline: 4.3% in Stage 0/1, 6.6% in Stage 2, 18.6% in Stage 3 and 21.6% in Stage 4 ($p = 0.08$) (Figure 11). No differences were found in secondary endpoints.

Conclusions. TAVI has an early beneficial impact on the left ventricular diastolic and right ventricular function. However, the extent of cardiac damage at baseline significantly affects the risk of mortality at 1-year after the procedure.

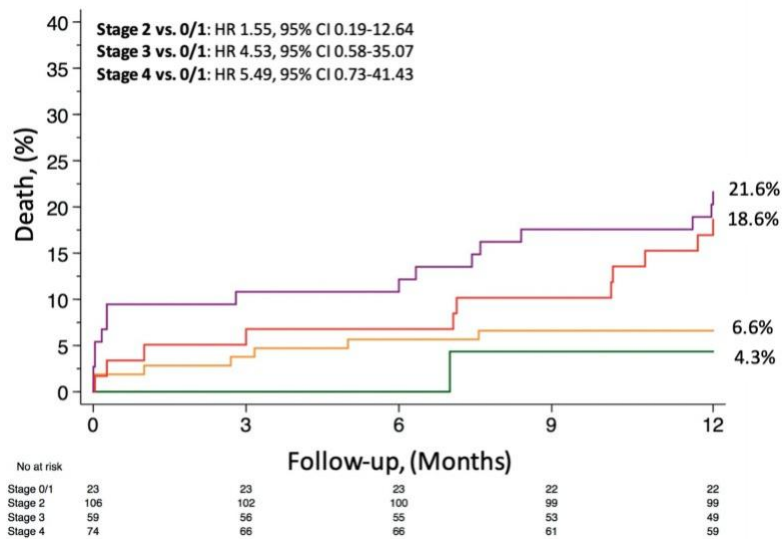


Figure 11. All-cause mortality according to the stage of cardiac damage

CHAPTER 15

Incidence, predictors, and prognostic impact of temporary left bundle branch block after transcatheter aortic valve replacement

Background. Little is known about temporary Left Bundle Branch Block (LBBB) after transcatheter aortic valve replacement (TAVR). We aim to evaluate the incidence, prognostic impact and predictors of temporary LBBB in TAVR patients.

Methods. Electrocardiograms (ECGs) obtained before and after TAVR, at discharge and at 30-day follow-up were anonymously analyzed by 5 cardiologists. Temporary LBBB included transient LBBB or persistent LBBB. The primary endpoint was all-cause mortality at 1-year after TAVR.

Results. Out of 198 patients, 55 (27.7%) developed temporary LBBB. No differences between groups were observed in primary endpoint. Left ventricular ejection fraction (LVEF) was identified as predictive factor of transient LBBB.

Conclusions. Temporary LBBB has no significant impact on survival at 1 year after the procedure. We sought to assess the impact of the extent of cardiac damage on survival among real-world patients with severe aortic stenosis (AS) undergoing transcatheter aortic valve implantation (TAVI).

CHAPTER 16

Impact of COVID-19 pandemic on timing and early clinical outcomes of transcatheter aortic valve implantation

Background. We sought to investigate the applicability and outcomes of a novel system to manage patients requiring transcatheter aortic valve implantation (TAVI) at a tertiary level hospital during the coronavirus disease-2019 (COVID-19) pandemic.

Methods. To analyze the impact of hospitalization pathways during the pandemic on clinical outcomes of TAVI patients, the study population was divided into two groups (pre-pandemic and pandemic groups) and all perioperative/follow-up data were compared. The primary endpoint was all-cause mortality at 30 days; secondary endpoints included procedural success and short-term complications.

Results. A total of 315 patients received TAVI during the study period. Pandemic group (n.77) showed a more complex baseline clinical profile (NYHA class III-IV, 70.1% vs. 56.3%; $p=0.03$). The overall time to procedure was significantly longer during pandemic (56.9 ± 68.3 vs. 37.7 ± 25.4 ; $p=0.004$) while intensive care unit stay was shorter (2.2 ± 1.4 vs. 3.7 ± 3.9 , $p<0.05$). Hospitalization length was similar in both groups as well as all-cause mortality rate and the incidence of major periprocedural complications. No case of infection by COVID-19 was reported among patients during the hospital stay.

Conclusions. Comparative analysis of early clinical outcomes showed that COVID-19 pandemic did not affect the safety and effectiveness of TAVI as similar rates of procedural complications and all-cause mortality were reported than before February 2020. Despite the increased time lag between diagnosis and procedure and a more complex clinical profile of patients at baseline, the revised

pathway of hospitalization allowed to resume inpatient procedures while not affecting patients' and healthcare workers' safety.

CHAPTER 17

Acute advanced aortic stenosis

Acute decompensation often represents the onset of symptoms associated with severe degenerative aortic stenosis (AS) and usually complicates the clinical course of the disease with a dismal impact on survival and quality of life. Several factors may derange the faint balance between left ventricular preload and afterload and precipitate the occurrence of symptoms and signs of acute heart failure (HF). A standardized approach for the management of this condition is currently lacking. Medical therapy finds very limited application in this setting, as drugs usually indicated for the control of acute HF might worsen hemodynamics in the presence of AS. Urgent aortic valve replacement is usually performed by transcatheter than surgical approach whereas, over the last decades, percutaneous balloon valvuloplasty gained renewed space as bridge to definitive therapy. This review focuses on the pathophysiological aspects of acute advanced AS and summarizes current evidence on its management.

