Volume 21 | Number 18 | September 2025
ISSN: 1774-024X (Print)
ISSN: 1969-6213 (Online)
www.eurointervention.com

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A state-of-the-art on antithrombotic therapy in complex PCI; optimal minimal stent areas after left main crossover stenting; VARC-HBR criteria validation for TAVI; the balloon-expandable DurAVR transcatheter heart valve; valve-in-valve TAVI and redo-TAVI; and more

For our last issue of the summer, we'll end the season in the best EuroIntervention style with a wide range of articles to capture your interest and help keep you up to date on the latest research and trends…

State-of-the-art on antithrombotic therapy in complex PCI

Covering the current state of antithrombotic therapies in complex percutaneous coronary intervention (PCI), **Domenico Simone Castiello, Raffaele Piccolo and colleagues** provide us with a state-of-the-art examining different types and durations of antithrombotic strategies. They also review management within specific settings, including patients with long-term indications for oral anticoagulation.

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Optimal minimal stent area after left main crossover stenting

Ju Hyeon Kim, Seung-Jung Park and colleagues analyse intravascular ultrasound-derived minimal stent area criteria for optimal stent expansion following left main crossover stenting. Using the 5-year major adverse cardiac events data available from their centre, the authors established three threshold values to serve as benchmarks for stent optimisation during left main PCI. **José M. de la Torre Hernandez** comments in an accompanying editorial.

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The new intra-annular balloon-expandable DurAVR valve

In this translational research bench study, **David Meier, Stephanie L. Sellers and colleagues** assess the hydrodynamic performance of the intra-annular balloon-expandable DurAVR transcatheter heart valve (THV) in native, valve-in-valve (ViV), and redo-TAVI procedures against other commercially available THVs. The valve demonstrated excellent hydrodynamics in all three scenarios, with minimal pinwheeling, especially in the ViV and redo-TAVI simulations.

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VARC-HBR criteria for risk stratification and prediction of bleeding risk in TAVI

In a subanalysis of the POPular PAUSE TAVI trial, **Daniël C. Overduin, Jurrien M. ten Berg and colleagues** evaluate the Valve Academic Research Consortium High Bleeding Risk (VARC-HBR) criteria for risk stratification and prediction of bleeding risk in transcatheter aortic valve implantation (TAVI) patients and then compare it to other bleeding risk criteria. The authors find that use of the VARC-HBR criteria in clinical practice may help identify patient subgroups who would benefit from additional measures for access site management. This article is accompanied by an editorial from **Kentaro Hayashida and Juri Iwata**.

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Redo-TAVI with a supra-annular self-expanding THV for short-frame THVs

Giuseppe Tarantini, Luca Nai Fovino and colleagues offer practical guidance for performing redo-TAVI with a supra-annular THV in failing short-frame THVs. In this research correspondence, the authors examine the specific preprocedural and procedural considerations needed to optimise outcomes.

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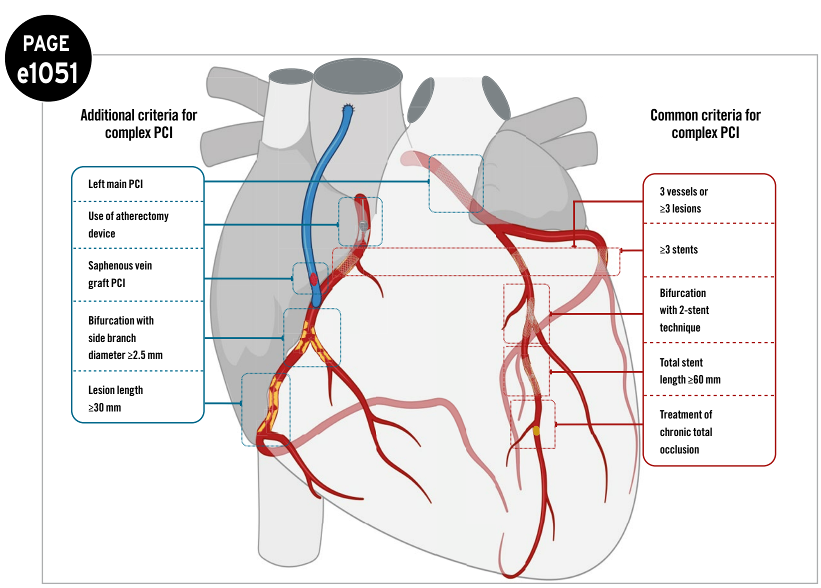

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Antithrombotic therapy in complex percutaneous coronary intervention
Domenico Simone Castiello, Angelo Oliva, Giuseppe Andò, Giampaolo Niccoli, Francesco Pelliccia, Elisabetta Moscarella, Rocco Antonio Montone, Felice Gragnano, Italo Porto, Paolo Calabrò, Salvatore De Rosa, Carmen Anna Maria Spaccarotella, Enrico Fabris, Giovanni Esposito, Ciro Indolfi, Gianfranco Sinagra, Pasquale Perrone Filardi, Raffaele Piccolo, on behalf of the Working Group of Interventional Cardiology of the Italian Society of Cardiology
EuroIntervention 2025;21:e1051-68.

EuroIntervention

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Publication : 24 numéros par an
Volume 21 - N°18 - Septembre 2025

Facteur d'impact : 9.5
2024 Journal Citation Reports®
(Clarivate Analytics, 2025)

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EuroIntervention est édité par la Société Europa Group, SAS au capital de 1 146 848 euros, siège social : 19, allées Jean-Jaurès, 31000 Toulouse, France, RCS Toulouse 342 066 727, APE 8230 Z.

MEDLINE abbreviation: EuroIntervention

Editeur
Ronnie Lassiaille

Président : 1987 SAS
Principal actionnaire : 1987 SAS

ISSN : 1774-024X
ISSN online : 1969-6213
Dépôt légal à parution

Aims and scope

EuroIntervention Journal is an international, English language, peer-reviewed journal whose aim is to create a forum of high-quality research and education in the field of percutaneous and surgical cardiovascular interventions.

It is released 24 times a year at regular intervals in electronic formats, and 4 of these issues will be available in print. EuroIntervention is indexed in Science Citation Index® (ISI), SciVerse Scopus, MEDLINE®/PubMed® (Abbreviation: EuroIntervention).

IMPACT FACTOR: 9.5 *2024 JOURNAL CITATION REPORTS® SCIENCE EDITION (CLARIVATE ANALYTICS, 2025)*

Publication information
Subscription fees are on the dedicated website:
https://subscribe.eurointervention.com
Issues are sent by standard mail (regular mail within Europe, air mail outside Europe). Claims for missing issues should be made in writing within six months after the date of dispatch.

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EuroIntervention
2025;21:e1043-e1044
published online e-edition September 2025
DOI: 10.4244/EIJ-E-25-00038

EDITORIAL

Evolving cutoff values for optimising left main stenting with intravascular imaging

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The value of intravascular imaging (IVI) to improve clinical outcomes after left main (LM) revascularisation has been the subject of multiple studies, with some attempting to identify specific minimum stent area (MSA) targets[1-3].

It is worth noting that it is not just a matter of using IVI but of using it in an actionable way and oriented towards achieving certain targets, since the observable long-term prognostic benefit will depend on this[4].

The group of investigators behind the study discussed in this editorial pioneered in defining these optimisation criteria, identifying an easy numerical series 5-6-7-8 mm² for the MSA cutoff values in the ostial left circumflex (LCx), ostial left anterior descending (LAD), LM polygon of confluence, and LM above the polygon of confluence, respectively[1].

These threshold values for MSA, derived from an Asian population, were notably lower than those found in a trial conducted in a Western population: 6, 7, and 10 mm² for the LCx, LAD, and LM, respectively[2].

Recently, the same authors revised the previous MSA criteria based on the 5-year clinical outcomes in patients undergoing upfront LM two-stenting. The MSA cutoff values for predicting major adverse cardiovascular events (MACE) were upgraded to 5.7, 8.3, and 11.8 mm² for the LCx, LAD, and distal LM, respectively[3].

In this issue of EuroIntervention, Kim et al[5] describe a study they conducted including 829 consecutive patients with LM disease who underwent intravascular ultrasound (IVUS)-guided percutaneous coronary intervention (PCI) with a single-stent crossover technique from the LM to the LAD. The MSA cutoff values best predicting 5-year MACE were 11.4 mm² for the proximal LM, 8.4 mm² for the distal LM, and 8.1 mm² for the LAD ostium. Based on these cutoff values, stent underexpansion in the proximal LM was significantly associated with an increased risk of 5-year MACE. Additionally, patients with simultaneous stent underexpansion in both the distal LM and LAD ostium exhibited a significantly higher risk of MACE compared with those having adequate expansion or only single-site underexpansion. The study is well executed and properly presented, as is typical of this research group.

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One of the aspects that should be highlighted is the modest predictive value of the identified MSA cutoff values, with an area under the curve (AUC) ranging from 0.57-0.62. This may be explained by their inability to predict events originating in the LCx artery. In fact, the LCx was involved in 78% of target lesion revascularisation cases, and the ostial LCx was the only site involved in 57%.

That said, it would have been very relevant to analyse the predictive value of the minimum lumen area and/or plaque burden at the level of the LCx ostium as predictors of events. This information could even lead to the identification of factors that could recommend the upfront use of two stents. However, in this study, preintervention IVUS was available in 30.6% of patients and a final IVUS run from the LCx was carried out in only 5.6%. Nevertheless, the minimum lumen area in the LCx was smaller and the plaque burden higher in patients with MACE.

Another aspect to consider is the definition of stent underexpansion. Obviously, stent expansion is a parameter subject to different definitions, sometimes not easy to establish at the level of the LM due to the absence of adequate luminal reference areas. In this study, the stent expansion index was defined as the MSA divided by the vessel area, and it failed to show any predictive value. This definition of stent expansion is highly conditioned by the degree of plaque burden and remodelling at the lesion level and does not consider the value of the luminal area in healthy or less diseased reference sites. Thus, a low expansion index does not necessarily mean that a stent is underexpanded, since a very large plaque burden at a point with positive remodelling will always be associated with a low expansion index, even if the stent size is well selected and the stent is fully expanded.

Overall, MSA cutoff values have a certain, though modest, predictive value. Nevertheless, these have a much more limited value at the individual level since there is variability in the size of the coronary tree and in the distribution of disease that can condition the feasibility of reaching certain MSA cutoff points. Thus, I consider it most convenient to pursue a range of acceptable MSA values rather than a precise value and maybe combine stent expansion, which is a relative criterion, with MSA, which is an absolute criterion, to achieve a balance with the individualised anatomy of the patient **(Figure 1)**.

The OPTIMAL trial (ClinicalTrials.gov: NCT04111770), currently in clinical follow-up, will be the first properly designed trial to provide definitive evidence on the clinical impact of IVUS guidance during LM PCI, as well as valuable information on optimisation targets[6].

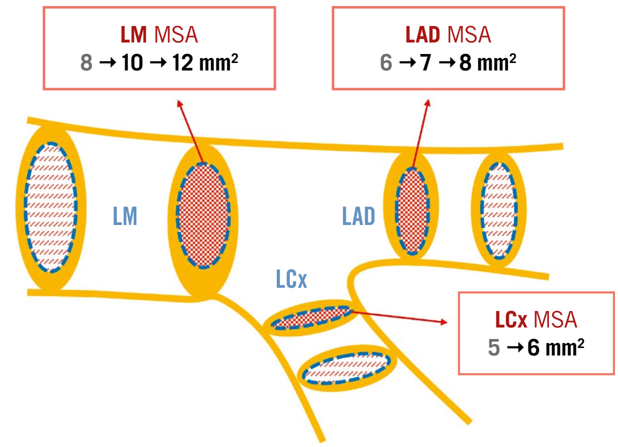

Figure 1. *Evolution in the cutoff values for MSA identified as predictive of MACE after LM stenting. The most supported values are in bold. LAD: left anterior descending artery; LCx: left circumflex artery; LM: left main coronary artery; MACE: major adverse cardiovascular events; MSA: minimum stent area*

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Conflict of interest statement

J.M. de la Torre Hernandez discloses grants from Abbott and Biotronik; consulting fees from Medtronic, Philips, Abbott, and Daiichi Sankyo; and honoraria from Boston Scientific, Abbott, and Medtronic.

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EuroIntervention
2025;21:e1045-e1046
published online e-edition September 2025
DOI: 10.4244/EIJ-E-25-00022

EDITORIAL

An ongoing quest to discern the optimal antithrombotic therapy after TAVI

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In this issue of EuroIntervention, Overduin and colleagues evaluate the Valve Academic Research Consortium High Bleeding Risk (VARC-HBR) criteria[1] for risk stratification and prediction of 30-day major bleeding risk in patients undergoing transcatheter aortic valve implantation (TAVI) with a concomitant indication for oral anticoagulation. The VARC-HBR criteria enabled the effective identification of three major bleeding risk subgroups in this study. Severe femoral artery calcification and tortuosity, anaemia, and conversion to open heart surgery were identified as the most contributive criteria. Patients who undergo TAVI are likely to be elderly and severely frail, and, given that periprocedural bleeding events are sometimes associated with fatal complications, bleeding risk stratification before TAVI is therefore essential. This study sheds light on current clinical practice to predict and avoid bleeding events during TAVI[2].

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One of the high bleeding risks in this study was severe calcification and tortuosity of the access vessels. Such poor vessel condition indicates severe arteriosclerosis, inevitably contributing to increasing not only bleeding but also thromboembolic risks. In the POPular PAUSE TAVI trial, bleeding events were more frequently observed in the periprocedural continuation group than in the interruption group[3]. On the other hand, that trial was not designed to assess the benefit of anticoagulation for thromboembolic events. The authors discuss that considering the risk for thromboembolic events with respect to a patient's underlying vascular or cerebrovascular diseases, the risk-benefit ratio of anticoagulation for patients with TAVI may differ from that of the general population. It is necessary to tailor treatment strategies based on the balance of bleeding and thromboembolic risks for each patient.

An appropriate antithrombotic therapy after TAVI still remains unclear. The current guidelines recommend single or double antiplatelet therapy after TAVI to potentially prevent hypoattenuated leaflet thickening (HALT), meaning leaflet thrombosis[4]. However, HALT within 30 days after TAVI may not be associated with patients' prognosis or haemodynamic performance during long-term follow-up, although further clarification is needed[5,6]. Moreover, given that the non-antithrombotic strategy after TAVI has suggested no association with an increased risk of cardiovascular death, stroke, myocardial infarction, or bleeding, it may be an acceptable alternative to the current antithrombotic therapy after TAVI[7]. We are now conducting a randomised controlled trial comparing an aspirin group with a group without any antiplatelet therapy in patients without an indication for oral anticoagulation (the NAPT trial; ClinicalTrials.gov: NCT06007222), which has the potential to offer new perspectives into anticoagulant therapy after TAVI in the future[8].

Lastly, this study included around 30% of female patients in each category. However, elderly women tend to be at higher bleeding risk. It would be beneficial to verify the outcomes in a larger cohort, including Asian patients or more female patients with higher bleeding risk.

In summary, the study by Overduin et al reveals that the assessment of bleeding risk after TAVI as measured by VARC-HBR criteria is effective. The stratification of bleeding risk is essential for patients who undergo TAVI to prevent fatal bleeding complications. Further studies are necessary to identify the optimal antithrombotic treatment strategies to minimise adverse events after TAVI.

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Conflict of interest statement

K. Hayashida is a clinical proctor for Edwards Lifesciences, Abbott, and Medtronic. J. Iwata has no conflicts of interest to declare.

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EuroIntervention
2025;21:e1047-e1050
published online e-edition September 2025
DOI: 10.4244/EIJ-D-25-00323

VIEWPOINT

Early interruption of dual antiplatelet therapy after an acute myocardial ischaemic syndrome: but what then?

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Patients after an acute myocardial ischaemic syndrome[1] (AMIS; formerly known as acute coronary syndrome [ACS]) are ideally treated with percutaneous coronary intervention (PCI) and drug-eluting stent (DES) implantation, which require the rapid introduction of dual antiplatelet therapy (DAPT; usually with aspirin plus prasugrel or ticagrelor – two $P2Y_{12}$ inhibitors with more favourable pharmacokinetics than clopidogrel), traditionally for up to 12 months[1,2]. The most recent European Society of Cardiology (ESC)[1] and American College of Cardiology/American Heart Association (ACC/AHA)[3] guidelines suggest the subsequent discontinuation of the $P2Y_{12}$ inhibitor to continue aspirin lifelong for most patients ("default strategy"). While the need for DAPT early on in this setting became clear after the completion of pivotal trials[3,4], its optimal duration has never been crystal clear, and the traditional 12-month duration has been challenged by new evidence. The rapid decline in ischaemic risk after AMIS in most patients who are now properly treated with optimal medical therapy, including extensive use of cholesterol-lowering agents, and the decreased incidence of stent thrombosis with less thrombogenic DES, along with increased awareness of the negative prognostic impact of bleeding, have now enabled a safe reduction in DAPT duration in high bleeding risk patients. Recently, in an attempt to improve safety and maintain an optimal antithrombotic efficacy, a generalised strategy based on early aspirin discontinuation while continuing ticagrelor monotherapy has been proposed[5]. We argue that the choice of which drug to maintain after early DAPT discontinuation is still uncertain, and the position of specifically preferring ticagrelor monotherapy over aspirin monotherapy is not based on solid objective evidence, as it lacks direct comparison within randomised clinical trials (RCTs).

In attempts to minimise bleeding without compromising efficacy, several RCTs evaluated the possibility of progressively shorter DAPT regimens, followed either by aspirin monotherapy after interruption of the $P2Y_{12}$ inhibitor (clopidogrel, ticagrelor, or prasugrel) or by $P2Y_{12}$ monotherapy, compared against the standard 12 months in patients undergoing PCI for either AMIS or non-AMIS. These RCTs were included in a systematic review and meta-analysis[6]. Eight trials (15,020 patients) compared 12-month DAPT with 6-month DAPT followed by aspirin monotherapy, and 4 trials (7,514 patients) compared 12-month with <6-month DAPT followed by aspirin monotherapy. Compared with 12-month DAPT, both of the shortened DAPT regimens were associated with similar relative risks (RR) for cardiovascular events (RR 1.11, 95% confidence interval [CI]: 0.86-1.45; RR 1.24, 95% CI: 0.89-1.72, respectively) and, close to statistical significance, a lower risk of major bleeding (RR 0.85, 95% CI: 0.56-1.28; RR 0.67, 95% CI: 0.43-1.04, respectively). Compared with 12-month DAPT, short-term DAPT followed by $P2Y_{12}$ inhibitor monotherapy was also associated with a similar RR for cardiovascular events (RR 0.97, 95% CI: 0.78-1.22) but a significantly lower RR for major bleeding (RR 0.69, 95% CI: 0.50-0.96), likely due to the higher potency of the RCT. Similar results were obtained in a subgroup analysis restricted to patients with AMIS: compared with 12-month DAPT, (a) the RR of aspirin monotherapy after both shortened DAPT regimens was 1.32 (95% CI: 0.83-2.09) and 1.17 (95% CI: 0.63-2.18) for cardiovascular events; and 0.70 (95% CI: 0.35-1.38) and

SUBMITTED ON 26/03/2025 - REVISION RECEIVED ON 1st 30/04/2025 / 2nd 26/05/2025 - ACCEPTED ON 03/06/2025

0.82 (95% CI: 0.47-1.42) for major bleeding, respectively; (b) the RR of $P2Y_{12}$ inhibitor monotherapy was 0.60 (95% CI: 0.32-1.14) for cardiovascular events and 0.64 (95% CI: 0.46-0.90) for major bleeding, respectively. An analysis of the hierarchy of treatment effectiveness and safety indicated that strategies based on short-term DAPT followed by aspirin monotherapy are the least effective to prevent ischaemic events but the most effective to prevent major bleeding.

RCTs published after the above-cited meta-analysis provided additional evidence with somewhat conflicting results. In the STOPDAPT-2 ACS RCT in patients with AMIS treated with successful PCI, clopidogrel monotherapy after 1-2 months of DAPT failed to achieve non-inferiority compared with 12-month DAPT for the net clinical benefit endpoint, primarily due to a numerical increase in cardiovascular events exceeding the reduction in bleeding[7]. However, in SMART-CHOICE[8], monotherapy with a $P2Y_{12}$ inhibitor (clopidogrel in 77% of cases) started after 3 months of DAPT was associated with non-inferior incidence of major adverse cardiac and cerebrovascular events (MACCE) and lower rates of bleeding at 12 months compared with continued DAPT. Therefore, the available evidence is inconclusive regarding whether $P2Y_{12}$ inhibition by clopidogrel monotherapy after early DAPT discontinuation is non-inferior in efficacy to standard 12-month DAPT. Lesser bleeding and lack of clear evidence of non-increased ischaemic events could be consequent to an inadequate pharmacological response to clopidogrel in about 30% of patients, due to its impaired biotransformation to the active metabolite[9].

More recently, the effects of monotherapy with one of the more efficient $P2Y_{12}$ inhibitors, ticagrelor or prasugrel, after early DAPT discontinuation have been tested. Results of the more relevant RCTs exploring de-escalations to ticagrelor monotherapy were synthesised in a patient-level meta-analysis including a total of 24,407 patients from 6 RCTs. This meta-analysis showed that, compared with standard 12-month DAPT, de-escalation to ticagrelor monotherapy was non-inferior for MACCE (a composite of all-cause death, myocardial infarction, or stroke; hazard ratio [HR] 0.91, 95% CI: 0.78-1.07; p=0.004 for non-inferiority), while significantly reducing Bleeding Academic Research Consortium (BARC) Type 3 or 5 bleeding (HR 0.43, 95% CI: 0.34-0.54; p<0.001 for superiority) and all-cause mortality (HR 0.76, 95% CI: 0.59-0.98; p=0.034 for superiority)[5]. Trial sequential analyses confirmed the evidence for MACCE non-inferiority and bleeding superiority but not for mortality[5]. The beneficial effect with respect to bleeding was particularly pronounced among patients with AMIS at baseline (p for interaction=0.022)[5]. The authors argued for the use of ticagrelor monotherapy after early DAPT discontinuation as a strategy to be adopted for most patients[5]. We believe that the preference of ticagrelor over aspirin monotherapy in the setting of shortened DAPT is questionable because of the lack of RCTs directly comparing the two drug regimens.

With the progressive waning of ischaemic risk after AMIS, seen in recent times[1,2,], it is conceivable that the intensity of antiplatelet therapy could be mitigated to improve safety by reducing bleeding events. Indeed, the above-cited meta-analysis[5] shows that extensive blocking of platelet function by DAPT may not be necessary 1 or 3 months after AMIS. The same "default" 12-month duration of DAPT, so widely adopted and still recommended by current guidelines, is not actually written in stone, since it is based on a disputable inference from the CURE study. In this study, the maximum duration of aspirin plus clopidogrel, compared to aspirin monotherapy, for patients with non-ST-elevation ACS was 12 months, while the actual mean duration was 9 months[3]. Patients initially treated with aspirin plus ticagrelor are likely to bleed more[10] than those treated with aspirin plus clopidogrel (4.5% vs 3.8%; p=0.03 for non-coronary bypass-related bleeding); the latter is associated with more bleeding than aspirin alone (3.7% vs 2.7%; p=0.001)[3]. Any de-escalation strategy is expected to be safer than 12-month DAPT and probably acceptable for efficacy given a decreasing ischaemic risk. However, this may not necessarily be true for all post-AMIS patients. The PEGASUS study, for instance, showed that some patients at high ischaemic risk and low bleeding risk who had survived 12-month DAPT without major bleeds may actually derive a net clinical benefit by prolonging DAPT with aspirin and ticagrelor (60 mg twice daily) beyond 12 months[11]. But, once we accept that some patients with a lower risk of recurrences can benefit from early de-escalation, how can we be reassured that the aspirin, instead of the ticagrelor component, of DAPT should be withheld?

Aspirin has the advantage of being a well-known, extensively studied agent, with fairly reproducible antiplatelet efficacy and bleeding similar to that of clopidogrel when used at the usual once-daily low doses (75-150 mg), deriving solely from its antihaemostatic effects rather than its gastrotoxicity[12]. Ticagrelor, however, is likely to be associated with more bleeding than aspirin (as shown by the higher rates of bleeding in the PLATO study compared with clopidogrel[10]). Consequently, is ticagrelor better than aspirin based on efficacy/safety considerations at that point? And, do we really need a "more effective" therapy with ticagrelor monotherapy instead of aspirin monotherapy, even in patients at low thrombotic risk, and for how long? The only RCT that has directly compared the antithrombotic efficacy of ticagrelor monotherapy and aspirin monotherapy failed to demonstrate superiority of ticagrelor in preventing stroke, myocardial infarction or death within 90 days in patients with acute non-severe ischaemic stroke or high-risk transient ischaemic attack[13]. Although the pathogenesis of thrombi in the coronary and cerebrovascular circulations partially differs, it must be noted that RCTs of antithrombotic drugs in patients with AMIS include the occurrence of stroke among the primary clinical endpoints (MACCE)[5].

To solve the question of the best efficacy/safety compromise after early interruption of DAPT, we need a head-to-head RCT comparing the interruption of aspirin with that of ticagrelor or prasugrel, as summarised in **Figure 1**. This RCT needs to enrol around 20,000 patients, will be expensive, and is unlikely to be funded by the industry, given that tested drugs are now all off patent. But before then, we cannot rely on the only meta-analysis-based evidence produced so far, which showed the superiority of ticagrelor monotherapy over DAPT only in terms of safety; we need a head-to-head comparison of the two (or three) single antiplatelet therapies

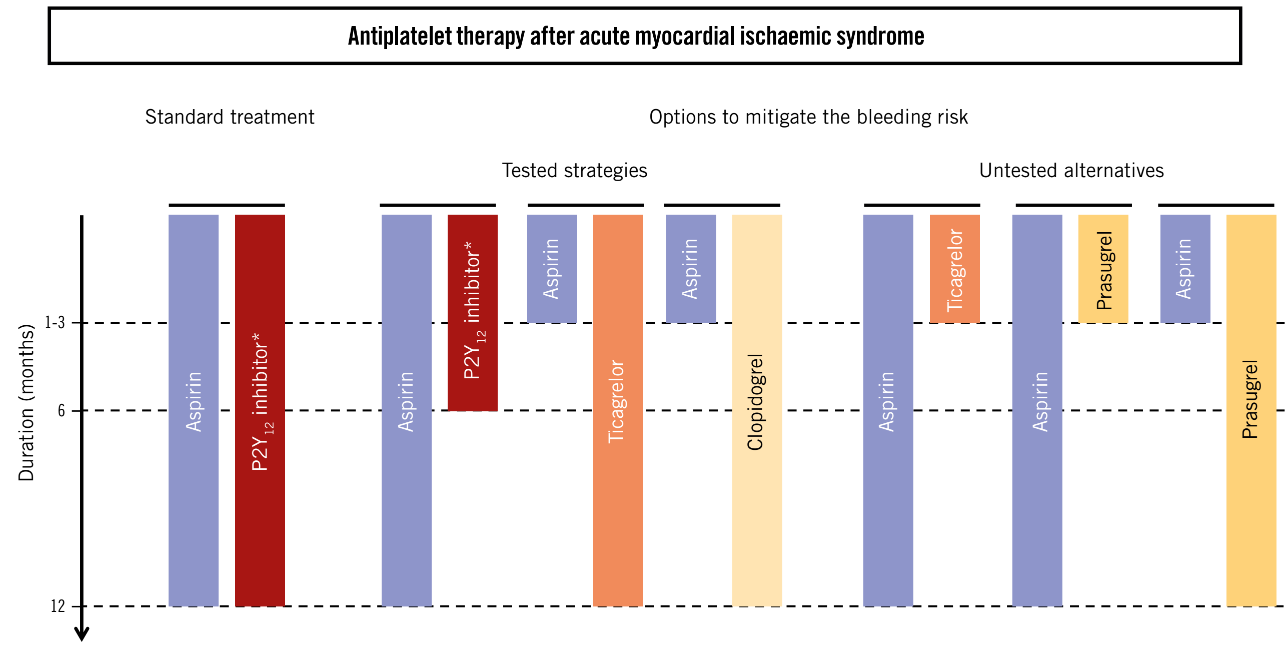

Figure 1. *Tested and untested alternatives for standard and shortened durations of dual antiplatelet therapies after an acute myocardial ischaemic syndrome. *Ticagrelor, prasugrel or clopidogrel*

under scrutiny. It is notable that both the 2023 ESC[1] and the 2025 ACC/AHA[2] ACS guidelines still recommend 12-month DAPT as the default treatment for most AMIS patients.

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Conflict of interest statement

R. De Caterina: consulting fees, honoraria for lecturing, and support to congress participation from Sanofi, Milestone, Daiichi Sankyo, Janssen, Pfizer, Bristol-Myers Squibb, Menarini, and Amarin, all unrelated to the topic under discussion. The other authors have no conflicts of interest to declare.

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EuroIntervention
2025;21:e1051-e1068
published online e-edition September 2025
DOI: 10.4244/EIJ-D-24-00992

State-of-the-Art
by EuroIntervention

Antithrombotic therapy in complex percutaneous coronary intervention

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ABSTRACT

Over the past decades, percutaneous coronary intervention (PCI) has become the most common modality for myocardial revascularisation, and it is increasingly used in patients with advanced coronary artery disease. Antithrombotic therapy, including antiplatelet and anticoagulant drugs, plays a key role and should be part of the optimal revascularisation strategy in the early phase as well as in the long-term prevention of ischaemic events. An antithrombotic therapy regimen of increased intensity and/or duration may mitigate part of the ischaemic burden associated with complex PCI. However, patients undergoing complex PCI are often at increased bleeding risk, challenging, therefore, the decision-making process. In this setting, the optimal antithrombotic treatment is still a matter of debate and has become a field of intensive research. In this state-of-the-art review, we analyse the evidence related to the different approaches regarding the periprocedural and long-term antithrombotic management of patients undergoing complex PCI. Since a "one-size-fits-all" approach cannot be justified in this clinical setting, our aim is to tailor the antithrombotic strategy to each patient's profile and PCI complexity. We discuss the type and duration of antithrombotic regimens that can be selected for patients undergoing complex PCI, with a focus on prolonged dual antiplatelet therapy, $P2Y_{12}$ receptor inhibitor monotherapy, and dual pathway inhibition. We also address antithrombotic management in specific scenarios (left main disease, coronary bifurcations, chronic total occlusion) and in patients undergoing complex PCI who require oral anticoagulant therapy.

KEYWORDS: anticoagulant therapy; antiplatelet therapy; antithrombotic therapy; complex PCI; coronary artery disease; $P2Y_{12}$ inhibitor monotherapy

SUBMITTED ON 29/10/2024 - REVISION RECEIVED ON 1st 07/12/2024 / 2nd 07/01/2025 - ACCEPTED ON 14/02/2025

In approximately 30% of cases, percutaneous coronary intervention (PCI) features a certain level of technical or anatomical complexity[1]. Antithrombotic therapy in the setting of PCI has the following aims: (i) to minimise thrombus burden and prevent the no-reflow phenomenon in patients with acute coronary syndrome (ACS); (ii) to reduce thrombotic complications secondary to the mechanical damage derived from coronary intervention (such as distal embolisation, plaque rupture, iatrogenic dissection, and occlusion of side branches); (iii) to prevent stent thrombosis; and (iv) to prevent ischaemic events outside the stented coronary segments[2,3].

