International PhD program in Cardiovascular Pathophysiology and Therapeutics

New insights for medical and interventional treatment in CAD and PAD patients

PhD Thesis

Donato Gerardi, MD

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Contents

Chapter 1

General introduction and outline of the thesis

In this thesis we present a summary of the activities carried out in the last 3 years. In the period we have been committed in clinical and interventional activities in the "San Carlo" Regional Hospital, Potenza, Italy, as a full-time MD assigned to the Cardiology Unit. The main areas of interest have been the following:

- interventional cardiology, mainly involved in percutaneous coronary intervention (PCI) in elective and emergent procedures as a reference center of the regional network for myocardial infarction "rete IMA";
- inpatient and outpatient clinical assistance;
- hospital referral for the diagnosis and treatment of patients with chronic coronary syndrome (CCS);
- hospital referral for cardiac assessment and management of patients undergoing non-cardiac surgery.

During the period in exam, our research was targeted to different areas but we always kept the focus both on coronary artery disease (CAD) and peripheral artery disease (PAD) and, in general, on multisite atherosclerotic disease (MSAD), which defines subjects at very high cardiovascular risk. We have generally analyzed "real-world" populations that reflect daily clinical practices in order to provide further insights respect to the highly controlled subject enrolled in clinical trials (RCTs).

We evaluated the predictors of adherence to medical therapy after acute coronary syndrome (ACS), which constitutes an important issue for the prognosis improvement after cardiovascular events; and safety and efficacy of potent P2Y12-inhibitors in an elderly (>75 year old), real-world population with ACS undergoing percutaneous coronary intervention (PCI), a subgroup slightly represented in RCTs.

In the field of PAD, we have examined the long-term results of the DAART (directional atherectomy and antirestenotic therapy) technique for the percutaneous treatment of common femoral artery (CFA) disease. We also report in this thesis a summary of the invited commentaries and literature reviews about PAD and MSAD; we have directed particular attention to carotid artery stenting (CAS) through the novel dual-layer stents and the different protection systems that can be used in this procedure.

During these years we also had the opportunity to study the permanent pacemaker implantation (PPMI) after TAVI with a balloon-expandable valve and a high implantation technique.

Outline of the thesis

The thesis is divided in the following parts:

Part I – Real world medical therapy after an acute coronary syndrome: from predictors of adherence to safety and efficacy of potent P2Y12 inhibitors in elderly patients.

In the first part of the thesis we report the works published (or waiting for submission) in the field of coronary artery disease, with particular interest in real-world populations and clinical practices. Starting from the assumption that the prognostic benefit observed in lasts decades in atherosclerotic cardiovascular diseases is partly due to the appropriate use of drugs prescribed in secondary prevention and that this benefit is attenuated by non-adherence to the prescribed therapy, our interest was initially directed to the identification of predictors of adherence after ACS. We subsequently focused on the assessment of efficacy and safety of potent P2Y12-inhibitors in a real-world population of elderly subjects with ACS, which represents a growing subgroup in daily clinical practice but slightly represented in randomized clinical trials.

Part II – Focus on peripheral arterial disease (PAD): novel techniques for percutaneous treatment of common femoral artery (CFA) disease.

The study of peripheral atherosclerotic disease (PAD) has been a focus of our research in recent years. It is well known that patients with peripheral atherosclerotic disease represent a very high risk subgroup. However, the optimal interventional treatment for some peripheral vascular districts such as the common femoral artery (CFA) still need to be clarified. We recently evaluated the efficacy and safety of percutaneous treatment in this district using directional atherectomy plus antirestenotic therapy (DAART): a no-stenting approach that can improve long-term patency without compromising future reinterventions or surgical procedures.

- **Part II.a – Reviews and editorial comments on peripheral arterial disease and multisite arterial disease.**

  Multisite artery disease is invariably associated with worse clinical outcomes. In this sub-section we report the short abstract of our published reviews discussing the incidence and diagnosis of multisite arterial disease and the available medical treatment strategies to improve outcomes in patients with lower extremity peripheral arterial disease (LE-PAD). We finally report in this section our editorial comments published in the field of carotid atherosclerotic disease, particularly regarding the growing evidences for the use of dual-layer stents and proximal and distal protection systems.

Part III – Focus on structural heart intervention: permanent pace-maker implantation predictors after TAVI.

In this section we report our study relative to the predictors of permanent pacemaker need after transcatheter aortic valve implantation (TAVI) with a balloon-expandable prosthesis with a high implantation technique. In this research an invasive electrophysiological study was performed before and after transcatheter aortic valve implantation. After this analysis, new insight about PPMI predictors were obtained.

Part IV – Discussion and conclusions

The last section of the thesis is a broad discussion of the addressed topics with the conclusions

PART I

Real-world medical therapy after an acute coronary syndrome: from predictors of adherence to safety and efficacy of potent P2Y12-inhibitors in elderly patients

Chapter 2

Predictors of adherence to composite therapy after acute coronary syndromes

Aims: Adherence to medical therapy following acute coronary syndrome (ACS) affects a patient's prognosis. In this cohort study, we sought to assess the factors that could affect a patient's adherence to therapy after ACS.

Methods: We prospectively collected information from patients (N = 964) hospitalized at the coronary care unit of the Federico II University Hospital, from 1 January 2015 to 30 June 2017, for ACS. Adherence to three classes of drugs including statins, antiplatelets [dual or single antiplatelet agent (SAPT)] and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACE-I/ARB) and their composites were assessed at 1 month, 1 and 2 years after discharge.

Results: At 30 days adherence to prescribed therapy was 94.4% for dual antiplatelet therapy (DAPT), 78.2% for statins, 92.7% for ACE-I/ARB and 70.7% for multitherapy. At 1 year, it was 91.1% for DAPT, 81.2% for ACE-I/ARB, 84.9% for statins and 71.4% for multitherapy. At 2 years, it was 97.1% for SAPT, 78.1% for ACE-I/ARB, 91.8% for statins, 72.8% for multitherapy. Multivariable logistic analysis demonstrated that at each time point, a telephone follow-up assessment predicts nonadherence to multitherapy and that a percutaneous coronary intervention at the index hospitalization is an independent predictor of adherence to composite therapy at 1 month and 1 year.

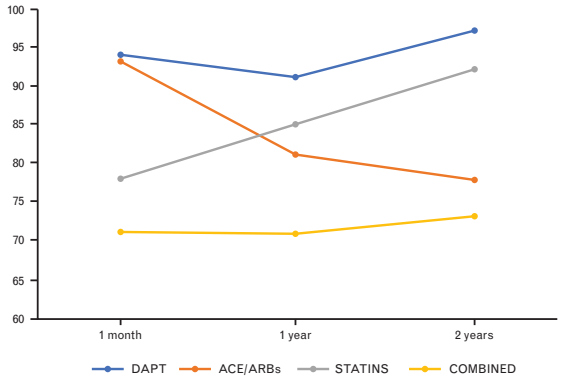

Figure 1. Adherence to therapy at 1 month, 1 year and 2 years of follow-up after ACS. Antiplatelets: The use of antiplatelets was considered a combination of aspirin and a P2Y12 inhibitor (dual antiplatelet therapy or DAPT) at 12 months and a single antiplatelet agent (aspirin or a P2Y12 inhibitor) (SAPT) at 24 months; ACE-I/ARBs: angiotensin- converting enzyme inhibitors or angiotensin receptor blockers; Composite: Adherence to Multitherapy. ACS, acute coronary syndrome.