(Figure 12)

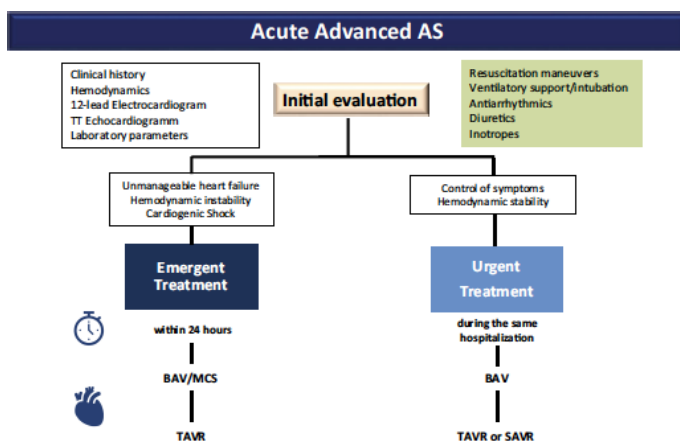


Figure 12. Management of patients with acute advanced aortic stenosis

PART V

Pharmacological treatment of atherosclerotic disease

CHAPTER 18

Antithrombotic Therapy in Peripheral Artery Disease: Current Evidence and Future Directions

Abstract. Patients with peripheral artery disease (PAD) are at an increased risk of major adverse cardiovascular events, and those with disease in the lower extremities are at risk of major adverse limb events primarily driven by atherothrombosis. Traditionally, PAD refers to diseases of the arteries outside of the coronary circulation, including carotid, visceral and lower extremity peripheral artery disease, and the heterogeneity of PAD patients is represented by different atherothrombotic pathophysiology, clinical features and related antithrombotic strategies. The risk in this diverse population includes systemic risk of cardiovascular events as well as risk related to the diseased territory (e.g., artery to artery embolic stroke for patients with carotid disease, lower extremity artery to artery embolism and atherothrombosis in patients with lower extremity disease). Moreover, until the last decade, clinical data on antithrombotic management of PAD patients have been drawn from subanalyses of randomized clinical trials addressing patients affected by coronary artery disease.

The high prevalence and related poor prognosis in PAD patients highlight the pivotal role of tailored antithrombotic therapy in patients affected by cerebrovascular, aortic and lower extremity peripheral artery disease. Thus, the proper assessment of thrombotic and hemorrhagic risk in patients with PAD represents a key clinical challenge that must be met to permit the optimal antithrombotic prescription for the various clinical settings in daily practice. The aim of this updated review is to analyze different features of atherothrombotic disease as well as current evidence of antithrombotic management in

asymptomatic and secondary prevention in PAD patients according to each arterial bed (**Figure 13**).

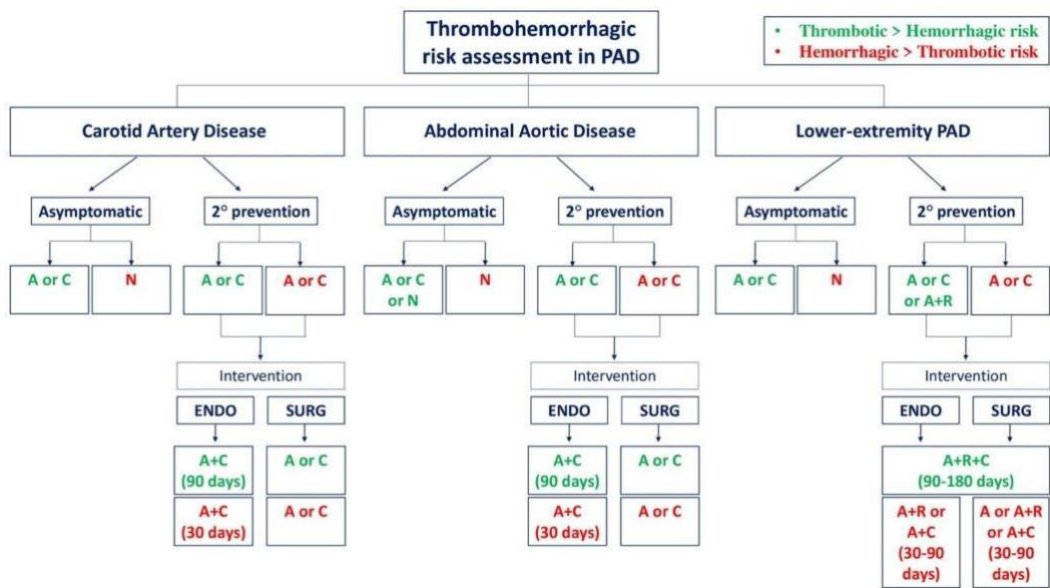


Figure 12. Proposed algorithm for antithrombotic management in patients with PAD asymptomatic or in secondary prevention.