In this state-of-the-art review, we summarise the currently available antithrombotic strategies in patients undergoing complex PCI and highlight the results of randomised clinical trials that have tested antithrombotic regimens in this setting **(Figure 1)**.

Methods

We searched MEDLINE (from its inception to October 2024). We used the search terms "complex" or "complexity" in combination with the terms "percutaneous coronary intervention" or "PCI" or "revascularisation". We selected publications from the past 10 years but did not exclude commonly referenced and highly regarded older publications. We also searched the reference lists of articles identified by this search strategy and selected those we judged relevant. Review articles are cited to provide readers with more details.

Complex PCI

Despite the lack of a universal definition, criteria for complex PCI generally include one of the following characteristics: treatment of 3 vessels or ≥3 lesions, implantation of ≥3 stents, treatment of bifurcation with a 2-stent technique, total stent length ≥60 mm, or a chronic total occlusion (CTO) as the target lesion[4]. Additional criteria, such as treatment of the left main (LM) or a saphenous vein graft (SVG), lesion length ≥30 mm, thrombus-containing lesions, the use of an atherectomy device for severely calcified lesions, or bifurcation lesions with a side branch diameter ≥2.5 mm, have also been reported **(Figure 2)**[5,6]. The concept of complex PCI differs from complex high-risk indicated PCI (CHIP-PCI), as the latter considers patient-related factors (e.g., elderly status, frailty, severe left ventricular dysfunction, or chronic kidney disease) and procedure-related factors (e.g., mechanical circulatory support)[7].

Patients undergoing complex PCI tend to have more comorbidities and incur a higher risk of both early and late ischaemic events compared to those undergoing non-complex PCI, particularly in the presence of multiple complexity features[1,2,4,6,8,9]. Factors such as longer procedural time, more extensive coronary manipulation, the presence of severe calcifications that hinder proper stent expansion, and an increased incidence of periprocedural complications contribute to an elevated early ischaemic risk. Conversely, incomplete revascularisation, the higher likelihood of stent failure, and accelerated disease progression play a greater role in late ischaemic events. Despite potentially being effective, antithrombotic therapy is invariably associated with an increased bleeding risk, which might override the ischaemic risk in certain populations[5,10]. Notably, major bleeding complications may portend a similar prognostic impact compared with thrombotic events[11]. While the link between complex PCI and ischaemic events is generally recognised, the impact of complex PCI on bleeding events is more controversial[4,12,13]. Since antithrombotic therapy can mitigate the risk of both stent-related and non-stent-related events, the selection of an antithrombotic regimen based on its efficacy and safety profiles may significantly influence the outcomes of patients undergoing complex PCI. Although recommendations on alternative antithrombotic regimens in current European Society of Cardiology (ESC) guidelines refer to patients with high ischaemic risk, several technical aspects are potential criteria for complex PCI (≥3 stents implanted, treatment of ≥3 lesions, total stent length >60 mm, LM PCI, treatment of bifurcation with a 2-stent technique, CTO PCI)[14,15].

Antithrombotic therapy before PCI

In patients with unknown coronary anatomy, anticipating complex PCI is highly unlikely. However, not all patients undergo *ad hoc* PCI, and in several instances the decision to proceed with PCI is delayed (e.g., after Heart Team evaluation). In patients with chronic coronary syndrome (CCS), the prior recommendation to pretreat with clopidogrel for at least 5 days is no longer present in the current ESC guidelines on CCS[14-18]. From a clinical standpoint, in patients scheduled for complex PCI and deemed at low bleeding risk based on their risk score (e.g., Academic Research Consortium

Abbreviations

ACS	acute coronary syndrome
ACT	activated clotting time
AF	atrial fibrillation
CCS	chronic coronary syndrome
CHIP-PCI	complex high-risk indicated percutaneous coronary intervention
CTO	chronic total occlusion
DAPT	dual antiplatelet therapy
DAT	dual antithrombotic therapy
DPI	dual pathway inhibition
ESC	European Society of Cardiology
GPI	glycoprotein IIb/IIIa inhibitors
HBR	high bleeding risk
LM	left main
MI	myocardial infarction
NOAC	non-vitamin K antagonist oral anticoagulant
NSTE-ACS	non-ST-segment elevation acute coronary syndrome
OAC	oral anticoagulant
PCI	percutaneous coronary intervention
STEMI	ST-segment elevation myocardial infarction
SVG	saphenous vein graft
TAT	triple antithrombotic therapy
UFH	unfractionated heparin
VKA	vitamin K antagonist

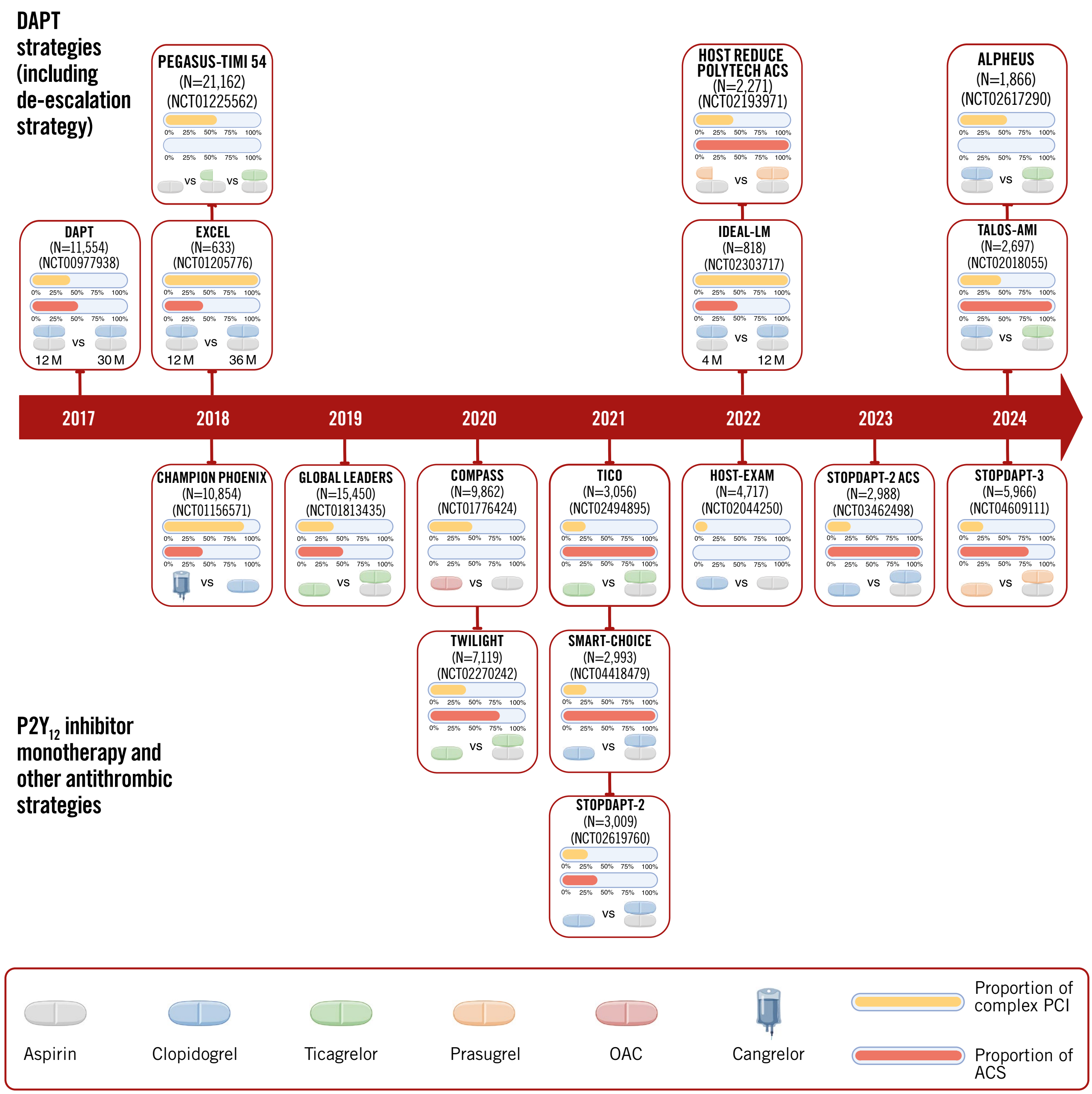


Figure 1. *Timeline of randomised trials testing antithrombotic strategies in complex percutaneous coronary intervention. The duration is shown only for trials comparing short-term versus long-term DAPT. The publication year refers to the substudies performed in a complex PCI setting. ACS: acute coronary syndrome; DAPT: dual antiplatelet therapy; OAC: oral anticoagulant; PCI: percutaneous coronary intervention*

for High Bleeding Risk [ARC-HBR])[10] and procedural aspects (e.g., radial access), pretreatment is a valuable option. In other cases, a loading dose of $P2Y_{12}$ inhibitors can be safely administered around the time of PCI[14,15,18].

In the setting of ACS, routine pretreatment with $P2Y_{12}$ inhibitors is no longer recommended for patients with non-ST-segment elevation ACS (NSTE-ACS) undergoing early invasive assessment within 24 hours (Class III, Level of Evidence A) and is weakly recommended for ST-segment elevation myocardial infarction (STEMI; Class IIb, Level of Evidence B)[14].

An intravenous bolus of unfractionated heparin (UFH) is recommended at the time of diagnosis in patients with STEMI (Class I, Level of Evidence C)[14]. Data from observational studies showed that pretreatment with UFH in patients with STEMI is associated with higher patency of the infarct-related artery at baseline angiography[19,20], and these data have been recently confirmed by a randomised trial[21].

In patients with NSTE-ACS, fondaparinux is recommended when an invasive strategy within 24 hours is not anticipated (Class I, Level of Evidence B)[14].

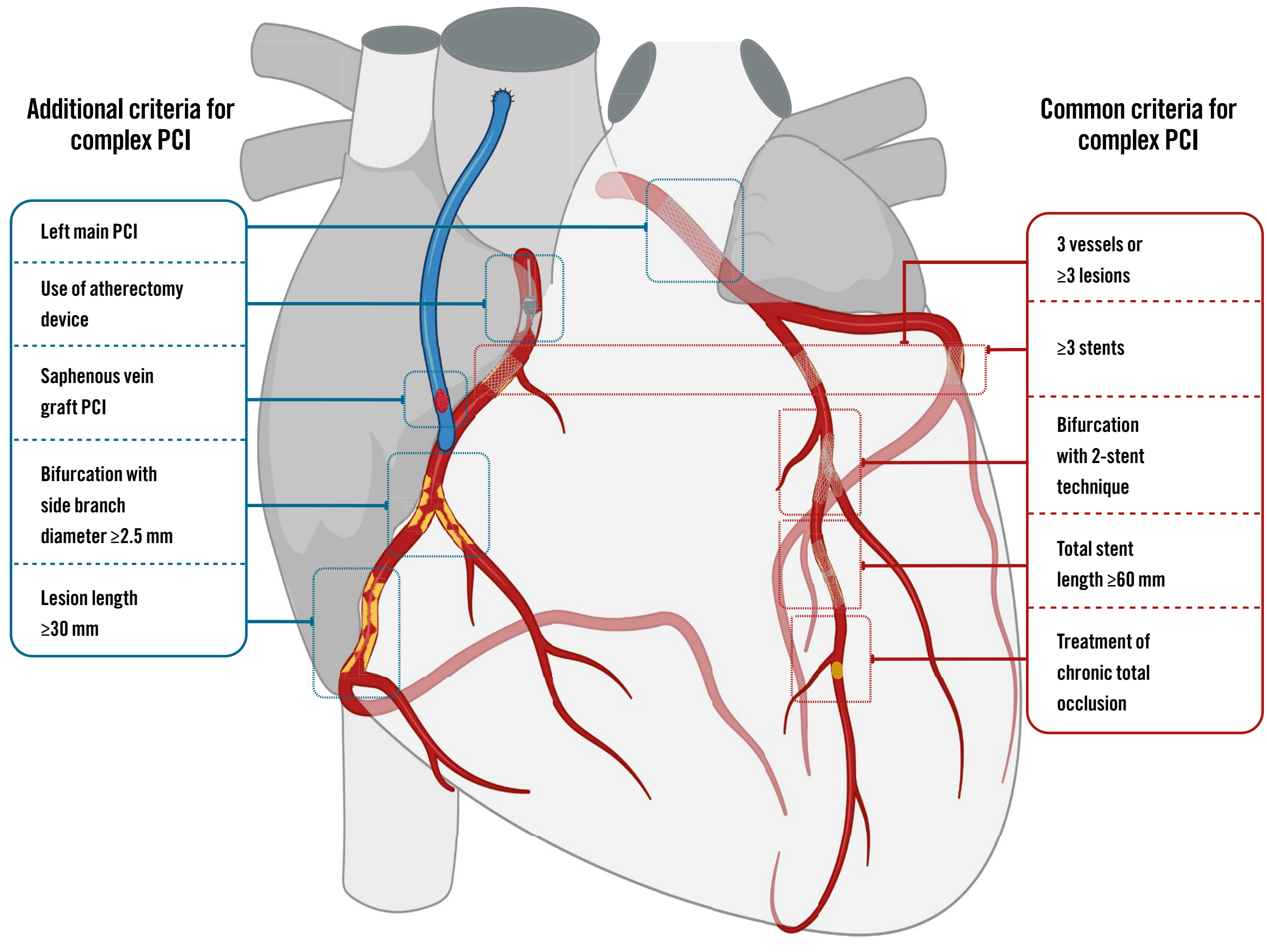


Figure 2. *Principal and additional criteria for complex percutaneous coronary intervention. PCI: percutaneous coronary intervention*

Antithrombotic therapy during PCI

Periprocedural antithrombotic therapy is mandatory during PCI to avoid thrombus formation on the surface of the intravascular equipment and at the site of local plaque rupture or dissection caused by balloon angioplasty and stent implantation[2]. Complex PCI is linked to a heightened risk of bleeding at the access site, particularly when using femoral access, larger sheath sizes, or mechanical circulatory support devices. Hence, determining the ideal periprocedural antithrombotic approach remains a subject of ongoing debate.

1. ANTICOAGULANT THERAPY

Parenteral anticoagulant therapy with intravenous UFH is the standard of care in patients undergoing PCI by virtue of its low cost, the immediate onset of action, the ease of periprocedural monitoring using activated clotting time (ACT) with the opportunity to titrate the infusion in order to deepen the antithrombotic effect, and the possibility of being rapidly antagonisable by protamine sulphate[22]. Bivalirudin and intravenous enoxaparin are two alternatives to UFH, based on data from randomised trials showing a decreased risk of major bleeding[23-25]. The rapid onset and stable antithrombotic effect of bivalirudin, with no need for repeated monitoring, are significant advantages for the use of bivalirudin in long, technically complex coronary procedures, even though the absence of a selective antagonist remains a concern for its use. Data on bivalirudin are more controversial in view of the increased risk of stent thrombosis and myocardial infarction (MI) reported by early trials[26-29], findings not confirmed by the three most recent trials[30-32]. Evidence interpretation about bivalirudin is also challenged by the variable use of glycoprotein IIb/IIIa inhibitors (GPI) in the control arms and the non-standardised scheme of bivalirudin infusion after PCI. Considering the shorter half-life of bivalirudin (25 min) compared with heparin (60-90 min), continuing a full dose of bivalirudin infusion for up to 2-4 h post-PCI may mitigate the early increased ischaemic risk after PCI, mainly driven by stent thrombosis, observed in previous trials. This hypothesis, initially supported by a *post hoc* analysis of the EUROMAX trial[33], was recently confirmed in a patient-level meta-analysis of six randomised trials with 15,254 patients[34]. Bivalirudin reduced the risk of all-cause mortality, cardiac mortality and major bleeding, although with an increase in reinfarction and stent thrombosis compared with UFH. However, in four trials with a 2- to 4-hour high-dose post-PCI infusion regimen, bivalirudin reduced cardiac mortality and major bleeding, without increasing the risk of reinfarction or stent thrombosis[34]. Of interest, a prolonged infusion of bivalirudin after PCI reduced procedural myocardial injury severity without increasing the risk of bleeding in patients with CCS in the Safety and Efficacy of Prolonged Use of Bivalirudin 4 Hours After elective PCI (COBER) study[35]. In approximately 20% of patients included in the CHAMPION PHOENIX trial, bivalirudin was used as the anticoagulant during PCI. Of interest, the decreased risk of ischaemic complications without bleeding liability was retained in patients receiving cangrelor and bivalirudin[36]. Hence, even if there is still a lack of data in patients undergoing complex PCI, bivalirudin might counterbalance the possibly higher risk of bleeding associated with the use of more potent $P2Y_{12}$ inhibitors and cangrelor.

Despite the lack of data regarding complex PCI, in a large meta-analysis of 23 randomised and non-randomised trials including 30,966 patients, enoxaparin (both intravenous and subcutaneous) significantly reduced mortality, MI, and the composite endpoint of death or MI compared with UFH, particularly in patients with STEMI undergoing primary PCI. Of note, major bleeding was reduced only with the intravenous route, a finding not observed in studies that used subcutaneous enoxaparin[25].

To summarise, although there are no specific data regarding the optimal periprocedural anticoagulant management in the complex PCI setting, UFH is widely used and remains the default strategy for anticoagulant therapy. However, bivalirudin and enoxaparin represent valuable alternatives for complex PCI, especially in patients at high risk of periprocedural bleeding events **(Central illustration)**.

However, when UFH is used, in some complex procedures (e.g., retrograde CTO PCI), achieving a higher ACT (>350 seconds) may be considered[37]. The results of several studies on ACT monitoring during PCI are conflicting. A *post hoc* analysis of the Treatment of Acute Coronary Syndromes With Otamixaban (TAO) trial represents, to date, the largest cohort with systematic blinded ACT monitoring[38]. In this cohort of patients with NSTE-ACS treated with UFH plus GPI undergoing PCI, there was no evidence of an ACT threshold predicting ischaemic complications, whereas peak procedural ACTs ≥250 seconds for femoral access and ≥290 seconds by radial approach were associated with increased bleeding risk[38].

2. ANTIPLATELET THERAPY

Periprocedural aspirin use, along with $P2Y_{12}$ inhibitor administration, is the mainstay in patients undergoing PCI and is also standard in complex PCI. Clopidogrel is usually the default $P2Y_{12}$ inhibitor in the setting of elective PCI, whereas ticagrelor or prasugrel are preferred in patients with ACS and may be considered in patients with CCS at high ischaemic risk (Class IIb, Level of Evidence C)[14,15,18]. Clopidogrel has been extensively used and remains the $P2Y_{12}$ inhibitor of choice in patients with CCS, even in complex PCI[15,39], although its use is limited by delayed antiplatelet efficacy and high variability in the antiplatelet effect. As of yet, there is no reason to replace clopidogrel with more potent $P2Y_{12}$ inhibitors to prevent periprocedural events in patients undergoing elective, complex PCI. Two randomised trials, Ticagrelor versus clopidogrel in elective percutaneous coronary intervention (ALPHEUS) and Strategies of Loading With Prasugrel Versus Clopidogrel in PCI-Treated Biomarker Negative Angina (SASSICAIA), failed to demonstrate the superiority of more potent $P2Y_{12}$ inhibition using ticagrelor or prasugrel, respectively, compared with clopidogrel. These trials aimed to decrease periprocedural and cardiovascular events in patients with CCS undergoing high-risk PCI[40,41]. Consistently, in the ALPHEUS substudy, randomisation to ticagrelor versus clopidogrel did not decrease periprocedural or 30-day cardiovascular events in patients with CCS undergoing complex PCI[42].

Cangrelor is an intravenous $P2Y_{12}$ inhibitor that acts as a direct reversible $P2Y_{12}$ receptor antagonist, with rapid onset and offset after infusion discontinuation[36]. It is currently approved (Class IIb, Level of Evidence A) for oral $P2Y_{12}$ inhibitor-naïve patients presenting with ACS undergoing PCI[14]. Compared to clopidogrel, cangrelor achieves faster and more potent platelet inhibition, and this finding has been confirmed in patients undergoing complex PCI[43]. In a pooled analysis of three trials, including 24,910 patients, cangrelor significantly reduced the risk of early ischaemic events at 48 hours after PCI compared with clopidogrel[44]. Although there was no significant difference in terms of the primary safety endpoint, the risk of major bleeding based on other criteria was significantly increased in patients randomised to cangrelor. Because the risk of periprocedural MI is significantly higher in patients undergoing complex compared to non-complex PCI, even using multiple definitions[8], cangrelor may represent a valid alternative in patients naïve to $P2Y_{12}$ inhibitors who are not at high bleeding risk (HBR). In this respect, the greatest absolute risk reduction in ischaemic events with cangrelor has been reported in patients with the highest number of high-risk features[45].

GPI are potent intravenous antiplatelet agents, which were routinely added to UFH in patients with ACS in the early era of PCI. However, in view of the increased risk of major bleeding, GPI are currently indicated only as a bailout strategy in case of no-reflow or thrombotic complications during PCI. Recent ESC guidelines on ACS indicate the potential use of GPI in patients undergoing high-risk PCI and naïve to $P2Y_{12}$ inhibitors[14].

Antithrombotic therapy after PCI

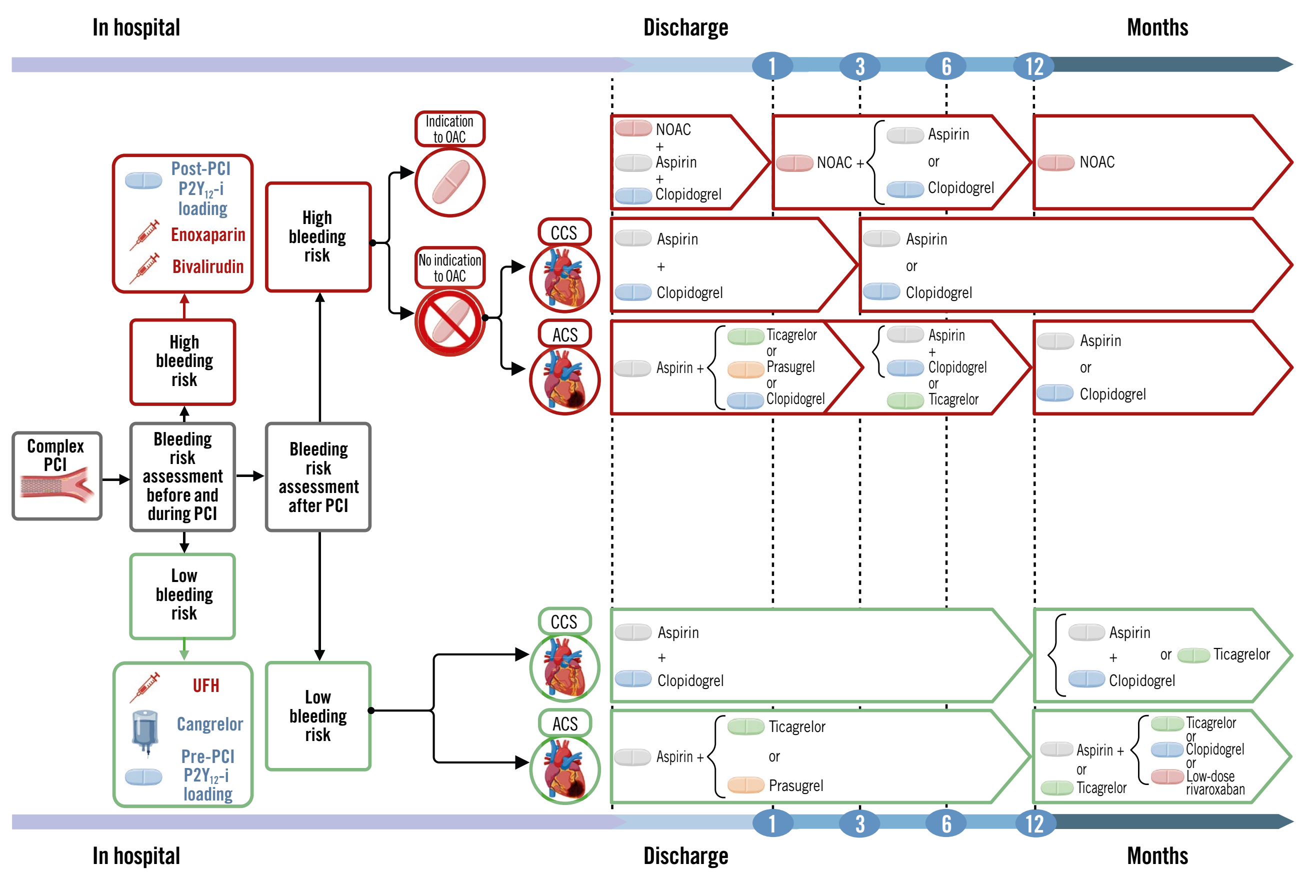
1. DUAL ANTIPLATELET THERAPY

In patients undergoing PCI, a variable duration of dual antiplatelet therapy (DAPT), consisting of a combination of aspirin and a $P2Y_{12}$ inhibitor, is recommended for all patients and still remains the cornerstone of secondary prevention.

In real-world clinical practice, 20-40% of patients continue DAPT beyond 1 year after revascularisation, and complex PCI is a major independent predictor of DAPT persistence[46]. In a patient-level meta-analysis including nearly 9,500 patients from 6 randomised trials, long-term DAPT (≥12 months), compared with short-term DAPT (3-6 months), yielded a significant reduction of major adverse cardiovascular events in the complex PCI group, a finding not observed in the non-complex PCI stratum (p for interaction=0.01). Moreover, the benefit associated with long-term DAPT gradually increased with the number of complex PCI features. However, long-term DAPT was associated with a significantly higher risk of major

EuroIntervention Central Illustration

Antithrombotic strategies for patients undergoing complex percutaneous coronary intervention.



Domenico Simone Castiello *et al.* • *EuroIntervention* 2025;21:e1051-e1068 • DOI: 10.4244/EIJ-D-24-00992

The algorithm shows periprocedural and long-term antithrombotic strategies based on bleeding risk. All patients undergoing complex PCI are assumed to be at high ischaemic risk. Patients requiring OACs are assumed by default to be at HBR.
ACS: acute coronary syndrome; CCS: chronic coronary syndrome; HBR: high bleeding risk; NOAC: non-vitamin K antagonist oral anticoagulant; OAC: oral anticoagulant; $P2Y_{12}$-i: $P2Y_{12}$ inhibitor; PCI: percutaneous coronary intervention; UFH: unfractionated heparin

bleeding, both in complex PCI and in non-complex PCI strata[4]. A subsequent meta-analysis combined the risk of bleeding with PCI complexity in 8 trials and showed that in patients undergoing complex PCI without HBR features, prolonging DAPT (12 or 24 months) was associated with a decreased absolute risk of ischaemic events without bleeding liability, compared with short DAPT (3 or 6 months). In patients undergoing complex PCI and at HBR, prolonging DAPT increased the risk of bleeding without a parallel ischaemic benefit[13]. In a *post hoc* analysis of the DAPT trial, long-term DAPT (12-30 months), mainly with clopidogrel and prasugrel, was associated with a reduction of MI and stent thrombosis rates at the expense of an increased bleeding rate, a finding that was similar for patients with and without anatomical complexity[6]. Consistently, in a prespecified subanalysis of the Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis In Myocardial Infarction 54 (PEGASUS-TIMI 54) trial, extended DAPT with ticagrelor significantly reduced the risk of cardiovascular death, MI, or stroke, whereas it increased the risk of major bleeding, as compared to aspirin plus placebo, irrespective of multivessel coronary artery disease angiographic evidence[47]. Taken together, these data **(Table 1)** support a strategy of DAPT prolongation beyond 1 year after PCI in patients undergoing complex PCI when the thrombotic risk is prevalent (e.g., patients with ACS) and the bleeding risk is low **(Central illustration)**. Extended DAPT (beyond 12 months) should be considered in patients without HBR and with high ischaemic risk, including those presenting with complex PCI (Class IIa, Level of Evidence A) according to current ESC guidelines on the management of ACS and CCS[14,15].

2. $P2Y_{12}$ INHIBITOR MONOTHERAPY

$P2Y_{12}$ INHIBITOR MONOTHERAPY FROM PCI TO 1 YEAR

Different types of $P2Y_{12}$ inhibitors and varying timings of aspirin discontinuation (e.g., 1-3 months after PCI) have been tested in randomised trials, showing a satisfactory safety and efficacy profile overall **(Table 2)**[48].

Clopidogrel monotherapy was investigated in three trials[49-51]. Across these studies, clopidogrel monotherapy reduced major bleeding rates without increasing ischaemic events as compared with standard 12-month DAPT, regardless of PCI complexity[52-54]. However, in a pooled analysis of nearly 6,000 patients, clopidogrel monotherapy after 1-month DAPT, compared with 12 months of DAPT, was associated with a numerical increase in cardiovascular events among patients with ACS, but not in patients with CCS, suggesting a possible safety issue with clopidogrel monotherapy in patients with ACS[55].

In the "Comparative effectiveness of 1 month of ticagrelor plus aspirin followed by ticagrelor monotherapy versus a current-day intensive dual antiplatelet therapy in all-comers patients undergoing percutaneous coronary intervention with bivalirudin and BioMatrix family drug-eluting stent use" (GLOBAL LEADERS) trial, 23-month ticagrelor monotherapy after 1-month DAPT was compared with 12-month DAPT with ticagrelor or clopidogrel followed by aspirin monotherapy among 15,968 patients undergoing PCI[56]. In a *post hoc* analysis of the study, ticagrelor monotherapy significantly reduced the risk of the primary endpoint, a composite of all-cause death or new Q-wave MI, in patients with complex PCI but not in those with non-complex PCI features (p for interaction=0.015), a benefit that was mainly driven by a significant interaction for treatment effect in patients presenting with ACS; moreover, no significant difference in bleeding was shown[57]. Ticagrelor monotherapy after 3-month DAPT was evaluated in 7,119 high-risk patients enrolled in the Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention (TWILIGHT) trial and in 3,056 patients presenting with ACS in the Ticagrelor Monotherapy After 3 Months in the Patients Treated With New Generation Sirolimus Stent for Acute Coronary Syndrome (TICO) trial[58,59]. In the TWILIGHT-COMPLEX substudy, a total of 2,342 patients underwent complex PCI and, in line with the parental trial, ticagrelor monotherapy was associated with a significant reduction of major bleeding and similar ischaemic risk compared with ticagrelor plus aspirin, irrespective of periprocedural complexity[60]. In the TICO trial, when the clinical characteristics (e.g., diabetes and chronic kidney disease) were combined with procedural complexity criteria, no significant interaction was evident for ticagrelor monotherapy after 3-month DAPT compared with 12-month DAPT with ticagrelor[61]. More recently, in a pooled analysis including 7,529 patients with ACS from the TICO and TWILIGHT trials, ticagrelor monotherapy significantly reduced major bleeding, without increasing adverse events, with no evidence of interaction according to PCI complexity[62].

Prasugrel monotherapy was investigated in the recent Short and Optimal Duration of Dual Antiplatelet Therapy After Everolimus-Eluting Cobalt-Chromium Stent-3 (STOPDAPT-3) trial. In 1,230 patients with ACS or HBR undergoing complex PCI, low-dose prasugrel (3.75 mg/day) monotherapy showed similar ischaemic and bleeding outcomes at 1 month compared with low-dose prasugrel-based DAPT[63]. However, it should be noted that there was an excess of unplanned revascularisation and subacute definite or probable stent thrombosis in the aspirin-free group[63,64].