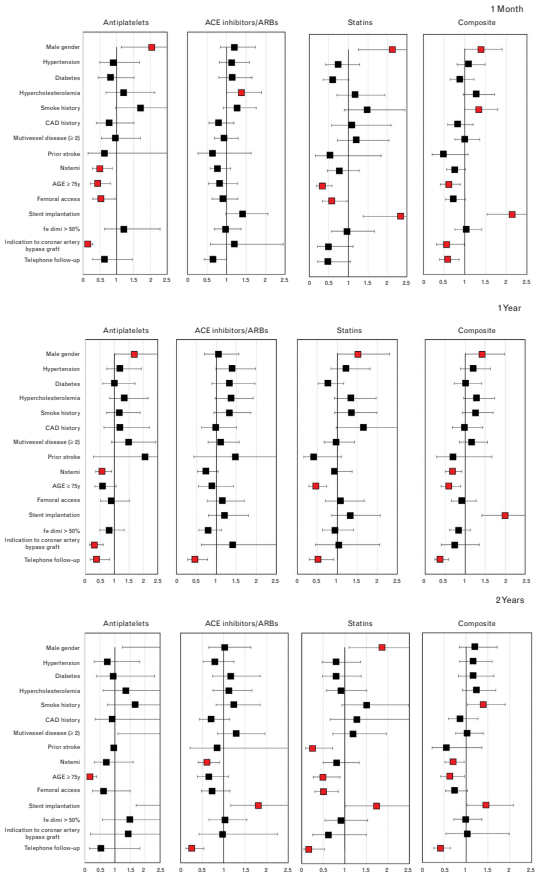

Figure 2. Predictors of patients' adherence to therapy at different follow-up time points after ACS. Forest Plot depicting predictors of patients' adherence to therapy at different timepoint after hospital admission for ACS (Upper: 1 month, Mid: 1 year, Bottom: 2 years). Antiplatelets: The use of antiplatelets was considered a combination of aspirin and a P2Y12 inhibitor (dual antiplatelet therapy or DAPT) at 12 months and a single antiplatelet agent (aspirin or a P2Y12 inhibitor) (SAPT) at 24 months; ACE-I/ARBs: angiotensin-converting enzyme inhibitors or angiotensin receptor blockers; Composite: Adherence to Multitherapy. In red the statistically significant variables ($P < 0.05$), in black the not statistically significant variables. ACS, acute coronary syndrome.

Conclusion: Up to 2 years after ACS, three out of four patients are adherent to multitherapy prescription; percutaneous coronary intervention during the index hospitalization improves a patient's adherence, whereas telephone follow-up is associated with reduced adherence to multitherapy.

Chapter 3

Clopidogrel versus Ticagrelor in elderly patients with acute coronary syndrome undergoing percutaneous coronary intervention: a retrospective monocentric study

Aim of the study: Investigate the safety and efficacy of Clopidogrel compared with Ticagrelor in real-world population aged ≥ 75 years with STEMI-ACS or NSTEMI-ACS undergoing percutaneous coronary revascularization.

Methods: This is a retrospective observational study. From 01/01/2018 to 12/31/2020, 297 patients aged ≥ 75 years with a diagnosis of STEMI-ACS or NSTEMI-ACS, treated with coronary angioplasty at the "San Carlo" Regional Hospital, Potenza, Italy, were identified. The diagnosis of acute myocardial infarction and its classification were made in accordance with the fourth universal definition of myocardial infarction. Subjects who were treated with medical or surgical therapy, patients who had contraindications to one of the antiplatelet drugs or to a DAPT duration of one year were excluded. No further exclusion criteria were added, to try to be as consistent as possible with daily clinical reality. Therefore, 109 patients were excluded. The remaining 188 patients were enrolled in our registry, including 108 patients diagnosed with STEMI-ACS and 80 patients diagnosed with NSTEMI-ACS. All patients underwent coronary angiography and coronary angioplasty. All patients were prescribed double antiplatelet therapy, consisting of Aspirin and a P2Y12 receptor antagonist (Ticagrelor or Clopidogrel), which was chosen according to comorbidities and specific contraindications, to be continued for at least 12 months after the acute event. Adverse events that occurred before discharge were assessed by consulting medical records, while one-year follow-up data were assessed by telephone interview. 53 patients were lost to follow-up after discharge; therefore, one-year data are available for the remaining 135 patients (71.8% of the initially enrolled population). During the hospital stay and at one-year follow-up, the incidence of acute myocardial infarction, stroke, cardiovascular death, death from all causes, bleeding according to the BARC classification, composite endpoint of major cardiovascular events or MACE (major adverse cardiovascular events) consisting of acute myocardial infarction, stroke and death. Net clinical benefit, a composite endpoint of net clinical adverse events (NACE) including MACE (including all-cause death) and BARC 3-5 bleeds, was also assessed at one-year follow-up.

Results: 188 patients were enrolled in the study (57% men; 57% STEMI; 43% NSTEMI). 70% of patients were prescribed with Ticagrelor; patients treated with Clopidogrel vs Ticagrelor were older (84.4 years vs 81.1; p<0.01). At 1-year follow-up available for 135 patients, MACE (CV death, MI, stroke) occurred in 23% of all patients, without significant differences between Ticagrelor vs Clopidogrel (24.2% vs 20%; p=0.59). A BARC 2-5 bleeding event occurred in 17.8% of all patients, with no significant difference between Ticagrelor and Clopidogrel (15.8% vs 22.5%; p=0.35).

