

ADVANCING CONTEMPORARY CORONARY DIAGNOSTICS AND INTERVENTIONS

Integrating Imaging, Pharmacology, and Procedural Innovation to Optimize Patient Outcomes

Valeria Paradies

Propositions pertaining to the PhD

Advancing Contemporary Coronary Diagnostics and Interventions:
Integrating Imaging, Pharmacology, and Procedural Innovation to Optimize Patient Outcomes

1. Up to 50% of ACS patients exhibit multivessel coronary artery disease, which significantly worsens prognosis (this thesis)

2. There is an urgent need for antiplatelet strategies that balance ischemic and bleeding risks in contemporary percutaneous coronary intervention (PCI) practice. (this thesis)

3. Women remain underrepresented in randomized trials investigating acute coronary syndrome and antithrombotic therapy, despite exhibiting distinct clinical and pharmacodynamic profiles. (this thesis)

4. The use of intravascular imaging has become increasingly central to contemporary PCI, particularly for the assessment and treatment of complex lesions. (this thesis)

5. Invasive coronary function testing remains the gold standard for diagnosis and endotype classification of ANOCA patients. (this thesis)

6. The complexity of PCI is determined not only by coronary anatomy but also by patient-specific and procedural factors (N Engl J Med. 2016;375:2223–2235)

7. The clinical benefit of new coronary devices is increasingly determined by implantation technique rather than by the device itself. (Lancet. 2024;403(10429):824-837)

8. First, do no harm (inspired by Hippocrates: “Primum non nocere”)

9. Poor shared decision-making is associated with worse physical and mental outcomes and lower adherence to therapy (European Heart Journal (2024) 00, 1–123)

10. Nothing in life is to be feared, it is only to be understood. Now is the time to understand more, so that we may fear less (inspired by Marie Curie)

11. The major virtue of human beings is the continuous pursuit of virtue and knowledge (inspired by Dante Alighieri, Inferno: “Fatti non foste a viver come bruti, ma per seguir virtute e conoscenza”)

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Prologue

Chapter 1

Introduction

Introduction and Outline of the Thesis

Ischaemic heart disease remains one of the foremost causes of morbidity and mortality globally.[1] In recent decades, the management of coronary artery disease (CAD) has undergone a profound transformation, driven by significant advances in stent technology, intracoronary imaging, physiological assessment, and pharmacological therapy. These innovations have contributed to improved clinical outcomes in a broad range of patients. Nevertheless, considerable challenges remain—particularly in those with acute coronary syndrome (ACS) presentations, anatomical complexity, high bleeding risk, or angina in the absence of obstructive coronary disease.

The overarching objective of this thesis is to explore how innovation in imaging, physiology, pharmacology, and procedural strategy can be integrated to optimize diagnostic accuracy, procedural outcomes, and long-term prognosis in both obstructive and non-obstructive coronary disease. Through results of clinical trials, mechanistic studies, state-of-the-art reviews, and expert consensus documents, the thesis aims to address key gaps in contemporary coronary intervention and propose more personalized, physiology- and imaging-guided approaches to care.

The thesis is structured into three interrelated parts:

Part I: Pharmacological Strategies and Revascularization Approaches in ACS patients

Patients presenting with acute coronary syndromes (ACS) are at increased risk of adverse cardiovascular events. Up to 50% of ACS patients exhibit multivessel coronary artery disease (MVD), which significantly worsens prognosis.[2] Numerous clinical trials have demonstrated the benefit of complete revascularization in this population, showing reductions in spontaneous myocardial infarction, cardiovascular mortality, and unplanned revascularization.[3-6]

This section of the thesis explores procedural and pharmacological strategies aimed at optimizing outcomes in ACS, with particular emphasis on approaches to reduce bleeding risk such as early discontinuation of aspirin followed by $P2Y_{12}$ inhibitor monotherapy.

A central element of this section is the COMPARE STEMI ONE trial, which targets patients with ST-segment elevation myocardial infarction (STEMI).[7] The trial evaluates the efficacy and safety of abbreviated DAPT followed by $P2Y_{12}$ inhibitor monotherapy. Recognizing the complex nature of STEMI with multivessel disease, the trial also investigates the benefit of optical coherence tomography (OCT)-guided complete revascularization, underscoring the increasing interest in leveraging intravascular imaging to optimize procedural outcomes.

Complementing this, the TARGET-FIRST trial examines the safety of early DAPT discontinuation followed by $P2Y_{12}$ monotherapy in selected low-risk acute MI patients undergoing complete revascularization within one week.[8] This study responds to the urgent need for de-escalation strategies that balance ischemic and bleeding risks in contemporary PCI practice.

This part includes a chapter on the evolving understanding of vulnerable plaques in non-culprit lesions through multimodality intravascular imaging. This highlights the need for a more comprehensive risk stratification and secondary prevention approach that extends beyond the treatment of the infarct-related artery.[9-11]

Finally, sex-based differences in ACS presentation, treatment response, and outcomes are also critically addressed. Women remain underrepresented in randomized trials, despite exhibiting distinct clinical and pharmacodynamic profiles. A dedicated consensus statement included in this section offers updated, sex-specific recommendations for antithrombotic therapy in women with ACS, contributing to more personalized cardiovascular care.[12,13]

Part II: Device Innovation, Imaging Guidance, and Strategic Planning in Complex PCI

Beyond clinical presentation, a range of anatomical, procedural, and patient-related factors contribute to the overall complexity of percutaneous coronary intervention (PCI).[14] Notably, up to 45% of PCI patients may be classified as having high bleeding risk (HBR).[15] This condition is frequently associated with an increased risk of thrombotic

complications, negatively impacting both short- and long-term outcomes.[16] As a result, selecting an optimal antithrombotic regimen post-PCI becomes particularly challenging in this patient group.

Advances in stent technology such as the development of newer-generation drug eluting stents (DES) with thinner struts, have reduced thrombotic complications and may allow for shorter durations of DAPT.[17] Thinner struts are associated with less flow disturbance, reduced inflammation, and faster endothelial healing, which lowers thrombogenicity.[18] These features make thin and ultra-thin strut DES particularly attractive for HBR patients. The COMPARE 60/80 HBR trial directly addresses this evidence gap by evaluating the safety and efficacy of ultrathin- versus thin-strut DES in patients with HBR, aiming to guide more personalized stent selection strategies for this patient population.[19]

In parallel, the increasing use of intravascular imaging has become central to contemporary PCI, particularly for the assessment and treatment of complex lesions. Imaging now plays a critical role in optimizing lesion preparation and guiding stent implantation, supported by a class I recommendation in the latest chronic coronary syndrome ESC guidelines.[20] This section of the thesis includes studies focusing on the use of imaging to assess calcium modification and fracture, stent expansion in calcified lesions, and the performance of stents with differing strut thickness under these challenging anatomical conditions.

A state-of-the-art review discusses strategic planning for left main coronary artery (LMCA) bifurcation PCI. The chapter covers the technical aspects of optimal provisional stenting, criteria for escalation to two-stent techniques, and reviews both angiographic and intravascular imaging determinants. It also integrates data from key randomized controlled trials and real-world registries to provide a comprehensive overview of best practices in this complex and high-risk anatomical subset.[21]

Finally, the concluding section offers an in-depth exploration of in-stent restenosis (ISR)—the most frequent cause of stent failure after PCI—and its management using emerging technologies, with a particular focus on the role of drug-coated balloons (DCBs).[22]

Part III: Physiological Guidance in Obstructive and Non-Obstructive Coronary Disease

This final section explores the expanding role of coronary physiology in both obstructive and non-obstructive CAD. Special focus is given to patients with ANOCA/INOCA, who account for up to 25% of individuals undergoing angiography for chest pain and yet exhibit no obstructive lesions.[23] Despite the absence of significant stenosis, many of these patients continue to experience debilitating ischaemic symptoms.[24]

The underlying mechanisms are heterogeneous and include coronary microvascular dysfunction (CMD) and vasomotor disorders, such as epicardial or microvascular spasm.[25,26] Invasive coronary function testing (CFT), using endothelium-dependent and endothelium-independent stimuli, remains the gold standard for diagnosis and endotype classification.[27] However, conventional techniques—such as bolus-thermodilution and Doppler-derived flow assessment—are limited by technical complexity and the need for pharmacologic hyperaemia.

Emerging technologies, particularly continuous thermodilution, provide a novel means of assessing absolute coronary flow and microvascular resistance without hyperaemic agents.[28] Ongoing research evaluates the diagnostic value of these metrics across ANOCA endotypes and their correlation with established physiological indices.[29]

This section also includes expert reviews highlighting the pathophysiology of CMD and the need for personalized diagnostic and treatment strategies, especially given the lack of standardised therapeutic pathways.[30,31] Finally, a clinical consensus statement from the European Association of Percutaneous Cardiovascular Interventions (EAPCI) provides updated recommendations for integrating applied coronary physiology in PCI planning, lesion assessment, and post-procedural optimization, underscoring its relevance in both obstructive and non-obstructive CAD.[32]

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Part I – Pharmacological Strategies and Revascularization Approaches in ACS patients

Chapter 2

Prasugrel monotherapy versus standard DAPT in STEMI patients with OCT-guided or angio-guided complete revascularisation: design and rationale of the randomised, multifactorial COMPARE STEMI ONE trial

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Abstract

Monotherapy with a potent P2Y12 receptor antagonist after 1 month of dual antiplatelet therapy (DAPT) may reduce bleeding in the absence of increased ischaemic events compared to 12-month DAPT in patients with acute coronary syndrome undergoing percutaneous coronary intervention (PCI). PCI guidance with optical coherence tomography (OCT) may enhance stent expansion. COMPARE STEMI ONE is an international, multicentre, open-label, randomised controlled trial. In 1,656 ST-segment elevation myocardial infarction (STEMI) patients, prasugrel monotherapy after 1 month of DAPT, as compared to standard 12-month prasugrel-based DAPT, will be tested for non-inferiority for the primary composite endpoint of net adverse clinical events – defined as all-cause death, myocardial infarction, stroke, or Bleeding Academic Research Consortium Type 3 or 5 bleeding events – at 11 months after randomisation. Furthermore, an ancillary substudy will test the superiority of OCT-guided versus angiography-guided staged complete revascularisation in achieving a larger minimal stent area (MSA) in non-culprit lesions during staged procedures. COMPARE STEMI ONE is the first randomised controlled trial assessing an abbreviated 1-month DAPT regimen followed by prasugrel monotherapy in the context of STEMI. The trial will also study the value of OCT-guided PCI in terms of the MSA of non-culprit lesions and may elucidate potential synergies between intravascular imaging-guided PCI and abbreviated DAPT regimens. (ClinicalTrials.gov: NCT05491200)

Introduction

Antiplatelet therapy plays a pivotal role in reducing thrombotic complications and systemic ischaemic events among acute coronary syndrome (ACS) patients undergoing percutaneous coronary intervention (PCI), albeit with an increased risk of bleeding1. In the early phase following PCI for ACS, an aggressive antithrombotic therapy outweighs the risk of bleeding complications. In the maintenance phase (after 30 days), this benefit is counteracted by subsequent higher rates of major bleeding complications, particularly in real-life clinical settings, where patient complexity impacts both haemorrhagic and thrombotic risks2. New-generation drug-eluting stents (DES) and the adoption of intravascular imaging to optimise PCI have reduced the incidence of stent thrombosis

and may justify a less intensive antithrombotic therapy3,4. Recent randomised controlled trials (RCTs) have explored the hypothesis that abbreviated dual antiplatelet therapy (DAPT) with potent P2Y12 antiplatelet drugs may mitigate bleeding risk without increasing ischaemic events5-7. In the absence of compelling data supporting the superiority of one agent over the other, the choice between prasugrel and ticagrelor is primarily driven by physician preference, relative contraindications, market availability, and patient characteristics. This has resulted in an increased use of ticagrelor at discharge8. Although the ISAR-REACT 5 Trial demonstrated a lower incidence of the composite endpoint of death, myocardial infarction (MI) or stroke with prasugrel than ticagrelor in 4,018 ACS patients, limited data are available for abbreviated prasugrel-based DAPT in ACS9-11. Up to 50% of patients with ACS present with multivessel disease (MVD)12. Multiple studies have validated the importance of complete revascularisation, demonstrating fewer unplanned revascularisations and reductions in cardiovascular mortality and spontaneous MI13-16. The European Society of Cardiology (ESC) guidelines endorse a Class I recommendation for complete revascularisation in ST-segment elevation MI (STEMI) patients with MVD, either during the index procedure or within 45 days17. Intravascular imaging optical coherence tomography (OCT) may provide valuable insights into plaque characteristics, including fatty content, fibrous cap thickness, lesion severity, lesion length, and stent landing zones before treatment. It may also help assess stent expansion, apposition, lesion coverage and possible complications after PCI17,18. However, no data exist on the use of intravascular imaging in the context of complete revascularisation or an abbreviated DAPT regimen in the context of STEMI.

Methods

OBJECTIVES AND STUDY DESIGN

COMPARE STEMI ONE is an international, multicentre, open-label, randomised controlled trial with a 1:1 randomisation comparing prasugrel-based short DAPT (30-45 days) followed by prasugrel monotherapy versus a standard DAPT regimen in STEMI patients in terms of net adverse clinical events (NACE). In the subgroup of STEMI patients with MVD, a subrandomisation compares OCTguided complete revascularisation versus

angiography-guided complete revascularisation in terms of efficacy and safety endpoints.

The primary objective of this study is to demonstrate the non-inferiority of 30-45 days of DAPT followed by prasugrel monotherapy versus standard 12-month DAPT (acetylsalicylic acid [ASA]+prasugrel) in patients admitted for STEMI treated with primary PCI regarding the net composite endpoint of ischaemic and bleeding events.

The ancillary objective of the study is to demonstrate the superiority of OCT-guided revascularisation of non-culprit lesion(s) compared to an angiography-guided approach in terms of minimal stent area (MSA) in patients with MVD who undergo staged complete revascularisation after primary PCI. The clinical investigation is being conducted in up to 20 centres across Europe. A total of 1,656 STEMI patients, 50% with MVD, will be enrolled and followed up for 3 years. Patients with MVD who have been randomised to either angio- or OCT-guided PCI and who do not fulfil the eligibility criteria for DAPT randomisation at 30-45 days will be included in the analysis of the co-primary endpoint (post-PCI MSA) and will remain in a parallel registry, receiving clinical follow-up at 1 year. The study design appears in Figure 1.

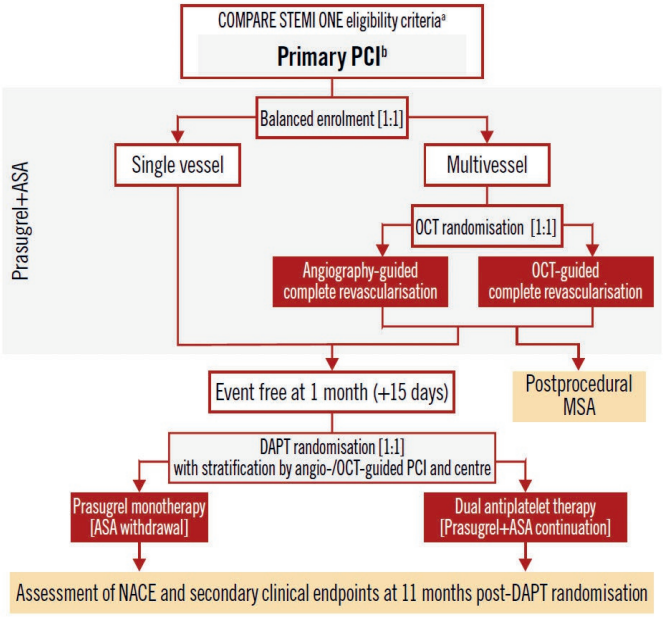


Figure 1. Study design flowchart. aLoading with prasugrel is among the inclusion criteria. bRevascularisation of only the culprit lesion is recommended. ASA: acetylsalicylic acid; DAPT: dual antiplatelet therapy; MSA: minimal stent area; NACE: net adverse clinical events; OCT: optical coherence tomography; PCI: percutaneous coronary intervention

RANDOMISATION AND TREATMENT ALLOCATION

Patients are screened for inclusion immediately after STEMI diagnosis. Patients will be screened and enrolled to achieve a 1:1 trial population of single-vessel disease (SVD) and MVD patients. During the index procedure, only the culprit lesion will be treated as per standard of care. Patients with MVD will undergo staged complete revascularisation within 15 days.

During the staged procedure, patients will be randomised 1:1 to OCT-guided or angio-guided PCI. All patients will undergo an OCT study at the end of PCI.

At 30-45 days, patients with SVD and MVD will be randomised to prasugrel monotherapy (ASA discontinuation) or standard prasugrel-based DAPT if no ischaemic or major bleeding event and no protocol violation have occurred (Figure 2). Among patients with MVD, randomisation to prasugrel monotherapy or DAPT at 30-45 days will be stratified based on the staged revascularisation strategy (OCT- or angio-guided) to ensure balance in the study treatment algorithms. Prasugrel monotherapy or prasugrel-based standard DAPT will be given in an open-label manner.

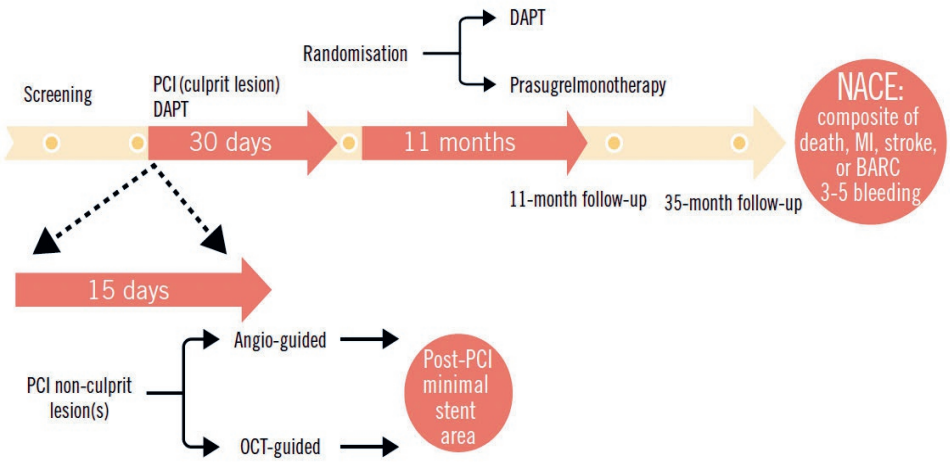


Figure 2. Timeline of COMPARE STEMI ONE. BARC: Bleeding Academic Research Consortium; DAPT: dual antiplatelet therapy; NACE: net adverse clinical events; OCT: optical coherence tomography; PCI: percutaneous coronary intervention

BALANCED SCREENING AND ENROLMENT

Patients will be screened and enrolled to achieve a 1:1 trial population of SVD and MVD patients. Out of every group of 30 patients screened and enrolled per site, 15 patients should present with MVD. After the enrolment of 15 patients with SVD, screening and enrolment of those patients will be temporarily halted until the target number of MVD patients in each group has been reached and vice versa.

STUDY POPULATION, INCLUSION AND EXCLUSION CRITERIA

Consecutive patients admitted for STEMI undergoing primary PCI will be screened and considered for inclusion in the study. Eligible patients will receive ASA as per standard of care and a prasugrel loading dose of 60 mg, followed by 30-45 days of DAPT (ASA+prasugrel 10 mg). In patients with multivessel disease, only primary PCI of the culprit lesion will be allowed during the index procedure. Staged PCI of the non-culprit lesion(s) will be planned within 15 days. During the staged PCI procedure, OCT will be performed at the end of PCI of each vessel, but patients will be randomly assigned 1:1 to OCT- or angio-guided stent optimisation. The XIENCE everolimus-eluting platform (Abbott) will be the preferred stent for the study. Other DES platforms will be used as bailout options. Details on study devices and study procedures are shown in Supplementary Appendix 1 and Supplementary Appendix 2. All patients with no ischaemic or major bleeding event at the 1-month office visit following primary PCI will be randomised 1:1 to receive prasugrel monotherapy (ASA discontinuation) for 11 months or DAPT continuation for 11 months (standard 12-month DAPT duration). The randomisation will occur at 1 month, within a 15-day window, to take into account those patients with MVD undergoing staged complete revascularisation. Figure 1 displays the trial randomisation schemes for STEMI patients with SVD and MVD. Inclusion and exclusion criteria that are relevant during the index procedure and the 1-month clinical follow-up visit are tabulated in Table 1. Further details on investigational procedures, and

concomitant treatments are shown in Supplementary Appendix 3 and Supplementary Appendix 4

Table 1. Inclusion and exclusion criteria

Inclusion criteria
Eligibility at index procedure - Patients of 18 years and above. - Written or witnessed oral consent. - All STEMI patients who are planned to be treated with PCI: *ST segment elevation myocardial infarction* Chest discomfort suggestive of cardiac ischemia ≥20 min at rest with 1 of the following ECG features: • ST segment elevation ≥2 contiguous ECG leads • new or presumably new left bundle branch block **Eligibility at DAPT randomization visit (30-45 days)** - All patients who have provided informed consent - Compliance to DAPT with no regimen modifications (Non-adherence Academic Research Consortium 0 - No occurrence of significant event (such as MI, unplanned revascularisation, stent thrombosis, stroke, major vascular complication/bleeding BARC Types 3 or greater). - Successful revascularization: - Successful delivery and deployment of the Study device(s), with final residual stenosis of <30% (visually) for all target lesions. - Complete revascularization performed when more than 1 significant lesion, in staged procedure(s) occurring within 15 days from the index procedure. Physiologic assessment highly recommended for lesions with stenosis between 50% and 90%
Exclusion criteria
- Patients on oral anticoagulation - Contraindication to P2Y12 inhibitors and/or to Cardioaspirin or to any of the excipients (hypersensitivity, history of any stroke or transient ischemic attack within the last 12 months, active bleeding or haemorrhagic diathesis, fibrin-specific fibrinolytic therapy less than 24 h before randomization, severe hepatic dysfunction (Child-Pugh C), history of asthma induced by the administration of salicylates or substances with a similar action, notably non-steroidal anti-inflammatory medicines, history of gastrointestinal perforation or acute gastrointestinal ulcers, severe cardiac failure (NYHA grade III or IV), combination with methotrexate at doses of 15 mg/week or more). - Patients who have received P2Y12 inhibitors other than Prasugrel in the ambulance (Ticagrelor or Clopidogrel loading dose) or are already on P2Y12 inhibitors, may be enrolled in the protocol, provided that the Prasugrel loading dose is administered at admission, according to current guidelines recommendations. - Concomitant oral or i.v. therapy with strong CYP3A inhibitors (e.g., ketoconazole, itraconazole, voriconazole, telithromycin, clarithromycin, nefazodone, ritonavir, saquinavir, nelfinavir, indinavir, atazanavir, grapefruit juice >1L/day), CYP3A substrates with narrow therapeutic indices (e.g., cyclosporine, quinidine), or strong CYP3A inducers (e.g., rifampin) - rifampicin, phenytoin, carbamazepine, dexamethason, phenobarbital - Platelet count <100.000/µL at the time of screening - Anemia (hemoglobin <10 g/dL) at the time of screening - Comorbidities associated with life expectancy <1 year

- Pregnancy, giving birth within the last 90 days, or lactation (see appendix III for women of childbearing potential) - PCI indication for stent thrombosis or previous history of definite stent thrombosis - Non-deferrable major surgery on DAPT after PCI - Cardiogenic shock - Out of hospital cardiac arrest (OHCA) unless survivors of ventricular arrythmia with prompt return of spontaneous circulation (ROSC)

BARC: Bleeding Academic Research Consortium; DAPT: dual antiplatelet therapy; ECG: electrocardiogram; MI: myocardial infarction; NYHA: New York Heart Association; PCI: percutaneous coronary intervention; STEMI: ST-segment elevation myocardial infarction

ENDPOINTS PRIMARY ENDPOINTS

The study will primarily assess the following endpoints: - NACE: composite endpoint of all-cause death, myocardial infarction, stroke or Bleeding Academic Research Consortium (BARC) Type 3 or 5 bleeding at 11 months post-DAPT randomisation; - postprocedural MSA: final post-PCI MSA assessed by OCT in each randomised arm, measured at an independent OCT core laboratory blinded to imaging modality assignment.

SECONDARY ENDPOINTS

The following secondary endpoints will be assessed at 2, 11 and 35 months: - major adverse cardiac and cerebrovascular events (MACCE): composite endpoint of cardiovascular death, myocardial infarction or stroke; - BARC Type 3 or 5 bleeding; - incidence of target vessel failure: composite of cardiac death, target vessel myocardial infarction (per-protocol [PP] MI definition), or ischaemia-driven target vessel revascularisation; - incidence of stent thrombosis (definite or probable as defined by the Academic Research Consortium [ARC]). Procedural outcomes and additional clinical endpoints are listed in Table 2. Definitions are provided in Supplementary Appendix 5.

Table 2. Inclusion and exclusion criteria.

Inclusion criteria

Eligibility at index procedure

- Patients of 18 years and above.
- Written or witnessed oral consent.
- All STEMI patients who are planned to be treated with PCI:
  <u>*ST segment elevation myocardial infarction*</u>
  Chest discomfort suggestive of cardiac ischemia ≥20 min at rest with 1 of the following ECG features:
  - ST segment elevation ≥2 contiguous ECG leads
  - new or presumably new left bundle branch block

Eligibility at DAPT randomization visit (30-45 days)

- All patients who have provided informed consent
- Compliance to DAPT with no regimen modifications (Non-adherence Academic Research Consortium 0
- No occurrence of significant event (such as MI, unplanned revascularisation, stent thrombosis, stroke, major vascular complication/bleeding BARC Types 3 or greater).
- Successful revascularization: - Successful delivery and deployment of the Study device(s), with final residual stenosis of <30% (visually) for all target lesions.
- Complete revascularization performed when more than 1 significant lesion, in staged procedure(s) occurring within 15 days from the index procedure. Physiologic assessment highly recommended for lesions with stenosis between 50% and 90%

Exclusion criteria

- Patients on oral anticoagulation
- Contraindication to P2Y12 inhibitors and/or to Cardioaspirin or to any of the excipients (hypersensitivity, history of any stroke or transient ischemic attack within the last 12 months, active bleeding or haemorrhagic diathesis, fibrin-specific fibrinolytic therapy less than 24 h before randomization, severe hepatic dysfunction (Child-Pugh C), history of asthma induced by the administration of salicylates or substances with a similar action, notably non-steroidal anti-inflammatory medicines, history of gastrointestinal perforation or acute gastrointestinal ulcers, severe cardiac failure (NYHA grade III or IV), combination with methotrexate at doses of 15 mg/week or more).
- Patients who have received P2Y12 inhibitors other than Prasugrel in the ambulance (Ticagrelor or Clopidogrel loading dose) or are already on P2Y12 inhibitors, may be enrolled in the protocol, provided that the Prasugrel loading dose is administered at admission, according to current guidelines recommendations.
- Concomitant oral or i.v. therapy with strong CYP3A inhibitors (e.g., ketoconazole, itraconazole, voriconazole, telithromycin, clarithromycin, nefazodone, ritonavir, saquinavir, nelfinavir, indinavir, atazanavir, grapefruit juice >1L/day), CYP3A substrates with narrow therapeutic indices (e.g., cyclosporine, quinidine), or strong CYP3A inducers (e.g., rifampin)
- rifampicin, phenytoin, carbamazepine, dexamethason, phenobarbital
- Platelet count <100.000/μL at the time of screening
- Anemia (hemoglobin <10 g/dL) at the time of screening
- Comorbidities associated with life expectancy <1 year
- Pregnancy, giving birth within the last 90 days, or lactation (see appendix III for women of childbearing potential)
- PCI indication for stent thrombosis or previous history of definite stent thrombosis
- Non-deferrable major surgery on DAPT after PCI
- Cardiogenic shock
- Out of hospital cardiac arrest (OHCA) unless survivors of ventricular arrythmia with prompt return of spontaneous circulation (ROSC)

All procedural outcomes are OCT defined (OCT core laboratory assessed). Subjects in the angiography-guided arm will undergo a post-PCI OCT run. Assessed per target lesion. EEL: external elastic lamina; MLA: minimal lumen area; MSA: minimal stent area; OCT: optical coherence tomography; PCI: percutaneous coronary intervention

SAMPLE SIZE CALCULATION

With respect to the antiplatelet therapy study component, a sample size of 1,500 subjects was deemed necessary to assess the non-inferiority of short DAPT followed by prasugrel monotherapy compared with standard prasugrel-based DAPT, with 80% power at a 1-sided α of 0.025. This calculation was based on the assumptions of an anticipated event rate of 3.5% in both groups at 11 months following randomisation (i.e., 12 months post-PCI), consistent with previous studies on DAPT duration after contemporary DES implantation; a non-inferiority margin of 2.0%, corresponding to a hazard ratio of 1.59; an accrual period of 42 months; and a 1:1 treatment allocation ratio. The analysis will be primarily conducted in the per-protocol population. Considering an expected rate of dropout and protocol violations of 10%, the final sample size was increased to 1,6505,6,10,19. With respect to the intravascular imaging guidance study component, in patients with multivessel disease undergoing early staged complete revascularisation, OCT-guided stent optimisation was assumed to produce a 0.4 mm^2 mean reduction in MSA after PCI compared with angiography-guided stent optimisation, assuming a common standard deviation of 2.0 mm^2 20. The analysis will be primarily conducted in the intention-to-treat (ITT) population. Patients will undergo 1:1 stratification in terms of antithrombotic treatment. A sample size of 788 subjects was deemed necessary to test superiority with 80% power at a 2-sided α of 0.05. Considering an expected rate of dropout and protocol violations of 5%, the final sample size was increased to 828. Considering that the reported prevalence of MVD in STEMI patients is 50%, doubling the intravascular imaging guidance study sample size of 828 subjects led to a total of 1,656. In conclusion, a sample size of 1,656 subjects was determined to comprehensively encompass both components of COMPARE STEMI ONE.

PRESPECIFIED SUBGROUP ANALYSIS

Analysis of the primary endpoints will be performed in prespecified subgroups defined by the following: • Age (<75, ≥75 years old) • Sex (male/female) • Diabetes mellitus (yes/no) • High bleeding risk according to the ARC High Bleeding Risk (ARC-HBR) definition (yes/no) • Bifurcation lesion treated with 2 stents • Complex high-risk indicated procedures defined as at least one of the following: a. Angiographic heavy calcification b. Ostial lesion c. True bifurcation lesion involving side branch ≥2.5 mm d. Left main lesion e. Chronic total occlusion f. In-stent restenosis g. Long lesion (estimated stent length >28 mm) h. Patient with an indication for PCI for any lesion and in need of elective mechanical circulatory support-assisted PCI (staged procedure) Subgroup analyses will be performed with the Cox proportional hazards model after testing for interaction between the variable defining the subgroup and treatment effect.

STATISTICAL ANALYSIS

The following analysis population sets will be defined for the assessment of study endpoints. The ITT population consists of enrolled subjects who have been randomised. Subjects will be analysed according to the treatment group they were assigned. The co-primary endpoint of MSA will be analysed from the ITT population. The primary endpoint of NACE will be assessed in the PP population. This population will include all randomised participants who completed the 11-month follow-up without prasugrel or DAPT disruption and remained free of ischaemic and major bleeding. Based on the MASTER DAPT trial results, the anticipated rate of discontinuation of prasugrel will be less than 10%. Here below is the preliminary list of major protocol deviations that will lead to exclusion from the PP population: • inclusion/exclusion criteria not fulfilled or randomisation criteria not fulfilled; • non-compliance to the treatment assigned by the randomisation. Like sensitivity, non-inferiority will be tested in the ITT population. Details on statistical analysis are displayed in Supplementary Appendix 6.

DATA COLLECTION AND ANALYSIS

The co-primary endpoint of post-PCI MSA assessed by OCT in each randomised arm will be measured at an independent OCT core laboratory (CERC, Massy, France) blinded to imaging modality assignment. An independent clinical events committee (CEC) will

adjudicate all primary and secondary endpoints. Definitions of all primary and secondary endpoints are summarised in Table 2. An independent data safety monitoring board (DSMB) will oversee the safety and wellbeing of the participating subjects, ensure the study's scientific integrity, and recommend actions based on potential safety issues, including study suspension or termination based on prespecified suspension criteria. The organisation and composition of the DSMB and CEC are described in Supplementary Table 1 and Supplementary Table 2. Details on follow-up in Supplementary Appendix 7.

Discussion

The conventional approach to STEMI patients undergoing PCI involves aggressive antithrombotic therapy with DAPT, despite the known increased risk of bleeding, especially in the maintenance phase post-PCI2. The COMPARE STEMI ONE trial investigates the non-inferiority of an abbreviated DAPT regimen of 1 month followed by prasugrel monotherapy. The rationale is grounded in the hypothesis that a reduced DAPT duration curtails bleeding risks without compromising its antithrombotic efficacy in reducing ischaemic events7. A few randomised trials focusing on DAPT regimen in ACS (6 vs 12 months in SMART-DATE and DAPT-STEMI and 3 vs 12 months in REDUCE) have attempted to shed light on the optimal timing for DAPT discontinuation, aiming to shorten the duration of P2Y12 inhibitor administration. Results were concordant in reporting the non-inferiority of an abbreviated (3-6 months) DAPT regimen as compared to the standard 12-month DAPT regimen21-23. There is a paucity of head-to-head comparison data for ASA versus P2Y12 inhibitor monotherapy following a short period of DAPT24. A recent meta-analysis involving 73,126 patients showed a significantly higher risk of myocardial infarction and a similar risk of bleeding with ASA monotherapy as compared to P2Y12 inhibitor monotherapy following short-term DAPT after PCI25. Recent trials exploring abbreviated DAPT have yielded favourable results for a single P2Y12 inhibitor strategy. A non-prespecified post hoc analysis of the GLOBAL LEADERS trial in ACS patients investigated the efficacy of ticagrelor monotherapy compared to ASA plus ticagrelor after 1 month of DAPT. Between 1 and 12 months post-PCI, ASA was associated with an increased bleeding risk (1.5% vs 0.8%; p for superiority=0.004) and did not appear to enhance the benefit of ticagrelor on ischaemic events (2.0% vs 1.5%; p for

superiority=0.07)26. The findings from the TWILIGHT trial revealed that administering ticagrelor monotherapy following an uneventful 3-month DAPT post-PCI in high-risk patients led to less bleeding without increased ischaemic events5. In the TICO Study (3,056 ACS patients), 3 months of DAPT followed by ticagrelor monotherapy resulted in a significant reduction of major bleeding and cardiovascular events at 1 year compared to 12-month ticagrelor-based DAPT27. In line with previous studies, the ULTIMATE-DAPT RCT showed that ACS patients can benefit from discontinuing ASA and maintaining ticagrelor monotherapy after 1 month of DAPT, resulting in less bleeding and similar major adverse cardiac event rates28. Consistently, in 2,850 ACS patients undergoing PCI, 1-month DAPT followed by ticagrelor monotherapy was non-inferior and superior to 12-month DAPT for the 1-year composite outcome of death, myocardial infarction, stent thrombosis, stroke, or major bleeding29. However, these results have not been consistent across trials investigating different P2Y12 inhibitors. In patients with ACS and successful PCI, clopidogrel monotherapy after 1 to 2 months of DAPT failed to demonstrate non-inferiority compared to standard 12-month DAPT for the net clinical benefit10. The STOPDAPT-3 trial failed to achieve the primary endpoint of superiority in reducing bleeding events (BARC 3 or 5) and showed a potential increase in the risk of subacute stent thrombosis in patients allocated to prasugrel monotherapy at a dosage of 3.75 mg/day immediately following PCI10,11. Several RCTs are currently investigating either a prasugrel-based or ticagrelor-based single antiplatelet regimen after 0-3 months of DAPT in ACS patients (Figure 3). The design of the COMPARE STEMI ONE trial is unique in focusing exclusively on a full-dose prasugrel-based regimen in the context of STEMI30,31. The potentially better ischaemic profile of prasugrel over ticagrelor, which was demonstrated in the ISAR-REACT 5 Trial, adds to the rationale of our trial9. In addressing the multifaceted nature of STEMI patients, the COMPARE STEMI ONE trial takes a step further by examining the benefit of OCT-guided complete revascularisation in patients with MVD and addressing the growing interest in leveraging intravascular imaging to optimise procedural outcomes4,20,32,33. Recently, the Impact of IntraVascular UltraSound Guidance on Outcomes of Xience Prime Stents in Long Lesions trial (IVUS-XPL Study), conducted at 20 centres in the Republic of Korea, revealed a significant interaction between intravascular ultrasound (IVUS) use and DAPT duration,

suggesting that IVUS-guided stent optimisation may yield more favourable results with shorter DAPT34. The COMPARE STEMI ONE RCT will explore synergies between a shortened DAPT duration and OCT-guided revascularisation for STEMI patients with MVD. The potential implications of this dual approach for optimising patient outcomes remain a particular point of interest. We recognise that the choice of an absolute non-inferiority margin of 2.0 results in a relative non-inferiority margin that is higher than those used in previous trials. This decision, however, was driven by the low, but realistic, expected event rates in our study population. In this context, our approach reflects a pragmatic balance between feasibility and statistical rigour.

Trial	Population	Intervention	Control	Outcomes
COMPARE STEMI ONE NCT05491200	1,656 STEMI	30-45 d DAPT-> P monotherapy	P+ASA 12 m	12-month NACE
TARGET-FIRST NCT04753749	2,246 ACS	1 m DAPT-> T/P monotherapy	T/P+ASA 12 m	12-month NACE and BARC 2 bleeding
LEGACY NCT05125276	3,090 NSTEMI	PCI-> T/P monotherapy	T/P+ASA 12 m	12-month MACE and BARC ≥ 2 bleeding
MATE NCT04937699	2,856 ACS	1 m DAPT-> 5 m T monotherapy->C	T+ASA 12 m	12-month NACE
NEOMINDSET NCT04360720	3,400 ACS	PCI->T/P monotherapy	T/P+ASA 12 m	12-month MACE and BARC ≥ 2 bleeding

Figure 3. Overview of current RCTs investigating P2Y12 inhibitor monotherapy in ACS patients. ACS: acute coronary syndrome; ASA: acetylsalicylic acid; BARC: Bleeding Academic Research Consortium; C: clopidogrel; DAPT: dual antiplatelet therapy; MACE: major adverse cardiac events; NACE: net adverse clinical events; NSTEMI: non-STEMI; P: prasugrel; PCI: percutaneous coronary intervention; STEMI: ST-segment elevation myocardial infarction; T: ticagrelor

Conclusions

In summary, the multicentre, randomised, open-label COMPARE STEMI ONE trial addresses critical clinical questions regarding the optimal strategy and choice of antiplatelet therapy in STEMI patients undergoing PCI. By integrating intravascular imaging into the paradigm of complete revascularisation, the trial may also provide meaningful insights into the optimal antithrombotic treatment of STEMI patients with MVD.

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SUPPLEMENTARY DATA https://eurointervention.pcronline.com/article/prasugrel-monotherapy-versus-standard-dapt-in-stemi-patients-with-oct-guided-or-angio-guided-complete-revascularisation-design-and-rationale-of-the-randomised-multifactorial-compare-stemi-one-trial

Chapter 3

Completeness of revascularisation in acute coronary syndrome patients with multivessel disease

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State of the art

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Abstract

A significant proportion of patients presenting with acute coronary syndromes (ACS) have multivessel disease (MVD). Despite the abundance of clinical trials in this area, several questions regarding the procedure of complete coronary revascularisation remain unanswered. This state-of-the-art review summarises the latest evidence on complete revascularisation (CR) in this subset of patients and critically appraises clinical decision making based on non-culprit lesion (NCL) assessment. Future areas of research are put into perspective.

Introduction

In a substantial proportion of patients with acute coronary syndromes (ACS), the pathophysiological process of coronary artery disease (CAD) is not limited to one single vessel, and multivessel disease (MVD) can be found in 50% of the cases1,2. Complete revascularisation (CR) has been associated with decreased risk of composite outcomes driven mainly by reduced subsequent revascularisations, with recent studies supporting the benefit of non-culprit lesion (NCL) percutaneous coronary intervention (PCI) on hard clinical endpoints3-7. The optimal timing for the treatment of NCLs and how to identify the amenable lesions are still matters of debate. Furthermore, whether the goal of CR should be the treatment of ischaemia-related lesions or vulnerable plaques prone to thrombosis has yet to be determined. Despite the evidence supporting the safety of deferred PCI in patients with ACS on the basis of pressure-derived measurements, the reliability of physiological assessment of NCLs in the acute phase of ACS has not yet been defined5,6,8-11. The presence of chronic total occlusions (CTO) among NCLs may dramatically impact on the prognosis of those patients and imposes a tailored decision-making strategy12. For cardiogenic shock (CS) patients presenting with MVD (nearly 80%), the available data are highly controversial and the treatment strategy remains extremely challenging13. Overall, this review provides a comprehensive assessment of the latest results of randomised controlled rials (RCTs), highlights the current guideline recommendations and sheds light on future directions for the treatment of patients with ACS and MVD.

Multivessel disease in patients with ACS presenting with ST elevation

The primary objective of PCI in ST-elevation myocardial infarction (STEMI) patients is to restore epicardial flow in the culprit vessel and myocardial perfusion14. Despite robust data favouring CR, the optimal timing for NCL revascularisation has still to be determined14. In the PRAMI trial, angiography-guided CR yielded a 65% reduction in the composite primary endpoint when compared to culpritonly revascularisation during the index procedure3. The CvLPRIT trial randomised STEMI patients with MVD to a culprit-only strategyor to an angiography-guided CR approach. CR, performed either at the time of index procedure (64%) or before hospital discharge (36%), resulted in a 55% reduction of the primary composite endpoint of all-cause mortality, recurrent myocardial infarction (MI), heart failure, and ischaemia-driven revascularisation at 12 months of follow-up 4. A fractional flow reserve (FFR)-guided CR approach versus culprit lesion-only treatment was investigated in DANAMI-3- PRIMULTI and in the COMPARE-ACUTE trial. In both trials, CR was found to be associated with a benefit in terms of the composite primary endpoint, driven largely by the need for repeat revascularization 5,6.

The COMPLETE trial is by far the largest and the only powered study to address hard endpoints7. More than 4,000 patients were randomised. Angiography-guided CR (with FFR performed in 50 to 69% stenosis) proved to reduce the composite outcome of cardiovascular (CV) death and MI at a median of 36 months of follow-up (7.8% in the CR group vs 10.5% in the culprit-only group – hazard ratio [HR] 0.74, 95% confidence interval [CI]: 0.60 to 0.91; p=0.004)7. Data from these five trials are summarized in Supplementary Table 1. The benefit of CR in terms of CV mortality was confirmed in a recent meta-analysis based on 10 RCTs and 7,030 patients. A reduced CV death and MI rate (both as combined and as individual endpoints) was found, regardless of whether immediate or staged CR was performed. The results were consistent whether an FFR-guided or an angiography-guided approach was performed 15.

KEY MESSAGE

RCTs and meta-analyses support the benefit of CR in STEMI patients with MVD, regardless of the mode of selection and the timing of NCL treatment (Figure 1).

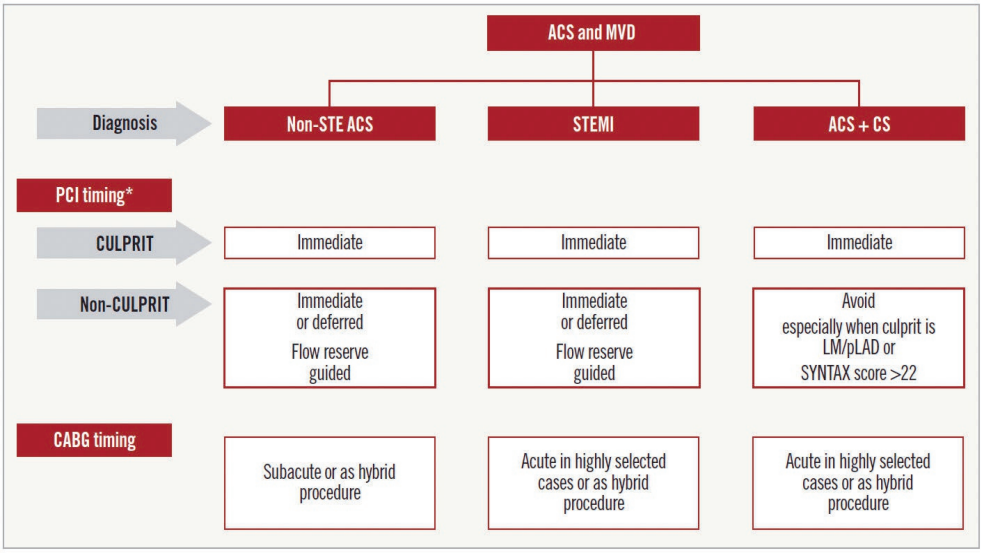


Figure 1. Schematic representation of proposed revascularisation strategies in patients with ACS and MVD. *PCI timing is relative to the time of coronary angiography. ACS: acute coronary syndromes; CS: cardiogenic shock; MVD: multivessel disease

Multivessel disease in patients with ACS presenting without ST elevation

Contrary to the case for STEMI where reperfusion of the infarctrelated artery was established as a therapeutic goal in the 1980s, the treatment of patients presenting with NSTEMI was more conservative, with antithrombotic therapies and optimal medical therapy. Early studies probably classified a large proportion of patients as having unstable angina because (high-) sensitive or even cardiac- specific biomarkers were not available. When an early invasive strategy for NSTEMI was established as being superior, the comparator was non-invasive or watchful waiting with crossover permitted. It is important to recognise that NSTEMI presenters, compared to STEMI patients, are older, more often diabetics and present with more diffuse coronary disease, including more prior revascularisations without a clear culprit lesion 16. As a result, the ruling principle in these early studies was CR engaging each treatable lesion. In the pivotal FRISC II trial, equipoise almost existed between the number of patients having PCI versus coronary artery bypass graft (CABG), 44% versus 38%, respectively, most within 10 days of the index event17. This Scandinavian study was the first to demonstrate a significant

difference in 12-month mortality, favouring an invasive strategy with intended CR (2.2% vs 3.9%), recommending CABG for those with left main stenosis (LMS) and/or triple vessel disease. Later studies on this topic and their pooled individual patient-level data confirmed the benefit of an early invasive strategy on recurrent MI with a trend towards lower mortality 18.

Indirect evidence for the benefit of an early and CR strategyin NSTEMI patients is the high crossover rate in the early studies comparing invasive versus conservative management, reaching almost 50% in long-term follow-up 18,19. Recently published propensity-matched data from a UK registry of NSTEMI patients demonstrated a reduced all-cause mortality for complete versus incomplete revascularisation19. The timing of the intervention itself, when occurring within the first week, seems of minor importance in haemodynamically stable patients 20-22. Contemporary all-comers studies in NSTEMI patients suggest that the rate of CABG might be declining (closer to 7-12%), possibly due to better stent technology, staged PCI and increased experience with CTO techniques. Consequently, increased rates of CR in patients with NSTEMI and MVD undergoing PCI have been observed over the past decade, leading to improved survival16,21,23 (Supplementary Figure 1). Centre preferences and expertise might explain the wide span in completeness of revascularisation in NSTEMI patients across centres, varying from 38% to 79% in one study 20.

KEY MESSAGE

Indirect evidence supports the benefit of CR in NSTEMI patients with MVD with decreased mortality and readmission for MI and repeat revascularisation (Figure 1).

Completeness of revascularisation in patients with ACS presenting with or developing cardiogenic shock

PREVALENCE OF MVD

The worst outcomes among ACS patients are observed in those 5-10% who present with or develop CS, reaching 80-90% mortality among patients with mechanical complications 24. In ACS accompanied by CS, the mortality has remained rather constant for the past three decades at almost 50% within the first month 25,26. Acute angiography

is recommended in this high-risk population where three quarters present with MVD and/or left main (LM) involvement 14,27.

REVASCULARISATION STRATEGY BEFORE CULPRIT-SHOCK TRIAL

For almost two decades the guiding principle for treatment in shock patients was CR based on data from the SHOCK trial which compared revascularisation to conservative management with 38% in the revascularisation arm receiving CABG and 55% treated with PCI 25. This strategy has been recommended by both American and European guidelines 28,29. An aggressive strategy with CR, regardless of whether PCI or CABG is performed, in those individuals with a high risk of PCI failure does seem to incur an early hazard; however, this is, to some extent, mitigated by the long-term effects 25,30,31. Registry data recently supported the hypothesis that complete or multivessel PCI in CS would lead to myocardial protection, relieve the global ischaemic burden and result in improved long-term survival 32.

REVASCULARISATION STRATEGY AFTER THE CULPRITSHOCK TRIAL

Eventually, a prospective randomised study on MVD versus culprit- only PCI in patients with CS was published. The CULPRITSHOCK trial, with a composite endpoint of death and renal replacement, actually demonstrated harm from immediate multivessel PCI compared to culprit-only PCI after 30 days and one year (55.4% vs 45.9% and 59.5% vs 52%, respectively) 26,27. However, the post hoc landmark analysis revealed that the mortality difference was confined to the first month, with no difference in total mortality or CV mortality thereafter. Actually, there were numerically fewer deaths in the multivessel PCI arm at 12 months (5.3% vs 6.7%)27. Undoubtedly, immediate multivessel PCI leads to longer procedures, which in earlier studies have been associated with more complications including stroke, but also excess of contrast loads, i.e., 60 ml in the CULPRIT-SHOCK trial. Deeper dives into the same trial have demonstrated that a higher baseline SYNTAX score is associated with more depressed LV function, a higher need for mechanical ventricular support, longer procedure times and a lower success rate when treating the culprit artery. Importantly, higher SYNTAX scores independently predicted 30-day and one-year outcomes with no interaction between the SYNTAX score and the revascularisation strategy 33. Patients with a culprit lesion in the LM or proximal left

anterior descending (LAD) are particularly vulnerable to further multivessel PCI, with an absolute excess in one-year mortality of almost 20% (69.9% vs 50%) 34.

KEY MESSAGES

– Immediate multivessel PCI in acute CS has been associated with higher rates of death and renal failure as compared to culpritonly PCI.

– More complex CAD and the presence of the culprit lesion in the LM or proximal LAD are associated with worse outcomes when a multivessel PCI is performed (Figure 1).

Assessment of non-culprit lesions

STEMI PATIENTS

The optimal time and the preferred modality to assess the NCLs in STEMI patients remain a real diagnostic challenge. Most of the observational and randomised studies so far have used angiographic diameter stenosis severity to determine the NCLs requiring further intervention. In the acute STEMI setting, coronary vasoconstriction due to alpha-adrenergic stimulation may lead to angiographic overestimation of NCL stenosis degree by approximately 10% and to unnecessary overtreatment 35.