A= low-dose aspirin, C= clopidogrel 75mg/day, N= no medical therapy, R= rivaroxaban 2.5mg/twice daily, ENDO = endovascular revascularization, SURG = surgical revascularization.

CHAPTER 19

Safety and efficacy of bempedoic acid: a systematic review and meta-analysis of randomized controlled trials

Background. Bempedoic Acid (BA) is a novel Lipid-Lowering Therapy (LLT). We performed a systematic review and meta-analysis to assess the efficacy and safety of BA in patients with hypercholesterolemia.

Methods. PubMed, Scopus, and Cochrane library databases were searched for randomised controlled trials evaluating the efficacy and/or safety of BA compared with placebo. Trials investigating dosages other than 180 mg/die were excluded. Major adverse cardiovascular events (MACE) were the primary efficacy endpoint. LDL-cholesterol reduction was the primary laboratory endpoint. Pre-specified safety endpoints included muscle-related adverse events, newonset diabetes, and gout. The protocol was registered on PROSPERO (temporary ID:399,867).

Results. Study search identified 275 deduplicated results. 11 studies, encompassing 18,315 patients (9854 on BA vs 8461 on placebo/no treatment) were included. BA was associated with a reduced risk of MACE (OR 0.86, 95% CI 0.79– 0.95), myocardial infarction (OR 0.76, 95% CI 0.64–0.88) and unstable angina (OR 0.69, 95% CI 0.54–0.88) compared to control, over a median follow up of 87 (15–162) weeks. BA was associated with a reduction of LDL-Cholesterol (mean difference [MD]–22.42,95% CI – 24.02% to – 20.82%), total cholesterol (– 16.50%,95% – 19.21% to – 13.79%), Apo-B lipoprotein (– 19.55%, – 22.68% to – 16.42%) and high-sensitivity CRP (– 27.83%, – 31.71% to – 23.96%) at 12 weeks. BA was associated with a higher risk of gout (OR 1.55, 95% CI 1.27–1.90) as compared with placebo. Efficacy on laboratory endpoints was confirmed, with a

variable extent, across patients on statin or ezetimibe background therapy (Figure 14).

Conclusions. The improved cholesterol control achieved with BA translates into a reduced risk of MACE, including myocardial infarction and coronary revascularization. The drug has a satisfactory safety profile except for an increased risk of gout.

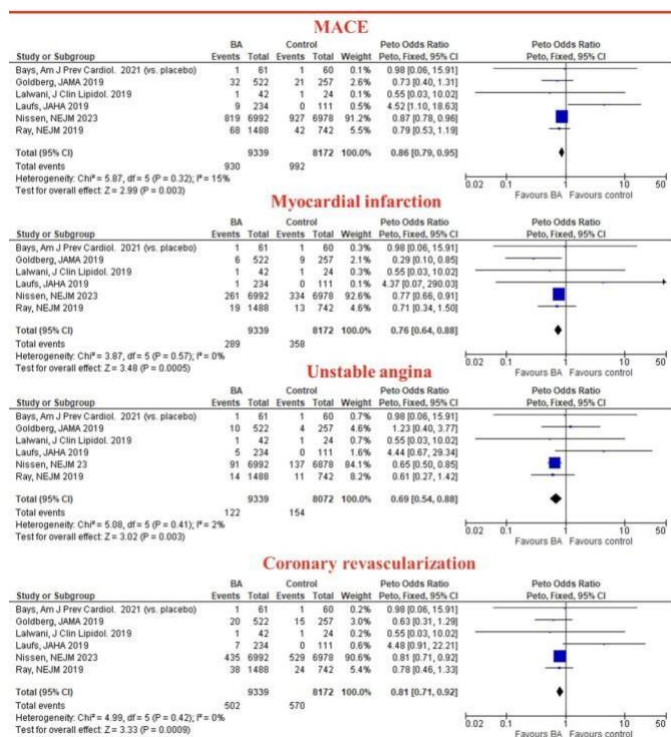


Figure 14. Peto odds ratio for major adverse cardiovascular events (MACE), myocardial infarction, unstable angina and coronary revascularization. BA: bempedoic acid; CI: confidence intervals.

Part VI

Artificial Intelligence application in cardiovascular medicine

CHAPTER 20

International evaluation of an artificial intelligence-powered electrocardiogram model detecting acute coronary occlusion myocardial infarction

Aims. A majority of acute coronary syndromes (ACS) present without typical ST elevation. One-third of non-ST-elevation myocardial infarction (NSTEMI) patients have an acutely occluded culprit coronary artery [occlusion myocardial infarction (OMI)], leading to poor outcomes due to delayed identification and invasive management. In this study, we sought to develop a versatile artificial intelligence (AI) model detecting acute OMI on single-standard 12-lead electrocardiograms (ECGs) and compare its performance with existing state-of-the-art diagnostic criteria.