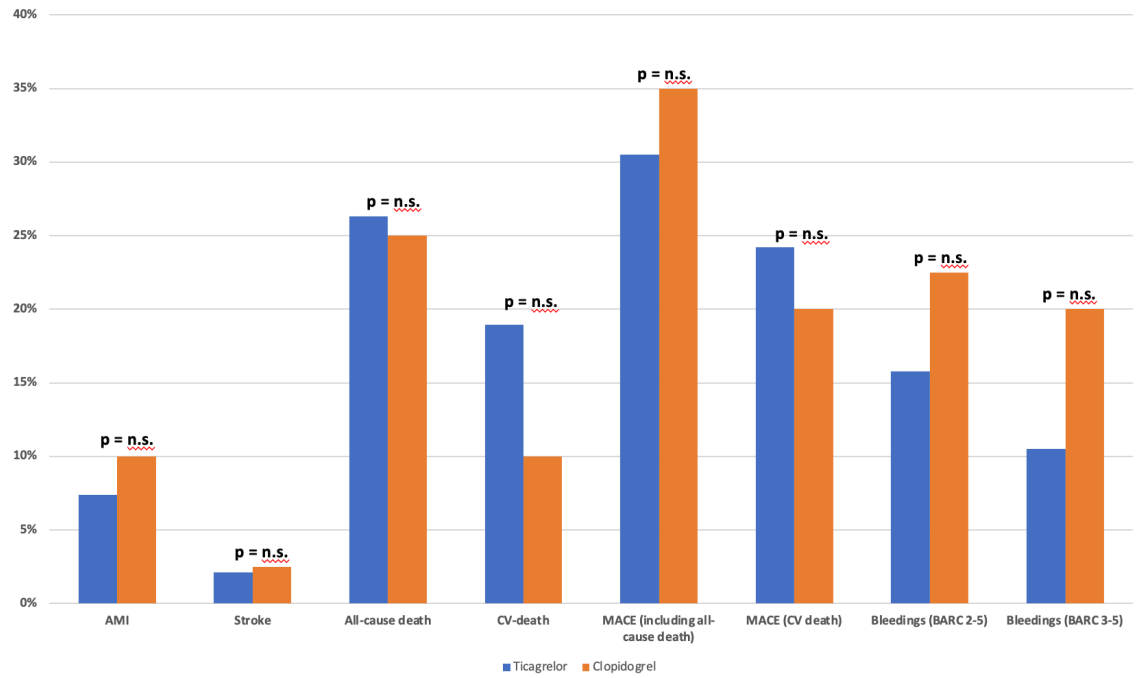

Figure 3. One-year adverse events in STEMI+NSTEMI patients

Conclusions: The present study suggests the safety of Ticagrelor in comparison with Clopidogrel in a real-world elderly population with acute coronary syndrome undergoing coronary percutaneous revascularization. These results could promote the use of Ticagrelor in high bleeding risk patients.

Part II

Focus on peripheral arterial disease (PAD): novel techniques for percutaneous treatment of common femoral artery (CFA) disease

Chapter 4

Three-years outcome of directional atherectomy and anti-restenotic therapy (DAART) for the treatment of common femoral artery steno-occlusive lesions

Background. Endarterectomy is considered the gold standard therapy for common femoral artery (CFA) steno-occlusive lesions, but a significant risk of perioperative mortality and complications has been reported.

Objective. Aim of this study is to evaluate the efficacy at a long-term follow-up of patients with CFA steno-occlusive lesions treated with directional atherectomy and anti-restenotic therapy (DAART).

Material and methods. In this single-centre registry, 78 patients (male: 80.7%; age: 71±15 years; occlusions: 25%) with 80 CFA lesions were included, with 39.7% of them undergoing DAART due to critical limb ischemia and 60.3% due to lower-limb intermittent claudication. The long-term follow-up was completed by 75 patients (three years). The 31 patients with critical ischemia (39.7%) were further subdivided into 20 (25.6%) patients with pain at rest and 11 (14.1%) with trophic changes, ulcers and / or tissue loss.

Results. The primary outcome measure was freedom from binary restenosis as determined by a peak systolic velocity ratio (PSVR) ≥2.4 on duplex or >50% stenosis on digital subtraction angiography at 36 months and was obtained in 84% of patients. The secondary outcome was freedom from clinically driven target lesion revascularization (CD-TLR) at 36 months and was obtained in 86.7%. Freedom from MALE was obtained in 98.6% of patients.

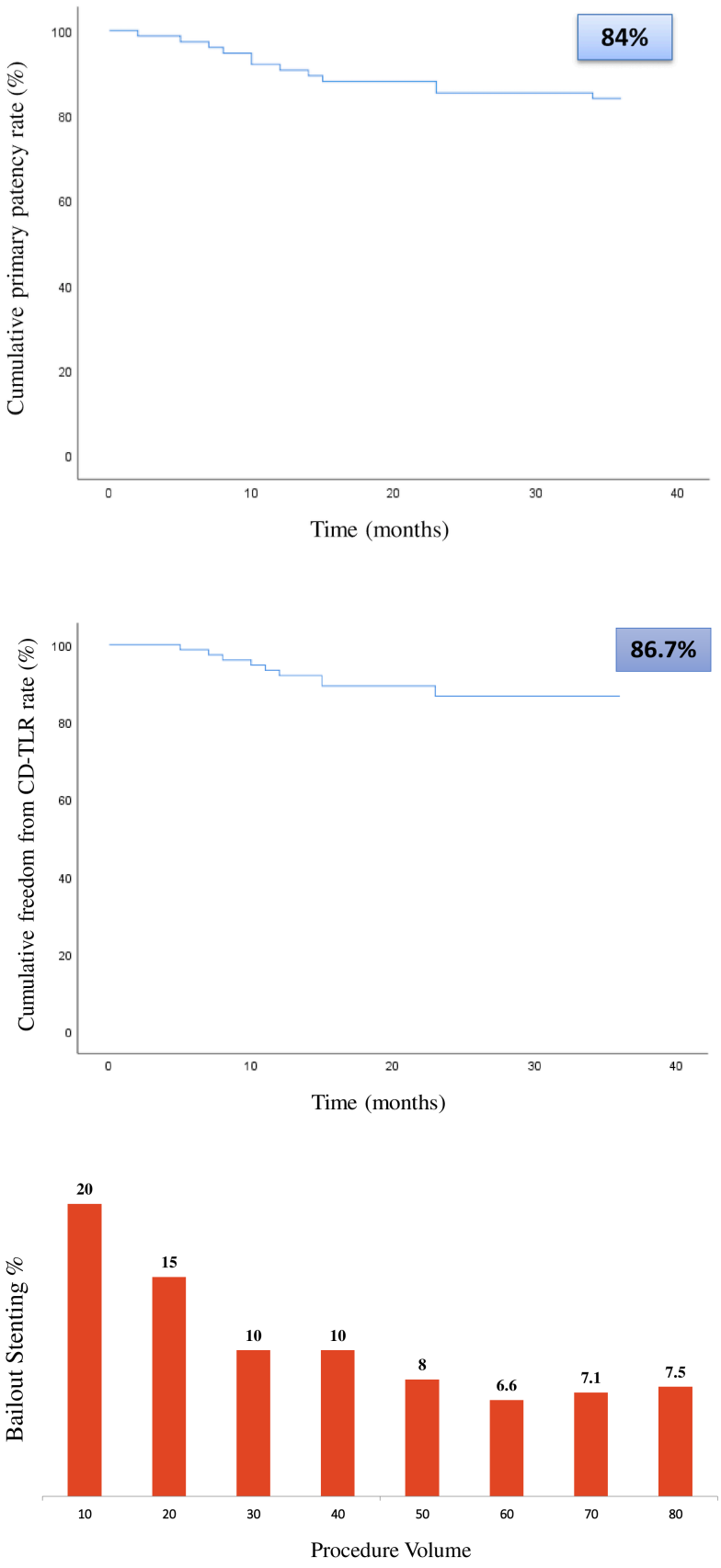

Figure 4. Upper panel: cumulative PP after DAART; central panel: cumulative feeedom from CD-TLR after DAART; lower panel: incidence of bailout stenting after DAART according to procedural volume. PP: primary patency; DAART: directional atherectomy and anti-restenotic treatment; CD-TLR: clinically-driven target lesion revascularization.

Conclusions. This study demonstrates the long-term efficacy of combined directional atherectomy and anti-restenosis therapy (DAART) for the treatment of common femoral artery steno-occlusive lesions.

Part II.A

Reviews and editorial comments on peripheral arterial disease and multisite arterial disease

Chapter 5

Focus on Prevention: Peripheral Arterial Disease and the Central Role of the Cardiologist

Abstract: Peripheral artery disease (PAD) is a manifestation of systemic atherosclerotic disease. PAD patients have a poor prognosis with an increased risk of cardiovascular (CV) events, including myocardial infarction (MI), stroke, limb ischemia and CV death; therefore, it is important to detect and treat PAD early. PAD and coronary artery disease (CAD) share a common pathogenesis and risk factors for development; therefore, cardiologists are in a unique position to screen, diagnosis and treat PAD. Moreover, PAD and CAD also share some treatment goals, including an aggressive modification of risk factors to reduce the risk of CV events. However, PAD remains an underdiagnosed and undertreated disease with medico-legal implications. As the role of cardiologists is expanding, the purpose of this review was to awaken the clinicians to the significance of PAD.