PHYSIOLOGICAL ASSESSMENT OF NCLs

FFR measurement of NCLs has been extensively and safely used in large RCTs to guide CR in the STEMI setting, resulting in lower acute and repeat revascularisation rates compared to angioguided revascularization 5,6. However, the diminished sensitivity of the purinergic adenosine receptors associated with an increased level of endothelin-1, higher left ventricular (LV) end-diastolic pressure and myocardial oedema may all contribute to a decreased hyperaemic flow in NCLs and a consequent underestimation of their FFR significance in the acute STEMI setting 36. A recent substudy of the REDUCE-MVI trial showed a mean decrease of 0.03 of FFR values between the index procedure and one-month follow-up, more evident in larger infarcts 37. On the other hand, the instantaneous wave-free ratio (iFR) measurement is affected by an increased resting flow in NCLs in the acute setting, resulting in an overestimation of lesion significance. The iSTEMI substudy found a mean discrepancy of 0.03 in iFR values

between the index procedure and a staged procedure performed at a median of 16 days (IQR: 5-32) 38.

NSTEMI PATIENTS

PHYSIOLOGICAL ASSESSMENT OF NCLs

The evaluation of NCLs is even more challenging in the NSTEMI setting. At least two of the angiographic criteria (intraluminal filling defect, plaque ulceration, plaque irregularity, dissection, or impaired flow) may be found in more than one lesion in up to 40% of NSTEMI patients 39-42. Both the FAMOUS-NSTEMI trial (n=350) and the ACS subgroup of the FAME trial (n=328) were not powered to assess the superiority of FFR-guided over angiography-guided revascularization in terms of clinical outcomes. They included physiology assessment of both culprit and NCLs, resulting in less robust evidence than for STEMI patients 43,44. Limited data are available for non-hyperaemic indices in ACS patients. The pooled analysis of the DEFINE-FLAIR and iFRSWEDEHEART randomised trials showed similar safety in deferring revascularisation with both iFR and FFR, despite the higher rate of deferral with iFR 45.

IMAGING ASSESSMENT

The haemodynamic paradigm alone, based on physiological indices, may not provide all the information needed to guide a safe revascularisation of NCLs. Moreover, both iFR and FFR are continuous variables being reported in RCTs and considered for decision making in a dichotomous fashion. Both STEMI and NSTEMI patients may have underlying ruptured or eroded plaques also in NCLs. The PROSPECT study demonstrated that non-angiographic significant NCLs with a large plaque burden, a small luminal area, or a combination of both features detected by intravascular ultrasonography (IVUS) imaging were associated with the same major adverse cardiac event (MACE) rates of culprit lesions at three-year follow-up 46. Both systemic effects and local inflammation of NCLs in ACS patients might contribute to plaque instability. The presence of a minimum lumen area (MLA) <3.5 mm2, fibrous cap thickness <75 mm, lipid arc circumferential extension >180°, and optical coherence tomography (OCT)-defined macrophage infiltration yielded a higher rate of MACE in the 1,003 patients (53.4% ACS) of the CLIMA study 47.

Interestingly, a sub-analysis from the COMPLETE trial showed that nearly half of the patients undergoing OCT had an obstructive non-culprit lesion (>70% visual diameter stenosis) with vulnerable plaque. These findings may explain the reduced MI rates associated with a strategy of routine PCI of obstructive NCLs 48.

KEY MESSAGES

– Physiological assessment of NCLs in ACS patients is safe and results in reduced repeat revascularisation rates.

– Transient physiological changes in the acute setting may impact on NCL severity assessment in the acute STEMI setting, with potentially underestimated and overestimated severity by FFR and iFR, respectively. This should be kept in mind when obtaining borderline values for significance (Figure 2).

– Intravascular imaging could provide further insights for the evaluation of the plaque morphology and high-risk plaque features. However, the role of these techniques in guiding clinical decision making has yet to be determined (Figure 2).

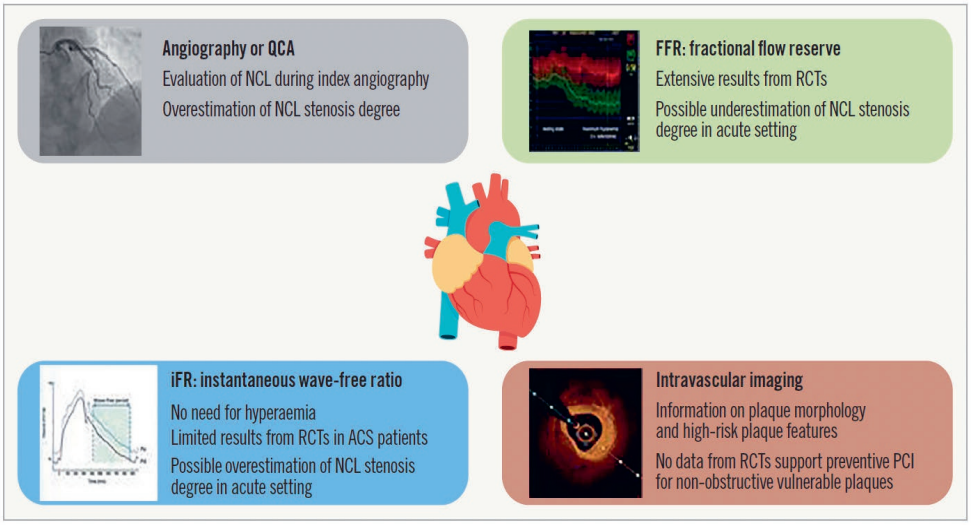


Figure 2. Schematic overview of modes of NCL assessment.

Complex non-culprit lesions

CHRONIC TOTAL OCCLUSION LESIONS

The presence of a concurrent chronic total occlusion (CTO) in NCLs in the setting of ACS is frequent and is a substantial determinant of the prognosis of patients. A CTO is found in approximately every tenth patient with STEMI 49,50 and, despite the scarce data, its prevalence in NSTEMI patients shows comparable rates51. In patients with ACS complicated by CS, a CTO lesion is even more frequent and present in every fourth to every fifth patient 49,50,52. The mortality rate for ACS patients with a concurrent CTO is almost twice as high after 3-5 years compared to ACS patients without a concurrent CTO, even after adjustment for age, comorbidities and Killip class 49,52. The main mechanism might be the additional extent of myocardium at risk due to acute blockade of the infarct-related artery which supplies not only its own myocardial target area but also (via collaterals) remote myocardium in the area of the CTO artery 49,53.

Data about revascularisation of a bystander CTO in ACS patients are extremely limited since the vast majority of RCTs investigating culprit-only PCI versus multivessel PCI excluded patients with a concomitant CTO, and retrospective analyses addressing this question imply the risk of a relevant selection bias 4,5. Inclusion of CTO in NCLs in the recent COMPLETE trial was extremely selected and limited to a non-representative subgroup of only 2% of the study population7. Although not powered to detect differences in MACE rates, the EXPLORE trial was the only RCT evaluating the benefit of an early PCI of a concurrent CTO in ACS patients54. The primary outcomes of LV ejection fraction and LV end-diastolic volume measured by cardiac magnetic resonance (CMR) imaging after four months were not different between the early CTO-PCI arm (N=150) and the conservative treatment arm (N=154). However, there was a significant interaction regarding location of the CTO, with a favourable outcome for the revascularisation strategy in patients with a CTO located in the LAD. Both this specific subgroup and the entire study population had comparable MACE rates between the treatment arms up to a median follow-up of 3.9 years. Moreover, the quality-of life benefit, in terms of a significantly lower rate of freedom from angina in the CTO-PCI arm at one year, faded away in the subsequent years of follow-up55. Potential biases of these findings, such as lack of any viability test prior to CTO PCI and a relatively low success rate of 73% according to the core lab adjudication, might have weakened the effect of CTO PCI.

LEFT MAIN STENOSIS (LMS)

NCL LMS is rare in patients with ACS (Supplementary Figure 2).

A registry-based study from Korea revealed an LMS as the NCL in only 99 of 7,655 patients with MI (1.3%)56. Focusing on the location of NCLs in STEMI patients, a large meta-analysis of eight STEMI trials found significant LMS in 807 out of 12,710 patients (6.4%) 57. Most of the RCTs investigating culprit-only versus multivessel PCI in different ACS settings excluded patients with an indication for urgent CABG affecting the majority of patients with an NCL LMS3,5,6,25,58. COMPLETE and CvLPRIT included only ≤10 ACS patients with LMS as the NCL, not allowing the generation of any evidence for this specific subgroup 4,7. Unless there is a critical degree of stenosis and any sign of an unstable morphology, e.g., thrombotic lesion, ulceration or plaque rupture related to the NCL LMS, a deferred revascularisation approach is recommended for most patients with CS and patients with STEMI after primary PCI of the culprit lesion.

KEY MESSAGES

– In general, there are no data to recommend PCI of a bystander CTO in patients with ACS in the acute phase. A CTO PCI may be considered in a few cases based on symptoms, ischaemia, and viability after stabilisation and optimal medical therapy, as recommended for stable CAD.

– The decision to pursue NCL LMS PCI remains an individualdecision, taking into account the clinical setting, lesion morphology and complexity, and the operator`s experience, preferably after Heart Team discussion.

Current guidelines, grey areas and future perspectives

Current European guidelines, giving a class IIA recommendation to routine revascularisation of NCLs before hospital discharge, were developed before the publication of the COMPLETE trial wherein the benefit of CR was observed regardless of whether NCL PCI was performed during the index hospitalisation or after discharge 7,14,28. These results were achieved in the first RCT powered to determine a meaningful reduction in the risk of the clinically important outcome of CV death or MI and are likely to influence future guidelines on this topic (Figure 3).

Whether an immediate CR approach is non-inferior to staged CR (within six weeks after the procedure) will be investigated in the BIOVASC trial (NCT03621501). The MULTISTARS AMI trial will compare index procedure CR to staged revascularization of NCLs within 19-45 days (NCT03135275). An immediate versus staged FFR-guided NCL PCI strategy was planned to be investigated in 4,052 STEMI patients enrolled in the FULL-REVASC trial. This study was designed to detect differences in one-year all-cause mortality and MI (NCT02862119). However, the trial has halted recruitment in the light of the COMPLETE trial results.

The clinical relevance of FFR-guided NCL revascularization has recently been assessed in the FLOWER-MI trial where STEMI patients were randomised after successful primary PCI in a 1:1 fashion to either FFR-guided or angio-guided CR during the index procedure or a staged procedure before discharge (≤5-day) (NCT02943954). The primary outcome of all deaths, MI, or unplanned hospitalisation leading to urgent revascularisation at 12 months occurred in 5.5% of the FFR-guided group compared with 4.2% of the angiography-guided group. The hypothesis of superiority of an FFR-guided versus an angiography-guided complete revascularisation within the same hospitalisation was not met in this trial (HR 1.32, 95% confidence interval: 0.78 to 2.23; p=0.31). However, the lower than expected incidence of events and the wide confidence intervals for the estimate of effect do not allow a conclusive interpretation 58. Finally, the iMODERN trial will compare an iFR-guided approach of NCLs during the acute setting with a deferred stress perfusion CMR-guided strategy during the outpatient follow-up in a cohort of 1,146 STEMI patients with MVD (NCT03298659). In contrast to the STEMI setting, the optimal timing for CR in NSTEMI patients has so far been investigated in only one RCT. The complete single-stage strategy yielded less MACE than staged multivessel PCI, driven mainly by repeat revascularization (HR 0.55, 95% CI: 0.36-0.83, p=0.004)59. However, exclusion of patients with an estimated glomerular filtration rate (eGFR) <60 ml/min in this trial greatly limits the transferability to a realworld NSTEMI population.

Despite the lack of RCTs, the vast majority of available data favour a CR strategy in patients presenting with NSTEMI. Our interpretation of the data to pursue CR is in line with the recently published ESC guidelines (Class IIa/level of evidence C) 60.

Regarding the optimal timing, the guidelines recommend that revascularisation of NCLs may be considered during the index procedure (Class IIb, B) (Figure 3). However, we would propose an individual assessment based on procedural aspects of culprit lesions and NCLs, operator experience, and patient characteristics.

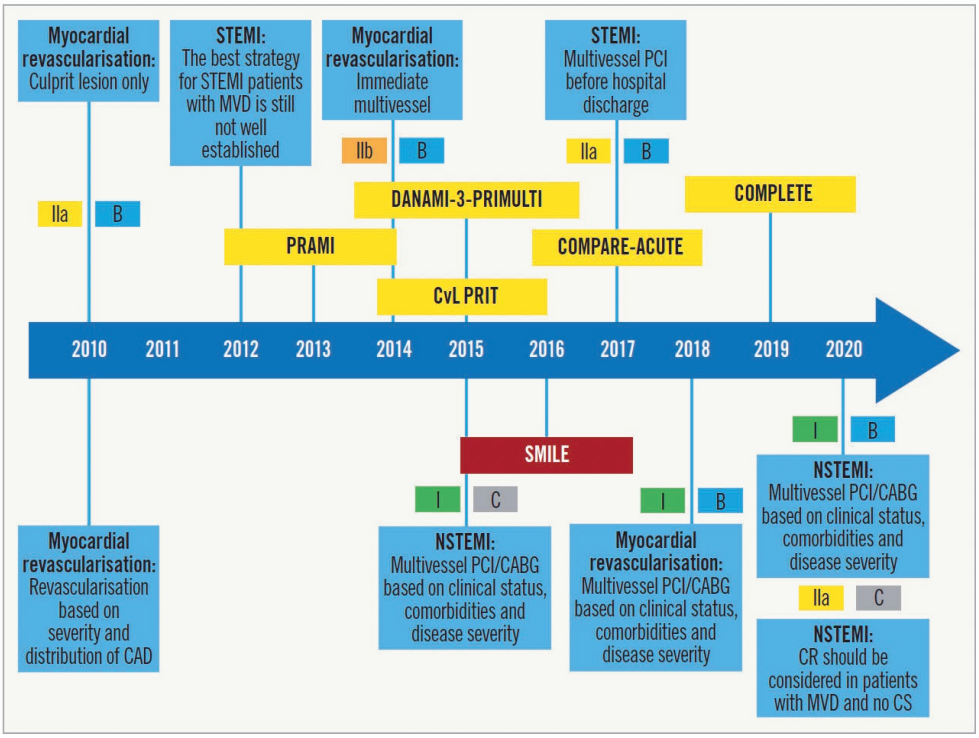


Figure 3. Revascularisation strategy for NSTEMI/STEMI with MVD. Evolution of guidelines and RCTs.

Conclusions

All ACS patients, except for those presenting with CS, should be offered CR. This means PCI of the culprit lesion as well as NCLs during the index procedure, before discharge or at least within the first month, when the coronary anatomy is suitable. In daily practice, an individualised approach is preferred according to patient factors, anatomic findings and institutional experience. PCI, despite its dominance in ACS, cannot be offered to all, and the treatment spectrum in ACS ranges from medical management to CABG; complex cases should always be evaluated by the Heart Team.

Tribute to Professor Anthony Gershlick

All the authors of this manuscript would like to pay tribute to a pioneering interventional cardiologist, Professor Anthony Gershlick, a leading expert in this field.

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Supplementary data https://eurointervention.pcronline.com/article/completeness-of-revascularisation-in-acute-coronary-syndrome-patients-with-multivessel-disease

Chapter 4

Should we be fully complete in multivessel AMI?

Pieter Cornelis Smits; Valeria Paradies

Editorial

Published in *Eurointervention Journal*

In 2012, the European Society of Cardiology (ESC) Guidelines for the management of acute ST-segment elevation myocardial infarction (STEMI) stated that primary percutaneous coronary intervention (PCI) should be limited to the culprit vessel with the exception of cardiogenic shock (Class IIa, Level of Evidence B recommendation) and, in case of multivessel disease with non-culprit lesions suitable for revascularisation stress testing, or imaging for ischaemia or viability is indicated (Class I, Level of Evidence A recommendation).

In the past 10 years, these recommendations have shifted almost in the opposite direction. It started with the PRAMI study, the first randomised controlled trial (RCT) that challenged the concept that primary PCI should be limited to the culprit vessel only and disregarded the need for additional ischaemia testing for non-culprit lesions1. PRAMI randomised patients between culprit-only treatment and angiography-guided complete revascularisation by PCI (preventive PCI) and showed that a preventive PCI strategy significantly reduced the composite endpoint of cardiac death, recurrent non-fatal myocardial infarction and refractory angina. Even without the "soft" endpoint of refractory angina, the study was positive for the composite of the two "hard" endpoints of cardiac death and myocardial infarction. The PRAMI trial was followed by the smaller CvLPRIT trial, showing a similar benefit in the composite of major adverse cardiac events (MACE; all deaths, non-fatal myocardial infarction, ischaemia-driven revascularisation and heart failure) with an angiography-guided complete revascularisation strategy2.

Simultaneously to PRAMI and CvLPRIT, two other RCTs were conducted with a slightly different approach. Both the DANAMI-3-PRIMULTI and COMPARE-ACUTE trials also challenged the concept of infarct-only treatment but incorporated fractional flow reserve (FFR) testing of nonculprit lesions in the subacute or acute setting of the complete revascularisation arm3,4. Again, both RCTs showed an early significant benefit in MACE of a complete revascularisation (FFR-guided) against a culprit-only strategy. This benefit remained intact and became even more significant at 27- and 36-month follow-up, respectively, for the DANAMI-3-PRIMULTI and COMPARE-ACUTE trials. The final verdict on the culprit-only strategy came from the mother of all multivessel STEMI trials, the COMPLETE trial5. This large RCT (4,041 patients) provided, for the first time, evidence on individual hard endpoints (cardiovascular death or new myocardial

infarction) indicating that an early complete revascularisation strategy is significantly better compared to a culprit-only strategy.

If you think that this was the end of the discussion, then you are mistaken. Although the recent FIRE trial6 also confirmed that (physiology-guided) complete revascularisation was significantly better on hard endpoints compared to the conservative culprit-only strategy in elderly acute myocardial infarction patients, the recent FULL REVASC results have shaken up the discussion again7. FULL REVASC was a large-scale (1,542 patients) RCT comparing an FFR-guided complete revascularisation strategy to a culprit-only strategy in a mix of STEMI and non-STEMI (NSTEMI) patients. It showed no benefit in the composite of all-cause death, myocardial infarction or unplanned revascularisation. The FULL REVASC trial has some issues. After 3 years, only 38% of the intended 4,052 patients were enrolled, and trial enrolment was stopped prematurely because of feasibility and ethical reasons after the COMPLETE trial publication. Even after changing the primary endpoint and extending the follow-up from 1 to 4.8 years, the study power remained below 80%. In addition, the trial did not exclusively enrol STEMI patients, but also high-risk NSTEMI patients. This is different compared to the previously mentioned trials (except from FIRE) which exclusively enrolled STEMI patients, in whom the culprit lesion is much easier to identify and often has a different aetiology compared to NSTEMI lesions. Nevertheless, the FULL REVASC trial raises questions about the validity of an FFR-guided complete revascularisation strategy in acute myocardial infarction patients with multivessel disease as it did not show any signal of reducing hard endpoints such as death and myocardial infarction.

What should be done in case of inconsistent or insufficient evidence from different studies? Meta-analysis is one of the answers.

In this issue of EuroIntervention, Laudani et al report a very comprehensive and contemporary meta-analysis of the 14 major RCTs in the field of multivessel disease and acute myocardial infarction, in which they adopted the frequentist five-node analysis which combines both the timing and guidance of non-culprit lesion revascularisation8. Considering the multiple treatment strategies and the mixed results across studies investigating similar approaches, this paper holds significant clinical relevance. It helps to distil the optimal treatment strategy in this frequently occurring clinical scenario. By

including all recent non-shock trials, and performing multiple sensitivity analyses, this network analysis paper is a thorough piece of work.

Laudani and colleagues found that complete revascularisation, whether angiography- or physiologyguided, reduces recurrent myocardial infarction compared with culprit-only revascularisation strategy. This benefit was most prominent in an immediate complete revascularisation strategy. In our eyes, the latter remains a topic of discussion. By study design it is impossible to accurately detect periprocedural myocardial infarction in an immediate revascularisation strategy, and part of the benefit is caused by periprocedural myocardial infarctions in a staged complete revascularisation strategy. In any case, good clinical judgement remains the best advice on when to perform complete revascularisation in STEMI patients.

Is this the end of the discussion? No. Many questions remain, like what is the role of physiology compared to intravascular imaging or angiography guidance, and do we obtain the same strategy results in multivessel NSTEMI patients? In the absence of patient-level meta-analyses (unlike the network meta-analyses by Laudani et al), in order to better determine which patients or lesions might benefit from which strategy, we must eagerly await the results of the ongoing COMPLETE-2 trial – wire-based physiology-versus angiography-guided complete revascularisation (ClinicalTrials.gov: NCT05701358), FRAME-AMI2 – IVUS- versus FFRguided complete revascularisation (NCT05812963), and COMPARE STEMI ONE – OCT- versus angiography-guided complete revascularisation (NCT05491200).

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Chapter 5

Early Discontinuation of Aspirin after PCI in Low-Risk Acute Myocardial Infarction

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Abstract

BACKGROUND

An appropriate duration of dual antiplatelet therapy after percutaneous coronary intervention for acute myocardial infarction that has been treated with guideline-recommended complete revascularization and a contemporary drug-eluting stent remains unclear.

METHODS We conducted a multicenter, open-label, randomized trial at 40 European sites. Adults with acute myocardial infarction who had undergone successful complete revascularization within 7 days after the infarction and had subsequently completed 1 month of dual antiplatelet therapy with no ischemic or major bleeding events were randomly assigned to transition to a P2Y12 inhibitor as monotherapy or to continue dual antiplatelet therapy for an additional 11 months. The primary outcome was a composite of death from any cause, myocardial infarction, stent thrombosis, stroke, or major bleeding (defined by the Bleeding Academic Research Consortium [BARC] as a bleeding event of type 3 or 5) at 11 months after randomization (tested for noninferiority with a margin of 1.25 percentage points). The main secondary outcome was BARC type 2, 3, or 5 bleeding (clinically relevant bleeding) at 11 months after randomization (tested for superiority).

RESULTS Among the 2246 enrolled patients, 1942 underwent randomization: 961 to receive P2Y12-inhibitor monotherapy and 981 to continue dual antiplatelet therapy. A primary-outcome event occurred in 20 patients (2.1%) in the P2Y12-inhibitor monotherapy group and in 21 patients (2.2%) in the dual antiplatelet therapy group (difference, −0.09 percentage points; 95% confidence interval [CI], −1.39 to 1.20; P = 0.02 for noninferiority). BARC type 2, 3, or 5 bleeding occurred in 2.6% of the patients in the P2Y12-inhibitor monotherapy group and in 5.6% of those in the dual antiplatelet therapy group (hazard ratio, 0.46; 95% CI, 0.29 to 0.75; P = 0.002 for superiority). Stent thrombosis was infrequent, and the incidence was similar in the two groups. The incidence of serious adverse events appeared to be similar in the two groups.

CONCLUSIONS Among low-risk patients with acute myocardial infarction who had undergone early complete revascularization and had completed 1 month of dual

antiplatelet therapy without complications, P2Y12-inhibitor monotherapy was noninferior to continued dual antiplatelet therapy with respect to the occurrence of adverse cardiovascular and cerebrovascular events and resulted in a lower incidence of bleeding events. (Funded by MicroPort [France]; TARGET-FIRST ClinicalTrials.gov number, NCT04753749.)

Introduction

The advent of drug-eluting stents revolutionized the management of ischemic heart disease by substantially reducing the risk of restenosis. However, first-generation stents were associated with late thrombotic complications, which led to recommendations for prolonged dual antiplatelet therapy, particularly in patients with increased platelet activation and thrombotic risk associated with acute coronary syndrome.1,2 Despite its effectiveness, dual antiplatelet therapy increases the risk of bleeding across the spectrum of patients with ischemic heart disease, including those who are not at high risk for bleeding. Observational studies, such as ADAPT-DES (Assessment of Dual Antiplatelet Therapy with Drug-Eluting Stents), have linked dual antiplatelet therapy to complications and death after percutaneous coronary intervention (PCI) in all-comer populations.3,4 The introduction of newer-generation drug-eluting stents, with lower doses of drugs and improved biocompatibility, has markedly reduced the risk of late stent thrombosis; there has been a renewed interest in refining antiplatelet strategies, including earlier deescalation to monotherapy on the basis of individual risk profiles.5,6 Although abbreviated dual antiplatelet therapy has been studied in patients with a high bleeding risk,7 in unselected patient populations,8,9 and in East Asian patients with an acute coronary syndrome,8,10-12 only a few trials have evaluated early discontinuation of aspirin specifically in patients with acute myocardial infarction. It would be important to evaluate the effects of early discontinuation of aspirin in patients with acute myocardial infarction who had undergone early complete revascularization with a contemporary stent — particularly in cases in which the risk of bleeding may outweigh the residual ischemic risk, which could make antiplatelet de-escalation a beneficial option. Therefore, we conducted a multicenter, randomized trial in which early

discontinuation of aspirin at 1 month was compared with standard dual antiplatelet therapy in low-risk patients with acute myocardial infarction who had been treated with PCI and a contemporary drug-eluting stent.

Methods

Trial Design and Oversight

TARGET-FIRST was a prospective, multicenter, open-label, randomized, controlled trial that was conducted at 40 sites across Europe. The trial design has been described previously.[13] The trial protocol (available with the full text of this article at NEJM.org) was designed by the steering committee, approved by applicable regulatory authorities and ethics committees, and conducted in accordance with the principles of the Declaration of Helsinki. The sponsor (MicroPort [France]) oversaw the conduct and monitoring of the trial, which were performed by a contract research organization (the Cardiovascular European Research Center [France]). The steering committee and the sponsor vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. The data analysis involved contributions from a contract research organization (Valos [Genoa, Italy]). The first author wrote the first draft of the manuscript, and the sponsor and all the authors agreed to submit the manuscript for publication. An independent data safety monitoring board periodically reviewed the safety data against the predefined stopping criteria. An independent clinical events committee adjudicated all the outcome events. A detailed list of the participating sites and committees is provided in the Supplementary Appendix (available at NEJM.org).

Trial Population

Patients were eligible for enrollment if they were at least 18 years of age, were hospitalized for ST-segment elevation myocardial infarction (STEMI) or non-STEMI (NSTEMI), and had undergone complete revascularization with an abluminal biodegradable-polymer rapamycin-eluting stent (Firehawk Liberty, MicroPort) without complications. Complete revascularization was defined as treatment of all clinically significant lesions (as determined on angiography) during the index or staged (within 7 days after myocardial infarction) PCI procedure. The final decision regarding the lesion treatment strategy was at the investigator's discretion. Patients were excluded if they

had a high risk of bleeding (i.e., if they had secondary fibrinolysis, were receiving oral anticoagulant therapy, had an estimated glomerular filtration rate of <30 ml per minute per 1.73 m^2 of body-surface area or were undergoing dialysis, had active bleeding, had a pre-PCI hemoglobin level of <13 g per deciliter [men] or <12 g per deciliter [women], had liver cirrhosis, had a history of bleeding diathesis, or had thrombocytopenia). Patients were also excluded if they had a high risk of an ischemic event (i.e., if they had undergone complex PCI, had a chronic total occlusion, had left main coronary artery disease, had received stents that totaled >80 mm in length, or had severe calcification). Full inclusion and exclusion criteria are provided in Table S1 in the Supplementary Appendix.

Randomization

After at least 30 days of dual antiplatelet therapy (aspirin plus a P2Y12 inhibitor), patients were evaluated. If they were free from ischemic or major bleeding events, they were randomly assigned in a 1:1 ratio to transition to P2Y12-inhibitor monotherapy (intervention) or to continue receiving dual antiplatelet therapy (control) for an additional 11 months. Randomization was performed with the use of a computer-generated sequence with random block sizes of two or four and stratified according to trial site, diabetes status, and type of myocardial infarction (STEMI or NSTEMI).

Treatments and Follow-up

The choice of P2Y12 inhibitor (prasugrel, ticagrelor, or clopidogrel) was determined by the investigator and aligned with the guidelines of the European Society of Cardiology and local practice. Investigators were encouraged to use a potent P2Y12 inhibitor (prasugrel or ticagrelor) and to use the same P2Y12 inhibitor throughout the trial unless there was a clinical reason to switch. Follow-up assessments were conducted by means of a telephone call or office visit at 6 months after PCI and by a mandatory on-site visit at 12 months after PCI. Information regarding patient-reported adherence to the assigned therapy, concomitant medications, and adverse events were documented at each visit. Nonadherence to the assigned therapy was defined according to the criteria listed in Table S2.

Outcomes

The primary outcome was net adverse clinical and cerebrovascular events, defined as a composite of death from any cause, myocardial infarction, stent thrombosis, stroke, or

major bleeding (defined by the Bleeding Academic Research Consortium [BARC] as a bleeding event of type 3 or 5)[14] at 11 months after randomization. The main secondary outcome was BARC type 2, 3, or 5 bleeding (clinically relevant bleeding, which ranges from overt bleeding for which medical attention is warranted [type 2] to fatal bleeding [type 5]) at 11 months after randomization. Key additional prespecified secondary outcomes were the individual components of the primary and main secondary outcomes; a device-oriented outcome, defined as a composite of death from cardiac causes, target vessel–related myocardial infarction, or ischemia-driven revascularization of the target lesion; a patient-oriented outcome, defined as a composite of death from any cause, myocardial infarction, definite or probable stent thrombosis (according to Academic Research Consortium criteria[14]), stroke, ischemia-driven repeat revascularization, or BARC type 2, 3, or 5 bleeding; major adverse cardiovascular events, defined as a composite of death from cardiovascular causes, myocardial infarction, or ischemia-driven revascularization of the target vessel; and individual components of these additional secondary outcomes. Serious adverse events were also recorded. A description of the outcomes is provided in Table S3.

Statistical Analysis

The sample size was calculated under the assumption that a primary-outcome event would occur in 3.5% of the patients in the dual antiplatelet therapy group and in 2.5% of those in the P2Y12-inhibitor monotherapy group; a sample of 1908 randomly assigned patients would provide the trial with 80% power at a one-sided alpha level of 2.5%. The planned enrollment of 2246 patients accounted for expected attrition. The anticipated incidence of a primary-outcome event was informed by previous randomized trials in which abbreviated dual antiplatelet therapy was investigated in patients with low-risk acute coronary syndrome[8 10 15], as well as by internal data derived from feasibility assessments at participating sites.

The primary analysis evaluated whether P2Y12-inhibitor monotherapy was noninferior to dual antiplatelet therapy with respect to net adverse clinical and cerebrovascular events at 11 months after randomization. Noninferiority was defined as an absolute difference between the groups in the incidence of events not exceeding 1.25 percentage

points; noninferiority would be concluded if the upper boundary of the two-sided 95% confidence interval was less than 1.25 percentage points.

If noninferiority for the primary outcome was shown, then superiority for BARC type 2, 3, or 5 bleeding (the main secondary outcome) would be tested by means of a hierarchical approach. The same use of a Cox proportional-hazards model and reported as hazard ratios and 95% confidence intervals. Adjustment for multiplicity was addressed by application of the prespecified hierarchical testing strategy. Cumulative incidence functions were estimated with the use of the Kaplan–Meier method or, when applicable, a competing-risks approach that accounted for death as a competing event. Missing data were handled by censoring at the time of last known contact. No interim analyses were planned. Between-group differences with respect to the primary outcome were calculated with the use of the Com-Nougue method with Greenwood's variance[16].

The intention-to-treat population included all the patients who had undergone randomization; patients were assessed according to their assigned treatment group. The per-protocol population consisted of patients who had undergone randomization and had had no major protocol deviations that could have affected the primary or main secondary outcomes, including adherence to the assigned therapy. The as-treated population included all the patients who had undergone randomization and were assessed according to the treatment they had actually received. The primary analysis was performed in the intention-to-treat population. The per-protocol and as-treated analyses were prespecified in the statistical analysis plan (which is included with the protocol) as sensitivity analyses. Subgroup analyses of the primary and main secondary outcomes were also prespecified and were evaluated with the use of interaction terms in Cox proportional-hazards models. All analyses were performed with the use of SAS software, version 9.4 (SAS Institute).

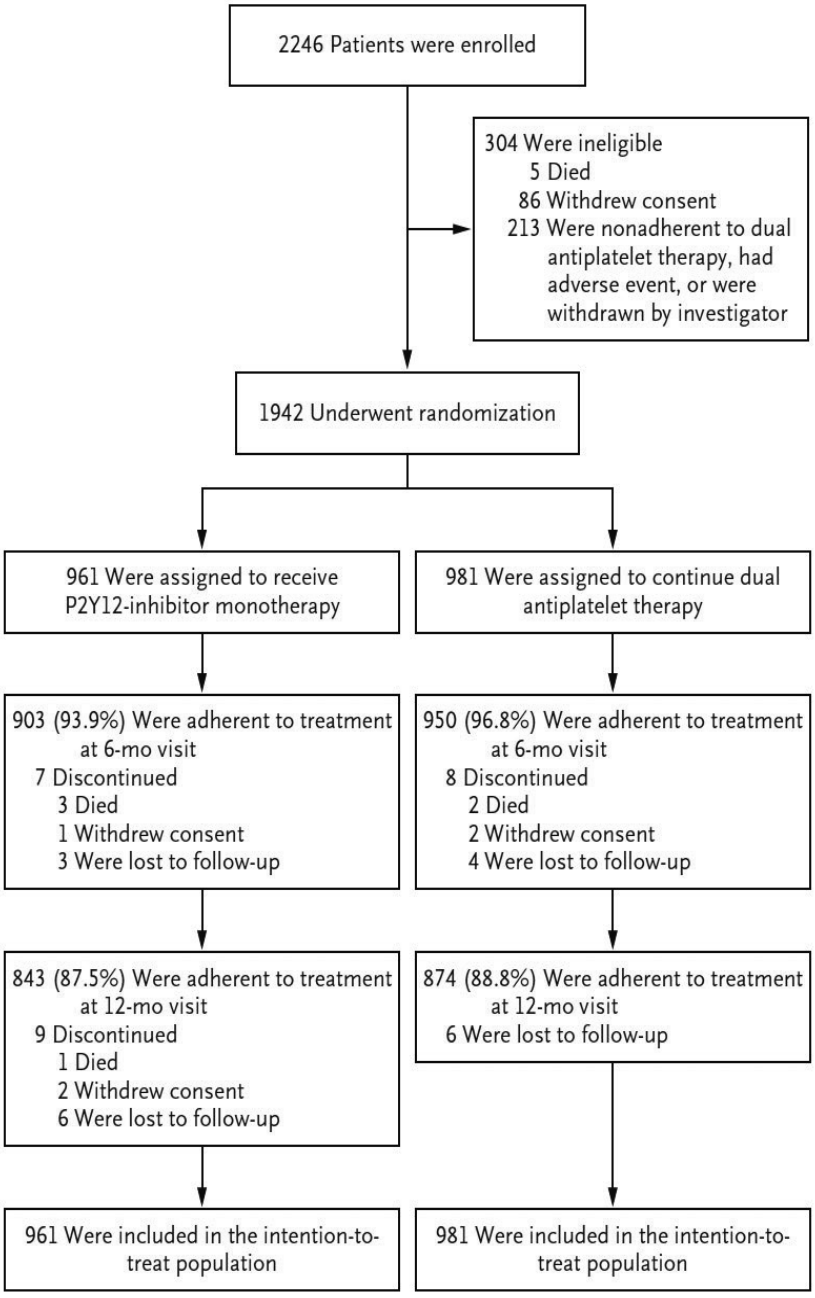


Figure 1. Enrollment, Randomization, and Follow-up. The percentage of patients who adhered to the assigned treatment was calculated with the use of Kaplan–Meier estimates based on the criteria listed in Table S2.

Results

Trial Population

From March 2021 through March 2024, a total of 2246 patients were enrolled at 40 European sites. One month after PCI, 1942 of these patients (86.5%) underwent randomization: 961 to the P2Y12-inhibitor monotherapy group and 981 to the dual antiplatelet therapy group (Fig. 1). The final patient underwent randomization in April 2024, and the database was locked in May 2025. Details regarding patients who did not undergo randomization, major protocol deviations, treatment adherence, and follow-up are provided in Tables S4 through S8. The median time from PCI to randomization was 37 days in each group. Overall, the mean (±SD) age of the patients who had undergone randomization was 61.0 ± 10.6 years; 78.4% of the patients were men and 21.6% were women (Table 1). A total of 14.5% of the patients had diabetes mellitus, 38.7% had hypertension, and 27.8% had hypercholesterolemia; 50.4% of the patients were hospitalized with STEMI, and 49.6% with NSTEMI. The representativeness of the trial population is presented in Table S9. Procedural characteristics appeared to be similar in the two groups, with a median of 1 implanted stent per patient (interquartile range, 1 to 2) in each group and a mean (±SD) total stent length of 30.3 ± 16.2 mm in the P2Y12-inhibitor monotherapy group and 30.8 ± 16.5 mm in the dual antiplatelet therapy group. Additional procedural characteristics are shown in Table S10. Complete revascularization was achieved in 99.9% of the patients. At the time of randomization, ticagrelor was the most commonly prescribed P2Y12 inhibitor (in 74.0% of the patients), followed by prasugrel (in 20.9%) and clopidogrel (in 5.1%). Cardiovascular therapies at the time of randomization included statins in 97.0% of the patients, beta-blockers in 79.1%, and angiotensin-converting–enzyme inhibitors or angiotensin-receptor blockers in 76.7% (Table S11).

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline (Intention-to-Treat Population).*

Characteristic	P2Y12-Inhibitor Monotherapy (N = 961)	Dual Antiplatelet Therapy (N = 981)
Age — yr	61.0 ±10.8	61.0±10.5
Female sex — no. (%)	223 (23.2)	197 (20.1)

Body-mass index†	26.7±4.7	27.4±4.4
Current smoker — no./total no. (%)	402/959 (41.9)	410/981 (41.8)
Diabetes mellitus — no./total no (%)	135/961 (14.0)	146/981 (14.9)
Type 1, treated with insulin	10/959 (1.0)	6/981 (0.6)
Type 2, treated with insulin	26/959 (2.7)	27/981 (2.8)
Hypertension — no. (%)	367 (38.2)	384 (39.1)
Hypercholesterolemia — no. (%)	271 (28.2)	269 (27.4)
Chronic kidney disease — no. (%)	15 (1.6)	21 (2.1)
Family history of coronary disease — no./total no. (%)	260/949 (27.4)	243/970 (25.1)
Peripheral vascular disease — no. (%)	34 (3.5)	25 (2.5)
Previous myocardial infarction or previous PCI — no./total no. (%)	57/959 (5.9)	67/975 (6.9)
Previous cerebrovascular accident — no. (%)	15 (1.6)	20 (2.0)
Left ventricular ejection fraction <40% — no./total no. (%)	25/704 (3.6)	33/702 (4.7)
Indication for PCI — no. (%) STEMI	482 (50.2)	497 (50.7)
Indication for PCI — no. (%) NSTEMI	479 (49.8)	484 (49.3)
Duration of dual antiplatelet therapy after PCI — days	37.0±4.6	37.0±4.6
P2Y12 inhibitor at 1-month visit — no./total no. (%) Ticagrelor	706/961 (73.5)	731/980 (74.6)
P2Y12 inhibitor at 1-month visit — no./total no. (%) Prasugrel	209/961 (21.7)	196/980 (20.0)
P2Y12 inhibitor at 1-month visit — no./total no. (%) Clopidogrel	46/961 (4.8)	53/980 (5.4)

* Plus–minus values are means ±SD. NSTEMI denotes non–ST-segment elevation myocardial infarction, PCI percutaneous coronary intervention, and STEMI ST-segment elevation myocardial infarction. † The body-mass index is the weight in kilograms divided by the square of the height in meters. Data were available for 949 patients in the P2Y12-inhibitor monotherapy group and for 967 patients in the dual antiplatelet therapy group.

Treatment Adherence

Overall, 87.5% of the patients in the P2Y12-inhibitor monotherapy group and 88.8% of those in the dual antiplatelet therapy group were adherent to the assigned antiplatelet regimen at 11 months (Fig. S2 and Table S6). Adherence to treatment was more than 95% for at least 6 months in the P2Y12-inhibitor monotherapy group and for at least 10 months in the dual antiplatelet therapy group. Reasons for nonadherence are provided in Table S12.

Primary and Secondary Outcomes

Death from any cause, myocardial infarction, stent thrombosis, stroke, or BARC type 3 or 5 bleeding (the composite primary outcome) occurred in 20 patients (2.1%; 95% confidence interval [CI], 1.4 to 3.2) in the P2Y12-inhibitor monotherapy group and in 21

patients (2.2%; 95% CI, 1.4 to 3.3) in the dual antiplatelet therapy group. The between-group difference was −0.09 percentage points (95% CI, −1.39 to 1.20), which met the criterion for noninferiority (P = 0.02) (Fig. 2).

The incidence of death from any cause was 0.4% in the P2Y12-inhibitor monotherapy group and 0.2% in the dual antiplatelet therapy group (hazard ratio, 2.04; 95% CI, 0.37 to 11.14). Myocardial infarction occurred in 0.7% of the patients in the P2Y12-inhibitor monotherapy group and in 1.1% of those in the dual antiplatelet therapy group (hazard ratio, 0.72; 95% CI, 0.27 to 1.88). Definite or probable stent thrombosis occurred in 0.1% of the patients in the P2Y12-inhibitor monotherapy group and in no patients in the dual antiplatelet therapy group. Stroke was reported in 0.3% and 0.2% of the patients in the respective groups (hazard ratio, 1.53; 95% CI, 0.26 to 9.18). BARC type 3 or 5 bleeding occurred in 0.7% of the patients in each group (hazard ratio, 1.02; 95% CI, 0.36 to 2.91) (Table 2). The results of prespecified subgroup analyses are shown in Figure 3 and Table S13, and the results of a post hoc analysis of the primary outcome involving the patients at the highest enrolling sites are shown in Table S14.

BARC type 2, 3, or 5 bleeding (the main secondary outcome), which was tested for superiority, occurred in 25 patients (2.6%; 95% CI, 1.8 to 3.9) in the P2Y12-inhibitor monotherapy group and in 54 patients (5.6%; 95% CI, 4.3 to 7.2) in the dual antiplatelet therapy group. The hazard ratio was 0.46 (95% CI, 0.29 to 0.75; P = 0.002 for superiority) (Table 2 and Fig. 2).

Table 2. Primary and Secondary Outcomes at 11 Months after Randomization (Intention-to-Treat Population).*

Outcome	P2Y12-Inhibitor Monotherapy (N = 961)	Dual Antiplatelet Therapy (N = 981)	Hazard Ratio (95% CI)	P Value
Primary outcome: net adverse clinical and cerebrovascular events	20 (2.1)	21 (2.2)	—	0.02
Death from any cause	4 (0.4)	2 (0.2)	2.04 (0.37–11.14)	—
Myocardial infarction	7 (0.7)	10 (1.1)	0.72 (0.27–1.88)	—
Stent thrombosis, definite or probable	1 (0.1)	0	—	—
Stroke	3 (0.3)	2 (0.2)	1.53 (0.26–9.18)	—

BARC type 3 or 5 bleeding	7 (0.7)	7 (0.7)	1.02 (0.36–2.91)	—
Type 3a	1 (0.1)	1 (0.1)	—	—
Type 3b	6 (0.6)	3 (0.3)	—	—
Type 3c	0	3 (0.3)	—	—
Main secondary outcome: BARC type 2, 3, or 5 bleeding	25 (2.6)	54 (5.6)	0.46 (0.29–0.75)	0.002
Death from cardiovascular causes	3 (0.3)	2 (0.2)	1.53 (0.26–9.16)	—
Patient-oriented composite outcome	43 (4.5)	71 (7.2)	0.61 (0.42–0.89)	—
Major adverse cardiovascular events	15 (1.6)	16 (1.6)	—	**
Device-oriented composite outcome: target-lesion failure	10 (1.1)	8 (0.8)	1.28 (0.50–3.23)	—
Ischemia-driven revascularization of target lesion	5 (0.5)	6 (0.6)	0.85 (0.26–2.79)	—
Ischemia-driven revascularization of target vessel	7 (0.7)	7 (0.7)	1.02 (0.36–2.91)	—

* The percentages of patients with events were calculated as Kaplan–Meier estimates of the incidence at 11 months after randomization (335 days). The P value for the primary outcome was for noninferiority, and the P value for the main secondary outcome was for superiority.
† Net adverse clinical and cerebrovascular events were defined as a composite of death from any cause, myocardial infarction, stent thrombosis, stroke, or major bleeding (defined by the Bleeding Academic Research Consortium [BARC] as a bleeding event of type 3 or 5).
‡ Type 3a indicates overt bleeding with a decrease in the hemoglobin level of 3 to 5 g per deciliter or the use of transfusion. Type 3b indicates overt bleeding with a decrease in the hemoglobin level of more than 5 g per deciliter, the occurrence of cardiac tamponade, surgical intervention (nonminor), or the use of intravenous vasoactive agents. Type 3c indicates intracranial bleeding, intraspinal bleeding, or vision-threatening intraocular bleeding.
§ BARC type 2, 3, or 5 bleeding indicates clinically relevant bleeding, which ranges from overt bleeding for which medical attention is warranted (type 2) to fatal bleeding (type 5).
¶ This outcome was defined as a composite of death from any cause, myocardial infarction, definite or probable stent thrombosis (according to Academic Research Consortium criteria), stroke, ischemia-driven repeat revascularization, or BARC type 2, 3, or 5 bleeding.
‖ Major adverse cardiovascular events (also known as MACE) were defined in this trial as a composite of death from cardiovascular causes, myocardial infarction, or ischemia-driven revascularization of the target vessel.
** The difference between the groups in the restricted mean survival time was −1.3 days (95% CI, −3.6 to 0.9).
†† Target-lesion failure was defined as a composite of death from cardiac causes, target vessel–related myocardial infarction, or ischemia-driven revascularization of the target lesion.

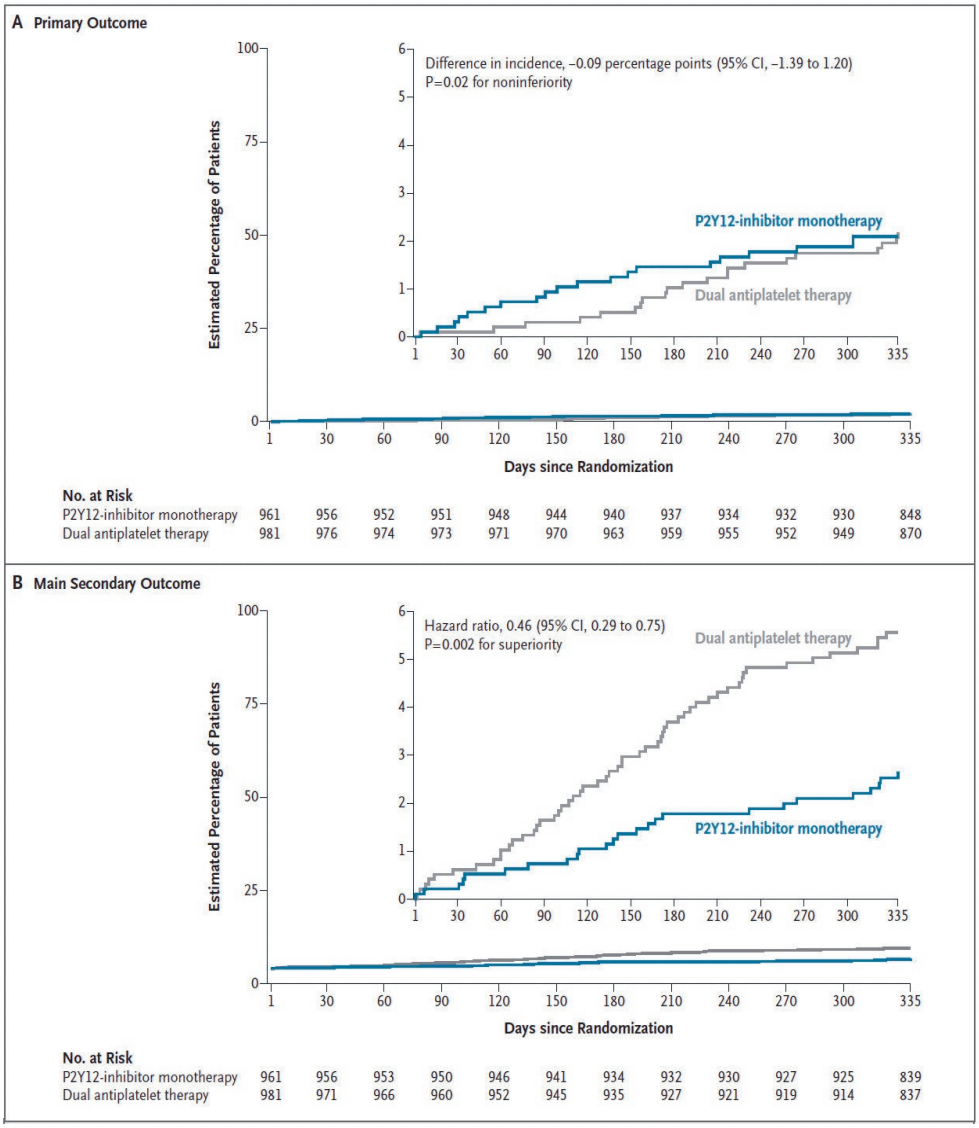


Figure 2. Primary and Main Secondary Outcomes.
Panel A shows the incidence of net adverse clinical and cerebrovascular events, defined as a composite of death from any cause, myocardial infarction, stent thrombosis, stroke, or major bleeding (defined by the Bleeding Academic Research Consortium [BARC] as a bleeding event of type 3 or 5) (the primary outcome). Panel B shows the incidence of BARC type 2, 3, or 5 bleeding (clinically relevant bleeding) (the main secondary outcome). In each panel, the inset shows the same data on an expanded y axis.

Other Secondary Outcomes

Death from cardiovascular causes occurred in 3 patients (0.3%) in the P2Y12-inhibitor monotherapy group and in 2 patients (0.2%) in the dual antiplatelet therapy group. Death

from any cause, myocardial infarction, stent thrombosis, stroke, ischemia-driven repeat revascularization, or BARC type 2, 3, or 5 bleeding (the patient-oriented composite outcome) occurred in 43 patients (4.5%) in the P2Y12-inhibitor monotherapy group and in 71 patients (7.2%) in the dual antiplatelet therapy group. Major adverse cardiovascular events—a composite of death from cardiovascular causes, myocardial infarction, or ischemia-driven revascularization of the target vessel—occurred in 1.6% of the patients in each group.

Death from cardiac causes, target vessel–related myocardial infarction, or ischemia-driven revascularization of the target lesion (the device-oriented composite outcome) occurred in 10 patients (1.1%) in the P2Y12-inhibitor monotherapy group and in 8 patients (0.8%) in the dual antiplatelet therapy group. Ischemia-driven revascularization of the target vessel occurred in 0.7% of the patients in each group (Table 2). The results of analyses of other secondary outcomes are provided in Tables S15 and S16.