Methods and results. An AI model was developed using 18 616 ECGs from 10 543 patients with suspected ACS from an international database with clinically validated outcomes. The model was evaluated in an international cohort and compared with STEMI criteria and ECG experts in detecting OMI. The primary outcome of OMI was an acutely occluded or flow-limiting culprit artery requiring emergent revascularization. In the overall test set of 3254 ECGs from 2222 patients (age 62 ± 14 years, 67% males, 21.6% OMI), the AI model achieved an area under the curve of 0.938 [95% confidence interval (CI): 0.924–0.951] in identifying the primary OMI outcome, with superior performance [accuracy 90.9% (95% CI: 89.7–92.0), sensitivity 80.6% (95% CI: 76.8–84.0), and specificity 93.7 (95% CI: 92.6–94.8)] compared with STEMI criteria [accuracy 83.6% (95% CI: 82.1–85.1), sensitivity 32.5% (95% CI: 28.4–36.6), and specificity 97.7% (95% CI: 97.0–98.3)] and with similar performance compared with ECG experts [accuracy 90.8% (95% CI: 89.5–91.9), sensitivity 73.0% (95% CI: 68.7–77.0), and specificity 95.7% (95% CI: 94.7–96.6)] (**Figure 15**).

Conclusion. The present novel ECG AI model demonstrates superior accuracy to detect acute OMI when compared with STEMI criteria. This suggests its potential to improve ACS triage, ensuring appropriate and timely referral for immediate revascularization.

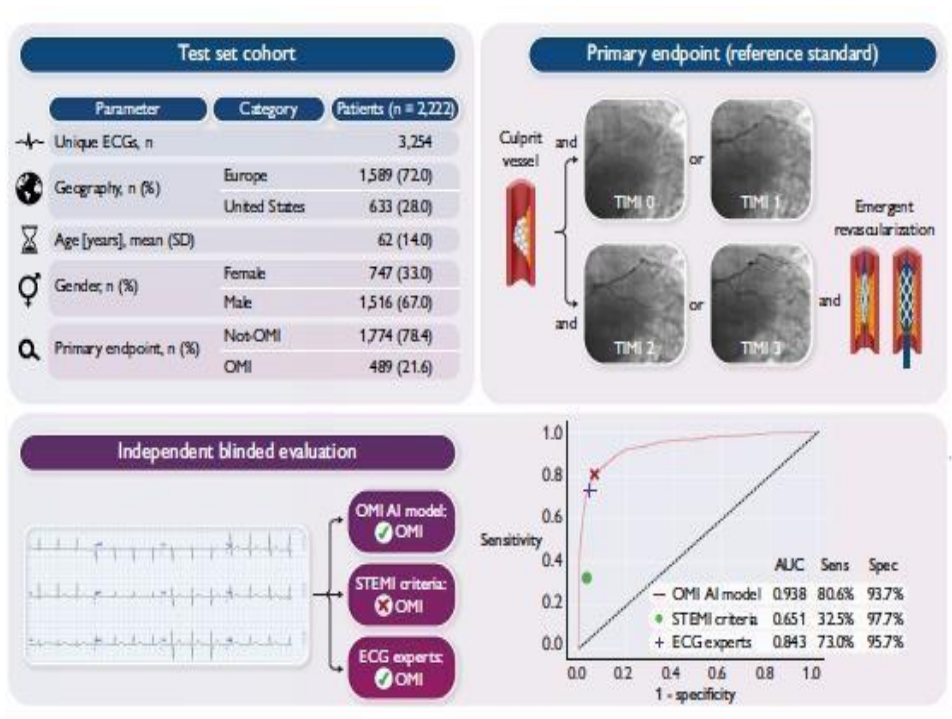


Figure 15. Study design and results

Part VII

Discussion and conclusions

Discussion

Part I. Advances in coronary artery disease treatment

With the advancement of devices and the broadening indications for PCI, the field of coronary artery disease has expanded significantly. Our research has contributed to this growing body of evidence in some of the most challenging clinical scenarios:

- Bifurcation lesions
- Chronic Total Occlusions (CTO)
- Left main revascularization
- ISR

In recent years, improvements in device technology have led to a further reduction in stent strut thickness, introducing a new class of “ultrathin strut DES”. Although there is no universally accepted definition, ultrathin DES are typically considered stents with a strut thickness of less than 70 μm . The potential benefits of these devices include better deliverability, reduced vessel injury, and less disturbance to side branch flow.

In our analysis of the ULTRA registry, we evaluated the performance of ultrathin-strut DES in 1,801 patients who underwent PCI in complex lesions, specifically in the left main stem, bifurcations, or CTO lesions. The clinical outcome data demonstrated high efficacy and satisfactory safety, even in these challenging lesion types. Several clinical predictors of poor outcomes following PCI, such as diabetes, impaired LVEF, chronic kidney disease, and ST-elevation Myocardial Infarction (STEMI) treatment, have been well established by previous studies.(6, 7)

In our cohort, characterized by highly complex coronary disease, we confirmed the significant impact of these variables despite using state-of-the-art devices.

Several patient-related characteristics, such as advanced age, diabetes, impaired renal function, reduced left ventricular function, cardiogenic shock at admission, and STEMI as an admission diagnosis, were associated with an increased risk of target Lesion Failure (TLF) while a positive effect was observed with the use of intracoronary imaging both in the overall study population and in the subset treated for bifurcation lesions.