Two recent meta-analyses showed a consistent reduction in the risk of major bleeding during $P2Y_{12}$ inhibitor monotherapy in patients undergoing complex PCI, without an increased risk of ischaemic events[65,66]. Despite the accumulated evidence, the current guidelines recommend $P2Y_{12}$ inhibitor monotherapy only in patients with ACS at high bleeding risk (Class IIb, Level of Evidence B) or in patients with CCS at high ischaemic risk in the absence of HBR features (Class IIb, Level of Evidence C) **(Central illustration)**[14,15].

$P2Y_{12}$ INHIBITOR MONOTHERAPY AFTER 1 YEAR

Although aspirin remains the treatment of choice for long-term secondary prevention after PCI, $P2Y_{12}$ inhibitor monotherapy is emerging as a novel strategy **(Table 2, Table 3)**. A recent patient-level meta-analysis of 7 randomised trials compared $P2Y_{12}$ inhibitor monotherapy versus aspirin monotherapy for long-term secondary prevention in patients with established coronary artery disease. $P2Y_{12}$ inhibitor monotherapy was superior to aspirin monotherapy in terms of ischaemic outcomes, whereas the rate of major bleeding was similar between the two strategies[67]. In the Harmonizing Optimal Strategy for Treatment of Coronary Artery Stenosis-EXtended Antiplatelet Monotherapy (HOST-EXAM) trial, clopidogrel monotherapy was associated with lower risks of both thrombotic and bleeding events compared with aspirin among more than 5,000 patients. A subgroup analysis of PCI complexity showed consistent benefit of clopidogrel monotherapy with no significant interaction[68]. A landmark analysis of the GLOBAL LEADERS trial at 12-month follow-up showed that ticagrelor versus aspirin monotherapy significantly reduced ischaemic events (all-cause death, any MI, or any stroke), although it numerically increased the risk of bleeding. This result was consistent in patients undergoing both complex and non-complex PCI[69]. Of note, clopidogrel monotherapy has been endorsed by ESC guidelines on CCS as a safe and effective alternative to aspirin for long-term post-PCI secondary prevention (Class I, Level of Evidence A)[15].

3. SWITCHING, ESCALATION AND DE-ESCALATION OF ANTITHROMBOTIC THERAPIES

Switching between antithrombotic drugs can involve both anticoagulant and antiplatelet agents. As a general approach, switching between anticoagulants should be avoided unless fondaparinux has been used before PCI[14].

Switching between $P2Y_{12}$ inhibitors can involve switching between two oral $P2Y_{12}$ inhibitors (escalation, de-escalation, or change) or can involve an intravenous $P2Y_{12}$ inhibitor (bridge or transition). Both escalation and de-escalation approaches can be guided or unguided, according to whether genetic tests to identify carriers of CYP2C19 loss-of-function alleles or platelet function tests are performed or not, respectively. In general, switching between oral $P2Y_{12}$ inhibitors should occur with the administration of a loading dose in the setting of ACS, whereas reloading is not required in the context of CCS, with the exception of ticagrelor[70]. Despite the lack of data on complex PCI, a meta-analysis of both randomised and non-randomised trials showed that guided escalation is associated with a decreased risk of ischaemic events without

Table 1. Studies comparing short-term versus long-term DAPT strategies in patients undergoing complex PCI.

Study - year	Complex PCI patients	ACS patients	Follow-up	Complex PCI criteria	Short-term DAPT	Long-term DAPT	Results
Patient-level meta-analysis of 6 RCTs[4] -2016	17.5% (1,680/ 9,577)	43.7% (4,189/ 9,577)	12 months*	≥1 of the following: 3 vessels treated, ≥3 stents implanted, ≥3 lesions treated, bifurcation with 2 stents implanted, total stent length >60 mm, CTO PCI	3 to 6 months of DAPT (aspirin and clopidogrel)	≥12 months of DAPT (aspirin and clopidogrel)	Long-term DAPT yielded a significant reduction in MACE in the complex PCI group versus the non-complex PCI group
DAPT trial[6] -2017	32.2% (3,730/ 11,554)	46.3% (5,359/ 11,554)	30 months	≥1 of the following: unprotected LM, ≥2 lesions per vessel, lesion length ≥30 mm, bifurcation lesion with side branch ≥2.5 mm, saphenous vein graft, thrombotic lesions	12 months of DAPT (aspirin and clopidogrel or prasugrel)	30 months of DAPT (aspirin and clopidogrel or prasugrel)	Long-term DAPT reduced ischaemic events, irrespective of the presence of anatomically complex lesions, but increased moderate/severe bleeding
EXCEL trial -2018	100% (633/633)	38.7% (245/633)	36 months	LM PCI	12 months of DAPT (aspirin and clopidogrel, prasugrel or ticagrelor)	36 months of DAPT (aspirin and clopidogrel or ticagrelor)	Long-term DAPT was not associated with improved event-free survival in complex PCI patients
PEGASUS-TIMI 54 trial[47,86] -2018	59.4% (12,558/ 21,162)	0% (0/ 21,162)	36 months†	Multivessel CAD	12 months of DAPT (aspirin and ticagrelor)	36 months of DAPT (aspirin and ticagrelor)	Long-term DAPT reduced ischaemic events, but increased TIMI major bleeding (not ICH or fatal bleeding) in multivessel PCI patients
Patient-level meta-analysis of 8 RCTs[13] -2019	20.8% (3,118/ 14,963)	55.5% (8,312/ 14,963)	24 months	≥1 of the following: 3 vessels treated, ≥3 stents implanted, ≥3 lesions treated, bifurcation with 2 stents implanted, total stent length >60 mm, CTO PCI	3 to 6 months of DAPT (aspirin and clopidogrel, prasugrel or ticagrelor)	12 to 24 months of DAPT (aspirin and clopidogrel, prasugrel or ticagrelor)	Long-term DAPT in non-HBR patients reduced ischaemic events in both complex and non-complex PCI groups, but not among HBR patients, regardless of PCI complexity
IDEAL-LM trial[87] -2022	100% (818/818)	40.4% (331/818)	24 months	LM PCI	4 months of DAPT (aspirin and clopidogrel, prasugrel or ticagrelor)	12 months of DAPT (aspirin and clopidogrel, prasugrel or ticagrelor)	4 months of DAPT was non-inferior to 12 months of DAPT with respect to the ischaemic composite endpoint in LM PCI patients

*Median follow-up time: 392 days. †Median follow-up time: 33 months. ACS: acute coronary syndrome; CAD: coronary artery disease; CTO: chronic total occlusion; DAPT: dual antiplatelet therapy; HBR: high bleeding risk; ICH: intracranial haemorrhage; LM: left main; MACE: major adverse cardiovascular events; PCI: percutaneous coronary intervention; RCT: randomised clinical trial; TIMI: Thrombolysis in Myocardial Infarction a trade-off in bleeding[71]. In this respect, an expert consensus statement supported the use of platelet-function testing to escalate $P2Y_{12}$ inhibitors in patients undergoing complex PCI (multivessel PCI, ≥3 stents implanted, bifurcation PCI with 2 stents, total stent length >60 mm, CTO PCI)[72].

A de-escalation strategy has been tested exclusively in patients with ACS across 6 trials (2 functional-guided, 1 genotype-guided, 3 unguided trials)[73]. Except for one trial[74], all the studies met their primary endpoint and showed significant reductions of net adverse clinical events and major bleeding, without increasing ischaemic events. Recently, four of these trials were pooled in an individual patient-data meta-analysis of 10,133 patients[75]. Guided or unguided de-escalation provided consistent results and was associated with both decreased ischaemic and bleeding endpoints. There was no interaction for either ischaemic or bleeding outcomes in patients undergoing multivessel versus single-vessel PCI nor in those undergoing PCI with ≥3 versus <3 implanted stents, which are considered proxies for complex PCI. Consistently, there was no interaction according to PCI complexity for both ischaemic and bleeding outcomes in the Harmonizing Optimal Strategy for Treatment of Coronary Artery Diseases Trial - Comparison of REDUCTION of prasugrEl Dose & POLYmer TECHnology in ACS Patients (HOST REDUCE POLYTECH) and TicAgrelor Versus CLOpidogrel in Stabilized Patients With Acute Myocardial Infarction (TALOS-AMI) trials, which showed reduced bleeding events with unguided prasugrel or ticagrelor de-escalation, respectively **(Table 3)**[76,77]. Current ESC guidelines on ACS recommend a de-escalation strategy after 30 days to prevent bleeding (Class IIb, Level of Evidence A)[14].

A transition from cangrelor to clopidogrel or prasugrel should occur at the end of cangrelor infusion, or 30 minutes before the cangrelor infusion is stopped when prasugrel is used. Transition from cangrelor to ticagrelor is not affected by drug-drug interaction and therefore can occur at any time during PCI[70,78,79].

4. DUAL PATHWAY INHIBITION

Dual pathway inhibition (DPI) consists of a simultaneous inhibition of both platelet activity and coagulation cascade by the administration of an antiplatelet agent combined with an anticoagulant drug. This strategy is aimed to target the residual cardiovascular ischaemic risk in patients who present with ACS and/or undergo coronary revascularisation[80]. The Apixaban for Prevention of Acute Ischemic and Safety Events (APPRAISE) trial showed that among patients with ACS with high-risk clinical features (44% treated with PCI), the addition of a full dose of apixaban (5 mg twice daily) to DAPT increased the risk of major bleeding without a significant reduction in ischaemic events as compared with standard DAPT[81]. The Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome 2–Thrombolysis in Myocardial Infarction 51 (ATLAS ACS 2–TIMI 51) trial tested rivaroxaban on a background of single or dual antiplatelet therapy in patients with recent ACS and showed a significant reduction of ischaemic events and mortality with low-dose rivaroxaban (2.5 mg twice daily) as compared to placebo, counterbalanced by an increase of major bleeding[82]. Similarly, in the Cardiovascular OutcoMes for People Using Anticoagulation StrategieS (COMPASS) trial, a low dose of rivaroxaban (2.5 mg twice daily) on top of aspirin decreased the rates of major adverse cardiovascular events and cardiovascular mortality, at the expense of bleeding events, in patients with CCS (60% with a clinical history of MI or peripheral artery disease)[83]. This benefit was preserved in a prespecified subgroup analysis including patients with CCS treated with PCI, of whom a substantial proportion (38%) underwent complex, multilesion PCI[84]. Based on the available evidence **(Table 3)**, a DPI strategy with rivaroxaban in addition to aspirin should be considered for extended long-term (beyond 12 months) prevention in patients without HBR and with high ischaemic risk, including those presenting with complex PCI (Class IIa, Level of Evidence A) according to current ESC guidelines on the management of ACS **(Central illustration)**[14].

Specific settings

Some complexity features, such as LM, bifurcation and CTO lesions, have been associated with worse prognostic impact and increased rates of ischaemic events. For this reason, some studies have evaluated the optimal antithrombotic therapy in these subsets of patients[5]. On the other hand, patients with a chronic indication to oral anticoagulation undergoing complex PCI represent a unique cohort with a higher bleeding risk.

1. LEFT MAIN DISEASE

LM PCI represents one of the most challenging scenarios in view of the large area of myocardium at risk with a potentially catastrophic impact of thrombotic complications related to LM stenting. Indeed, unprotected LM disease can substantially affect myocardial supply and has a critical role in long-term outcomes in patients undergoing PCI, with a higher long-term risk of ischaemic events[85]. In a *post hoc* analysis of the Evaluation of XIENCE Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization (EXCEL) trial, continuation of DAPT beyond 1 year was not associated with improved outcomes, and trends toward harm were noted with extended DAPT after propensity adjustment[86]. In the randomised Improved Drug-Eluting stent for All-comers Left Main (IDEAL-LM) study, among 818 patients undergoing PCI of the LM, a biodegradable-polymer everolimus-eluting stent followed by 4 months of DAPT resulted in non-inferior outcomes compared to a durable-polymer everolimus-eluting stent followed by 12 months of DAPT. However, major adverse cardiovascular events and its individual components trended numerically higher in the biodegradable-polymer stent with the 4-month DAPT group[87]. Along the same line, in a prospective observational study enrolling 3,865 patients undergoing LM PCI and at low bleeding risk, a longer duration (>12 months) of DAPT was associated with a significant reduction of ischaemic events without a concomitant increase in clinically relevant bleeding as compared with ≤12-month DAPT[88]. Interestingly, in a large retrospective analysis including 700 patients undergoing LM PCI, the rate of target lesion failure in patients treated with a two-stent technique was significantly higher than in the one-stent group only when DAPT was interrupted before 1 year[89]. Given the

Table 2. Studies comparing $P2Y_{12}$ inhibitor monotherapy versus DAPT in patients undergoing complex PCI.

Study - year	Complex PCI patients	ACS patients	Follow-up	Complex PCI criteria	$P2Y_{12}$ inhibitor monotherapy regimen	DAPT regimen	Results
GLOBAL LEADERS trial[57] -2019	28.6% (4,570/15,968)	45.4% (7,260/15,968)	24 months	≥1 of the following: 3 vessels treated, ≥3 stents implanted, ≥3 lesions treated, bifurcation with 2 stents implanted, total stent length >60 mm	23-month ticagrelor monotherapy following 1-month DAPT (aspirin and ticagrelor)	12-month aspirin monotherapy following 12-month DAPT (aspirin and ticagrelor or clopidogrel)	Ticagrelor monotherapy significantly reduced the risk of the primary ischaemic endpoint in complex PCI patients, but not in the non-complex PCI group
TWILIGHT trial[60] -2020	32.8% (2,342/7,119)	64.8% (4,614/7,119)	15 months	≥1 of the following: 3 vessels treated, ≥3 lesions treated, bifurcation with 2 stents implanted, total stent length >60 mm, CTO PCI, atherectomy device use, LM PCI, surgical bypass graft PCI	12-month ticagrelor monotherapy following 3-month DAPT (aspirin and ticagrelor)	12-month DAPT (aspirin and ticagrelor)	Ticagrelor monotherapy significantly reduced the risk of the primary bleeding endpoint in complex PCI patients without an increased risk of ischaemic events
TICO trial[61] -2021	13.3% (409/3,056)*	100% (3,056/3,056)	12 months	≥1 of the following†: ≥3 stents implanted, total stent length >60 mm, bifurcation with 2 stents implanted, LM PCI, CTO PCI, history of DM or CKD	9-month ticagrelor monotherapy following 3-month DAPT (aspirin and ticagrelor)	12-month DAPT (aspirin and ticagrelor)	Ticagrelor monotherapy after short-duration DAPT was not associated with an increased risk of ischaemic or bleeding events in high-ischaemic risk patients
SMART-CHOICE trial[52] -2021	16.6% (498/2,993)	100% (2,993/2,993)	12 months	≥1 of the following: 3 vessels treated, ≥3 stents implanted, ≥3 lesions treated, bifurcation with 2 stents implanted, total stent length >60 mm	9-month $P2Y_{12}$ inhibitor monotherapy (mostly clopidogrel) following 3-month DAPT (aspirin and mostly clopidogrel)	12-month DAPT (aspirin and mostly clopidogrel)	$P2Y_{12}$ inhibitor monotherapy, mostly clopidogrel, after short-duration DAPT was not associated with an increased risk of ischaemic events in complex PCI patients
Pooled population of STOPDAPT-2[53] -2021 and STOPDAPT-2 ACS trials[54] -2023	16.7%‡ (999/5,997)	68.9%§ (4,136/5,997)	12 months	≥1 of the following: 3 vessels treated, ≥3 stents implanted, ≥3 lesions treated, bifurcation with 2 stents implanted, total stent length >60 mm, CTO PCI	11-month clopidogrel monotherapy following 1-month DAPT (aspirin and clopidogrel)	12-month DAPT (aspirin and clopidogrel)	Clopidogrel monotherapy after short-duration DAPT showed comparable ischaemic and bleeding outcomes compared to 12-month DAPT in complex PCI patients
STOPDAPT-3 trial[63] -2024	20.6% (1,228/5,966)	75% (4,474/5,966)	12 months	≥1 of the following: 3 vessels treated, ≥3 stents implanted, ≥3 lesions treated, bifurcation with 2 stents implanted, total stent length >60 mm, CTO PCI	Low-dose prasugrel monotherapy	1-month DAPT (aspirin and low-dose prasugrel)	Low-dose prasugrel monotherapy showed comparable ischaemic and bleeding outcomes compared to 1-month DAPT in the complex PCI cohort. However, an excess of unplanned revascularisation and subacute definite or probable stent thrombosis was found in the no-aspirin group

*Complex PCI patients: 409; non-complex PCI patients: 2,647. †Information for the *post hoc* analysis of the TICO trial refers to patients defined as at high ischaemic risk, which included those undergoing complex PCI, having chronic kidney disease, or diabetes mellitus. ‡Complex PCI patients from the STOPDAPT-2 cohort: 509 (16.9%); complex PCI patients from STOPDAPT-2 ACS: 490 (16.3%). §ACS patients from the STOPDAPT-2 cohort: 1,148 (38.1%); ACS patients from STOPDAPT-2 ACS: 2,988 (100%). ACS: acute coronary syndrome; CKD: chronic kidney disease; CTO: chronic total occlusion; DAPT: dual antiplatelet therapy; DM: diabetes mellitus; HBR: high bleeding risk; LM: left main; PCI: percutaneous coronary intervention available evidence **(Table 1)**, even if LM PCI does not appear to be a treatment modifier for oral antithrombotic therapy, it is well recognised as a procedural risk enhancer for ischaemic events. For this reason, LM PCI is considered an ischaemic risk condition, allowing for extended antithrombotic therapy (with DAPT or DPI) beyond 6 and 12 months in patients with CCS and ACS, respectively (Class IIa, Level of Evidence A)[14,15]. In patients with CCS undergoing complex LM PCI, potent $P2Y_{12}$ inhibitors may be an alternative to clopidogrel in selected cases (Class IIb, Level of Evidence C)[15].

2. BIFURCATION PCI

Bifurcation lesions have a critical prognostic impact on ischaemic outcomes with a 2-year major adverse cardiovascular events rate of 10% and a higher risk of stent thrombosis[4,5,85]. Bifurcation stenting is considered an ischaemic risk criterion, justifying the recommendation of extended antithrombotic therapy (with both DAPT or DPI) beyond 6 and 12 months in patients with CCS and ACS, respectively (Class IIa, Level of Evidence A), and the opportunity to replace clopidogrel with potent $P2Y_{12}$ inhibitors in patients with CCS (Class IIb, Level of Evidence C)[14,15]. In 2,082 patients who underwent bifurcation stenting in the Coronary Bifurcation Stenting (COBIS) II registry and who were event-free at 12 months, prolonged DAPT was associated with a reduced incidence of all-cause death, MI and stent thrombosis at 4-year follow-up compared with a short-term strategy (<12 months). Interestingly, the beneficial role of prolonged DAPT was not significantly affected by lesion location or stenting technique[90]. Similarly, in the European Bifurcation Club registry, prolonged DAPT was associated with a significantly lower risk of ischaemic events as compared with both the short-term DAPT group (<6 months) and standard DAPT group (6-12 months) at 2-year follow-up. Furthermore, event-free survival was significantly lower in the group of DAPT duration <6 months[91]. However, the currently available evidence about antithrombotic therapy in bifurcation PCI is not derived from major dedicated trials, and observational studies may be inexorably biased. A decision-making algorithm for DAPT duration based primarily on the clinical presentation, the baseline bleeding risk, the stenting strategy, and the possible use of intracoronary imaging in patients who are not candidates for anticoagulant therapy has recently been proposed and may inform clinician decisions[92].

3. CTO PCI

As previously described, patients with a CTO are considered at increased ischaemic risk. Notably, extensive calcification, a common CTO lesion feature, hinders stent expansion and leads to a higher risk of both acute and late stent thrombosis. Most of the time, CTO PCI is performed as a scheduled intervention in patients with CCS; thus, aspirin and clopidogrel are the standard DAPT regimen, even if ticagrelor or prasugrel may be considered (Class IIb, Level of Evidence C). Regarding the DAPT duration, prolonged DAPT (>6 months) should be considered according to European guidelines (Class IIa, Level of Evidence A)[14,15]. Lee et al compared ≤12-month with >12-month DAPT in 512 patients undergoing CTO PCI. In a propensity score-matched population, the rate of ischaemic events was similar between the two groups[93]. More recently, Sachdeva et al found that prolonged DAPT (>12 months) was associated with a lower incidence of death or MI without an increase in bleeding rate in 1,069 patients undergoing CTO PCI[94]. Further dedicated prospective studies are required to assess the optimal antithrombotic strategy in this distinct subgroup.

4. SVG PCI

PCI of SVG disease represents a technical challenge considering that the pathophysiological mechanisms are distinct from those of native coronary artery disease. Despite their poor mid- and long-term patency rates, venous grafts are still commonly used in patients undergoing surgical myocardial revascularisation[95]. SVG PCI is frequently performed in the setting of ACS. Among 8,582 patients enrolled in the ADAPT-DES study, 405 (4.7%) underwent SVG PCI. In this cohort, patients who underwent SVG PCI had a higher risk of ischaemic events compared with patients undergoing PCI of native coronary arteries. For this reason, SVG PCI is considered, in some cases, a complex PCI criterion; prolonged antithrombotic therapy therefore provides potential benefits[96]. However, further studies are warranted to investigate this particular cohort, and, to date, no specific recommendations are available.

5. PATIENTS WITH ATRIAL FIBRILLATION REQUIRING ORAL ANTICOAGULATION

Patients with atrial fibrillation (AF) requiring oral anticoagulants (OACs) undergoing PCI are at increased risk for thromboembolic and bleeding events. Current guidelines recommend triple antithrombotic therapy (TAT) consisting of DAPT with clopidogrel plus an OAC agent for a short peri-interventional 1-week time frame, followed by dual antithrombotic therapy (DAT) with clopidogrel plus OAC for up to 6 or 12 months after PCI for patients with CCS and ACS, respectively (Class I, Level of Evidence A)[14,15,97]. This recommendation largely relies on four major trials comparing DAT, mainly based on non-vitamin K antagonist oral anticoagulants (NOACs), with vitamin K antagonist (VKA)-based TAT in patients with AF presenting with ACS and/or undergoing PCI[98-100]. Across these trials, DAT was associated with a significant reduction of major bleeding, a similar incidence of ischaemic stroke, numerically higher risks of MI and stent thrombosis, and an overall neutral effect on all-cause mortality. A *post hoc* analysis of Open-Label, Randomized, Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects with Atrial Fibrillation who Undergo Percutaneous Coronary Intervention (PIONEER AF-PCI) and Randomized Evaluation of Dual Antithrombotic Therapy with Dabigatran versus Triple Therapy With Warfarin in Patients With Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention (RE-DUAL PCI) showed consistent risk estimates between a DAT and/or NOAC-based strategy as compared with VKA-based TAT regardless of PCI complexity[101,102]. However, the individual trials were underpowered for ischaemic outcomes, and two large meta-analyses found a significant association between DAT and the risk of stent thrombosis occurrence[103,104]. For this reason, when the ischaemic risk outweighs the bleeding risk, TAT can be extended up to 1 month after PCI in patients with CCS (Class IIa, Level of Evidence B) and ACS (Class IIa,

Table 3. Studies comparing other antithrombotic strategies versus a standard strategy in patients undergoing complex PCI.

Study - year	Complex PCI patients	ACS patients	Follow-up	Complex PCI criteria	Antithrombotic experimental regimen	Standard regimen	Results
CHAMPION PHOENIX trial[45] -2018	83.3% (9,037/10,854)	41.6% (4,518/10,854)	48 hours	≥1 of the following: long lesions, LM lesions, bifurcation lesions, thrombotic lesions, calcified lesions, multilesion PCI	Cangrelor (30 µg/kg i.v. bolus followed by a 4 µg/kg/min infusion i.v.)	Clopidogrel (loading dose of 600 mg or 300 mg)	Cangrelor reduced MACE within 48 hours after PCI in both CCS and ACS, compared to an LD of clopidogrel in ADP receptor inhibitor-naïve patients
COMPASS trial[84] -2020	38.0% (3,775/9,862)	0% (0/9,862)	24 months	Multivessel PCI (patients with previous PCI)	DPI with rivaroxaban (2.5 mg twice a day) and aspirin	Aspirin monotherapy	DPI reduced MACE and mortality compared with aspirin, but increased major bleeding in CCS patients with multivessel PCI
HOST REDUCE POLYTECH trial[76] -2022	31.0% (705/2,271)	100% (2,271/2,271)	12 months	≥1 of the following: ≥3 stents implanted, ≥3 lesions treated, bifurcation PCI, total stent length ≥60 mm, LM PCI, heavily calcified lesions	DAPT with prasugrel dose de-escalation (5 mg once a day) following 1-month DAPT with the conventional prasugrel dose	12-month DAPT with the conventional prasugrel dose (10 mg once a day)	Prasugrel dose de-escalation DAPT did not increase the risk of MACE, but decreased bleeding events compared with the conventional dose
HOST-EXAM trial[68] -2022	3% (152/4,717)	0% (0/4,717)	72 months*	1 of the following: 3 vessels treated, ≥3 stents implanted, ≥3 lesions treated, bifurcation with 2 stents implanted, total stent length >60 mm, CTO PCI	Clopidogrel monotherapy following 12±6 months of DAPT with clopidogrel	Aspirin monotherapy following 12±6 months of DAPT with clopidogrel	Clopidogrel monotherapy showed a lower risk of both thrombotic and bleeding events compared with aspirin monotherapy
TALOS-AMI trial[77] -2024	29.2% (788/2,697)[†‡]	100% (2,697/2,697)	12 months	≥1 of the following: history of DM or CKD, multivessel PCI, ≥3 lesions treated, total stent length >60 mm, ≥3 stents implanted, LM PCI, bifurcation with 2 stents implanted	11-month clopidogrel-based DAPT (aspirin and clopidogrel) following 1 month of ticagrelor-based DAPT (aspirin and ticagrelor)	12-month ticagrelor-based DAPT (aspirin and ticagrelor)	An unguided de-escalation strategy to clopidogrel-based DAPT reduced bleeding events without a significant difference in ischaemic outcomes, regardless of the presence of high ischaemic risk features
ALPHEUS trial[42] -2024	48.3% (910/1,866)	0% (0/1,866)	1 month	≥1 of the following: total stent length >60 mm, bifurcation with 2 stents implanted, LM PCI, bypass graft PCI, CTO PCI, use of atherectomy, multiple stents implanted	Ticagrelor-based DAPT (aspirin and ticagrelor)	Clopidogrel-based DAPT (aspirin and clopidogrel)	Ticagrelor-based DAPT did not reduce periprocedural MI and ischaemic events compared with clopidogrel in CCS patients undergoing complex PCI

*Median follow-up time: 5.8 years. †Complex PCI patients: 788; non-complex PCI patients: 1,909. ‡Information for the *post hoc* analysis of the TALOS-AMI trial refers to patients defined as at high ischaemic risk, which included those undergoing complex PCI, and having a history of diabetes mellitus or chronic kidney disease. ACS: acute coronary syndrome; ADP: adenosine diphosphate; CCS: chronic coronary syndrome; CKD: chronic kidney disease; CTO: chronic total occlusion; DAPT: dual antiplatelet therapy; DM: diabetes mellitus; DPI: dual pathway inhibition; LD: loading dose; LM: left main; MACE: major adverse cardiovascular events; MI: myocardial infarction; PCI: percutaneous coronary intervention

Level of Evidence C). ESC guidelines on both ACS and CCS provide several high ischaemic risk criteria for extended treatment with TAT that include complex PCI characteristics: diffuse multivessel disease, implantation of ≥3 stents, treatment of ≥3 lesions, total stent length >60 mm, bifurcation with two stents implanted, and treatment of a CTO[14,15]. Furthermore, European guidelines on ACS indicate that continuation with one antiplatelet agent (aspirin or clopidogrel) beyond 1 year after ACS may be considered for patients having high-risk features of stent-driven recurrent ischaemic events. A similar approach is endorsed by the North American consensus recommending long-term continuation of single antiplatelet therapy only for selected patients at high risk for ischaemic recurrence and low bleeding risk[14,105]. These recommendations should be interpreted, however, in view of recent trials showing a reduced risk of major bleeding with sole continuation of the OAC agent in the longstanding phase of coronary artery disease[106].

FUTURE PERSPECTIVES

As the landscape of antithrombotic therapy continues to evolve, several innovative agents and strategies are poised to enhance the outcomes of patients undergoing complex PCI. The development of subcutaneous, self-administered $P2Y_{12}$ inhibitors like selatogrel, currently being tested in the SOS-AMI trial (ClinicalTrials.gov: NCT04957719), and the novel subcutaneously administered GPI zalunfiban (RUC-4), being evaluated in the CELEBRATE trial (NCT04825743), represents a shift towards more accessible, rapid-acting therapies for acute MI, which may revolutionise early intervention for patients with complex coronary artery disease.

Tailored antithrombotic strategies are also being explored specifically for high-risk complex PCI populations, such as switching from ticagrelor- to clopidogrel-based DAPT at 6 months (TAILORED-CHIP; ClinicalTrials.gov: NCT03465644), utilising low-dose prasugrel or low-dose ticagrelor DAPT (E5TION; NCT04734353), prolonging DAPT with aspirin and prasugrel (ATTEMPT; NCT04014803), and comparing long-term clopidogrel and aspirin monotherapy (SMART-CHOICE3; NCT04418479). Additionally, the advent of factor XIa inhibitors promises to target residual thrombotic risk while decoupling haemostasis and thrombosis, mirroring the benefits of DPI, but with a potentially lower risk of bleeding. Among the factor XIa inhibitors in development, milvexian is currently being tested in the phase III LIBREXIA-ACS trial (NCT05754957), enrolling patients with ACS undergoing PCI[3]. As these novel strategies continue to be validated through clinical trials, they have the potential to transform the standard of care for complex PCI, offering more personalised, safer, and more effective treatment options for high-risk patients. Furthermore, these studies could be helpful to better define the profile and unique definition of patients undergoing complex PCI.

Conclusions

As complex PCI is associated with a higher ischaemic risk, adjunctive antithrombotic therapy plays a key role and should be part of the optimal revascularisation strategy. Some very high-risk patients may derive clinical benefit from extending DAPT beyond the period mandated by clinical guidelines, but bleeding risk status should always be considered in the decision. New strategies including early aspirin withdrawal followed by monotherapy with a potent $P2Y_{12}$ inhibitor or implementation of DPI have shown promising results and may be attractive strategies in this setting, particularly in patients at high bleeding or ischaemic risk, respectively. To summarise, in patients undergoing complex PCI, the evaluation of bleeding risk is pivotal: in patients with HBR features, ticagrelor or clopidogrel monotherapy, after a short course of DAPT, should be the antithrombotic strategy of choice; conversely, in patients without bleeding concerns, prolonged DAPT represents the gold standard antithrombotic therapy, even if $P2Y_{12}$ inhibitor monotherapy or DPI are promising strategies in this setting. Hence, we have proposed an algorithm to guide antithrombotic therapy strategies integrating bleeding risk and indication to oral anticoagulation after complex PCI **(Central illustration)**. However, a standardised definition of complex PCI is still lacking, which partly hampers the comparability of previous studies. Moreover, it is important to acknowledge that the available evidence on the safety and efficacy profiles of antithrombotic strategies in complex PCI, as well as in specific subsets, is derived from subgroup analyses of randomised trials, which might be underpowered to assess heterogeneity in the treatment effect between patients undergoing complex and non-complex PCI. Although the definition of complex PCI is increasingly becoming "prespecified" in trial protocols, the presence of subgroup phenomena can bias the interpretation of results. Finally, it is also important to recognise that some PCI criteria for complexity are unplanned or might not become evident upon PCI completion. Even if this aspect poses challenges, dedicated randomised trials for patients undergoing complex PCI are warranted to find the optimal antithrombotic strategy in this specific population and, in this way, optimise outcomes.