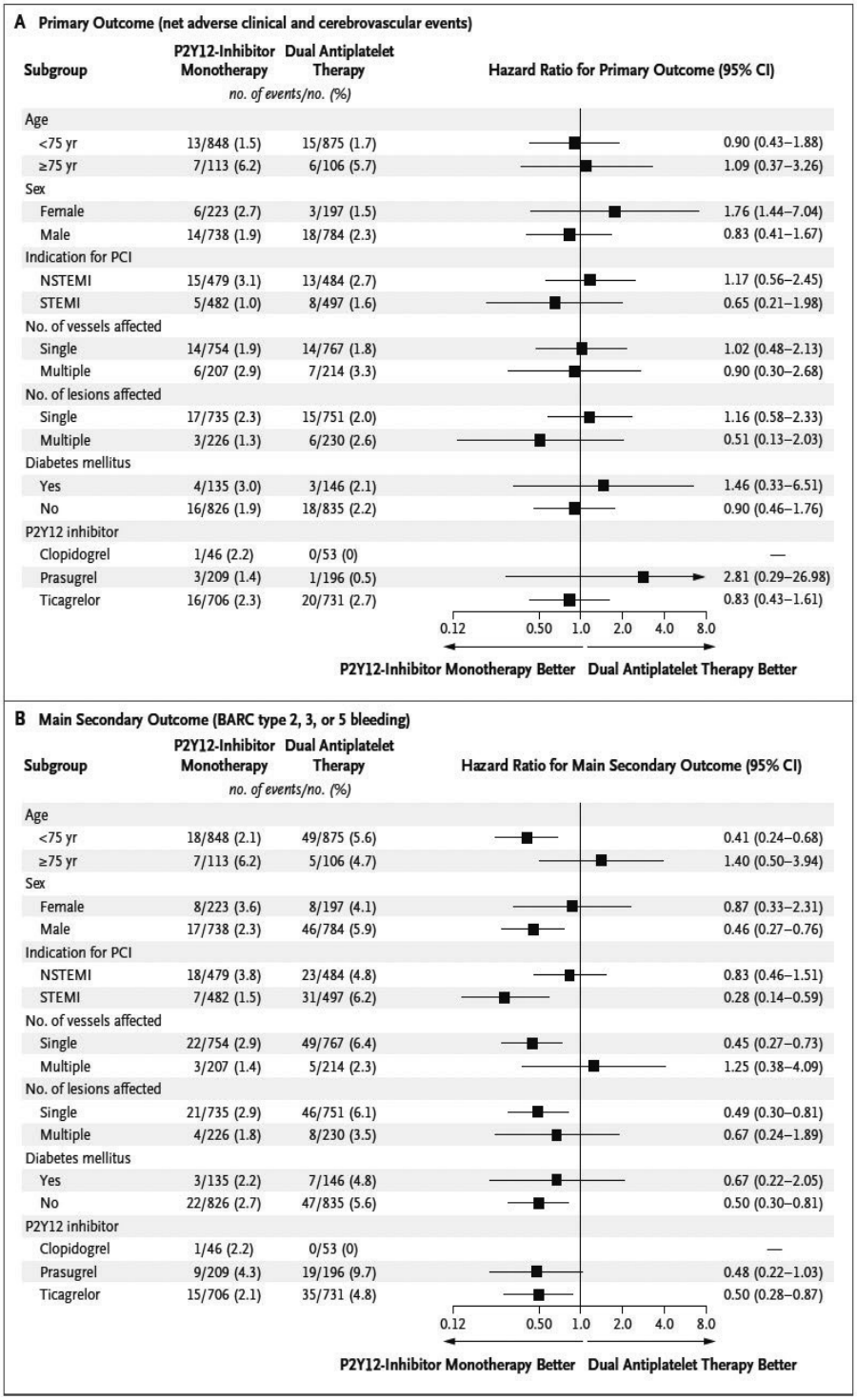

A Primary Outcome (net adverse clinical and cerebrovascular events)
Subgroup
P2Y12-Inhibitor Monotherapy
Dual Antiplatelet Therapy
no. of events/no. (%)
Hazard Ratio for Primary Outcome (95% CI)
Age
<75 yr 13/848 (1.5) 15/875 (1.7) 0.90 (0.43–1.88)
≥75 yr 7/113 (6.2) 6/106 (5.7) 1.09 (0.37–3.26)
Sex
Female 6/223 (2.7) 3/197 (1.5) 1.76 (1.44–7.04)
Male 14/738 (1.9) 18/784 (2.3) 0.83 (0.41–1.67)
Indication for PCI
NSTEMI 15/479 (3.1) 13/484 (2.7) 1.17 (0.56–2.45)
STEMI 5/482 (1.0) 8/497 (1.6) 0.65 (0.21–1.98)
No. of vessels affected
Single 14/754 (1.9) 14/767 (1.8) 1.02 (0.48–2.13)
Multiple 6/207 (2.9) 7/214 (3.3) 0.90 (0.30–2.68)
No. of lesions affected
Single 17/735 (2.3) 15/751 (2.0) 1.16 (0.58–2.33)
Multiple 3/226 (1.3) 6/230 (2.6) 0.51 (0.13–2.03)
Diabetes mellitus
Yes 4/135 (3.0) 3/146 (2.1) 1.46 (0.33–6.51)
No 16/826 (1.9) 18/835 (2.2) 0.90 (0.46–1.76)
P2Y12 inhibitor
Clopidogrel 1/46 (2.2) 0/53 (0) —
Prasugrel 3/209 (1.4) 1/196 (0.5) 2.81 (0.29–26.98)
Ticagrelor 16/706 (2.3) 20/731 (2.7) 0.83 (0.43–1.61)
0.12 0.50 1.0 2.0 4.0 8.0
P2Y12-Inhibitor Monotherapy Better
Dual Antiplatelet Therapy Better
B Main Secondary Outcome (BARC type 2, 3, or 5 bleeding)
Subgroup
P2Y12-Inhibitor Monotherapy
Dual Antiplatelet Therapy
no. of events/no. (%)
Hazard Ratio for Main Secondary Outcome (95% CI)
Age
<75 yr 18/848 (2.1) 49/875 (5.6) 0.41 (0.24–0.68)
≥75 yr 7/113 (6.2) 5/106 (4.7) 1.40 (0.50–3.94)
Sex
Female 8/223 (3.6) 8/197 (4.1) 0.87 (0.33–2.31)
Male 17/738 (2.3) 46/784 (5.9) 0.46 (0.27–0.76)
Indication for PCI
NSTEMI 18/479 (3.8) 23/484 (4.8) 0.83 (0.46–1.51)
STEMI 7/482 (1.5) 31/497 (6.2) 0.28 (0.14–0.59)
No. of vessels affected
Single 22/754 (2.9) 49/767 (6.4) 0.45 (0.27–0.73)
Multiple 3/207 (1.4) 5/214 (2.3) 1.25 (0.38–4.09)
No. of lesions affected
Single 21/735 (2.9) 46/751 (6.1) 0.49 (0.30–0.81)
Multiple 4/226 (1.8) 8/230 (3.5) 0.67 (0.24–1.89)
Diabetes mellitus
Yes 3/135 (2.2) 7/146 (4.8) 0.67 (0.22–2.05)
No 22/826 (2.7) 47/835 (5.6) 0.50 (0.30–0.81)
P2Y12 inhibitor
Clopidogrel 1/46 (2.2) 0/53 (0) —
Prasugrel 9/209 (4.3) 19/196 (9.7) 0.48 (0.22–1.03)
Ticagrelor 15/706 (2.1) 35/731 (4.8) 0.50 (0.28–0.87)
0.12 0.50 1.0 2.0 4.0 8.0
P2Y12-Inhibitor Monotherapy Better
Dual Antiplatelet Therapy Better

Figure 3 Primary and Main Secondary Outcomes in Prespecified Subgroups.
Panel A shows the subgroup analysis of net adverse clinical and cerebrovascular events, defined as a composite of death from any cause, myocardial infarction, stent thrombosis, stroke, or major bleeding (defined by the BARC as a bleeding event of type 3 or 5) (the primary outcome). The arrow on the confidence interval bar indicates that upper boundary of the confidence interval is off the scale. Panel B shows the subgroup analysis of BARC type 2, 3, or 5 bleeding (clinically relevant bleeding) (the main secondary outcome). NSTEMI denotes non–ST-segment elevation myocardial infarction, PCI percutaneous coronary intervention, and STEMI ST-segment elevation myocardial infarction.

Discussion

The TARGET-FIRST trial was a multicenter, randomized trial that evaluated whether early discontinuation of aspirin (at 1 month) and receipt of P2Y12-inhibitor monotherapy was noninferior to dual antiplatelet therapy for a period of 11 months in patients with acute myocardial infarction who had undergone early complete revascularization with a contemporary drug-eluting stent and were at low risk for ischemic and bleeding events. Our trial showed that P2Y12-inhibitor monotherapy was noninferior to continued dual antiplatelet therapy with respect to a composite of death from any cause, myocardial infarction, stent thrombosis, stroke, or BARC type 3 or 5 bleeding at 1 year (11 months after randomization) (the primary outcome). In addition, the incidence of bleeding complications (BARC type 2, 3, or 5 bleeding) was significantly lower (by 54%) with P2Y12-inhibitor monotherapy than with dual antiplatelet therapy, and this finding appeared to be consistent across most prespecified subgroups. Earlier trials that evaluated an abbreviated duration of dual antiplatelet therapy after PCI involved patients with acute myocardial infarction as a subgroup; focused on higher-risk[9], unselected[8], or predominantly East Asian patient populations[10–12,17]; or examined discontinuation of aspirin after a longer duration of dual antiplatelet therapy than that assessed in the TARGET-FIRST trial[9,10,17,18]. It is important to note that none of these trials enrolled only patients with acute myocardial infarction—a clinical context in which thrombotic involvement may substantially affect both the patient's prognosis and the efficacy of antithrombotic strategies. Another distinctive feature of our trial was that the choice of P2Y12 inhibitor was at the discretion of the investigator, although the use of a potent P2Y12 inhibitor was recommended; a potent P2Y12 inhibitor was used in more than 90% of the patients. Although the overall incidence of ischemic events during the trial appeared to be low, this finding may reflect the effectiveness of modern stent

technology, a high incidence of procedural success, adherence to evidence-based medical therapy, and the low-risk patient population enrolled in the trial. Taken together, our trial provides targeted evidence regarding the noninferiority of early cessation of aspirin at 1 month as compared with continued dual antiplatelet therapy for a low-risk European patient population treated with modern PCI strategies and optimized medical therapy.

The benefit of P2Y12-inhibitor monotherapy with respect to bleeding was accompanied by a low incidence of key ischemic-outcome events, including death from any cause, myocardial infarction, stroke, and stent thrombosis. The incidence of stent thrombosis was particularly low, reinforcing the safety of this approach among patients who had been carefully selected for low ischemic risk. Our results align with and contribute to the growing body of evidence that supports tailored antiplatelet strategies that are based on individual bleeding and ischemic-risk profiles. Our findings contrast with those of the STOPDAPT-2 ACS (Short and Optimal Duration of Dual Antiplatelet Therapy after Everolimus-Eluting Cobalt-Chromium Stent-2 in Patients with an Acute Coronary Syndrome) trial[11], in which 1 month of dual antiplatelet therapy was not noninferior to 12 months of dual antiplatelet therapy. However, in the STOPDAPT-2 ACS trial, the completeness of revascularization was unknown and recurrent ischemic events were often linked to untreated lesions rather than to stent failure. Our trial suggests that when complete revascularization is achieved with the use of a latest-generation stent platform, the justification for extended dual antiplatelet therapy in low-risk patients may differ from current practice because residual anatomical ischemic risk has already been addressed.

Our trial required complete revascularization within a narrow window of time after the index PCI in order to eliminate the possibility of residual high-grade or flow-limiting lesions being present at the time of randomization to ensure a consistent anatomical baseline across the trial population. Although most of the patients had single-vessel disease, which is consistent with a low residual ischemic risk, this uniform revascularization strategy enabled a reliable evaluation of the balance between ischemic protection and bleeding risk and of the effect of early antiplatelet de-escalation. The results of previous trials such as the COMPLETE (Complete vs. Culprit-Only

Revascularization to Treat Multi-Vessel Disease after Early PCI for STEMI) trial[19] showed the benefits of complete revascularization; however, the timing of complete revascularization in the COMPLETE trial could have occurred up to 45 days after the index PCI, and the trial involved higher-risk patients. Our findings should be interpreted in the specific context of early, anatomically complete revascularization in a carefully selected population and may not be directly generalizable to the broader, more heterogeneous populations studied previously.

Our trial has limitations that merit consideration. First, although the noninferiority criterion was formally met, the observed effect size was smaller than anticipated. The lower-than-expected incidence of primary-outcome events led to an increase in the relative inferiority margin. Second, although noninferiority was shown in the intention-to-treat and as-treated analyses (Table S18 and Fig. S3), it was not shown in the per-protocol analysis (Tables S19, S20, and S21 and Fig. S4). The per-protocol analysis may have had reduced statistical power owing to the reduced sample size; nonetheless, it showed a similar direction of treatment effect with no safety signals and with a favorable bleeding outcome. Third, the trial was not powered to detect between-group differences in rare events such as stent thrombosis, stroke, and death from cardiovascular causes. Although the assumed incidence of events was based on previous trials and feasibility data, the observed incidence was lower. This finding may reflect a population free from early adverse events, with high procedural success, low ischemic risk, and excellent adherence to therapy that involved the widespread use of potent P2Y12 inhibitors, contemporary stents, and optimized secondary prevention.

Fourth, the focus on patients who completed 1 month of dual antiplatelet therapy without major events and underwent complete revascularization may limit generalizability to higher-risk patients or more complex populations with myocardial infarction. A fifth limitation is that the open-label design could have introduced bias; however, blinded adjudication of major events mitigates this concern.

Sixth, the subgroup analyses of the primary and secondary outcomes were exploratory, were based on small numbers, and should be interpreted cautiously. Seventh, the exclusive use of a single-stent platform may limit extrapolation of the results to other types of devices. Eighth, no platelet-function testing or genotyping was performed in the

small percentage of patients (5.1%) treated with clopidogrel. Finally, the trial population was highly selected, reflecting strict inclusion and exclusion criteria, a mandated narrow window for anatomically complete revascularization (within 7 days), and a low overall incidence of events. Indeed, a substantial percentage of enrolled patients (13.5%) were excluded before randomization, largely owing to early clinical events, incomplete revascularization, or site-level discretion. Modest baseline imbalances between patients who had undergone randomization and those who had not were noted, but none of the imbalances meaningfully affected the heterogeneity of the treatment effect.

The results of this trial showed that, among low-risk patients with acute myocardial infarction who had undergone complete revascularization and had subsequently received 1 month of dual antiplatelet therapy, P2Y12-inhibitor monotherapy was noninferior to continued dual antiplatelet therapy with respect to the occurrence of adverse cardiovascular or cerebrovascular events and resulted in a lower incidence of bleeding events at 1 year than dual antiplatelet therapy.

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Chapter 6

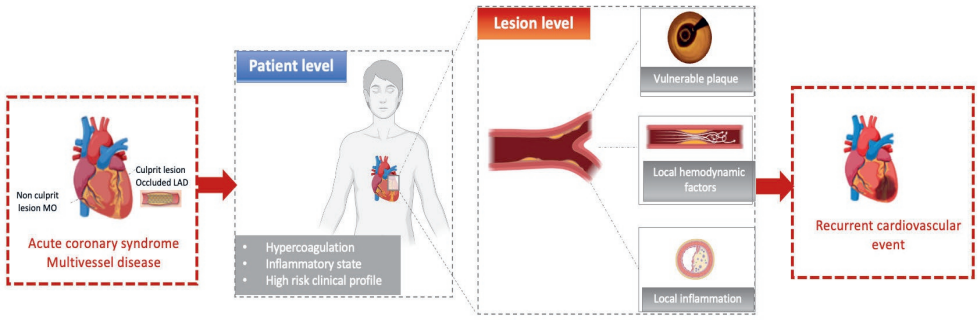
Unveiling the Complexity of Vulnerable Plaques in non-culprit vessels of patients with Acute Coronary Syndrome: Insights from Multimodality Imaging Approach

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Abstract

Vulnerable coronary plaques in non-culprit lesions are increasingly recognized as key drivers of recurrent events in patients presenting with acute coronary syndromes (ACS). Despite successful treatment of the culprit lesion, ACS patients remain at high residual risk due to the presence of other unstable plaques. Advances in intracoronary imaging—particularly optical coherence tomography (OCT) and intravascular ultrasound (IVUS)—have enhanced our understanding of the morphological and compositional features that define plaque vulnerability. However, the optimal preventive management of these high-risk lesions remains uncertain. Most subsequent events originate from angiographically mild but biologically active plaques, challenging the traditional paradigm of treating only flow-limiting stenoses. Intensified systemic pharmacotherapy and pre-emptive percutaneous coronary intervention (PCI) guided by imaging have both been proposed, but robust evidence for either approach is still lacking. This review will specifically focus on ACS populations, summarizing the current evidence on the detection, prognostic significance, and management of non-culprit vulnerable plaques. It will also discuss the integration of plaque imaging, physiology, and clinical risk profiling to guide personalized treatment strategies aimed at reducing recurrent events in this high-risk group.



Graphical abstract. Non-culprit plaque instability results from systemic vulnerability combined with local plaque factors.

Patient-level and lesion-level risk factors contributing to an increased risk of events associated with vulnerable plaques. These include systemic factors such as hypercoagulation and inflammatory states, as well as local factors beyond plaque composition, such as localized shear stress and inflammation.

Introduction

Obstructive coronary artery disease extends beyond the culprit lesion in up to 50% of patients presenting with Acute Coronary Syndrome (ACS) and is associated with worse outcomes.[33,34]. Extensive evidence supports the class I guideline recommendation of preventive percutaneous coronary intervention (PCI) of non-culprit lesions (NCLs) based on angiographic severity in ST-segment elevation myocardial infarction (STEMI), with fewer data guiding the management of patients presenting with Non ST-segment elevation myocardial infarction (NSTEMI) and Multivessel Disease (MVD).[6,35,36]

Identification and interrogation of NCLs in the context of STEMI holds clinical importance, as complete revascularization has been associated with a 26% lower risk of a composite of cardiovascular death or myocardial infarction (MI) over a median follow-up of 3 years, compared with a strategy focused solely on culprit-lesion PCI.[6] However, plaque instability may not be confined to culprit lesions or angiographically severe NCLs.[9] While the benefit of revascualrization is well established for angiographically significant lesions, its impact on lesions that are not angiographically significant remains unclear. High-risk features of NCLs have been linked to an up to 11-fold increase in major adverse cardiovascular events (MACE).[11] Intravascular imaging modalities may provide additional insights into plaque characterization and identify pathological features associated with subsequent events. Nevertheless, the concept of preventive revascularization of vulnerable plaque is questioned by observations that thin-cap fibroatheromas (TCFAs) are common and may persist for years without causing clinical events. [10,37]

Natural history studies on plaque progression suggest that only a minority of lesions with high-risk morphological features progress to ACS. [11] Thus, the optimal method (beyond angiographic visual estimation) for identifying high-risk NCLs that would benefit from preventive therapies remains unsettled. Herein we review the morphological characteristics and prevalence of vulnerable plaques in NCLs of patients with ACS and multivessel coronary artery disease, their relation to outcomes and various treatment options.

Morphological features of vulnerable plaques

Pathological intimal thickening (PIT) is a widely accepted precursor of complex fibroatheroma formation.[38,39] Transition from PIT to atheroma is marked by an accumulation of lipid-laden cells beneath the endothelium. [40,41] Further plaque evolution is marked by an aggressive inflammatory process that may progress to core necrosis along with thinning of the fibrous cap. This thin-cap fibroatheroma (TCFA), appears the dominant plaque phenotype in ACS. [39,41,42] In TCFA, the unstable core is separated from the vessel lumen by a thin layer of epithelial cells (< 65 microns thickness) and features macrophages, lymphocytes and type I collagen but no or minimal smooth muscle cells. Other hallmarks of high-risk lesions are lipid pools, cholesterol crystals, macrophages, a large necrotic core, small luminal area, intraplaque hemorrhage and microcalcifications. Figure 1-2

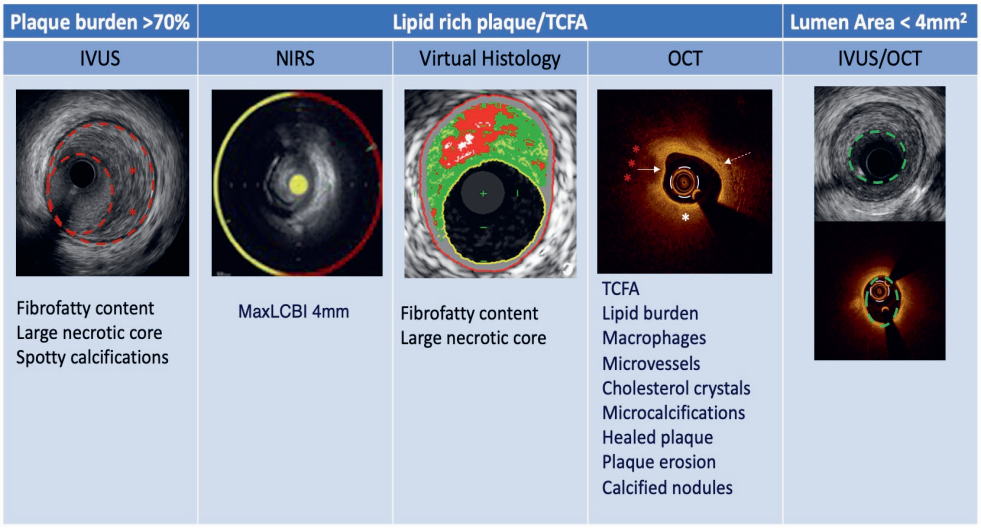


Figure 1. Detection of high-risk vulnerable plaque by intravascular imaging modalities.

From left to right: Intravascular Ultrasound (IVUS) image demonstrating key plaque characteristics, including echo-attenuated areas indicative of lipid-laden (red asterisks) within intermediate echogenic plaque indicative of fibrotic plaque between two red dotted areas. The chemogram of Near-Infrared Spectroscopy (NIRS) imaging showing a maximum lipid core burden index (MaxLCBI) over 4 mm, indicative of a significant lipid-rich plaque. Virtual Histology Intravascular Ultrasound (VH-IVUS) image showing fibrofatty content

(highlighted in green) and a large necrotic core (highlighted in red), providing detailed compositional insights into the atherosclerotic plaque. Optical Coherence Tomography (OCT) image demonstrating key plaque features. The thin-cap fibroatheroma (TFCA) is indicated by a white arrow. The dashed white arrow highlights the presence of microvessels within the plaque. Cholesterol crystals are marked with a white asterisk, while lipid burden is denoted by a red asterisk.

A lumen area of less than 4 mm² (dashed green line) on both IVUS (upper panel) and OCT (lower panel).

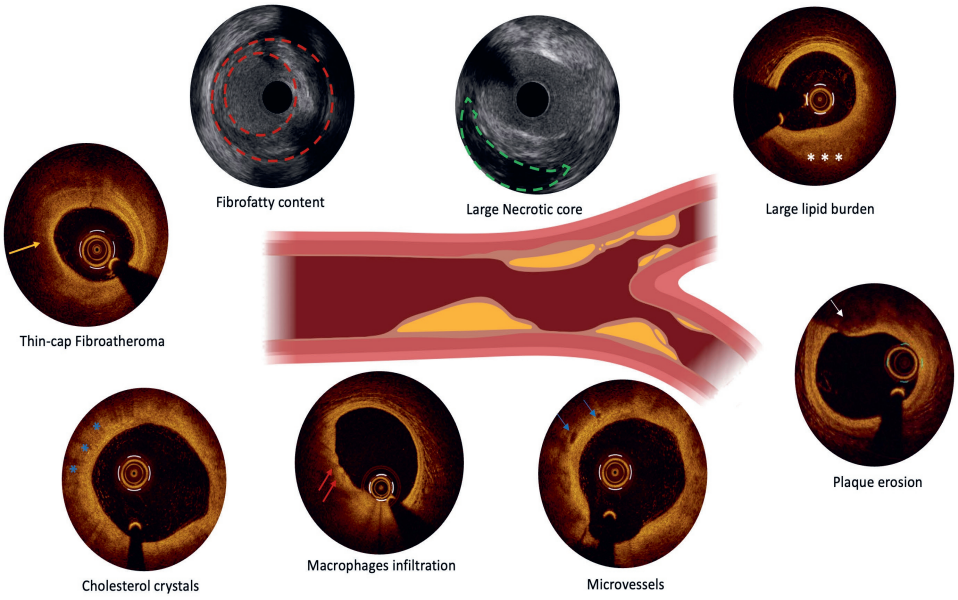


Figure 2. High-Risk Vulnerable Plaque Hallmarks Identified by IVUS and OCT

This figure highlights hallmark features of high-risk vulnerable plaques as visualized by intravascular imaging. On IVUS, fibrofatty content is delineated by red dashed lines, and a large necrotic core is outlined by green dashed lines, with significant lipid burden indicated by asterisks representing lipid accumulation. On OCT, plaque erosion is identified by a white arrow, while microvessels are marked with blue arrows. Macrophage infiltration is highlighted by red arrows, cholesterol crystals are represented by blue asterisks, and a thin-cap fibroatheroma (TFCA) is marked with a yellow arrow.

TCFA are susceptible to tears and ruptures in response to shear stress or inflammation and may cause instant endoluminal occlusive thrombus formation.[43] Additionally, many ACS events can be triggered by surface plaque erosion.[44] Post-mortem assessments of patients suffering an ACS revealed that approximately 60% of CV events appeared to be caused by plaque rupture while 40% were caused by plaque erosion. [41,42] Other less

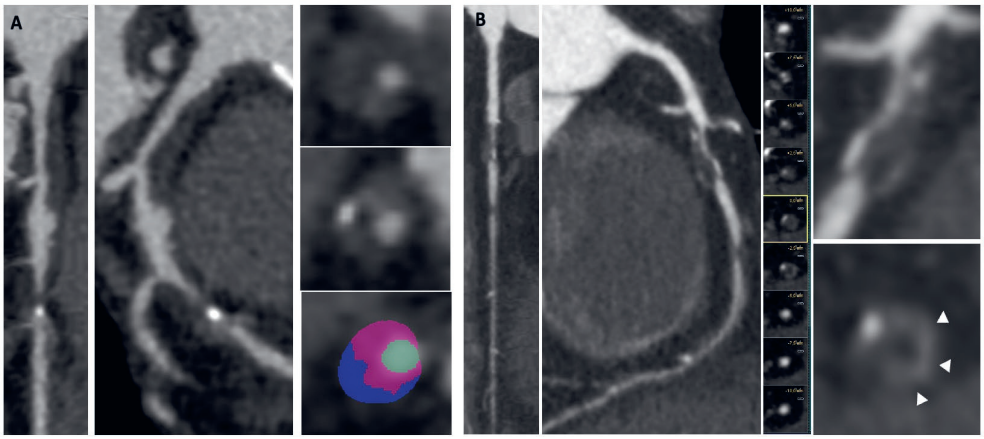
common forms of plaque morphologies found in ACS include occlusive fibrocalcific plaques and erupted calcific nodules. [45]

The two clinical subtypes of ACS, STEMI and non-STEMI, may be linked to distinct coronary atherosclerotic lesion characteristics and pathophysiologic mechanisms. In vivo studies with intravascular imaging demonstrated a higher prevalence of plaque rupture and high-risk plaque features at the culprit site in patients with STEMI as compared with NSTEMI.[46] While limited evidence exists regarding differences in NCLs plaque morphology between NSTEMI and STEMI, studies have shown a higher prevalence of plaque rupture (8.2% vs. 4.8%; p=0.018), microvessels (57.5% vs. 45.2%; p<0.001), and calcification (40.7% vs. 30.2%; p=0.003) in patients with STEMI compared to patients with NSTEMI.[47]

Detection of Vulnerable Plaques by Non-Invasive Imaging Modalities

Non-invasive imaging modalities traditionally play a crucial role in detecting coronary artery disease by identifying obstructive stenoses and coronary calcium (via anatomic testing such as Computed Tomography Coronary Angiography (CCTA) and assessing ischemia or infarction through perfusion imaging.[48] Efforts are now focused on identification and detection of non-obstructive vulnerable plaques.

CCTA is highly effective for large-scale surveillance of at-risk populations, providing accurate detection of coronary disease and calcium with high sensitivity and specificity. [49,50] Key CT plaque features such as low attenuation, positive remodeling, spotty calcification, and the "napkin-ring sign" have been associated with future ischemic events; however most patients with these features remained event-free in large cohort studies, indicating low positive predictive value of high-risk non-obstructive plaques and subsequent clinical outcomes. [51,52] Figure 3-4



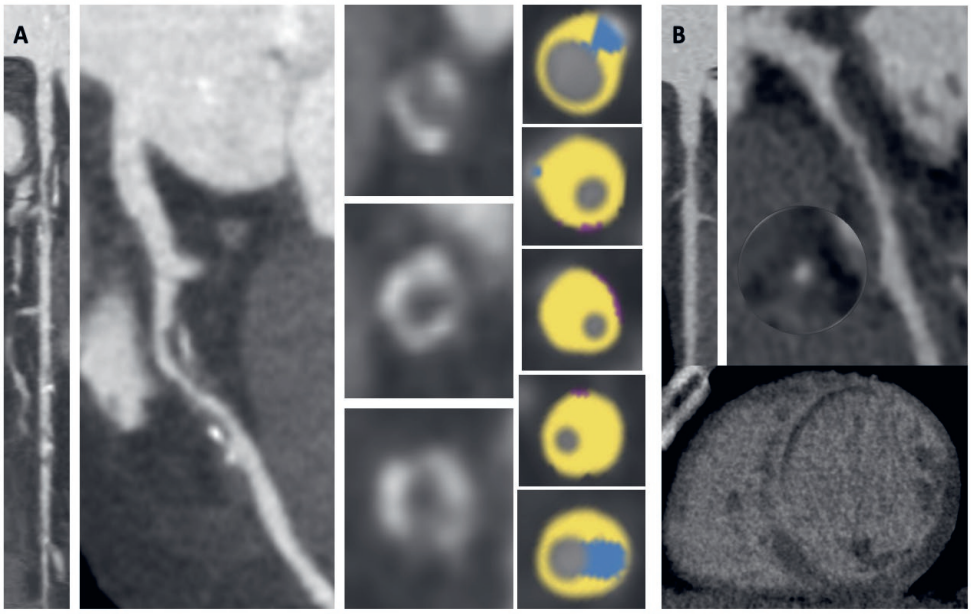
Coronary CT Depiction of High-Risk Atherosclerotic Plaques: Positive Remodeling, Low-Attenuation Components, and Napkin-Ring Sign

Figure 3A

Longitudinal lumen and curved multiplanar reconstructions of the proximal and mid left anterior descending artery reveal two predominantly non-calcified plaques with high-risk features. Short-axis cross-sectional views demonstrate positive remodeling (arrow), low-attenuation plaque components <30 HU (asterisk), and spotty calcification (arrowhead). Color-coded attenuation mapping, generated with dedicated software, shows low-attenuation plaque in blue (<30 HU) and fibrotic components in pink (50–180 HU).

Figure 3B

Longitudinal lumen, curved multiplanar, and cross-sectional reconstructions of the mid right coronary artery reveal two predominantly non-calcified plaques causing subocclusion of the vessel. Enlarged short-axis views demonstrate the napkin-ring sign (arrowheads), defined as a peripheral rim of higher attenuation encircling a central low-attenuation core—an imaging feature associated with high-risk of MACE.



High-Risk Plaques on Coronary CT: Volumetric Plaque Analysis and Correlation With Myocardial Injury

Figure 4A

Longitudinal lumen, curved multiplanar, and cross-sectional reconstructions of the proximal left anterior descending artery in a 61-year-old man with effort angina reveal a mixed, predominantly non-calcified plaque causing severe luminal stenosis. Dedicated plaque analysis demonstrates a large non-calcified component (462 mm^3, highlighted in yellow).

Figure 4B

Longitudinal lumen, curved multiplanar, and cross-sectional reconstructions of the proximal left anterior descending artery in a 32-year-old man reveal a non-calcified plaque with positive remodeling and low-attenuation components. The lower panel shows a short-axis CT image with late iodine enhancement, revealing extensive transmural ischemic scar with microvascular obstruction in the territory of the culprit lesion, involving the anterior septum and mid anterior wall (arrowheads).

A study by Lee et al. involving ACS patients found that non-invasive hemodynamic assessment using computational fluid dynamics on CTCA may help identify high-risk plaques that lead to ACS recurrence.[53] However, this method shows only moderate diagnostic accuracy for detecting ischemia in remote infarcted areas of STEMI patients with MVD compared to invasive FFR.[54] The pericoronary fat attenuation index (FAI), assessed via CTCA, is a novel imaging correlate of coronary inflammation that has been

assoicated with plaque vulnerability, stenosis severity, and local inflammatory responses.[55,56]

Photon-counting computed tomography (PCCT) introduces multi-energy capabilities for enhanced spatial resolution, and superior soft tissue contrast.[57,58] It allows for a more detailed assessment of atherosclerotic plaque composition with less noise and radiation. Small studies report enhanced characterization of coronary calcification and non-calcified plaques, especially fibrotic and lipid-rich components with PCCT.[59,60] However, further clinical validation is needed to confirm its diagnostic accuracy for idenfication of non-obstructive vulnerable plaques and their subsequent impact on outcomes.

Magnetic Resonance Imaging (MRI) is a radiation-free imaging technique able to differentiate between various tissue types, such as calcification, fibrous tissue, fibrocellular areas, and fatty tissue, based on distinct signal intensities.[61-65] Coronary MRI combined with contrast-enhanced methods can identify high-risk plaque features, including reduced fibrous cap thickness (FCT) and intraplaque hemorrhage, as well as intraplaque inflammation through gadolinium or iron oxide, which accumulate in activated macrophages. [64,65] In a small study, CMR successfully identified lipid-rich, calcified, and fibrotic plaques in coronary arteries, with high sensitivity and specificity for calcified plaques (100% and 90%) and lipid-rich plaques (90% and 75%) when compared to histology.[66] While CMR tends to overestimate coronary wall thickness compared to Intravascular Ultrasound (IVUS), it can detect positive vessel remodeling.[67] The application of CMR is limited by logistic challenges, cardiac and pulmonary motion, and its lower spatial and temporal resolution that hinders the evaluation of plaques in smaller vessels.

Dedicated molecular imaging Positron Emission Tomography (PET) is a nuclear imaging technique which can assess high-risk features of atherosclerotic plaques. Radiotracers such as 18F-FDG and 18F-NaF provide insights into plaque vulnerability by visualizing inflammation and microcalcifications.[68,69]

18F-FDG, which highlights macrophage-driven inflammation, is limited in coronary imaging due to non-specific uptake by glycolytic cells and the myocardium, as well as requiring specific preparation.[70,71] In contrast, 18F-NaF binds to hydroxyapatite, effectively identifying microcalcifications without myocardial interference. Its uptake

correlates with high-risk plaque features like positive remodeling and necrotic cores, making it a promising tool for evaluating plaque vulnerability.[72] PET imaging provides complementary information to other modalities and excels in metabolic assessment through parameters like the target-to-background ratio, which quantifies macrophage activity and inflammation within plaques.

Emerging radiotracers such as 68Ga-DOTATATE, 18F-FMCH, and 11C-PK11195, commonly used in oncology, are being investigated for vascular inflammation imaging and may offer improved specificity.[68] Among these developments, 18F-NaF stands out, with its prognostic value currently under investigation in large-scale studies like the PREFFIR trial (NCT02278211).

Despite significant advancements in non-invasive imaging, these modalities primarily focus on specific aspects of plaque vulnerability that can be captured visually. While techniques such as CTCA, PCCT, MRI, and PET have shown promise in identifying high-risk plaque features, their ability to fully assess the complex pathophysiology of ACS remains limited. Crucial factors like hypercoagulability and systemic vascular inflammation, which play a key role in plaque destabilization, cannot be comprehensively evaluated through imaging alone. Moreover, the widespread clinical adoption of these technologies is hindered by practical challenges, including high costs, limited accessibility, and the lack of standardized imaging protocols. While some advanced modalities such as PCCT and PET offer superior plaque characterization, their routine use is restricted to research settings or specialized centers.[73,74] CTCA, with its broad availability and strong diagnostic performance, represents a more scalable approach for large-scale cardiovascular risk assessment.[74] Future efforts should focus on cost-effectiveness analyses and the development of standardized protocols to optimize the clinical utility of these imaging techniques and ensure broader accessibility.

Detection of Vulnerable Plaques by Intravascular Imaging

Invasive imaging techniques such as IVUS, optical coherence tomography (OCT) and nearinfrared spectroscopy (NIRS) can characterize various morphological features of vulnerable plaques. Figure 1

The introduction of greyscale IVUS in the late 1990s enabled in vivo assessment of plaque burden and distribution of atherosclerotic plaque.[75]

IVUS can identify large plaque burden, lipid core, spotty calcification and outward remodeling.[76-78] Color coding of different histological subtypes in virtual histology IVUS (VH-IVUS) can improve plaque composition definition and identification of high-risk features such as fibrofatty content and large necrotic core. [75]

However, the limited resolution of IVUS restricts its ability to quantify in detail the lipid burden, thrombus volume, and FCT. To address these limitations, NIRS has been combined with IVUS to evaluate lipid content. NIRS-IVUS provides simultaneous visualization of plaque structure and quantification of the lipid pool. Limitations include IVUS's inadequate resolution for finer measurements such as cap thickness and NIRS's inability to differentiate between superficial and deep lipid content .[79]

OCT offers a higher spatial resolution (10–20 μm) and [80,81] can detect TCFA and different stages of vulnerable plaque progression, including plaque rupture, healed plaque, plaque erosion, and calcific nodules .[82] Figure 1-2

Prevalence and clinical impact of vulnerable plaques in non culprit lesions of Acute Coronary Syndrome patients

In the PROSPECT trial (a prospective natural-history study of coronary atherosclerosis), 697 patients with ACS underwent coronary angiography and three-vessel gray-scale and radiofrequency IVUS imaging after PCI of the culprit lesion. A total of 596 thin-cap fibroatheromas (TCFAs) were identified in 313 of 623 patients.[11] Plaque burden ≥ 70%, TCFA, and an MLA ≤ 4 mm^2 at IVUS were independent predictors of adverse events in NCLs of ACS patients. (HR 5.03; 95% confidence interval [CI], 2.51 to 10.11; P<0.001; 3.21; 95% CI, 1.61 to 6.42; P = 0.001; 3.35; 95% CI, 1.77 to 6.36; P<0.001; respectively). The presence of all morphological high-risk features was associated with a 11-fold higher risk of MACE. [11]

The PROSPECT II trial (Identification of vulnerable plaques and patients by intracoronary near-infrared spectroscopy and ultrasound), found that untreated NCLs often showed one or more criteria of vulnerable plaque including max lipid core burden index

(LCBI)≥324.7, plaque burden ≥70% or MLA ≤4.0 mm^2 in 58.8%, 59.0% and 75.6% of patients, respectively. [83] In this trial, a 4-fold increase in MACE was observed during 1-year follow-up in 898 ACS patients with high LCBI. Moreover, lesions with both large plaque burden (defined as ≥70% by intravascular ultrasound) and large lipid-rich cores (defined as maxLCBI4mm > 400 by NIRS) had a 4-year NCL related MACE rate of 7·0% (95% CI 4·0–10·0). [83]

The Lipid-Rich Plaque (LRP) Study investigated the use of near-infrared spectroscopy combined with intravascular ultrasound (NIRS-IVUS) to detect lipid-rich plaques (LRPs) in the coronary arteries. Patients and plaques with a high maxLCBI4mm value (≥250 or ≥400) showed a significantly increased risk of future adverse cardiovascular events, including myocardial infarction and cardiac death, compared with those without large LRPs.[84]

The CLIMA trial (Relationship between coronary plaque morphology of the left anterior descending artery and 12 months clinical outcome), which included a total of 1776 lesions from 1003 patients (19.8% with STEMI presentation), found by OCT an MLA <3.5 mm^2 in 39.5% of lesions, FCT <75 μm in 18.2%, maximum lipid arc >180° in 40.9%, and macrophage infiltration in 57.5%. [85] The presence of multiple OCT high-risk features was associated with a 7-fold increased risk of experiencing the composite primary endpoint of target-segment MI and/or cardiac death (HR 7.54, 95% CI, 3.1–18.6;p<0.001). [85]

The COMBINE OCT-FFR study, which investigated patients with diabetes undergoing coronary angiography (CAG), found that OCT imaging of non-flow-limiting lesions revealed a higher incidence of target lesion-related major adverse cardiac events (MACE) in patients with TCFA compared to those without TCFA (13.3% vs. 9.7%) at the 18-month follow-up. However, only 25% of the patients in this study presented with an ACS at baseline.[86]

The PECTUS-obs trial (Identification of Risk Factors for Acute Coronary Events by OCT After STEMI [ST-segment elevation MI] and NSTEMI [non-STEMI] in Patients With Residual Non–flow Limiting Lesions) evaluated by OCT all FFR-negative non-culprit lesions in patients presenting with MI. High-risk plaques were identified based on the presence of at least two of the following criteria: (1) a lipid arc of at least 90°, (2) a FCT less than 65 μm, and (3) either plaque rupture or the presence of thrombus. OCT imaging

analysis revealed that 143 patients (34.0%) had at least one high-risk plaque.[87,88] This trial reported a higher incidence of MACE at 2-year follow-up in patients with high-risk plaques compared to those without (hazard ratio, 1.93 [95% CI, 1.08-3.47]; p:0.02). This difference was primarily driven by an increased number of unplanned revascularizations in patients with high-risk plaques (14 of 143 [9.8%] vs. 12 of 277 [4.3%]; p:0.02).[87]

In the specific context of STEMI presentation with MVD, an imaging substudy of the COMPLETE trial identified at least one TCFA at a NCL site in 47% of patients who underwent OCT assessment. TCFAs were more commonly found in obstructive lesions (defined as >70% visual diameter stenosis) that also contained higher features of lesion complexity. However, 21% of TCFAs were detected in non obstructive coronary arteries.[89]

In a study of 491 ACS patients, the prevalence of TCFA was twice as high in obstructive lesions compared with nonobstructive lesions; of note, OCT-derived TCFA, but not angiographic obstructive stenosis, was independently predictive of recurrent MACEs.[90]

In a more stable setting (84% with stable angina) in the Preventive Percutaneous Coronary Intervention versus Optimal Medical Therapy Alone for the Treatment of Vulnerable Atherosclerotic Coronary Plaques (PREVENT) trial, vulnerable plaque criteria were identified through different modalities in 45% of 3562 patients with non-flow-limiting (fractional flow reserve >0.80) intermediate lesions. Among these lesions, 89% had at least two imaging-defined prespecified vulnerable plaque features as assessed by the imaging core laboratory, with minimal luminal area (MLA) less than 4.0 mm^2 and plaque burden greater than 70% being the most represented. [91] The PREVENT trial reported a target vessel failure rate at 2 years, defined as a composite of cardiac death, target vessel myocardial infarction (TV-MI), ischemia-driven target vessel revascularization (ID-TLR), or hospitalization for unstable or progressive angina, of 0.4% in the PCI + OMT group compared to 3.4% in the OMT alone group (hazard ratio [HR] 0.11, 95% CI 0.03-0.36, p = 0.0003).[91] This benefit was primarily driven by a reduction in ischemia-driven TLR. The number needed to treat (NNT) to prevent one primary outcome event over two years was 45.4, while the NNT to prevent one cardiac death or TV-MI over the same period was 87.7. However, the positive predictive value of vulnerable plaque characteristics identified by intravascular imaging in natural history

studies was less than 20%, suggesting that only a minority of those lesions with all morphological high-risk features eventually progress to ACS. (Table1).

Table 1. Predictive positive values of vulnerable plaques in natural history studies

	PROSPECT	**CLIMA**	**PROSPECT II**	**COMBINE**
Year	2011	2020	2021	2021
Patients (n)	697	1003	898	550
ACS presentation (%)	100	53.4	100	23.9
Imaging modality	IVUS	OCT	IVUS + NIRS	OCT
NLCs related MACE (%)	11.6	NA	8.0	NA
Follow-up	3.4 yrs	1 yr	3.7 yrs	1.5 yrs
Lesion hazard ratio with all high-risk features (95% CI)	11.05 (4.39–27.82)	7.54 (3.1–18.6)	11.33 (6.10–21.03)	4.65 (1.99–10.89)
PPV with all high-risk features	18.0	19.4	7.0	13.3

ACS Acute Coronary Syndromes, IVUS Intravascular Ultrasound, MACE Major Adverse Cardiovascular Events, NCLs Non Culprit Lesions, NIRS Near-Infrared Spectroscopy, OCT Optical Coherence Tomography, PPV Positive Predictive Value

Imaging studies reveal a high prevalence of vulnerable plaques in non-culprit lesions among ACS patients, reflecting the generalized pathophysiology of atherosclerosis. Nonetheless, these techniques only provide a snapshot of the plaque during the acute phase. A vulnerable plaque may or may not rupture and heal, or instigate a major adverse cardiac event (MACE)[92].

Vulnerable plaque treatment

Lipid-lowering therapies

Multiple studies using serial intracoronary imaging have demonstrated the significant role of lipid-lowering therapies in stabilizing vulnerable plaques. [93,94-97]

The addition of intensive lipid-modifying therapies to statin therapy, has resulted in significantly greater coronary plaque regression in non–infarct-related arteries. [98,99] The PACMAN-AMI (Effects of the PCSK9 Antibody Alirocumab on Coronary Atherosclerosis in Patients With Acute Myocardial Infarction) and HUYGENS (High-Resolution Assessment of Coronary Plaques in a Global Evolocumab Randomized Study) trials investigated the effects of alirocumab and evolocumab, respectively, when added to high-intensity statin therapy on non-flow-limiting NCLs in patients who had recently experienced an ACS. In the HUYGENS trial, plaque morphology was assessed solely using OCT, while the PACMAN-AMI trial employed both OCT and NIRS-IVUS. [98,99] PCSK9 inhibitors reduced plaque burden observed by IVUS and the maximum LCBI index measured by NIRS. Additionally, a significant increase in FCT was noted by OCT. [98,99] A key limitation of these trials was that the lesions analyzed for plaque regression and morphological changes had a relatively modest plaque burden, ranging from 40% to 55%. Consequently, the effects of intensive lipid-lowering therapy on more advanced, high-risk plaques—characterized by a plaque burden of 70% or greater, a well-developed necrotic core, and a TCF—remain understudied. Further research is needed to determine how such therapies influence the progression or stabilization of more complex and vulnerable atherosclerotic lesions. A patient's risk profile may influence the response to intensive lipid-lowering therapy. In a pre-specified sub-analysis of the FOURIER trial, evolocumab reduced the risk of MACE by 19% in patients with a recent MI, with a number needed to treat of 27 over three years. This suggests that recent MI identifies patients whose underlying disease processes are more responsive to LDL-C reduction.[100]

The EVOLVE-MI trial (NCT05284747) is currently evaluating whether early administration of evolocumab alongside standard lipid management in the acute phase can reduce MACE in 6,019 ACS patients. Elevated lipoprotein(a) is a marker of cardiovascular risk, especially for early-onset atherosclerotic disease. Lipoprotein(a)-lowering strategies are currently under investigation in phase 3 cardiovascular outcomes trials for secondary prevention.[101] However, the role of lipoprotein(a) in guiding treatment

and as an independent therapeutic target requires further study, and there are currently no data on its effect on plaque stabilization.

It remains to be determined whether novel lipid-lowering therapies (e.g. inclisiran, bempedoic acid) or improved risk stratification will provide additional benefits in plaque regression and stabilization.

Anti-inflammatory therapies

The low positive predictive value of vulnerable plaques and outcomes may be attributed not only to the dynamic nature of plaque vulnerability but also to the role of various local and systemic factors. Both vascular and systemic inflammation contribute to atherosclerotic plaque formation and the development of ACS. [102]

Colchicine reduces cardiovascular risk in patients with coronary heart disease.[103,104] The COLCOT (Effect of Colchicine on Coronary Plaque Stability in ACS as Assessed by Optical Coherence Tomography) trial provided key evidence, not only showing a reduction in ischemic events but also demonstrating for the first time that colchicine positively affects coronary plaque stability.[105] In 128 ACS patients with at least one intermediate-severity lipid-rich NCL (30-70% stenosis), colchicine significantly increased minimal FCT and lowered inflammatory markers, including high-sensitivity C-reactive protein (hs-CRP) ($p = 0.046$), IL-6 ($p = 0.025$), and MPO ($p = 0.047$).[105] Administration of low-dose colchicine (0.5 mg once a day) in ACS patients with high ischemic risk profile or recurrent events, has received a class IIb recommendation by the 2023 ESC Guidelines for the management of ACS and class IIa recommendation by the 2024 Guidelines for the management of chronic coronary syndromes.[20,106] However, the recent findings from the CLEAR SYNERGY trial challenged these recommendations, demonstrating no additional benefit of colchicine early after MI nor for a median of three years in reducing the incidence of the composite primary outcome. Several factors limit the generalizability of these results, including deviations from the original study protocol due to a high drug discontinuation rate, an unexpectedly high all-cause mortality likely influenced by the COVID-19 pandemic, and the absence of consistent CRP measurements. These limitations raise important questions about patient selection and whether certain high-risk subgroups would respond to colchicine therapy.[100]

Other agents with different targets of inflammatory pathways are currently under investigation in selected ACS patients .

A Research Study to Look at How Ziltivekimab Works Compared to Placebo in People With a Heart Attack (ARTEMIS) phase III trial (NCT06118281) will evaluate the effect of Ziltivekimab (fully human monoclonal antibody directed against the IL-6 ligand) versus placebo in 10,000 NSTEMI and STEMI patients receiving PCI and with an increased cardiovascular profile.

Glucose-lowering agents

Patients with diabetes experience a more rapid progression of plaque burden markers, such as percentage atheroma volume, and exhibit a higher prevalence of high-risk plaque characteristics.

Recent studies have highlighted the cardioprotective effects of GLP-1 receptor agonists, suggesting their potential role in treating various cardiovascular diseases. GLP-1 receptor agonists have been shown to inhibit plaque progression and enhance plaque stabilization by reducing plaque growth and altering its composition. iMAP-IVUS analysis demonstrated that patients receiving GLP-1 therapy had larger fibrotic plaque components and smaller necrotic and calcified plaque components compared to controls. [107] These findings, along with previous research, suggest that the plaque-modifying effects of GLP-1 receptor agonists may be mediated in part by their anti-inflammatory properties.[108] However, the precise mechanisms underlying these effects remain unclear and warrant further investigation. Additionally, the therapeutic benefits of GLP-1 in advanced atherosclerosis may be partially attributed to its influence on serum lipid profiles.

<u>Percutaneous Coronary Intervention</u>

Current guidelines recommend complete revascularization of NCLs based on angiographic severity, with a Class I indication for STEMI patients and a Class IIa indication for NSTEMI patients.[106] Despite a correlation between instability features and adverse outcomes, there is currently no consensus supporting the preventive PCI of non-obstructive, nonculprit lesions based on intravascular imaging in the context of ACS. This

is in part because in the prospective trials do date, the majority of MACE events prevented are no "hard" events such as cardiac death or MI, but rather ACS presentations and/or repeat revascularization. This has led to a suggestion that rather than pre-emptively revascularizing, intensive medical therapy plus watchful waiting may be an appropriate strategy without incurring the penalty of adverse death/MI events.