In the context of left main revascularization, we conducted a meta-analysis of randomized controlled trials (RCTs) and adjusted observational studies comparing outcomes of PCI and CABG for left main disease based on age. Among younger patients, PCI was associated with a significantly higher risk of all-cause death and repeat revascularization compared to CABG. However, this mortality benefit was not confirmed when the analysis was restricted to RCTs alone. Conversely, in older patients, PCI and CABG showed similar risks for all-cause death, myocardial infarction, and repeat revascularization.

Recent studies have consistently shown that advanced age, independent of surgical risk scores, is associated with worse outcomes after cardiac surgery.⁽⁸⁾ The challenges posed by general anesthesia, sternotomy, extended hospital stays, and postoperative complications can be particularly severe in elderly patients, making recovery more difficult. Frailty, common in this population, has been identified as a significant risk factor for perioperative and long-term mortality after cardiac surgery.⁽⁹⁾ In this context, the results of our meta-analysis provide valuable insights for heart teams making clinical decisions in patients with unprotected left main disease.

DES-ISR remains a significant clinical challenge, exhibiting higher rates of Target Lesion Revascularization (TLR) compared to PCI for de novo lesions. Evidence on the efficacy of ultrathin DES with biodegradable polymers in the context of DES-ISR is limited. This lack of data may be attributed to concerns that ultrathin strut stents could provide insufficient radial force for the rigid, plaque-laden coronary lesions often seen in ISR. While reassuring data from RCTs have led to the widespread adoption of ultrathin DES, it is essential to acknowledge that these devices may yield less favorable outcomes in heavily calcified lesions, where stronger scaffolding is required for optimal treatment.⁽¹⁰⁾ Our study aimed to evaluate the efficacy and safety of ultrathin DES compared to second-generation thin-strut DES and drug-eluting balloons (DEB) for DES-ISR. The findings indicate that ultrathin DES may be associated with a lower risk of TLR in cases of diffuse DES restenosis compared to second-generation thin-strut DES or DEB. For focal DES restenosis, however, the outcomes were similar across all devices. While our results corroborate existing data suggesting that DES (both second-generation thin-strut and ultrathin) are generally associated with more favorable outcomes compared to DEB, they also highlight that ultrathin DES may represent an optimal therapy for the first occurrence of DES-ISR. Ultrathin DES offers the advantage of maximizing luminal gain, particularly in high plaque-burden lesions, where they provide more effective scaffolding than DEBs, especially when results following predilation are suboptimal. Moreover, the reduced strut thickness of ultrathin DES limits the endothelial inflammatory response and curbs neointimal proliferation compared to second-generation DES.⁽¹¹⁾ Based on these findings, we propose that repeated DES implantation with ultrathin DES should be considered first choice for more aggressive cases, such as diffuse or occlusive ISR, while DEBs

may be suitable for focal ISR.(12) Future randomized controlled trials exploring the optimal treatment strategy for DES-ISR, with the latest-generation ultrathin DES as the standard of care, are warranted.

Part II. Periprocedural Myocardial Infarction and impact on outcomes

Periprocedural MI and myocardial injury are adverse events that can diminish the benefits of elective percutaneous revascularization. In the context of chronic coronary syndromes (CCS), the early risk of periprocedural MI is crucial when weighing the risks and benefits of myocardial revascularization against a conservative approach. Indeed, when considering all MI events, PCI has a neutral effect on MI risk due to a trade-off between spontaneous and periprocedural events—the former being avoided at the expense of the latter.

Over the past decade, various academic groups have proposed multiple definitions of periprocedural MI, though not all have shown a clear association with mortality.(13–15) Identifying patients at higher risk for periprocedural MI, as well as establishing a definition with prognostic relevance, along with understanding its frequency and mechanisms, could improve decision-making regarding the risk-benefit ratio of elective PCI. It could also encourage the adoption of strategies to mitigate the risk of periprocedural MI in high-risk scenarios.

We first conducted a study on 1,010 patients undergoing elective PCI, aiming to compare the frequency of myocardial injury and periprocedural MI in relation to PCI complexity. The results clearly demonstrated that the risk of periprocedural MI increases in patients undergoing complex PCI, a finding consistent across various definitions. As a result, the risk of periprocedural MI should be carefully considered during procedural planning for patients undergoing complex PCI.

In another study, we characterized the frequency, mechanisms, and clinical course of periprocedural MI diagnosed using Society for Cardiovascular Angiography and Interventions (SCAI) criteria, comparing creatine kinase-

myocardial band fraction (CK-MB) and high-sensitivity cardiac troponin (hs-cTn) measurements. Using hs-cTn instead of CK-MB led to a substantial increase in the diagnosis of SCAI-defined periprocedural MI, though these additional events were not prognostically relevant in the absence of concurrent CK-MB elevations.

Unlike definitions solely based on elevated cardiac biomarkers after PCI, the Fourth Universal Definition of MI (UDMI) requires the presence of at least one of the following: ischemic Electrocardiogram (ECG) changes, cardiac imaging abnormalities, or angiographic complications. In our last study on this topic, we evaluated the prognostic significance of these criteria and found that the risk of death is significantly higher in patients meeting two or three supporting criteria for periprocedural MI, but not in those meeting only one.

The results of our studies suggest that hs-cTn should not be considered a substitute for CK-MB in defining SCAI periprocedural MI and that adopting a two- or three-criteria approach may help harmonize UDMI criteria. This approach could also reduce the incidence of periprocedural MI by focusing on clinically significant events.