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Acknowledgements
D.S. Castiello, A. Oliva, G. Andò, G. Niccoli, and F. Pelliccia conceived and designed the project. R. Piccolo, E. Moscarella, R.A. Montone, F. Gragnano, and I. Porto supervised the project. P. Calabrò, S. De Rosa, E. Fabris, and G. Sinagra contributed to the acquisition, analysis and interpretation of data. D.S. Castiello, A. Oliva, and R. Piccolo drafted the manuscript. C.A.M. Spaccarotella, G. Esposito, C. Indolfi, and P.P. Filardi critically revised the manuscript for important intellectual content and the final approval of the version to be published. All authors have read and agreed to the published version of the manuscript.

Funding
This work is supported by a research grant from the Italian Ministry of Education (PRIN PNRR P2022RJS7X and PRIN 2022497RZ4 to R. P.).

Conflict of interest statement
The authors have no conflicts of interest to declare that could have appeared to influence the work reported in this paper.

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EuroIntervention
2025;21:e1069-e1080
published online e-edition September 2025
DOI: 10.4244/EIJ-D-25-00122

ORIGINAL RESEARCH

Optimal minimal stent area after crossover stenting in patients with unprotected left main coronary artery disease

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This paper also includes supplementary data published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-25-00122

ABSTRACT

BACKGROUND: Intracoronary imaging-guided percutaneous coronary intervention (PCI) has demonstrated clinical benefit over angiography-guided PCI for left main coronary artery (LM) disease. However, the optimal minimal stent area (MSA) thresholds to predict cardiovascular outcomes remain incompletely defined.

AIMS: This study aimed to evaluate intravascular ultrasound (IVUS)-measured segmental MSA after LM crossover stenting.

METHODS: We identified 829 consecutive patients who underwent IVUS-guided PCI for unprotected LM disease using a single-stent crossover technique. The final MSA was measured at the proximal LM, distal LM, and left anterior descending artery (LAD) ostium. The primary outcome was 5-year major adverse cardiac events (MACE), including all-cause death, myocardial infarction, and target lesion revascularisation.

RESULTS: The MSA cutoff values best predicting 5-year MACE were 11.4 mm² for the proximal LM (area under the curve [AUC] 0.62), 8.4 mm² for the distal LM (AUC 0.58), and 8.1 mm² for the LAD ostium (AUC 0.57). Based on these cutoff values, stent underexpansion in the proximal LM was significantly associated with increased risk of 5-year MACE (adjusted hazard ratio [HR] 2.34; $p<0.001$). Additionally, patients with simultaneous stent underexpansion in both the distal LM and LAD ostium exhibited a significantly higher risk of 5-year MACE compared with those having adequate expansion or only single-site underexpansion (adjusted HR 2.57; $p<0.001$).

CONCLUSIONS: Achieving sufficient stent expansion in the proximal LM and preventing underexpansion in both the distal LM and LAD ostium are critical for improving long-term clinical outcomes. The identified MSA thresholds may serve as practical benchmarks for stent optimisation during LM PCI.

KEYWORDS: crossover; intravascular ultrasound; left main; minimal stent area; stent underexpansion

SUBMITTED ON 03/02/2025 - REVISION RECEIVED ON 1st 09/04/2025 / 2nd 22/05/2025 - ACCEPTED ON 28/05/2025

The advantages of using intracoronary imaging guidance during percutaneous coronary intervention (PCI) are most evident when treating patients with high-risk lesions[1-3], particularly those with unprotected left main coronary artery (LM) disease, for which accumulating data suggest a mortality benefit over angiography guidance alone[4-6]. Current guidelines recommend the use of intravascular ultrasound (IVUS) during LM stenting to optimise PCI results by ensuring well-apposed and adequately expanded stents[7-9]. Although there is no standardised consensus on the definition of stent underexpansion[10], the minimal stent area (MSA) assessed via IVUS is considered the most reliable predictor of future adverse events in post-PCI patients[11-13]. However, the relationship between the MSA and cardiovascular outcomes in patients undergoing IVUS-guided PCI for unprotected LM disease has not been fully elucidated in the literature.

Previously, we proposed the "5-6-7-8" criteria for stent expansion in patients undergoing LM stenting to predict the risk of angiographic restenosis (i.e., soft endpoints)[14]. The study included a non-Western population that underwent either a single-stent (72%) or an upfront two-stent (28%) procedure. Recently, we revised these MSA criteria based on the 5-year clinical outcomes in patients undergoing upfront LM two-stenting using the crush technique[15]. The revised criteria suggested larger areas than previously proposed and showed similar MSA values to those from the Evaluation of XIENCE Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization (EXCEL) trial[16]. However, a knowledge gap remains regarding the optimal MSA threshold levels for LM PCI using a provisional one-stent strategy. Here, we investigated IVUS-derived segmental MSA cutoffs in patients who underwent LM crossover stenting to predict 5-year major adverse cardiac events (MACE).

Editorial, see page e1043

Impact on daily practice

This study established optimal minimal stent area thresholds for single-stent crossover in patients with unprotected left main coronary artery (LM) disease (proximal LM ≥11.4 mm², distal LM ≥8.4 mm², left anterior descending artery [LAD] ostium ≥8.1 mm²). To ensure favourable long-term outcomes in this high-risk patient population, adequate stent expansion in the proximal LM and avoidance of simultaneous underexpansion in both the distal LM and LAD ostium segments are essential. These results provide practical intravascular ultrasound-based optimisation targets for interventional cardiologists performing LM crossover stenting.

Methods

STUDY POPULATION

The study included all consecutive patients with unprotected LM disease – regardless of bifurcation involvement or lesion location – who underwent IVUS-guided PCI using a single-stent crossover technique from the LM to the left anterior descending artery (LAD) with drug-eluting stent (DES) implantation, at Asan Medical Center, Seoul, Republic of Korea, between March 2005 and December 2022. The exclusion criteria were as follows: (1) patients who required a second stent at the left circumflex artery (LCx) ostium; (2) patients who underwent crossover stenting from the LM to the LCx; (3) patients with a history of coronary artery bypass grafting (CABG); and (4) patients with in-stent restenosis lesions in the LM. All study participants underwent a final post-stenting IVUS pullback from the LAD. The study protocol was approved by the Ethics Committee of Asan Medical Center, and all patients provided their written informed consent to participate in the study.

STUDY PROCEDURE

Coronary lesion severity was evaluated by visual assessment performed by two experienced interventional cardiologists. Significant stenosis was defined as a diameter narrowing of ≥50%. The extent of disease at the LAD and LCx ostia was assessed using the Medina classification system.

PCI was performed according to current clinical practice guidelines. The use of adjunctive devices and pharmacological agents, such as cutting balloons and rotational atherectomy, was left to the operator's discretion. IVUS assessments prior to stent implantation were recommended. During the procedure, IVUS measurements guided the sizing of stents and the selection of post-dilation balloons. Additionally, repeated IVUS assessments during adjunctive post-dilation were recommended to ensure complete stent apposition and optimal expansion.

INTRAVASCULAR ULTRASOUND ANALYSIS

The final post-stenting IVUS imaging and offline IVUS analyses were performed as previously described[14,15]. The final MSA within the prespecified segments was assessed, including the LAD ostium (5 mm distal to the carina), distal LM segment (5 mm proximal to the carina), and proximal LM (proximal segment of the stent). The cross-sectional area of the external elastic membrane at the MSA site was measured using two-dimensional planimetry and defined as the vessel area. The stent expansion index was defined as the MSA divided by the vessel area[10].

STUDY OUTCOMES

The primary outcome was 5-year MACE, defined as a composite of all-cause death, target lesion-related myocardial infarction

Abbreviations

DES	drug-eluting stent
IVUS	intravascular ultrasound
LAD	left anterior descending artery
LCx	left circumflex artery
LM	left main coronary artery
MACE	major adverse cardiac events
MI	myocardial infarction
MSA	minimal stent area
PCI	percutaneous coronary intervention
TLR	target lesion revascularisation

(MI), and clinically driven target lesion revascularisation (TLR). Cardiovascular death and the individual components of the primary outcome comprised the secondary outcomes. Unless an incontrovertible non-cardiovascular cause was identified, all deaths were classified as cardiovascular deaths. MI was defined as elevated cardiac biomarker levels with concomitant ischaemic symptoms or signs and was supported by documentation from non-invasive (electrocardiography or imaging) or invasive (coronary angiography) examinations. Events not related to the index PCI but attributable to the target lesion (i.e., the LM ostial, shaft, or bifurcation segments) were classified as target lesion-related MI. LM-related TLR was defined as revascularisation for LM restenosis, involving the proximal or distal segments (within 5 mm) adjacent to the LM-to-LAD stent and the LCx ostium (within 5 mm distal to the carina). Isolated in-stent restenosis in the distal segments without ostial LAD involvement was not considered LM-related TLR. Any surgical revascularisation for LM restenosis was also classified as TLR.

Follow-up evaluations were performed at 1, 6, and 12 months post-PCI, and then annually through in-office visits or telephone calls. Clinical data were gathered from the prospective ASAN-MAIN registry by independent personnel at the Clinical Research Center, Asan Medical Center, Seoul, Republic of Korea, using a prespecified electronic case report form. All clinical outcomes of interest were validated using the collected source documentation and adjudicated by an independent group of clinicians who were blinded to both the initial PCI procedures and post-stenting IVUS images.

STATISTICAL ANALYSIS

Categorical data are shown as counts and percentages, whereas continuous variables are presented as means and standard deviations or medians and interquartile ranges (IQRs), as deemed suitable. Group comparisons were conducted using either a parametric unpaired t-test or a non-parametric Mann-Whitney U test for continuous variables. Categorical variables were compared using either the χ^2 test or Fisher's exact test. The optimal cutoff values for the final MSA that accurately predicted the primary outcome were obtained by examining time-dependent receiver operating characteristic curves. A restricted cubic spline curve was generated to analyse the correlation between the MSA within each segment, treated as a continuous variable, and the unadjusted risk of the primary outcome. Cumulative occurrences were calculated using the Kaplan-Meier method and compared using log-rank tests.

Additionally, a Cox proportional hazards model analysis was performed to obtain the hazard ratio (HR) and 95% confidence intervals (CIs) for each study outcome. Patients were censored either at the time of the incident or on the date of the last follow-up, up to 5 years after the index PCI. The Schoenfeld residuals test validated the proportional hazards assumption, with no significant violations detected. Model 1 was adjusted for age, body mass index, body surface area, diabetes mellitus, chronic kidney disease, peripheral artery disease, and a left ventricular ejection fraction (LVEF) ≤50%. Model 2 included all covariates from model 1, with simultaneous adjustment for both MSA and the stent expansion index within each specific segment separately. Model 3 included all covariates from model 1, with concurrent adjustment for MSA from all three segments together, without considering the stent expansion index. Model 4 included all covariates from model 1, with additional adjustment for underexpansion in the proximal LM and underexpansion in both the distal LM and LAD ostium. Continuous variables (age, body mass index, body surface area, and MSA measurements) were standardised using Z-score transformation to calculate standardised HRs, representing the effect of a 1-standard deviation increase in each variable. None of these variables exhibited multicollinearity in the variance inflation factor analysis. Statistical analyses were conducted using R statistical software, version 4.4.2 (R Foundation for Statistical Computing). Two-sided results were considered statistically significant at a significance level of $p<0.05$.

Results

The data supporting the findings of this study are available from the corresponding author upon request.

STUDY POPULATION

A total of 879 patients underwent IVUS-guided PCI for unprotected LM disease using a provisional one-stent strategy at Asan Medical Center between March 2005 and December 2022. Of these, 50 patients who required a second stent in the LCx ostium were excluded. Consequently, 829 patients who underwent a single-stent LM-to-LAD crossover and had complete post-stenting IVUS images from the LAD pullback were included in the final analysis **(Supplementary Figure 1)**.

The clinical characteristics of the study population are summarised in **Table 1**. The mean age of the overall population was 64.2±10.2 years. Among the patients, 79.0% were male, and 37.9% had acute coronary syndrome as the clinical indication for the index PCI. The mean LVEF was 60.0±7.7%, with 7.6% of patients having an LVEF ≤50%. Coronary angiography revealed the extent of disease as follows: 3.4% LM only, 35.5% LM with 1-vessel disease, 34.9% LM with 2-vessel disease, and 26.3% LM with 3-vessel disease. The LM lesion was located in the ostium or midshaft in 26.9% of cases and at the distal bifurcation in 73.1%. The majority of patients (75.9%) had Medina 1,1,0 lesions, while angiographically significant LCx ostial involvement was identified in 19.9% of cases. Right coronary artery disease was present in 45.5% of patients.

When comparing patients with and without MACE at 5-year follow-up, significant differences were noted in several parameters. Patients with MACE were older, had a lower body mass index, and had a lower body surface area. They also had a higher incidence of comorbidities, including heart failure, cerebrovascular accidents, peripheral artery disease, chronic kidney disease, and atrial fibrillation. Additionally, the mean LVEF was lower in patients with MACE, with a higher proportion exhibiting an LVEF ≤50%.

PROCEDURAL CHARACTERISTICS

The procedural characteristics of the study population are summarised in **Table 2**. An intra-aortic balloon pump or extracorporeal membrane oxygenation was used in 2.3%

Table 1. Clinical characteristics.

Characteristics	Overall population (N=829)	Major adverse cardiac events		*p*-value
		No (N=722)	Yes (N=107)	
Demographics				
Age, years	64.2±10.2	63.4±9.9	69.8±10.3	<0.001
Male sex	655 (79.0)	574 (79.5)	81 (75.7)	0.439
BMI, kg/m²	24.5±3.0	24.6±3.0	23.6±2.6	0.001
BSA*, m²	1.72±0.2	1.72±0.2	1.67±0.2	0.001
Acute coronary syndrome	306 (37.9)	256 (36.6)	50 (46.7)	0.056
Medical history				
Current smoker	196 (23.6)	179 (24.8)	17 (15.9)	0.098
Hypertension	577 (69.6)	492 (68.1)	85 (79.4)	0.024
Diabetes	295 (35.6)	248 (34.3)	47 (43.9)	0.068
Dyslipidaemia	627 (75.6)	549 (76.0)	78 (72.9)	0.558
History of MI	54 (6.5)	42 (5.8)	12 (11.2)	0.057
History of PCI	137 (16.5)	112 (15.5)	25 (23.4)	0.057
History of HF	18 (2.2)	9 (1.2)	9 (8.4)	<0.001
History of CVA	59 (7.1)	41 (5.7)	18 (16.8)	<0.001
History of PAD	41 (4.9)	24 (3.3)	17 (15.9)	<0.001
Chronic kidney disease	31 (3.7)	11 (1.5)	20 (18.7)	<0.001
Chronic lung disease	14 (1.7)	12 (1.7)	2 (1.9)	1.000
Atrial fibrillation	11 (1.3)	7 (1.0)	4 (3.7)	0.058
Echocardiography				
LVEF, %	60.0±7.7	60.7±6.8	55.2±11.3	<0.001
LVEF ≤50%	63 (7.6)	42 (5.8)	21 (19.6)	<0.001
Coronary angiography				
Disease extent				0.016
LM only	28 (3.4)	27 (3.7)	1 (0.9)	
LM with 1-vessel disease	294 (35.5)	265 (36.7)	29 (27.1)	
LM with 2-vessel disease	289 (34.9)	252 (34.9)	37 (34.6)	
LM with 3-vessel disease	218 (26.3)	178 (24.7)	40 (37.4)	
LM lesion location				0.182
Ostium or midshaft	223 (26.9)	188 (26.0)	35 (32.7)	
Distal bifurcation	606 (73.1)	534 (74.0)	72 (67.3)	
Medina classification				0.332
1,1,1	165 (19.9)	137 (19.0)	28 (26.2)	
1,1,0	629 (75.9)	554 (76.7)	75 (70.1)	
1,0,0	32 (3.9)	28 (3.9)	4 (3.7)	
0,1,0	3 (0.4)	3 (0.4)	0 (0)	
Right CAD	377 (45.5)	315 (43.6)	62 (57.9)	0.008

Values are presented as numbers (percentages) or means±standard deviation. *BSA was calculated using the Mosteller formula. BMI: body mass index; BSA: body surface area; CAD: coronary artery disease; CVA: cerebrovascular accident; HF: heart failure; LM: left main coronary artery; LVEF: left ventricular ejection fraction; MI: myocardial infarction; PAD: peripheral artery disease; PCI: percutaneous coronary intervention

of the study population. Direct stenting was performed in 21.4% of cases. The mean total number of stents used per patient was 2.0±1.2, and the mean total length of stents was 50.8±29.6 mm. For LM stenting, the mean stent diameter was 3.6±0.4 mm, and the mean stent length was 27.2±7.3 mm. Final kissing balloon inflation was performed in 11.4% of procedures. Regarding the type of DES used, 15.2% were first-generation stents, and 84.8% were second- or newer-generation stents.

POST-STENTING MINIMAL STENT AREA AND CLINICAL OUTCOMES

The mean MSA was 11.9±2.5 mm² in the proximal LM, 10.1±2.2 mm² in the distal LM, and 8.7±1.9 mm² at the

Table 2. Procedural characteristics.

Characteristics (N=829)	Overall population	Major adverse cardiac events		*p*-value
		No (N=722)	Yes (N=107)	
Use of IABP or ECMO	19 (2.3)	12 (1.7)	7 (6.5)	0.005
Direct stenting	141 (21.4)	124 (21.5)	17 (20.5)	0.947
Total stent number (per patient)	2.04±1.2	2.04±1.1	2.07±1.2	0.756
Total length of stents, mm	50.8±29.6	50.8±29.5	51.2±30.3	0.898
LM-to-LAD crossover stent				
Stent diameter, mm	3.62±0.4	3.63±0.4	3.58±0.3	0.217
Length of stents, mm	27.2±7.3	27.1±7.4	27.6±7.0	0.535
Final kissing balloon inflation	94 (11.4)	86 (12.0)	8 (7.5)	0.229
Drug-eluting stent type				0.826
First-generation	126 (15.2)	111 (15.4)	15 (14.0)	
Second- or newer-generation	703 (84.8)	611 (84.6)	92 (86.0)	

Values are presented as numbers (percentages) or means±standard deviation. ECMO: extracorporeal membrane oxygenation; IABP: intra-aortic balloon pump; LAD: left anterior descending artery; LM: left main coronary artery

LAD ostium in the overall population **(Supplementary Table 1)**. **Supplementary Figure 2** illustrates the final MSA distribution within each segment, along with the corresponding median values and IQRs. To predict 5-year MACE, the MSA cutoff value for each segment was 11.4 mm² for the proximal LM (area under the curve [AUC] 0.62), 8.4 mm² for the distal LM (AUC 0.58), and 8.1 mm² for the LAD ostium (AUC 0.57) **(Supplementary Figure 3)**. Using these MSA criteria, 46.2%, 19.2%, and 41.1% of the patients had stent underexpansion in the proximal LM (<11.4 mm²), distal LM (<8.4 mm²), and LAD ostium (<8.1 mm²), respectively.

The primary and secondary outcomes at 5 years are summarised in **Table 3** and **Supplementary Table 2**. The median follow-up was 5.7 years (IQR 4.2-9.3 years). The primary outcome, MACE at 5 years, was observed in 107 patients when only the first event was counted in patients with multiple events. A gradual linear relationship between the unadjusted risk of 5-year MACE and the MSA within each segment was evident using the spline regression model **(Supplementary Figure 4)**. **Figure 1** illustrates the cumulative incidence of MACE and all-cause death according to stent underexpansion within each segment. Compared with patients with adequate stent expansion, those with underexpansion in the proximal LM showed increased risks of 5-year MACE (log-rank p<0.001) and all-cause death (log-rank p=0.013).

Patients with stent underexpansion in both the distal LM and LAD ostium (group 2) showed the highest rate of 5-year MACE (24.2%) compared with those who had stent underexpansion in either the distal LM or LAD ostium (group 1) and those who had no underexpanded segments in either the distal LM or LAD ostium (group 0) **(Central illustration)**. Compared with group 0, group 2 demonstrated significantly increased risks of 5-year MACE (adjusted HR 2.34; p<0.001) **(Figure 2A)**, all-cause death (adjusted HR 1.81; p=0.04) **(Figure 2B)**, and clinically driven TLR (adjusted HR 4.30; p<0.001) **(Figure 2C)**.

Of the 33 patients who underwent clinically driven TLR (at a median of 450 days), 2 patients required CABG, while the remaining 31 patients underwent PCI with DES implantation (n=22), drug-coated balloon (DCB; n=8), or thrombus aspiration for acute stent thrombosis in the LM shaft (n=1). Among these TLR cases, 26 involved ostial LCx stenosis. Of these, 19 presented as isolated LCx stenosis with a patent crossover stent. In this subset, 5 were treated with a DCB, and 14 received DES implantation in the LCx ostium using two-stent techniques (reverse crush, n=9; T and protrusion, n=5).

Table 3. Clinical outcomes at 5 years according to stent underexpansion in the proximal LM.

	Overall population (N=829)	Proximal LM MSA ≥11.4 mm² (N=446)	Proximal LM MSA <11.4 mm² (N=383)	*p*-value
Primary outcome: MACE†	107 (12.9)	39 (8.7)	68 (17.8)	<0.001
Secondary outcomes				
All-cause death	75 (9.0)	30 (6.7)	45 (11.7)	0.017
Cardiovascular death	53 (6.4)	20 (4.5)	33 (8.6)	0.022
LM-related MI	3 (0.4)	0 (0)	3 (0.8)	0.196
LM-related TLR	33 (4.0)	9 (2.0)	24 (6.3)	0.003

Values are presented as numbers (percentage). The percentages presented in the table may differ from cumulative incidence estimates derived by the Kaplan-Meier method. †MACE was defined as a composite of all-cause death, LM-related MI, and clinically driven LM-related TLR. LM: left main coronary artery; MACE: major adverse cardiac events; MI: myocardial infarction; MSA: minimal stent area; TLR: target lesion revascularisation

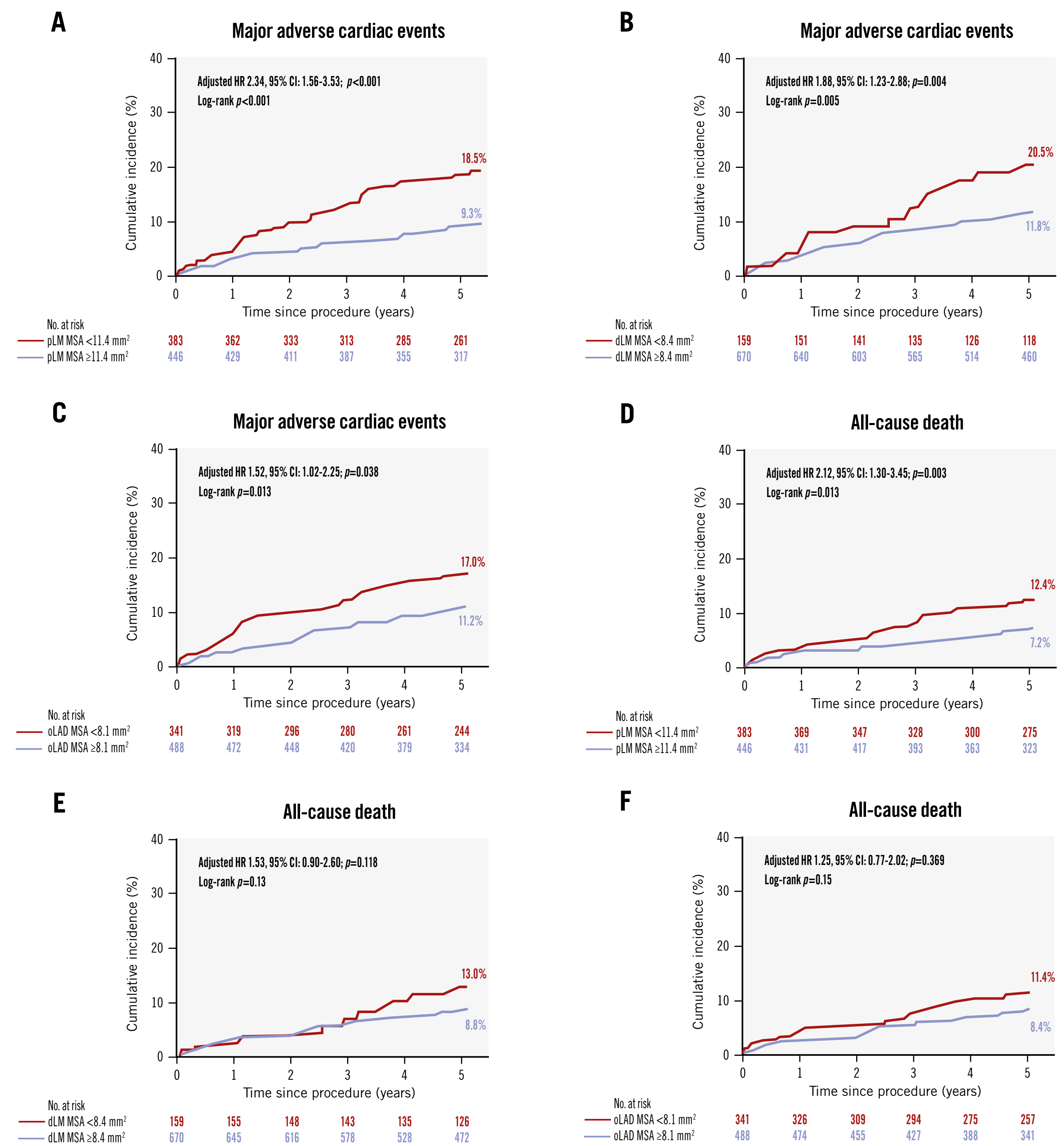
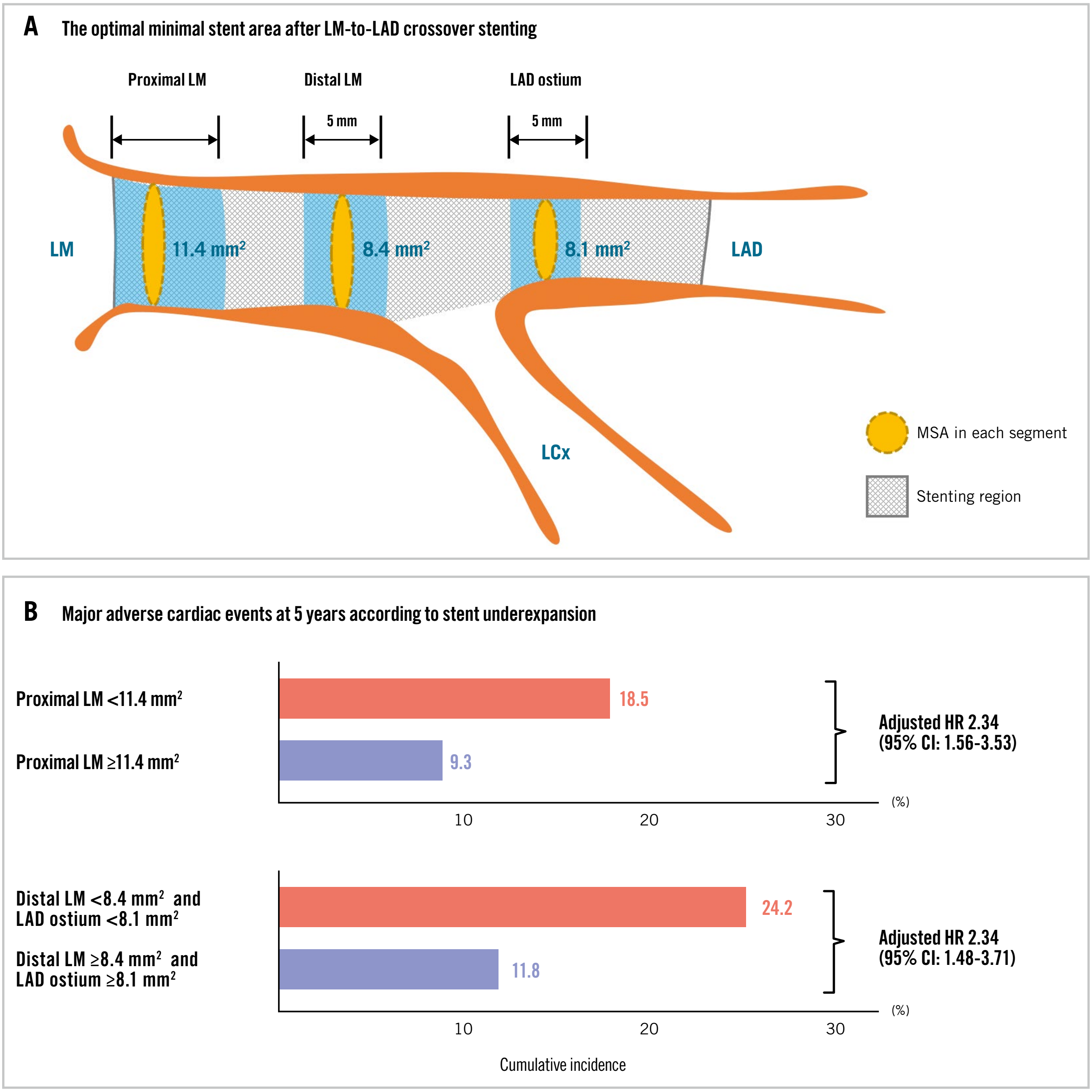


Figure 1. *Cumulative incidences of major adverse cardiac events and all-cause death. The cumulative incidences of 5-year MACE according to the optimal MSA cutoff within the proximal LM (A), distal LM (B), and LAD ostium (C) are shown. The cumulative incidences of 5-year all-cause death according to the optimal MSA cutoff within the proximal LM (D), distal LM (E), and LAD ostium (F) are shown. CI: confidence interval; dLM: distal left main coronary artery; HR: hazard ratio; LAD: left anterior descending artery; LM: left main coronary artery; MACE: major adverse cardiac events; MSA: minimal stent area; oLAD: ostial left anterior descending artery; pLM: proximal left main coronary artery*

The multivariable-adjusted independent predictors of the primary outcome are shown in **Table 4**. Model 1 represents values adjusted individually for each variable while controlling for clinical covariates. Model 2 included three segment-specific models (for proximal LM, distal LM, and LAD ostium, respectively), each incorporating both MSA and stent expansion index. In all three models, the stent expansion index failed to show independent prognostic significance. Model 3, which adjusted concurrently for MSA values from all three segments, identified only MSA within the proximal LM as

EuroIntervention Central **Illustration**

Optimal minimal stent area after left main crossover stenting and 5-year MACE.