Focal treatment with PCI using a bioresorbable vascular scaffold was investigated in the PROSPECT Absorb trial. This approach was safe, improved the MLA and reduced lipid burden; however, it did not decrease the risk of TLF at 24 months as compared to guidelines directed medical therapy alone (4.3% vs. 4.5%; p . 0.96).[83] Table 2

Table 2. Overview of RCTs investigating preventive PCI of vulnerable plaques

Study	**Year**	**N**	**ACS (%)**	**Modality of assessment**	**Control**	**Intervention**	**Follow-up**	**Main findings**
VELETI	2009	57	71.5	IVUS	Intensive lipid-lowering therapy	PCI DES	1 yr	12-m FU MACE related to the target SVG was 19% in the medical treatment group versus 3% in the PES group (P 0.091).
SECRITT	2012	10	24	IVUS/OCT	GDMT	PCI self-expanding vShield device	6 mo	At 6 mo FU vShield treatment was associated with DS decrease 18.7±16.9%.
Prospect Absorb	2021	182	100	NIRS-IVUS	GDMT	PCI BVS	2 yrs	At 24 months TLF occurred in similar rates of BVS-treated and GDMT alone–treated patients (4.3%

								vs. 4.5%; p . 0.96)
Pectus	2020	34	100	OCT	GDMT	PCI BVS	2 yrs	At 2 years, the composite endpoint occurred 3 times (18.8%) in the BVS group and 1 time (6.3%) in the GDMT group
Prevent	2024	1606	15.5	NIRS-IVUS/OCT	GDMT	PCI DES or BVS*	2 yrs	At 2 years, the primary outcome occurred in three (0·4%) patients in the PCI group and in 27 (3·4%) patients in the GMDT group (p=0·0003).

BVS Bioresorbable vascular scaffolds, DES Drug Eluting Stents, GDMT Guidelines directed medical therapy, IVUS Intravascular Ultrasound, MACE Major Adverse Cardiovascular Events, NIRS Near-Infrared Spectroscopy, OCT Optical Coherence Tomography, PCI Percutaneous Coronary Intervention, SVG Saphenous Venous Graf, TLF Target Lesion Failure, *BVS (Absorb; Abbott, Santa Clara, CA, USA) used for initial recruitment. Following the withdrawal of BVS from the market, cobalt–chromium everolimus-eluting metallic stents (Xience; Abbott, Santa Clara, CA, USA) were used for the default device of PCI.

The PROSPECT studies revealed that most nonculprit lesions causing follow-up MACE events were angiographically mild at baseline, with mean diameter stenosis of only 32.3% and 47% in PROSPECT and PROSPECT II, respectively. This indicates that an angiography-guided revascularization approach may overlook a significant number of potentially clinically relevant lesions.[109] However, given that many of these MACE events

involve unplanned revascularizations, an alternative approach could be watchful waiting combined with intensive medical therapy.

Pathology studies have shown that most plaque rupture events are asymptomatic, and healing after plaque rupture is the predominant mechanism for plaque progression, eventually leading to severely obstructive stenosis, which often becomes the substrate for a CCS. [98,110,111]

The PREVENT trial demonstrated that preventive PCI, targeting focal plaques with angiographic stenosis >50% and signs of vulnerability on intravascular imaging, combined with OMT, is superior to OMT alone in improving clinical outcomes over two years, primarily driven by a reduction in ischemia-driven TLR. However, the majority of enrolled patients (83.5%) presented with chronic coronary syndrome (CCS), and only 1% had a STEMI presentation. [91] Notably, the study was primarily conducted in Asian patients, limiting its generalizability to more diverse populations, and the preponderance of CCS patients may not fully capture the dynamic nature of vulnerable plaques described in previous studies on ACS patients. [11,83]Additionally, vulnerable plaques were identified in segments with at least 50% visual angiographic diameter stenosis and negative FFR and most lesions were identified based on MLA and plaque burden, whereas TCFA accounted for less than 10% of the qualifying criteria. This may partially explain why the observed benefit was more closely associated with reduced revascularization rates rather than a significant impact on MI-related adverse events. Furthermore the lower-than-expected event rates limit the generalizability of these findings.

To date, the only strategy proven to reduce cardiovascular death and MI in patients presenting with STEMI and MVD is angiography-based revascularization of obstructive lesions, which reduced the first co-primary outcome of CV death or new MI by 26% (7.8% vs. 10.5%; hazard ratio: 0.74; 95% confidence interval: 0.60 to 0.91; p = 0.004), primarily driven by a reduction in new, spontaneous MI in the COMPLETE trial.[6]

Preliminary data have explored the use of paclitaxel drug-coated balloons (DCBs) for the treatment of lipid-rich vulnerable plaques in patients with ACS, demonstrating a significant reduction in lipid burden (maxLCBI4mm) at 9-month follow-up. [112]

The straightforward and widely adopted approach of revascularizing nonculprit lesions based on angiographic severity may overcome the limitations of a physiology-guided

approach, which cannot identify biologically active but physiologically negative plaques. Moreover, the higher presence of high-risk plaques in obstructive lesions supports the hypothesis that the benefit of complete revascularization is derived not only from sealing vulnerable plaques but also from reducing residual ischemia.

Future directions

Advancing Atherosclerosis Detection

Atherosclerosis is driven by complex biological and mechanical processes that go beyond plaque morphology. Local inflammation, thrombogenicity, and shear stress contribute to plaque progression and destabilization. [113] In recent years, emerging techonologies like hybrid intravascular imaging—either through co-registration of complementary modalities or dual-probe catheters—provide a more comprehensive understanding of plaque vulnerability.[79] (Figure 5)

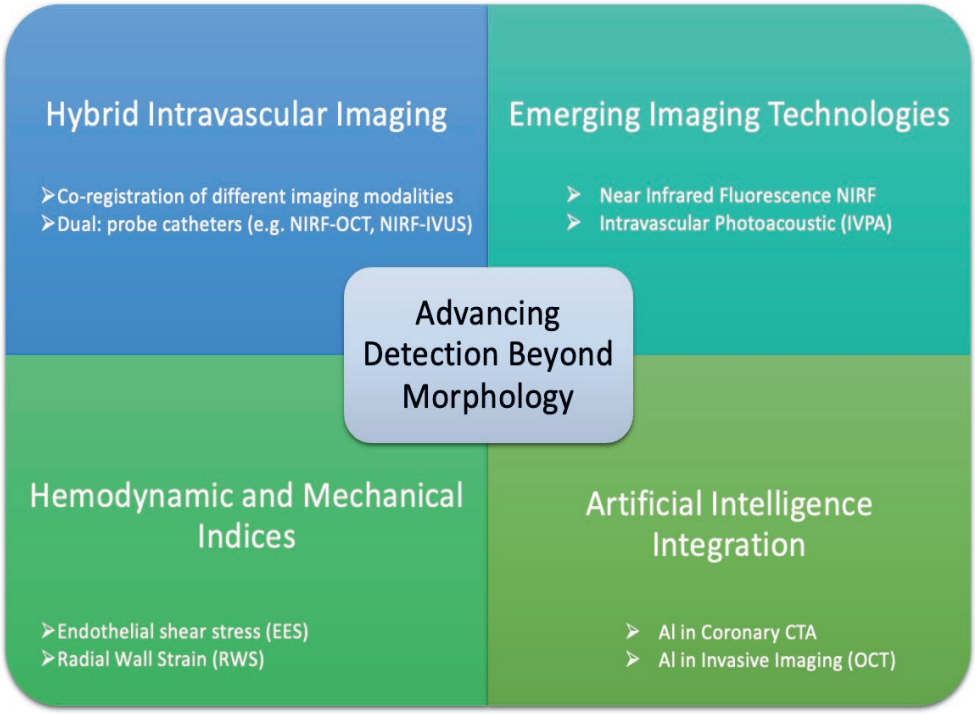


Figure 5 Multidimensional Strategies for High-Risk Plaque Detection

This schematic highlights four key domains shaping the future of coronary plaque assessment: hybrid intravascular imaging, novel molecular imaging technologies, hemodynamic and mechanical indices, and artificial intelligence integration.

Moreover a growing emphasis has been placed on technologies that move beyond structural imaging to capture the dynamic biological environment of coronary atherosclerosis. OCT can detect additional aspects of vulnerable plaques, like macrophages infiltration and neovascularization, but lacks molecular insights. [85,114,115] The interest for the role of inflammation in plaque progression has led to the devolpment of alternative invasive imaging techniques. The Near Infrared Fluorescence Molecular Imaging (NIRF) allows visualization of in vivo atheroma inflammation, angiogenesis, apoptosis, oxidative stress, and calcifications by detecting tissue autofluorescence.[116] Dual-probe intravascular imaging catheters are under investigation to synergize molecular and structural imaging methods (NIRF-OCT, NIRF-IVUS).[79]

Similarly, intravascular photoacoustic (IVPA) imaging has emerged as novel technique which uses short laser pulses to generate ultrasound signals through optical absorption, enabling the identification of lipids relative to the lumen border as demonstrated *in a* swine model. [117] Advancing higher-speed IVPA/IVUS systems remains a crucial step toward clinical translation, to limit the need for flushing and enhance signal-to-noise ratio. Polarization-sensitive OFDI (PS-OFDI) offers a novel functional dimension to plaque assessment by mapping tissue birefringence and depolarization—biophysical signatures that reflect collagen content and tissue integrity. Compatible with commercial catheters, PS-OFDI adds functional imaging to conventional morphological assessment. [118–120] However, hybrid imaging remains invasive, costly, and mainly confined to research settings.[79,116]

Beyond imaging, biomechanical metrics such as low endothelial shear stress (ESS) and coronary strain are gaining interest. EES promotes lipid accumulation and inflammation, while coronary strain reflects wall stiffness and plaque load. [121,122] Angiography-derived radial wall strain (RWS) correlates with OCT vulnerability markers and may offer a low-cost, real-time biomechanical assessment—though vessel motion, imaging angles, and projection quality might limit accuracy.[123]

Future directions in coronary atherosclerotic plaque analysis involve the integration of artificial intelligence (AI).[124] Applied to CTA, AI has shown high diagnostic accuracy in coronary CTA for detecting stenosis and assessing plaque composition.[125] AI has enabled detailed, non invasive morphological plaque evaluation through quantitative coronary plaque and hemodynamic analysis softwares offering not only robust characterization of the plaque type, volume, burden, and stenosis but also strong prognostic stratitification.[125-128] When applied to invasive imaging, AI-powered OCT further enhances precision by automatically detecting lipid-rich plaques, thin-cap fibroatheromas, and calcifications.[129-131] (Table 3).

Table 3 Emerging Techniques and Future Directions in Coronary Atherosclerosis Imaging

Technology/Method	**Principle**	**Target Features**	**Current Status**
Hybrid Imaging (OCT + IVUS/NIRF)	Dual-modal structural + molecular imaging	Plaque structure, inflammation	Research phase
NIRF Imaging	Autofluorescence for molecular targets	Inflammation, apoptosis, angiogenesis	Preclinical/early human
IVPA	Laser-induced ultrasound imaging	Lipid content near lumen	Preclinical (animal studies)
PS-OFDI	Polarization-based tissue analysis	Birefringence, plaque composition	Early human studies
Radial Wall Strain (RWS)	Angiography-based strain analysis	Biomechanical plaque vulnerability	Early human studies
AI for CTA & OCT	Deep learning for image interpretation	Stenosis, plaque burden, risk stratification	Emerging clinical application

AI – Artificial Intelligence, CTA – Computed Tomography Angiography, IVPA – Intravascular Photoacoustic Imaging, IVUS – Intravascular Ultrasound, MI – Myocardial Infarction, NIRF – Near-Infrared Fluorescence, OCT – Optical Coherence Tomography, OFDI – Optical Frequency Domain Imaging, PS-OFDI – Polarization-Sensitive Optical Frequency Domain Imaging, RWS – Radial Wall Strain, RWSmax – Maximum Radial Wall Strain, ESS – Endothelial Shear Stress

Conclusions

Contemporary invasive and non-invasive imaging techniques can identify non-flow-limiting vulnerable plaques, but their management remains controversial. Optimal pharmacotherapy and the value of preemptive revascularization require further research.

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Chapter 7

Antithrombotic drugs for acute coronary syndromes in women: sex-adjusted treatment and female representation in randomised clinical trials. A clinical consensus statement of the European Association of Percutaneous Cardiovascular Interventions (EAPCI) and the ESC Working Group on Thrombosis

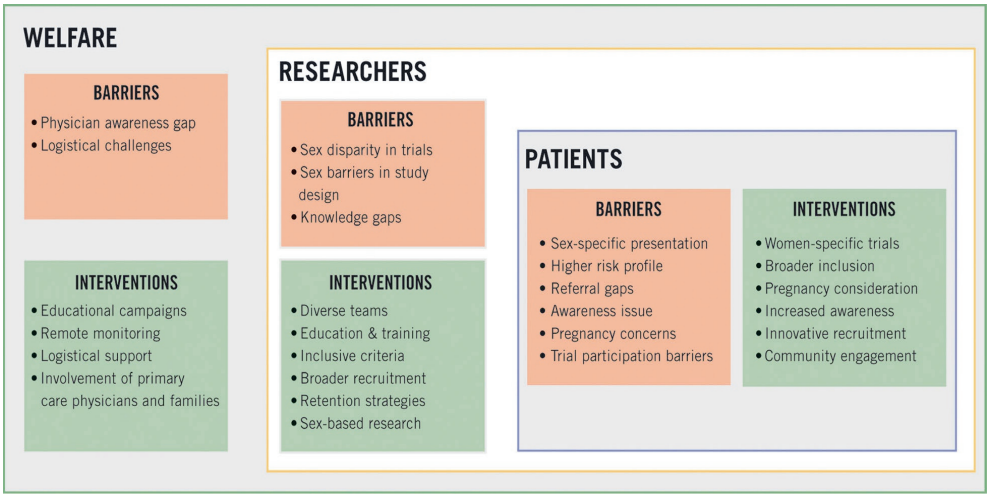
Valeria Paradies[*], *Giulia Masiero*, *Andrea Rubboli*, *Heleen M M Van Beusekom*, *Francesco Costa*, *Piera Capranzano*, *Sophie Degrauwe*, *Diana A Gorog*, *Claudia Moreira Jorge*, *Gill Louise Buchanan*, *Mirvat Alasnag*, *Daniela Trabattoni*, *Chiara Fraccaro*, *Dirk Sibbing*, *Dariusz Dudek*, *Gemma Vilahur*, *Alaide Chieffo*, *Roxana Mehran*, *Davide Capodanno*, *Emanuele Barbato*, *Jolanta M Siller-Matula*

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Abstract

Thrombotic and bleeding risks differ between sexes, partly in relation to distinct biology and hormonal status, but also due to differences in age, comorbidities, and body size at presentation. Women experience frequent fluctuations of prothrombotic and bleeding status related to menstrual cycle, use of oral contraceptives, hormone replacement therapy, or menopause. Although clinical studies tend to underrepresent women, available data consistently support sex-specific differences in the baseline thrombotic and haemorrhagic risks. Compared with men, women feature an increased risk of in-hospital bleeding related to invasive procedures, as well as long-term out-of-hospital bleeding events. In addition, the inappropriate dosing of antithrombotic drugs, which is not adapted to body weight or renal function, is more frequently associated with an increased risk of bleeding in women compared to men. While acute coronary syndrome (ACS) studies support similar antithrombotic drug efficacy, irrespective of sex, women may receive delayed treatment due to bias in their referral, diagnosis, and invasive treatment decisions. The current clinical consensus statement highlights the need for an increased awareness of sex-specific risks and biases in ACS management, with a focus on sex-specific bleeding mitigation strategies, antithrombotic management in special conditions (e.g., myocardial infarction with non-obstructive coronary arteries), and barriers to female representation in cardiovascular trials. This manuscript aims to provide expert opinion, based on the best available evidence, and consensus statements on optimising antithrombotic therapy according to sex, which is critical to improve sex-based disparities in outcome.



Graphical Abstract Current barriers and potential interventions to improve the recruitment of women in cardiovascular trials

Introduction

Sex-based differences in the pathophysiology, epidemiology, clinical presentation, therapy, and outcome of acute coronary syndrome (ACS) are well described[1–4]. Although sex-based disparities in the invasive management of patients with ACS and percutaneous coronary intervention (PCI) have narrowed in recent years, clinical outcomes after ACS remain worse for female compared to male patients[5]. Data consistently show that female patients experience greater delays in the diagnosis and treatment of ACS compared to male patients, these being associated with the consequent late administration of antithrombotic agents during ongoing cardiac ischaemia[6]. Although there is a sex-based bias in referral by both healthcare practitioners and patients[7], differences in coronary anatomy and function, peripheral vascular anatomy and comorbidities, psychosocial factors, and vascular and neural stress responses may contribute to the observed differences in the safety and efficacy of antithrombotic drugs between sexes[8–9]. As women are often underrepresented in randomised controlled trials (RCTs) of antithrombotic treatment, new data and adequately powered trials in women are required to identify independent associations between sex and the efficacy/safety of

antithrombotic treatment. Considering these unique challenges to optimising antithrombotic treatment based on sex, the aim of the current consensus statement, led by the European Association of Percutaneous Cardiovascular Interventions (EAPCI) and the European Society of Cardiology (ESC) Working Group on Thrombosis, is to provide consensus-based guidance, founded on the best available evidence and expert opinion.

Sex and antithrombotic therapies

Baseline differences between sexes in the coagulation system

The risk of coronary thrombosis differs between females and males. This is especially true before the menopause due to oestrogen and progesterone fluctuations influencing blood platelets and procoagulant factors[10–11]. Oestrogen promotes prostacyclin production, improves nitric oxide availability, and reduces platelet aggregation, which might be protective against the premature onset of coronary artery disease[11]. Fluctuations in hormonal status associated with menstrual cycles, oral contraceptive use, menopause, and hormone replacement therapy all influence thrombotic and bleeding risks[6 12–13] (Supplementary Appendix 1). Of note, lower platelet reactivity in premenopausal women has been related to the presence of oestrogen receptors on the platelet surface[14]. Some reports have also indicated more pronounced platelet adhesion to injured vessels in males[15], but greater agonist-induced platelet activation and aggregation in females[11 16–18] (Figure 1). There are also differences in protease-activated receptor (PAR) signalling pathways between sexes, with platelet PAR1 signalling shown to be reduced in women and increased in men during myocardial infarction (MI)[19]. Increased endothelial shear stress, which is associated with significantly smaller epicardial coronary arteries in females, may influence vascular lipid accumulation, pathological remodelling, and plaque instability. This contributes to distinct coronary atherosclerosis characteristics, including a more diffuse and non-obstructive pattern, reduced overall plaque burden and calcification, and fewer signs of necrosis in the plaque core[20] (Figure 1).

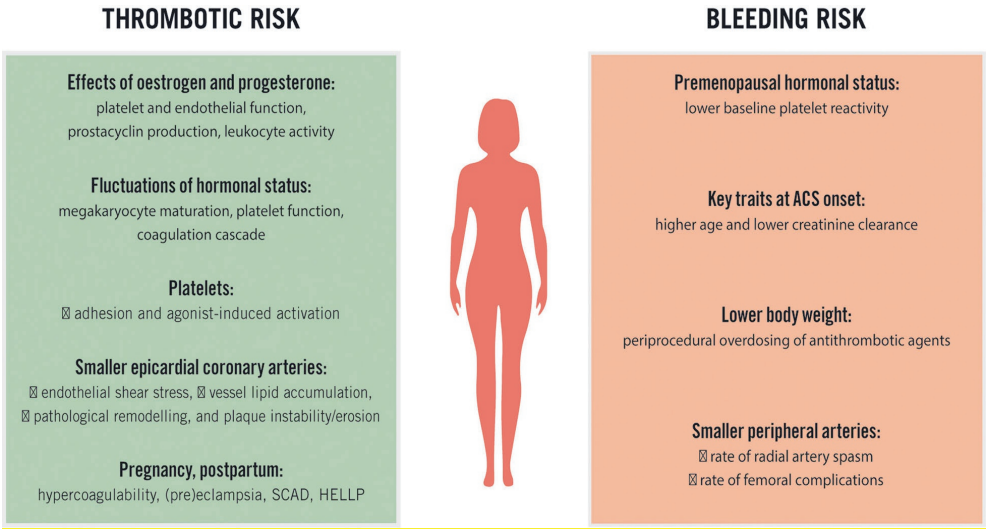


Figure 1 Factors associated with thrombotic and bleeding risks in women. ACS: acute coronary syndrome; HELLP: haemolysis, elevated liver enzymes and low platelets; SCAD: spontaneous coronary artery dissection

Thrombotic/ischaemic risk according to sex in patients treated with antithrombotic agents

The major adverse cardiovascular event (MACE) rate after ACS is higher in female than male patients, which might be due to sex-based disparities in clinical characteristics and treatment[6 21]. Women tend to present with ACS at an older age and with a higher burden of comorbidities such as diabetes, hypertension, and chronic kidney disease, compared to men[1]. The available evidence shows a similar efficacy of antithrombotic agents for ACS/PCI in both sexes. In the Antithrombotic Trialists' (ATT) Collaboration meta-analysis, there was no interaction between sex and the efficacy of aspirin versus placebo for secondary cardiovascular disease (CVD) prevention[22]. As far as dual antiplatelet (DAPT) therapy is concerned, a meta-analysis comparing clopidogrel plus aspirin versus aspirin alone in patients presenting with ACS and/or undergoing PCI showed that the absolute risk of MACE was higher in women than in men, and the relative benefit of clopidogrel therapy appeared attenuated in women versus men (7% vs 16% reduction)[23]. In the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel–Thrombolysis in Myocardial Infarction 38 (TRITON-TIMI 38 trial), which evaluated prasugrel versus clopidogrel on top of aspirin therapy in ACS

patients undergoing PCI, there was no significant interaction between the efficacy of prasugrel and sex, but the magnitude of the effect was greater in men at 15-month follow-up[24] (Supplementary Table 1). Similarly, in the PLATelet inhibition and patient Outcomes (PLATO) trial, which compared ticagrelor to clopidogrel in aspirin-treated patients with ACS, no significant sex-related difference was found for MACE reduction at 1 year[25] (Supplementary Table 2). Similar results were observed in the The Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment 5 (ISAR-REACT 5) trial[26] (Supplementary Table 3).

Some interest over the combination of antiplatelet therapy and direct oral anticoagulants has emerged. In the Anti-Xa Therapy to Lower cardiovascular events in addition to Aspirin with or without thienopyridine therapy in Subjects with Acute Coronary Syndrome 2–Thrombolysis in Myocardial Infarction 51 (ATLAS ACS 2-TIMI 51) trial, rivaroxaban (2.5 mg or 5 mg twice daily) added to aspirin plus clopidogrel reduced the risks of MACE across both sexes[27].

In ACS/PCI patients with an indication for oral anticoagulation and antiplatelet therapy, no significant interaction between sex and major efficacy outcomes was observed (Supplementary Table 4).

Clinical consensus statements: antithrombotic agents

There is no significant sex-related difference in the efficacy of antithrombotic drugs for secondary CVD prevention.

Delays in ACS diagnosis and invasive treatment should be addressed to enable timely initiation of treatment with antithrombotic drugs.

Bleeding risk according to sex in patients treated with antithrombotic agents

Although primary analyses of pivotal trials on antithrombotic therapies in ACS do not indicate an interaction between sex and bleeding outcomes (Supplementary Table 1–Supplementary Table 4), there is a wealth of additional data from multivariate analyses of dedicated substudies demonstrating a higher risk of bleeding and vascular complications in females versus males, especially when femoral access for PCI is used[6 10 28 29]. Female ACS patients tend to be older, with more comorbidities when compared to their male

counterparts[30]. In this context, it should be noted that female ACS patients may receive higher antithrombotic drug doses than appropriate for their body weight or renal function[31].

The ESC Guidelines for the management of acute coronary syndromes advocate an early invasive approach and use of weight-adjusted unfractionated heparin (UFH) as the first-line anticoagulant agent for most patients with non-ST-segment elevation acute coronary syndrome (NSTE-ACS)[32]. In patients undergoing coronary angiography (CAG) outside of the recommended time window, antithrombotic "bridging" with fondaparinux prior to angiography was associated with significantly fewer Bleeding Academic Research Consortium (BARC) 3–5 (adjusted [adj.] hazard ratio [HR] 0.21) and access site-related bleeding events (adj. HR 0.49) compared to enoxaparin in a contemporary patient population[33] and in pivotal fondaparinux trials[34] [35]. In the Fifth Organization to Assess Strategies in Acute Ischemic Syndromes (OASIS-5) trial, fondaparinux substantially reduced the occurrence of major bleeding events and access site-related bleeding in both sexes compared to enoxaparin, but the magnitude of the effect on bleeding risk reduction was greater in women than in men (HR 0.45 vs 0.60, respectively)[34] [35].

The age-dependent risk of bleeding is even more pronounced in premenopausal women, being 4-fold higher for Thrombolysis in Myocardial Infarction (TIMI) major/minor bleeding events in females younger than 50 years of age, compared to males in the same age category[36]. This increased bleeding risk in young females might be partly related to the differential effects of sex hormones on platelet activity, with lower baseline platelet activity in the presence of platelet oestrogen receptors in premenopausal females[1] [6] [14]. Additionally, young patients, regardless of sex, tend to be treated with excessive doses of anticoagulants in the setting of ACS and PCI; still, this excess dosing is associated with significantly higher bleeding rates in young females than in young males[37]. Importantly, women presenting with cardiogenic shock had a higher risk of major bleeding events compared to men (adj. odds ratio [OR] 1.23; 95% confidence interval [CI]: 1.12–1.34)[38].

Beyond non-modifiable factors such as age, creatinine clearance, and other comorbidities, the modifiable factor of arterial access selection also differs between sexes; femoral access was more frequently used (5–50%) in females than in males in the majority of studies and accounts for almost half of bleeding events[36] [39–41]. An effort

should be made regarding the proper training and awareness of interventional cardiologists in strategies such as ultrasound-guided access, smaller sheath sizes, and earlier sheath removal in order to mitigate the bleeding events associated with vascular puncture[41 42]. Radial access remains an effective method to reduce access site bleeding complications[43]. Various prevention approaches, including medications like vasodilators and calcium channel blockers, aim to reduce radial artery spasm[44]. Equipment-related prevention includes the use of hydrophilic tools, special 6-in-5 Fr sheaths, minimising catheter exchanges, and avoiding cold intra-arterial injections[45].

Consensus statements: mitigation of bleeding risks

Strategies aiming to mitigate the bleeding risks associated with the femoral access site are advisable (Figure 2):

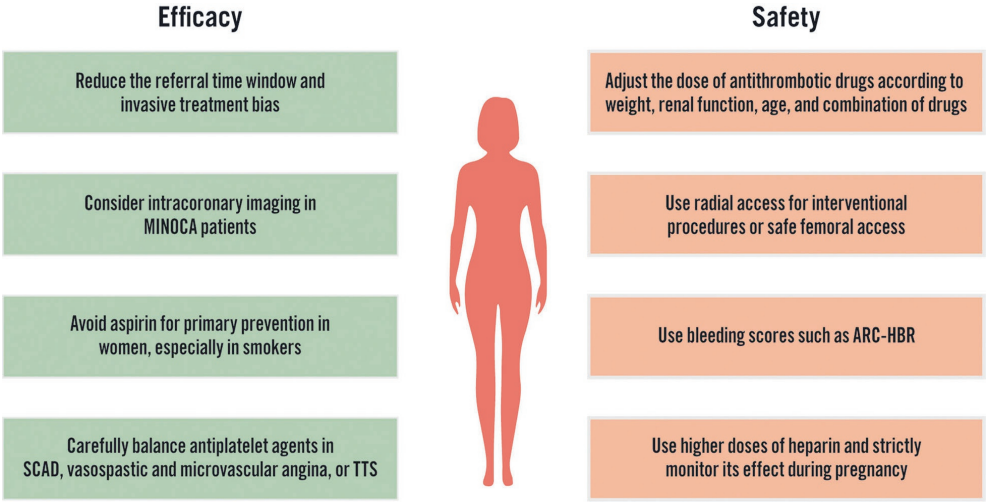


Figure 2 Strategies to improve the efficacy and safety of antithrombotic agents in women. ACS: acute coronary syndrome; ARC-HBR: Academic Research Consortium for High Bleeding Risk; MINOCA: myocardial infarction with non-obstructive coronary arteries; SCAD: spontaneous coronary artery dissection; TTS: Takotsubo syndrome

- Favour radial access over femoral access, with emphasis on spasm prophylaxis and the use of dedicated radial equipment.
- Utilise ultrasound-assisted puncture when femoral artery access is needed.

- Avoid excess dosing of periprocedural anticoagulants and antiplatelet agents (Figure 2):
- Body weight and/or renal function-adjusted dosing of periprocedural antiplatelet agents (the P2Y12 inhibitor cangrelor or the glycoprotein [GP] IIb/IIIa inhibitors tirofiban or eptifibatide) and anticoagulants (UFH, low-molecular-weight heparins [LMWH], bivalirudin) should be used. When a combination of UFH and GPIIb/IIIa inhibitors is applied, it is advisable to reduce the dose of UFH from 70-100 U/kg to 50-70 U/kg and to monitor its effect using activated clotting time testing.
- For NSTE-ACS patients without an immediate invasive strategy, anticoagulants with a favourable safety profile are preferable. It is advisable to select fondaparinux over enoxaparin.
- Long-term selection of antithrombotic treatment type or duration after ACS/PCI should be based on patient comorbidities rather than sex, recognising the higher comorbidity burden in women compared to men (Figure 2).
- Use of guideline-endorsed bleeding scores (such as Academic Research Consortium for High Bleeding Risk [ARC-HBR] and PRECISE-DAPT46,47) is advisable (Table 1).

Table 1

Ischaemic and bleeding risk scores for the secondary prevention of events following ACS and PCI, and the role of sex.

Risk scores[#]	C-statistic	Predictors	Role of sex and/or strongest (significant) predictor
GRACE (I)*	0.7	Systolic blood pressure, age, Killip class, heart rate, cardiac arrest, serum creatinine levels, ST-segment deviation, cardiac biomarker increase	No interaction between sexes for primary endpoints
CRUSADE (B)[#]	0.6-0.8	Female sex, diabetes, peripheral arterial disease, heart rate, systolic blood pressure,	HR female sex 1.31 (95% CI: 1.23-1.39)

Risk scores[#]	C-statistic	Predictors	Role of sex and/or strongest (significant) predictor
		congestive heart failure, haematocrit level, creatinine clearance	
GRACE + CRUSADE (I + B)	n.a.	See above	OR cardiac death/bleeding: female: 27.42 (95% CI: 21.64-34.74) male: 34.80 (95% CI: 28.89-41.91)
PARIS CTE (I)	0.7	Diabetes, ACS, smoking, creatinine clearance, prior PCI or CABG	No sex strata
PARIS MB (B)	0.7	Age, BMI, smoking, anaemia, creatinine clearance, triple therapy	No sex strata
DAPT (I + B)*	0.6-0.7	Myocardial infarction, PCI, diabetes, stent diameter <3 mm, smoking, paclitaxel stent, heart failure or low ejection fraction, vein graft intervention, age	No sex strata
CHA_2DS_2-VASc (I)[#]	0.6	Female sex, age, heart failure, hypertension, CVA, venous embolism, vascular disease, diabetes	OR female sex 2.53 (95% CI: 1.08-5.92)
ACUITY (B)[#]	0.7	Female sex, age, creatinine, white blood cell count, anaemia, ST-segment elevation	OR female sex 2.32 (95% CI: 1.98-2.72)
HAS-BLED (B)	0.7	Hypertension, abnormal renal and liver function, stroke, prior bleeding, labile INR, alcohol or drug use, predisposition to bleeding (e.g., medication)	No sex strata
PRECISE-DAPT (B)*	0.7	Age, creatinine clearance, haemoglobin levels, white blood cell count, previous spontaneous bleeding	No sex strata

#Taking female sex into account. *Recommended by (ESC) guidelines; C-statistic for risk prediction. ACS: acute coronary syndrome; B: bleeding risk score; BMI: body mass index; CABG: coronary artery bypass grafting; CI: confidence interval; CVA: cerebrovascular accident; ESC: European Society of Cardiology; HR: hazard ratio; I: ischaemic risk score; INR: international normalised ratio; n.a.: not applicable; OR: odds ratio; PCI: percutaneous coronary intervention

Antithrombotic agents in the settings of MINOCA

Myocardial infarction with non-obstructive coronary arteries (MINOCA)[48] is classified into epicardial and microvascular disease. In the absence of critical coronary stenoses, the main pathological findings are plaque rupture or erosion, epicardial or microvascular spasm, thromboembolism, or spontaneous coronary artery dissection (SCAD)[49]. Data are scarce regarding which antithrombotic drug should be used for the treatment of MINOCA, and underlying pathologies should be addressed.

Plaque erosion

In the small EROSION trial (n = 60; < 15% women), patients with ACS and plaque erosion were treated with antithrombotic therapies (aspirin, ticagrelor, UFH) without PCI and had favourable 1-year outcomes[50]. In the EROSION III trial in ST-segment elevation MI patients with early infarct artery patency (n = 226; 20% women), optical coherence tomography [OCT]-based diagnosis and conservative treatment with antithrombotic therapies (aspirin, ticagrelor, UFH) resulted in comparable MACE rates in both the conservative and PCI-treated arms[51].

Spontaneous coronary artery dissection

The majority of SCAD patients are female and undergo conservative management. However, for these patients, there is a lack of consensus regarding the utilisation and duration of either aspirin alone or DAPT. A small study of patients on DAPT who underwent repeat angiography showed dissection healing in nearly all cases of SCAD[52]. Conversely, a small registry of conservatively managed SCAD patients showed that, at 1 year, patients on DAPT had a higher MACE rate than those on single antiplatelet therapy (SAPT)[53].

Vasospasm

Vasomotor dysfunction (both epicardial and microvascular) is more common in women, with vasoreactivity induced by lower doses of acetylcholine compared to men[54]. Data to support the use of aspirin in patients with vasospasm are lacking. High-dose aspirin (>325 mg daily) inhibits prostacyclin production, and can aggravate vasospasm[55]. Low-dose aspirin (<100 mg) can inhibit thromboxane A_2 (TXA_2), which is implicated in spasm, but clinical results are conflicting, with some studies showing that low-dose aspirin was also associated with frequent coronary spasm[56].

Takotsubo syndrome

Takotsubo syndrome (TTS) is more common in women than in men. Despite aspirin use, women with TTS have been shown to have impaired endothelial function with excess TXA_2 formation and enhanced platelet reactivity[57]. In the international Takotsubo registry, aspirin use was not associated with a lower risk of major adverse cardiac or cerebrovascular events at 30 days or 5 years[58]. A subsequent meta-analysis also indicated a higher incidence of cardiovascular events with long-term antiplatelet therapy[59].

Coronary microvascular dysfunction

The hallmark of coronary microvascular dysfunction (CMD) is enhanced coronary vasoconstriction, and it is much more common in women. TXA_2 leads to arterial constriction, platelet aggregation, and vascular injury, while aspirin reduced endothelial platelet adhesion and conferred microvascular protection in mice[60]. Whilst unsupported by evidence, low-dose aspirin could be useful in CMD by reducing platelet-rich microembolism and downstream events, if confirmed in clinical studies.

Consensus statements: antithrombotics in MINOCA PATIENTS

Intravascular imaging is advised to confirm plaque erosion in MINOCA patients who may benefit from a conservative approach consisting of DAPT (potent $P2Y_{12}$ inhibitor and aspirin) for 12 months without undergoing PCI.

In the overall MINOCA population, the choice to treat patients with either DAPT or only aspirin should be based on underlying pathophysiological mechanisms, irrespective of sex.

In patients with conservatively managed SCAD, vasospastic and microvascular angina, or Takotsubo syndrome, the adoption of DAPT is not advisable based on current available data.

Underrepresentation of women in RCTs investigating antithrombotic therapies

Participation-to-prevalence ratio and screening failures in RCTs of chronic and acute coronary syndromes

Despite the call from regulatory bodies for equal representation, women remain underrepresented in clinical trials, especially in CVD studies, with inclusion rates varying greatly based on disease type[61–65] (Table 2). The participation-to-prevalence ratio (PPR; the percentage of women among trial participants/percentage of women among disease population) has been used to establish female representation in clinical trials relative to their prevalence in the diseased population[66]. After accounting for age and sex-specific disease prevalence, a substantial underrepresentation of women (PPR <0.6) was found for trials in the chronic coronary syndrome (CCS) and ACS domains, and the representation of women was particularly low in studies where the average participants' age was between 61 and 65 years[66,67]. Of note, the PPR strictly depends on disease type and epidemiological data quality, with a potential misalignment between clinical trials and population-based data[66]. Another suggested driver for the unbalanced representation of women was the selection of sex-biased inclusion criteria. A recent analysis of clinical trials supporting U.S. Food and Drug Administration (FDA) approval of cardiovascular drugs, focusing on the percentages of screening failure in both sexes, has shown that only one ACS trial reported a higher percentage of screened-out women as compared to men (32% vs 23%, respectively), hence a lower enrolment of women could not be completely ascribed to this phenomenon[66]. Female patients are better represented in the transcatheter treatment of severe aortic stenosis compared to the coronary field, particularly in early landmark trials[5]. Evidence suggests that women may

derive greater benefit from transfemoral aortic valve implantation than from surgical treatment. However, the PPR remains consistently around 0.73[68].

Table 2
Sex-specific analysis of the most relevant RCTs on antiplatelet therapies.

	INFUSE-AMI	PLATO	CHAMPION PHOENIX	TROPICAL-ACS	GLOBAL LEADERS	ISAR-REACT 5	MASTER DAPT
Year of publication	2014	2014	2016	2019	2020	2021	2023
NCT number	NCT00976521	NCT00391872	NCT01156571	NCT01959451	NCT01813435	NCT01944800	NCT03023020
Study design	Multicentre, open-label, controlled, single-blind, randomised 2 × 2 factorial trial	Multicentre, randomised, double-blind trial	Multicentre, randomised, double-blind, double-dummy trial	Multicentre, randomised, parallel-group, open-label, assessor-blinded trial	Multicentre, randomised, open-label trial	Multicentre, randomised, open-label trial	Multicentre, randomised, open-label trial
Population	452 anterior STEMI patients	18,624 ACS patients	11,145 patients undergoing elective or urgent PCI	2,610 ACS patients	15,968 all-comers patients	4,018 ACS patients planned for invasive strategy	4,579 HBR patients randomised at 1 month after PCI to abbreviated or

	INFUSE-AMI	PLATO	CHAMPION PHOENIX	TROPICAL-ACS	GLOBALLEADERS	ISAR-REACT 5	MASTER DAPT
							standard DAPT
Female	26%	28%	28%	21%	23%	24%	30.7%
Antiplatelet therapy	Abciximab vs placeboThrombectomy vs placebo	Loading dose of ticagrelor vs loading dose of clopidogrel within 24 h of the most recent cardiac ischaemic symptoms and before any planned or urgent PCI	Cangrelor (I.V. bolus then infusion) vs clopidogrel before PCI	Guided de-escalation from prasugrel to clopidogrel or standard DAPT therapy	Experimental DAPT(1 month followed by 23 months of ticagrelor monotherapy) vs reference strategy (12 months of DAPT followed by 12 months of aspirin monotherapy)	Loading dose of ticagrelor as soon as possible after randomisation vs prasugrel loading dose once coronary anatomy was known	Abbreviated (immediate DAPT discontinuation, followed by single APT for≥ 6 months) or standard regimen (DAPT for≥ 2 additional months, followed by single APT for 11 months)
Results	Higher rate of MACE in women (30 days)No	Female sex was not an indepen	Cangrelor reduced the	The 1-year incidence of the	Similar risk of the primary	No significant interacti	Abbreviated DAPT was associated

	INFUSE-AMI	PLATO	CHAMPION PHOENIX	TROPICAL-ACS	GLOBAL LEADERS	ISAR-REACT 5	MASTER DAPT
	difference in infarct size (30 days) (p for interaction = 0.71)	dent risk factor for adverse clinical outcomes in moderate-to-high risk ACS patients at 1 year (p for interaction = 0.78)	odds of the primary endpoint by 35% in women and by 14% in men compared with clopidogrel at 48 hours (p for interaction = 0.23)	primary endpoint did not differ in guided de-escalation vs control group patients (p for interaction = 0.60)	endpoint at 2 years (p for interaction = 0.63)Higher risk of BARC 3 or 5 bleeding and haemorrhagic stroke in women at 2 years (p for interaction = 0.09)	on between sex and study drug effect (p for interaction = 0.275)The superior efficacy of prasugrel was more evident in men	with comparable NACE rates in men and women (p for interaction = 0.65)There was evidence of heterogeneity of treatment effect by sex for MACCE, with a trend towards benefit in women (p for interaction = 0.04)

ACS: acute coronary syndrome; APT: antiplatelet therapy; BARC: Bleeding Academic Research Consortium; DAPT: dual antiplatelet therapy; HBR: high bleeding risk; I.V.: intravenous; MACCE: major adverse cardiac and cerebrovascular events; MACE: major adverse cardiovascular events; NACE: net adverse clinical events; PCI: percutaneous coronary intervention; STEMI: ST-segment elevation myocardial infarction

Participation of women in RCTs on antithrombotic therapy and sex reporting

We conducted a systematic review of all RCTs on antithrombotic therapies with the goal of determining temporal trends in female enrolment and patterns of sex reporting. There were 29,398 interventional clinical trials on cardiovascular disease registered in the ClinicalTrials.gov database between 1 January 2001 and 31 December 2021 with reported results. Search strategy criteria and details of the trials are displayed in Supplementary Table 5-Supplementary Table 7. Of those, 1,156 were selected based on the following search criteria: ACS, CCS, PCI, atherosclerosis, antiplatelet, antithrombotic, aspirin, P2Y12 inhibitor, prasugrel, ticagrelor, clopidogrel, and cangrelor. After excluding duplicates, phase I and II RCTs, and those with a sample size <500 patients, there remained 64 studies with a publication year between 2001 and 2021, and these were included in the final analysis (Supplementary Figure 1). The overall female representation was 26.6%, with a decreasing enrolment rate per year of publication over the analysed period (Figure 3). Sex-specific analyses of the primary outcome were reported in 42 clinical trials (65.6%). Importantly, only 8 trials (12.5%) reported sex-specific baseline characteristics. In this analysis, women were significantly older than men (mean ± standard deviation: 68.79 ± 4.32 years vs 63.77 ± 4.84 years; p = 0.03) but had similar body mass index (BMI; 27.15 ± 1.06 kg/m² vs 27.53 ± 0.75 kg/m²; p = 0.49). The prevalence of diabetes mellitus was similar in both sexes (26.78 ± 8.68% in women vs 23.71 ± 6.04% in men; p = 0.49). The proportion of patients with a history of myocardial infarction was slightly lower in women than in men (16.32 ± 8.07% vs 22.35 ± 10.59%; p = 0.22). In line with a previous sex-specific analysis of the most relevant RCTs on antiplatelet therapies, our analysis showed a later onset of clinical manifestations of CCS/ACS in women[69].

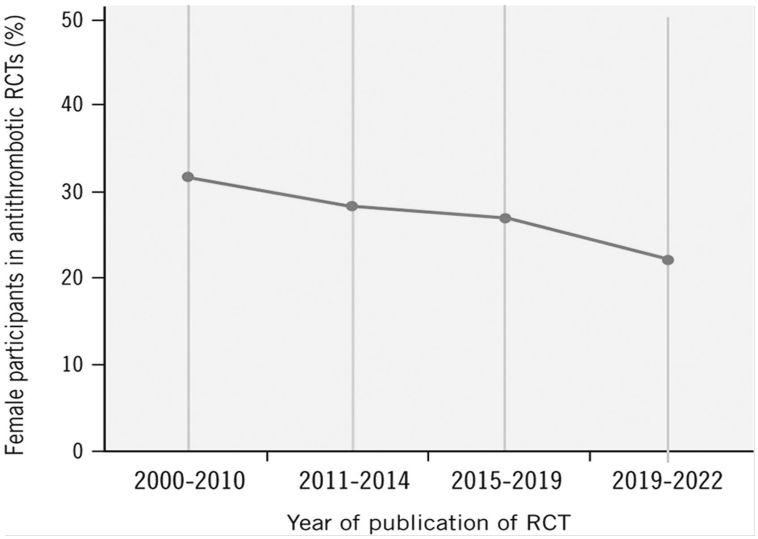


Figure 3 Mean enrolment rate of female participants in antithrombotic trials by year of publication. RCT: randomised controlled trial

Current pitfalls of RCTs

Sample size adjustments and sex-specific subanalysis

The underenrolment of women in cardiovascular (CV) trials has been increasingly recognised, and various strategies to improve female representation have been proposed[30]. To detect meaningful differences in both main treatment effects and interaction effects between women and men, the sample size of such trials would need to increase significantly[70]. This may be challenging because of increased costs and the lack of infrastructure to enrol so many patients within a reasonable timeframe. In addition, limitations arise from the phase before drug testing enters human clinical research, as animal studies have historically relied on male subjects[71]. Important features of a well-designed trial to provide robust sex-specific evidence include randomisation stratified by sex as well as the avoidance of exclusion criteria that (predominantly) affect women. With regard to the latter, pregnant and lactating women are often excluded based on a protection-by-exclusion strategy, even though this strategy deprives pregnant and lactating women of the benefits of contemporary therapies that would potentially improve their outcomes[72]. Moreover, barriers are routinely placed on women of childbearing potential in participating in clinical trials of antithrombotic therapies

owing to concerns about adverse foetal effects of treatment. Nonetheless, anticoagulation poses unique challenges for women of reproductive age, and contraception recommendations in clinical trials may allow equity and access in clinical research[66].

Historical data revealed that three-quarters of clinical cardiovascular trials published in leading general medical and cardiology journals did not report sex-specific analyses[73]. Despite federal legislation, national calls, and several author and reviewer guidelines underlining the importance of such analyses, this practice has not changed over the last decade[74],[75].

The Lancet was the first journal to adopt a policy of encouraging researchers to enrol women and ethnic groups into clinical trials of all phases and to plan analyses of data by sex and race, including the enrolment of women in clinical trials and separate reporting of data by sex[76]. Clinical research studies published in the New England Journal of Medicine must include a table in the supplementary appendix that provides background information on the disease to ensure that study participants properly represent the patients affected by the condition being studied[77].

Drug discontinuation

Among the current pitfalls of RCTs on antithrombotic therapies, study drug discontinuation and study retention among women should be listed. Higher odds of premature study drug discontinuation in women versus men may attenuate the observed treatment effect in intention-to-treat analyses and may blunt a potential safety signal. In 135,879 men and 51,812 women enrolled in 11 phase 3 and 4 trials conducted by the TIMI Study Group, and after adjusting for baseline differences, women had a 22% higher odds of premature drug discontinuation (adj. OR 1.22; 95% CI: 1.16–1.28) and were also more likely to withdraw consent compared with men (adj. OR 1.26; 95% CI: 1.17–1.36). The reason behind a higher drug discontinuation rate in women remains incompletely understood. This phenomenon is not explained by differences in age or comorbidities, appears in both active and placebo arms, and has been related and unrelated to bleeding complications[75],[76]. Withdrawal of consent and loss to follow-up may compound the interpretation of a possible drug's efficacy or safety.

Current barriers to women's enrolment and sex disparities in the research system

From 1993, the FDA started implementing guidelines encouraging women to participate in clinical trials. The action plan encouraged the completeness, quality, and transparency of demographic subgroup data. However, there is currently no FDA legal requirement for clinical trials to be powered to identify effects for subgroups based on sex, age, or other characteristics. Major barriers to the enrolment of women and minorities are related to cultural, social, and economic constraints. Although poorly investigated, factors such as competing priorities, caregiver roles, or transportation barriers may account for poor female enrolment and premature study discontinuation (Central illustration). Inadequate disease education and poor communication with the research team generate and amplify mistrust in the research system. The leaky pipeline of diversity in the leadership of clinical trials translates into the lack of diversity in enrolled populations. Women currently represent only 1 in 10 lead authors of cardiovascular trials published in high-impact journals, with a minority of first and last authors in cardiovascular research publications[78]. Trials led by female investigators enrol a greater proportion of females (7% higher mean in a recent study) and racial minorities, generating better evidence to assess for sex, race, or ethnicity as effect modifiers of intervention[79],[80]. Editorial leadership remains male dominated, and sex bias still affects the peer-reviewing process[81]. Sex disparities in the research system warrant further attention, both to ascertain causes of lower female study enrolment and to target actions that effectively improve female representation in clinical trials contributing to treatment recommendations.

Consensus statement: underrepresentation of women in RCTs

It is advised to publish sex-specific data, such as the participation-to-prevalence ratio, withdrawal of consent, subanalyses including sex-treatment interaction, reporting adverse events and drug discontinuation by sex, and to provide full access to sex-disaggregated data in RCTs.

Sample size adjustments and randomisation stratification by sex may be needed to detect relevant differences in treatment effect between women and men, although it may be difficult for economic and logistical reasons.

All stakeholders from the research system (referring clinicians, investigators and coordinators in research teams, healthcare systems, healthcare administrations, funders, sponsors, professional, and community organisations) should act consistently to ensure the adequate representation of women in RCTs as participants and investigators.

Action should be taken to increase female patient representation in RCTs such as organising educational campaigns, sharing of experiences by enrolled women, providing logistical support where needed, such as rideshare, childcare, or older adult care, limiting the number of onsite visits, making remote monitoring possible, offering flexible onsite study visitation hours, providing free transportation to study visits, proposing at-home follow-up, evaluating the reasons for study drug discontinuation and withdrawal of consent, expanding inclusion criteria, including pregnant and lactating women after satisfying results in pregnant animals, and involving primary care physicians and family members.

Institutions, funding agencies and pharmaceutical companies should commit to advancing sex equality in academia at the level of principal investigators and leadership in RCTs. Such actions should have a measurable impact that is assessed through regular and transparent monitoring along the academic seniority pathway and should be incorporated in the rankings of universities and institutions.

Limitations

While transgender-inclusive trials have increased in the past two decades, most have focused on infectious diseases and mental health[82]. There remains a need for greater inclusion of transgender individuals in trials evaluating drugs and biologics for chronic diseases. Consequently, this consensus statement does not address cardiovascular health or provide recommendations on antithrombotic use in transgender women due to the limited quantity and quality of available data.

Conclusions

Despite significant advances in pharmacological and interventional treatments, CVD remains the leading cause of death among women. Differences between sexes in the risks of bleeding and thrombosis should be taken into consideration when using antithrombotic drugs. Importantly, the enrolment and retention of women in RCTs of antithrombotic therapy remain suboptimal and determine important gaps in evidence of drug safety. Barriers to the equal enrolment of women in CV trials have been attributed to several reasons, including patient characteristics, clinical research strategies, and behavioural, socioeconomic, and cultural factors[83],[84]. Clinical researchers, sponsors, community organisations, and federal agencies must work together to ensure that representative patient populations are enrolled in future studies.