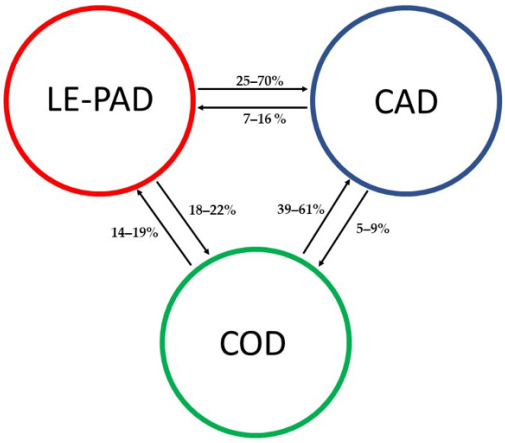

Figure 5. Multisite artery disease and ranges of other localizations of atherosclerosis in patients with a specific arterial disease. LE-PAD: lower extremities peripheral arterial disease; CAD: coronary artery disease; COD: carotid occlusive disease (severe carotid artery stenosis ≥ 70%)

Chapter 6

Carotid artery stenting with dual layer stent: expanding evidences with a randomized trial

According to current guidelines, carotid artery stenting (CAS) is a less-invasive alternative to carotid endarterectomy (CEA) for symptomatic and asymptomatic selected patients. Overall, the 30-day rate of any stroke in symptomatic patients enrolled in randomized clinical trials (RCTs) comparing CAS vs. CEA was higher following stenting (ranging from 5.5% to 9.2% after CAS and from 3.2% to 6.1% for CEA) (Aboyans, 2018), being a perioperative stroke able to impair the long-term survival (Hill, 2012). In a pooled analysis of four largest RCTs comparing CAS and CEA in symptomatic patients, after the periprocedural period, the annual rates of ipsilateral stroke per person-year were similar for the two treatments (0.60%, 95%CI:0.46–0.79 for CEA and 0.64%, 95%CI:0.49–0.83 for CAS). This similar outcome in the postprocedural period after revascularization confirmed a good durability for both treatments although in this analysis the long-term outcomes (combined periprocedural and postprocedural risks) continued to favor CEA (Brott, 2019). It's clear that stroke is still the Achille's heel of carotid percutaneous revascularization (although reduced by the use of embolic protection devices – EPD – and increasing operator's experience (Stabile, 2014)) and a procedural improvement is needed in order to minimize peri and postprocedural embolization risk. Such risk has been related to plaque protrusion through the struts of conventional (single-layer) carotid stents and depends not only on plaque morphology and/or symptomatic status, but also stent design and free cell area (Stabile, 2018). With conventional stents, a relation between neurological events and free cell area has been demonstrated: in the ERCAS study the use of an open-cell design stent with a free-cell area >7.5mm^2 significantly increased 30-day stroke risk, highlighting the importance of carotid stent design in minimizing neurological complications following CAS (Stabile, 2016).

This led to the development of new generation of dual-layered mesh-covered carotid stent systems (DLS). These devices basically consist of novel thin-strut nitinol stents combined with mesh covering (made of nitinol or of polyethylene terephthalate). This design allows the device to trap and exclude thrombus and/or plaque debris in order to prevent embolic events from the target lesion. Optical coherence tomography (OCT) studies demonstrated a very low proportion of patients with plaque prolapse (less than one-tenth), explaining

the sustained antiembolic action of the DLS, demonstrated by the lack of cerebrovascular events at 30-day follow-up (Umemoto, 2017). In the CARNET trial diffusion weighted magnetic resonance imaging (DW-MRI) has been used to demonstrate a low periprocedural embolism rate (37%) with a small lesion size (0.039 ±0.08 cm3) in CAS with DLS (Shofwer, 2015): a 2-fold reduction in DW-MRI lesion(s) prevalence and over 10-fold reduction in mean lesion volume when DLS rather than a conventional carotid stent is used in the PROFI study patients treated under similar distal neuroprotection (Bijuklic, 2012). The safety of DLS use for the guideline-based percutaneous treatment of extracranial carotid artery stenosis has been proved in meta-analytical data (at a 1 year follow-up, the cumulative stroke rate was 3.56%, the overall death and stroke rate was 3.77%) (Stabile, 2020), however, at present, the advantage of a closed-over an open-cell stent design has not been proved in a randomized fashion. Today a a robust scientific evidence has been added to the available data of CAS with a DLS.
In this issue of the *Journal*, Karpenko et al present a 1:1 randomized controlled trial comparing procedure-related ipsilateral cerebral embolism with conventional stent (Acculink, Abbott Vascular) versus DLS (CGuard, InspireMD) in filter-protected CAS. 100 patients were enrolled in the study which was powered for the primary endpoint of at least 50% reduction in ipsilateral DW-MRI lesion average volume 48h post-procedure. Compared to conventional stent, DLS significantly reduced the number of lesions and the mean volume of new cerebral lesion (per-affected patients and per-lesion). On the other side, conventional stent significantly increased the risk of detecting multiple cerebral lesions post procedure . At 30 days the CAS-related permanent lesion occurrence was reduced with the DLS by ≈70%, with a >90% volume reduction consistent with a lasting impact of the stent type choice in CAS. The authors concluded that DLS significantly reduced peri-procedural, and abolished post-procedural cerebral embolism in relation to a conventional carotid stent. We praise the authors for the effort made in this well conducted trial comparing the use of DLS vs conventional stent in CAS in a 1:1 randomized fashion, providing unique and useful clinical informations.
Some limitations are present, like the single-center design trial, conducted in a high-volume institution, by well experienced operators (two operators, each with >500 CAS experience, performing the interventional procedure assisting each other) which is hardly comparable with real-world practices. An important concern is about the choice, as comparator, of the open-cell stent with the largest free-cell area (>7.5 cm^2) which is known to be associated with a significant increase in stroke risk at 30 days; this could

potentially affect the results in favor of DLS. This is important considering that a randomized comparison between DLS and closed cell stent showed no significant differences between groups at 72-hours DW-MRI (Capoccia, 2019), but in the latter study a low-risk asymptomatic population was enrolled, differently from the population enrolled by the authors, where one out four patients was symptomatic, representing the group expected to show the most profound difference after randomization. Moreover their all-comer protocol minimizes the proportion of trial-unrepresented patients to whom the tested intervention is designed to apply. It is true that the 2 devices used in this trial share a similar platform and substantially differ for the presence of the MicroNet sleeve in the DLS and it is known that plaque prolapse occurs also in closed- cell design stent (de Donato, 2013); therefore remains still to be explored the question whether the advantage of DLS when compared to an open-cell stent could be preserved when compared to a closed-cell stent in an all- comer population, or with the use of proximal protection devices (in the present study, a distal filter was adopted), because a substantial body of evidence indicates that proximal neuroprotection can minimize the risk of intra-procedural cerebral embolization (Grunwald, 2014). In conclusion, considering the equipoise between CAS and CEA in the long-term outcome, the reduction of periprocedural complications and in particular the risk of stroke in CAS is the main objective of research in this area. The technological progress of devices used in the CAS (i.e. EPD, DLS) seem to progressively improve the outcome; new generation stents as DLS could potentially offer the final optimization of the CAS compared to CEA, but large-scale studies are needed.