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A) The optimal minimal stent area cutoff values for each segment were 11.4 mm² for the proximal LM, 8.4 mm² for the distal LM, and 8.1 mm² for the LAD ostium. B) The cumulative incidences of 5-year major adverse cardiac events (MACE) according to stent underexpansion in the proximal LM, distal LM, and LAD ostium are shown. The hazard ratio was adjusted for age, body mass index, body surface area, diabetes mellitus, chronic kidney disease, peripheral artery disease, and a left ventricular ejection fraction ≤50%. CI: confidence interval; HR: hazard ratio; LAD: left anterior descending artery; LCx: left circumflex artery; LM: left main coronary artery; MSA: minimal stent area

a significant prognostic factor (p=0.003); the MSAs within the distal LM and LAD ostium were not significant. In Model 4, underexpansion in the proximal LM and underexpansion in both the distal LM and LAD ostium were simultaneously included. Both remained independent predictors of 5-year MACE (adjusted HRs 1.93 and 1.94, respectively).

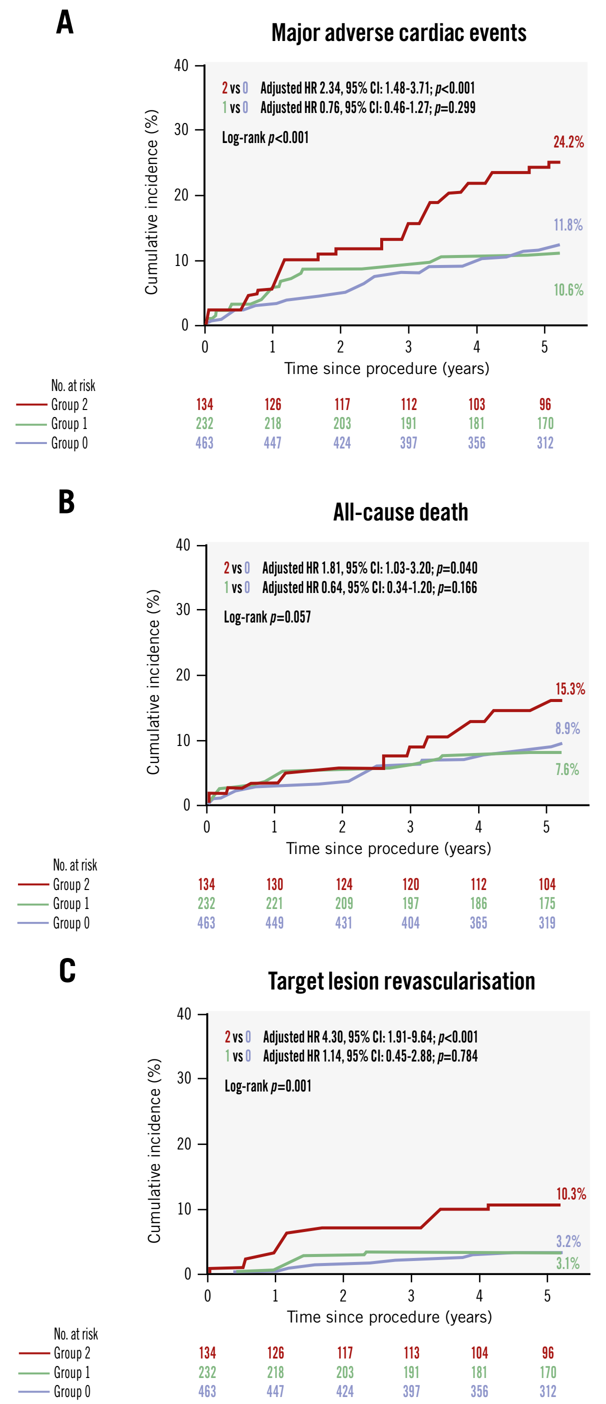

Figure 2. *Cumulative incidences of major adverse cardiac events and its components. The cumulative incidences of 5-year MACE (A), all-cause death (B), and clinically driven target lesion revascularisation (C) in patients with stent underexpansion in both the distal LM and LAD ostium (group 2) are shown compared with those who had stent underexpansion in either the distal LM or LAD ostium (group 1) and those who had no underexpanded segments in either the distal LM or LAD ostium (group 0).*
CI: confidence interval; HR: hazard ratio; LAD: left anterior descending artery; LM: left main coronary artery; MACE: major adverse cardiac events

ADDITIONAL ANALYSIS

The cumulative incidence of 5-year MACE was similar between patients with second- or newer-generation (13.9%) and first-generation DES implantation (11.9%; log-rank p=0.53). Postprocedural IVUS analysis revealed comparable MSAs within the proximal and distal LM between DES subgroups **(Supplementary Table 3)**. Among patients with second- or newer-generation DES implantation (n=703), the proximal LM MSA was significantly associated with 5-year MACE (p=0.003), while the MSA values within the distal LM and LAD ostium did not show significant associations **(Supplementary Table 4)**. In Model 2, when both MSA and the stent expansion index were incorporated into the same statistical model, the stent expansion index showed no independent predictive value for 5-year MACE.

Preintervention IVUS imaging was available for 254 patients (30.6%), while a post-stenting IVUS pullback from the LCx was available in only 47 patients. The pre-stenting IVUS findings are described in **Supplementary Table 5**. The minimal luminal area in the LCx ostium was significantly smaller in patients with 5-year MACE compared with those without MACE (4.4±1.8 mm² vs 5.5±2.8 mm²; p=0.006). In addition, plaque burden in the LCx ostium was significantly greater in patients with MACE (58% vs 52%; p=0.027).

Discussion

This study evaluated IVUS-derived MSA criteria for optimal stent expansion based on 5-year adverse events in patients who underwent PCI using a single-stent crossover technique for unprotected LM disease. We found that the final MSA values within the proximal LM (<11.4 mm²), distal LM (<8.4 mm²), and LAD ostium (<8.1 mm²) were significantly associated with the risk of 5-year MACE. When concurrently adjusted for MSA values from all three segments, only the MSA within the proximal LM was independently associated with the adjusted risk of 5-year MACE, whereas the MSA values in the distal LM and LAD ostium were not predictive of long-term outcomes. Furthermore, patients with stent underexpansion in both the distal LM and LAD ostium exhibited a significantly higher incidence of 5-year MACE compared with those who had either no underexpanded segments or underexpansion in only one of these segments.

LM disease, characterised by a large, jeopardised myocardium, exhibits distinct anatomical and pathophysiological characteristics, including diffuse involvement and positive remodelling[17,18]. Conventional angiographic assessment of LM lesions is fundamentally limited by its two-dimensional nature; therefore, current guidelines recommend IVUS for the evaluation of LM lesion severity[7,8]. IVUS guidance provides valuable anatomical information for preprocedural planning and enables detection of potential complications during and after stent deployment, including stent underexpansion, incomplete apposition, edge dissection, and significant residual disease[19,20]. Several observational studies and randomised trials with limited sample sizes support the benefit of intracoronary imaging, especially IVUS, in improving clinical outcomes in LM stenting[4-6,21-23]. However, standardised IVUS-guided optimisation protocols and criteria for LM stenting have not yet been specified, and the prognostic significance of the LM MSA as a predictor of long-term cardiovascular outcomes remains unclear[24].

Recently, an IVUS subgroup analysis of the Nordic-Baltic-British Left Main Revascularization (NOBLE) trial including 224 patients (single-stent crossover: 67.4%) showed that the final LM MSA (12.5±3.0 mm^2) was negatively associated with the TLR rate at 5 years, but not with the harder clinical endpoints[25]. Subgroup analysis of the EXCEL trial comprising 504 patients showed that the final LM MSA was 9.9±2.3 mm^2 and that the smallest tertile of the LM MSA was associated with a higher rate of the composite outcome (all-cause death, MI, and stroke at 3 years) than the largest tertile[16]. Similarly, another study proposed IVUS-guided LM optimisation criteria using relative stent expansion (MSA >90% of the reference lumen) and found that patients with a median LM MSA of 11.8 mm^2 (n=124, single-stent crossover: 85.5%) exhibited a lower incidence of composite outcomes (cardiac death, MI, and TLR at 1 year) than those guided by angiography alone[26].

Our study exclusively included patients (n=829) who underwent single-stent crossover with a complete final IVUS pullback from the LAD. The distribution of the proximal LM MSA (median 11.6 mm^2) and distal LM MSA (median 9.9 mm^2) in our study was comparable to those of previous studies[15,16,25-27]. A smaller final MSA might reflect an anatomically smaller vessel size rather than stent underexpansion. However, when comparing patients who had MACE with those who did not, the vessel area was equivalent in both groups. The stent expansion index was much lower in patients who had MACE, indicating that the stented LM segment was not adequately expanded. Interestingly, when both the MSA and the stent expansion index were simultaneously adjusted for within each segment, only MSA remained a significant predictor of clinical outcomes **(Table 4)**. Accordingly, stent underexpansion in our analysis was defined solely based on absolute MSA values within each segment, without incorporating relative expansion indices. Indeed, a lower stent expansion index does not necessarily indicate true underexpansion, particularly in vessels with significant plaque burden and positive remodelling. This highlights the value of absolute MSA as a practical procedural target in IVUS-guided LM PCI.

Due to the modest AUC values, the MSA in either the distal LM alone or LAD ostium alone was not predictive of 5-year MACE after adjustment with the proximal LM MSA **(Table 4)**. The observed limitation in predictive accuracy likely reflects that MSA assessment of either the distal LM alone or the LAD ostium alone fails to encompass adverse events originating from the LCx ostium. However, underexpansion in both the distal LM and LAD ostium was a significant predictor, as was underexpansion in the proximal LM **(Table 4)**. These

Table 4. Multivariable Cox proportional hazards model analysis for 5-year major adverse cardiac events.

Variables	Model 1		Model 2		Model 3		Model 4	
	Adjusted HR (95% CI)	*p*-value	Adjusted HR (95% CI)	*p*-value	Adjusted HR (95% CI)	*p*-value	Adjusted HR (95% CI)	*p*-value
Proximal LM, MSA*	0.61 (0.49-0.77)	<0.001	0.68 (0.52-0.88)	0.004	0.60 (0.43-0.84)	0.003		
Proximal LM, stent expansion index*	0.68 (0.55-0.85)	<0.001	0.83 (0.65-1.07)	0.154				
Proximal LM, underexpansion	2.34 (1.56-3.53)	<0.001					1.93 (1.24-2.99)	0.003
Distal LM, MSA*	0.73 (0.59-0.91)	0.006	0.71 (0.55-0.93)	0.011	1.03 (0.74-1.44)	0.859		
Distal LM, stent expansion index*	0.87 (0.70-1.08)	0.210	1.05 (0.82-1.35)	0.700				
Distal LM, underexpansion	1.88 (1.23-2.88)	0.004						
LAD ostium, MSA*	0.79 (0.64-0.98)	0.030	0.78 (0.61-1.00)	0.052	0.99 (0.76-1.30)	0.954		
LAD ostium, stent expansion index*	0.90 (0.74-1.09)	0.297	1.02 (0.81-1.29)	0.841				
LAD ostium, underexpansion	1.52 (1.02-2.25)	0.038						
Underexpansion in both the distal LM and LAD ostium	2.57 (1.67-3.95)	<0.001					1.94 (1.22-3.09)	0.005

*Continuous variables were standardised using Z-score transformation, resulting in standardised hazard ratios that represent the effect of a 1-standard deviation increase in each variable. Model 1 was adjusted for age, body mass index, body surface area, diabetes mellitus, chronic kidney disease, peripheral artery disease, and an LVEF ≤50%. Model 2 included all covariates from model 1, with simultaneous adjustment for both the MSA and stent expansion index within each specific segment separately (proximal LM, distal LM, and LAD ostium). Model 3 included all covariates from model 1, with concurrent adjustment for the MSA from all three segments together in the same model, without considering the stent expansion index. Model 4 included all covariates from model 1, with additional adjustment for underexpansion in the proximal LM and underexpansion in both the distal LM and LAD ostium. Stent underexpansion was defined as a final MSA value of <11.4 mm^2 in the proximal LM, <8.4 mm^2 in the distal LM, and <8.1 mm^2 in the LAD ostium. CI: confidence interval; HR: hazard ratio; LAD: left anterior descending artery; LM: left main coronary artery; LVEF: left ventricular ejection fraction; MSA: minimal stent area findings suggest that avoiding stent underexpansion through IVUS guidance can directly improve clinical outcomes during LM PCI. In fact, the use of intracoronary imaging guidance has led to the selection of larger stent sizes and superior stent expansion, primarily due to the use of non-compliant balloons for postadjunctive dilatation with high-pressure inflation[1,5,28-31]. In a prospective application of contemporary optimisation criteria for LM lesions (MSA >7 mm^2 for the distal segment and >8 mm^2 for the proximal segment)[32], the intracoronary imaging-guided LM PCI group (60.1% of whom achieved optimisation) had a significantly lower risk of composite cardiovascular events than the angiography-guided LM PCI group[5].

Limitations

This study has certain limitations. First, the prospective observational design may have led to a selection bias and unmeasured confounding factors. Although randomised controlled trials are considered the gold standard of evidence, they are only feasible for a selected subset of patients treated for LM disease; therefore, evidence from all-comers registries remains essential, and our findings should be interpreted with caution. Second, our study did not examine whether intracoronary imaging could identify distal LM lesions better suited to a two-stent approach rather than the standard provisional strategy. The necessity for bailout implantation of a second stent arises in up to 22% of LM bifurcation lesions initially treated with a stepwise provisional technique[27,33]. Future research should focus on identifying lesion characteristics predictive of the need for LCx ostial stenting, thereby improving procedural planning and efficiency. Third, this analysis from a single tertiary centre, which performs a high volume of LM stenting procedures[34], limits the generalisability of our findings. Additional randomised studies in diverse clinical settings are needed for validation.

Conclusions

This study evaluated the IVUS-derived segmental MSA cutoffs in patients undergoing LM-to-LAD crossover stenting for unprotected LM disease. Achieving optimal stent expansion in the proximal LM and preventing underexpansion in both the distal LM and LAD ostium are critical for improving long-term clinical outcomes. The optimal MSA thresholds identified herein may serve as practical benchmarks for stent optimisation during LM PCI.

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Funding

This work was supported by the Korea Medical Device Development Fund grant funded by the government of the Republic of Korea (the Ministry of Science and ICT; the Ministry of Trade, Industry and Energy; the Ministry of Health & Welfare; the Ministry of Food and Drug Safety; Project Number: 2710000054, RS-2022-00141289).

Conflict of interest statement

The authors have no conflicts of interest relevant to the contents of this study to declare.

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Supplementary data

Supplementary Table 1. Post-stenting IVUS findings within each segment.

Supplementary Table 2. Incidence of primary and secondary outcomes at 5 years.

Supplementary Table 3. Post-stenting IVUS findings according to the type of DES.

Supplementary Table 4. Multivariable Cox proportional hazards model in patients with second- or newer-generation DES implantation.

Supplementary Table 5. Pre-stenting IVUS findings within each segment.

Supplementary Figure 1. Flowchart of the study population.

Supplementary Figure 2. Cumulative frequency of minimal stent area.

Supplementary Figure 3. The optimal cutoff value for IVUS-measured MSA that best predicts the occurrence of 5-year MACE.

Supplementary Figure 4. The association of IVUS-measured MSA with the risk of MACE at 5 years.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-25-00122

EuroIntervention
2025;21:e1081-e1089
published online e-edition September 2025
DOI: 10.4244/EIJ-D-24-01066

ORIGINAL RESEARCH

VARC-HBR criteria validation in TAVI patients on oral anticoagulation

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This paper also includes supplementary data published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-24-01066

ABSTRACT

BACKGROUND: Bleeding remains a frequent complication after transcatheter aortic valve implantation (TAVI). Recently, the Valve Academic Research Consortium High Bleeding Risk (VARC-HBR) criteria were introduced to identify patients at (very) high risk of bleeding.

AIMS: This study aimed to evaluate the validity of the VARC-HBR criteria for predicting bleeding risk in TAVI patients and to compare its performance with other existing criteria.

METHODS: Data were obtained from the POPular PAUSE TAVI trial, a randomised clinical trial that evaluated the safety and efficacy of continuation versus interruption of oral anticoagulation during TAVI. Major and minor bleeding risk criteria were identified at baseline, and bleeding events were recorded up to 30 days after TAVI. Patients were classified into three groups: those with ≤1 minor criterion (moderate risk), those with 1 major or 2 minor criteria (high risk), and those with ≥2 major or ≥3 minor criteria (very high risk).

RESULTS: A total of 856 patients were included: 332 (39%) were classified at moderate bleeding risk, 337 (39%) at high bleeding risk, and 187 (22%) at very high bleeding risk. Major bleeding occurred in 4.2% of moderate-risk patients, 9.5% in the high-risk group, and 15.0% in the very high-risk group ($p<0.001$). Receiver operating characteristic analysis showed moderate discriminative performance (area under the curve=0.64, 95% confidence interval: 0.58-0.70). Despite higher-than-expected event rates, the VARC-HBR criteria demonstrated good calibration with observed outcomes.

CONCLUSIONS: The VARC-HBR criteria effectively identified distinct subgroups with a stepwise increase in major bleeding post-TAVI. However, their predictive performance for individual risk was moderate.

KEYWORDS: bleeding risk; high bleeding risk; oral anticoagulation; TAVI; VARC-HBR criteria

SUBMITTED ON 19/11/2024 - REVISION RECEIVED ON 1st 23/01/2025 / 2nd 25/02/2025 - ACCEPTED ON 25/02/2025

Transcatheter aortic valve implantation (TAVI) is a well-established treatment for patients with symptomatic severe aortic stenosis[1]. Despite numerous technical advancements in recent years, procedure-related bleeding complications remain frequent[2]. This is particularly true in patients with a concomitant indication for oral anticoagulation, who represent about 35% of the current TAVI population[3]. Major bleeding occurs in 3-10% of patients and has been associated with up to a threefold increase in mortality[2,4]. It is also associated with reduced mental and physical quality of life, longer hospitalisation and higher healthcare costs[5]. To anticipate and potentially avoid these events, preprocedural bleeding risk assessment has been recommended to guide preventive strategies[4,6]. As standardised bleeding risk criteria for patients with valvular heart disease were limited, the Valve Academic Research Consortium High Bleeding Risk (VARC-HBR) criteria were recently introduced[7]. Twenty-one clinical, anatomical, and procedural factors were combined, weighted as 15 major and 6 minor criteria. These criteria were developed based on expert consensus; hence, they require empirical validation to substantiate their use in clinical practice. Therefore, we evaluated the VARC-HBR criteria for risk stratification and prediction of 30-day major bleeding risk in patients undergoing TAVI with a concomitant indication for oral anticoagulation.

Editorial, see page e1045

Impact on daily practice

The Valve Academic Research Consortium High Bleeding Risk (VARC-HBR) criteria effectively identify three distinct subgroups of patients with a stepwise increase in major bleeding risk after transcatheter aortic valve implantation. Applying these criteria in clinical practice may help select subgroups of patients who could benefit most from precautionary measures for access site management (e.g., radial secondary access, heparin reversal with protamine, and the use of an additional closure device). Given the significant association with bleeding, alternative approaches could be considered for patients with severe calcification or tortuosity of the iliofemoral arteries. For individual risk prediction, the discriminative performance observed in our data was moderate but outperformed other bleeding scores. While moderate, the VARC-HBR performs comparably to other bleeding scores, for example in studies evaluating the Academic Research Consortium High Bleeding Risk criteria in patients undergoing percutaneous coronary intervention.

Methods

STUDY DESIGN

This study is a subanalysis of the POPular PAUSE TAVI (ClinicalTrials.gov: NCT04437303) trial, a randomised clinical trial, conducted at 22 European sites, that evaluated the safety and efficacy of continuing versus interrupting oral anticoagulation during TAVI. Details of the design of the study have been described previously[8]. Briefly, patients were eligible if they were on any oral anticoagulant and scheduled to undergo transfemoral or transsubclavian TAVI. Patients randomised to the continuation strategy maintained oral anticoagulation throughout the periprocedural period, including on the day of the TAVI procedure. Patients randomised to the interruption strategy interrupted oral anticoagulation at least 48 hours before TAVI. Bridging with low-molecular-weight heparin was not recommended. Oral anticoagulation was restarted after TAVI, as soon as deemed safe by the operator and/or treating physician. The TAVI procedures were performed according to the local protocol of each participating study site, including the choice of valve type, whether cerebral embolic protection was used, the amount of periprocedural heparin, the amount of protamine (when administered), and the type of vascular closure device used. Follow-up visits were performed at discharge and 30 days after TAVI. If necessary, the patient's primary care physician and/or treating specialist was contacted for additional information. The trial was approved by the national authorities and ethics committees and by the institutional review board at each participating site.

PATIENTS

Patients planned for transfemoral or transsubclavian TAVI, who were using long-term oral anticoagulation and provided written informed consent, were included. The exclusion criteria were the presence of a mechanical heart valve prosthesis, intracardiac thrombus, venous thromboembolism within 3 months before TAVI or transient ischaemic attack or stroke in patients with atrial fibrillation within 6 months before TAVI.

BLEEDING RISK CRITERIA

Baseline and procedural characteristics, including the VARC-HBR criteria, were registered in standardised electronic case report forms. Slightly modified definitions of severe hepatic disease, prior ischaemic stroke and active malignancy were used. A full list of the criteria and their respective definitions is provided in **Supplementary Table 1**. Patients were classified at moderate risk if no more than one minor criterion was met, at high risk if one major or two minor criteria were met, and at very high risk if at least two major or three minor criteria were met[7]. To compare the VARC-HBR criteria with existing bleeding risk scores, the criteria of the HAS-BLED, ORBIT, DOAC and PREDICT-TAVR bleeding risk scores were also

Abbreviations

BARC	Bleeding Academic Research Consortium	**ROC-AUC**	area under the receiver operating characteristic curve	**VARC**	Valve Academic Research Consortium
CI	confidence interval	**TAVI**	transcatheter aortic valve implantation	**VARC-HBR**	Valve Academic Research Consortium High Bleeding Risk

assessed[9-12]. Full lists of these criteria and their respective definitions, adapted to the current study, are provided in **Supplementary Table 2**.

BLEEDING DEFINITIONS

Bleeding events were collected until 30 days after TAVI and adjudicated by a blinded clinical events committee. Adjudication was based on the Bleeding Academic Research Consortium (BARC) criteria and the Valve Academic Research Consortium (VARC)-3 criteria[13,14]. For this analysis, major bleeding was defined as BARC Type 3-5 bleeding occurring within 30 days after TAVI[7]. The VARC-3-based major bleeding definition (Type 2-4) was used as a sensitivity analysis[14]. BARC and VARC-3 bleeding definitions are detailed in **Supplementary Table 3**.

STATISTICAL ANALYSIS

The analysis population included all patients who had undergone randomisation and subsequent TAVI. Continuous variables are summarised as mean±standard deviation (SD) or as median and interquartile range, as appropriate. Categorical variables are presented as numbers and percentages. Proportions of major bleeding were compared between risk groups using the chi-square test. The discriminative ability of the VARC-HBR criteria, as well as the other bleeding risk scores, was assessed based on the area under the receiver operating characteristic curve (ROC-AUC) with corresponding 95% confidence intervals (CIs). The VARC-HBR criteria were assessed as a three-class risk score (moderate, high, very high risk) and as a point-based score, where minor criteria were given one point and major criteria two points. Calibration was evaluated by comparing predicted probabilities with observed frequencies of major bleeding per risk group. Multivariate logistic regression analysis was performed to assess the relative contribution of each criterion, which is expressed as odds ratios (ORs) with corresponding 95% CIs. Since the main trial did not show non-inferiority of the continued oral anticoagulation strategy, the impact of continuation of oral anticoagulation for the different VARC-HBR risk groups was evaluated. Additional logistic regression analyses were conducted, considering continuation of oral anticoagulation as a major criterion, to evaluate its impact both independently and in combination with other variables. There were no missing data in the evaluated criteria or bleeding outcomes. Statistical analyses were performed using R software, version 4.1 (R Foundation for Statistical Computing).

Results

BASELINE CHARACTERISTICS

Between November 2020 and December 2023, a total of 869 patients were enrolled. Thirteen patients were excluded because TAVI was not initiated or they withdrew informed consent before the procedure. The mean±SD age of the patients was 81.1±5.9 years, and 34.5% were female. The indication for long-term oral anticoagulation was atrial fibrillation in 94.9% of the patients. The majority (81.6%) of patients used a direct oral anticoagulant, of whom 30.4% were on a reduced dose. Out of 856 patients included, 332 (39%) were classified at moderate bleeding risk, 337 (39%) at high bleeding risk, and 187 (22%) at very high bleeding risk. Patients in the higher bleeding risk categories had a greater prevalence of cardiovascular risk factors and comorbidities, consistent with the VARC-HBR criteria. Randomisation to a continued oral anticoagulation strategy was not significantly different between the groups (p=0.43). Baseline and procedural characteristics are detailed in **Table 1** and **Supplementary Table 4**, respectively.

PREVALENCE OF VARC-HBR CRITERIA

The prevalence of VARC-HBR criteria, when present in at least 1% of the patients, is summarised in **Central illustration A.** The most common criterion was severe femoral artery calcification and tortuosity, which was present in 26.8% of the patients. Other prevalent criteria were dual antithrombotic therapy (oral anticoagulation+antiplatelet therapy; 12.5%), history of ischaemic stroke (10.5%), and anaemia (haemoglobin <11 g/dL) at hospital admission (11.6%). The following criteria were rarely observed: non-deferrable major surgery (0.4%), severe hepatic disease (0.7%), history of haemorrhagic stroke (0.9%), dual antiplatelet therapy (meaning triple therapy in this population; 0.5%), conversion to open-heart surgery (0.4%), and spontaneous bleeding >6 and <12 months before TAVI (0.4%). Severe thrombocytopaenia (platelet count <50x10^9/L) at baseline was not observed.

RISK STRATIFICATION

Major bleeding occurred in 4.2% of patients classified at moderate risk, in 9.5% classified at high risk, and 15.0% at very high risk (p<0.001), as shown in **Central illustration B.** Fatal bleeding (BARC Type 5) occurred in 6 patients: 3 (0.9%) in the high-risk group and 3 (1.6%) in the very high-risk group **(Table 2)**. Access site bleeding was the most common bleeding phenotype, which occurred in 4.5% of the moderate-risk group, in 7.1% of the high-risk group and in 10.2% of the very high-risk group. Further details regarding the sites of bleeding across the VARC-HBR subgroups are provided in **Supplementary Table 5**. Major bleeding according to the VARC-3 definition occurred in 6.3% of patients classified at moderate risk, in 10.4% classified at high risk, and 15.5% at very high risk. Bleeding events adjudicated by the VARC-3 criteria are displayed in **Supplementary Table 6**.

RISK PREDICTION

The ROC-AUC of the VARC-HBR criteria was 0.64 (95% CI: 0.58-0.70) when assessed as a three-class risk score and 0.65 (95% CI: 0.58-0.71) when assessed as a point-based score **(Figure 1)**. The ROC-AUC of the HAS-BLED score was 0.52 (95% CI: 0.45-0.60), the ORBIT score 0.54 (95% CI: 0.48-0.60), the DOAC score 0.55 (95% CI: 0.48-0.62), and the PREDICT-TAVR score 0.54 (95% CI: 0.47-0.61) **(Figure 2)**. Although the observed event rates were slightly higher than predicted, the VARC-HBR criteria showed overall good calibration with observed outcomes **(Central illustration B)**. Based on logistic regression analysis, severe femoral artery calcification and tortuosity (OR 2.5, 95% CI: 1.5-4.3), anaemia at baseline (OR 2.2, 95% CI: 1.1-4.2), and conversion to open-heart surgery (OR 21.2, 95% CI: 1.8-491.5) appeared to be the most influential predictors. The VARC-HBR model, showing the univariate and multivariate

Table 1. Baseline characteristics.

	Moderate bleeding risk (n=332)	High bleeding risk (n=337)	Very high bleeding risk (n=187)
Age, years	80.1±5.6	81.9±5.7	79.2±6.6
Female sex	114 (34.3)	128 (38.0)	53 (28.3)
Body mass index, kg/m²	27.9±4.6	27.3±4.8	26.6±4.6
EuroSCORE II, %	3.4±3.5	3.9±4.0	4.6±5.0
NYHA Class III or IV	191 (57.5)	209 (62.0)	130 (70.6)
Atrial fibrillation	319 (96.1)	323 (95.8)	176 (94.1)
Paroxysmal	154 (48.7)	135 (41.9)	87 (49.4)
CHA_2DS_2-VASc	4.07±1.3	4.6±1.4	4.9±1.4
Hypertension	256 (77.1)	253 (75.1)	150 (80.2)
Diabetes			
None	243 (73.2)	249 (73.9)	115 (61.5)
Non-insulin dependent	68 (20.5)	60 (17.8)	48 (25.7)
Insulin dependent	21 (6.3)	28 (8.3)	24 (12.8)
Coronary artery disease	128 (38.6)	171 (50.7)	113 (60.4)
History of myocardial infarction	40 (12.0)	56 (16.6)	40 (21.4)
Previous cerebrovascular event	33 (9.9)	79 (23.4)	55 (29.4)
Peripheral artery disease	32 (9.6)	63 (18.7)	68 (36.4)
Chronic obstructive pulmonary disease	51 (15.4)	43 (12.8)	22 (11.8)
Chronic renal insufficiency	151 (45.5)	173 (51.3)	108 (57.8)
Previous heart valve surgery	23 (6.9)	26 (7.7)	15 (8.0)
Previous spontaneous bleeding[$]	15 (4.5)	31 (9.2)	38 (20.3)
Active malignancy[#]	0 (0)	21 (6.2)	26 (13.9)
Type of oral anticoagulation			
Vitamin K antagonist	48 (13.0)	66 (19.6)	45 (24.1)
Direct oral anticoagulant	289 (87.0)	271 (80.4)	142 (75.9)
Randomised to continuation of OAC	168 (50.6)	162 (48.1)	101 (54.0)

Data are presented as mean±SD or n (%). [#]Excluding non-melanoma skin cancer. [$]Requiring hospitalisation or transfusion. EuroSCORE: European System for Cardiac Operative Risk Evaluation; NYHA: New York Heart Association; OAC: oral anticoagulation; SD: standard deviation

associations of the individual criteria with the occurrence of major bleeding, is presented in **Table 3**. Additionally, in **Supplementary Table 7**, the randomised strategy was evaluated as a major criterion and showed no significant interaction in either univariate or multivariate analyses (OR 1.1, 95% CI: 0.7-1.9). Accordingly, multivariate logistic regression models of the other bleeding scores are reported in **Supplementary Table 8-Supplementary Table 11**. The sensitivity analysis, in which the VARC-HBR criteria were applied to predict major bleeding based on the VARC-3 definition, yielded similar results (ROC-AUC of 0.64 [95% CI: 0.58-0.70]).