Part III. Evaluation of coronary microvascular function

The clinical significance of coronary microvascular dysfunction (CMD) is increasingly recognized, as it is associated not only with symptoms and reduced quality of life but also with higher mortality.⁽¹⁶⁾ However, the reported prevalence of CMD varies widely, likely due to the heterogeneous clinical definitions and the lack of an accurate, specific, reproducible, and quantitative measure to assess microvascular function.⁽¹⁷⁾

In our first study on the topic, we investigated 175 patients to compare CFR and MRR using bolus and continuous thermodilution. The key findings are as follows:

1. Continuous thermodilution produced significantly lower measurements compared to bolus thermodilution.
2. There was only moderate agreement between the two techniques for diagnosing CMD, with a fair correlation for MRR and CFR.

3. Importantly, continuous thermodilution demonstrated three times the precision in measuring MRR and CFR compared to bolus thermodilution.

Based on these results, we conducted the first study evaluating CMD in heart HF patients using continuous thermodilution. Our aim was to characterize the presence and extent of CMD in patients with de novo HF and nonobstructive CAD, while also exploring differences in CMD patterns between HF with preserved ejection fraction (HFpEF) and HF with reduced ejection fraction (HFrEF) and evaluating the incidence of CMD in HFrEF patients stratified by the presence of left ventricular (LV) reverse remodeling at follow-up. The main findings were:

1. In the HFrEF cohort, absolute coronary flow (at rest and hyperemia) was significantly higher, and microvascular resistance (both at rest and hyperemia) was lower compared with HFpEF.

2. CMD was present in 52% of the entire study population, with similar prevalence in both HFpEF and HFrEF.

3. HFrEF patients predominantly exhibited a functional CMD pattern.

Our research underscores the value of a comprehensive invasive physiological assessment of microcirculation in HF patients. It highlights the importance of systematically evaluating microcirculatory dysfunction in patients with HF, regardless of the presence of epicardial stenoses.

In our final study on this subject, we examined the physiological changes in microcirculatory function using continuous intracoronary thermodilution to assess both resting and hyperaemic absolute coronary flow and microvascular resistance in patients with severe aortic stenosis, before TAVI, immediately after TAVI, and at 6-month follow-up. We observed no significant changes in absolute coronary blood flow (both resting and hyperaemic) immediately post-TAVI or at 6 months in a subgroup of 20 patients. However, in patients with reverse LV remodeling, hyperaemic perfusion increased over time. This suggests that while coronary autoregulation remained intact, it could not fully explain the cause of exercise-induced angina in aortic stenosis (AS) patients. The inverse relationship between hyperaemic perfusion and LV hypertrophy regression suggests that the mismatch between perfusion and LV mass may contribute to this phenomenon, implying that hyperaemic perfusion may not adequately meet the demands of increased LV mass in AS, leading to symptoms.

These findings illustrate the complex interaction between coronary perfusion, LV remodeling, and exercise-induced angina in patients undergoing TAVI. Further research is needed to better understand these

mechanisms and optimize the timing of interventions to alleviate symptoms in this patient population.

Part IV. Aortic stenosis and Transcatheter Aortic Valve Implantation

Current guidelines recommend intervention in patients with AS based on the severity of the disease and the presence of symptoms.(18) However, the benefits of valve replacement may be limited in patients with advanced myocardial structural and functional changes. A recently proposed staging classification for AS suggests a continuum in the pathophysiology of LV structural and functional changes induced by AS.(19)

We conducted a study to evaluate the prognostic performance of this staging classification in a real-world cohort of patients undergoing TAVI and to investigate the procedure's impact on the extent of extra-aortic valve cardiac damage. The key findings of our analysis are as follows:

1. The AS-related cardiac damage staging classification, originally derived from a randomized trial, retains its prognostic value in real-world TAVI patients.
2. TAVI induces an early reversal of cardiac dysfunction, primarily by improving LV diastolic and right ventricular (RV) function.
3. The extent of extra-aortic valve cardiac damage at baseline significantly influences survival at 1-year post-procedure.

In a further study, we assessed the prognostic value and reclassification potential of right heart catheterization (RHC) compared with transthoracic echocardiography (TTE) in characterizing CD staging over a 3-year follow-up in patients with clinically significant AS. Our goal was to identify patients who might benefit from RHC for better prognostic stratification and to test the prognostic utility of a combined CD staging approach.

Our data confirmed that both TTE and RHC reliably map CD in patients with AS, offering valuable prognostic insights. Notably, more advanced stages of

CD correlated with progressively higher mortality. However, RHC-derived staging provided superior discrimination in the mortality curves, particularly in stages assessing RV damage (stages 3 and 4).

The combined CD staging, which integrates both TTE and RHC, enhances stratification of CD severity and allows for more accurate prognosis in patients with moderate/asymptomatic severe AS and severe symptomatic AS compared to TTE alone. Our findings suggest that incorporating RHC into the diagnostic work-up, especially in elderly patients with atrial fibrillation (AF) and elevated filling pressures on TTE, may improve prognostic stratification. Taken together, these data contribute to a better understanding of which parameters should be considered in clinical decision-making and how they should be interpreted.