Chapter 7

Carotid artery stenting with DLS: new insights for long-term outcome.

Carotid artery stenting (CAS) is nowadays considered a less-invasive alternative to carotid endarterectomy (CEA) for the treatment of symptomatic and asymptomatic patients with carotid artery stenosis . CAS still presents a higher rate of periprocedural stroke compared to CEA in symptomatic patients in RCTs (Aboyans, 2018) and even if the long-term outcome is similar between the two treatments, the outcome continues to favor CEA (Brott, 2019).

Many different procedural improvements were introduced to minimize the risk of periprocedural complications, one of these is the adoption in the clinical practice of the dual-layered mesh-covered carotid stent systems (DLS). These devices basically consist of novel thin-strut nitinol stents combined with mesh covering (made of nitinol or of polyethylene terephthalate) (Stabile, 2021). A design allowing the device to trap and exclude thrombus and/or plaque debris in order to prevent post procedural embolic events from the target lesion (Stabile, 2018).

The efficacy of DLS in reducing plaque prolapse (Umemoto, 2017) and periprocedural embolization (Shofer, 2015) has been demonstrated and a very low rate of early stroke (Sirignano, 2020; Pini, 2022) and embolism at diffusion-weighted magnetic resonance imaging have been proved in previous experiences (Karpenko, 2021). Some evidences of good long-term outcome exist: when compared with single-layer stents (SLS), DLS demonstrated a significantly improved outcome in term of a 80% relative-risk reduction of ipsilateral stroke at 1 year (Mazurek, 2022). The multicenter, large IRONGUARD2 registry enrolled more than 700 (mostly asymptomatic) patients with carotid stenosis treated with the C-Guard (CG) (InspireMD, Boston, Massachussetts) DLS and demonstrated its safety with a very low rate of stroke at a 1-year follow-up (0.68%) (Sirignano, 2021); a patient-level meta-analysis including more than 500 CAS with CG and Roadsaver (RS) (Terumo Corp., Tokyo, Japan) confirmed a low rate of stroke (<2%) at 1-year, with symptomatic status being the only predictor of the event, even if this subgroup was poorly represented (Stabile, 2020). Moreover, the 1-year follow-up of the randomized comparison between DLS and SLS demonstrated a significant reduction of the composite endpoint of MACE and in-stent restenosis or occlusion with DLS (Karpenko, 2023) and some data at very long-term follow-up (5 year) in small population are encouraging (Bramucci).

However, these data need to be consolidated and some questions remain about the durability of DLS treatment, given the increased metallic coverage with this new stent technology and the potential for an increased risk of long-term complications, like restenosis and thrombosis.

In this issue of CRM, *Bramucci et al.* performed a retrospective analysis of 301 patients with symptomatic and asymptomatic internal carotid artery stenosis treated with CAS with either a DLS or a SLS; at a 1-year follow-up very few events occurred and DLS significantly reduced the incidence of stroke in symptomatic patients compared to SLS (0 stroke *vs* 2 stoke; p=0.04).

At univariate analysis, DLS use was the only protective factor against stroke. No difference in term of patency was reported in this study for DLS and SLS.

We congratulate the authors for provided new evidence about of long-term efficacy for the use of DLS in symptomatic patients with carotid stenosis, which is a population poorly represented in clinical trials, in whom a potential advantage of DLS use could be hypothesized, for the presence of unstable plaque more prone to prolapse.

Nonetheless, some considerations should be done: a) in this study, among symptomatic patients, the majority were treated with a DLS and strokes were concentrated in the few patients who received a SLS: for this reason we could hypothesize that, given the increased risk associated to the symptomatic status, the real benefit of DLS might be even higher; b) symptomatic patients treated with SLS mostly received a wide, open-cell stent, whose design is known to favor the incidence of periprocedural and post procedural stroke (Stabile, 2016) so that a potential bias could affect the results in the present study. We should remember that the comparison between DLS and closed-cell stent has shown no difference in terms of stroke in previous studies, at least in the periprocedural phase (Capoccia, 2019).

In the complex, this finding might suggest that the benefit in using DLS in avoiding unstable plaque prolapse might occur even after stent placement and last for longer period. However, this retrospective, non randomized study, limited by a small sample-size, should be useful for hypothesis-generating.

A future prospective, randomized study comparing DLS and closed-cell SLS is still needed to confirm the long term outcome of DLS in carotid artery stenting, also in relation to long-term patency results which are still not clarified.

Previous meta-analysis data have showed that DLS vs SLS increased the risk of 1-year in-stent restenosis (ISR) (Mazurek, 2022) and that among DLS, CG significantly reduced

1-year ISR compared to RS, possibly for design reasons (Stabile, 2018). In the present study there were no differences in long term patency rates between DLS and SLS nor between C-Guard and Roadsaver.

The awaited results of the multicenter, observational Roadsaver study will shed light on the long term outcome of DLS use in a real-world clinical practice and will provide valuable insights into the contemporary European treatment trends and outcomes of elective carotid artery stenting (Kedev, 2022).

Chapter 8

Proximal versus distal protection: dissecting clinical trials.

Carotid artery stenting (CaS) is a valid alternative to conventional carotid endarterectomy for treatment of carotid artery stenosis. distal embolization of atherosclerotic debris causing cerebrovascular accidents during CaS has been the most significant concern limiting widespread application of CAS technology. A variety of embolic protection devices (EPDs) with different mechanism of action, have been designed to minimize the risk of major embolization causing stroke and their use is recommended by current guidelines. Two general types of EPDs are available: proximal protection devices (PPDs) and distal protection devices (DPDs). However, there is no convincing clinical evidence of the clinical superiority of one device over another. This review will examine the different types of available devices and also innovative devices and techniques, including strengths and weaknesses of each, and present the available evidence and rationale for their routine use during CaS.

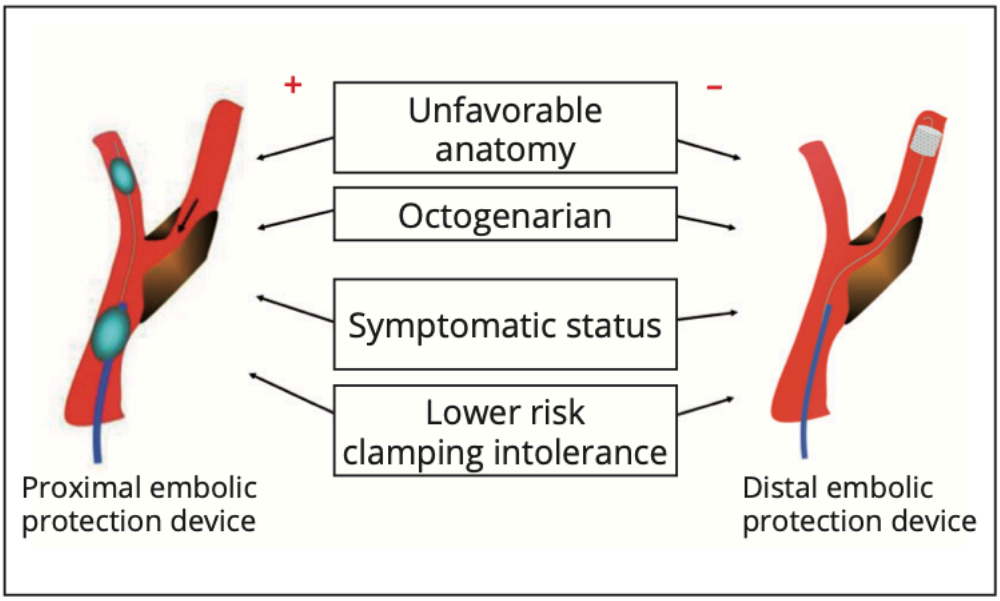

Figure 6. Decision diagram to select embolic protection devices in patient undergoing carotid artery stenting