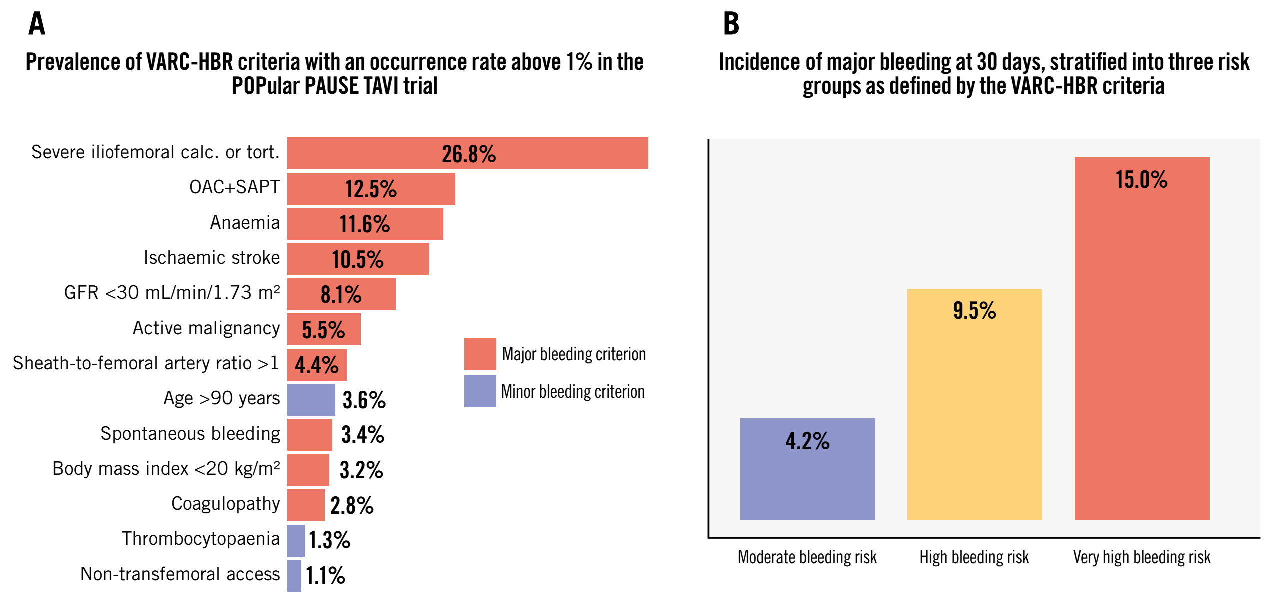
Discussion

In this subanalysis of the POPular PAUSE TAVI trial, we evaluated the VARC-HBR criteria for risk stratification and prediction of 30-day major bleeding risk in patients undergoing TAVI with a concomitant indication for oral anticoagulation. The main findings were as follows: (1) the VARC-HBR criteria effectively identified three well-distributed subgroups, with a stepwise increase in major bleeding risk across the risk categories; (2) for individual risk prediction, the discriminative performance of the VARC-HBR criteria was moderate, yet, it appeared to outperform existing bleeding risk scores in this population; (3) severe femoral artery calcification and tortuosity, anaemia, and conversion to open-heart surgery were identified as the most contributory criteria.

In contemporary studies, major bleeding has been reported in 3-10% of patients within 30 days after TAVI[4,15-18]. The observed bleeding rate in our study was slightly higher, which could be attributed to the fact that we evaluated a subgroup of patients receiving oral anticoagulation, half of whom continued their therapy throughout the periprocedural period[8]. These high rates of bleeding emphasise the need for adequate risk assessment[7]. Based on the current findings, the VARC-HBR criteria seem to be a valuable tool for this purpose. The clinical implications of identifying patients at (very) high risk of bleeding may lie in adopting precautionary measures for access site management, since access site bleeding appeared to be the most common bleeding phenotype early after TAVI. For example, the use of the radial artery for secondary vascular access, protamine administration for heparin reversal at the end of the procedure, and the use of an additional vascular closure device may mitigate the bleeding risk in these

Euro**Intervention** Central **Illustration**

VARC-HBR criteria and bleeding risk in the POPular PAUSE TAVI trial.



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A) Prevalence of VARC-HBR criteria (occurrence >1%). B) 30-day major bleeding incidence stratified by VARC-HBR risk. calc.: calcification; GFR: glomerular filtration rate; OAC: oral anticoagulation; SAPT: single antiplatelet therapy; TAVI: transcatheter aortic valve implantation; tort.: tortuosity; VARC-HBR: Valve Academic Research Consortium High Bleeding Risk

Table 2. BARC bleeding types stratified according to VARC-HBR risk groups.

Bleeding type	Moderate (n=332)	High (n=337)	Very high (n=187)
Minor bleeding (Type 2)	63 (19.0)	53 (15.7)	40 (21.4)
Major bleeding (Type 3-5)	14 (4.2)	32 (9.5)	28 (15.0)
Type 3a	7 (2.1)	16 (4.8)	19 (10.2)
Type 3b	6 (1.8)	13 (3.9)	6 (3.2)
Type 3c	1 (0.3)	-	-
Type 5a	-	-	-
Type 5b	-	3 (0.9)	3 (1.6)

Data are n (%). BARC: Bleeding Academic Research Consortium; VARC-HBR: Valve Academic Research Consortium High Bleeding Risk

patients[17-19]. Recently, a dedicated stepwise vascular closure algorithm was shown to be associated with a major vascular complication rate (including major bleeding) of less than 1%[20]. This systematic approach may particularly be useful in patients at (very) high risk of bleeding.

Regarding the choice of antithrombotic therapy, the additional value of the VARC-HBR criteria may be limited, particularly in this subpopulation using oral anticoagulation, since interrupting oral anticoagulation before TAVI and restarting oral anticoagulation monotherapy after TAVI seems to be the appropriate strategy in general[8,15]. Dual antiplatelet

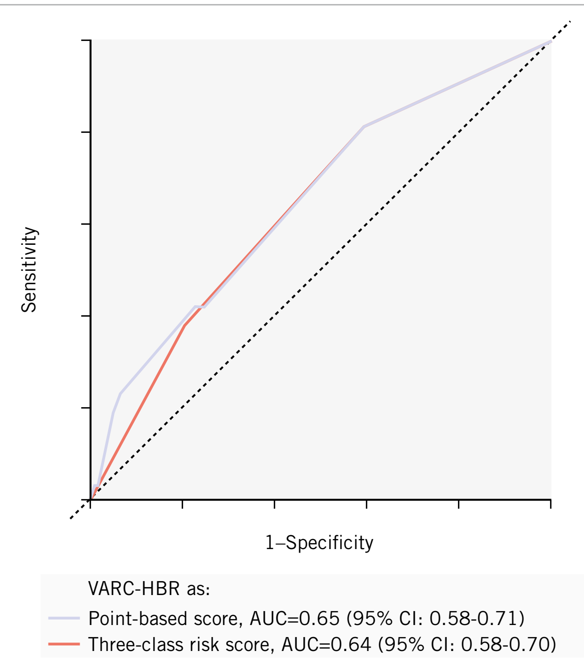

Figure 1. *ROC curves of VARC-HBR criteria. AUC: area under the curve; CI: confidence interval; ROC: receiver operating characteristic; VARC-HBR: Valve Academic Research Consortium High Bleeding Risk*

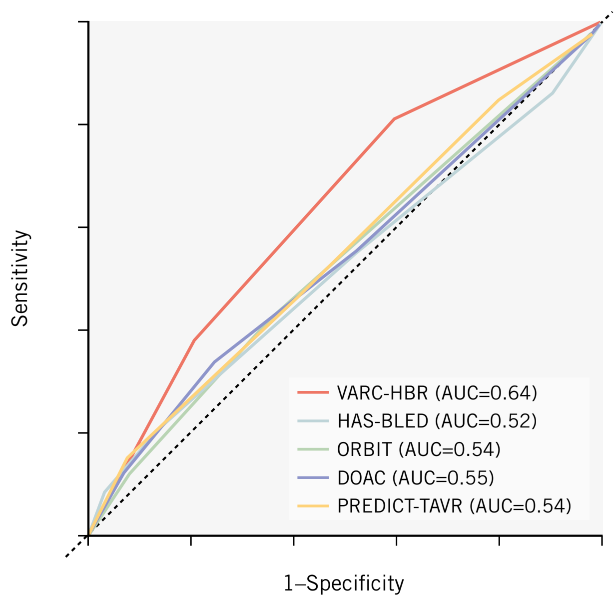

Figure 2. *Performance of the VARC-HBR criteria compared to other bleeding risk scores. AUC: area under the curve; VARC-HBR: Valve Academic Research Consortium High Bleeding Risk*

therapy in addition to oral anticoagulation (triple therapy) is discouraged based on current literature. Our dataset showed that it was potentially an important predictor (OR 3.8, 95% CI: 0.17-34.62). Switching from a vitamin K antagonist to a direct oral anticoagulant after TAVI may be best avoided in (very) high-risk patients, as this has been associated with an increased risk of major bleeding[21]. Interestingly, in patients without a concomitant indication for oral anticoagulation or antiplatelet therapy, the need for lifelong single antiplatelet therapy has recently been questioned in high bleeding risk patients[22]. However, randomised controlled trials are needed before omitting antiplatelet therapy can be recommended. The ongoing Non-antithrombotic Therapy After TAVI Trial (NAPT; ClinicalTrials.gov: NCT06007222) and the Personalized, CT-guided Antithrombotic Therapy Versus Lifelong Single Antiplatelet Therapy to Reduce Thromboembolic and Bleeding Events in Non-atrial Fibrillation Patients After TAVI trial (POPular ATLANTIS; ClinicalTrials.gov: NCT06168370) are expected to provide further evidence on this topic[23].

To the best of our knowledge, PREDICT-TAVR is the only other bleeding risk score specifically developed for patients undergoing TAVI[12]. Previous external validation showed a much better predictive performance than our data. This may be due to our evaluation of the version of the model without serum iron and our assessment of the common femoral artery diameter as a binary variable (<6 mm or not) instead of the original per-millimetre variable. The HAS-BLED, ORBIT and DOAC scores were specifically designed for patients on oral anticoagulation, but independent of the need for TAVI[9-11]. Their limited predictive performance in this setting is likely due to the fact that these scores were developed to predict spontaneous bleeding rather than procedure-related bleeding, which involves different risk factors. The VARC-HBR criteria

Table 3. Logistic regression analysis.

VARC-HBR criteria*	Univariate OR (95% CI)	*p*-value	Multivariate OR (95% CI)	*p*-value
Minor criteria				
Age >90 years	1.14 (0.27-3.31)	0.84	1.40 (0.32-4.27)	0.60
Dual antiplatelet therapy (besides OAC)	3.56 (0.17-28.18)	0.27	3.79 (0.17-34.62)	0.28
Non-transfemoral access	1.33 (0.07-7.37)	0.79	0.79 (0.04-4.72)	0.83
Major criteria				
BMI <20 kg/m²	1.33 (0.31-3.94)	0.64	1.37 (0.31-4.32)	0.63
Chronic kidney disease (eGFR <30 mL/min/1.73 m²)	1.43 (0.61-2.96)	0.37	1.05 (0.40-2.40)	0.91
Active malignancy	1.94 (0.77-4.24)	0.12	1.80 (0.67-4.23)	0.20
Anaemia (Hb <11 g/dL)	2.11 (1.11-3.80)	0.02	2.16 (1.06-4.21)	0.03
Previous ischaemic stroke	1.37 (0.64-2.66)	0.38	1.37 (0.61-2.80)	0.42
Chronic bleeding diathesis	1.53 (0.36-4.58)	0.50	1.60 (0.34-5.48)	0.49
Spontaneous bleeding#	1.73 (0.50-4.62)	0.32	1.19 (0.29-3.83)	0.79
Dual antithrombotic therapy (OAC+SAPT)	1.91 (1.01-3.42)	0.04	1.53 (0.74-2.96)	0.22
Non-deferrable major surgery	5.34 (0.25-56.40)	0.17	3.60 (0.15-44.46)	0.33
SFAR >1	1.64 (0.55-4.00)	0.32	1.21 (0.38-3.19)	0.72
Severely calcified and tortuous iliofemoral arteries	2.26 (1.38-3.68)	0.001	2.50 (1.46-4.29)	0.001
Immediate conversion to open-heart surgery	21.69 (2.05-470.18)	0.012	21.20 (1.77-491.47)	0.02

*Due to limited occurrence, associations for the following variables could not be estimated: moderate thrombocytopaenia, first spontaneous bleeding >6 and <12 months before TAVI, severe hepatic disease, severe thrombocytopaenia, previous intracranial haemorrhage, and oral anticoagulation (applied to everyone). #Defined as spontaneous (non-intracranial) bleeding requiring hospitalisation or transfusion in the previous 6 months (or at any time if recurrent). BMI: body mass index; CI: confidence interval; eGFR: estimated glomerular filtration rate; Hb: haemoglobin; OAC: oral anticoagulation; OR: odds ratio; SAPT: single antiplatelet therapy; SFAR: sheath-to-femoral artery ratio; VARC-HBR: Valve Academic Research Consortium High Bleeding Risk provide a more comprehensive approach, distinguishing factors that impact periprocedural and non-periprocedural bleeding, or both. Still, the discriminative performance observed in our data was only moderate, quite similar to what has been reported in studies evaluating the ARC-HBR criteria in patients undergoing percutaneous coronary intervention[24,25]. In a large-scale observational study, the ROC-AUC of the ARC-HBR criteria was 0.64 (95% CI: 0.61-0.66) when assessed as a two-class variable, which increased to 0.68 (95% CI: 0.65-0.71) when assessed as a point-based variable[25]. Such an improvement was not observed in our analysis. This may be related to the fact that the VARC-HBR definition was designed as a three-class instead of a two-class system, thus providing a more granular approach. Upon exploration of our data, we observed that the point-based scores were clustered in three groups (1 point, 3 points, and 5 points), indicating that the three-class risk score appropriately described the degree of variation in our data.

Severe iliofemoral calcification and tortuosity are widely recognised risk factors for major bleeding[26,27]. However, the VARC-HBR document provides no specific guidance on how this criterion should be determined. Considering its prevalence and contributory value, a more specific definition may improve the predictive value of the VARC-HBR criteria. Previous studies have shown that ventral (or anterior) common femoral artery calcification seems to be more relevant than overall iliofemoral calcification[28]. Also, the degree of longitudinal and especially circumferential extent of calcification appears to be associated with major bleeding risk[29]. Finally, considering severe femoral tortuosity as an independent criterion, given its distinct aetiology, may further enhance predictive performance[26,27].

Limitations

Our findings should be interpreted considering the following limitations. Although all 21 VARC-HBR criteria were included in the dataset, three variables had to be slightly modified because of data availability. Second, due to the limited sample size, the predictive value of uncommon criteria could not be assessed. Additionally, for a few variables, this resulted in wide confidence intervals, which should be interpreted with caution. Third, follow-up was limited to 30 days after TAVI, which resulted in access-related bleeding being more prominent compared to the 1-year major bleeding defined by VARC-HBR. Finally, almost all patients were treated using the transfemoral approach, so the results should not be generalised to other access site approaches for TAVI. The same applies to patients not using oral anticoagulation.

Conclusions

Among patients with a concomitant indication for oral anticoagulation, the VARC-HBR criteria identified three well-distributed subgroups, with a stepwise increase in major bleeding risk within 30 days after TAVI. However, for individual risk prediction, the discriminative performance of the VARC-HBR criteria were moderate but appeared to outperform existing bleeding risk scores in this population. Severe femoral artery calcification and tortuosity, anaemia, and conversion to open-heart surgery were identified as the most contributory criteria.

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Funding

The POPular PAUSE TAVI trial (ClinicalTrials.gov: NCT04437303) was supported by grants from the Netherlands Organization for Health Research and Development and the St. Antonius Research Fund. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the manuscript, and its final contents.

Conflict of interest statement

Y. Kobari has received consulting fees from Boston Scientific. O. De Backer has received institutional research grants and consulting fees from Abbott, Boston Scientific, and Medtronic. F. van der Kley has received consulting/lecturer fees from Edwards Lifesciences, Boston Scientific, and Abbott. N.M. Van Mieghem has received grants or contracts from Abbott, Boston Scientific, Medtronic, Edwards Lifesciences, Daiichi Sankyo, AstraZeneca, and Teleflex; and consulting/lecturer fees from Abbott, Boston Scientific, Medtronic, Daiichi Sankyo, PulseCath BV, Siemens, Teleflex, JenaValve, Anteris, and Amgen. M.

Voskuil has received lecturer fees from Edwards Lifesciences, Medtronic, and Abbott. A.J.J. IJsselmuiden has received consulting/lecturer fees from Angiocare, Meril Life Sciences, and Medtronic. R.S. Hermanides has received lecturer fees from Abbott, Amgen, Edwards Lifesciences, and Novartis. E. Barbato has received lecturer fees from Abbott, Insight Lifetech, and Boston Scientific. D. Mylotte has received consulting fees from Boston Scientific, Medtronic, and MicroPort. M.J. Swaans has received consulting/lecturer fees from Abbott, Bioventrix Inc., Boston Scientific, Cardiac Dimensions, Edwards Lifesciences, GE HealthCare, Medtronic, Philips Healthcare, and Siemens Healthineers. T. Adriaenssens has received consulting fees from Abbott. J.M. Montero-Cabezas has received lecturer fees from Penumbra, Inc.; and a research grant from Shockwave Medical. J.J. Wykrzykowska has received institutional research grants from Medtronic; lecturer fees from Boston Scientific, Meril Life Sciences, Abbott, SMT, Cordis, and Medis Medical Imaging; and participates on the advisory board of Medtronic and Novo Nordisk. A.W.J. van 't Hof has received institutional research grants from Medtronic, AstraZeneca, and Boehringer Ingelheim; consulting fees from CeleCor Therapeutics; and participates in the Data Safety Monitoring Board for Diagram Research. N. van Royen has received institutional research grants from Abbott, Biotronik, Medtronic, and Philips; and lecturer fees from Abbott, Bayer, MicroPort, and Rainmed. R. Delewi has received institutional research grants and consulting fees from Abiomed, Amgen, Boston Scientific, Edwards Lifesciences, and Novartis. J.M. ten Berg has received institutional research grants from ZonMw, AstraZeneca, and Daiichi Sankyo; and consulting/lecturer fees from AstraZeneca, Daiichi Sankyo, CeleCor Therapeutics, and Boehringer Ingelheim. The other authors have no conflicts of interest relevant to the contents of this paper to declare.

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Supplementary data

Supplementary Table 1. VARC-HBR definitions.

Supplementary Table 2. HAS-BLED, ORBIT, DOAC and PREDICT-TAVR definitions.

Supplementary Table 3. BARC and VARC-3 bleeding definitions.

Supplementary Table 4. Procedural characteristics.

Supplementary Table 5. Major bleeding sites.

Supplementary Table 6. VARC bleeding types stratified according to VARC-HBR risk groups.

Supplementary Table 7. Logistic regression analysis including randomised strategy.

Supplementary Table 8. Prevalence and logistic regression: HAS-BLED criteria.

Supplementary Table 9. Prevalence and logistic regression: ORBIT criteria.

Supplementary Table 10. Prevalence and logistic regression: DOAC criteria.

Supplementary Table 11. Prevalence and logistic regression: PREDICT-TAVR criteria.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-24-01066

EuroIntervention
2025;21:e1090-e1101
published online e-edition September 2025
DOI: 10.4244/EIJ-D-24-01000
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ORIGINAL RESEARCH

DurAVR – a novel biomimetic balloon-expandable transcatheter valve for TAVI, valve-in-valve TAVI and redo-TAVI

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This paper also includes supplementary data published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-24-01000

ABSTRACT

BACKGROUND: The DurAVR transcatheter heart valve (THV) is a novel biomimetic balloon-expandable valve with promising early clinical results.

AIMS: We aimed to assess the hydrodynamic performance of the DurAVR THV in native, valve-in-valve (ViV), and redo-transcatheter aortic valve implantation (TAVI) procedures against commercially available THVs on the bench.

METHODS: The hydrodynamic function of the DurAVR THV was assessed by simulating native valve deployments at 0 mm, 3 mm, and 6 mm depths, compared to SAPIEN 3 (S3), Evolut PRO, Navitor, and ACURATE *neo*2 (ACn2) valves. For ViV simulations, THVs were implanted in 21 mm and 23 mm Magna Ease, Mosaic, and Hancock bioprostheses. For redo-TAVI simulations, the DurAVR THV was assessed within S3, Evolut PRO, Navitor, and ACn2 valves.

RESULTS: For native TAVI simulations, the DurAVR THV demonstrated superior or comparable hydrodynamic performance, independent of implant depth, with an effective orifice area (EOA) ≥3 cm^2 and a mean gradient (MG) <6 mmHg. The DurAVR THV had nil to mild pinwheeling (0-2%) at all depths, while the S3 and Evolut PRO showed moderate pinwheeling at 6 mm depth. For ViV simulations, the DurAVR THV exhibited larger EOAs and lower MGs than the comparator THVs and showed no more than mild pinwheeling in all ViV configurations. For redo-TAVI simulations, the DurAVR THV exhibited larger EOAs and lower MGs in each simulation compared to all other THVs tested, with no more than mild pinwheeling observed in all configurations except when implanted within the Evolut PRO.

CONCLUSIONS: In this bench study, the DurAVR THV demonstrated excellent hydrodynamic performance in native, ViV, and redo-TAVI simulations. Future large-scale studies are needed to confirm these findings in clinical application and further characterise the valve's short- and long-term performance.

KEYWORDS: bench study; DurAVR; hydrodynamics; redo-TAVI; transcatheter aortic valve implantation

SUBMITTED ON 03/11/2024 - REVISION RECEIVED ON 1st 06/01/2025 / 2nd 10/02/2025 - ACCEPTED ON 21/02/2025

The use of transcatheter aortic valve implantation (TAVI) is now transitioning towards a younger patient population with greater anticipated longevity[1]. Thus, there is an increasing need for devices with optimal haemodynamic performance in both the short and long term. One of the main challenges for current and future transcatheter heart valve (THV) platforms is to engineer leaflets resistant to different modes of degeneration[2]. Post-TAVI thrombosis is poorly understood, and one mechanism may be related to prosthesis expansion and flow within the neosinuses[3,4]. Therefore, a THV that functions well across a wide range of deployment configurations and/or restores near-physiological flow may be advantageous and help improve long-term durability.

Presently, operators can choose between short-frame balloon-expandable (BE) and tall-frame self-expanding (SE) THVs. SE valves may have a better haemodynamic profile, particularly in the context of a small annulus, valve-in-valve (ViV) TAVI, or redo-TAVI, even if the impact on hard clinical endpoints and durability is debated[5-7]. Conversely, BE THVs are associated with lower pacemaker rates and improved coronary access in clinical practice[8]. On the bench, BE valves are generally associated with a higher degree of pinwheeling, a phenomenon that is potentially linked to reduced leaflet durability[9,10]. Thus, a short-frame BE THV with little to no pinwheeling and improved haemodynamics would be of great interest.

The recently developed DurAVR system (Anteris Technologies) is a TAVI platform built around a biomimetic BE THV with a single-piece, moulded bovine pericardial tissue leaflet intended to mimic the shape of the native aortic valve. The first-in-human implantations of the DurAVR valve have been performed successfully, with excellent early clinical outcomes and restoration of near-physiological aortic flow[11]. While clinical data on the DurAVR THV is growing, additional insight is needed. Therefore, to further evaluate the capabilities of this novel BE THV, we performed an *in vitro* bench study to assess the performance of the valve in three different important procedural settings: native valve TAVI, ViV TAVI, and redo-TAVI, in comparison to other commercially available THV devices.

Impact on daily practice

The DurAVR transcatheter heart valve (THV) is an intra-annular balloon-expandable THV that has shown promising results in early feasibility clinical experience. In this bench study, the DurAVR THV showed excellent hydrodynamic performance in native transcatheter aortic valve implantation (TAVI), valve-in-valve TAVI, and redo-TAVI simulations, compared to SAPIEN 3, Navitor, Evolut PRO, and ACURATE *neo*2 valves. The performance and characteristics of both the current and anticipated larger DurAVR THV sizes need to be assessed in future *in vitro* testing, and a larger clinical series is required to validate these findings *in vivo*.

Methods

OBJECTIVES

The present study had the following objectives:

1) To assess the hydrodynamic function of the DurAVR THV on the bench at three different depths (0 mm, 3 mm, and 6 mm) and compare this to four commercially available THV platforms: SAPIEN 3 (S3 [Edwards Lifesciences]), Evolut PRO (Medtronic), Navitor (Abbott), and ACURATE *neo*2 (ACn2 [Boston Scientific]).
2) To evaluate the hydrodynamic function of the DurAVR THV when used in a ViV context within different types of surgical bioprostheses (Magna Ease [Edwards Lifesciences], Mosaic [Medtronic], and Hancock [Medtronic]) and compare this to four commercially available THV platforms (S3, Evolut PRO, Navitor, ACn2).
3) To evaluate the hydrodynamic function of the DurAVR THV when used in a redo-TAVI context within different types of THVs and compare this to the use of other THVs (S3, Evolut PRO, Navitor, ACn2).

STUDY METHODS

In vitro testing was performed in collaboration with the Cardiovascular Translational Laboratory (Vancouver, Canada) and Anteris Technologies (Minneapolis, MN, USA). This study was performed under physiological test conditions with no human or animal participants, and thus ethical approval was not required.

VALVES

The DurAVR THV is a BE THV, currently available in one size, with a short cobalt-chromium frame and large top cell intended for the treatment of native aortic annuli of 21 mm to 24 mm area-derived diameter, with a valve height of 23 mm. The THV has a trileaflet configuration built from a single piece of moulded bovine pericardium treated with an anticalcification tissue process (ADAPT [Anteris Technologies])[12] **(Figure 1A)**.

S3 is a BE THV with a cobalt-chromium frame, trileaflet bovine pericardial tissue valve, and polyethylene terephthalate fabric skirt.

Navitor is an SE THV incorporating a nitinol frame and an active sealing cuff. Unlike other SE THVs, the trileaflet bovine pericardial leaflets are positioned lower in the stent frame in an intra-annular position.

ACn2 incorporates an SE nitinol frame with three large open stabilisation arches, supra-annular trileaflet porcine pericardial leaflets, and a polyester fabric sealing skirt.

Abbreviations

ACn2	ACURATE *neo*2	**MG**	mean gradient	**SHV**	surgical heart valve
BE	balloon-expandable	**RF**	regurgitant fraction	**TAVI**	transcatheter aortic valve implantation
CT	computed tomography	**S3**	SAPIEN 3	**THV**	transcatheter heart valve
EOA	effective orifice area	**SE**	self-expanding	**ViV**	valve-in-valve

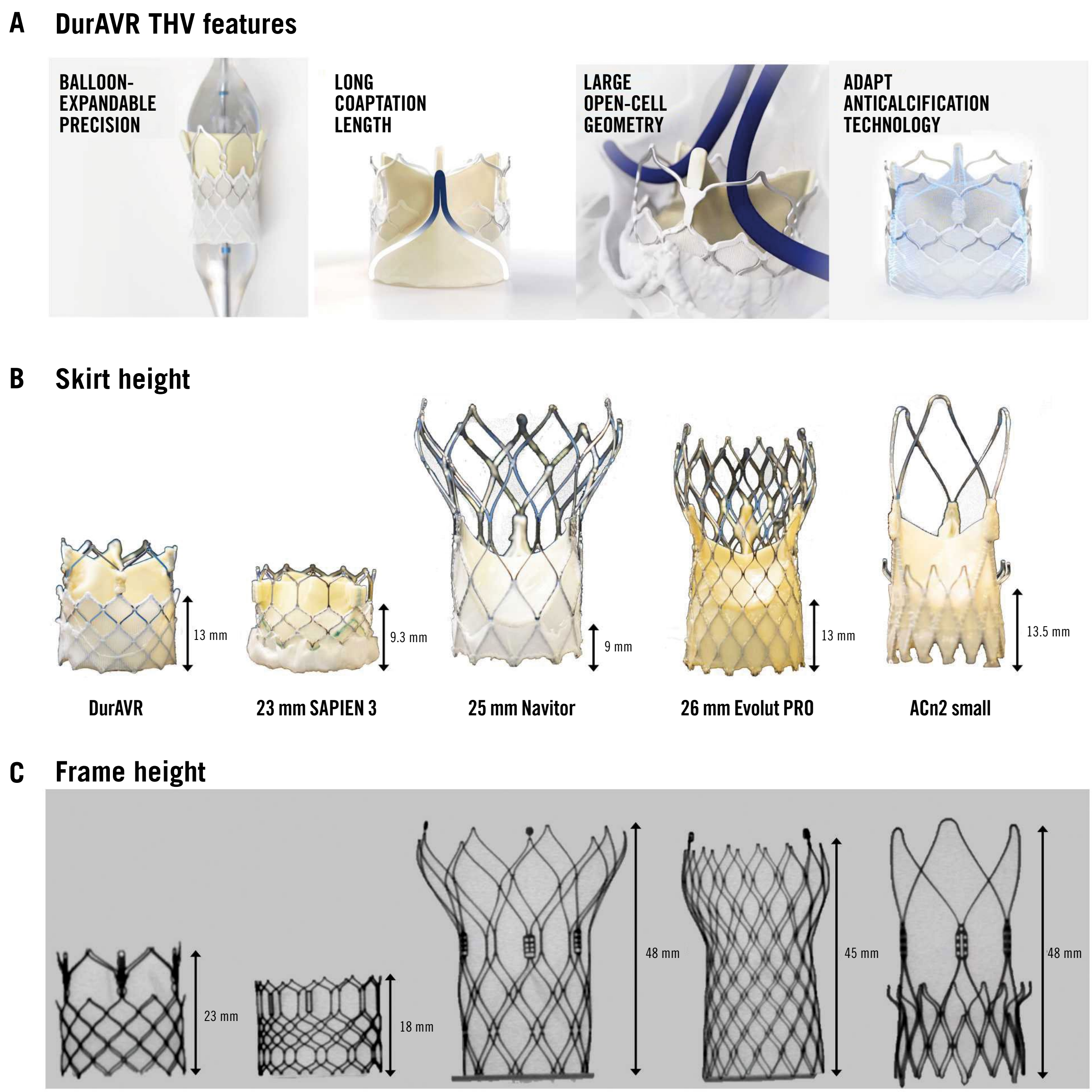


Figure 1. *DurAVR THV design analysis in comparison to leading THVs. A) Novel design and components of the DurAVR THV. B) Photographic images of the DurAVR THV and commercially available THVs used comparing skirt heights. C) Fluoroscopy of the DurAVR THV and comparators showing overall valve heights. ACn2: ACURATE neo2; THV: transcatheter heart valve*

Evolut PRO is also designed around an SE nitinol frame with supra-annular trileaflet porcine pericardial leaflets and a porcine pericardial skirt.

The DurAVR valve was assessed in comparison to 23 mm S3, 25 mm Navitor, 23 mm and 26 mm Evolut PRO, and ACn2 THVs. Size selection for the comparators was matched to the size range currently covered by the DurAVR THV. The THVs used in the study are shown in **Figure 1B** and **Figure 1C**.

For the ViV component of the study, three types of surgical heart valves (SHVs) were used as the modelled "failed" index valves: 21 mm and 23 mm Magna Ease (true internal diameter [ID] 19 mm and 21 mm, respectively), 21 mm and 23 mm Mosaic (true ID 17 mm and 19 mm, respectively), and 21 mm and 23 mm Hancock (true ID 17 mm and 19 mm, respectively). Size selection for the SHV was based on recommendations from the Aortic ViV app (KRUTSCH). Finally, for the redo-TAVI section of the study, a total of four THVs were used as "failed" index valves: 23 mm S3, 26 mm Evolut PRO, small ACURATE *neo*2, and 25 mm Navitor.