Part V. Pharmacological treatment of atherosclerotic disease

Antithrombotic therapy and LLT play crucial roles in reducing long-term cardiovascular risk in individuals with atherosclerotic disease, particularly those with polyvascular disease. While the benefits of antithrombotic therapy in CAD have been well established over the past decades, supported by dedicated RCTs, evidence for antithrombotic therapy in peripheral artery disease (PAD) has historically relied on subgroup analyses from CAD trials, often yielding limited and conflicting data.

In recent years, a new antithrombotic strategy has emerged in PAD research that combines an anticoagulant with standard antiplatelet therapy. However, it is crucial to evaluate thrombo-hemorrhagic risk when selecting the appropriate antithrombotic regimen, as PAD patients generally face a higher bleeding risk than those with CAD due to concomitant diseases.

In our review, we reported on the pharmacodynamic targets of antithrombotic drugs in peripheral artery disease as categorized by thrombotic pathways and proposed an updated algorithm for antithrombotic management in these patients, for both primary and secondary prevention. Among the LLTs for atherosclerotic cardiovascular disease, statins remain the most extensively studied and widely prescribed drugs. However, bempedoic acid (BA) is emerging as a promising new therapeutic agent. We conducted an updated systematic review and meta-analysis of RCTs examining BA for hypercholesterolemia treatment. Our study represents the largest meta-analysis investigating the clinical properties of BA, with a sample size sufficiently powered to evaluate the drug's efficacy on hard cardiovascular endpoints. The findings confirm that BA use is associated with improved cholesterol control, leading to significant reductions in major adverse cardiovascular events (MACE), MI, and myocardial revascularizations, all

while maintaining a satisfactory safety profile, aside from an increased risk of gout.

Part VI. Artificial Intelligence application in cardiovascular medicine

AI is making significant strides in all fields of medicine, including cardiovascular care. We developed and validated a novel, explainable AI model capable of detecting acutely occluded or obstructive culprit coronary arteries from a single 2.5-second 12-lead ECG recorded in patients with suspected Acute Coronary Syndrome (ACS) before undergoing cardiac catheterization. Our model outperforms conventional STEMI criteria and is comparable to the interpretations of expert ECG readers, who were blinded to all other clinical information, in identifying invasively confirmed acute coronary occlusion.

Given that only 25% of ACS patients present with typical ST-segment elevation on their initial ECG, and up to 35% of those without ST-segment elevation are later found to have total coronary occlusion on delayed angiography, there is a critical need to better identify patients at risk for OMI.(20–22) Compared to Non-ST-Elevation Myocardial Infarction (NSTEMI) patients with non-occlusive stenosis of the culprit artery, those with OMI experience significantly higher mortality and worse left ventricular function, despite being younger and having fewer comorbidities.(23)

Accurate and timely ECG-based diagnosis of ACS at the point of first contact could facilitate rapid coronary intervention, as is currently recommended for patients meeting standard STEMI criteria. Early reperfusion in these cases can significantly reduce myocardial injury and improve clinical outcomes. Notably, our model detected OMI on average three hours earlier than current guideline-based ECG standards, highlighting its potential to enhance the timely referral of ACS patients at risk for adverse outcomes.

Conclusions

Throughout this extensive research journey, we have investigated several key areas: (a) advancements in the treatment of CAD, providing new insights into coronary revascularization in complex scenarios; (b) the frequency, mechanisms, and impact of periprocedural MI in elective PCI; (c) the most accurate method to evaluate Coronary Microvascular Function and its clinical significance across various settings; (d) the role of proper staging classifications and timely interventions in AS management; (e) the importance of antiplatelet therapy and novel lipid-lowering agents in cardiovascular disease; and (f) the latest applications of AI in cardiovascular medicine. We believe our comprehensive translational research has provided critical answers to these important clinical questions.

List of abbreviations

AI: Artificial intelligence

ACS: acute coronary syndrome

AS: aortic stenosis

BA: Bempedoic acid

CABG: coronary artery bypass grafting

CAD: coronary artery disease

CCTA: coronary computed tomography angiography

CD: Cardiac damage

CFR: coronary flow reserve

Ck-mb: creatine kinase-myocardial band fraction

CMD: coronary microvascular dysfunction

CVD: Cardiovascular disease

DEB: Drug eluting balloon

DES: Drug eluting stent

ECG: Electrocardiogram

HF: heart failure

Hfref: HF reduced ejection fraction

Hfpref: HF preserved ejection fraction

Hs-cTn: high-sensitivity cardiac troponin

ISR: In-stent restenosis

LLT: Lipid-Lowering Therapy

LV: Left ventricular

MACE: major adverse cardiac events

MI: myocardial infarction

MRR: microvascular resistance reserve

NSTEMI: Non-ST-elevation myocardial infarction

OMI: Occlusion myocardial infarction

PAD: Peripheral artery disease

PCI: Percutaneous Coronary Intervention

RCTs: Randomized controlled trials

RHC: Right heart catheterization

RV: Right ventricular

SCAI: Society for Cardiovascular Angiography and Interventions

STEMI: ST- elevation myocardial infarction

TAVI: transcatheter aortic valve implantation

TTE: Transthoracic echocardiography

UDMI: Universal Definition of Myocardial infarction

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Evaluation of Dr. Leone Attilio

a) Scientific Production:

Dr. Leone has demonstrated excellent scientific productivity, producing high-quality research that reflects significant expertise and innovation in his field.

b) First Authorship in Papers:

The level of first-author publications by Dr. Leone is excellent, showcasing his ability to independently lead impactful research projects and contribute significantly to the academic community.

c) Acknowledgment of Affiliations and the CardioPaTh Program:

Dr. Leone has shown good adherence to acknowledging his institutional affiliations and the CardioPaTh program, ensuring proper recognition in his professional outputs.

d) Attendance to the Webinars:

His participation in the program's webinars has been excellent, underscoring his commitment to lifelong learning and active engagement with program activities.

e) Attendance to the Yearly Meeting:

Dr. Leone's excellent attendance at the yearly meetings reflects his strong commitment to the CardioPaTh program and its collaborative mission.

f) Research Training in a Non-Italian Campus:

Dr. Leone successfully completed a 12-month research training period at a non-Italian campus, fulfilling a key requirement of the CardioPaTh program and gaining valuable international research experience.

Final Evaluation:

Dr. Leone has complied with all the requirements of the Core Curriculum of the CardioPaTh program, excelling in nearly all evaluated areas.

Conclusion:

Dr. Leone is approved to proceed to the discussion of his final thesis.

Firma

Coordinatore del Dottorato
(Prof. Giovanni Esposito)

ANALYTICAL JUDGMENT ON DOCTORAL THESIS
PhD in Cardiovascular Pathophysiology and Therapeutics (CardioPath
Cycle 36°

EVALUER (name and surname) Tullio Tesorio

PROFESSOR\QUALIFICATION AT: Director Catheterization Laboratory Casa di Cura Montevergine

PhD STUDENT (name and surname) **Attilio Leone**

Analytical judgment on the thesis

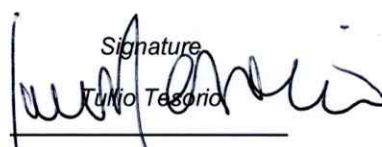
The thesis represents a comprehensive and well-structured contribution to the field of interventional cardiology, addressing several key areas in contemporary clinical practice and research. The focus on complex coronary lesions, treatment strategies, periprocedural myocardial infarction and the evaluation of novel technologies and methodologies demonstrates a clear understanding of the challenges in the discipline. The thesis offers valuable insights and contributes to ongoing discussions in the interventional cardiology community. The thesis is well-organized and presented in a clear, logical manner. The sections flow cohesively, with appropriate transitions between chapters. The author effectively discusses the broader implications of the research, particularly its impact on treatment strategies and patient outcomes. Recommendations for future research are insightful, addressing the evolving needs of interventional cardiology, such as advancements in coronary microcirculation and the long-term outcomes of TAVI.

Therefore:

☒ The PhD student mentioned above is admitted to the public discussion of the thesis in the ordinary session of the final exams;

☐ The doctoral student mentioned above is admitted to the public discussion of the thesis with reference to extraordinary session of final exams *;

Date 07/11/2024

Signature

Tullio Tesorio

* the extraordinary session of the final exams will be set by 30 June 2025 (or with extension, pursuant to **Legislative Decree 34 of 19/05/2020, art. 236, paragraph 5)**

ANALYTICAL JUDGMENT ON DOCTORAL THESIS
PhD in Cardiovascular Pathophysiology and Therapeutics (CardioPath
Cycle 36°

EVALUER (*name and surname*) Fabrizio D'Ascenzo

Associate Professor at University of Turin

PhD STUDENT Attilio Leone

Analytical judgment on the thesis

Dr Leone performed a high-quality thesis reporting a relevant number of papers he co-authored in the field of coronary intervention.

Regarding the third chapter, he should focus on integration of FFR-CT in real life, and how to implement its use.

Regarding chapters 4 and 6, in the discussion he should describe the predictors of failure of the procedure, and why they still hold true also in ultrathin stent era

In chapter 7, Dr. Leone should focus on the different impact on prognosis across the different definitions of peri procedural MI, as done in chapter 8 with Ck-MB and in chapter 9.

Regarding part 3, in the first chapter Dr. Leone should write if he compared the different methods of thermos dilution with a non-invasive gold standard like CMR.

Regarding part 4, in chapter 15, De Leone should add if he followed these patients also from a electrocardiography point of view (e.g 24 hours Holter)

In part V, the Candidate should describe his clinical experience regarding bempedoic acid.

In summary, the Candidate should be congratulated for performing a high-quality research covering a wide range of cardiovascular research.

Therefore:

☒ The PhD student mentioned above is admitted to the public discussion of the thesis in the ordinary session of the final exams;

☐ The doctoral student mentioned above is admitted to the public discussion of the thesis with reference to extraordinary session of final exams *;

Date 15/11/2024

Signature

Fabrizio D'Ascenzo



* the extraordinary session of the final exams will be set by 30 June 2025 (or with extension, pursuant to **Legislative Decree 34 of 19/05/2020, art. 236, paragraph 5**)