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Supplementary data

Supplementary Appendix 1. Bleeding and ischaemic risk scores.

While many clinicians recognize sex as a variable considered to weight bleeding risk after stent implantation, the actual impact of sex on the independent risk of bleeding is controversial[1].

Various risk scores for estimating bleeding risk are advisable for guidance of antithrombotic treatment post PCI[2]. The controversy surrounding female sex as a dependent vs. independent risk factor for bleeding is also reflected in those scores as female sex accrues the predicted bleeding hazard among most risk scores. In models predicting in-hospital risk of bleeding events, which are more closely related to the impact of invasive procedures and dose-adjusted parenteral antithrombotic agents, female sex was an independent bleeding predictor in the CRUSADE score (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines)[3], the REPLACE score (Randomized Evaluation of PCI Linking Angiomax to Reduced Clinical Events)[4], the ACTION score (Acute Coronary Treatment and Intervention Outcomes Network Registry-Get With the Guidelines)[5], and the ACUITY-HORIZONS-AMI score (Acute Catheterization and Urgent Intervention Triage strategY trial and the Harmonizing Outcomes with RevasculariZatiON and Stents in Acute Myocardial Infarction trial)[6]. All these scores included common variables as female sex, anemia, renal function, and age as predictive factors, in addition to others[7],[8].

In contrast, sex did not appear to be associated with an increased bleeding risk in the out-of-hospital phase. Sex was not an independent predictor of out-of-hospital bleeding events in a large post-PCI population treated with DAPT, and the predictive ability of the score was consistent irrespective of sex at external validation[9]. The ARC-HBR (Academic Research Consortium High Bleeding Risk), proposed as a consensus of experts collecting the most important long-term bleeding risk features, does not include female sex, but age, renal function, and anemia, in addition to other variables[7],[10]. Importantly, the ARC-HBR score was significantly higher among women than men (0.82 vs 0.60), 43% of women and 32% of men were qualified as at HBR (defined by the presence of at least 2 minor or 1 major ARC-HBR criterion), confirming the role of comorbidities for a different long-

term bleeding risk between women and men[11]. In fact, in HBR patients defined according to the ARC-HBR criteria, no interaction for sex and HBR status was observed for the explored ischemic and bleeding endpoints[12]. In contrast, in almost 17,000 PCI-treated patients (26% women), female sex was an independent predictor of access-site bleeding irrespective of ARC-HBR criteria[11]. This finding underlines the need for strategies to reduce femoral access-site bleeding especially among women, irrespective of the bleeding risk status, and that overall, 1-year bleeding risk after PCI should not be assessed based on sex but on the other bleeding predictors.

Ischemic risk scores

Importantly, female sex was not independently associated with MACE in ischemic/thrombotic risk scores such as GRACE (Global Registry of Acute Coronary Events) or PARIS-CTE (the Patterns of Nonadherence to Antiplatelet Regimens in Stented Patients registry, for coronary thrombotic events; Table 1). Recently, a GRACE 3.0 score was proposed, which reduces sex inequalities in risk stratification as it better performs in men and women, as the older GRACE 2.0 score underestimated in-hospital mortality in female patients with NSTE-ACS[13].

Recently, sex differences in outcome of the high-risk patients were found when a combination of the GRACE and CRUSADE scores was used: ACS patients with high-risk for both bleeding and ischemia, especially females, were less likely to receive guideline-recommended therapy and experienced significantly worse outcome[14].

Potency and duration of DAPT in women

The ESC Guidelines for the management of acute coronary syndromes underline the importance of using bleeding scores and recommend the ARC-HBR score in the decision-making process about the potency and duration of DAPT[15],[16]. In line with the current guidelines, a preferential use of potent P2Y12 inhibitors (prasugrel>ticagrelor) for >12 months is advisable in NSTE-ACS patients at low bleeding risk[15],[16]. For patients with high or very high bleeding risk, shorter treatment of DAPT for 1 or 3 months, possibly followed by a P2Y12 inhibitor and the implementation of less potent P2Y12 inhibitor clopidogrel may be appropriate[17],[18].

This strategy is especially relevant for female patients, as more women (43 in 100) than men (32 in 100) fulfill the criteria to shorten the duration and adapt the potency of DAPT according to the ARC-HBR score (1 major point or 2 minor points in the ARC-HBR score)[11]. Accordingly, the benefits of short DAPT were shown for both sexes. Of importance, recent meta-analyses indicate that short DAPT improves the net-benefit and decreases bleeding risk, irrespective of PCI complexity[20],[21].

Supplementary data https://eurointervention.pcronline.com/article/antithrombotic-drugs-for-acute-coronary-syndromes-in-women-sex-adjusted-treatment-and-female-representation-in-randomised-clinical-trials-a-clinical-consensus-statement-of-the-european-association-of-percutaneous-cardiovascular-interventions-eapci-and-the-esc-working-group-on-thrombosis

Part II – Device Innovation, Imaging Guidance, and Strategic Planning in Complex PCI

Chapter 8

Comparison of Supraflex Cruz 60 µm Versus Ultimaster Tansei 80 µm Stent Struts in High Bleeding Risk PCI Patients: Study design and Rational of Compare 60/80 HBR trial

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Abstract

Up to 45% of patients who underwent percutaneous coronary intervention (PCI) may have a high bleeding risk (HBR), depending on the bleeding risk definition[1]. This condition is often associated with an enhanced risk of thrombotic events with a negative impact on short- and long-term outcomes[2–8], making the choice of an appropriate antithrombotic regimen after PCI particularly challenging.

Advances in stent technologies, in which the introduction of newer generations of thinner strut drug-eluting stents (DES), have significantly reduced the rate of thrombotic complications and may justify a shorter dual antiplatelet therapy (DAPT) duration. Both in vitro and in vivo studies have shown that local hemodynamic factors may critically affect the natural history of atherosclerosis. Strut thickness correlates with flow disturbances and endothelial shear stress. Flow separation within struts determines areas of recirculation with low endothelial shear stress, which promotes local concentration of activated platelets[9].

By mitigating inflammation, vessel injury, and neointimal proliferation, thin and streamlined struts have been associated with faster vascular healing and re-endothelization and have resulted in lower rates of thrombotic events after PCI[10,11].

The use of thin strut and ultra-thin strut stents may lead to a favorable trade-off in bleeding and ischemic events in patients with HBR. However, dedicated studies evaluating the performance of thin strut versus ultra-thin strut stents in patients with HBR are lacking.

Background

HBR definition and impact of bleeding events on outcome after PCI

Bleeding complications may occur in up to 10% of patients after PCI[12–14] according to the definition used. A consensus definition of the bleeding risk in patients who underwent PCI has been developed by the Academic Research Consortium for High Bleeding Risk (ARC-HBR) and extensively validated in contemporary PCI patients, solving the ambiguity

about how to effectively identify patients with HBR and the inclusion criteria adopted by randomized controlled trials[1].

Post-PCI bleeding has been correlated with an increased risk of short-term and long-term adverse events such as stent thrombosis[2], recurrent myocardial infarction (MI)[4], stroke[15], and death[2–5]. Possible explanations for this relationship include medical therapy cessation after bleeding, adverse effects of blood transfusions, and greater prevalence of comorbidities in patients suffering from these complications[16]. Observational studies show that the deleterious effect of bleeding is not to be restricted to a limited time interval after the event but persists after the bleeding event resolves, depending on its type and severity. A subanalysis of the TRITON-thrombolysis in MI (TIMI) 38 trial showed that the impact of instrumented or traumatic bleedings on mortality was of short duration (i.e., 1 week), whereas the effect of spontaneous ones tended to be up for 1 month[17].

Multiple studies have investigated the net benefit of dropping aspirin shortly after coronary stent implantation, with the aim of reducing bleeding events in patients with HBR[18–25]. The Management of High Bleeding Risk Patients Post Bioresorbable Polymer-Coated Stent Implantation With an Abbreviated Versus Standard DAPT Regimen (MASTER-DAPT) trial randomized patients with HBR, who had undergone implantation of a biodegradable polymer sirolimus-eluting stent and did not have postprocedural ischemic events, to receive either 1-month or at least 3-month DAPT. The discontinuation of DAPT at a median of 34 days after PCI was noninferior to the continuation of treatment for a median duration of 193 days with regard to the incidence of net adverse clinical events and major adverse cardiac or cerebral events and was associated with a lower incidence of major or clinically relevant nonmajor bleeding[25].

Current evidence suggests that bleeding is not only associated but also a driver for mortality in patients who underwent PCI[26]. For this reason, efforts should be to reduce hemorrhagic complications after PCI, aiming to avoid a concomitant increase in thrombotic events.

DAPT after PCI in patients with HBR-current recommendations

Current European and American guidelines recommend a 1-month to 3-month DAPT period after PCI for stable coronary artery disease in patients with HBR without a concomitant indication to oral anticoagulant (OAC) therapy, whereas at least a 6-month DAPT duration is still recommended for patients with HBR who underwent PCI for acute coronary syndrome (ACS)[27,28]. By contrast, the concomitant indication to OAC therapy, either for preexisting or new-onset conditions requiring anticoagulation, inevitably enhances the risk of hemorrhagic events after PCI[29]. Therefore, current guidelines recommend early cessation of the triple therapy (up to 1 month), followed by dual therapy consisting of OAC with clopidogrel[27,28,30] or aspirin for 6 to 12 months.

Ultrathin strut DES and SupraflexCruz DES

Procedural and clinical outcomes after PCI are influenced by several DES characteristics, including the composition and location of biodegradable or durable polymers, the polymer resorption rate, drug-release kinetics, stent design and strut configuration, stent composition (metal alloy or absorbable polymer), and delivery systems. The progressive reduction of DES strut thickness represents one of the main developments in contemporary stent technology. First-generation DES were made of stainless steel and had thicker struts (>130 μm) to achieve adequate radial strength and radio-opacity. The introduction of second-generation DES, formulated with newer materials such as cobalt–chromium, platinum–chromium, or cobalt–nickel, enabled a reduction in strut thickness (<100 μm), resulting in greater deliverability and faster endothelial coverage without loss of radial force or radio-opacity[10].

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of strut thickness (<100 μm) resulting in greater deliverability and faster endothelial coverage without a concomitant loss in radial force and radio-opacity[10].

Recently, "ultrathin" strut DES have been introduced in clinical practice. These devices are characterized by a further reduction in strut thickness (<70 μm), and their performance have been tested by several studies and by 2 large meta-analyses[10],[31]. In the meta-analysis from Bangalore et al (>11,500 patients), the ultrathin strut DES reduced the risk of TLF by 16% compared with a conventional new-generation DES (relative risk, 0.84; 95% confidence interval [CI], 0.72 to 0.99). These results were consistent in a subsequent larger meta-analysis (20,701 patients) where ultrathin strut DES were associated with a lower risk of TLF and target vessel failure at a mean 2.5 years of follow-up. No significant interaction was found according to the stent type in the ultrathin strut group; however, most of the trials included in both meta-analyses investigated the ultrathin strut Orsiro bioresorbable polymer sirolimus-eluting stent (BP-SES) (Biotronik).

The Supraflex Cruz is an ultrathin BP-SES made of cobalt–chromium, which represents the successor of the Supraflex BP-SES with an improved stent design: 2 long dual-Z connectors from "valley to valley" between the struts and a re-designed proximal shaft to enhance flexibility and pushability. Differently than the Orsiro BP-SES, for which the strut thickness is 60 μm for the 2.25 to 3.0 mm and 80 μm for the 3.5 to 4.0-mm sizes, the Supraflex Cruz strut thickness is 60 μm in all its sizes from 2.0 to 4.5 mm. The Supraflex BP-SES showed noninferiority in 12 months TLF as compared with the Xience degradable-polymer everolimus-eluting stent (DP-EES) in the TALENT (Thin Strut Sirolimus-Eluting Stent in All Comers Population vs Everolimus-Eluting Stent) trial (4.9% versus 5.3% for Supraflex and Xience, respectively; $p < 0.0001$ for noninferiority)[32].

Strut apposition and tissue endothelialization of the Supraflex Cruz BP-SES have been tested by early optimal coherence tomography (OCT) studies. The TAXCO (Comparison of neointimal coverage between ultrathin biodegradable polymer-coated sirolimus-eluting stents and durable polymer-coated everolimus-eluting stents) study investigated the OCT-derived neointimal coverage of the Supraflex Cruz BP-SES, showing that 97.6% of the device struts are endothelialized at 6 months after PCI, which is comparable to the neointimal coverage of the Xience DP-EES. Equally, no significant difference was found with respect to 6 months uncovered and malapposed struts between the 2 devices[33].

Similarly, the SiBi (Healing and early stent coverage after ultrathin strut biodegradable polymer-coated sirolimus-eluting stent implantation) study evaluated the early (4 to 6 weeks) OCT-derived neointimal coverage of the Supraflex Cruz BP-SES, demonstrating an excellent healing profile with a mean of 91.26% strut coverage at 35.3 ± 5 days after the index PCI[34]. Taken together, these results indicate an appropriate balance between neointimal thickness and amount of strut coverage.

Several ongoing studies will provide evidence on the performance of Supraflex Cruz SES in different settings, including high-risk subgroups. The prospective, open-label, multicenter, 2 × 2 factorial, randomized, controlled study Ultra-ThinstrUt Supraflex Cruz versus XiencE in a Diabetic pOpulation with multi-vessel disease-2 (TUXEDO-2 India) will randomize 1,800 patients with diabetes mellitus and multi-vessel disease to either Supraflex Cruz or Xience stents. The study will establish whether biodegradable polymer-coated ultrathin Supraflex Cruz stent is an attractive option for PCI in diabetic patients with multi-vessel disease[35].

Whether the ultrathin Supraflex Cruz BP-SES will be noninferior in terms of net adverse clinical endpoint (NACE) then the Ultimaster Tansei BP-SES in patients with HBR will be investigated in The Comparison of the Supraflex Cruz 60-μm stent strut versus the Ultimaster Tansei 80-μm stent strut in HBR PCI population (COMPARE 60/80 HBR) study. The technical characteristics of the 2 study stents are summarized in Figure 1.

	Supraflex Cruz BP-SES	Ultimaster Tansei BP-SES
		
Manufacturer	Sahajanand Medical Technologies	Terumo
Stent material	Cobalt Chromium L-605	Cobalt Chromium L-605
Strut thickness	60 µm	80 µm
Active drug	Sirolimus	Sirolimus
Active drug dose	1.4 µg/mm^2	3.9 µg/mm of length
Polymer	Blend of biodegradable polymers (Poly-L-lactide; Poly L-lactide-co-caprolactone; Polyvinyl pyrrolidone)	Poly (DL-lactide-co-caprolactone)
Active drug release time	80% within 1 month; 20% within 4 months	3-4 months

Figure1. Comparison of Supraflex and Ultimaster biomechanical characteristics.

Methods

Study design and patient selection

The Comparison of the Supraflex Cruz 60-mm stent strut versus the Ultimaster Tansei 80-mm stent strut in HBR PCI population (COMPARE 60/80 HBR) study is an investigator-initiated, Dutch multicenter, randomized clinical trial evaluating the safety and efficacy of PCI with the Supraflex Cruz BP-SES as compared with the Ultimaster BP-SES, in patients with HBR. The primary hypothesis is that the Supraflex Cruz BP-SES is noninferior to Ultimaster Tansei BP-SES in terms of NACE at 12 months follow-up. In case noninferiority is met, superiority testing will be performed.

Eligible patients are aged 18 or more, with at least one native coronary artery lesion deemed eligible for PCI with DES. No restrictions apply in number of lesions and stents, vessel size, or lesion complexity, apart from stent thrombosis as indication for

revascularization. HBR status is defined according to the ARC-HBR criteria[36]. Staged procedures are allowed but should be planned within 6 weeks after the index PCI and this should be indicated at index PCI. Detailed inclusion and exclusion criteria and ARC-HBR criteria are listed in Table 1, Table 2 whereas a comprehensive flowchart of the study design is reported in Figure 2.

Randomization and treatment protocol

Eligible patients will be randomized to PCI with either Supraflex Cruz BP-SES or Ultimaster BP-SES after successful wiring of the first target lesion during the index procedure. The randomization will be web-based and will be stratified for center, ACS, and diabetes mellitus.

Patients will be treated with the assigned randomized device from the day of randomization till the last planned staged PCI. Patients will be kept blinded for the randomization arm till the end of the study when they will be informed about the results. There are no restrictions on number of target lesions or complexity of the lesions to be treated, including chronic total occlusion, bifurcation, ostial, calcified, thrombotic etc. Any form of lesion preparation is allowed and is left at the discretion of the operator, and the usage of intravascular imaging and physiological assessment. Equally, no restrictions apply on the use of adjunct antithrombotic drugs (like GPIIb/IIIa receptor blockers or cangrelor). In case of unsuccessful delivery or deploymentIn case of unsuccessful delivery or deployment of one of the randomized stents, cross-over to the other DES type is required after optimal attempts to deliver the designated one. In case of unsuccessful delivery or deployment of one of the randomized stents, cross-over to the other DES type is required after optimal attempts to deliver the designated one. In case of unsuccessful delivery or deployment of any study stent, any other new-generation DES can be used.

The DAPT regimen after PCI in this HBR population will be based according to European guidelines[27,30]. Specifically, in patients not on OAC (either vitamin K antagonists or new OAC) up to 3 months DAPT (aspirin + clopidogrel) is recommended for stable coronary artery disease, whereas up to 6 months DAPT (aspirin + ticagrelor or prasugrel) is recommended for ACS. In patients on OAC therapy, early cessation of the triple therapy

(up to 1 month after the index PCI) is recommended, followed by 6 months of dual therapy and then by OAC only thereafter. Compared with the Ultimaster Tansei BP-SES, the Supraflex Cruz BP-SES has a wider range of sizes and lengths. Specifically, the diameter of the Supraflex Cruz BP-SES ranges from 2 to 4.5 mm whereas that of the Ultimaster Tansei BP-SES is from 2.25 to 4 mm. As for length, the Supraflex Cruz BP-SES ranges from 8 to 48 mm whereas the Ultimaster Tansei BP-SES is from 9 to 38 mm. However, the expansion capacity of both the 4.5 mm Supraflex Cruz BP-SES and the 4.0 Ultimaster Tansei BP-SES reaches up to 5.5 mm. In addition, no restrictions apply on the length of the lesions or the number of stents to be used. For these reasons, we do not expect a relevant number of patients crossing over or violating assignment.

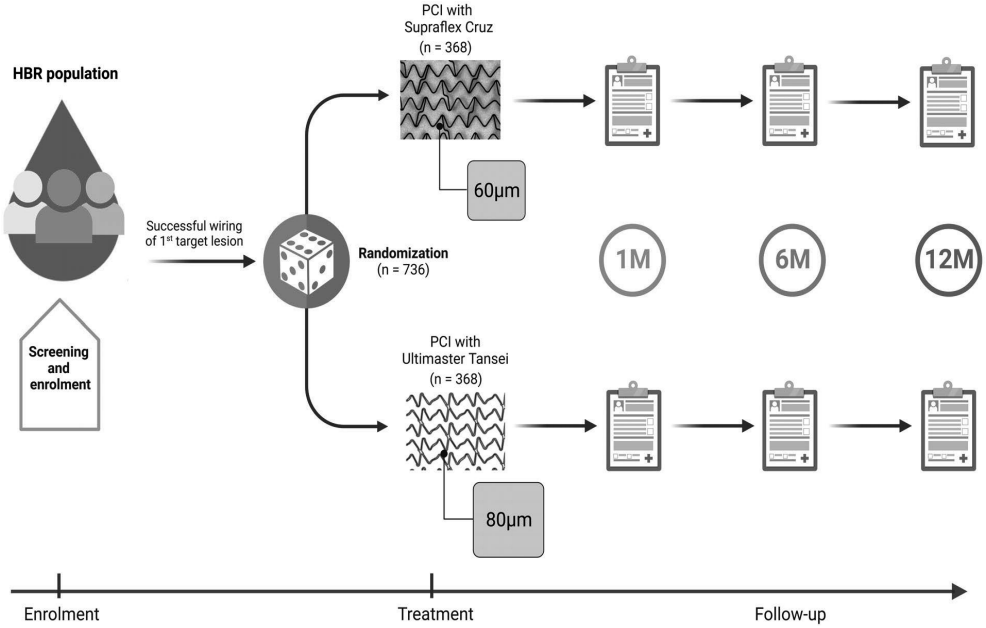
Table 1. Inclusion and exclusion criteria.

Inclusion criteria	**Exclusion criteria**
- Patients of 18 years and above. - Written or witnessed oral consent. - Native coronary artery lesions eligible for PCI with stents with no restrictions in number of lesions and stents, vessel size or lesion complexity, apart from stent thrombosis. - Patients are at high risk for bleeding according to the HBR-ARC criteria* (≥1 major or ≥2 minor).	- Treated with stents other than Supraflex Cruz or Ultimaster within 6 months prior to index PCI. - Stent thrombosis. - Venous or arterial coronary grafts disease. - Treated for stent thrombosis in 12 months prior to index PCI. - Treated with a bioresorbable scaffold 3 years before index PCI. - Cardiogenic shock. - Active confirmed/suspected SARS-CoV-2 infection. - Inability to provide informed consent. - Under judicial protection, tutorship or curatorship. - Unable to understand and follow study-related instructions or to comply with study protocol. - Active BARC≥2 bleeding at index PCI. - Life expectancy less than one year. - Known hypersensitivity or allergy for aspirin, clopidogrel, ticagrelor, prasugrel, cobalt chromium or sirolimus. - Any anticipated PCI after index PCI, unless planned and scheduled at index PCI. - Participation in another stent or drug trial.
Abbreviations: ARC-HBR: Academic Research Consortium for High Bleeding Risk; PCI: percutaneous coronary intervention; BARC: Bleeding Academic Research Consortium. *HBR status is defined if ≥1 major or ≥2 minor criteria are met.	

Table 2. ARC-HBR criteria for defining high bleeding risk

Major criteria*	**Minor criteria***
- Anticipated use of long-term OAC. - Severe or end-stage CKD (eGFR < 30 mL/min) - Hb < 11 g/dL. - Spontaneous bleeding requiring hospitalization or transfusion in the past 6 months, or any time, if recurrent. - Moderate or severe thrombocytopenia (platelet count < $100x10^9$/L). - Chronic bleeding diathesis. - Liver cirrhosis with portal hypertension. - Active malignancy (excluding skin non-melanoma) within past 12 months. - Previous spontaneous intracranial hemorrhage. - Previous traumatic intracranial hemorrhage within the past 12 months. - Brain AVM. - Moderate or severe ischemic stroke (NIHSS score ≥ 5) within the past 6 months.	- Age ≥ 75 years. - Moderate CKD (eGFR 30-59 mL/min). - Hb 11-12.9 g/dL (men) and 11-11.9 g/dL (women). - Spontaneous bleeding requiring hospitalization or transfusion within the past 12 months not meeting the major criterion. - Long term use of oral NSAIDs or steroids. - Any ischemic stroke at any time not meeting the major criterion.
Abbreviations: AVM: arteriovenous malformation; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; Hb: hemoglobin; NIHSS: National Institutes of Health Stroke Scale; NSAIDs: non-steroidal anti-inflammatory drugs; OAC: oral anticoagulation. *HBR status is defined if ≥1 major or ≥2 minor criteria are met.	

Figure 2. Study design with antithrombotic recommendations.



Follow-up

Follow-up visits will be scheduled at 1, 6, and 12 months after the index PCI. All the follow-ups will be preferably scheduled as outpatient clinic visits. If the patient is unable or unwilling to come for a visit, the 1-month and 6-month follow-up can be performed through telephone call, whereas the 12-month follow-up must be performed as an outpatient clinic visit. At each follow-up assessment, the following information will be collected: occurrence of major adverse and cerebrovascular events, stent thrombosis, any clinically overt bleeding event, and any coronary revascularization. In addition, the compliance to the antiplatelet regimen will be assessed.

A subject will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted. Survival status will be collected within legal and ethical boundaries for all the patients included in the study and will be searched in public sources at the end of the follow-up period. If vital status is known at the last study visit, the subject will not be considered lost to follow-up.

Study endpoints

The primary endpoint of the COMPARE60/80HBR study is NACE at 12 months, defined as a composite of cardiovascular death, MI, Target Vessel Revascularization (TVR), stroke, major bleeding (Bleeding Academic Research Consortium [BARC] 3 and 5).[137] The following secondary endpoints will also be assessed: major adverse and cerebrovascular events defined as a composite of cardiac death, MI, TVR and stroke; major or clinically relevant nonmajor bleeding defined as a composite of type 2, 3, and 5 BARC bleeding events; target lesion failure (TLF) defined as the composite of cardiac death, target vessel MI, or clinically indicated target lesion revascularization; target vessel failure defined as the composite of cardiac death, target vessel MI, or clinically indicated TVR; the individual components of the composite primary endpoint; the composite of cardiovascular death, MI and stroke; the composite of cardiovascular death, MI, stroke and major bleed (BARC 3 and 5); stent thrombosis; MI; urgent TVR; non-TVR (urgent and nonurgent); clinically indicated TVR; bleeding events according to the BARC, TIMI and global use of streptokinase and tissue Plasminogen Activator (t-PA) for occluded coronary arteries (GUSTO) classifications; transfusion rates; event rates according to the Predicting Bleeding Complications in Patients Who underwent Stent Implantation and Subsequent DAPT (PRECISE-DAPT) score; device success; procedural success. Device success is defined as deployment of the assigned stent without system failure or device-related complication, with attainment of a <20% final residual stenosis. Procedural success is defined as device success without the occurrence of in-hospital death, MI, or TVR.[38]

Statistical methods and determination of sample size

Main analysis of the primary endpoint is performed on the full analysis population under application of the intention-to-treat principle based on Clinical Event Committee-adjudicated events. Follow-up is censored at the last date of known outcome status or at 1 year, whichever comes first.

Rates of primary endpoints are estimated as the cumulative incidence from the date of randomization to 365 days after the index PCI by the Kaplan–Meier methods. Rate differences are defined as the rate under the Ultimaster Tansei arm minus that under the

Supraflex Cruz arm. Noninferiority in terms of NACE is declared if the 95% CI of the rate difference excludes 4.0%, whereas superiority is declared if the 95% CI of the rate difference excludes 0%, which is equivalent to $p < 0.05$ for the log-rank test. Use of 95% CI is equivalent to noninferiority testing with a one-sided type I error (α) of 0.025.

Considering the shorter DAPT duration in the HBR population, the 12-monthly rates of the primary endpoint NACE are based on conservative assessments of previous trials of patients with HBR who underwent PCI.[18 20 25] Thus, NACE rates are estimated to be 10% for the Ultimaster Tansei BP-SES and 8% for the Supraflex Cruz BP-SES. With an additional 3% attrition rate, a final sample size of 2 × 368 patients (736 in total) is required to reach a >80% power to establish the noninferiority in NACE with a noninferiority margin of 4.0%.

Secondary endpoints will be analyzed as appropriate (according to the distribution of each outcome), comparing the difference between the Ultimaster Tansei and the Supraflex Cruz groups at the specified follow-up visits. In all analyses of the secondary endpoints, statistical uncertainties are expressed in 95% two-sided confidence intervals. A p value of <0.05 will indicate statistical significance. For the secondary endpoint analysis, the study does not have significant statistical power to demonstrate noninferiority or superiority, so the results will be considered hypothesis-generating. Statistical calculations will be based on all available data. No missing value imputations will be performed.

Prespecified subgroup analysis

The following prespecified subgroup analyses will be performed: PCI for ACS, PRECISE-DAPT score tertiles, gender, creatinine clearance ≥ or <60 ml/min, age ≥ or <75 years, diabetic status, single versus multivessel PCI, bifurcation treatment, PCI of a large vessel (≥3.5-mm diameter), PCI of a small vessel (≤2.75-mm diameter).[234]

Study organization, timelines, and conclusions

The COMPARE60/80HBR study is an investigator-initiated trial, sponsored by the Research Maatschap Cardiologen Rotterdam Zuid (Maasstad Hospital, Rotterdam, The

Netherlands), which received an unrestricted research grant from Sahajanand Medical Technologies, Surat, India.[1]

The operational committee is responsible for daily management of study execution at operational level under supervision of the Steering Committee. The Steering Committee is comprised of the coordinating principal investigator and local lead investigators. The Data Monitoring Committee is an independent, multidisciplinary board composed of qualified members who are not directly involved in the conduct of the trial and is responsible for ensuring the safety of the patients included in the trial. All the investigator-reported potential endpoint events are adjudicated by the Clinical Event Committee, comprised of qualified physicians who are not investigators in the trial and are blinded for the treatment arms.[1]

The Maasstad Cardiovascular Research department will be responsible for monitoring all the sites, except for the Maasstad Hospital site. For the Maasstad Hospital site, monitoring will be done by Medwave Clinical Research (Rotterdam, The Netherlands).[1]

The first study patient was enrolled on September 14, 2020, and enrollment was completed on August 1, 2022. Final results are projected to be presented by Q4 2023.[1]

Publication policy and data availability

Data or study-related material will not be released without the express permission of the Steering Committee. The authors of the primary manuscript include the Steering Committee members and investigators according to the number of patients and quality of data. The publication and/or presentation of results from a single trial site are not allowed until publication and/or presentation of the multi-center results.[1]

To promote scientific collaboration and facilitate reproducibility, anonymized data of the patients will be made available to other researchers upon a reasonable request.[1]

Subject to compliance with data use agreements and approval from the Steering Committee, thereby fostering transparency while upholding patient confidentiality and privacy.[1]

Declaration of Competing Interest

The authors have no competing interest to declare.

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Chapter 9

Comparison of Ultrathin- Versus Thin-Strut Stents in Patients With High Bleeding Risk PCI: Results From the COMPARE 60/80 HBR Trial: An Open-Label, Randomized, Controlled Trial.

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Abstract

BACKGROUND: No randomized data exist on ultrathin-strut stents in patients at high bleeding risk (HBR) undergoing an abbreviated dual antiplatelet therapy after coronary stenting. The aim of this study was to compare the safety and effectiveness of the ultrathin-strut biodegradable-polymer sirolimus-eluting Supraflex Cruz stent with the thin-strut biodegradable-polymer sirolimus-eluting Ultimaster Tansei stent in patients at HBR with abbreviated dual antiplatelet therapy after stenting.

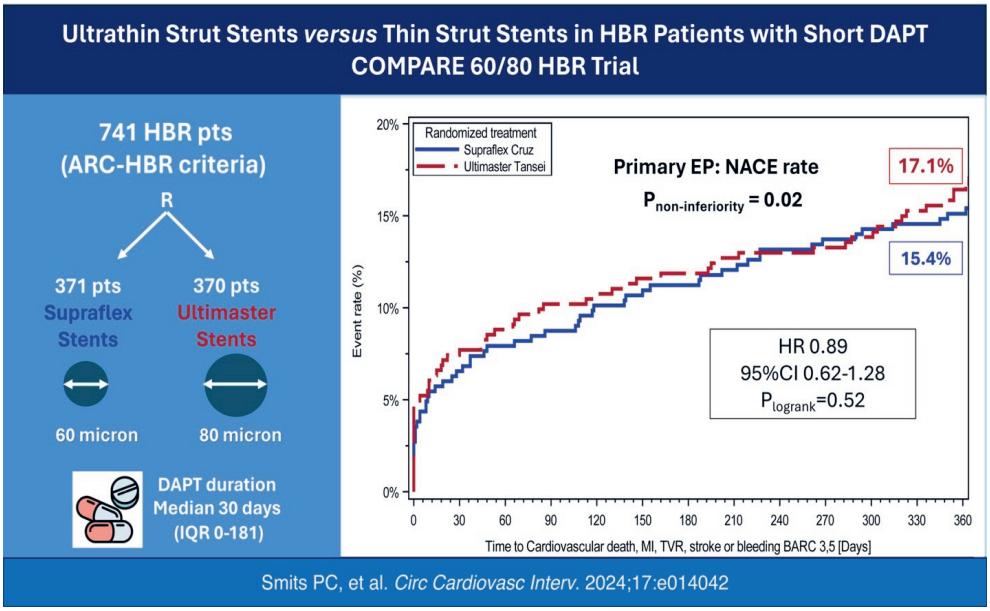
METHODS: In the investigator-initiated, randomized, open-label COMPARE 60/80 HBR trial (Comparison of the Supraflex Cruz 60 Micron Stent Strut Versus the Ultimaster Tansei 80 Micron Stent Strut in HBR Percutaneous Coronary Intervention Population), 741 patients at HBR according to the Academic Research Consortium HBR criteria were randomized to receive either the ultrathin-strut biodegradable-polymer sirolimus-eluting Supraflex Cruz stent or thin-strut biodegradable-polymer sirolimus-eluting Ultimaster Tansei stent. Dual antiplatelet therapy was recommended according to the applicable guidelines and trial data for patients at HBR. The primary outcome was net adverse clinical events, the composite of cardiovascular death, myocardial infarction, target vessel revascularization, stroke, and major bleeding, and was powered for noninferiority with an absolute margin of 4.0% at 1-sided 2.5% alpha.

RESULTS: Between September 2020 and August 2022, 371 patients were randomized to the ultrathin-strut biodegradable-polymer sirolimus-eluting Supraflex Cruz stent and 370 patients to the thin-strut biodegradable-polymer sirolimus-eluting Ultimaster Tansei stent at 11 sites in the Netherlands. At 1 year, the primary outcome was observed in 56 (15.4%) patients in the ultrathin-strut biodegradable-polymer sirolimus-eluting Supraflex Cruz stent group and 61 (17.1%) in the thin-strut biodegradable-polymer sirolimus-eluting Ultimaster Tansei stent group (risk difference, −1.65%; upper boundary of the 1-sided 95% CI, 3.74; P=0.02 for noninferiority at a 0.025 significance level and P=0.55 for 2-sided superiority at a 0.05 significance level).

CONCLUSIONS: Among patients at HBR with abbreviated dual antiplatelet therapy post-stenting, the use of an ultrathin-strut biodegradable-polymer sirolimus-eluting Supraflex Cruz stent was noninferior compared with the use of a thin-strut biodegradable-polymer sirolimus-eluting Ultimaster Tansei stent.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT04500912.

Graphical abstract



WHAT IS KNOWN

• Abbreviated dual antiplatelet therapy after coronary stenting with thin-strut biodegradable-polymer or durable-polymer sirolimus-eluting stents is safe regarding ischemic events and reduces the risk of bleeding events in patients at high bleeding risk (HBR).

• Unknown is whether ultrathin-strut drug-eluting stents have similar or additional benefits compared with thin-strut drug-eluting stents in patients with HBR receiving abbreviated dual antiplatelet therapy.

WHAT THE STUDY ADDS

• In the COMPARE 60/80 HBR (Comparison of the Supraflex Cruz 60 Micron Stent Strut Versus the Ultimaster Tansei 80 Micron Stent Strut in HBR Percutaneous Coronary Intervention Population) trial, the first prospective trial enrolling patients with HBR according to the Academic Research Consortium HBR criteria and receiving abbreviated dual antiplatelet therapy after coronary stent implantation, the ultrathin-strut

biodegradable-polymer sirolimus-eluting Supraflex Cruz stent had a similar safety and efficacy profile compared with the thin-strut biodegradable-polymer sirolimus-eluting Ultimaster Tansei stent.

INTRODUCTION

Ultrathin-strut stents have shown in vivo to be less thrombogenic compared with thicker-strut stents due to lower endothelial shear stress and flow disturbances, which limit platelet activation[1,2]. This is reflected in clinical trials and meta-analyses showing lower target lesion failure rates with ultrathin-strut stents compared with thin-strut stents[3–5]. No data exist on ultrathin-strut stents in patients with high bleeding risk (HBR) during and after percutaneous coronary intervention (PCI), in whom short dual antiplatelet therapy (DAPT) regimens are prescribed. Because of the shorter DAPT regimens, we hypothesized that the benefit of ultrathin-strut stents might be enhanced in this specific subset of patients. Therefore, we designed and conducted the randomized COMPARE 60/80 HBR trial (Comparison of the Supraflex Cruz 60-Micron Stent Strut Versus the Ultimaster Tansei 80-Micron Stent Strut in HBR PCI Population), in which an ultrathin-strut stent is compared with the thin-strut Ultimaster stent. The Ultimaster stent was selected as the comparator due to its use in the pivotal MASTER-DAPT trial (Management of High Bleeding Risk Patients Post Bioresorbable Polymer Coated Stent Implantation With an Abbreviated Versus Standard DAPT Regimen), which demonstrated safety and efficacy of abbreviated DAPT in a large HBR post-PCI population[6].

METHODS

The data, analytic methods, and study materials will not be made available to other researchers for the purposes of reproducing the results or replicating the procedure.

Study Design

The COMPARE 60/80 HBR trial (https://www.clinicaltrials.gov; NCT04500912) is an investigator-initiated, randomized, open-label, noninferiority trial with sequential superiority testing in largely unselected patients at HBR who same biodegradable-polymer sirolimus-eluting Supraflex Cruz (Sahajanand Medical Technologies Ltd, Surat, India) stent or a thin-strut (80 μm) biodegradable-polymer sirolimus-eluting Ultimaster

(Terumo Corporation, Tokyo, Japan) stent. A detailed description of the study design is described elsewhere.^7 In summary, the trial was performed at 11 sites in the Netherlands. The study protocol was approved in each center. All patients gave written informed consent. An independent data safety monitoring board regularly reviewed the conduct of the trial and the safety of the patients. Trial organization and participating sites are mentioned in the Supplemental Material.

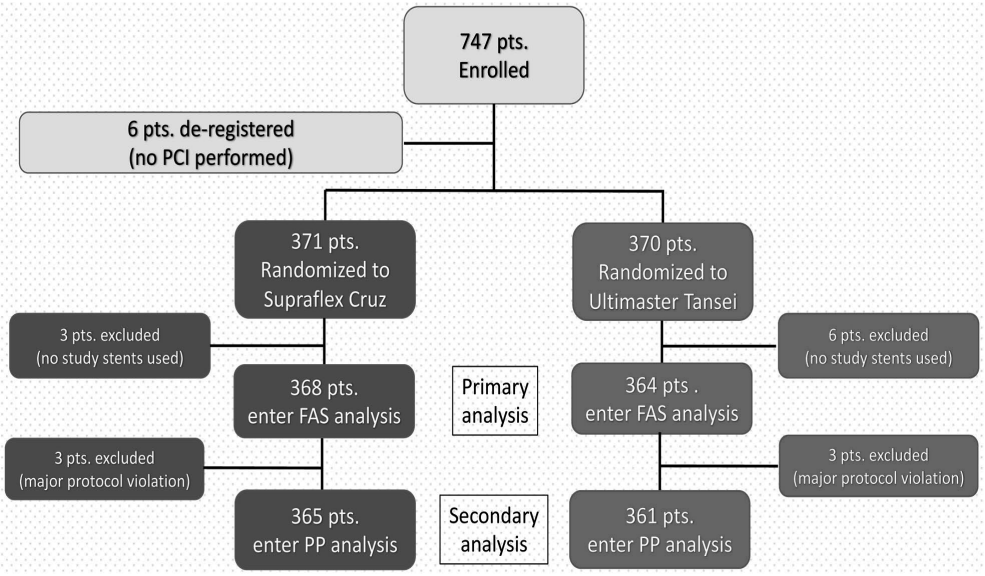


Figure 1. Patient flow. FAS indicates full analysis set; PCI, percutaneous coronary intervention; and PP, per protocol.

Patients

Patients at high risk for bleeding according to the Academic Research Consortium on HBR (ARC-HBR) criteria,^8 who underwent PCI of native coronary artery lesions, irrespective of clinical presentation (chronic coronary or acute coronary syndrome) at index procedure and with no restrictions in number of lesions, stents, vessel size, or lesion complexity, were eligible if at least 1 major or 2 minor ARC-HBR criteria were present. Exclusion criteria were minimal, with the most important ones being implantation of the thin-strut biodegradable-polymer sirolimus-eluting Ultimaster

Tansei or ultrathin-strut biodegradable-polymer sirolimus-eluting Supraflex Cruz stent within the previous 6 months, or bioresorbable scaffold implantation within 3 years before the index procedure, or treatment because of a stent thrombosis or treatment of a venous or arterial graft stenosis, or presentation with cardiogenic shock. Detailed inclusion and exclusion criteria are provided in the Supplemental Material.

Table 1. Baseline Patient Characteristics

Characteristics	Supraflex Cruz (N=368)	Ultimaster Tansei (N=364)
Age, y	74.8 (8.1)	75.4 (7.5)
Male sex	265 (72.0%)	272 (74.7%)
White	361 (98.1%)	353/363 (97.3%)
Non-White	7 (1.9%)	10/363 (2.7%)
Family history of coronary artery disease	141/363 (38.8%)	140/363 (38.6%)
Arterial hypertension	265 (72.0%)	270 (74.2%)
Uncontrolled hypertension	18 (4.9%)	11 (3.0%)
Diabetes	110 (29.9%)	104 (28.6%)
Insulin-dependent	31 (8.4%)	33 (9.1%)
Non–insulin-dependent	79 (21.5%)	71 (19.5%)
Hyperlipidemia	214 (58.2%)	226/362 (62.4%)
Smoking (current + former)	206 (56.0%)	225/361 (62.3%)
Current	178 (48.4%)	182/361 (50.4%)
Former	28 (7.6%)	43/361 (11.9%)
LVEF, %	48.5 (12.4; n=209)	48.7 (11.7; n=202)
Hyperdynamic (>70%)	4/313 (1.3%)	1/310 (0.3%)
Normal (50–70%)	192/313 (61.3%)	195/310 (62.9%)
Mild dysfunction (40–49%)	53/313 (16.9%)	56/310 (18.1%)
Moderate dysfunction (30–39%)	44/313 (14.1%)	38/310 (12.3%)
Severe dysfunction (<30%)	20/313 (6.4%)	20/310 (6.5%)
Medical history		
Peripheral vascular disease	57 (15.5%)	66 (18.1%)
Heart failure	67 (18.2%)	76 (20.9%)
Prior myocardial infarction	99 (26.9%)	102 (28.0%)
Prior PCI	124 (33.7%)	119 (32.7%)
Prior CABG	34 (9.2%)	40 (11.0%)
Prior valve intervention	17 (4.6%)	12 (3.3%)
Prior cerebrovascular event	76 (20.7%)	73 (20.1%)
Stroke	41 (11.4%)	44 (12.1%)
TIA	41 (11.4%)	34 (9.3%)
Prior bleeding	21 (5.7%)	17 (4.7%)
Chronic pulmonary disease	37 (10.1%)	63 (17.3%)
Chronic kidney disease*	83 (22.6%)	93 (25.6%)
Atrial fibrillation	193/366 (52.7%)	199 (54.7%)
History of cancer	100 (27.2%)	71 (19.5%)
Active cancer	18 (4.9%)	11 (3.0%)
Hematologic/coagulation disorder	15 (4.1%)	7 (1.9%)
Chronic steroids or NSAIDs	19 (5.2%)	31 (8.5%)
Need for OAC/NOAC	240 (65.2%)	230 (63.2%)
PRECISE-DAPT score		

≤28	185/336 (55.1%)	185/334 (55.4%)
>28	151/336 (44.9%)	149/334 (44.6%)
ARC-HBR		
≥1 major criterion	285 (77.5%)	267/362 (73.8%)
≥2 minor criteria	184 (50.0%)	211 (58.0%)
ARC-HBR score	1.7 (0.7)	1.6 (0.6)
Clinical presentation		
Non-ACS	261 (70.9%)	250 (68.7%)
Stable angina	235 (63.9%)	219 (60.2%)
Silent ischemia	26 (7.1%)	31 (8.5%)
Acute coronary syndrome	107 (29.1%)	114 (31.3%)
NSTEMI	74 (20.1%)	84 (23.1%)
STEMI	8 (2.2%)	4 (1.1%)
Unstable angina	25 (6.8%)	26 (7.1%)
Single-vessel disease	260 (70.7%)	266 (73.1%)
Multivessel disease	108 (29.3%)	98 (26.9%)
Chronic heart failure	12 (3.3%)	17 (4.7%)
Cardiac arrest	1 (0.3%)	2 (0.6%)
Heart rate, beats/min	72.0 (15.9)	73 (16.0)
Systolic blood pressure, mm Hg	142.3 (24.5)	144.9 (24.1)

Data are mean (SD), n (%), or n/n (%) in the case of missing data. ARC-HBR indicates Academic Research Consortium on High Bleeding Risk; LVEF, left ventricular ejection fraction; NOAC, nonvitamin K antagonist oral anticoagulation; NSAID, nonsteroidal anti-inflammatory drug; NSTEMI, non–ST-segment–elevation myocardial infarction; OAC, vitamin K antagonist oral anticoagulation medication; PRECISE-DAPT, Predicting Bleeding Complications in Patients Undergoing Stent Implantation and Subsequent Dual Anti-Platelet Therapy; and STEMI, STsegment–elevation myocardial infarction.

*Defined as kidney damage (pathological abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies) or estimated glomerular filtration rate <60 mL/min per 1.73 m² for ≥3 mo.

†PRECISE-DAPT, predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy.

‡ARC-HBR, academic research consortium for high bleeding risk. ARC-HBR score (major criterion, 1; minor criterion, 0.5).

Table 2. Procedural Characteristics

Characteristic	Supraflex Cruz (N=368)	Ultimaster Tansei (N=364)
Radial artery access site	305/367 (83.1%)	309 (84.9%)
IVUS pre- or post-procedure	8/367 (2.2%)	11 (3.0%)
OCT pre- or post-procedure	3/367 (0.8%)	4 (1.1%)
No. of staged PCI procedures - 0	358 (97.3%)	351 (96.4%)
No. of staged PCI procedures - 1	10 (2.7%)	10 (2.8%)
No. of staged PCI procedures - 2	0 (0.0%)	3 (0.8%)
No. of lesions treated	499	497
No. of lesions per patient	1.4 (0.6)	1.4 (0.6)
1 lesion	253/367 (68.9%)	262 (72.0%)
2 lesions	96/367 (26.2%)	74 (20.3%)
≥3 lesions	18/367 (4.9%)	28 (7.7%)
Predilatation per lesion	401 (80.4%)	416 (83.7%)
No. of stents used	665	677
No. of stents per patient	1.8 (1.0)	1.9 (1.2)
Stent length used, mm	22.8 (9.6)	22.9 (9.0)
Stent diameter used, mm; median (Q1; Q3)	3.0 (2.8; 3.5)	3.0 (2.5; 3.5)

Maximum deployment pressure, Atm	14.7 (3.1; n=664)	14.7 (3.1; n=674)
Postdilatation per lesion	279 (55.9%)	270 (54.3%)
Overlapping stents per lesion	132/496 (26.6%)	134/493 (27.2%)
TIMI flow 3 post-procedure	494 (99.0%)	495 (99.8%)
Total amount of contrast, mL	140.3 (64.4)	145.1 (70.4)

Data are mean (SD), n (%), or n/n (%) in the case of missing data. IVUS indicates intravascular ultrasound; OCT, optical coherence tomography; PCI, percutaneous coronary intervention; and TIMI, Thrombolysis in Myocardial Infarction.

Randomization, Masking, and Procedures

After successful passage of the guidewire through the first target lesion, patients were centrally randomized (1:1 ratio) to an open-label thin-strut biodegradable-polymer sirolimus-eluting Ultimaster Tansei or ultrathin-strut biodegradable-polymer sirolimus-eluting Supraflex Cruz stent. Randomization was concealed using a web-based system; randomization sequences were computer-generated, blocked, with randomly selected block sizes of 2, 4, or 6, and were stratified by site, the presence of acute coronary syndrome, or the presence of diabetes at index procedure. Staged PCI procedures were allowed but had to be planned within 6 weeks after the index PCI, and this had to be indicated at index PCI. Patients were treated according to the randomized regimen from the day of randomization until the last planned staged PCI procedure. Patients were kept blinded to the randomization arm until the end of the study. There were no restrictions on the number or complexity of target lesions to be treated, including chronic total occlusions, bifurcations, ostial, calcified, or thrombotic lesions. Any lesion pretreatment procedure was allowed, such as balloon dilatation, rotational atherectomy, thrombosuction, or lithotripsy (shockwave). Decisions regarding the pretreatment strategy, the use of optical coherence tomography, intravascular ultrasound, intravascular physiology guidance (fractional flow reserve, instantaneous wave-free ratio, or resting full-cycle ratio), and adjunct antithrombotic drugs (such as glycoprotein IIb/IIIa receptor blockers or cangrelor) were left to the operator's discretion. In case of unsuccessful delivery or deployment of one of the randomized stents, crossover to the opposite stent type was required after vigorous attempts to deliver the assigned device. the designated stent type as per randomization. In the case of unsuccessful delivery or deployment of any study stent, any other new-generation drug-eluting stent type could be used according to the discretion of the operator. DAPT treatment (combination and

duration) was initially according to the 2018 Guidelines of the European Society of Cardiology for Myocardial Revascularization.^9 For patients not on vitamin K antagonist oral anticoagulant (OAC)/nonvitamin K antagonist oral anticoagulant (NOAC), 3-month DAPT (aspirin+clopidogrel) and 6-month DAPT (aspirin+ticagrelor or prasugrel) were initially recommended for chronic coronary syndromes and acute coronary syndromes, respectively. For patients on OAC/NOAC, initially, 1-month triple therapy (aspirin+OAC/NOAC+clopidogrel) followed by 11 months dual therapy (OAC/NOAC+clopidogrel) was recommended However, after publication of the 2020 European Guidelines on Non–ST-Segment–Elevation Myocardial Infarction^10 and publication of the MASTER-DAPT trial,^6 the DAPT treatment recommendation in this study was modified. For patients on OAC/NOAC, it changed to 1-week triple therapy, followed by at least 5 months of dual therapy. For patients not on OAC/ NOAC,1- to 3-month DAPT was recommended, irrespective of clinical presentation. Follow-up visits were done at 1, 6, and 12 months postindex PCI procedures with a window of 14 days. Two independent clinical research organizations (Maasstad Cardiovascular Research Department, Rotterdam, the Netherlands; Medwave Clinical Research, Rotterdam, the Netherlands) performed on-site and remote monitoring visits, verified the source documents, and collected source material for event adjudication. All events were adjudicated by an independent adjudication committee (Center of European Cardiovascular Research, Massy, France) that was unaware of the treatment allocations. An independent quantitative coronary angiography core laboratory (Center of European Cardiovascular Research) analyzed the preprocedure and postprocedure angiograms of the first 200 consecutive randomized patients. All data were stored in a central database (Maasstad Cardiovascular Research Department, Maasstad Hospital, Rotterdam, the Netherlands).

Outcomes

The primary end point was a net adverse clinical event (NACE) at 12-month follow-up, defined as a composite of cardiovascular death, myocardial infarction, target vessel revascularization, stroke, and major bleeding according to Bleeding Academic Research Consortium (BARC) 3 or 5 bleeding events.[8] The major secondary outcomes were target

lesion revascularization; major adverse cardiac and cerebral event, defined as the composite of cardiovascular death, myocardial infarction, and stroke; and major and clinically relevant nonmajor bleeding according to the BARC classifications: BARC 2, 3, or 5 bleeding events. All outcomes were prespecified[7] and summarized in the Supplemental Material. All analyses evaluated the occurrence of the adjudicated outcomes between randomization and 365 days.