THV CONFIGURATIONS

Supplementary Figure 1 outlines the overall configurations used in testing for native TAVI, ViV TAVI, and redo-TAVI. For native TAVI testing, the DurAVR THV, 23 mm S3, 25 mm Navitor, 26 mm Evolut PRO, and small ACn2 were utilised. For each THV, three different implant depths were used: 0 mm, 3 mm, and 6 mm. For the ViV TAVI testing, the DurAVR THV, 23 mm S3, 23 mm or 26 mm Evolut PRO, 25 mm Navitor, and small ACn2 were used. These THVs were implanted in three types of SHV (Magna Ease, Mosaic, and Hancock) with two sizes for each SHV (21 mm and 23 mm) as described above. This represents a total of 27 ViV configurations, as the Navitor was not tested in the 21 mm SHVs because an appropriately sized Navitor was not available. Only one implant depth of 0 mm was tested for all ViV configurations. Images and fluoroscopy of ViV configurations are shown in **Supplementary Figure 2** and **Supplementary Figure 3**.

Redo-TAVI performance was assessed using the 23 mm S3, 26 mm Evolut PRO, small ACn2 and 25 mm Navitor as the "failed" index THVs. The DurAVR THV and 23 mm S3 were implanted in all redo-TAVI configurations. However, as the implant of a tall-frame THV in a failed tall-frame valve is an unlikely clinical combination, ACn2, Navitor, and Evolut PRO were not assessed in other tall-frame valves and were only evaluated when implanted in S3 THVs. Overall, a total of 11 combinations were tested. For redo-TAVI, when Evolut PRO served as the "failed" index valve, the S3 and DurAVR THV were placed at node 5, as is commonly performed clinically. All deployments were performed in nominal conditions, and images and fluoroscopy of redo-TAVI configurations are shown in **Supplementary Figure 4**.

HYDRODYNAMIC ASSESSMENT

A pulse duplicator test system (BDC Laboratories) was used to assess hydrodynamic performance for all TAVI configurations. The THVs, index SHVs and index THVs were placed into a holder fabricated from silicone. The holder compliance was chosen in accordance with International Organization for Standardization (ISO) 5840-3:2021[13]. For assessment, THVs were then directly deployed into holders for TAVI or into index SHVs and index THVs placed in holders for ViV TAVI and redo-TAVI testing, respectively. No post-dilatation was performed.

All testing was completed in a saline solution at 37°C, and results were taken for 20 consecutive cycles, repeated 3 times, and then averaged. High-speed video filming was performed to assess index valve kinematics from the outflow and inflow. Pulsatile forward flow performance was measured at a nominal beat rate of 70±1 beats/min, systolic duration of 35±5%, mean aortic pressure of 100±2 mmHg, and simulated cardiac output of 5±0.1 L/min. The mean gradient (MG; mmHg), regurgitant fraction (%), and effective orifice area (EOA; cm^2) were assessed. The maximum allowable regurgitant fraction in accordance with ISO 5840-3:2021 is <20%[13]. The total regurgitant fraction, which included closing and intervalvular regurgitation, was assessed. The EOA was computed according to a simplified version of the Bernoulli equation, as previously described in ISO 5840[13]. Of note, for ACn2, hydrodynamic data are only available for 0 mm and 3 mm depths due to interaction between the holder and the THV upper crown at 6 mm depth. The opening index was calculated from still imaging taken from the hydrodynamic video and represents the ratio of the maximal area for opening and the dimension of the free edge in systole.

IMAGING PROTOCOL

Fluoroscopy of the THVs alone and in ViV combinations was performed using the OEC 9900 Elite Mobile C-arm X-ray system (GE HealthCare). High-resolution photography was performed at a prespecified magnification and fixed camera height. High-speed video from the hydrodynamic testing was also captured.

PINWHEELING

Pinwheeling, as defined by the ISO guideline for THV testing, refers to twisting of the free edges of the leaflets, resulting from excessive leaflet redundancy. A pinwheeling index (PWI) was calculated as previously reported[14], using images from the high-speed videos. The PWI of each leaflet's free edge was measured, and the mean PWI (%) of the valve was obtained from the average. Pinwheeling was classified as mild (<5%), moderate (5-9%) or severe (≥10%).

STATISTICS

Hydrodynamic variables, EOA, pressure gradients, and total regurgitation fraction are reported as mean values.

Results

HYDRODYNAMIC PERFORMANCE FOR THE NATIVE SIMULATIONS

Photographic and fluoroscopic images of the DurAVR THV and comparator THVs are shown in **Figure 1**, along with skirt and frame heights. Overall, use of the DurAVR THV resulted in excellent hydrodynamic performance, independent of implant depth **(Figure 2A, Figure 2B)**. The EOA was consistently ≥3 cm^2 and MG <6 mmHg. The other THVs used as comparator valves also showed good performance, independent of implant depth, with an EOA >2 cm^2 and an MG <10 mmHg. However, the EOA was greater and the MG was lower for the DurAVR THV at all three implant depths compared to the other THVs tested, with the increased opening index of DurAVR THV being visually appreciable **(Figure 1C)**. Comparison of the DurAVR THV to the S3 at 3 mm depth exemplifies this, with an 82% opening index for the DurAVR THV compared to 72% for the S3. Representative cycles of hydrodynamic function at 3 mm implant depth are shown in **Moving image 1**.

PINWHEELING FOR THE NATIVE TAVI SIMULATIONS

Analysis of video from the hydrodynamic assessment of THVs simulating native TAVI implantion showed that the DurAVR THV resulted in very mild pinwheeling (between 0% and 2%) at all implant depths tested. This was also the case for ACn2 and Navitor. However, Evolut PRO displayed moderate pinwheeling at 6 mm depth, and S3 displayed moderate pinwheeling at 3 and 6 mm depths **(Figure 3)**.

HYDRODYNAMIC PERFORMANCE FOR THE VIV TAVI CONFIGURATIONS

Photographic and fluoroscopic images of the ViV combinations are displayed in **Supplementary Figure 2** and **Supplementary Figure 3**. ViV configurations resulted in diminished hydrodynamic performance compared to native THVs. However, in the ViV context, the DurAVR THV was associated with larger EOAs and lower MGs than the

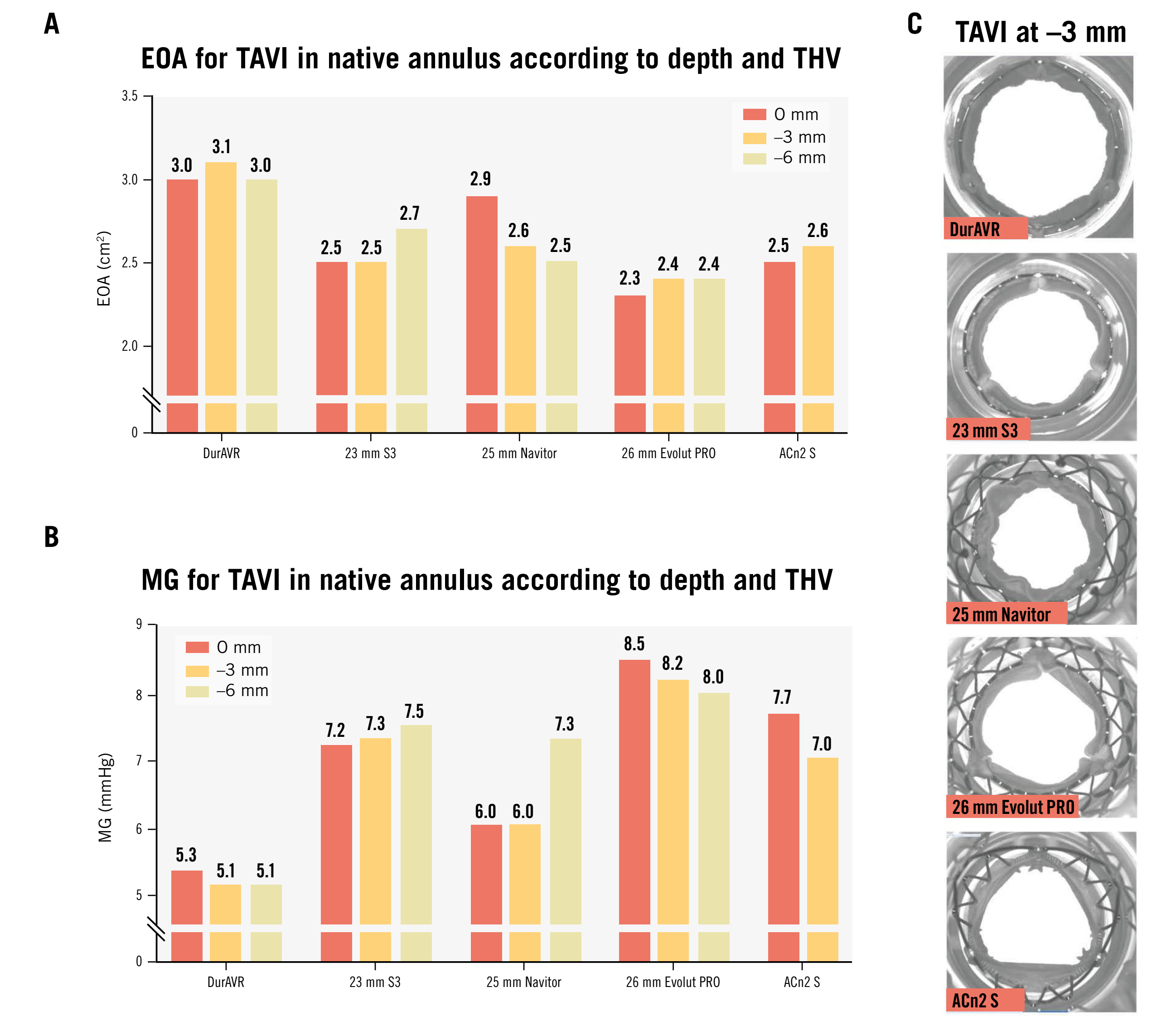


Figure 2. *Effective orifice area and mean gradient of the THVs in the native TAVI simulations at varying depths. EOA (A) and mean gradient (B) of the THVs in the native simulations at 0 mm, 3 mm, and 6 mm depths with representative images of valve opening at 3 mm depth (C). ACn2 S: ACURATE neo2 small; EOA: effective orifice area; MG: mean gradient; S3: SAPIEN 3; TAVI: transcatheter aortic valve implantation; THV: transcatheter heart valve*

comparators, with the greatest difference seen with implants in the 21 mm surgical valves **(Figure 4A, Figure 4B)**. In particular, within the 21 mm Hancock, the DurAVR THV was the only THV with an MG below the acceptable threshold according to ISO guidelines (16.4 mmHg for DurAVR THV vs 19.7 mmHg, 21.1 mmHg, and 20.2 mmHg for S3, Evolut PRO, and ACn2, respectively). The smallest difference was noted for the 23 mm Magna Ease, where all THVs had an MG <10 mmHg. Of note, the advantage of the DurAVR valve was more marked in the porcine leaflet valves (Hancock and Mosaic) which had smaller true ID than in the Magna Ease (pericardial leaflets). **Moving image 2** shows hydrodynamic function examples for ViV.

PINWHEELING FOR THE VIV TAVI CONFIGURATIONS

Pinwheeling was generally more marked in the ViV configurations than for the native THV implant alone, except for the DurAVR THV, which showed no more than mild pinwheeling (range 0-3%) for any of the surgical valve sizes and types tested **(Figure 5)**. Similar to native TAVI configurations, a lower extent of pinwheeling was seen for ACn2, except for the 21 mm and 23 mm Hancock valves, where moderate pinwheeling was noted. Evolut PRO had severe pinwheeling in the 21 mm surgical valves and moderate pinwheeling in the 23 mm surgical valves. S3 had severe pinwheeling in the 21 mm surgical valves and moderate to severe pinwheeling in the 23 mm surgical valves. Finally, Navitor had a variable (from mild to severe) degree of pinwheeling depending on the surgical valve type.

HYDRODYNAMIC PERFORMANCE FOR THE REDO-TAVI CONFIGURATIONS

Supplementary Figure 4 displays photographic and fluoroscopic images of the redo-TAVI simulations. The

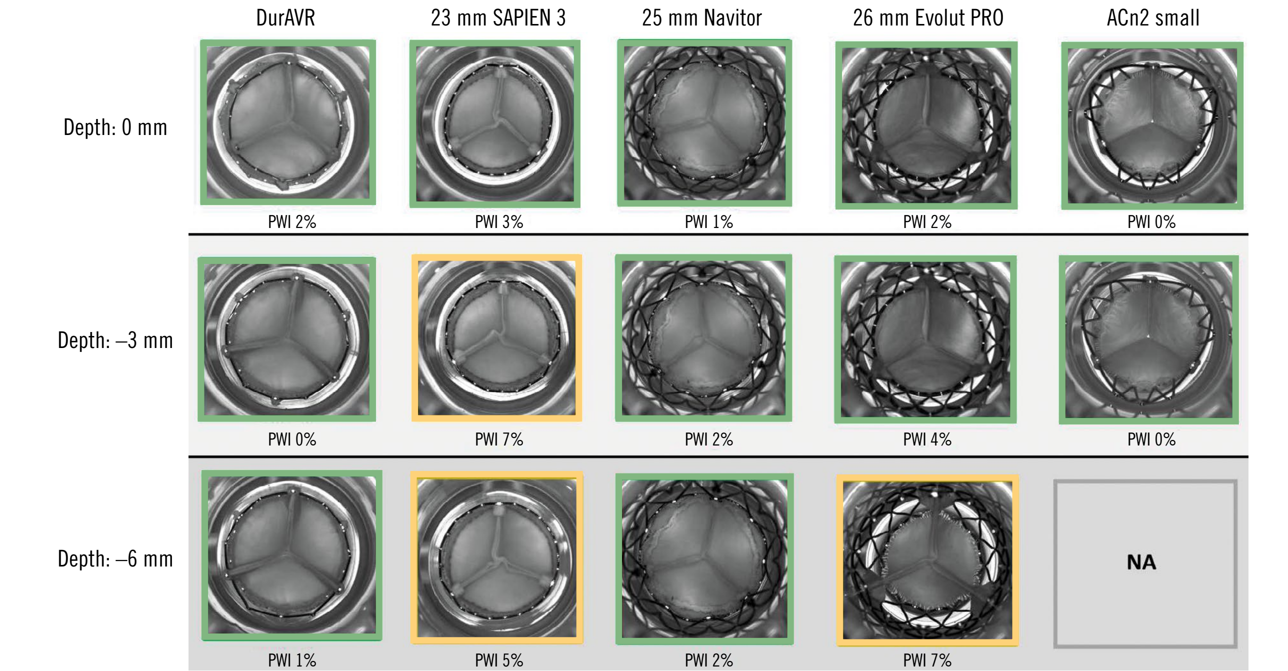


Figure 3. *Pinwheeling index and representative hydrodynamic testing images in diastole of the THVs in the native simulations according to implant depth. ACn2 could not be assessed at –6 mm. Green: mild; yellow: moderate. ACn2: ACURATE neo2; NA: not applicable; PWI: pinwheeling index; THV: transcatheter heart valve*

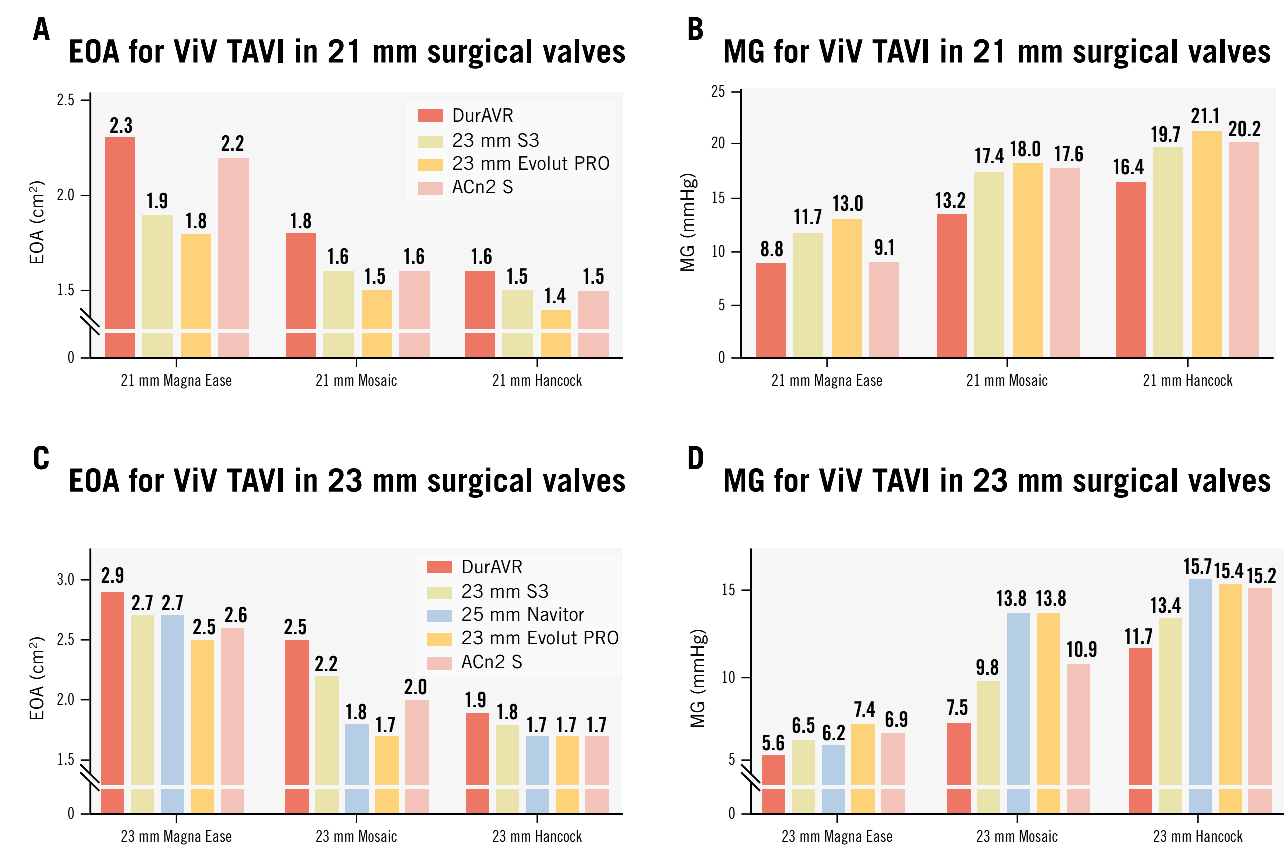


Figure 4. *Effective orifice area and mean gradient in ViV TAVI simulations. Effective orifice area (EOA) and mean gradient (MG) of ViV configuration in 21 mm index surgical valves (A, B) and in 23 mm index surgical valves (C, D). ACn2 S: ACURATE neo2 small; S3: SAPIEN 3; TAVI: transcatheter aortic valve implantation; ViV: valve-in-valve*

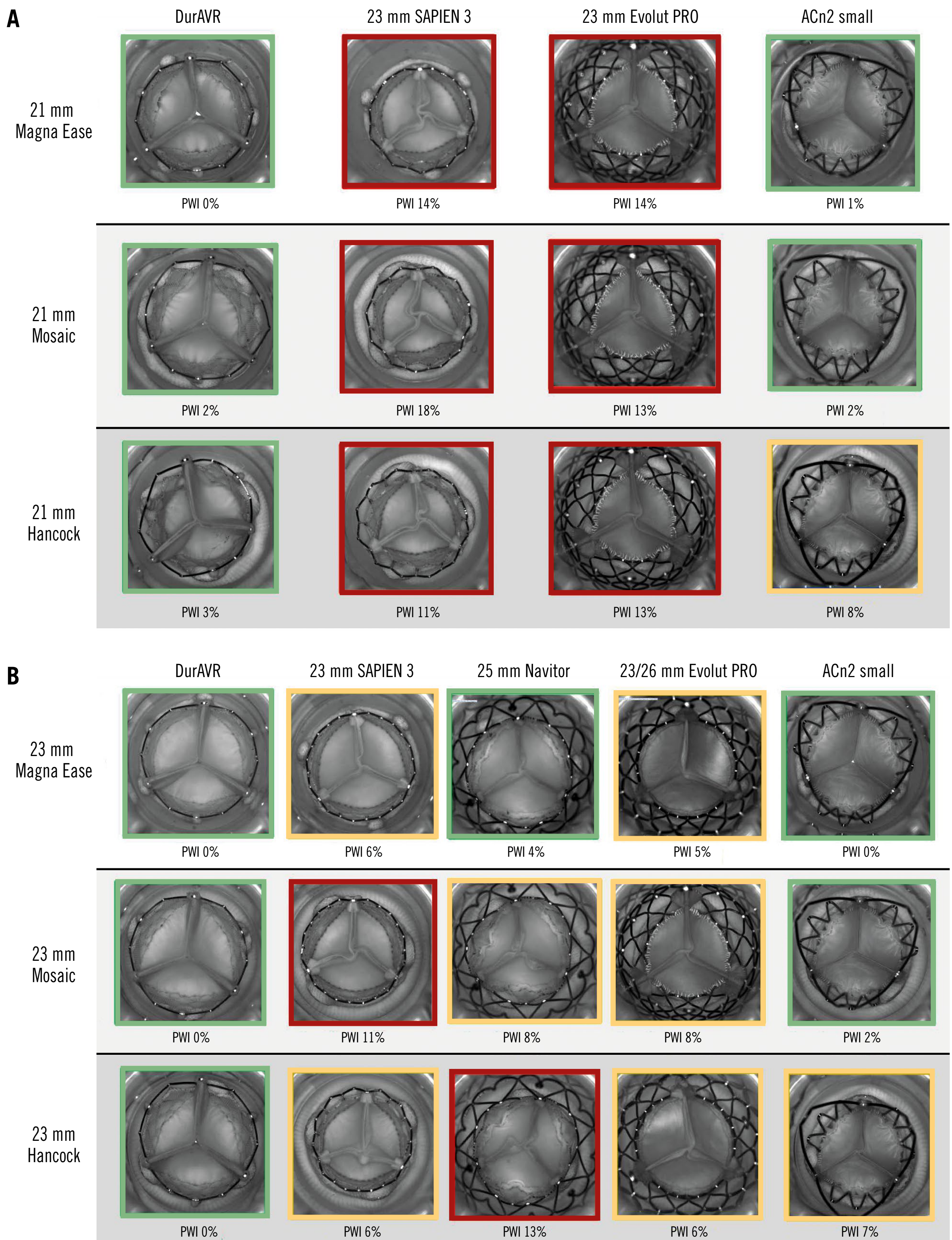


Figure 5. *Pinwheeling index and representative hydrodynamic testing images in diastole of the THVs in ViV configurations. PWI of ViV configurations in 21 mm index surgical valves (A) and in 23 mm index surgical valves (B). Green: mild; yellow: moderate; red: severe. ACn2: ACURATE neo2; PWI: pinwheeling index; THV: transcatheter heart valve; ViV: valve-in-valve*

DurAVR THV exhibited larger EOAs and lower MGs than its comparators in each index THV configuration **(Figure 6A, Figure 6B)**. In all four configurations, the DurAVR THV demonstrated an MG ≤8 mmHg and an EOA ≥2.4 cm².

PINWHEELING FOR THE REDO-TAVI CONFIGURATIONS

Figure 6C, **Supplementary Figure 5** and **Moving image 3** present the different degrees of pinwheeling observed in the various redo-TAVI configurations. When redo-TAVI was modelled in a failed S3, the DurAVR THV and ACn2 showed no pinwheeling (0%). In contrast, other THVs (Evolut PRO, Navitor, S3) demonstrated moderate to severe pinwheeling when implanted in an S3. In the case of redo-TAVI modelled in a failed Navitor, ACn2, and S3, DurAVR THV was compared to S3 only. In these configurations, the DurAVR THV showed notably less pinwheeling than the S3. However, due to the extent of leaflet overhang, pinwheeling measurements were not possible at all in the cases modelled in a failed Evolut PRO, and in one case modelled in a failed ACn2, only visual estimation was possible.

Discussion

In this bench evaluation of the DurAVR TAVI system, we demonstrate that this new platform has (1) excellent hydrodynamic performance in native simulations compared to other platforms; (2) superior hydrodynamic performance to other platforms when tested in ViV TAVI and redo-TAVI configurations; and (3) less susceptibility to pinwheeling than other platforms **(Central illustration)**.

Early clinical experience has shown promising valve performance with the DurAVR TAVI system[11]. In lieu of clinical comparative data with other commercially available THVs, we show on the bench that the DurAVR THV is consistently associated with MGs <10 mmHg and large EOAs, independent of implant depth. These results are consistent with the observed data in the first-in-human experience[11], which demonstrated stable haemodynamics up to 1 year. Although the DurAVR THV presented with numerically lower values than the comparators, MGs were similar across platforms.

In the ViV TAVI configurations, where THVs are generally constrained by the surgical valve, the DurAVR THV performed better than the comparator THV platforms. This benefit was

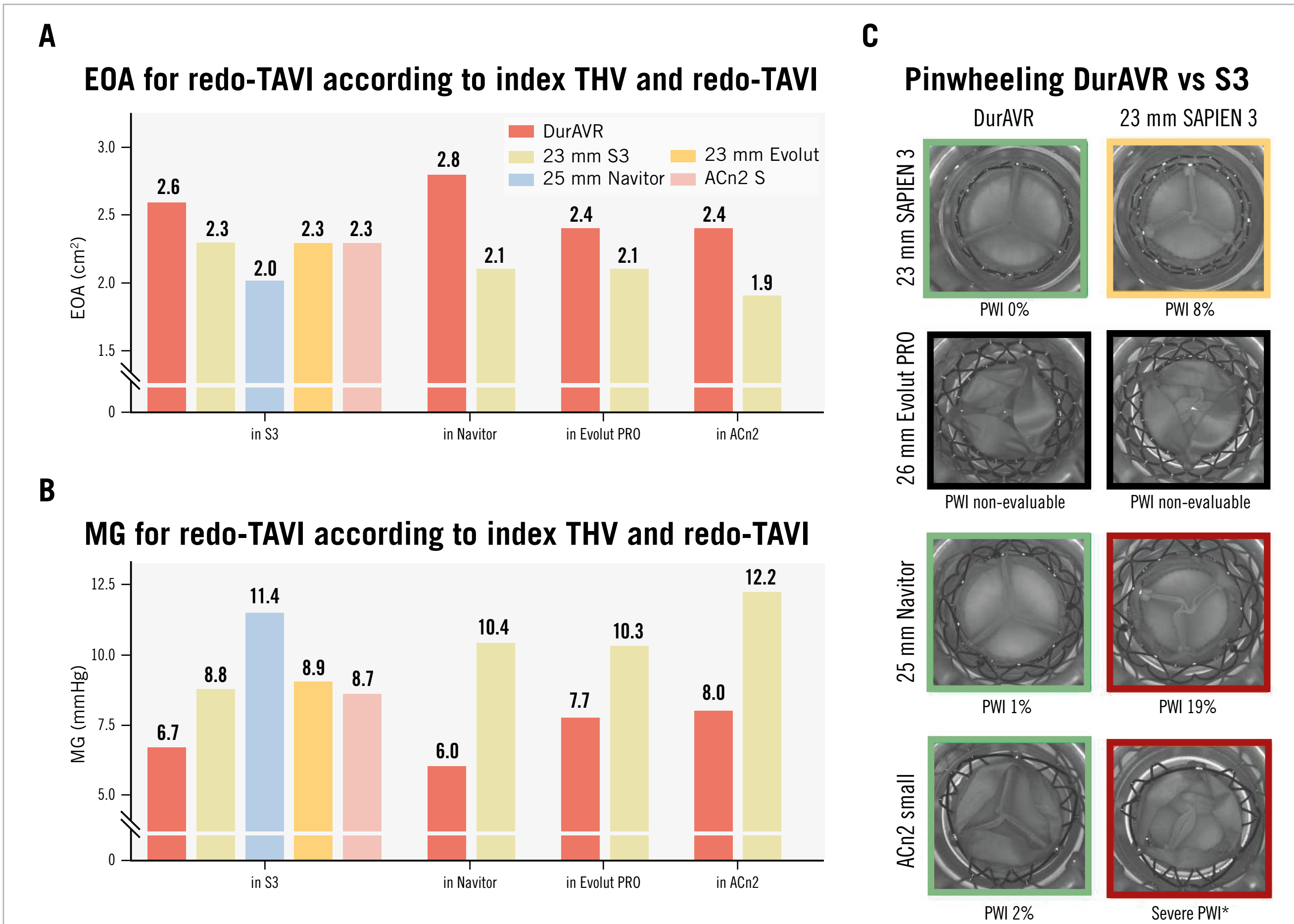


Figure 6. *Effective orifice area, mean gradient and pinwheeling index in redo-TAVI simulations. Effective orifice area (EOA), mean gradient (MG) (A, B) and pinwheeling index (PWI) with representative hydrodynamic testing images in diastole (C). Green: mild, yellow: moderate, red: severe. *Visual estimation. ACn2 S: ACURATE neo2 small; S3: SAPIEN 3; TAVI: transcatheter aortic valve implantation*

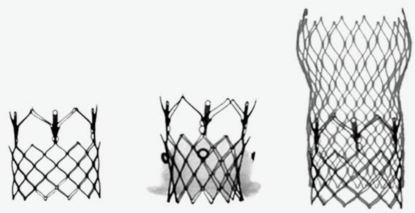
Functional assessment of the DurAVR THV in TAVI simulations.

DurAVR for TAVI, ViV TAVI and redo-TAVI

Multimodality *ex vivo* evaluation of the DurAVR with hydrodynamic testing, fluoroscopy and high-speed videos

A STUDY PROCEDURES

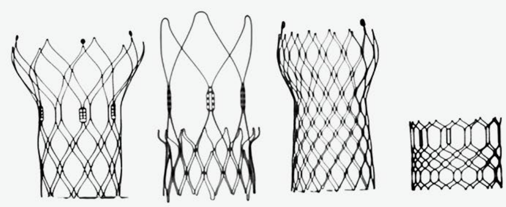
DurAVR



Native TAVI | ViV TAVI | Redo-TAVI

DurAVR tested in three settings (native, ViV and redo-TAVI)

Comparators

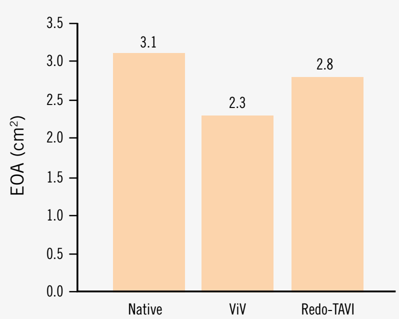


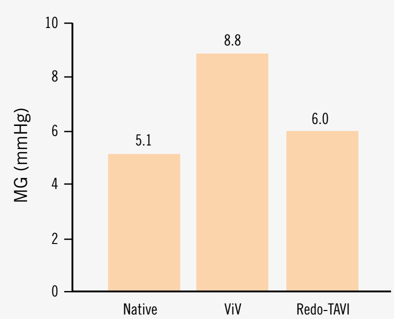
Navitor | ACURATE *neo2* | Evolut PRO | SAPIEN 3

Comparison with 4 of the most commonly used transcatheter heart valves

Total of 52 combinations

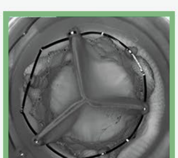
B MAIN RESULTS





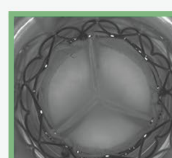
DurAVR generally showed excellent hydrodynamic performance and almost no pinwheeling

Native TAVI
PWI 0%



ViV TAVI in Hancock
PWI 3%

Redo-TAVI in S3
PWI 0%



Redo-TAVI in Navitor
PWI 1%

C ON THE BENCH, THE DURAVR THV DEMONSTRATED SUPERIOR HYDRODYNAMIC PERFORMANCE IN NATIVE TAVI, ViV TAVI AND REDO-TAVI SIMULATIONS COMPARED TO OTHER AVAILABLE THVS.