Part III

Focus on structural heart intervention: permanent pace-maker implantation predictors after TAVI

Chapter 9

Conduction delays after transcatheter aortic valve implantation with balloon-expandable prosthesis and high implantation technique

Background: Performing transcatheter aortic valve implantation with high implantation technique, i.e. with an aorto-ventricular ratio >60/40, reduces the need for permanent pacemaker implantation. Valve calcification and prosthesis oversizing are predictors of permanent pacemaker implantation but there are no available data on their role when transcatheter aortic valve implantation is performed with an aorto-ventricular ratio >60/40. The aim of this study is to evaluate the effect of leaflets/annulus calcification and prosthesis oversizing on the incidence of permanent pacemaker implantation after transcatheter aortic valve implantation with a high implantation technique

Methods and Results: Transcatheter aortic valve implantation was performed in 48 patients implanting a balloon-expandable transcatheter heart valve with an aorto-ventricular ratio >60/40. Calcium burden was assessed by preprocedural multidetector computed tomography. An invasive electrophysiological study was performed before and after transcatheter aortic valve implantation. Five patients (10.4%) needed permanent pacemaker implantation. At univariate analysis, baseline right bundle branch block and postprocedural PR, QRS and His-Ventricle interval elongation significantly predicted permanent pacemaker implantation ($p<0.05$). Receiver-operating characteristic curve analysis showed a correlation between transcatheter heart valve oversizing and permanent pacemaker implantation need, with the best cut-off being >17% (AUC=0.72, p=0.033). Linear regression analysis demonstrated that QRS interval elongation was related to total, left and non-coronary leaflet calcification ($p<0.05$).

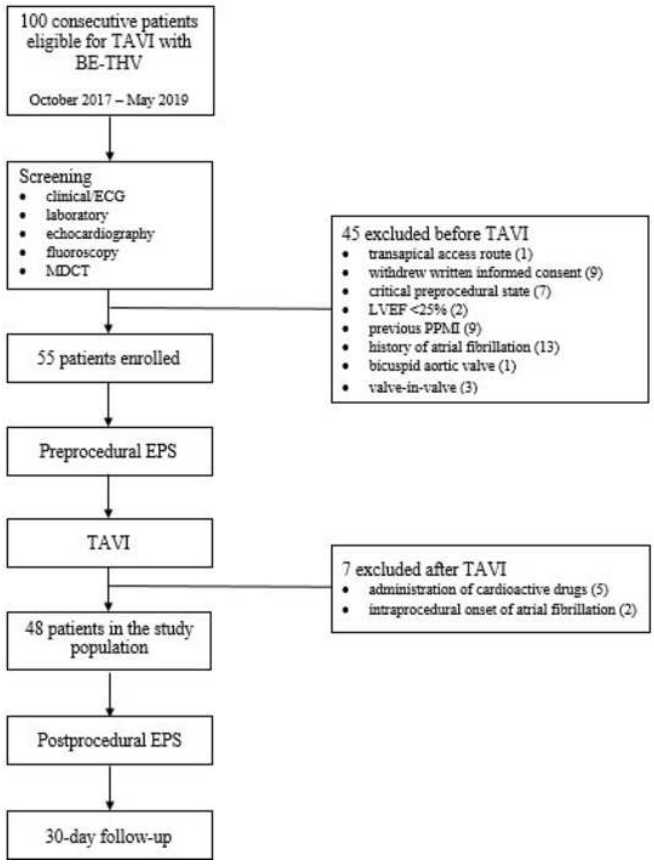

Figure 7. Study flow chart

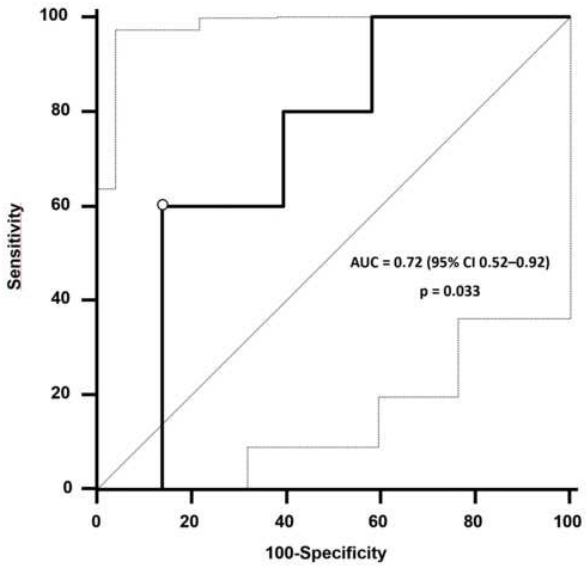

Figure 8. Receiver-operating characteristic curve analysis for prosthesis oversizing in predicting the need of PPMI. The circle marks the value (>17%) with the highest Youden's index. Dotted lines indicate 95% confidence intervals of the curve.

Conclusions: This study demonstrates that, when transcatheter aortic valve implantation is performed using a balloon-expandable transcatheter heart valve deployed with an aorto-ventricular ratio >60/40, the presence of leaflets/annulus calcification or the need to oversize the prosthesis correlate with the occurrence of pathological cardiac conduction delays.

PART IV

Discussion and conclusions

PART I

Predictors of adherence to composite therapy after acute coronary syndromes

In this study we have demonstrated that up to 2 years after the index hospitalization for an ACS: 1) almost three out of four patients are still adherent to composite therapy prescription; 2) a PCI during the index hospitalization increases the likelihood of medication adherence; 3) a dedicated institutional program for clinical follow-up assessment improves a patient's adherence to composite therapy. Evidence from randomized clinical trials supports the use of several pharmacological therapies in the secondary prevention of coronary artery disease (CAD). Although substantial attention has been focused appropriately on improving the prescription of evidence-based therapies by physicians in the hospital and at the time of hospital discharge, much less attention has been paid to understanding and improving long-term adherence of patients to physician prescription. This research project has been conducted in a clinical setting that mirrors regional contemporary clinical practice. Indeed, the clinic-demographic characteristics and mortality outcomes of the current study were consistent with those observed in large clinical trials investigating pharmacological therapies for ACS patients (1). Moreover, the rate of NSTE-ACS and STEMI patients receiving a conservative strategy or undergoing coronary angiography, with a consequent percutaneous or surgical revascularization during hospitalization was consistent with what was observed in the EmploYEd Antithrombotic Therapies in Patients With Acute Coronary Syndromes HOspitalized in iTalian Coronary Care Units (EYE- SHOT) registry that depicted the contemporary management of patients 1 to 3 years from acute myocardial infarction (AMI) in Italy (2). As observed in other prospective MI registries, adherence to medical therapies has been persistently suboptimal in the first 6–12months following hospitalization for an acute MI (3-5). Similar results were noted among stable outpatients, as fewer than half of patients with clinical atherosclerotic CVD remained on all secondary prevention medications at 1 year of follow-up (6). However, there remains a paucity of data describing the longitudinal use of medical therapy beyond 12 months among ACS patients. It is well known that the immediate discharge period is a time of high risk for nonadherence, which can occur in up to 25% of the patients (3). Of the patients who are initially adherent, half of them will discontinue antihypertensive medications within 6 – 12 months, and only a third will continue statin