Statistical Analysis

The trial was designed to test whether the population randomized to the ultrathin-strut biodegradable-polymer sirolimus-eluting Supraflex Cruz stent would be noninferior in comparison to the population randomized toward the thin-strut Ultimaster Tansei stent regarding NACE, as determined by the difference in the cumulative incidence at 365 days (Supraflex Cruz group minus Ultimaster Tansei group). The upper limit of the 2-sided 95% CI for the difference in the cumulative incidence had to exclude 4.0% for NACE. In case noninferiority was met, superiority testing was performed. These hypotheses were hierarchically tested, with the preservation of alpha (a 1-sided alpha of 0.025 corresponding to a 2-sided alpha of 0.05). We calculated that the enrollment of 714 patients would provide the trial with >80% power to show noninferiority using a noninferiority margin of 4% regarding NACE under an assumed cumulative incidence of 10.0% for the Ultimaster Tansei group and 8.0% for the Supraflex Cruz group. The final sample size was increased to 736 patients to account for an anticipated 3.0% loss of patients because of nonadherence to the use of study stents (in case no study stent left the tip of the guiding catheter) to the loss to follow-up or withdrawal of consent. Baseline and procedural characteristics are reported by the treatment group as means (±SD), medians, and interquartile ranges or numbers and percentages, as appropriate. The primary analysis of NACE on the full analysis set was performed according to the intention-to-treat principle. The full analysis set includes all randomized patients in which a study stent passed the guiding catheter. A secondary analysis of NACE on the per-protocol population was performed, which excluded patients who did not meet the selection criteria or did not receive one of the randomized stents for the treated lesions. The time to the primary end point was evaluated using the Kaplan-Meier curves and the

log-rank test. Risk differences were calculated for cumulative events up to 12 months. In addition, Cox proportional hazards models were fitted, and hazard ratios with their corresponding 95% CIs were calculated. Furthermore, the analysis was stratified by acute coronary syndrome and diabetes. For the secondary end points, we also considered the competing risk due to death. Therefore, we evaluated cumulative incidence functions and compared them using the Gray test. We also fitted Fine and Gray models and reported the subdistribution hazard ratios along with their 95% CIs. Subgroup analyses of the primary end point for the acute coronary syndrome, PRECISE-DAPT score (Predicting Bleeding Complications in Patients Undergoing Stent Implantation and Subsequent Dual Anti-Platelet Therapy), gender, creatinine clearance, age, diabetes, multivessel treatment, small vessel treatment, large vessel treatment, and bifurcation treatment were performed. In addition, PRECISE-DAPT score subgroup analyses were also performed for the end point target lesion failure, major or clinically relevant nonmajor bleeding, and major adverse cardiac and cerebral events. P values for testing homogeneity of the hazard ratio in subgroups of patients were derived in Cox proportional hazards models using a likelihood ratio test. The 95% CIs and P values were not adjusted for multiplicity and should not be used to infer definitive treatment effects. Device success was compared between treatment groups by means of a logistic generalized estimating equations model using an exchangeable working correlation matrix. The odds ratio with a 95% CI was calculated. All analyses are performed with SAS software, version 9.4.

Role of the Funding Source

The study was sponsored by Research Maatschap Cardiologen Rotterdam Zuid (Maasstad Hospital) and received grant support from Sahajanand Medical Technologies. The sponsor and funder had no role in the study design, data collection, data monitoring, analysis, interpretation, or writing of the report.

RESULTS

From September 14, 2020, to August 1, 2022, 747 patients were enrolled, and 741 patients were randomized. Eventually, 732 patients entered the full analysis set analysis (368 patients in the Supraflex Cruz arm and 364 in the Ultimaster Tansei arm) as 9 patients

were excluded because, in those cases, no study stent had passed the guiding catheter tip. See Figure 1 for the patient and analysis flow chart. Baseline and procedural characteristics are described in Tables 1 and 2 and Table S1. All characteristics were well balanced between both arms. The overall mean±SD age was 75.1±7.8 years with an average ARC-HBR score of 1.6. On average, 29.2% of patients received treatment for diabetes. The indication for coronary stenting was chronic coronary syndrome for 69.8% of patients, and the need for prolonged oral anticoagulation was present in 64.2% of the patients. In the Supraflex Cruz arm, patients were discharged with DAPT, dual therapy, and triple therapy in 35.3%, 35.0%, and 29.5%, respectively. In the Ultimaster Tansei arm, this was 36.6%, 35.2%, and 27.4%, respectively. The median (interquartile range) DAPT duration was 30 (0–181) days, in the Supraflex Cruz arm 29 (0–179) days, and in the Ultimaster Tansei arm 30 (0–183) days. More detailed information on the antiplatelet and antithrombotic medication is shown in Figure 2 and Table S2. At 12-month follow-up, in the Supraflex Cruz arm, 56 NACE events occurred with a cumulative event rate of 15.4% versus 61 NACE events (17.1%) in the Ultimaster Tansei arm (hazard ratio, 0.89 [95% CI, 0.62–1.28]; P=0.52). With the risk difference of 1.65% (95% CI, −∞ to −3.74), the primary analysis of noninferiority for NACE was significantly met (P=0.02). The secondary superiority analysis for NACE was not met (P=0.55). The primary and secondary end points at 12-month follow-up are shown in Table 3. No end points were significantly different between both arms. Time-to-event curves of the primary end point NACE and its individual components and stent thrombosis are shown in Figures 3 and 4. The time-to-event curve for target lesion failure and the Forrest plot of the subgroup analysis are shown in Figures S1 and S2. The results of this trial were consistent with the per-protocol analysis showing noninferiority and similar outcomes to the primary analysis. Detailed information is depicted in Table S3.

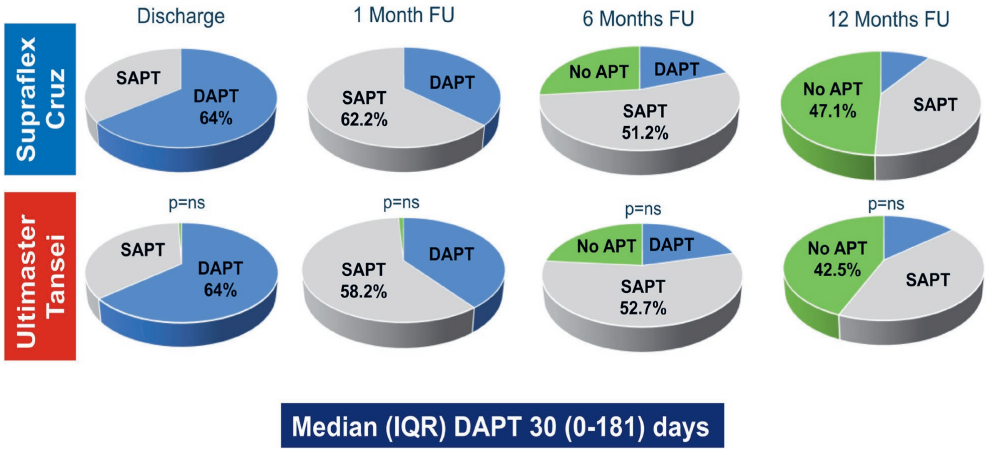


Figure 2. Antiplatelet usage at discharge and 1-, 6-, and 12-month follow-up (FU). Median (interquartile range [IQR]) dual antiplatelet therapy (DAPT) duration (days) was equal in both study arms. APT indicates antiplatelet therapy; and SAPT, single antiplatelet therapy.

Table 3. Clinical Outcomes at 12 Months Post-Randomization (Full Analysis Set and Intention-to-Treat Analysis)

Event	Supraflex Cruz arm (N=368)	Ultimaster Tansei arm (N=364)	HR (95% CI)	Risk difference	Log-rank P value
NACE	56 (15.4%)	61 (17.1%)	0.89 (0.62 to 1.28)	−1.65 (−∞ to −3.74)	0.52
Cardiovascular death	14 (3.8%)	14 (3.8%)	0.99 (0.47 to 2.08)		0.98
Myocardial infarction	24 (6.6%)	32 (8.8%)	0.69 (0.41 to 1.17)		0.17
Periprocedural myocardial infarction	12 (3.3%)	14 (3.8%)	0.85 (0.40 to 1.82)		0.67
Target vessel revascularization	11 (3.0%)	20 (5.6%)	0.54 (0.26 to 1.13)		0.10
Clinically indicated	11 (3.0%)	19 (5.3%)	0.57 (0.27 to 1.20)		0.13
Stroke	10 (2.8%)	4 (1.1%)	2.49 (0.78 to 7.94)		0.11
Bleeding BARC 3 or 5	18 (4.9%)	18 (5.0%)	1.00 (0.53 to 1.88)		0.99
MACCE	46 (12.9%)	49 (13.9%)	0.89 (0.59 to 1.32)		0.55
Cardiovascular death, myocardial infarction, stroke, and major	52 (14.3%)	53 (14.7%)	0.95 (0.65 to 1.38)		0.78

bleeding BARC 3 or 5					
Cardiovascular death, myocardial infarction, and stroke	42 (11.6%)	41 (11.4%)	0.95 (0.62 to 1.46)		0.83
Target vessel failure	32 (8.8%)	40 (11.1%)	0.77 (0.49 to 1.22)		0.26
Target lesion failure	31 (8.5%)	39 (10.8%)	0.76 (0.48 to 1.22)		0.26
All-cause death	22 (6.0%)	29 (8.0%)	0.72 (0.42 to 1.25)		0.25
Cardiac death	12 (3.3%)	12 (3.3%)	0.99 (0.45 to 2.21)		0.98
Target vessel–related myocardial infarction	18 (4.9%)	23 (6.3%)	0.74 (0.41 to 1.36)		0.34
Target lesion revascularization	10 (2.7%)	19 (5.3%)	0.52 (0.24 to 1.11)		0.09
Clinically indicated	10 (2.7%)	18 (5.0%)	0.55 (0.25 to 1.19)		0.12
Definite or probable stent thrombosis	8 (2.2%)	10 (2.8%)	0.79 (0.31 to 2.01)		0.62
Definite stent thrombosis	7 (1.9%)	7 (1.9%)	1.00 (0.35 to 2.83)		0.99
Bleeding BARC 2, 3, or 5	35 (9.6%)	31 (8.9%)	1.10 (0.69 to 1.75)		0.69
BARC 2	19 (5.2%)	16 (4.4%)	1.18 (0.62 to 2.25)		0.61
BARC 3a	9 (2.5%)	6 (1.7%)	1.41 (0.53 to 3.71)		0.49
BARC 3b	9 (2.5%)	6 (1.7%)	1.37 (0.52 to 3.64)		0.52
BARC 3c	1 (0.3%)	5 (1.4%)	0.20 (0.02 to 1.69)		0.10
BARC 5	1 (0.3%)	1 (0.3%)	0.99 (0.06 to 15.77)		0.99
TIMI major bleed	10 (2.7%)	14 (3.9%)	0.64 (0.29 to 1.40)		0.26
Device success	470/497 (94.6%)	455/495 (91.9%)	1.57† (0.91 to 2.73)		0.11

Device success is defined by all the following conditions: successful delivery, balloon expansion, and deployment of the first assigned device, at the intended target lesion, successful withdrawal of the device delivery system, and attainment of a final in-stent or in-scaffold residual stenosis of <20% with final data reported by investigator.

MACCE is defined as a composite of cardiovascular death, myocardial infarction, target vessel revascularization, and stroke. NACE is defined as a composite of cardiovascular death, myocardial infarction, target vessel revascularization, stroke, and BARC 3 or 5 bleeding events at 12-mo follow-up after the index PCI. BARC indicates Bleeding Academic Research Consortium; HR, hazard ratio; MACCE, major cardiac and cerebral event; NACE, net adverse clinical event; PCI, percutaneous coronary intervention; and TIMI, Thrombolysis in Myocardial Infarction.

*P value for 1-sided noninferiority testing using a 4% noninferiority margin at 0.025 significance level.

†Odds ratio and 95% CI.

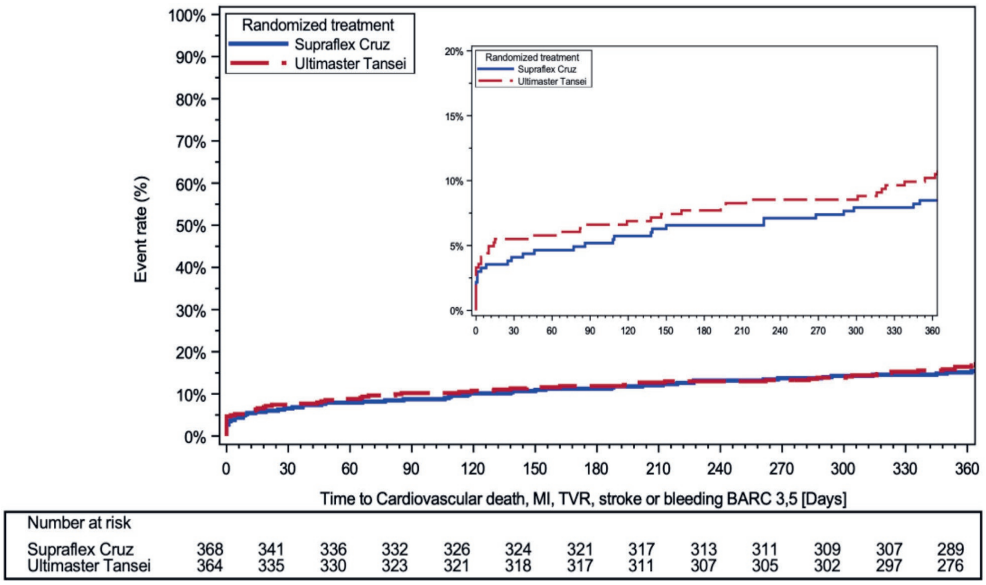


Figure 3. Kaplan-Meier time-to-event curves for the primary outcome.
The primary was the composite of cardiovascular death, myocardial infarction (MI), target vessel revascularization (TVR), stroke, and Bleeding
Academic Research Consortium (BARC) bleeding 3 or 5.

Quantitative Coronary Angiography Subgroup

Analysis The preprocedure and postprocedure quantitative coronary angiography analyses of the first 200 consecutive patients in the trial with 262 lesions showed similar acute in-lesion and in-segment gain between the Supraflex Cruz and Ultimaster Tansei arms, indicating the equal acute angiographic performance of both stents (Figure S3).

DISCUSSION

The main finding from the COMPARE 60/80 HBR trial is that the ultrathin-strut biodegradable-polymer sirolimus-eluting Supraflex stent is noninferior for NACE at 12 months compared with the thin-strut biodegradable-polymer sirolimus-eluting Ultimaster Tansei stent in an HBR population with short DAPT duration post-PCI. This finding has the following implication that it is safe and effective to use the ultrathin-strut biodegradable-polymer sirolimus-eluting Supraflex Cruz stent in an HBR population with short DAPT

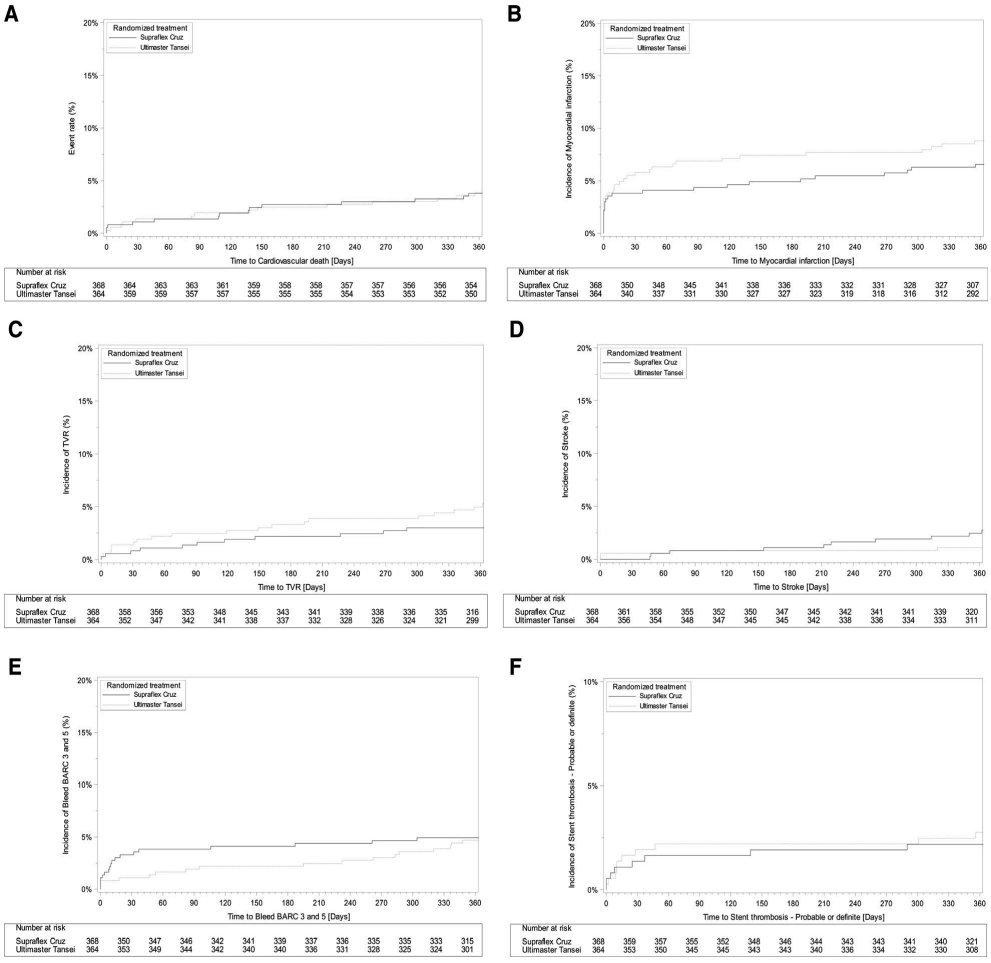


Figure 4. Kaplan-Meier time-to-event curve for the components of the primary end point and stent thrombosis.
Death from cardiovascular causes (A), myocardial infarction (B), target vessel revascularization (TVR; C), stroke (D), major bleeding according to the Bleeding Academic Research Consortium (BARC) 3 or 5 (E), and definite or probable stent thrombosis (F).

duration. Specifically, in a changing landscape in search for optimal DAPT durations for specific patient populations, the choice of stent that has shown to be safe and effective under different DAPT strategies becomes increasingly important. Our study failed to show the superiority of the ultrathin-strut biodegradable-polymer sirolimus-eluting Supraflex Cruz stent over the thin-strut biodegradable-polymer sirolimus-eluting Ultimaster Tansei stent for the composite end point of NACE at 12-month follow-up though, on myocardial infarction, target lesion and target vessel revascularization, and

the composite end point of target lesion failure, the event rates for the Supraflex Cruz stent were numerically lower compared with the Ultimaster Tansei stent. Although these findings could be a result of change, they are in line with several other studies in which ultrathin-strut stents were compared with thicker strut stents, reporting lower event rates for myocardial infarction and target lesion revascularization and target lesion failure.[3–5] The in vivo findings of less thrombus formation, less vessel wall injury, and faster endothelization with less intimal hyperplasia response in ultrathin-strut stents compared with thicker strut stents[1,2] correspond well with our observations of numerically lower myocardial infarction and target lesion revascularization rates with the ultrathin-strut stent in this trial. This effect is likely to be more pronounced in a population with an indication for shorter DAPT duration. Larger sized studies are needed to prove this hypothesis. The NACE event rates were higher than expected in our study. It is highly likely that this was the result of using the ARC-HBR criteria as inclusion criteria and few exclusion criteria on anatomy and lesion complexity, resulting in a truly high bleeding and high ischemic risk population. The COMPARE 60/80 HBR is the first prospective randomized trial to use the ARC-HBR criteria to define an HBR population. On average, 75% of the population had ≥1 major HBR criteria and >50% had ≥2 minor criteria, resulting in an average ARC-HBR score of 1.6 (major criteria, 1 point; minor criteria, 0.5 point). The prevalence of patients on OAC in COMPARE 60/80 HBR was high (64%) and likely was the result of using the ARC-HBR criteria for inclusion. The cumulative NACE rates at 12 months for the ultrathin-strut biodegradable-polymer sirolimus-eluting Supraflex Cruz stent (15.4%) and thin-strut biodegradable-polymer sirolimus-eluting Ultimaster Tansei stent (17.1%) seem, in this trial, much higher compared with the NACE rate (7.5%) of the thin-strut biodegradable-polymer sirolimus-eluting Ultimaster Tansei stent in the MASTER-DAPT trial with abbreviated DAPT regimen.[6] However, in the MASTER-DAPT trial, randomization was performed at 1 month post-stent procedure, and the cumulative NACE event rates were evaluated from 1 to 12 months. If one disregards the NACE event rates of the first month in the COMPARE 60/80 HBR trial (6.6% and 7.7% for Supraflex Cruz and Ultimaster Tansei, respectively), the NACE rates between both trials are much more in line. In comparison to the ONYX ONE trial (A Randomized Controlled Trial With Resolute Onyx in One Month DAPT for

High-Bleeding Risk Patients),^11 the myocardial infarction rates in COMPARE 60/80 HBR were much lower. In the ONYX ONE trial, the durable-polymer zotarolimus-eluting Resolute Onyx stent was compared with the polymer-free biolimus–coated Bio-Freedom stent in patients at HBR with 1-month DAPT therapy. Myocardial infarction rates for both stents were almost twice as high as compared with our trial, presumably because of a different definition for periprocedural myocardial infarction. ONYX ONE used the Third Universal Definition of Myocardial Infarction^12 with a relatively low threshold of periprocedural myocardial infarction (5× upper reference limit for cardiac troponin for PCI and 10× upper reference limit for CABG) in comparison to the used Society of Cardiovascular Angiography and Interventions definition[13] in our trial with a threshold of (70× upper reference limit for cardiac troponin or 35× upper reference limit in combination with new left bundle branch block or Q wave). Other event rates between ONYX ONE and our trials, such as cardiac death, target lesion and vessel revascularization, stent thrombosis, and BARC 3 or 5 bleeding, were comparable. The recent BIOFLOW-DAPT trial (Prospective, Randomized, Multi-Center Study to Assess the Safety of the Orsiro Mission Stent Compared to the Resolute Onyx Stent in Subjects at High Risk for Bleeding in Combination With 1-Month DAPT)^14 compared the biodegradable-polymer sirolimus-eluting Osiro stent with the durable-polymer zotarolimus-eluting Resolute Onyx stent in an HBR population with a 1-month DAPT duration. Although the inclusion and exclusion criteria were similar to ONYX ONE and slightly different compared with our trial, the ischemic event rates in BIOFLOW-DAPT were overall much lower compared with ONYX ONE and COMPARE 60/80 HBR trials. The myocardial infarction rates in BIOFLOW-DAPT were, respectively, 10-fold and 6- to 8-fold lower compared with ONYX ONE and COMPARE 60/80 HBR, respectively. Unlike the previously mentioned trials, BIOFLOW-DAPT selected the Academic Research Consortium-2 myocardial infarction definition,[15] however, without core-laboratory assessment for angiographic evidence of ischemia. Furthermore, a lower proportion of patients presenting with myocardial infarction in BIOFLOW-DAPT were included compared with ONYX ONE and COMPARE 60/80 HBR, and this may further explain the low rates of cardiac death, myocardial infarction, and stent thrombosis. The frequency of BARC 3 or 5 bleeding (3.5% and 3.8%) was little lower compared with ONYX ONE (4.4%

and 4.9%) and clearly lower compared with our trial (4.9% and 5.0%), which included patients with HBR solely on the ARC-HBR criteria. In general, patients with HBR post-PCI remain at higher risk for events compared with the general PCI population. This increased risk is likely attributed to the older age of patients with HBR (on average, 10 years) and other HBR characteristics such as renal insufficiency, active malignancy, age, and oral anticoagulation therapy. Every randomized trial has its strengths and weaknesses. Notably, the COMPARE 60/80 HBR trial stands out for being the first prospective trial using the ARC-HBR criteria for the inclusion of patients with HBR. The higher-than-expected NACE event rates reflect truly a high-risk population, both for bleeding and ischemic risk, which made the noninferiority margin of 4.0% more than adequate. Furthermore, the median DAPT duration of ≈30 days in both arms made this trial comparable to other trials in the field.[6,11,14]

Limitations

Several limitations must be acknowledged. Our trial was an open-label study, making the study results susceptible to selection and treatment bias. DAPT duration and type of antiplatelet selection in combination or as monotherapy were at the discretion of the operator and, therefore, heterogeneous. However, this reflects clinical practice and corresponds to current guidelines. Furthermore, the follow-up was limited to 1 year, and the long-term outcome remains to be investigated. Finally, the sample size was underpowered to detect significant outcome differences between both stents. This would have required a sample size of ≈5000 randomized patients.

Conclusions

In an HBR population with minimal angiographic restrictions and abbreviated DAPT duration, the ultrathin-strut biodegradable-polymer sirolimus-eluting Supraflex Cruz stent was noninferior for NACE at 12 months compared with the thin-strut biodegradable-polymer sirolimus-eluting Ultimaster Tansei stent.

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SUPPLEMENTAL MATERIAL

https://www.ahajournals.org/doi/10.1161/CIRCINTERVENTIONS.123.014042?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed

Chapter 10

30-Day DAPT in Patients at High Bleeding Risk Undergoing PCI With Biodegradable-Polymer Sirolimus-Eluting Ultra-Thin Stent

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ABSTRACT

Background: There is limited evidence on the safety and efficacy of biodegradable-polymer sirolimus-eluting ultra-thin stent (BP-SES) in patients at high bleeding risk (HBR) undergoing percutaneous coronary intervention[1] (PCI).

Aims: This study aims to evaluate the clinical outcomes of HBR patients treated with BP-SES and ≤ 30-day dual antiplatelet therapy (DAPT) regimen.

Methods: A systematic review was conducted to identify relevant studies involving HBR patients who underwent PCI with BP-SES (Supraflex Cruz). Individual patient-level data were extracted from the included studies. The primary endpoint was the composite of cardiovascular death, myocardial infarction, or clinically driven target lesion revascularization at 1-year. The safety endpoint was the 1-year occurrence of Bleeding Academic Research Consortium (BARC) type 3–5.

Results: The study population included 1691 patients. Of these, 928 patients (55%) received a ≤ 30-day DAPT, while 763 patients (45%) received a longer DAPT regimen. In the ≤ 30-day DAPT group, primary outcome events occurred in 89 patients (9.5%, 95% CI: 7.7%–11.6%). The upper limit of the one-sided 95% CI of 11.6% was below the pre-specified non-inferiority margin of 14%. There was no significant difference in the primary endpoint between the ≤ 30-day DAPT group and the >30-day DAPT group (propensity score adjusted HR: 0.95, 95% CI: 0.67–3). Notably, the incidence of BARC 3–5 bleeding events was significantly lower in the ≤ 30-day DAPT group.

Conclusions: In HBR patients treated with BP-SES, a ≤ 30-day DAPT regimen is associated with a low rate of ischemic events and a significant reduction in major bleeding events.

Trial Registration: PROSPERO CRD42024524208.

INTRODUCTION

Advancements in percutaneous coronary intervention (PCI) have made it possible to treat older, sicker, and more comorbid patients. As a result, it is unsurprising that over one-third of patients undergoing PCI are at high bleeding risk (HBR)[1,2]. Numerous studies have demonstrated that, in HBR patients, the protective benefit of dual antiplatelet therapy (DAPT) is often outweighed by bleeding complications, undermining the overall benefit-risk balance[1,2]. Consequently, consensus guidelines recommend short (< 3-month, possibly ≤ 1-month) DAPT regimen in this population[3]. The latest generations of drug-eluting stents (DES) have shown an improved safety profile, even as DAPT durations have been progressively reduced from 12 months to ≤ 30 days. However, this evidence primarily stems from studies including stents with strut thicknesses ≥ 80 μm[4,5]. Few studies investigated the safety of ≤ 30-day DAPT regimen with ultra-thin (≤ 60 μm) DES[6,7], which might show additional benefit compared to thicker strut stents.

The Supraflex Cruz (Sahajanand Medical Technologies Ltd.) is a biodegradable-polymer sirolimus-eluting ultra-thin stent (BP-SES). Previous studies have demonstrated its non-inferiority to the gold-standard durable-polymer everolimus-eluting stent (DP-EES)[8], with favorable outcomes in terms of stent thrombosis and in-stent restenosis, even in patients with complex coronary artery disease[9–12]. However, robust evidence about its efficacy and safety with ≤ 30-day DAPT remains limited.

Given the clinical importance of understating and demonstrating the safety and efficacy of BP-SES in HBR patients undergoing PCI and receiving ≤ 30-day DAPT, we conducted an individual patient meta-analysis of clinical studies including HBR patients treated with Supraflex Cruz.

METHODS

The Evidence Accumulated Regarding Therapeutic strategy in HBR patients (EARTH-HBR) individual patient meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The protocol was registered in the PROSPERO registry before the start of the analyses (id: CRD42024524208). A comprehensive search was performed using PubMed, Google

Scholar, Biomed Central, and Cochrane databases to identify clinical studies involving HBR patients who underwent PCI with implantation of the BP-SES Supraflex Cruz (Supporting Information S1: Figure 1). The search terms included: (HBR AND PCI AND [Supraflex Cruz stent]) (the full search strategy is available in the Supporting Information S1: Material online). Clinical studies enrolling fewer than 20 patients, as well as abstracts, conference presentations, or studies not published in English or in peer-reviewed journals, were excluded from the analysis. Two independent reviewers (G.C. and R.P.) screened the studies based on the search criteria. Any disagreements regarding study inclusion were resolved through discussion with a third reviewer (S.B.). All studies were carefully examined to eliminate any irrelevant duplicates. Ethics committees at each participating site approved the study protocols, and all patients provided written informed consent. The primary objective of this individual patient meta-analysis was to demonstrate that the 1-year incidence of ischemic outcomes in patients treated with BP-SES and ≤ 30-day DAPT regimen is noninferior to a pre-established cutoff based on previous studies[1–6]. The secondary objective was to compare the rate of ischemic and bleeding outcomes in patients treated with BP-SES and receiving ≤ 30-day DAPT versus those receiving a longer DAPT regimen.

Study Population

The corresponding authors of the clinical studies that met the search criteria were contacted to obtain individual patient-level data. From the original database of each clinical study (Supporting Information S1: Tables 1–2), patients were selected based on the following criteria: (i) HBR, and (ii) PCI and implantation of BP-SES Supraflex Cruz. The criteria for defining HBR were established in accordance with the Academic Research Consortium HBR (ARC-HBR) document, and both major and minor HBR criteria were systematically collected within the electronic Case Report Form (eCRF) by the investigators[3]. Patients were categorized as HBR if they fulfilled at least one major criterion or two minor criteria[3]. On top of this, for each patient, the PRECISE DAPT and the ARC-HBR scores were calculated (for the ARC-HBR score 1 point was attributed for each major criterion and 0.5 point for each minor criterion). Duration of the DAPT regimen was at the discretion of the investigators. However, each study protocol

recommended, in agreement with available consensus document[3], a ≤ 30-day DAPT for HBR patients. In cases where oral anticoagulant therapy was indicated, the study protocols recommended dual antithrombotic therapy, consisting of clopidogrel and a novel oral anticoagulant. A common data set was created, including baseline patient characteristics, angiographic data, treatment details, and clinical outcomes. These data were reviewed by each trial investigator and cross-referenced with previously published results from the respective studies.

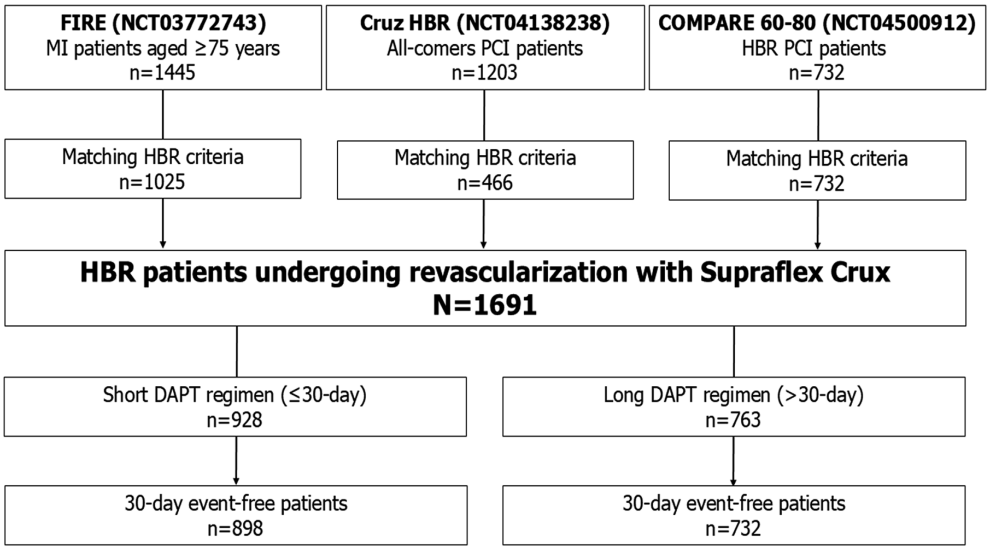


FIGURE 1 Study flowchart.

COMPARE 60–80, Comparison of the Supraflex Cruz 60-micron stent strut versus the Ultimaster Tansei 80-micron stent strut in HBR PCI population. DAPT, dual antiplatelet therapy; HBR, high bleeding risk; FIRE, Functional Assessment in Elderly MI Patients with Multivessel Disease.

Study Endpoints

The primary outcome was the device-oriented composite endpoint (DOCE), defined as the composite of cardiovascular death, any myocardial infarction (not clearly attributable to a nontarget vessel), or clinically-driven target lesion revascularization. Secondary outcomes included the individual components of the primary endpoint, cardiovascular

death or MI, all-cause mortality, any stroke, any MI, any revascularization, and definite and probable stent thrombosis. Safety endpoints focused on Bleeding Academic Research Consortium (BARC) type 3–5 bleedings. Endpoint definitions used in each trial adhered to those used in the original trials and are provided in Supplementary material (Supporting Information S1: Table 3). In each study, adverse events were adjudicated by an independent blinded committee. These independent blind committees also determined whether MI and revascularization events were attributable to the target vessel, specifically the vessel treated with the Supraflex Cruz stent.

G.C. and M.S. had full access to all the data and took responsibility for its integrity and data analysis. The data underlying this article can be requested from the EARTH-HBR study Executive Committee under reasonable conditions. For the primary analysis, which examined the occurrence of the DOCE in HBR patients treated with ≤ 30-day DAPT, it was assumed that the 1-year DOCE occurrence would be approximately 10%, based on the risk profile of the population[1–6]. A non-inferiority margin of 4% was established, in line with previous similar studies. To achieve 80% power for demonstrating non-inferiority with a one-sided type I error of 0.05, a minimum study population of 696 HBR patients treated with the BP-SES Supraflex Cruz and receiving ≤ 30-day DAPT was required. The analysis used a one-stage approach, which simultaneously included all data from the trials. Continuous variables were summarized with means (SD) or median [IQR], and comparisons were made using the Student t-test or the Wilcoxon test, as appropriate. Categorical variables were presented as frequencies and percentages, and comparative analyses were conducted using either the Pearson chi-square or Fisher's exact test, as appropriate. Time-to-event data were assessed using Kaplan–Meier estimates and Cox proportional-hazards models. The proportionality assumption was tested using Schoenfeld residuals and was confirmed ($p > 0.05$ for all outcomes). Due to the observed disparities in characteristics between ≤ 30-day DAPT and > 30-day DAPT groups, a propensity score (PS) model was developed. This model used a logistic regression model, incorporating significant variables identified during the analysis. The score was then included as an adjustment covariate in the multilevel Cox proportional hazards model to assess the association between ≤ 30-day DAPT versus > 30-day DAPT

and outcomes. Statistical analyses were performed using the STATA statistical software version 16 (StataCorp LLC, College Station, TX, USA).

RESULTS

The search strategy was carried out in April 2024, yielding 76 results (Supporting Information S1: Figure 1). Three studies met the selection criteria: Cruz HBR[13], Functional Assessment in Elderly MI Patients with Multivessel Disease (FIRE)[10], and Comparison of the Supraflex Cruz 60-micron stent strut versus the Ultimaster Tansei 80-micron stent strut in HBR PCI population (COMPARE 60/80 HBR)[7]. As shown in Figure 1, the three studies enrolled 3380 patients, of whom 2223 (66%) met the ARC-HBR definition (Figure 1). Among these, 1691 (76%) were treated exclusively with BP-SES for all coronary lesions requiring PCI (Figure 1). The median age of the population was 79 years [75–83], with ages ranging from 40 to 90 years, and 599 patients (35%) were female. The median ARC-HBR average score was 2 [1, 2], with values ranging from 1 to 5. The median PRECISE-DAPT value was 30 [24–36], with values ranging from 13 to 83. The majority of patients (n = 1015, 60%) were hospitalized for MI. Overall, 928 patients (55%) received a DAPT regimen of ≤ 30 days, while 763 patients (45%) received a longer DAPT regimen (Table 1). DAPT prescription patterns over time in the two study groups are depicted in Figure 2 (red line, ≤ 30-day DAPT; blue line > 30-day DAPT). Baseline, procedural, and treatment characteristics significantly differ between the two groups (Table 1).

TABLE 1 Baseline characteristics of HBR populations.

Characteristic	All (n = 1691)	≤ 30-day DAPT (n = 928)	>30-day DAPT (n = 763)	p
Age—years	80 [75–84]	80 [76–84]	79 [75–83]	< 0.001
Male sex—no. (%)	1092 (64)	587 (63)	505 (66)	0.228
Hypertension	1412 (83)	759 (82)	653 (86)	0.042
Dyslipidemia	981 (58)	514 (55)	467 (61)	0.018
Diabetes	531 (31)	268 (29)	263 (35)	0.015
Current smoker	141 (8)	71 (8)	70 (9)	0.298
Prior MI	500 (29)	282 (30)	218 (29)	0.446
Prior PCI	630 (37)	308 (33)	322 (42)	< 0.001
History of AF	317 (19)	241 (26)	76 (10)	< 0.001
eGFR < 60 mLmin	958 (57)	527 (57)	431 (56)	0.94
PAD	316 (19)	168 (18)	148 (19)	0.537
CVA	174 (10)	99 (11)	75 (10)	0.628

STEMI—no. (%)	283 (16.7)	206 (22)	77 (10)	< 0.001
NSTEMI—no. (%)	732 (43)	461 (50)	271 (35)	
CCS—no. (%)	676 (40)	261 (28)	415 (55)	
LVEF—%	50 [40-58]	50 [40-58]	50 [40-58]	0.460
Radial access—no. (%)	1481 (87)	865 (93)	616 (81)	< 0.001
Treated vessels Median [IQR]	2 [1–2]	2 [1–2]	2 [1–2]	0.567
Left main coronary artery	84 (3)	48 (3)	36 (4)	< 0.001
Left anterior descending artery	890 (34)	561 (35)	329 (33)	
Circumflex artery	769 (30)	431 (27)	338 (33)	
Right coronary artery	782 (30)	501 (33)	281 (28)	
Ramus Intermedius artery	58 (22)	36 (2)	22 (2)	
Aspirin	1467 (87)	716 (77)	751 (98)	< 0.001
Clopidogrel	1447 (86)	810 (87)	637 (82)	0.103
Newer P2Y12i	232 (14)	116 (13)	116 (15)	
Vitamin K antagonist	121 (7)	63 (7)	58 (7)	0.654
Novel oral anticoagulant	591 (35)	402 (43)	189 (24)	< 0.001
Triple antithrombotic therapy	505 (30)	258 (28)	247 (33)	< 0.001
Dual antithrombotic therapy	207 (12)	207 (22)	0 (0)	
Dual antiplatelet therapy	965 (57)	461 (50)	504 (66)	

Abbreviations: AF, atrial fibrillation; CCS, chronic coronary syndrome; CVA, cerebrovascular accident; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSTEMI, no ST-segment elevation MI; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation MI.

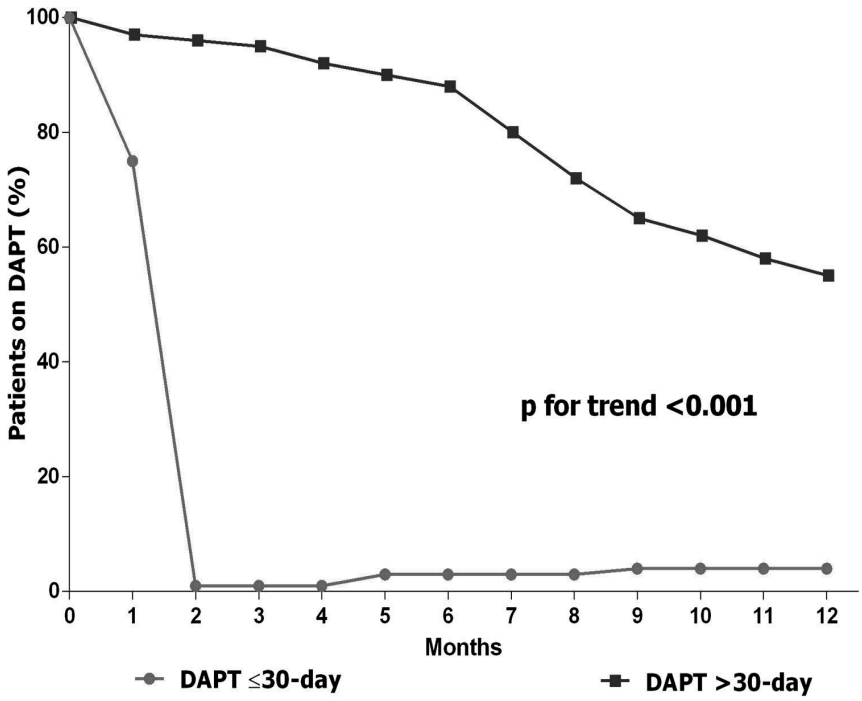


FIGURE 2 Rate of adherence to DAPT in patients. Blue: >30-day DAPT group. Red: ≤30 DAPT group. DAPT, dual antiplatelet therapy.

Ischemic Outcomes in ≤ 30-day DAPT Group

In HBR patients treated with ≤ 30-day DAPT, 50 (5.3%) cardiovascular death, 33 (3.5%) MI, and 43 (4.6%) clinically-driven target lesion revascularization occurred at 1-year (Table 2). A primary outcome event occurred in 89 patients (9.5%, 95% CI 7.7%–11.6%). The upper limit of the one-sided 95% CI of 11.6% was below the pre-specified 14% required demonstrating the non-inferiority (p for non-inferiority < 0.001). (Figure 3). The occurrence of the secondary ischemic endpoints was reported in Table 2. Definite/probable stent thrombosis was observed in 12 patients (1.2%, 0.6%–2.2%) (Table 2). Notably, only 4 (0.4%, 95% CI 0.1%–1.1%) definite stent thrombosis occurred after the 30-day window.

TABLE 2 Clinical outcomes.

Outcome	≤ 30-day DAPT (n = 928) no. (%)	>30-day DAPT (n = 763) no. (%)	Unadjusted HR (95% CI)	Propensity-matched adjHR (95% CI)
Composite of CV death, myocardial infarction, or clinically-driven TLR	89 (9.5)	60 (7.8)	1.21 (0.87–1.68)	0.95 (0.67–1.33)
CV death or MI	77 (8.3)	45 (5.9)	1.40 (0.97–2.02)	1.10 (0.75–1.62)
Death	97 (10.4)	79 (10.3)	1.01 (0.74–1.34)	0.86 (0.63–1.18)
Cardiovascular death	50 (5.3)	32 (4.1)	1.27 (0.81–1.98)	0.92 (0.58–1.46)
Myocardial infarction	33 (3.5)	17 (2.2)	1.06 (0.69–1.62)	0.99 (0.63–1.56)
Clinically-driven TLR	43 (4.6)	29 (3.8)	1.23 (0.77–1.97)	1.05 (0.64–1.73)
Any revascularization	49 (5.2)	44 (5.7)	0.92 (0.61–1.39)	0.85 (0.55–1.31)
Stroke	11 (1.2)	17 (2.2)	0.53 (0.25–1.13)	0.45 (0.20–1.13)
Definite/probable stent thrombosis	12 (1.2)	10 (1.2)	1.01 (0.51–2.23)	1.17 (0.48–2.88)
Definite stent thrombosis	10 (1)	8 (1)	1.03 (0.40–2.59)	1.33 (0.49–3.61)
Probable stent thrombosis	2 (0.2)	2 (0.2)	0.82 (0.11–5.77)	0.67 (0.08–5.32)
BARC 3–5	28 (3)	57 (7.5)	0.39 (0.25–0.62)	0.34 (0.21–0.54)

Abbreviations: BARC, Bleeding academic Research Consortium; CV, cardiovascular; DAPT, dual antiplatelet therapy; HR, hazard risk; MI, myocardial infarction;
TLR, target lesion revascularization; 95%CI, 95% confidence interval.

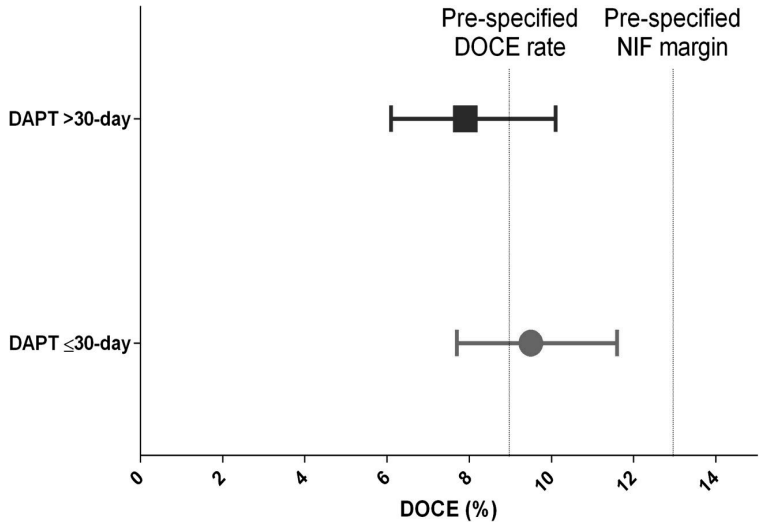


FIGURE 3 Occurrence of DOCE in the study groups. The dot and horizontal lines show the occurrence of DOCE (95%CI) in patients of the study groups. The vertical lines represent the pre-specified DOCE rate and non-inferiority (NIF) margin. Blue: >30-day DAPT group. Red: ≤ 30 DAPT group.

Ischemic Outcomes According to DAPT Groups

The occurrence of ischemic events in HBR patients treated with > 30-day DAPT regimen is reported in Table 2 and Figure 3. The occurrence of the primary endpoint did not differ between the two groups (9.5% in the ≤ 30-day DAPT vs. 7.8% in the > 30-day group, unadjusted HR 1.21, 95% CI 0.87–1.68) (Table 2 and Figure 4). No significant difference was observed in any of the secondary ischemic endpoints between the groups (Table 2), including the occurrence of definite/probable stent thrombosis (1.2% in the ≤ 30-day DAPT vs. 1.2% in the > 30-day group, unadjusted HR 1.01, 95% CI 0.51–1.23). After adjusting the analyses using a PS model – which included variables such as age, arterial hypertension, dyslipidemia, prior PCI, history of atrial fibrillation, clinical presentation, and treated vessels—no significant differences were observed between the ≤ 30-day DAPT and > 30-day DAPT groups (adjusted HR 0.95, 95% CI 0.67–1.33) (Table 2). This finding was consistent across the other ischemic outcomes as well (Table 2).

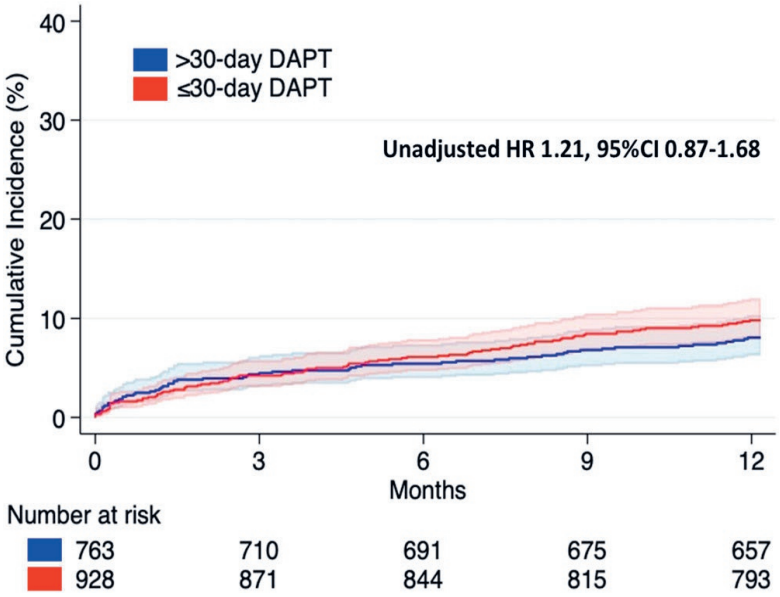


FIGURE 4 Cumulative occurrence of DOCE stratified according to DAPT length. Solid lines: cumulative occurrence in the study groups. Colored areas: 95% confidence interval in the study subgroups. Blue: >30-day DAPT group. Red: ≤ 30-day DAPT group.

Bleeding Outcomes According to DAPT Groups

A total of 28 patients in the ≤ 30-day DAPT group and 57 patients in the > 30-day DAPT group experienced a BARC 3–5 bleeding event (Table 2). The incidence of BARC 3–5 bleeding was significantly lower in the ≤ 30-day DAPT group (unadjusted HR 0.39, 95% CI 0.25–0.62) (Table 2 and Figure 5). This finding remained consistent after adjustment using the PS model (adjusted HR 0.34, 95% CI 0.21–0.54) (Table 2).

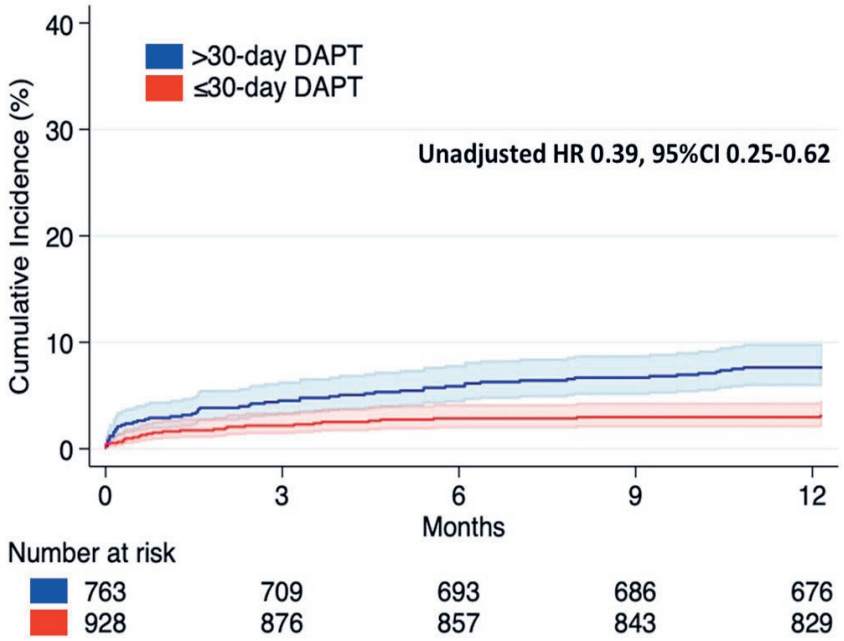


FIGURE 5 Cumulative occurrence of BARC 3–5 bleedings stratified according to DAPT length. Solid lines: cumulative occurrence in the study groups. Colored areas: 95% confidence interval in the study subgroups. Blue: > 30-day DAPT group. Red: ≤ 30 DAPT group.