David Meier *et al.* • *EuroIntervention* 2025;21:e1090-e1101 • DOI: 10.4244/EIJ-D-24-01000

A) Functional assessment of the DurAVR THV and other THV platforms was performed (total of 52 combinations) with pulsatile testing allowing for measurement of MG/EOA. High-speed videos were recorded to assess leaflet motion and pinwheeling. B) Main results of bench testing of EOA and MG for DurAVR at 3 mm depth of native TAVI, in 21 mm Magna Ease ViV, and in Navitor redo-TAVI configurations. C) Study conclusions. EOA: effective orifice area; MG: mean gradient; PWI: pinwheeling index; TAVI: transcatheter aortic valve implantation; THV: transcatheter heart valve; ViV: valve-in-valve more pronounced in the smaller SHVs and was different according to SHV type. This is a potentially important finding since ViV TAVI is often associated with an elevated residual gradient[15], and some data have suggested that in small SHVs, BE short-frame THVs might have higher residual gradients[6]. Moreover, there is perception that tall-frame SE THVs are associated with a better haemodynamic profile for both index and ViV TAVI. Here, we show the importance of performing a detailed assessment of a new THV design without assuming a class effect. Indeed, the short-frame BE DurAVR THV had a comparative or better hydrodynamic profile than the SE comparators. This may be related to the moulded single-leaflet design.

In the redo-TAVI setting, the DurAVR THV displayed larger EOAs and lower, single-digit gradients compared to the other THV platforms, including SE tall-frame valves. This is a key finding to note, as redo-TAVI with tall-frame SE platforms has generally been associated with superior haemodynamics[16].

Another important finding of this study is the minimal degree of pinwheeling observed in the DurAVR THV in native, ViV and redo-TAVI simulations. The difference compared to the other THV platforms was, however, much more marked in the ViV and redo-TAVI simulations. With the current THV platforms, pinwheeling is a phenomenon generally seen in the context of valve underexpansion[17], which, in turn, has been associated with increased propensity for leaflet thrombus formation and may have negative clinical implications for the patient[18,19]. On the bench, pinwheeling has been shown to cause more leaflet strain, impact turbulent flow and reduce durability. Studies assessing underexpanded S3 and ACn2 valves subjected to pinwheeling through 200 million cycles in ViV configurations showed a larger degree of leaflet histological ultrastructure damage compared to fully expanded valves[10,20-22]. However, despite its short frame, which is only slightly taller than the S3, and its visible underexpansion in the ViV configurations, the DurAVR THV displayed almost no pinwheeling. This suggests that the single-piece leaflet design with a long coaptation surface area could potentially offer a protective effect against pinwheeling, which, in turn, could reflect the near-physiological flow that has been observed during early clinical experience.

Limitations

The study is presented with the known limitations inherent to bench testing. THV expansion might be somewhat different within a calcified annulus or a degenerated SHV or THV, as these factors were not represented in this study. Nevertheless, the present work suggests that in similar conditions, the DurAVR THV performs at least as well as its comparators. Additionally, only one size of THV was tested and one sample was used for each combination, and it remains unknown whether similar findings would have been obtained with larger index surgical valves and THVs. Additional bench studies are needed to investigate the impact of varying degrees of commissural alignment on hydrodynamic function, the outcomes of accelerated wear testing on function and leaflet integrity, and the implications of the DurAVR valve design on neoskirt height and any subsequent impact on the feasibility of coronary access. Future studies could also consider comparing systolic and diastolic flow between platforms and assessing susceptibility to calcification or thrombosis. While this bench study provides needed insight into the function of the DurAVR THV compared to other THV platforms, ultimately the evaluation of valve function and durability will need to be determined through ongoing and future clinical trials.

Conclusions

In this study, the novel DurAVR THV demonstrated excellent hydrodynamic performance in native TAVI, ViV TAVI, and redo-TAVI simulations compared to other commercially available balloon-expandable and self-expanding THVs.

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Funding

This work was supported by Anteris Technologies.

Conflict of interest statement

D. Meier has received an institutional grant from Edwards Lifesciences. S.L. Sellers is a consultant for Edwards Lifesciences, Anteris Technologies, Excision Medical, and Medtronic; and has received research support from Edwards Lifesciences, Medtronic, and HeartFlow. J.L. Cavalcante has received consulting fees from 4C Medical, Abbott, Anteris Technologies, Boston Scientific, Edwards Lifesciences, JenaValve, and Medtronic; has received research grants from Abbott, Allina Health Foundation, JenaValve, and NIH/NHLBI; and he has received honoraria or consultation fees from 4C Medical, Abbott, Alleviant, Anteris Technologies, Boston Scientific, Edwards Lifesciences, JenaValve, JC Medical, Medtronic, Novo Nordisk, Siemens Healthineers, VDyne, and Zoll. M. Settergren is a consultant for Anteris Technologies, Edwards Lifesciences, and Boston Scientific. C.U. Meduri is the chief medical officer of Anteris Technologies; and serves as a consultant to Boston Scientific, Abbott, Alleviant, VDyne, Cardiovalve, xDot Medical, and V2V; he has received research funding from Edwards Lifesciences and Medtronic. A.W. Asgar has been a consultant for/on an advisory board for Medtronic and Abbott; and has been a consultant for Edwards Lifesciences. R.T. Hahn reports speaker fees from Abbott, Baylis Medical, Edwards Lifesciences, Medtronic, Philips, and Siemens Healthineers; institutional consulting contracts for which she receives no direct compensation with Abbott, Edwards Lifesciences, Medtronic, and Novartis; and she is Chief Scientific Officer for the Echocardiography Core Laboratory at the Cardiovascular Research Foundation for multiple industry-sponsored tricuspid valve trials, for which she receives no direct industry compensation. J. Sathananthan is an employee of Boston Scientific; has been a consultant to Edwards Lifesciences, Medtronic, and Anteris Technologies; and has received research support from Medtronic, ViVitro Labs, and Edwards Lifesciences. The other authors have no relevant conflicts of interest to declare.

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Supplementary data

Supplementary Figure 1. Schematic outlining test configurations for native TAVI, ViV TAVI, and redo-TAVI.

Supplementary Figure 2. Photographic and fluoroscopic views of valve-in-valve implants within the 21 mm surgical valves.

Supplementary Figure 3. Photographic and fluoroscopic views of valve-in-valve implants within the 23 mm surgical valves.

Supplementary Figure 4. Photographic and fluoroscopic views of redo-TAVI configurations.

Supplementary Figure 5. Pinwheeling index (PWI) and representative hydrodynamic testing images in diastole of the redo-TAVI with Navitor, Evolut PRO, and ACn2 in SAPIEN 3.

Moving image 1. Hydrodynamic testing for native TAVI implants at 3 mm depth.

Moving image 2. Hydrodynamic testing for valve-in-valve implants in 21 mm Magna Ease.

Moving image 3. Hydrodynamic testing for redo-TAVI configurations with implantation in SAPIEN 3.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-24-01000

EuroIntervention
2025;21:e1102-e1105
published online e-edition September 2025
DOI: 10.4244/EIJ-D-25-00255

RESEARCH CORRESPONDENCE

Redo-TAVI with the ACURATE platform for failure of short-frame transcatheter heart valves

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This paper also includes supplementary data published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-25-00255

Editorial note

On 28 May 2025, the manufacturer announced the global discontinuation of sales of its ACURATE *neo*2 and ACURATE Prime aortic valve systems. The following correspondence, submitted and accepted prior to the market withdrawal, discusses clinical experience with this device. Though no longer relevant for current practice, the Editorial Board believes it is important to document these findings in the interest of transparency and completeness of the scientific record. Accordingly, we are publishing this work as a Research Correspondence, with acknowledgement of the device's discontinued status.

As transcatheter aortic valve implantation (TAVI) is now performed in patients with longer life expectancy, the need for a second aortic valve procedure is expected to increase. Balloon-expandable short-frame SAPIEN 3/Ultra transcatheter heart valves (THVs; Edwards Lifesciences) are frequently selected for younger patients undergoing TAVI due to their lower likelihood of impairing coronary access and a design that may facilitate future redo-TAVI procedures[1]. Consequently, a consistent proportion of reinterventions is anticipated to involve degenerated short-frame THVs. While redo-TAVI with a same-sized SAPIEN 3/Ultra THV is usually feasible, recent bench studies indicate that the ACURATE platform (*neo*2/Prime [Boston Scientific]) might offer more favourable haemodynamic performance and minimal pinwheeling, particularly in smaller valve sizes[2]. Furthermore, the large-cell design of the ACURATE THV may more easily facilitate future coronary access compared to other supra-annular closed-cell THVs[3]. This paper is the first to provide practical guidance for performing redo-TAVI with the ACURATE THV in failing short-frame THVs, based on initial real-world clinical experience.

PREPROCEDURAL PLANNING

As with all redo-TAVI cases, assessing neoskirt height, coronary ostia height, valve-to-coronary (VTC), and valve-to-aorta (VTA) distances is critical to evaluate the risk of coronary flow impairment and feasibility of the procedure[4]. In this particular configuration – placement of a tall-frame THV within a short-frame THV – the leaflets of the degenerated valve are anticipated to be completely displaced upward following deployment of the second valve. The latest ACURATE platforms feature an outer sealing skirt that extends to the lower edge of the upper crown that typically caps the native leaflets (14-17 mm from S to XL). These upper crowns are designed to prevent ventricular movement and create space for coronary access, projecting 2.5 mm beyond the nominal valve size at 3 locations in between the commissures. Complete ACURATE THV expansion requires positioning the upper crown above the SAPIEN THV's outflow, resulting in a neoskirt higher than the stent frame of the failing valve. Consequently, preprocedural computed tomography (CT) should measure the VTC and VTA distances relative to the predicted neoskirt height, considering the risk of sinus sequestration **(Figure 1A)**. In general, when the coronary ostia are located below the level of the neoskirt, a VTC or VTA distance of less than 4 mm should prompt consideration of coronary protection strategies, including the potential use of chimney stenting. Even if a higher neoskirt does not impair coronary perfusion, upper crowns in smaller aortic root anatomies could complicate selective coronary engagement **(Figure 1B)**.

SIZING AND POSITIONING

Based on bench data, ACURATE *neo*2/Prime sizing recommendations for the treatment of SAPIEN 3/Ultra failure

SUBMITTED ON 09/03/2025 - REVISION RECEIVED ON 26/04/2025 - ACCEPTED ON 05/05/2025

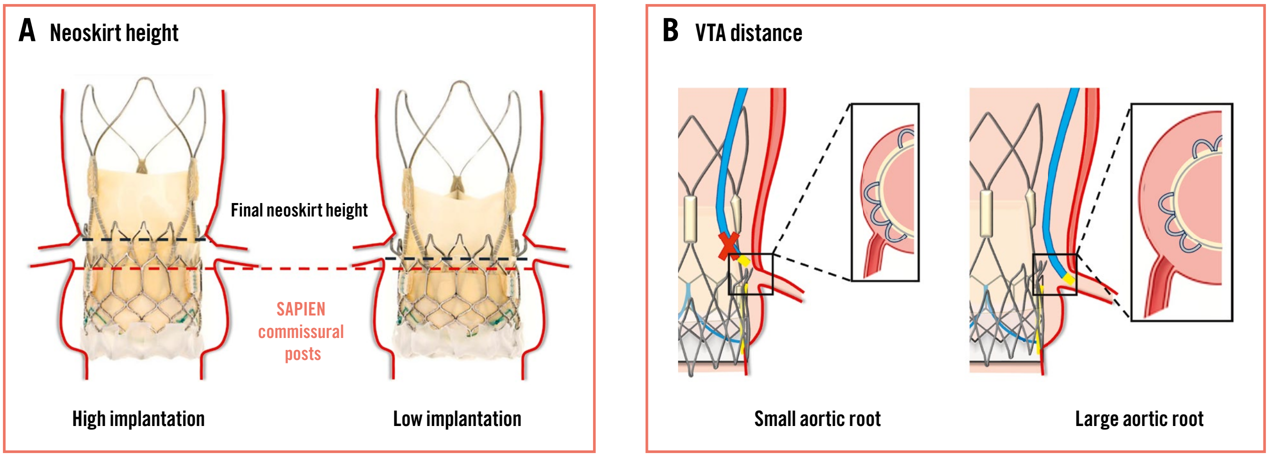

Figure 1. *Preprocedural assessment of the risk of coronary obstruction and coronary access impairment with ACURATE-in-SAPIEN redo-TAVI. A) Neoskirt height and risk of sinus sequestration with low versus high ACURATE THV implantation. B) Possible coronary access impairment despite preserved coronary artery perfusion in patients with small versus large aortic root anatomies. TAVI: transcatheter aortic valve implantation; THV: transcatheter heart valve; VTA: valve-to-aorta*

are reported in **Supplementary Table 1**. When the original THV is appropriately sized and expanded, haemodynamic performance after redo-TAVI is minimally influenced by the native annular dimensions[2]. However, the expansion of the SAPIEN THV should also be carefully assessed on CT imaging, as the measured true internal diameter and area directly impact the sizing of the ACURATE THV.

As previously explained, to ensure full expansion of the ACURATE THV, its upper crown must be positioned above the SAPIEN THV outflow. Higher implantation (upper crowns approximately 3 mm above the SAPIEN 3 stent frame) has demonstrated slightly lower (<3 mmHg) anterograde gradients *in vitro*, especially in the 20 mm and 23 mm short-frame THVs[2]. The clinical impact of this haemodynamic variation requires further real-world studies. The potential benefits of a higher implantation must be weighed against the increased risk of sinus sequestration, especially in patients with a narrow sinotubular junction.

PROCEDURAL CONSIDERATIONS

The first case series of redo-TAVI using the ACURATE platform in a short-frame THV is reported in **Supplementary Figure 1-Supplementary Figure 7**. Based on this initial clinical experience, the key procedural recommendations include the following:

1) Predilatation: strongly consider predilatating the failed THV to ensure optimal ACURATE THV expansion, particularly when the failure mechanism is stenosis.
2) Commissural alignment: this should always be pursued to facilitate future coronary access. Notably, the cusp-overlap projection should be calculated based on the native aortic root CT scan (if available) or on the coronary position at the pre-redo-TAVI CT scan (i.e., “coronary overlap view”) **(Figure 2A)**. Alignment of the failing short-frame valve is of little importance, given the futility of bioprosthetic or native aortic scallop intentional laceration to prevent iatrogenic coronary artery obstruction (BASILICA) during TAVI in this type of redo-TAVI combination. Implantation techniques to achieve commissural alignment should be performed as previously reported in TAVI for native aortic stenosis[5].
3) Eliminating parallax: before deployment, ensure no parallax on the SAPIEN THV in both the 3-cusp and cusp-overlap views.
4) Deployment strategy: start ACURATE deployment **(Figure 2B)** only after confirming that the upper crown hooks will open just above the SAPIEN 3 outflow. Ignore the annular radiopaque marker and focus on the upper crown’s position relative to the SAPIEN frame. If the upper crown has been opened within the stent frame of the SAPIEN frame, it might be possible to reposition the upper crown above the outflow part by careful wire manipulation, especially if only one side of the upper crown is hooked inside the SAPIEN frame. Final positioning (low vs high implant) can be adapted once the opening of knob 1 has been completed, based on preprocedural considerations about sinotubular junction dimensions and the risk of coronary flow impairment. However, the last movement of the delivery catheter before opening knob 2 should always be forward.
5) Delivery system removal: centralise the system by retracting the wire loop to ensure safe removal.
6) Evaluate outcomes: always evaluate valve expansion at fluoroscopy (both in the 3-cusp and cusp-overlap views) and measure invasive gradients to verify haemodynamic results and decide on post-dilatation. Given the presence of the protruding upper crowns, the possible risk of aortic root injury with post-dilatation should always be considered, particularly in smaller aortic root anatomies **(Supplementary Figure 8)**. The upper crown extends maximally 2.5 mm beyond the ACURATE valve waist in each sinus; there may be less protrusion if the degenerated SAPIEN leaflets are bulky/calcified and thus prevent the ACURATE frame fully extending to the edge of the SAPIEN valve.

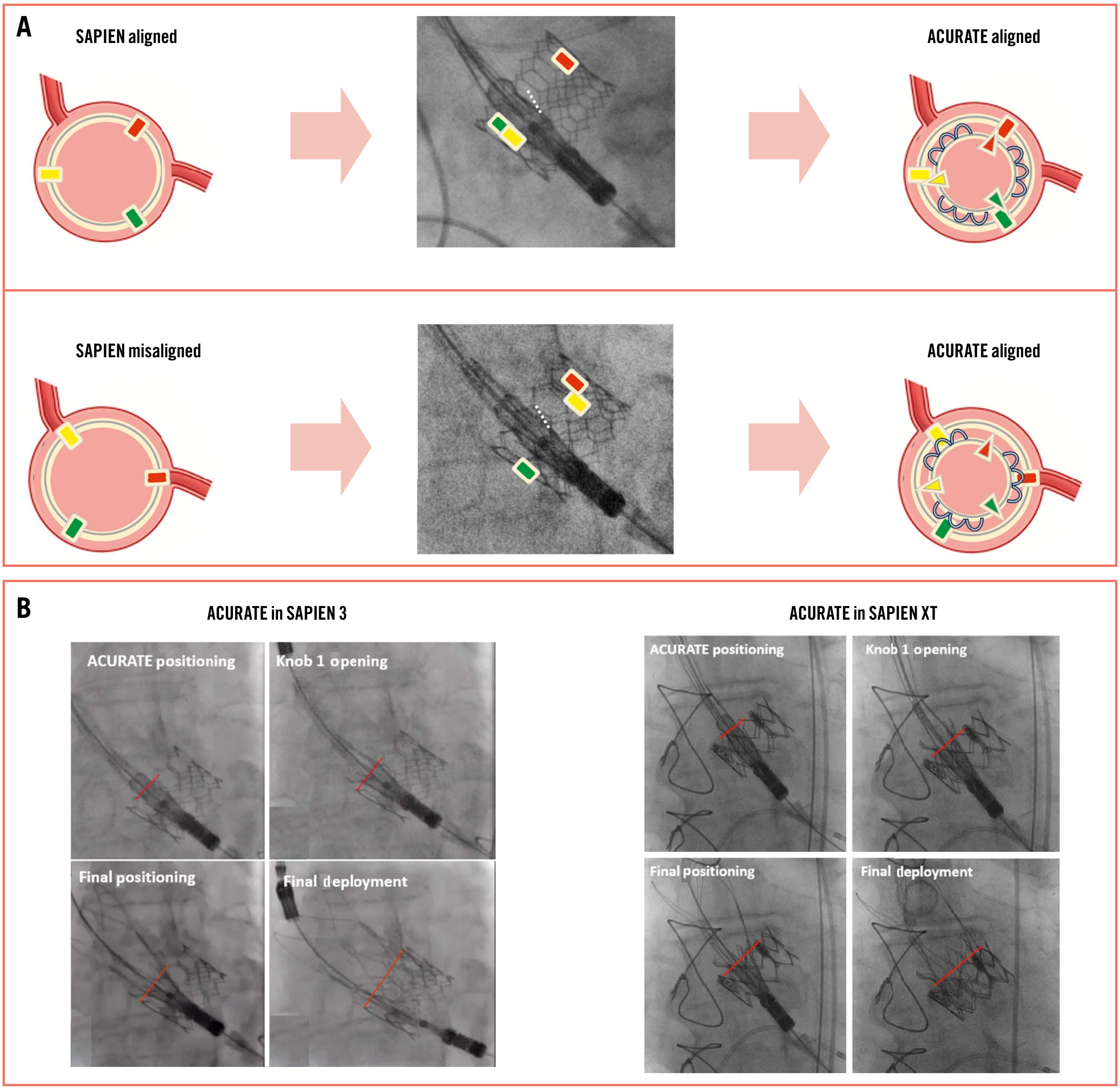

Figure 2. *Procedural considerations during ACURATE-in-SAPIEN redo-TAVI. A) Commissural alignment of the ACURATE THV. The cusp-overlap view should be calculated based on native aortic valve anatomy, disregarding the position of the SAPIEN THV commissural posts. B) Step-by-step deployment of an ACURATE neo2 valve in a degenerated SAPIEN 3 (left) and SAPIEN XT (right) THV. The operator needs to check that the upper crown is positioned above the short-frame THV outflow to ensure the complete expansion of the ACURATE THV. TAVI: transcatheter aortic valve implantation; THV: transcatheter heart valve*

Conclusions

The use of supra-annular THVs with a large-cell design for failing short-frame THVs offers theoretical advantages in haemodynamic performance and future coronary access. Understanding the specific preprocedural and procedural considerations of this redo-TAVI combination is vital to mitigate risks and optimise outcomes. Our initial clinical experience underscores the necessity for larger studies to validate the safety and long-term effectiveness of this approach.

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Conflict of interest statement

G. Tarantini reports honoraria for lectures/consulting from Medtronic, Edwards Lifesciences, Boston Scientific, Abbott, and SMT. W.-K. Kim reports personal fees from Abbott, Boston Scientific, Edwards Lifesciences, JenaValve, and Meril Life Sciences; and institutional fees from Boston Scientific. N. Mangner received research and an educational grant from Abiomed to his institution, outside the submitted work; an educational grant from Boston Scientific to his institution, outside the submitted work; received personal fees from Edwards Lifesciences, Medtronic, Biotronik, Novartis, Sanofi Genzyme, AstraZeneca, Pfizer, Daiichi Sankyo, Abbott, Abiomed, B. Braun, and Boston Scientific, outside the submitted work. R. Parma reports honoraria for lectures from Edwards Lifesciences. L. Nai Fovino reports honoraria for lectures/consulting from Edwards Lifesciences; and a research grant from Medtronic. The other authors have no conflicts of interest to declare.

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Supplementary data

Supplementary Table 1. General ACURATE platform sizing recommendations based on failing SAPIEN 3/Ultra THV size.
Supplementary Figure 1. Clinical case #1.
Supplementary Figure 2. Clinical case #2.
Supplementary Figure 3. Clinical case #3.
Supplementary Figure 4. Clinical case #4.
Supplementary Figure 5. Clinical case #5.
Supplementary Figure 6. Clinical case #6.
Supplementary Figure 7. Clinical case #7.
Supplementary Figure 8. Case example of a patient with a small aortic root and high risk of aortic injury with redo-TAVI with ACURATE *neo*2/Prime, particularly if post-dilatation is required.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-25-00255

EuroIntervention
2025;21:e1106-e1107
published online e-edition September 2025
DOI: 10.4244/EIJ-D-25-00121

Calcium mapping by 3DStent technology

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This paper also includes supplementary data published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-25-00121

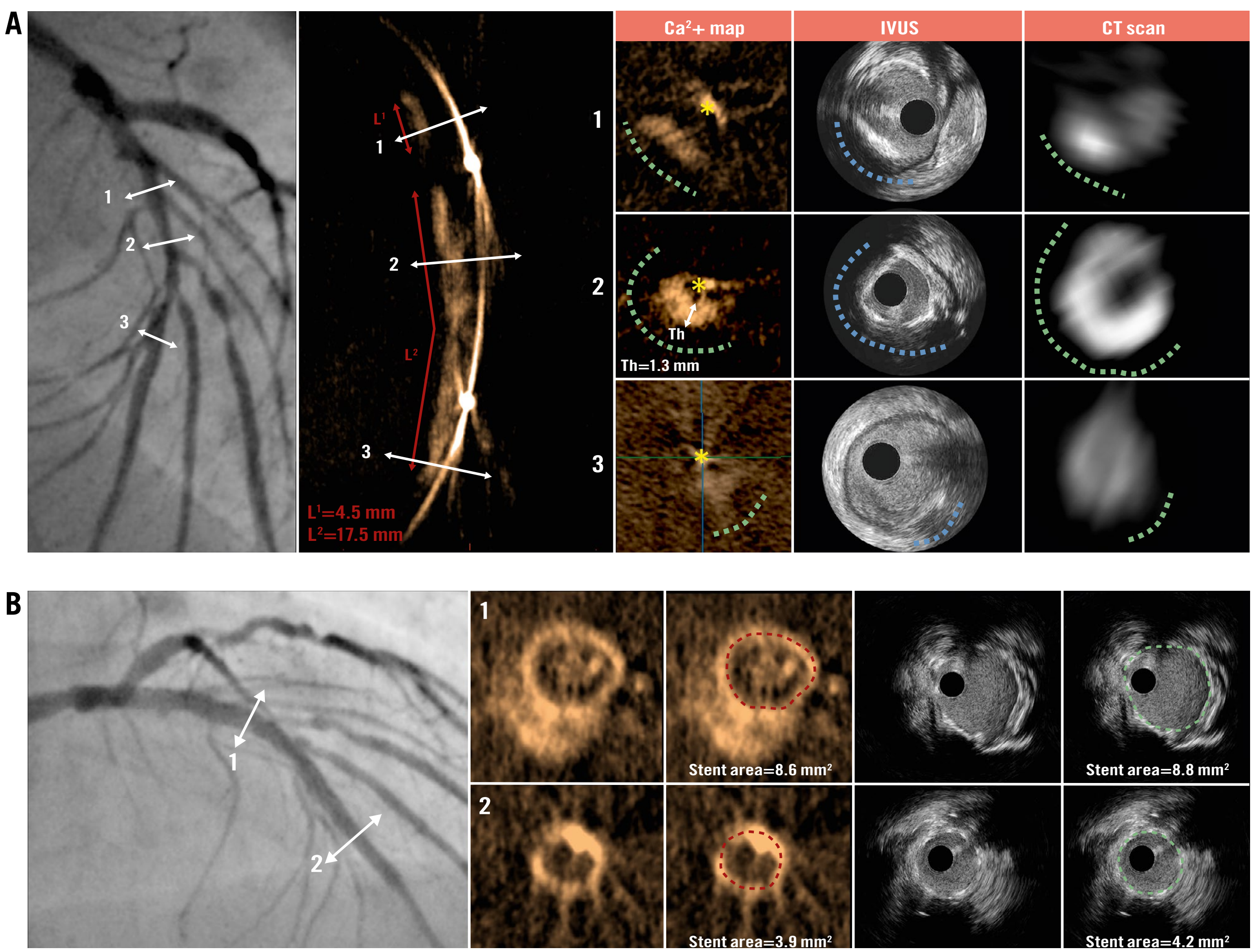

Figure 1. *Pre- and post-stenting LAD analysis. A) Multimodal calcium burden analysis in an LAD lesion. The head-to-head comparisons between Ca^{2+} mapping, IVUS, and CT scan are presented for different cross-sections within the LAD (1, 2 and 3). The X-ray-based methods and IVUS analyses displayed concordant results for calcium radial extent (green dashed lines for Ca^{2+} mapping and CT scan; blue dashed line for IVUS; yellow asterisk indicates the position of the wire), with a maximal arch of 270° (mid-LAD/section 2). In addition, Ca^{2+} mapping provided evaluation of calcification thickness and longitudinal extent. B) Post-stenting analysis by 3DStent and IVUS. The head-to-head comparisons between 3DStent and IVUS are presented for the proximal (1) and distal (2) parts of the stent. Each cross-section presents raw images and stent area measurement. Ca^{2+}: calcium; CT: computed tomography; IVUS: intravascular ultrasound; LAD: left anterior descending artery; Th: thickness*

SUBMITTED ON 03/02/2025 - REVISION RECEIVED ON 1st 07/03/2025 / 2nd 05/04/2025 - ACCEPTED ON 08/04/2025

A 78-year-old man with stable angina, a positive stress test, and a tight left anterior descending artery (LAD) with a mildly calcified lesion on computed tomography (CT) scan **(Moving image 1)** was referred for coronary angiography. The angiography confirmed the stenosis, and percutaneous coronary intervention (PCI) of this lesion was proposed.

We analysed the calcium burden with a multimodal approach to plan the intervention and the plaque preparation. After initial angiography **(Moving image 2)**, we performed X-ray-based calcium (Ca^2+) mapping through adaptation of the 3DStent technology (3DS; GE HealthCare) to the native vessel[1]. A deflated 2.0x15 mm PCI balloon was first placed within the target lesion, and a 200° rotational angiography was acquired **(Supplementary Figure 1)**. The data were processed through dedicated software which produced 0.1 mm voxel-based images that were visualised with different standard rendering methods, including a three-dimensional image that was analysable in different projections **(Supplementary Figure 1, Moving image 3)** and cross-section views **(Figure 1A)**. These images provided two- and three-dimensional representations of the calcifications within the plaque and allowed the relevant assessment of calcium arc radial extension, thickness, and length.

A pre-PCI intravascular ultrasound (IVUS) analysis was performed to confirm plaque composition and to determine stent diameter and length **(Moving image 4)**. The Ca^{2+} mapping, IVUS, and CT scan images correlated for the calcium radial and longitudinal extents **(Figure 1A)**. The maximal calcium arc radial extent was measured at 270° in the mid-LAD.

In view of these results, 3.0x15 mm non-compliant balloon predilation was performed and followed by 3.0x38 mm everolimus-eluting stent implantation and balloon post-dilation. Final angiography **(Moving image 5)**, 3DS, and IVUS **(Moving image 6)** analyses revealed a satisfactory result with adequate device expansion and an absence of complications, yet a mild distal myocardial bridge was observed **(Figure 1B)**. The final dose area product was 53.6 Gy·cm^2, including 16.6 Gy·cm^2 for Ca^{2+} mapping and 17.0 Gy·cm^2 for control 3DStent acquisition.

3DStent technology has been initially developed for post-PCI stent structure and expansion assessment[2,3]. Hence, this tool can identify and map any structure with a certain degree of radio-opacity (such as calcium sheets). This case illustrates the correct identification of calcifications within the plaque provided by the tool and the good correlations with intracoronary imaging and CT scan. In addition, Ca^{2+} mapping proposes three-dimensional reconstruction and therefore allowed in this case an evaluation of the calcium thickness that would not be feasible by IVUS (because of the acoustic shadowing inherent to this ultrasound-based technology). Hence, Ca^{2+} mapping might represent a new method to evaluate vessel calcium burden before PCI and might thus be an alternative option to intracoronary imaging when the latter is not available.

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Conflict of interest statement

N. Amabile and H. Benamer received consulting fees from GE HealthCare.

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Supplementary data

Supplementary Figure 1. Ca^{2+} mapping acquisition in the native vessel and examples of 3D representation of the lesion in different views.
Moving image 1. Baseline CT scan.
Moving image 2. Pre-PCI coronary angiography.
Moving image 3. Pre-PCI Ca^2+ mapping analysis.
Moving image 4. Pre-PCI IVUS analysis.
Moving image 5. Post-PCI angiography.
Moving image 6. Post-PCI IVUS analysis.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-25-00121