medications for 2 years after hospitalization for ACS (6,7). Primary nonadherence (not initially following the prescription written) leads to a significant increase in 1-year mortality after hospitalization for myocardial infarction. Secondary nonadherence (failure to follow the instructions or to refill the prescription) also increases mortality, hospitalizations, and costs (8). Patients with higher adherence rates have a significantly lower risk of CV events compared with those with lower rates (9). Our report confirms that the adherence to composite therapy is lower than the one observed with the single drug classes. Despite a higher adherence rate, this finding is consistent with what is reported in the literature in patients who have CAD, where self-reported adherence to medications was only 40% for the combination of aspirin, beta-blocker, and a lipid-lowering agent in follow-up surveys (10). The higher adherence rate observed in our registry could be related to the fact that we did not assess beta-blocker use, which has a lower adherence rate. We should consider that in our country there is a relatively comprehensive prescription plan with a small copay per prescription, allowing low-income patients to properly follow their necessary prescriptions. In our study, adherence to DAPT at 30 days, 1 year and 2 years of follow-up was the highest, suggesting that there is a high focus on this therapy from the medical and patient side. Adherence to DAPT was highly influenced by having received a stent implantation in contrast with CABG and indication to optimal medical therapy suggesting that receiving the implant of a coronary stent makes patients more aware of their medical condition and related risk (i.e. stent thrombosis after antiplatelet therapy discontinuation). These results provide the opportunity to identify those patients' subgroups in whom antithrombotic treatment should be radically implemented, such as medically managed patients and those undergoing surgical revascularization. The adherence rate to statins and ACE-I/ARB observed in our study is comparable with that observed in the EYESHOT registry. Observing the data, a progressive increase in adherence to statin therapy from the beginning of observation through the follow-up and an increase in the adherence to antiplatelet medications after 1 year can be noticed. We cannot exclude an influence on the antiplatelet regimen prolongation at 1year in high-risk patients and, for statins, an influence of cLDL levels at clinical evaluation. These hypotheses could be the basis for future investigational studies. In our analysis, the use of evidence-based medications was paradoxically lower among groups with the highest risk of poor outcomes and therefore who could potentially benefit the most from sustained therapy: elderly, patients with reduced ejection fraction and those hospitalized for NSTEMI. These findings suggest that it may be possible to design educational and

compliance intervention programs to reduce nonadherence in groups of patients at high risk. At 2 years from the index event, one patient out of four was not adherent to composite therapy. The reasons for nonadherence are often multifactorial. In-hospital methods shown to improve medication adherence are discharge medication counselling, positive interactions between clinician and patient, close follow-up with patients, low costs or co-payments for prescription medications, and simplified drug regimens like a polypill strategy, which has shown to improve global secondary CV prevention in the previous trials (11). The reported data confirm that continued efforts are needed to promote and maintain medical therapy use after ACS over time. A follow-up assessment based only on a phone call was strongly associated with nonadherence to therapy suggesting that patients who received a clinically based follow-up control were much more adherent to therapy and supporting the concept that communication between patients and physicians is an important target for any interventions aimed at increasing adherence to therapy. Among the possible reason why telephone follow-up predicted nonadherence, we should consider the lack of personal interaction that occurs during face-to-face visits. A clinically based follow-up assessment provides the patients with systematic medication counselling which can be a trigger to improve the following of prescriptions. This study demonstrates that the use of telephonic follow-up is associated with a reduced adherence rate; thus, in consideration of the potential increase in telemedicine use, we should put all our efforts into developing new communication strategies (i.e. web based) that could help to establish a more realistic and efficient physician-to-patient interaction. Finally, the use of a dedicated institutional clinical program of follow-up allows each patient to have a cardiologist as the most responsible physician, a feature that has been related to a better adherence rate (1).

Conclusions

The use of evidence-based therapies for CAD has improved but remains suboptimal. Nonadherence to medications remains a major problem for CV patients due to the related the increase in CV mortality. Up to 2 years after hospitalization for an ACS, one patient out of four is non-adherent to the combined therapy of antiplatelets, ACE/ARB-I and statins. Clinicians need to use multiple approaches to simple solutions to improve their patients' short- and long-term medication adherence. A dedicated institutional clinical program for follow-up assessment can improve a patient's adherence to multitherapy prescription.

Clopidogrel versus Ticagrelor in elderly patients with acute coronary syndrome undergoing percutaneous coronary intervention: a retrospective monocentric study

The management of antiplatelet therapy in elderly patients with acute coronary syndrome remains a highly debated topic due to the difficulty in balancing the ischemic and haemorrhagic risk. Current guidelines recommend dual antiplatelet therapy with Aspirin and a potent P2Y12 receptor antagonist (Ticagrelor or Prasugrel) regardless of age (12,13). The POPULAR AGE study was the first randomized trial that demonstrated a significant reduction in hemorrhagic events without an increase in ischemic events in patients with NSTE-ACS aged ≥ 70 years treated with Clopidogrel compared to Ticagrelor or Prasugrel (14). The results of our study however, despite a greater age in the Clopidogrel group, did not highlight any significant difference in ischemic and haemorrhagic events at one year follow-up between Clopidogrel and Ticagrelor in patients aged ≥ 75 years diagnosed with ACS-STEMI and ACS-NSTEMI treated with coronary angioplasty.

The different results of our study compared to POPULAR AGE could be due to various reasons:

1) POPULAR AGE included subjects aged ≥ 70 years, while in our study we included older subjects aged ≥ 75 years.
2) POPULAR AGE excluded patients with STEMI-ACS and included only patients with NSTE-ACS. In our study, however, we excluded patients with unstable angina and included patients with NSTEMI-ACS and STEMI-ACS.
3) In POPULAR AGE, patients with cardiogenic shock, which have a worse prognosis, were excluded, while they were included in our study.
4) In POPULAR AGE, patients who were already being treated with DAPT before the initial event were excluded, while this category of patients was included in our study.
5) POPULAR AGE included a minimal share of patients treated with Prasugrel, who were instead excluded from our study.
6) In POPULAR AGE, patients with an indication for anticoagulant therapy were included, but were excluded from our study due to the greater risk of bleeding.
7) In the POPULAR AGE, approximately half of the patients underwent coronary angioplasty, while in our study all patients underwent coronary angiography and angioplasty

Therefore, the population of our study, albeit with the limitations of the study design, reflects with greater similarity the complexities of the elderly patient in daily clinical reality.