DISCUSSION

This meta-analysis, based on individual patient-level data from three studies including 1691 HBR patients treated with implantation of BP-SES7,10,13, yielded several key findings. First, patients treated with BP-SES and ≤ 30-day DAPT showed a low 1-year occurrence of DOCE, non-inferior to prespecified cut-off based on similar studies with different stent technology. Second, in a direct comparison of BP-SES patients receiving ≤ 30-day DAPT versus those on longer DAPT regimen, there was no significant difference in the rate of ischemic endpoints, including stent thrombosis. Third, a ≤ 30-day DAPT regimen, when compared to longer ones, was associated with a significant reduction in bleeding outcomes.

In recent years, several studies have highlighted the negative prognostic implication of bleeding adverse events following PCI[14]. Specifically, a BARC 3–5 adverse event has been shown to carry the same prognostic weight for all-cause mortality as a recurrent MI[14]. For this reason, considerable efforts have been directed toward identifying patients who

are more likely to experience bleeding complications during DAPT, as opposed to ischemic events, and determining the optimal DAPT duration that balances the risks of bleeding and ischemia.

The development of the ARC-HBR classification has standardized the identification of HBR patients, providing clinicians with a practical tool to assess bleeding risk[3]. Additionally, the Management of HBR Patients Post Bioresorbable Polymer Coated Stent Implantation with an Abbreviated versus Standard DAPT Regimen (MASTER DAPT) trial confirmed that a short DAPT regimen (30–44 days, median 34 days) is optimal for HBR patients, offering significant reductions in bleeding events without a concomitant increase in ischemic complications[15].

The initial studies evaluating the benefit of short DAPT regimen were conducted in patients treated with polymer-free DES, based on the hypothesis that the stent polymer would carry a prothrombogenic effect[4]. However, subsequent studies have shown that both durable- and resorbable-polymer DES are effective and safe with short DAPT[5–7].

The Supraflex Cruz is an ultra-thin (60 μm in all the stent diameters) cobalt-chromium stent coated with biodegradable polymer and releasing sirolimus. The average coating thickness of Supraflex Cruz is between 4 μm and 6 μm. Previous studies have shown that Supraflex Cruz is non-inferior to durable-polymer DES in an all-comer PCI population[8]. Specifically concerning HBR patients, it has demonstrated noninferiority in a head-to-head comparison with a thin-strut biodegradable-polymer sirolimus-eluting stent, which was also utilized in the MASTER DAPT trial[7]. However, it is important to note that, in this trial, not all patients were treated with ≤ 30-day DAPT and it was not powered to confirm the efficacy and safety of the stent with this DAPT regimen[7]. Consequently, robust evidence demonstrating the efficacy and safety of Supraflex Cruz with ≤ 30-day DAPT remains absent.

This individual-patient meta-analysis has been conducted to fill this gap. From three different studies, individual data of HBR patients treated with BP-SES was collected. The criteria for ARC-HBR were reviewed and confirmed by an independent group of physicians. Adverse events, which were adjudicated in each trial, were reviewed and screened for their association with the stent. Finally, the population was divided into HBR patients treated with ≤ 30-day DAPT and those receiving longer DAPT, enabling

comparisons between groups concerning ischemic and bleeding outcomes. The findings are consistent: patients treated with ≤ 30-day DAPT exhibited a low occurrence of ischemic events, with no signals of concern regarding stent thrombosis, while also significantly reducing BARC 3–5 bleeding complications.

To better contextualize these findings, it is important to compare our patients with those in previous similar studies. Our cohort is older, with a median age of 80 years compared to a mean age of 75 years in prior studies and has a higher percentage of female participants (37% vs. around 30%)[4–6]. The bleeding risk profile of the population is high, as supported by the value of ARC-HBR score (median 2 [1, 2], mean 1.8 ± 0.7, vs. 1.6 ± 0.7 in the COMPARE 60–80) or by the PRECISE-DAPT score (median 30 [15–83], mean 31 ± 11, vs. 27 ± 11 in the MASTER-DAPT). Additionally, 22% of our population consisted of STEMI patients, who are considered at higher ischemic risk, a figure that is substantially higher than in many previous studies, where STEMI patients were either excluded[5], or comprised only 1.7%–6% of the population[4,6]. In general, the number of patients admitted for acute coronary syndromes is higher, being around 70%, as compared to 17%–45% of the previous ones[4–6]. Moreover, the mean number of treated vessels per patient in our study was greater (1.7 vs. 1.3 in previous studies)[4–6]. Despite these high-risk characteristics, the performance of the Supraflex Cruz stent was commendable, with a relatively low rate of ischemic complications; specifically, there were only 12 cases of stent thrombosis.

Our data carry two significant implications. First, the EARTH-HBR meta-analysis underscores the importance of accurately identifying HBR patients and treating them with a ≤ 30-day DAPT regimen. This very short regimen may guarantee the best balance between ischemic and bleeding outcomes. Second, the MATRIX-2 trial (Monotherapy with P2Y12 Inhibitors in Patients With Atrial Fibrillation Undergoing Supraflex Stent Implantation, NCT05955365) has commenced recruitment, aiming to evaluate the safety and efficacy of a monotherapy regimen with a P2Y12 inhibitor for 1 month, followed by direct oral anticoagulant (DOAC) monotherapy, compared to current standard care in atrial fibrillation patients undergoing PCI. The strong performance of the Supraflex Cruz stent, coupled with the very low rate of stent thrombosis observed in this meta-analysis, further supports the rationale for the MATRIX-2 trial.

Study Limitations

This study has certain limitations that must be acknowledged. First, the DAPT regimen was not randomized, as the final decision rested with the investigator. Second, only the COMPARE 60–80 trial randomized patients to two different stent technologies[7], which means that any indirect comparisons with other stents should be regarded as hypothesis-generating. Third, the overall rate of DOCE may appear high, particularly in comparison to similar studies; however, considering the mean age, risk profile, and percentage of MI patients, this is in line with expectations. Finally, while our database included the most relevant variables, we cannot exclude the potential presence of confounding factors, such as ethnicity or race, that may not have been captured in our analysis.

CONCLUSIONS

In HBR patients undergoing PCI with a biodegradable-polymer ultra-thin sirolimus-eluting stent, a short DAPT regimen (≤ 30 days) appears to be effective and safe, yielding a low incidence of ischemic outcomes while minimizing bleeding occurrences.

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Chapter 11

Polymers, thickness, dosage: just pieces of the whole puzzle

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Cardiovascular disease remains a significant global health con-cern, and percutaneous coronary intervention (PCI) has undergone remarkable advancements, transforming the management of coro-nary artery disease (CAD). The introduction and continuous tech-nological enhancements of drug-eluting stents (DES) have notably reduced the need for repeat revascularisations, as compared to bare metal stents (BMS)[1]. Newer-generation DES exhibit improvements in all key components, including the metallic scaffold, the active antiproliferative agent, and the polymer coating[2]. Modern mate-rials like cobalt-chromium have allowed for a gradual reduction in strut thickness, promoting faster endothelialisation while pre-serving both outer radial strength and radio-opacity[3]. Additionally, the transition from paclitaxel to the -limus family has significantly improved clinical outcomes[4]. However, concerns have arisen regarding the endothelial inflammatory response related to the persistence of the polymer coating. Biodegradable-polymer (BP) coatings have been conceived to mitigate the device-related risk of recurrent events by facilitating vascular healing while minimis-ing the persistent inflammatory response related to durable poly-mer (DP). Potential benefits of the biodegradable-polymer DES are expected at long-term follow-up, and the focus in recent years has been directed towards investigating whether the safety profile of biodegradable polymer is sustained and magnified over time[5].

The Targeted Therapy With a Localized Abluminal Groove, Low-Dose Sirolimus-Eluting Biodegradable Polymer Coronary Stent (TARGET All Comers) trial, the 1- and 3-year results of which have been previously published[67], randomised 1,653 patients across 10 European countries to PCI using either the BP siroli-mus-eluting stent (BP-SES), FIREHAWK (MicroPort), or the DP everolimus-eluting stent (DP-EES), XIENCE (Abbott).

At 1-year follow-up, the FIREHAWK BP-SES met the non-inferiority endpoint of target lesion failure (TLF) as compared to the XIENCE DP-EES. Neither TLF (6.1% vs 5.9%, respectively) nor the secondary outcomes significantly differed between the two stents. Notably, stent thrombosis occurred with similar frequency in both groups[6]. The 3-year results revealed comparable rates of TLF (11.9% vs 11.5% for FIREHAWK BP-SES and XIENCE DP-EES) and other secondary endpoints. Landmark analysis between 1 and 3 years demonstrated no significant differences in the performance of the two devices; however, a trend towards fewer very late definite or probable stent thromboses,

favouring the FIREHAWK BP-SES (0.8%), was observed after 12 months as compared to the XIENCE DP-EES (1.4%)[7]. Despite being rare, these events could be interpreted as a sign of a lower thrombo-genicity favoured by the bioresorbable polymer.

In this issue of EuroIntervention, Lanksy and colleagues report the long-awaited 5-year results of the TARGET All Comers trial which were anticipated to provide insights into the long-term per-formance of these stents[8]. Nearly 94% of patients completed the 5-year clinical follow-up, enhancing our understanding of the long-term performance of these devices. The primary endpoint, TLF, occurred in 17.1% of the FIREHAWK group and 16.3% of the XIENCE group at 5 years, with no statistically significant difference (p=0.68). Similarly, the patient-oriented composite endpoint (POCE), which comprised all-cause death, all myocardial infarctions, and all revascularisa-tions, showed similar rates in both groups. Notably, the previously suggested signs of reduced thrombogenicity with the FIREHAWK were not confirmed, as the rates of definite or probable stent thrombosis (acute, late, and very late) were observed to be compa-rable between the two study groups. Landmark analyses at 1 year showed no differences in TLF and its components, POCE, or stent thrombosis.

The study can be approached from two distinct perspectives: a purely technical one and a broader, clinical one.

With respect to the technical aspects, the FIREHAWK and the XIENCE share some similarities. They both employ cobalt-chro-mium for the metallic scaffold and exhibit a comparable strut thick-ness (86 μm and 81 μm, respectively). However, they incorporate different antiproliferative drugs from the -limus family (sirolimus and everolimus, respectively). Moreover, the FIREHAWK shows a novel feature of a unique set of recessed abluminal grooves con-taining a D,L-polylactic acid polymer of 10-μm thickness that are able to provide a controlled and targeted release of the antipro-liferative drug. The thin polymer coating completely dissolves within 6-9 months.

This finding is part of a broader context of extensive evidence, with some aligning and others conflicting, advocating that other mechanical features may be responsible for the device-related risk of recurrent events[9(10)]. Besides polymer coatings and drugs, differ-ences in strut thickness and geometry, coating distribution, drug release and polymer degradation kinetics can all have an impact on peristrut local haemodynamics

and, ultimately, on re-endothe-lialisation. Such a wide variety in stent features combined with a low rate of device endpoints in the past decade limit the potential to demonstrate the incremental benefits of newer technologies and overturn the concept of class effect among bioresorbable-polymer DES.

Beyond the technical perspective, this trial provides a highly comprehensive overview of the clinical progression of patients with CAD. The inclusion criteria were intentionally wide-rang-ing, and the enrolled patients fairly represent the typical caseload encountered in a cath lab on a daily basis. While the absence of significant differences between the two stent types in outcomes is noteworthy, a deeper analysis reveals intriguing nuances. Repeat revascularisation was a major contributor, occurring in 19.3% and 19.2% of the FIREHAWK and XIENCE groups, respectively. Importantly, fewer than one-third of these events were ischaemia-driven and target lesion-related, suggesting that factors beyond stent performance alone, such as patient- and lesion-related characteristics, play a significant role. This finding highlights the complexity of clinical decision-making in CAD management and underscores the need for a nuanced approach that considers not only the stent but also patient-specific factors and the clinical context. Ultimately, the TARGET All Comers trial reminds us that the path to improving cardiovascular care involves piecing together many elements, with metals, active drugs, and polymer coatings being just a few parts of a 1,000-piece puzzle.

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Chapter 12

Ultrathin- vs Thin- struts stent in calcified coronary lesion: A multicenter retrospective study.

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Abstract

Background.

Severe coronary calcification remains a major determinant of stent underexpansion and adverse outcomes. Strut thickness influences mechanical behaviour and deliverability, yet comparative data between ultrathin- and thin-strut drug-eluting stents (DES) in calcified lesions assessed with intravascular imaging are limited.

Methods.

We retrospectively analysed 158 de-novo calcified lesions (IVUS/OCT calcium score ≥2) treated with ultrathin-strut (60 μm; n=80) or thin-strut (80 μm; n=78) DES in two centres. All lesions underwent pre- and post-PCI intravascular imaging. The primary endpoint was relative stent expansion >80%. Secondary endpoints included expansion at the most calcified site, minimal stent area (MSA)/distal reference >90%, eccentricity index, and clinical outcomes at a median 33-month follow-up. Multivariable regression and propensity-score matching were performed as exploratory sensitivity analyses.

Results.

Baseline clinical characteristics were comparable, whereas anatomical complexity differed across groups: the 80-μm cohort presented more extensive circumferential calcium and larger reference vessel diameter, while the 60-μm cohort had numerically thicker calcium and more frequent bifurcations. Overall median expansion was 80.9%. Ultrafthin-strut DES achieved a higher rate of stent expansion >80% (66% vs 41%, p=0.005) and greater expansion at the most calcified segment (58% vs 48%, p=0.017). In exploratory adjusted analyses, implantation of a 60-μm DES was associated with lower odds of underexpansion, although residual confounding cannot be excluded. Clinical outcomes, including death, MACCE, TLF and TVR, were low and similar between groups, but the study was not powered for clinical endpoints.

Conclusion.

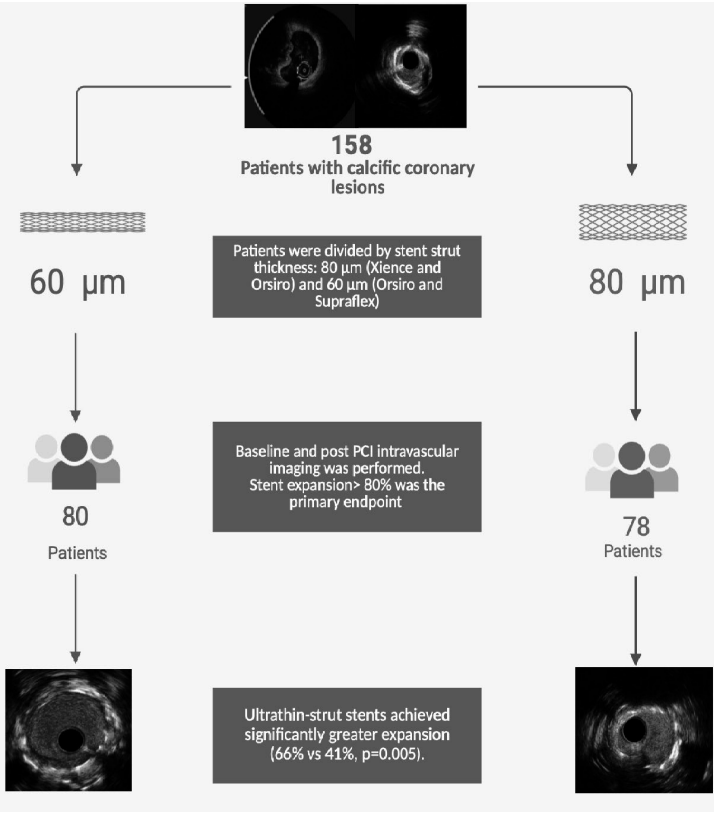
In this imaging-guided retrospective study of calcified coronary lesions, ultrathin-strut DES were associated with higher stent expansion compared with thin-strut DES. These findings, while hypothesis-generating, support the need for prospective studies with standardized lesion preparation algorithms to determine whether differences in mechanical performance translate into durable clinical benefit.

What is known?

- Calcified coronary lesions (IVUS/OCT calcium score ≥2) are at high risk of stent underexpansion and adverse events.
- Strut thickness influences expansion and conformability in rigid, calcified anatomy.
- Intravascular imaging is recommended to guide preparation, sizing, and optimization in complex lesions.

What is new?

- In a real-world cohort of calcified lesions with systematic imaging, ultrathin-strut (60 μm) DES achieved higher expansion than thin-strut (80 μm) DES.
- Imaging guidance was integral to lesion characterization and stent optimization across both groups.



Central Illustration

Introduction

Coronary calcification is a major determinant of percutaneous coronary intervention(PCI) complexity[1]. Circumferential and thick calcium impair device deliverability and stent expansion, predisposing to restenosis and thrombosis.

Strut thickness—through its effects on radial support, flexibility, and healing—may influence outcomes in this setting. However, data comparing ultrathin- and thin-strut drug eluting stent (DES) specifically in calcified lesions assessed by Intravascular Ultrasound IVUS) or Optical coherence tomography (OCT) are limited.

This study assessed expansion metrics and clinical outcomes in patients with de novo calcified lesions undergoing imaging-guided PCI with 60 μm vs 80 μm DES.

Methods

Consecutive patients with de novo calcified coronary lesions were included from 2 hospitals in Rotterdam, Netherlands (Maasstad Hospital and Erasmus Medical center). Patients were divided by stent strut thickness: 80 μm (Xience and Orsiro) and 60 μm (Orsiro and Supraflex). The OCT calcium score was defined assigning one point each for a maximum calcium arc >180°, a maximum calcium thickness >0.5 mm, and a calcium length >5 mm, while the IVUS calcium score is determined by the presence of specific intravascular ultrasound features, including a maximal superficial calcium angle greater than 270° over a length ≥5 mm, circumferential (360°) superficial calcium, calcified nodules, and a vessel diameter <3.5 mm[2][3].

Patients with calcium score <2, in-stent restenosis, or PCI performed exclusively with drug-eluting balloon were excluded.

Primary endpoint was relative stent expansion >80%. Stent expansion was calculated as the minimum stent area (MSA) divided by the average of the proximal and distal reference lumen areas, expressed as a percentage.

Secondary endpoint were expansion at the most calcified site, Minimal stent area (MSA) /distal reference area >90%, and eccentricity index. Clinical outcomes were assessed at 33-month median follow-up.

Intravascular imaging assessment

At OCT, calcified plaque was defined as a region of low or heterogeneous signal intensity with sharply delineated borders. Quantitative measurements were obtained every 1 mm along the treated lesion. Calcium thickness was measured as the maximum distance between the leading and trailing edges of the calcium signal, and calcium arc was calculated as the mean arc of calcium measured at 1-mm intervals throughout the lesion length. At IVUS, calcified plaque was defined as an echogenic area with acoustic shadowing, consistent with calcium deposition. Quantitative IVUS analyses were also performed at 1-mm longitudinal intervals along the lesion. All imaging analyses were performed by two independent investigators who were blinded to clinical data; in cases of disagreement, a third investigator adjudicated the final interpretation. A calcified nodule was defined as a calcific protrusion into the lumen, further categorized as eruptive (irregular surface without an overlying fibrous cap) or non-eruptive (smooth surface with an intact fibrous cap). Concentric calcium was defined as calcium with a mean arc greater than 180° along the analysed lesion segment.

Baseline imaging included arc, thickness, length of calcium, presence of nodules, and minimal lumen area (MLA). Post-stent analysis included proximal and distal reference areas, MSA, stent expansion, eccentricity index, malapposition, and edge dissections .

IVUS datasets were analysed using Boston IVUS Viewer and Avigo Plus; OCT datasets with Ultreon; additional IVUS with OsiriX.

Statistics

Statistical analysis were performed with STATA v17.0, continuous variables were expressed as mean±SD or median (IQR) and compared with t-test or Mann–Whitney U. Categorical variables were compared with χ^2 or Fisher's exact test. $p<0.05$ was significant, across-strata heterogeneity within each cohort was assessed using Kruskal–Wallis. We performed multivariable logistic regression including all clinically relevant covariates.

To reduce confounding, a propensity score (PS) was estimated using logistic regression including arc270, nodule, calcium length, MLA, bifurcation, and stent diameter. PS matching was performed using 1:1 nearest neighbour matching with a caliper of 0.05 on the standardized logit of the PS. Covariate balance was assessed using standardized mean

differences (SMDs). The average treatment effect on the treated (ATET) was estimated. Statistical significance was defined as $p<0.05$.

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Results

Baseline characteristics

A total of 158 patients were analysed, with 80 receiving ultrathin-strut DES (60 μm) and 78 treated with thin-strut DES (80 μm). The two groups were well balanced in terms of demographics and cardiovascular risk profile Table1. Median age was 71 years (IQR:16) in the 60 μm group and 71 years (IQR:12) in the 80 μm group (p=0.760). The prevalence of diabetes mellitus was similar (48.6% vs 51.0%, p=0.780), as were hypertension (66.0% vs 76.0%, p=0.137), chronic kidney disease (46.0% vs 30.0%, p=0.300), atrial fibrillation (8.7% vs 11.0%, p=0.387), and peripheral artery disease (4.3% vs 14.0%, p=0.400). Prior cardiovascular events and procedures were evenly distributed, with similar rates of prior PCI (27.0% vs 25.0%, p=0.541), coronary artery bypass graft (CABG) (3.7% vs 2.5%, p=0.670), and transient ischaemic attack (TIA) or stroke (8.7% vs 9.0%, p=0.387). Overall, baseline characteristics confirmed that the two groups represented a clinically homogeneous population, minimizing the risk of confounding from baseline imbalance.

Table 1 : Baseline Characteristics

Baseline Characteristics	**Overall N=158**	**Struts 60 µm N = 80 (51%)**	**Struts 80 µm N = 78 (49%)**	**p-value**
Age	71 (IQR: 14)	72 (IQR: 16)	71 (IQR: 12)	0.760
Diabetes	37 (23,0%)	18(48,6%)	19 (51,0%)	0,780
Familiar CAD	54 (34,0%)	31 (38,0%)	23 (29,0%)	0.220
Smoker	38 (25,0%)	27 (33,0%)	11(14,0%)	**0,004**
Hypertension	113 (71,0%)	53 (66,0%)	60 (76,0%)	0,137
Prior TIA or Strokes	14 (0,8%)	7 (8,75%)	7 (9,0%)	0,387
Prior PCI	44 (27,0%)	20 (25.0%)	24 (30,0%)	0.541
Prior CABG	5 (3,0%)	3 (3,75%)	2 (2.5%)	0.670
PAD	7 (11,0%)	1 (4.3%)	6 (14,0%)	0.400
Chronic HF	15 (9,0%)	6 (7,5%)	9 (24,0%)	0.048
AF	9 (14,0%)	2 (8.7%)	7 (11,0%)	0,387
CKD	61 (38,0%)	37 (46,0%)	24 (30,0%)	0.300

CAD= Coronary artery disease, TIA= Transient ischaemic attack, PCI: Percutaneous coronary intervention, CABG= Coronary artery bypass graft; PAD: Peripheral artery disease; HF= Heart Failure; AF= Atrial fibrillation; CKD: Chronic kidney disease.

Procedural characteristics

Clinical presentation at admission was also comparable, with stable coronary artery disease (CAD) in 50 % vs 47% (p=0.420), unstable angina in 12.5% vs 12.8% (p=0.780), non-ST elevation myocardial infarction (NSTEMI= in 36.2% vs 26.0% (p=0.208), and ST elevation myocardial infarction (STEMI) in 3.8% vs 6.4% (p=0.220). The left anterior descending (LAD) was the most frequently treated vessel in both groups (76.0% vs 65.0%, p=0.060), followed by the (right coronary artery) RCA, which was numerically more

common in the 80 µm cohort (8.1% vs 24.3%, p=0.060). Lesion complexity was high in the whole cohort. Type B2 lesions were significantly more common in the 80 µm group (52.0% vs 69.2% p=0.048), whereas bifurcation lesions were markedly more frequent in the 60 µm group (32.5% vs 7.7%, p=0.001). However, type C lesions, as well as chronic total occlusions, were evenly distributed. Lesion preparation strategies reflected this anatomical complexity. Non-compliant balloons alone were the default strategy (81.2% vs 83.3%). All other adjunctive devices were used in addition to non-compliant balloons: cutting balloons (8.7% vs 2.5%), IVL (1.2% vs 1.2%), rotational atherectomy (2.5% vs 2.5%), and orbital atherectomy (3.7% vs 10%).

Tables 2 Procedural Characteristics

Procedural Characteristics	**Overall N=158**	**Struts 60 µm N = 80 (51%)**	**Struts 80 µm N = 78 (49%)**	**p-value**
Stable CAD	80 (50%)	38 (47,0%)	42 (53,0%)	0.420
Unstable Angina	20 (12,6%)	10 (12,5%)	10 (12,8%)	0,780
STEMI	8 (5%)	3 (3,8%)	5 (6,4%)	0.220
NSTEMI	50 (31,1%)	29 (36,2%)	21 (26,0%)	0,208
Coronary Lesion	158	80	78	0.060
LM	5 (3.1%)	3 (3.75%)	2 (2.5%)	
LAD	112 (70%)	61 (76.0%)	51 (65.0%)	
RCx	15 (9%)	9 (11.2%)	6 (7.7%)	
RCA	26 (16%)	7(8.1%)	19 (24.3%)	
Lesion Type B2	96 (60%)	42 (52,0%)	54 (69,0%)	0.048
Lesion Type C	53 (33,5%)	31 (38,0%)	22 (28,0%)	0,387
CTO	1 (0,63%)	1 (1,2 %)	0	0,322
Bifurcation	32 (20%)	26 (32,0 %)	6 (7,7%)	**0,001**
Cutting Balloon	9 (5,69%)	7 (8,7 %)	2 (2,5%)	0.093
Intravascular Lithotripsy	2 (1,2%)	1 (1,2%)	1 (1,2%)	0.986
Non-Compliant (alone)	131 (82,0%)	67 (83,0%)	64 (82 ,0%)	0.777

Rotational Atherectomy	4 (2,5%)	2 (2,5%)	2 (2,5%)	0.980
Orbital Atherectomy	11 (6,9%)	3 (3,7%)	8 (10,0%)	0.108

CAD = coronary artery disease; STEMI = ST-elevation myocardial infarction; NSTEMI = non-ST elevation myocardial infarction; LM = left main; LAD = left anterior descending; RCx = left circumflex; RCA = right coronary artery; CTO = chronic total occlusion; NC = non-compliant balloon; MACCE = major adverse cardiac and cerebrovascular events.

Baseline intravascular imaging

Intravascular imaging was systematically performed to assess calcium severity, using IVUS or OCT according to operator choice. Distribution of modality was similar between groups. Lesions in the 80 μm group were characterized by a higher prevalence of extensive concentric calcification, with calcium arc >270° over >5 mm observed in 45.0% vs 73.0% of cases (p=0.010). Conversely, the 60 μm group showed numerically greater calcium thickness (1.10 mm vs 0.94 mm, p=0.328) and a trend toward smaller baseline MLA (2,92 mm^2 vs 3.3 mm^2, p=0.052). The prevalence of calcium nodules was comparable between groups (52% vs 42%, p=0.232). Notably, calcium length was higher in the 80 μm group (16 mm vs 28 mm; p=0.001) as was the reference vessel diameter (RVD; 3.0 mm vs 3.5 mm; p=0.005).

Table 3. Baseline Imaging Characteristics

Baseline Imaging Characteristics	**Overall N=158**	**Struts 60 μm N = 80 (51%)**	**Struts80 μm N = 78 (49%)**	**p-value**
IVUS	126 (79,0%)	61 (76,3%)	65 (83,3%)	0,268
OCT	32 (21,0%)	19 (23,7%)	13 (16,7%)	0,268
Calcium Score (IVUS/OCT)	2 (IQR: 1)	2 (IQR: 1)	2 (IQR: 1)	0,638

Calcium arc > 270° > 5mm	93 (58,0%)	36 (45,0%)	57 (73,0%)	**0,001**
360° Calcium	93 (58,0%)	49 (61,0%)	53 (67,0%)	**0,022**
Calcium Nodules	75 (47,0%)	34 (42,0%)	41 (52,0%)	0,232
MLA	3,1 (IQR : 1,61)	2,92(IQR 1,3)	3,3 (IQR : 1,59)	0,052
Calcium Lenght	24 (IQR: 28)	16 (IQR : 20)	28(IQR 28)	**0,001**
Calcium Thickness	1 (IQR :0,34)	1,10 (IQR :0,39)	0,94 (IQR:0,25)	0,328
Reference vessel diameter	3.0 (IQR : 0,5)	3.0 (IQR : 0,5)	3.5 (IQR : 0,5)	**0,005**

IVUS : Intravascular Ultrasound; OCT: Optical coherence tomography; MLA: Minimal Lumen Area

Post-PCI Intravascular imaging outcomes

The average expansion was 80.9%, ultrathin-strut DES achieved superior mechanical performance. Median MSA was slightly larger in the 80 μm group (6.4 mm^2 vs 7.5 mm^2, p=0.005). Importantly, the proportion of stents reaching an expansion >80% was significantly higher with ultrathin-strut DES (66.0% vs 41.0%, p=0.005), as was expansion assessed at the most calcified site (58.0% vs 48.0%, p=0.017). Eccentricity index was comparable (0.84 vs 0.85, p=0.133). Malapposition (18.7% vs 23.7%, p=0.504) and edge dissections (5.0% vs 1.3%, p=0.182) were infrequent and evenly distributed. Final stent size was higher in the 80 μm group (3.0 mm vs 3.5 mm; p=0.005).

Considering both nominal stent diameter and RVD, MSA increased with size in each cohort. Within the 60 μm cohort, MSA distributions differed across nominal stent diameter strata (Kruskal–Wallis χ^2 with ties = 15.18, P = 0.004) and across RVD (χ^2 = 16.49, P = 0.002). Median MSA increased from 4.6 mm^2 in stents with a 2.5-mm nominal diameter to 12.0 mm^2 in 4.0-mm stents, and from 5.0 mm^2 in vessels with RVD 2.5 mm to 9.0 mm^2 in RVD 4.0 mm. A similar size-dependent trend was observed in the 80-μm cohort (nominal diameter: χ^2 = 16.25, P = 0.003; RVD: χ^2 = 14.82, P = 0.011).

Direct head-to-head comparisons between 60 µm vs 80 µm within each size stratum showed a consistent advantage for 60 µm in terms of stent expansion and, in several strata, larger MSA. For the binary endpoint of >80% expansion, 60-µm stents outperformed 80- µm stents in several diameter categories with adequate sample size (e.g., 3.0 mm: 61.5% [32/52] vs 27.6% [8/29]; 3.5 mm: 86.7% [13/15] vs 65.6% [21/32]; 4.0 mm: 85.7% [6/7] vs 10.0% [1/10]) Tables 5,6 figure 1,2.

For continuous outcomes (MSA and expansion %), expansion percentage remained consistent across nominal stent diameter and RVD in the 60 µm cohort (diameter p= 0.161, RVD p= 0.107), whereas the 80 µm cohort showed nominal stent diameter-dependent variation (P = 0.001) but no RVD effect (p = 0.548). Tables 5,6 figure 1,2.

Table 4 Procedural Imaging Outcomes ; MSA: Minimal stent expansion

Procedural Imaging Outcomes	**Overall N=158**	**Struts 60 µm N = 80 (51%)**	**Struts 80 µm N = 78 (49%)**	**p-value**
MSA	6,9 (IQR : 3.30)	6,4 (IQR: 2,76)	7,5 (IQR : 3,45)	**0,005**
MSA at most calcified segment	7.50 (IQR : 3.50)	6.60 (IQR : 3.15)	8.16 (IQR : 3.35)	**0,006**
Eccentricityindex	0,84 (IQR : 0,10)	0,84(IQR : 0,12)	0,85 (IQR : 0,10)	0,133
StentExpansion > 80%	85 (53,0%)	53 (66,0%)	32 (41,0%)	**0,005**
StentExpansion > 80% at most calcific segment (or calcium nodule)	92 (58,0%)	54 (58,0%)	38 (48,0%)	**0,017**
MSA/distalLumen Area > 90%	104 (65,0%)	58 (72,0%)	46 (58,0%)	**0,073**
Edge dissection	5 (3,0%)	4 (5,0%)	1 (1,3%)	0,182
Malapposition	33 (20,0%)	15 (18,7%)	18 (23,7%)	0,504
Stent size	3.0 (IQR : 0,5)	3.0 (IQR : 0,5)	3.5 (IQR : 0,5)	**0,005**

Table 5 Stratified outcomes by reference vessel diameter (mm) ; MSA: Minimal stent expansion reported in mm²

Reference vessel Diameter	MSA median (Q1–Q3) – 60µm	MSA median (Q1–Q3) – 80µm	p-Value	Expansion % Median (Q1–Q3) – 60µm	Expansion % Median (Q1–Q3) – 80µm	p-Value	Stent expansion >80% 60µm (events/n, %)	Stent expansion >80%–80µm (events/n, %)	p-Value
2,5	5,03 (4,60–5,45)	6,10 (4,15–6,55)	0,606	73,6 (62,3–83,2)	60,4 (59,7–61,8)	0,24	3/9 (33,3%)	1/5 (20,0%)	1,0
3,0	6,40 (5,60–7,80)	6,75 (5,79–7,80)	0,523	84,9 (76,4–95,8)	75,1 (64,0–82,8)	0,003	28/45 (62,2%)	8/26 (30,8%)	0,014
3,5	7,80 (6,02–9,45)	8,15 (6,88–9,60)	0,348	87,5 (80,9–96,5)	77,7 (67,0–93,1)	0,15	11/13 (84,6%)	15/32 (46,9%)	0,024
4,0	9,00 (5,75–13,00)	9,13 (8,00–10,70)	0,732	83,0 (80,8–88,1)	76,0 (57,0–90,1)	0,403	9/11 (81,8%)	4/9 (44,4%)	0,16

Table 6 Stratified outcomes by nominal stent diameter (mm)

Nominal stent diameter	MSA median (Q1–Q3) – 60µm	MSA median (Q1–Q3) – 80µm	p-Value	Expansion % median (Q1–Q3) – 60µm	Expansion % median (Q1–Q3) – 80µm	p-Value	>80% – 60µm (events/n, %)	>80% – 80µm (events/n, %)	p-Value
2,5	4,60 (4,40–5,03)	5,96 (5,72–6,10)	0,095	62,7 (62,0–78,4)	55,3 (53,4–59,7)	0,095	1/5 (20,0%)	0/5 (0,0%)	1,0
3,0	6,35 (5,57–7,85)	6,90 (6,00–7,90)	0,317	83,3 (76,3–94,3)	72,8 (61,8–80,1)	0,002	32/52 (61,5%)	8/29 (27,6%)	0,005
3,5	7,30 (6,14–9,22)	8,95 (7,15–10,65)	0,039	89,6 (82,0–96,5)	88,0 (76,8–94,2)	0,64	13/15 (86,7%)	21/32 (65,6%)	0,175
4,0	12,00 (6,80–14,40)	8,30 (6,54–9,71)	0,315	85,7 (81,9–92,4)	67,1 (57,0–74,1)	0,014	6/7 (85,7%)	1/10 (10,0%)	0,004

MSA: Minimal stent expansion reported in mm²

Multivariable analysis

In the multivariable logistic regression including lesion-level calcium characteristics, bifurcation involvement, MLA, and maximum stent diameter, implantation of a 60-µm DES remained independently associated with a significantly lower risk of stent underexpansion. Specifically, 60-µm struts were associated with a 65% reduction in the odds of underexpansion (OR 0.35, 95% CI 0.15–0.82; p = 0.015).

Calcium nodules (OR 2.68, 95% CI 1.23–5.82; p = 0.013) and longer calcium length (trend, p = 0.066) were the strongest predictors of underexpansion, whereas MLA, bifurcation involvement, and calcium arc >270° were not independently associated.

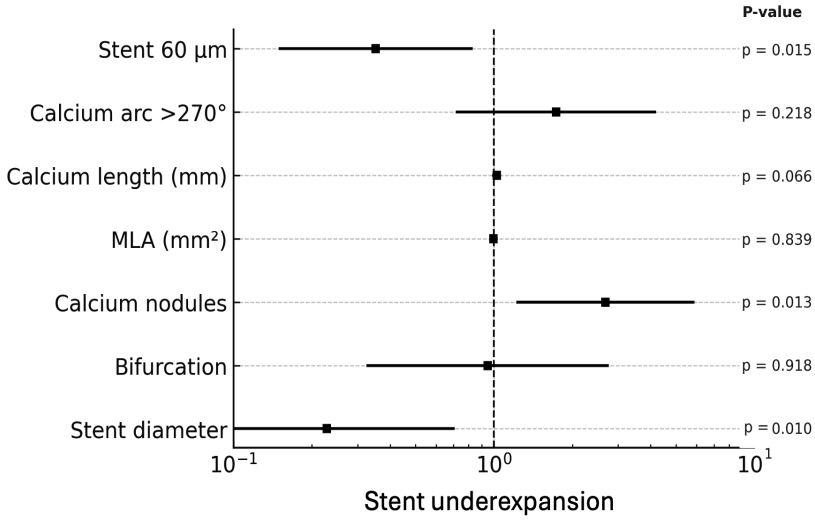


Fig 1. Forrest Plot. MLA: Minimal Lumen area.

Propensity-score matching

A propensity score for treatment with 60-µm DES was generated using the same anatomical and procedural covariates. After 1:1 nearest-neighbor matching with a 0.05 caliper, 150 of 151 lesions (99%) remained within the region of common support, with substantial improvement in covariate balance (mean standardized difference reduced from 44% to 16%; PS-R^2 from 0.247 to 0.044).

In the matched cohort, 60-µm DES continued to show a significantly lower risk of stent underexpansion (ATET −0.37 ± 0.14; p = 0.009), corresponding to a 36% absolute risk

reduction. Direction and magnitude of effect were consistent with the multivariable model.

Clinical outcomes

At a median follow-up of 33 months, no significant differences in clinical events were detected between groups. All-cause death occurred in a similar proportion of patients, as did target vessel revascularization (1.2% vs 5.0%, p=0.164), target lesion failure (1.2% vs 1.2%, p=0.986), and major adverse cardiac and cerebrovascular events (MACCE) (6.2% vs 6.4%, p=0.596).

Table 7 : Clinical Outcomes

Clinical Outcomes	**Overall N=158**	**Struts 60 µm N = 80 (51%)**	**Struts80 µm N = 78 (49%)**	**p-value**
All cause Death	16 (10.0%)	8(10.0%)	8 (9.0%)	0.135
TVR	5 (3.0%)	1 (1,2%)	4 (5.0%)	0.164
TLF	2 (1,2%)	1 (1,2%)	1 (1,2%)	0.986
MACCE	10 (6,3%)	5 (6,2%)	5 (6,4%)	0.596

TVR: Target Vessel Revascularization; TLF: Target Lesion failure; MACCE: Major Adverse Cardiac and Cerebrovascular Events

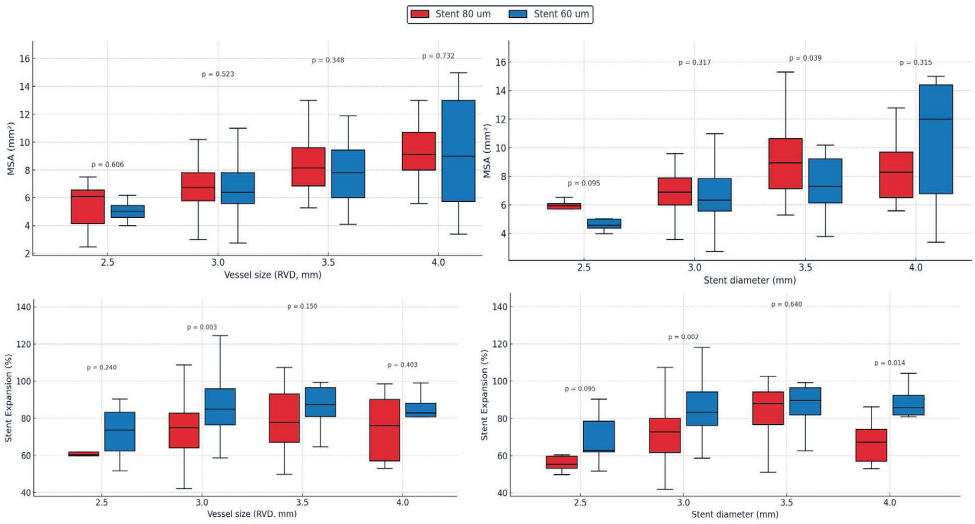


Figure 2: Stratified outcomes by reference vessel diameter and nominal stent diameter; RVD: Reference vessel diameter, MSA : Minimal stent area.

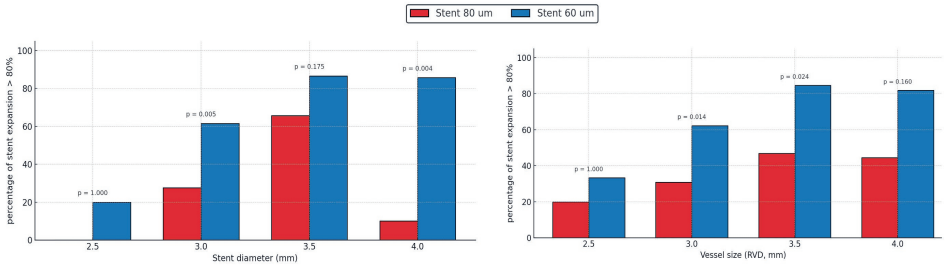


Figure 3: Percentage of achieved stent expansion>80% stratified by nominal stent diameter and reference vessel diameter; RVD: Reference vessel diameter.

Discussion

The main findings of our analysis are:

1. Even in complex anatomies use of IVI ensure reasonable expansion and is associated with low incidence of TLF
2. Ultrathin stents have demonstrated non-inferiority, and potentially superiority, compared with thin-strut stents, not only regarding device deliverability but also in achieving better stent expansion.

All lesions included in this analysis were complex by design: patients with an intravascular imaging calcium score <2 were excluded, so the present cohort uniformly comprised moderately to severely calcified lesions. In such anatomy, underexpansion is a leading driver of adverse outcomes, and meticulous procedural planning is mandatory. Accordingly, intravascular imaging was integral to the workflow in every case—pre- and post-PCI—and served three non-negotiable roles: (i) precise morphological characterization of calcium; (ii) guidance of lesion preparation strategy; and (iii) accurate stent sizing and optimization. This approach is consistent with contemporary recommendations for complex PCI[1] and reflects current practice in high-risk calcified disease. Although the 2024 ESC Guidelines on Chronic Coronary Syndromes[5] recommend the use of IVI in true bifurcations, long lesions, and left main PCI, they do not explicitly mention calcified lesions. This may be partly explained by the underrepresentation of calcific coronary disease in randomized clinical trials comparing intravascular imaging modalities (Illumien IV[6]: 11.5% calcified lesions; OCTOBER[7]: 14%; Renovate[8]: 14.2%; OCTIVUS[9]: 10.3%), as well as by the limited use of intravascular imaging in RCTs specifically addressing the treatment of calcified lesions. Furthermore, even in more recent clinical trials such as ECLIPSE[10], approximately 40% of patients did not undergo intravascular imaging, and in these cases calcium severity was adjudicated solely angiographically by the core lab, with no data reported on how many lesions would have met IVI-defined criteria for severe calcification.

The use of intravascular imaging is more sensitive than angiography in calcium detection, characterization, and distribution[11]. Different patterns of calcification can be properly identified, such as concentric rings, long calcified segments with thick calcium, superficial calcium, and calcified nodules[12]. This characterization is not merely descriptive but is also instrumental in guiding the decision-making process for lesion preparation. Such insights may explain why, as in the treatment of calcified lesions, the use of IVI results in greater therapeutic success in terms of stent expansion, as demonstrated in the CALIPSO and ECLIPSE RCTs[13]. In our dataset, the 80 μm cohort more frequently displayed concentric and circumferential calcium, while the 60 μm cohort tended to have thicker calcium and smaller baseline MLA. These differences help interpret the subsequent mechanical behaviour of the stent platforms and the response

to lesion preparation. Prior studies have shown that IVUS- and OCT-based calcium scores can reliably predict the risk of underexpansion and should guide lesion preparation[14 15].

Operators used a toolbox of adjunctive strategies including non-compliant balloons, cutting/scoring balloons, rotational and orbital atherectomy, and intravascular lithotripsy, according to calcium morphology and vessel size. Although the overall use of these tools was numerically similar between groups, the pattern of application reflected anatomical differences: for instance, the higher prevalence of bifurcation lesions in the 60 μm cohort likely influenced pre-dilatation strategy and post-dilation optimization, whereas the greater load of circumferential calcium in the 80 μm cohort may have prompted more extensive plaque modification before stenting. Imaging also clarified when aggressive plaque modification could be safely avoided, reducing unnecessary device escalation.

Moreover, intravascular imaging ensured accurate sizing and optimization. Reference lumen areas were measured proximally and distally, the stent was sized to the healthy reference, and high-pressure post-dilation was performed to target a post-PCI expansion above 80%. Edge dissections, tissue protrusion, and malapposition were identified and corrected interprocedurally when present. This meticulous image-guided pathway is central to the interpretation of our results. The principle that stent expansion above 80% is associated with improved long-term outcomes is supported by recent intravascular imaging studies[1]. The rate of TLF was low in this high-risk population, reflecting the advantage of IVI-guided PCI. Although underpowered for clinical endpoints, the trend toward higher repeat revascularization in underexpanded stents supports the mechanistic link between optimal expansion and long-term vessel patency, as described in contemporary literature[2–4].

Despite smaller vessels and more frequent bifurcations in the 60 μm cohort, ultrathin-strut DES achieved higher rates of optimal expansion, both overall and at the most calcified site. The use of ultrathin-strut stents may provide potential advantages not only in terms of improved stent expansion but also in reducing restenosis. Thinner struts are associated with less vessel wall injury and reduced flow disturbance, which in turn favourably modulates local endothelial shear stress, a critical determinant of neointimal

hyperplasia and restenosis[17,18]. By minimizing the protrusion of the struts into the lumen, ultrathin platforms promote a more physiological flow profile and reduce areas of low shear stress that are prone to neointimal proliferation. However, radial strength of stent hoops is primarily influenced by three factors: the metal alloy (or polymer), strut thickness, and stent architecture[19]. While a reduction in strut thickness could theoretically compromise radial strength, contemporary ultrathin designs employing optimized alloys and architectures achieve an adequate balance between radial force and deliverability, maintaining mechanical integrity while improving biological compatibility[20]. This suggests that increased conformability and flexibility may confer a mechanical advantage in rigid anatomy, enabling more complete apposition and lumen gain after adequate preparation. Conversely, the 80 μm cohort, with a higher prevalence of circumferential calcium, faced intrinsically greater resistance to expansion even with similar device use. The net result was a clear difference in expansion performance between platforms in this specific, high-risk substrate.

Data from RCTs confirm the excellent expansion and outcomes of ultrathin-strut stents, such as BIOFLOW V[21], which demonstrated excellent expansion and outcomes with ultrathin-strut DES, and a meta-analysis comparing ultrathin versus thin-strut devices; however, no data exist in calcified lesions treated with intravascular imaging guidance[22]. In the multivariable model, thinner 60-μm struts remained independently associated with a significantly lower risk of stent underexpansion, even after adjustment for calcium burden, nodularity, bifurcation involvement, MLA, and stent diameter. Notably, calcium nodules and calcium length emerged as the most powerful predictors of underexpansion, consistent with prior IVUS-based literature, whereas lesion eccentricity and bifurcation anatomy contributed minimally. Importantly, the propensity-score matched analysis—despite preserving nearly the entire cohort because of the high degree of overlap between treatment groups—confirmed the magnitude and direction of the association. The ATET indicated a 36% absolute reduction in underexpansion with 60-μm struts, providing convergent evidence that the effect is not driven by baseline imbalances or selection patterns. From a methodological standpoint, the preservation of 150 of 151 lesions within common support suggests that operators implanted the two stent platforms across broadly similar lesion subsets, thereby increasing the internal validity

of the comparison. Together, these adjusted analyses reinforce that the mechanical behaviour of ultrathin-strut DES may be intrinsically less favourable in heavily calcified or nodular lesions, and that incremental radial strength could translate into greater procedural efficiency when optimal expansion is the target.

The clinical follow-up in this study was deliberately reported but is not powered to detect small differences in events. Importantly, the absence of a difference in MACCE or target vessel revascularization (TVR) at approximately 33 months should not be interpreted as proof of clinical equivalence between strategies or platforms. Rather, it reflects the sample size and the influence of a uniform imaging-guided workflow, which likely minimized avoidable complications in both groups.

Several limitations merit emphasis. This was a retrospective analysis and, as such, is susceptible to selection bias and unmeasured confounding; the results are hypothesis-generating and require prospective validation. In addition, vessels in the 60 μm cohort were smaller, which may influence expansion metrics and device selection, and could partially account for procedural differences independent of strut thickness. No multivariable analyses were performed, by design, and the patterns of lesion preparation were operator-dependent. Finally, although the median follow-up was substantial, late events in heavily calcified disease can accrue beyond the reported horizon.

Conclusions

In this retrospective multicenter cohort of calcified lesions, imaging-guided PCI demonstrated that ultrathin-strut (60 μm) DES achieved higher expansion rates compared with thin-strut (80 μm) DES. Clinical outcomes were comparable, but greater expansion supports the hypothesis of a potential long-term prognostic benefit. These findings call for prospective, adequately powered studies comparing ultrathin- and thin-strut DES in calcified lesions with mandatory intravascular imaging, standardized preparation algorithms, and both mechanistic (MSA, expansion, symmetry, malapposition) and clinical endpoints over long-term follow-up. Such trials would determine whether the mechanical advantage observed here translates into durable clinical benefit.

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Chapter 13

Abluminus DES+ sirolimus-eluting stents versus everolimus-eluting stents in patients with diabetes mellitus and coronary artery disease: results from the ABILITY DIABETES GLOBAL randomised trial

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Summary

Background In patients with coronary artery disease, diabetes mellitus confers a high risk of restenosis and adverse cardiovascular events after percutaneous coronary intervention (PCI). Abluminus DES+ is a thin-strut cobalt–chromium sirolimus-eluting stent (SES) with abluminal and balloon-surface coating intended to enhance drug delivery to vessel wall. We aimed to compare the safety and efficacy of Abluminus DES+ (SES) versus the XIENCE durable-polymer everolimus-eluting stent (EES) in patients with diabetes undergoing PCI.