Our results are consistent with those observed in a subanalysis of the START-ANTIPLATELET registry, which demonstrated no statistically significant difference in ischemic and haemorrhagic events between Clopidogrel and Ticagrelor in patients diagnosed with acute coronary syndrome at high haemorrhagic risk. Age ≥ 75 years was one of the criteria to define patients at high bleeding risk and was present in approximately 80% of subjects in both treatment groups (15). Other studies in the literature show results consistent with our case study. The PHILO study, conducted in Asia, randomized 801 patients with ACS, of whom approximately 25% aged ≥ 75 years, to Clopidogrel or Ticagrelor and showed no significant differences in ischemic and hemorrhagic events between the two treatment groups (16). In a retrospective registry conducted in Canada, there was no significant difference in ischemic and hemorrhagic events between the two treatment groups in patients with ACS. Also in this study, the group treated with Clopidogrel was older and with more comorbidities (17). The meta-analysis by Dong Wang et al., which included 10 studies, also showed no significant differences in the risk of myocardial infarction, stroke and bleeding between the two treatment groups in patients with ACS (18).

Conclusions

The present study suggests the safety of Ticagrelor in comparison with Clopidogrel in a real-world elderly population with acute coronary syndrome undergoing coronary percutaneous revascularization. These results could promote the use of Ticagrelor in high bleeding risk patients.

PART II

Three-years outcome of directional atherectomy and antirestenotic therapy (DAART) for the treatment of common femoral artery steno-occlusive lesions

This study suggests that the combined use of directional atherectomy (DA) and drug-coated balloon (DCB) for the endovascular treatment of common femoral artery (CFA) obstructive disease is feasible and associated with good clinical outcome at a 3 years-follow-up. At our knowledge, this is the longest follow-up available for a large population of patients treated with DAART strategy for CFA lesions. The need for a less invasive strategy compared to surgery for the treatment of CFA stenosis has been addressed in several previous studies. Bonvini et al examined a large series of patients (n= 321) undergoing CFA angioplasty with provisional stenting (37%) and found a 74% PP and 84.1% freedom from TLR (19) at a 1-year follow-up. The landmark trial that added evidence to the endovascular treatment of CFA was the Endovascular Versus Open Repair of the Common Femoral Artery (TECCO) trial comparing endarterectomy to stenting in 117 patients with de novo CFA stenosis (20). At 24 months, there were no significant differences in freedom from TLR (HR 0.9; 95% CI 0.3-2.5; p=0.83) and primary patency (HR 1.7; 95% CI 0.5-5.6; p=0.42). Mehta et al analyzed 167 patients who underwent percutaneous CFA interventions with PTA only (68.2%), atherectomy ± PTA (22.8%) and provisional stenting (9%) for failed atherectomy ± PTA. The cumulative patency at 20 months was 85.9% in the atherectomy group and 70.7% in the angioplasty groups (21). Our working-group reported good results at a 1-year follow-up of a smaller population of patients (n: 30) with severely calcified CFA obstructions treated with DA and prolonged paclitaxel-coated balloon angioplasty that showed a 90% primary patency and a 93.3% freedom from TLR (22). In a recent experience, Guo et al. performed a 4-years follow-up of 90 patients with CFA lesions (81% IC) treated with PTA (n: 45) or DA (n: 31) with 87.1% PP in the atherectomy group and 66.7% PP in the PTA group (p=0.043) (23). Despite the long-term follow-up, this study included a smaller, lower-risk population compared to our study, nevertheless the long-term outcome was similar. Our results confirm that DAART strategy for the treatment of CFA lesions is effective at a long-term follow-up and could be considered as a good alternative to surgery.

CONCLUSIONS This study demonstrates good results up to three years follow-up of common femoral artery steno- occlusive lesions treated with DAART. These data are consistent with recent studies and suggest that DAART could be a safe and effective alternative to surgery for these patients.

PART III

Conduction delays after transcatheter aortic valve implantation with balloon-expandable prosthesis and high implantation technique

This study demonstrates that, when TAVI is performed using a balloon expandable (BE) transcatheter heart valve (THV) deployed with an aortic-valve ratio (AVR) >60/40:
1) the electrical cardiac function is still affected by THV implant;
2) a severe prosthesis oversizing still increases the PPMI rate;
3) the presence of leaflets/annulus calcification predicts IV cardiac conduction delays.
The origin of periprocedural conduction disturbances in TAVI patients depends on the close proximity between the aortic valve and the conduction system. This anatomical relation is the key of conduction disturbances in such patients, which are primarily determined by direct mechanical injury, associated with various degrees of edema, haematoma and ischemia (24). Different strategies to reduce the incidence of PPMI have been proposed, like limiting the size and the depth of the dilating balloon within the LVOT but also keeping the number of pre- and postdilations to a minimum. In a previous study, we observed that a BE-THV deployment with an AVR >60/40 was associated to a reduced PPMI rate (15) and this procedural strategy has been adopted in the present study too. EPS assessment of AV conduction after TAVI allowed to observe that both the AH (an estimate of AV nodal conduction time) and the HV interval (a measure of infranodal conduction) were elongated, thus demonstrating that the injury of the conduction system is not only limited to the infranodal portion. Consistently with previous reported literature data (25-26), the measured ECG (PR, QRS and corrected QT) and EPS (AH, H, HV, WP and AVNFRP) intervals were significantly prolonged after the procedure compared to baseline, confirming that conduction system is severely affected after valve implantation, even if a higher position of the THV is obtained at the implant. In particular, we have observed a significant relationship between pre-existing RBBB as well as TAVI-induced prolongation of PR, QRS and HV interval, and need for PPMI, which confirms the data obtained from procedure in which the AVR >60/40 was not adopted (25-26).
In a recently published study aiming at the identification of a risk score able to predict PPMI after S3-THV implantation, the authors did not include distal landing zone calcium burden as a risk factor in their analysis (27). Distal landing zone calcification has been

previously associated with PPMI among patients implanted with BE-THV in other studies (28,29). In our study the presence of valvular calcification but not the presence of calcification of the landing zone (i.e. LVOT) predicted the occurrence of conduction system dysfunctions, despite the high implantation technique. Finally, the association of PPMI and prosthesis oversizing ≥15.6% has been reported in literature (27). Although a difference of about 1% is within the range of measurement error, in our study a higher prosthesis oversizing (>17%) increases the likelihood of pathological procedural conduction delays requiring PPMI, confirming a potential effect of high-grade oversizing on conduction disturbances even when the THV is implanted with an AVR >60/40. In conclusion, conduction disturbances, also detected by EPS, could have a multifactorial etiology in such setting of patients: this is the reason why an high AVR is just one of the tricks that TAVI operators should put into practice in order to reduce postprocedural PPMI rate. Furthermore the findings of this study could support the heart team discussion with some useful informations for preprocedural planning. In fact, despite EPS could not be systematically reproducibile in all TAVI patients, it has been useful to confirm how much a careful evaluation of preprocedural MDCT scan (potential THV oversizing as well as calcification amount and location) is fundamental. EPS and MDCT would therefore allow to identify a priori such patients at higher risk of PPMI by TAVI-related conduction disorders.

Conclusion

In TAVI patients treated with BE-THV implanted with an AVR >60/40, we have observed an elongation of postprocedural conduction intervals. These phenomena significantly predicted PPMI but were correlated to the presence of leaflets/annulus calcification or the need for prosthesis oversizing.

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List of publications

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