Methods This was a prospective, randomised, open-label, multicentre trial conducted at 74 sites in 16 countries. Adults (≥18 years) with type 1 or type 2 diabetes mellitus undergoing PCI for at least one de novo coronary lesion due to chronic coronary syndrome or non-ST-segment elevation acute coronary syndrome were eligible. Participants were randomly assigned (1:1) to Abluminus DES+ SES or XIENCE EES. Randomisation was stratified by site using a secure web-based system with concealed allocation and randomly varying block sizes (4, 6, 8). Operators were unblinded whereas staff performing clinical follow-up and the independent clinical events committee were blinded. For Abluminus DES+ SES, ≥45-s balloon inflation was recommended to facilitate drug transfer; dual antiplatelet therapy was prescribed per guidelines and local practice. The primary hypothesis of the study was the non-inferiority of Abluminus DES+ SES compared with XIENCE EES for the two co-primary endpoints at 12 months, assessed in the per-protocol population: ischaemia-driven target-lesion revascularisation (idTLR) and target-lesion failure (TLF), defined as a composite of cardiovascular death, target-vessel myocardial infarction, or idTLR. Time-to-event analyses were conducted with Kaplan–Meier estimates and Cox proportional hazards models. Outcomes through 24 months were analysed according to the intention-to-treat principle.[91] This trial is registered with ClinicalTrials.gov NCT04236609 and has been completed.

Findings Between June 12, 2020, and Sept 9, 2022, 3032 patients were randomly assigned (1514 to Abluminus DES+ SES and 1518 to XIENCE EES); 2931 (96·7%) completed follow-up to death or the 24-month visit. At 12 months, in the per-protocol analysis, Abluminus DES+ SES did not meet the criteria for non-inferiority for idTLR (4·8% vs 2·1%; absolute

risk difference [ARD] 2·7%, 95% CI 1·3–4·1; non-inferiority [NI] margin 2·8%; p non-noninferiority = 0·44) and TLF (9·7% vs 6·2%; ARD 3·5%, 1·5–5·5; NI margin 3·0%; p non-inferiority = 0·68); for both endpoints, the lower bound of the 95% CI for the ARD excluded zero. At 24 months, in the intention-to-treat analysis, event rates remained significantly higher with Abluminus DES+ for both idTLR (6·6% vs 3·9%; HR 1·71, 95% CI 1·23–2·37) and TLF (12·4% vs 9·6%; HR 1·32, 1·06–1·65). No statistically significant differences were observed between 12 and 24 months in landmark analyses.

Interpretation In patients with diabetes undergoing PCI, the Abluminus DES+ SES was not non-inferior to the XIENCE EES stent, with higher rates of idTLR and TLF at 12-month follow-up. Event rates between 12 and 24 months were similar between groups. These findings highlight the persistent challenge of optimising outcomes in diabetic patients and underscore the need for continued innovation in stent design and adjunctive pharmacotherapy to reduce residual ischaemic risk in this population.

Funding Funded by Concept Medical

Trial registration ClinicalTrials.gov Identifier: NCT04236609

Key words: Diabetes mellitus; Percutaneous coronary intervention; Drug-eluting stents; Randomized controlled trial; Coronary Artery Disease

Research in context

Evidence before this study

We searched PubMed, Embase, and major cardiology meeting proceedings up to December 2024 without language restrictions, using the terms “diabetes,” “drug-eluting stents,” “PCI,” and “randomized clinical trial.” Previous randomized trials and meta-analyses consistently showed that patients with diabetes experience higher rates of restenosis and repeat revascularisation compared with non-diabetic patients, despite improvements in new-generation drug-eluting stents. Small mechanistic studies and observational studies of the Abluminus DES+ stent suggested feasibility and safety, but clinical evidence from large-scale randomized trials was lacking.

Added value of this study

The ABILITY Diabetes Global trial is the largest randomized study to date focused exclusively on patients with diabetes undergoing percutaneous coronary intervention. In

more than 3000 patients, the Abluminus DES+ sirolimus-eluting stent did not meet criteria for non-inferiority compared with the XIENCE everolimus-eluting stent for ischaemia-driven target lesion revascularisation and target lesion failure. The excess risk with Abluminus DES+ was confined to the first year, driven by higher rates of target-vessel myocardial infarction and revascularisation, whereas outcomes were similar thereafter. This trial provides definitive large-scale comparative data for two contemporary stent platforms in this high-risk population.

Implications of all the available evidence

Diabetic patients remain at elevated risk of adverse events after PCI. The lack of incremental benefit with Abluminus DES+ highlights the ongoing unmet need for innovation in stent technology and adjunctive therapies to reduce residual ischaemic risk in patients with diabetes and coronary artery disease requiring PCI. Future research should explore device designs and pharmacological strategies that specifically address the biological challenges of diabetes, while surgical revascularisation continues to remain the preferred option for patients with multivessel disease when feasible.

Introduction

Diabetes mellitus is a growing global health challenge, affecting more than 500 million individuals worldwide, a number projected to rise substantially over the coming decades.[1] Cardiovascular disease remains the leading cause of morbidity and mortality in this population, with coronary artery disease often presenting with a more aggressive and diffuse pattern of atherosclerosis compared with non-diabetic patients.[2] Hyperglycaemia, insulin resistance, and associated metabolic disturbances promote endothelial dysfunction, oxidative stress, and platelet hyperreactivity, facilitating pro-inflammatory and pro-thrombotic pathways.[3]

When myocardial revascularization is required, diabetic patients face an higher risk of major adverse cardiovascular events (MACE) and repeat revascularizations.[4] The FREEDOM trial established the superiority of coronary artery bypass graft over percutaneous coronary intervention (PCI) in diabetic patients with multivessel disease, showing lower rates of death and myocardial infarction; yet a substantial proportion of patients with diabetes still require PCI due to anatomical suitability, high surgical risk, or

patient preference.[5],[6] Outcomes after PCI remain suboptimal and mechanisms of failure and in-stent restenosis in diabetic patients are complex, including patient-related (e.g., diffuse disease, vessel calibre), metabolic-related (e.g., advanced glycation, endothelial dysfunction), and stent-related (e.g., strut thickness, polymer biocompatibility, drug resistance) factors.[7–9] Although new-generation drug-eluting stents (DES) have outperformed bare-metal stent and 1st generation DES in all-comer patients, improvement of long-term clinical outcomes in diabetic patients has been limited.[10–12]

The Abluminus DES+ (Concept Medical Inc., Tampa, FL, USA) is a novel, thin-strut, cobalt-chromium sirolimus-eluting stent platform specifically designed for diabetic patients.[13],[14] The anti-proliferative agent sirolimus is eluted from the abluminal surface of both the stent and the exposed parts of the delivery balloon (hence the term DES+). This technology is intended to ensure a uniform drug delivery within the lesions and the stent edges, addressing the risk of restenosis while guaranteeing an adequate re-endothelization.

The ABILITY Diabetes Global study aimed to compare the safety and efficacy of Abluminus DES+ stent versus the established durable-polymer everolimus-eluting XIENCE stent (Abbott Vascular, Santa Clara, CA, USA) in a large cohort of diabetic patients undergoing PCI.

Methods

Study design and participants

The ABILITY Diabetes Global trial was a prospective, international, multicentre, open-label, two-arm, parallel-group, randomised clinical trial conducted at 74 sites across 16 countries in Europe, South America, and Asia. The trial protocol was approved by local ethics committees at each site and is available with the full text of this article in the appendix 1; details of the study organization and the full list of participating sites is including in appendix 2 pp 2–6.

The Executive and Steering Committees, together with the sponsor (Concept Medical Inc., Tampa, FL, USA), were responsible for the trial design. The Cardiovascular European Research Center (CERC, Massy, France) coordinated study operations, site monitoring, and the angiographic core laboratory. The Icahn School of Medicine at Mount Sinai (New

York, NY, USA) oversaw data management, data analysis and coordinated both the independent Data and Safety Monitoring Board (DSMB) and blinded Clinical Events Committee (CEC).

Patients aged 18 years or older with either a previously documented diagnosis of type 1 or type 2 diabetes receiving pharmacological treatment or, alternatively, a new diagnosis of diabetes irrespective of treatment status, were considered eligible candidates for PCI for coronary artery disease presenting as chronic stable angina, silent ischaemia, or non-ST-segment elevation acute coronary syndrome. The angiographic inclusion criteria were the presence, by visual estimate, of at least one de novo coronary artery stenosis >50% in a native coronary artery amenable to treatment with one or more stents (reference vessel diameter 2·25–4·0 mm) (appendix 2, p7). Key clinical exclusion criteria included patients undergoing PCI for ST-segment elevation myocardial infarction (STEMI), cardiogenic shock, known allergy to study stent drug or protocol required medications, planned surgery requiring dual antiplatelet therapy discontinuation within 6 months after the index procedure, acute or chronic renal dysfunction (serum creatinine >3·0 mg/dL) or any serious medical illness reducing expected survival to <12 months; angiographic exclusion criteria were in-stent restenosis or lesions involving a bypass graft (appendix 2, p8). All patients provided written informed consent, and the study was conducted in accordance with the Declaration of Helsinki.

Randomisation and masking

Diabetic patients who were deemed clinically eligible and suitable for treatment with PCI were considered for enrolment in the study. After written informed consent was obtained, patients proceeded to the cardiac catheterisation laboratory for verification of angiographic inclusion and exclusion criteria. If all eligibility criteria were confirmed, randomisation was performed after successful guidewire crossing and lesion predilatation. Patients were randomly assigned in a 1:1 ratio to receive either the Abluminus DES+ sirolimus-eluting stent (SES) or the XIENCE everolimus-eluting stent (EES). The randomisation sequence was computer-generated using a permuted block design with randomly varying block sizes of 4, 6, and 8, stratified by investigational site, and used a secure web-based system with concealed allocation.

Operators were aware of the assigned study device; however, randomisation and device details were redacted from procedural reports and clinical documentation. Follow-up assessment was performed by research and clinical staff blinded to treatment allocation, and all clinical events were adjudicated by an independent Clinical Events Committee that remained blinded to study assignment.

Procedures

Stent implantation was performed in accordance with the instructions for use for either the Abluminus DES+ SES or the XIENCE EES depending on randomisation. For the Abluminus DES+ SES, an inflation of at least 45 seconds was recommended to allow adequate drug delivery from the balloon to the vessel wall. There were no restrictions on the number of treated lesions, number of vessels, or lesion length, and procedural strategy was left to the operator's discretion. However, all lesions within a patient were to be treated using the assigned study device; staged procedures were permitted within 45 days after the index procedure and had to use the same allocated device. Post-procedural management was at the discretion of the treating team, and dual antiplatelet therapy (consisting of aspirin plus a $P2Y_{12}$ inhibitor) was prescribed in accordance with current guideline recommendations and local practice.

Follow-up visits were scheduled at 1, 6, 12, and 24 months after randomisation; the 12-month visit was performed in person, whereas the other follow-ups could be conducted by telephone. At each visit, cardiovascular and diabetes-related medications, and HbA1c levels were recorded; the 12-month visit additionally included angina assessment, physical examination, 12-lead ECG, and standard laboratory testing. Patients could be withdrawn from the study upon withdrawal of consent, protocol violation precluding continued participation, or loss to follow-up.

Outcomes

The trial had two co-primary efficacy endpoints: (1) ischaemia-driven target lesion revascularisation (idTLR) and (2) target lesion failure (TLF), defined as a composite of cardiovascular death, target vessel myocardial infarction (TVMI), or idTLR. The key secondary endpoint was the composite of cardiovascular death or TVMI. Other

secondary clinical endpoints included the individual components of the co-primary endpoints, all-cause mortality, stent thrombosis, stroke, non-TLR target vessel revascularization (TVR), Bleeding Academic Research Consortium (BARC) type 2 or greater bleeding, and stent thrombosis.

The co-primary endpoint idTLR was defined according to the Academic Research Consortium-2 criteria as any repeat percutaneous or surgical revascularization of the target lesion (the treated segment including 5 mm proximal and distal margins) performed in the presence of clinical or objective evidence of ischaemia.[15] Evidence of ischaemia was defined by symptoms of angina, abnormal electrocardiographic findings, a positive noninvasive functional test, or by one of the following hierarchical criteria: (1) core laboratory fractional flow reserve ≤0.80 or instant wave-free ratio ≤0.89; (2) site-reported fractional flow reserve ≤0.80 or instant wave-free ratio ≤0.89; (3) quantitative coronary analysis (QCA) diameter stenosis >50% with recurrent symptoms or a positive noninvasive test; (4) QCA diameter stenosis >70% by the average of multiple views; or (5) QCA diameter stenosis >70% in the worst view regardless of other criteria.

Myocardial infarction was defined according to the Fourth Universal Definition of Myocardial Infarction.[16] Stent thrombosis was classified according to the Academic Research Consortium-2 consensus document.[15] All endpoints reported in this manuscript were pre-specified in the trial protocol. and are presented in accordance with the statistical analysis plan; full study endpoints definitions are reported in appendix 2, pp 9–15.

Statistical Analysis

The two primary hypotheses of the study were non-inferiority of the Abluminus DES+ SES compared with the XIENCE EES for the co-primary endpoints idTLR and TLF at 12 months in the per-protocol (PP) population. If non-inferiority was met for idTLR, sequential superiority testing was prespecified in the intention-to-treat (ITT) population. The ITT population included all randomised patients, irrespective of treatment received; the PP population consisted of all randomised patients treated exclusively with the assigned stent for all lesions and procedures with no major protocol deviations.

For idTLR, the sample size estimation assumed a 7·5% incidence at 1 year and a 2·8% non-inferiority margin. With an anticipated 8% attrition rate, a total of 3000 patients provided 80% power for non-inferiority with a one-sided type I error 0·025 and 80% power for sequential superiority with a minimum detectable effect size of 0·67. For TLF, based on an expected 9% incidence at 1 year and a 3·0% margin, 2252 patients were sufficient, but 3000 were planned to ensure adequate power for both co-primary endpoints, yielding 89% power for TLF. The one-year rates of the co-primary endpoints were estimated based on two previous trials investigating the XIENCE everolimus-eluting stent in patients with diabetes.[17],[18] Given the low event rates previously reported for the experimental device in observational studies,[19] non-inferiority margins for both endpoints were defined as thresholds considered unlikely to represent clinically meaningful differences.

During the study, the final sample size was increased to 3050 to preserve power for the PP analysis, accounting for the observed number of protocol deviations. Non-inferiority was assessed using Farrington–Manning test. Cumulative incidence was estimated with the Kaplan–Meier method, and hazard ratios with 95% CIs were calculated using Cox proportional-hazards models. Patients with incomplete follow-up were censored at the time of last contact. All other tests used two-sided α=0·05. No interim analyses were prespecified. Analyses were conducted with Stata version 18.0 (StataCorp, College Station, TX, USA) and SAS version 9.4 (SAS Institute, Cary, NC, USA) at the Icahn School of Medicine at Mount Sinai, with independent validation of primary endpoint analyses at the London School of Hygiene & Tropical Medicine. The study was registered with ClinicalTrials.gov, number NCT04236609.

Role of the funding source

The funder of the study contributed to the study design and reviewed the data included in this manuscript, but had no role in data collection, data analysis, data interpretation, or writing of the report.

Results

Between June 12, 2020, and Sept 9, 2022, 3032 patients were enrolled at 74 sites across 16 countries; of these 1514 (49·9%) were randomly assigned to Abluminus DES+ SES and 1518 (50·1%) to XIENCE EES. The trial profile is shown in figure 1; 2931 (96·7%) patients completed follow-up to death or the 24-month end of study. The median follow-up was 366 days (IQR 366–366) for the 12-month analysis and 726 days (IQR 724–728) for the 24-month analysis.

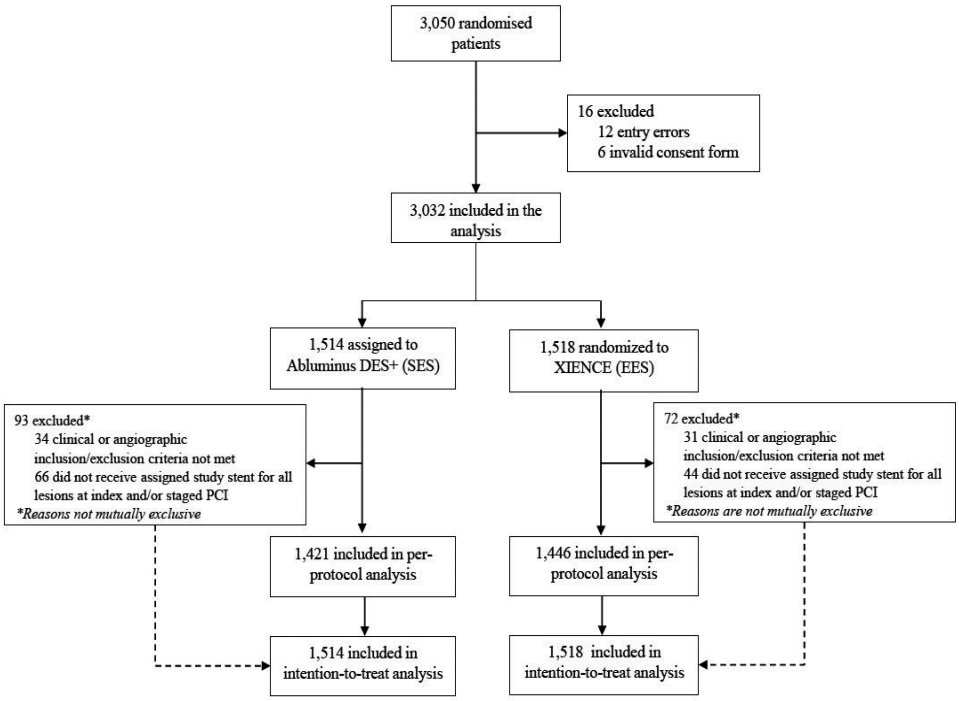


Figure 1. Trial profile.

The intention-to-treat population comprised all randomly assigned patients, regardless of device received. The per-protocol population consisted of all randomised patients treated exclusively with the assigned stent for all lesions and procedures, with no major protocol deviation. Reasons for exclusion were not mutually exclusive.

Baseline characteristics were well balanced between the two groups (table 1), as were index procedural characteristics (appendix 2, pp 16–17). Median age was 68·0 years (IQR 60–74); 879 (29·0%) of 3032 were females and 2153 (71·0%) were males; data on race or

ethnicity were not collected for this study. Of 3032 randomised patients, 2793 (92·1%) had type 2 diabetes with median HbA1c of 7.6% (IQR 6.8–8.7), 1065 (35·1%) received insulin and 2176 (71·8%) sensitizers, mainly metformin. Clinical presentation was non-ST-segment-elevation myocardial infarction in 681 (22·5%) of 3032, and 632 (20·8%) had a prior myocardial infarction. Radial access was used in 2521 (83·1%) of 3032; most procedures treated a single vessel with a mean of 1·7 (SD 1·0) stents implanted. Approximately one-third of cases (983 [32·4%] of 3032) were defined as complex PCI, with an even distribution between groups. Stent inflation time was longer with Abluminus DES+ (median 45 s [IQR 45–47]), and post-dilatation was performed in 2093 (69·5%) of 3010 procedures. Technical success was achieved in 2988 (98·9%) of 3022, with no significant between-group differences. Most patients were discharged on dual antiplatelet therapy (DAPT), predominantly with clopidogrel, with no between-group differences. Information on DAPT cessation and modalities throughout follow-up is provided in appendix 2, p 18.

Of the 3032 randomised participants comprising the intention-to-treat (ITT) population, 165 (5·4%) were excluded from the per-protocol (PP) primary analysis for major protocol violations, leaving 2867 (94·6%) patients (1421 Abluminus DES+ SES and 1446 XIENCE EES). At 12 months in the PP population, idTLR occurred in 67 (4·8%) of 1421 patients in the Abluminus DES+ SES arm versus 30 (2·1%) of 1446 receiving XIENCE EES (HR 2·31, 95% CI 1·50–3·55), with an absolute risk difference of 2·7% (95% CI 1·3–4·1). The prespecified criterion for non-inferiority was not met (p non-inferiority=0·44), and the lower bound of the 95% CI for the absolute risk difference excluded zero. Similarly, TLF occurred in 137 (9·7%) in Abluminus DES+ SES versus 89 (6·2%) in XIENCE EES (HR 1·59, 95% CI 1·22–2·07), with an absolute risk difference of 3·5% (95% CI 1·5–5·5). Non-inferiority was not met (p non-inferiority=0·68) and the lower bound of the 95% confidence interval of absolute risk difference excluded zero (figure 2). The composite of cardiovascular death or TVMI was significantly higher in the Abluminus DES+ SES arm (HR 1·55, 95% CI 1·15–2·10), driven by higher rates of TVMI (73 [5·2%] vs 44 [3·1%]; HR 1·70, 95% CI 1·17–2·47), while the difference in cardiovascular death was not statistically significant (41 [2·9%] vs 30 [2·1%]; HR 1·39, 95% CI 0·87–2·23). There were no statistically significant differences

in all-cause death or other secondary endpoints (table 2). Analyses at 12 months in the ITT population were consistent with primary PP results (appendix 2, p 19).

At 24-month, in the ITT population, idTLR occurred in 95 (6·6%) of 1514 in Abluminus DES+ SES versus 57 (3·9%) of 1518 in the XIENCE EES arm (HR 1·71, 95% CI 1·23–2·37), and TLF in 184 (12·4%) versus 142 (9·6%) (HR 1·32, 95% CI 1·06–1·65) (table 3, appendix 2 p 23). The composite of cardiovascular death or target-vessel MI was higher with Abluminus DES+ (139 [9·3%] vs 105 [7·1%]; HR 1·34, 95% CI 1·04–1·73). There were no statistically significant differences in all-cause death (87 [5·9%] vs 93 [6·3%]; HR 0·94, 95% CI 0·70–1·26) or cardiovascular death (63 [4·3%] vs 53 [3·6%]; HR 1·19, 95% CI 0·83–1·72). Definite or probable stent thrombosis occurred in 33 (2·2%) and 23 (1·6%) patients, respectively (HR 1·45, 95% CI 0·85–2·47). Other secondary outcomes are reported in table 3. Bleeding events stratified according to high bleeding risk status are reported in appendix 2 p 20.

Table 1. Summary of demographic and baseline clinical characteristics

	Abluminus DES+ (SES) N=1514 (49·9%)	**XIENCE (EES) N=1518 (50·1%)**
Age, years, median (IQR)	68 (60–75)	68 (61–74)
Sex, female	462 (30·6%)	417 (27·5%)
Sex, male	1052 (69·4%)	1101 (72·5%)
BMI, kg/m2 median (IQR)	28 (25–32)	29 (26–32)
Region of enrolment: Europe	1166 (77·0%)	1174 (77·3%)
Region of enrolment: South America	206 (13·6%)	206 (13·6%)
Region of enrolment: Asia	142 (9·4%)	138 (9·1%)
Silent ischemia	277 (18.4%)	293 (19.4%)
Stable angina	680 (45.1%)	695 (45.9%)
Unstable angina	203 (13.5%)	192 (12.7%)
NSTEMI	348 (23.1%)	333 (22.0%)
Current smoker	242 (16·2%)	233 (15·5%)
Hypertension	1246 (82·6%)	1294 (85·5%)
Hypercholesterolemia	999 (66·2%)	1003 (66·3%)
Family history of CAD	393 (26·2%)	418 (27·8%)
Congestive heart failure	152 (10·1%)	132 (8·7%)
LVEF, %, median (IQR)	55% (50–60)	55% (50–60)
Chronic kidney disease	173 (11·5%)	148 (9·8%)
Liver disease	23 (1·5%)	34 (2·2%)
Peripheral artery disease	137 (9·1%)	132 (8·7%)
Prior stroke	79 (5·2%)	92 (6·1%)
Prior MI	315 (20·9%)	317 (21·0%)
Prior PCI	349 (23·1%)	319 (21·1%)
Prior CABG	71 (4·7%)	55 (3·6%)
Atrial fibrillation	177 (11·7%)	164 (10·8%)
Chronic lung disease	114 (7·6%)	115 (7·6%)

High bleeding risk	508 (33·5%)	500 (32·9%)
Diabetes type 1	49 (3·2%)	57 (3·8%)
Diabetes type 2	1396 (92·5%)	1397 (92·4%)
Medically treated diabetes	1446 (95·8%)	1463 (96·6%)
Insulin	530 (35·1%)	535 (35·3%)
Sensitizers	1090 (72·2%)	1086 (71·7%)
Secretagogues	371 (24·6%)	367 (24·2%)
GLP1 or GIP agonists	77 (5·1%)	93 (6·2%)
DPP-4 inhibitors	220 (14·6%)	205 (13·5%)
SGLT2 inhibitors	190 (12·6%)	190 (12·5%)
HbA1c, %	7·6 (6·9-8·8)	7·5 (6·7-8·6)
Serum Creatinine, mg/dl	0·9 (0·8-1·2)	0·9 (0·8-1·2)
eGFR, ml/min/1·73m2	74·0 (60·0-90·0)	75·8 (60·0-90·0)
LDL, mg/dL	85·5±37·8	88·2±37·8
Aspirin at discharge	1407 (92·9%)	1421 (93·6%)
P2Y12 inhibitor at discharge	1480 (97·8%)	1486 (97·9%)
Clopidogrel	1171 (77·3%)	1197 (78·9%)
Ticagrelor	237 (15·7%)	205 (13·5%)
Prasugrel	72 (4·8%)	84 (5·5%)
OAC	182 (12·0%)	184 (12·1%)

Data are n (%), median (IQR), mean ±SD· Group· ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BMI = body mass index; CABG = coronary artery bypass graft; CAD = coronary artery disease;

SES = sirolimus-eluting stent; EES = everolimus-eluting stent; DPP-4 = dipeptidyl peptidase-4; eGFR = estimated glomerular filtration rate; GIP = glucose-dependent insulinotropic polypeptide; GLP-1 = glucagon-like peptide-1; HbA1c = hemoglobin A1c; HDL = high-density lipoprotein; LDL = low-density lipoprotein; LVEF= left ventricle ejection fraction; MI = myocardial infarction; OAC = oral anticoagulant; PCI = percutaneous coronary intervention; P2Y12 inhibitors = adenosine diphosphate receptor antagonists; SGLT2 = sodium–glucose cotransporter-2

Table 2. Primary analysis and secondary outcomes at 12-month in the per-protocol population

Per-protocol Analysis (12-month)	**Abluminus DES+ (SES) N=1421**	**XIENCE (EES) N=1446**	**Hazard Ratio (95% CI)**	**ARD, % (95% CI)**	**NI margin, %**	**P value noninferiority**
TLF	137 (9.7%)	89 (6.2%)	1.59 (1.22 - 2.07)	3·5 (1·5–5·5)	3.0	0.683*
idTLR	67 (4.8%)	30 (2.1%)	2.31 (1.50 - 3.55)	2·7 (1·3–4·1)	2.8	0.441*
CV Death	41 (2.9%)	30 (2.1%)	1.39 (0.87 - 2.23)			
Target-vessel MI	73 (5.2%)	44 (3.1%)	1.70 (1.17 - 2.47)			
- Periprocedural Target-vessel MI	31 (2.2%)	30 (2.1%)	1.05 (0.64 - 1.74)			
- Spontaneous Target-vessel MI	42 (3.0%)	14 (1.0%)	3.09 (1.68 - 5.65)			

CV death, target vessel MI	106 (7.5%)	70 (4.9%)	1.55 (1.15 - 2.10)			
All-cause death	52 (3.7%)	48 (3.3%)	1.10 (0.74 - 1.63)			
Definite or probable stent thrombosis	27 (1.9%)	16 (1.1%)	1.73 (0.93 - 3.21)			
Stroke	17 (1.2%)	20 (1.4%)	0.86 (0.45 - 1.65)			
TVR (non-TLR)	16 (1.2%)	11 (0.8%)	1.48 (0.69 - 3.19)			
Bleeding BARC 2-5	50 (3.6%)	51 (3.6%)	1.00 (0.68 - 1.48)			

*Absolute risk differences are shown with two-sided 95% CIs. Non-inferiority was assessed using Farrington–
Manning with a one-sided α=0·025. NI = non-inferiority; PP = per-protocol; ARD = absolute risk difference; CI =
confidence interval; TLF = target lesion failure (CV death, target-vessel MI, or idTLR); idTLR = ischaemia-driven
target lesion revascularisation; CV = cardiovascular; MI = myocardial infarction;

Table 3. Primary and secondary outcomes at 24-month in the intention-to-treat population

Intention-to-treat Analysis (24-month)	**Abluminus DES+ (SES) N=1514**	**XIENCE (EES) N=1518**	**Hazard Ratio (95% CI)**
TLF	184 (12·4%)	142 (9·6%)	1·32 (1·06 - 1·65)
idTLR	95 (6·6%)	57 (3·9%)	1·71 (1·23 - 2·37)
CV Death	63 (4·3%)	53 (3·6%)	1·19 (0·83 - 1·72)
Target-vessel MI	87 (5·9%)	57 (3·8%)	1·54 (1·11 - 2·16)
- Periprocedural Target-vessel MI	34 (2.2%)	32 (2.1%)	1.07 (0.66 - 1.73)
- Spontaneous Target-vessel MI	53 (3.8%)	25 (1.7%)	2.24 (1.39 - 3.59)
CV death, target vessel MI	139 (9·3%)	105 (7·1%)	1·34 (1·04 - 1·73)
All-cause death	87 (5·9%)	93 (6·3%)	0·94 (0·70 - 1·26)
Definite or probable stent thrombosis	33 (2·2%)	23 (1·6%)	1·45 (0·85 - 2·47)
Stroke	26 (1·8%)	28 (2·0%)	0·93 (0·55 - 1·59)
TVR (non-TLR)	28 (2·0%)	26 (1·8%)	1·08 (0·63 - 1·84)
Bleeding BARC 2-5	62 (4·2%)	64 (4·4%)	0·98 (0·69 - 1·38)

CI = confidence interval; TLF = target lesion failure (CV death, target-vessel MI, or idTLR); idTLR = ischaemia-driven target lesion revascularisation; CV = cardiovascular; MI = myocardial infarction

Table 4. Landmark analysis of co-primary endpoints and its components from 0–12 months and 12–24 months of follow-up in the intention-to-treat population

Intention-to-treat Analysis	**Time Period**	**Abluminus DES+ (SES) N=1514**	**XIENCE (EES) N=1518**	**Hazard Ratio (95% CI)**
TLF	0–12 months	151 (10·1%)	100 (6·7%)	1·54 (1·19 - 1·98)
	12–24 months	33 (2·6%)	42 (3·2%)	0·81 (0·51 - 1·28)
idTLR	0–12 months	75 (5·1%)	36 (2·4%)	2·13 (1·43 - 3·16)

	12–24 months	20 (1·5%)	21 (1·5%)	0·98 (0·53 - 1·81)
CV Death	0–12 months	46 (3·1%)	33 (2·2%)	1·40 (0·90 - 2·19)
	12–24 months	17 (1·2%)	20 (1·5%)	0·85 (0·45 - 1·63)
Target-vessel MI	0–12 months	81 (5·4%)	49 (3·3%)	1·67 (1·17 - 2·38)
	12–24 months	6 (0·5%)	8 (0·6%)	0·77 (0·27 - 2·22)

TLF = target lesion failure (CV death, target-vessel MI, or idTLR); idTLR = ischaemia-driven target lesion revascularisation; CV = cardiovascular; MI = myocardial infarction

In a landmark analysis from month 12 to month 24 — where time zero was set at 12 months after randomisation and only patients who were alive and event-free at that point were included — event rates were low and did not differ between groups for idTLR (20 [1·5%] vs 21 [1·5%]; HR 0·98, 95% CI 0·53–1·81), and TLF (33 [2·6%] vs 42 [3·2%]; HR 0·81, 95% CI 0·51–1·28) (table 4, appendix 2 p 24); when formally comparing hazard ratios across time intervals, the differences between the 0–12 month HR and the 12–24 month landmark HR were statistically significant for both co-primary endpoints (idTLR, p=0·04; TLF, p=0·02). An additional 30-day landmark analysis (appendix 2 p 25) further highlighted the concentration of early events.

Subgroup analyses at 24 months for the two co-primary endpoints in the ITT population yielded results consistent with the primary analysis (appendix 2 pp 26-27). Available core-laboratory QCA data for patients with adjudicated idTLR at 24 months are presented in appendix 2 p 21; the most frequent lesion location was in-stent for both groups, whereas edge restenosis was relatively less common with Abluminus DES+. Given the competing risk of death for the co-primary endpoint idTLR, we also performed a sensitivity analysis using a Fine–Gray subdistribution hazards model (appendix 2 p 22); results were consistent with the primary analysis at both the 12-month and 24-month time points.

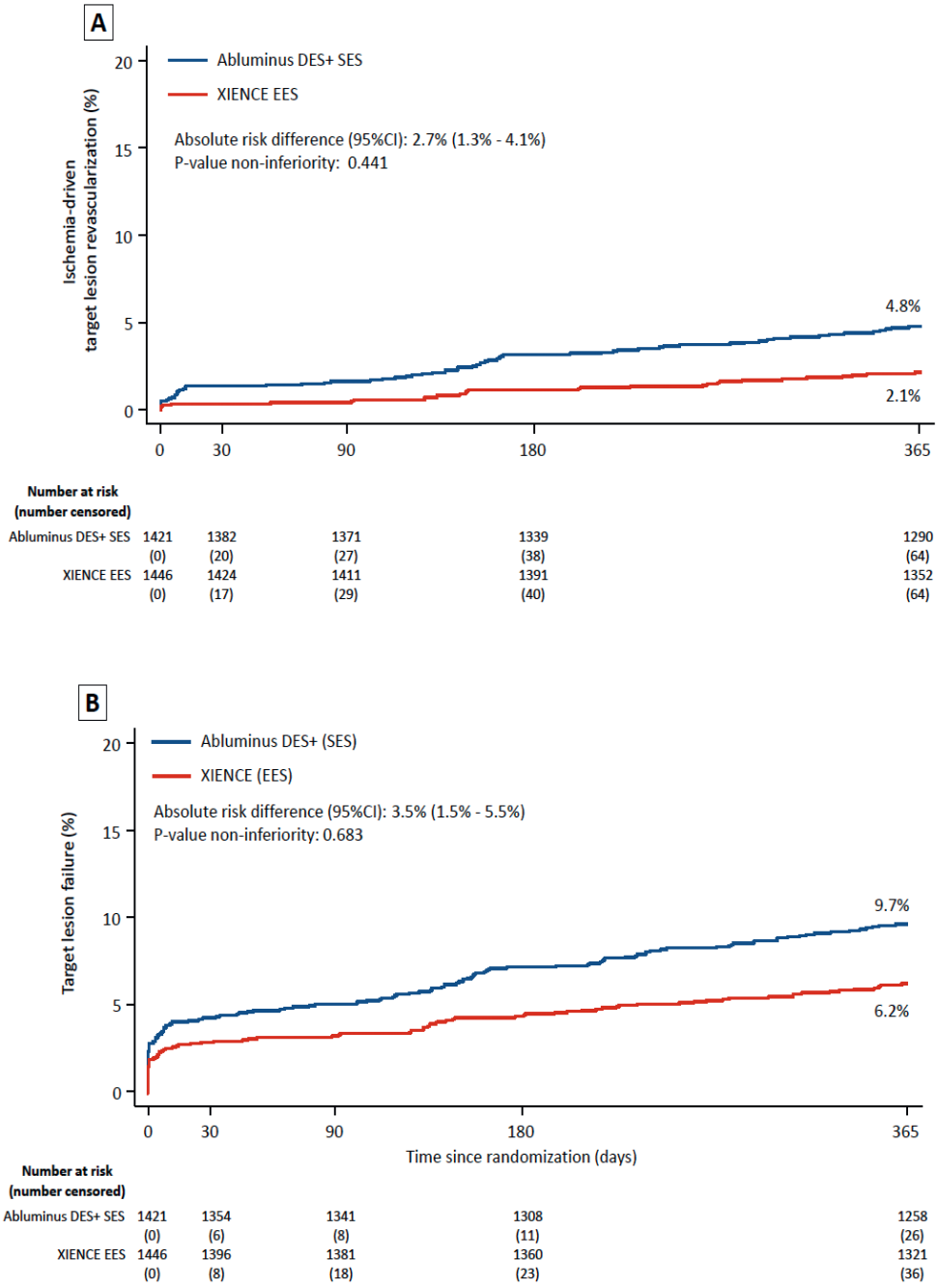


Figure 2. Kaplan–Meier curves for the co-primary efficacy endpoints ischemia-driven target lesion revascularization (idTLR) (Panel A) and target lesion failure (TLF) (Panel B) at 12 months in the perprotocol population

Discussion

In this large, international, randomised trial of more than 3000 patients with diabetes mellitus undergoing PCI, the Abluminus DES+ sirolimus-eluting stent did not meet the prespecified criteria for non-inferiority compared with the XIENCE everolimus-eluting stent for the two co-primary endpoints of ischaemia-driven target lesion revascularisation and target lesion failure at 12 months. Observed event rates were lower than anticipated, particularly in the control group, reflecting the good performance of the XIENCE platform. Abluminus DES+ stent was associated with higher rates of repeat revascularisation and TVMI, while there were no significant differences between groups in all-cause mortality, cardiovascular mortality, or stent thrombosis. Extended follow-up through 24 months confirmed these findings, with higher cumulative rates of idTLR and TVMI in the Abluminus DES+ arm. Landmark analyses indicated that the differences between groups were statistically significant before 1 year but not thereafter.

The design of the Abluminus DES+ aims to address the biological challenges of diabetes. The device incorporates a biodegradable polymer with sirolimus release, along with a coating on the exposed parts of the delivery balloon. This “hybrid” approach is intended to augment drug delivery to areas prone to in-stent restenosis, a phenomenon particularly aggressive in diabetes. In this trial, the Abluminus DES+ stent was compared with the XIENCE platform, which is characterized by a durable fluoropolymer and everolimus coating. The comparative efficacy of sirolimus- and everolimus-eluting stents in diabetic patients has yielded conflicting results. While some analyses reported similar outcomes between the two antiproliferative drugs[10],[11], others have suggested a potential advantage of everolimus[12],[13] in this population. In diabetic patients, the exaggerated smooth muscle proliferation and impaired endothelial repair are driven by upregulated PI3K/Akt/mTOR signaling and chronic inflammation[14]. Everolimus, with its higher lipophilicity and faster tissue penetration, may better suppress this hyperproliferative milieu and allow earlier endothelial recovery, whereas sirolimus’s slower uptake and prolonged retention may be less effective in counteracting the aggressive neointimal response of diabetes[15]. Nonetheless, large scale studies seem to indicate that diabetes

primarily increases the risk for repeat revascularization consistently across the spectrum of coronary artery disease complexity and irrespective of the stent platform[11].

Placed in the context of previous studies, the performance of the control arm in ABILITY exceeded its historical data[16]. Indeed, the XIENCE platform had demonstrated good outcomes in diabetic patients, with 2-year target lesion failure rates of 10·1% and target lesion revascularisation rates of 5·5% in a pooled analysis of SPIRIT II-IV and COMPARE trials[10]. Event rates were even lower in the TUXEDO trial, where the paclitaxel-eluting stent Taxus stent failed to achieve non-inferiority[17] and the primary endpoint of target vessel failure occurred in only 4·3% of patients treated with XIENCE stents at 2 years[17]. Recently, a small mechanistic study randomized 131 diabetic patients to Abluminus DES+ or XIENCE stents and used optical coherence tomography-derived neointimal volume at 9–12 months as the primary endpoint[14]. The trial did not demonstrate an advantage of Abluminus DES+ as there were no significant differences in neointimal volume, neointimal obstruction, or clinical outcomes between the two devices. In our study, the Abluminus DES+ did not provide further improvements beyond the benchmark set by the XIENCE platform, although its performance aligned with other contemporary stents tested in diabetic patients. In the SUGAR trial (n=1175), the polymer-free amphilimus (sirolimus + fatty acid) eluting stent Cre8 EVO was non-inferior and superior to the durable-polymer zotarolimus-eluting Resolute Onyx stent with respect to 1-year TLF, (7·2% vs 10·9%)[18]. However, at 2 years, differences between the stents were no longer statistically significant, with pooled TLF and TLR rates of approximately 11% and 7%, respectively[19]. Conversely, in ABILITY, landmark analyses from 12 to 24 months showed parallel event curves, indicating that the excess risk with Abluminus DES+ stent was confined to the first year and that outcomes thereafter were similar, excluding a persistent hazard. Of note, the SUGAR trial had a higher proportion of ACS and included STEMI patients, which may have influenced event rates; however, the late catch-up observed beyond 1 year is less likely related to clinical presentation. In contrast, although ABILITY was characterized by longer total stent length and a higher frequency of left-main and staged PCI—factors associated with complexity and ischemic risk—the study population was predominantly stable.

Several additional factors may help contextualize the findings of the present study. Nearly three-quarters of participating sites were new to Abluminus DES+, and more than 10% of patients did not receive implantation according to the instructions for use. The procedural requirement for prolonged balloon inflation (>45 seconds) to ensure uniform drug deposition may also have added technical difficulties, particularly in multivessel or complex lesions. To better clarify whether site volume and presence of a learning curve could have influenced outcome we performed multiple sensitivity analyses according to site volume and by excluding early cases. These analyses did not reveal meaningful differences from the primary results (data not shown). However, as the analyses were conducted at the site level, and operator-level data were not available, some degree of operator-specific experience cannot be fully excluded as a contributing factor. Additionally, this study found a higher incidence of TVMI with the Abluminus DES+, primarily driven by spontaneous rather than periprocedural events. The absence of a difference in periprocedural MI is reassuring, given the implantation technique of the Abluminus DES+, which requires longer balloon inflation times. Conversely, the increased rate of spontaneous MI diverges from previous observational studies with the Abluminus DES+, which reported lower event rates, and warrants further investigation[30],[31]. Mechanistically, potential explanations for the excess of spontaneous TVMI may relate to device-specific characteristics. Elution kinetic of Abluminus DES+ is designed to provide initial burst release in first 7 days and then sustain release for longer period beyond 90 days. While transient local inflammation or prothrombotic activity during polymer degradation cannot be excluded, preclinical studies of the Abluminus DES+ have shown complete early endothelialization and no evidence of increased inflammation[32]. On the other hand, the XIENCE's durable fluoropolymer coating is known to provide stable drug release and fluoropassivation properties associated with low thrombogenicity and enhanced endothelial healing[33–35]. Given the high and comparable adherence to DAPT, with similar antiplatelet type, duration, and cessation patterns across both groups with very few disruptions it is unlikely that differences in antiplatelet therapy exposure contributed meaningfully to the divergent outcomes observed. Overall, the observed imbalance in spontaneous TVMI should be interpreted with caution, as the absolute risk difference was approximately 2%, and the trial was not powered for

individual ischemic endpoints; thus, a chance finding rather than a true device-related effect cannot be excluded.

Beyond device-specific considerations, the results of this study highlight broader lessons about PCI in diabetes. Patients with diabetes remain at high risk of adverse outcomes even with the newest DES platforms, with rates of TLF exceeding 9% at 2 years. The FREEDOM trial established CABG as superior to PCI in diabetic patients with multivessel disease, yet many of those remain poor surgical candidates due to anatomical or clinical considerations, in addition to patient preference. Continuous innovation in DES design, optimisation of antithrombotic therapy, and adjunctive strategies to address diffuse atherosclerosis remain essential. In this context, this trial underscores the ongoing unmet need to reduce residual ischaemic risk in diabetic patients. New technologies such as drug-coated balloons may provide an alternative strategy for selected lesions by avoiding stent implantation, potentially reducing the burden of neointimal proliferation and late adverse events[36].

This study has limitations. First, since the operators were aware of the study device assignment, this may have introduced bias; however, the clinical team performing follow-up remained blinded, as did the independent clinical events committee responsible for endpoint adjudication. Second, the use of intravascular imaging was not systematically collected; because imaging use was left to operator discretion, we cannot exclude a potential influence of differential imaging guidance on outcomes, although such use was likely balanced by randomisation. Third, although the study was adequately powered for the prespecified non-inferiority analyses, lower-than-expected event rates were observed at 12 months. Fourth, the trial was not powered for mortality or other endpoints. Finally, follow-up was limited to 24 months, and longer observation might be needed to determine whether event rates remain stable over time.

In summary, to our knowledge, the ABILITY Diabetes Global trial is the largest randomised trial to date comparing two contemporary drug-eluting stent platforms in patients with diabetes undergoing PCI. At 12 months, the Abluminus DES+ sirolimus-eluting stent did not meet criteria for non-inferiority versus the XIENCE everolimus-eluting stent for the two co-primary endpoints of ischaemia-driven target lesion revascularisation and target lesion failure. Results were primarily driven by a higher

incidence of repeat revascularisation and target-vessel myocardial infarction. Although 24-month findings were consistent, event rates beyond the first year were low and comparable between groups. There were no differences in mortality or stent thrombosis between the two devices. These findings underscore the persistent residual risk in patients with diabetes and highlight the ongoing need for innovation in stent technology, procedural optimisation, and adjunctive pharmacotherapies to further reduce ischaemic risk in this population.

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Chapter 14

Provisional Strategy for Left Main Stem Bifurcation Disease

A State-of-the-Art Review of Technique and Outcomes

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Abstract

Left main coronary artery (LMA) disease jeopardizes a large area of myocardium and increases the risk of major adverse cardiovascular events. LMCA disease is found in 5% to 7% of all diagnostic coronary angiographies, and more than 80% of the patients enrolled in recent large randomized controlled left main trials had distal left main bifurcation or trifurcation disease. Emerging clinical evidence from prospective all-comer registries and randomized trials has provided a solid basis for percutaneous coronary intervention as a treatment option in selected patients with unprotected LMCA disease; however, to date, no uniform recommendations as to optimal stenting strategy for LMCA bifurcation lesions exist. This review provides an overview of provisional stenting technique and escalation to 2-stent strategies in LMCA bifurcation lesions. Data from randomized controlled trials and registries are reviewed. Technical characteristics of optimal provisional LMCA stenting technique and angiographic and intravascular determinants of escalation are also summarized

Introduction

More than 80% of the patients enrolled in recent large randomized controlled trials (RCTs) on left main coronary artery (LMCA) disease had distal disease.[1] Clinical evidence from prospective all-comer registries and randomized trials has provided a solid basis for percutaneous coronary intervention (PCI) as a valuable treatment option in unprotected LMCA disease.[2] [3] Yet, to date, no uniform recommendations as to optimal stenting strategy for LMCA bifurcation lesions exist.

The conventional mantra of a single stent for all bifurcation lesions has recently been challenged, especially for LMCA lesions.[4] [5] Continued iterations in drug-eluting stent (DES) platforms, growing adoption of intracoronary imaging, bifurcation simulation, and tailored antiplatelet therapy may potentially improve clinical outcomes. Also, operator experience (defined as 15 left main PCIs per year; mean 25 per year) may affect procedural and clinical outcomes in left main PCI.[6]

A single stent should suffice in isolated ostial or mid-shaft LMCA disease. True LMCA bifurcation lesions appear more challenging in terms of stent strategy selection. Recent RCTs support elective 2-stent techniques or a stepwise layered approach for true

bifurcation LMCA disease.[4] [5] This review summarizes the provisional LMCA PCI technique, the incidence and determinants of escalation to a 2-stent strategy, and how outcomes compare with an upfront 2-stent approach.

HIGHLIGHTS

Percutaneous coronary intervention (PCI) with drug-eluting stents (DES) is an evidence-based treatment option for left main bifurcation disease.

Intravascular imaging should be used to complement conventional angiography for the assessment of left main stem lesions and to guide provisional stent strategies.

Future research should focus on individualized approaches to optimize treatment strategies according to distal left main bifurcation phenotypes.

LMCA ANATOMY AND CLASSIFICATION

LMCA disease is rarely focal (Supplemental Tables 1 and 2). In all bifurcation lesions, atherosclerosis tends to localize at the outer walls of coronary arteries, with less involvement of the flow divider.[7] Intravascular ultrasound (IVUS) data have confirmed that plaques extend from the LMCA into the proximal left anterior descending artery (LAD), into the proximal left circumflex artery (LCx), or both branches in more than 90%, 66%, and 62% of cases, respectively. Isolated plaque at the ostia of the daughter branches occurred in 9% of LADs and 17% of LCxs.[8]

LMCA undergoes positive remodeling to preserve lumen dimension in response to plaque deposition, whereas the ostia of the LAD and LCX more often demonstrate negative remodeling.[9] LMCA lesions have less plaque burden, lower volume of necrotic core, and lower prevalence of thin-cap fibroatheroma as compared with LAD lesions.[10]

A greater plaque burden extending into all LMCA bifurcation segments may change hemodynamic flow patterns and promote intimal hyperplasia after stent implantation and has been associated with a significantly higher risk of 3-year target lesion revascularization compared with partial bifurcation involvement (24.9% vs 8.3%; adjusted HR: 2.84; 95% CI 1.43–5.64; P=0.003).[11] This effect was observed in the context of 1- or 2-stent techniques and in Medina 1,1,1 and 0,1,1 lesions (20.7% vs 26.8%; P=0.57).

LMCA disease is rarely focal, undergoes positive remodeling, and plaque features differ from other coronary locations.

FREQUENCY OF PROVISIONAL LMCA PCI IN REGISTRIES AND PCI VS CORONARY ARTERY BYPASS GRAFTING TRIALS

Secular trends in the characteristics and long-term outcomes of unprotected LMCA disease using real-world clinical experience from the IRIS-MAIN registry showed an increased rate of the simple 1-stent crossover technique over time.[12]

In the DELTA-2 study—the largest "all-comers" LMCA PCI registry with second-generation DES (n=3,986) covering 2006–2015—a single-stent strategy was chosen in almost 80% of cases, with 84% of lesions located at the distal LMCA.[1]

Combined data from the KOMATE multicenter registry and the COBIS II registry examined 1,353 distal bifurcation LMCA lesions. A single-stent strategy was adopted in 71.4% of patients, and up to 83.0% received current-generation DES.[13]

Six RCTs have compared PCI with CABG for LMCA disease, but only two—EXCEL and NOBLE—were conducted in the era of second-generation DES.[2] [12–16] Distal LMCA lesion rates ranged from 58% in the LE MANS trial to 81% in the EXCEL and NOBLE trials.[14] [16] [17] Provisional stenting was reported in 30%, 46.3%, 61.5%, 65%, and 63.2% in the study from Boudriot et al.[15] in the PRECOMBAT (Premier of Randomized Comparison of Bypass Surgery Versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease), SYNTAX (Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery), EXCEL and NOBLE trials, respectively.[17–20] No data were provided on provisional or 2-stent strategy rates for the LE MANS trial (Figure 1).[16]

Registry data demonstrate an increased adoption rate of provisional stenting over time. Provisional stenting rates in RCTs comparing PCI vs coronary artery bypass grafting for LMCA treatment range from 30% to 65%.

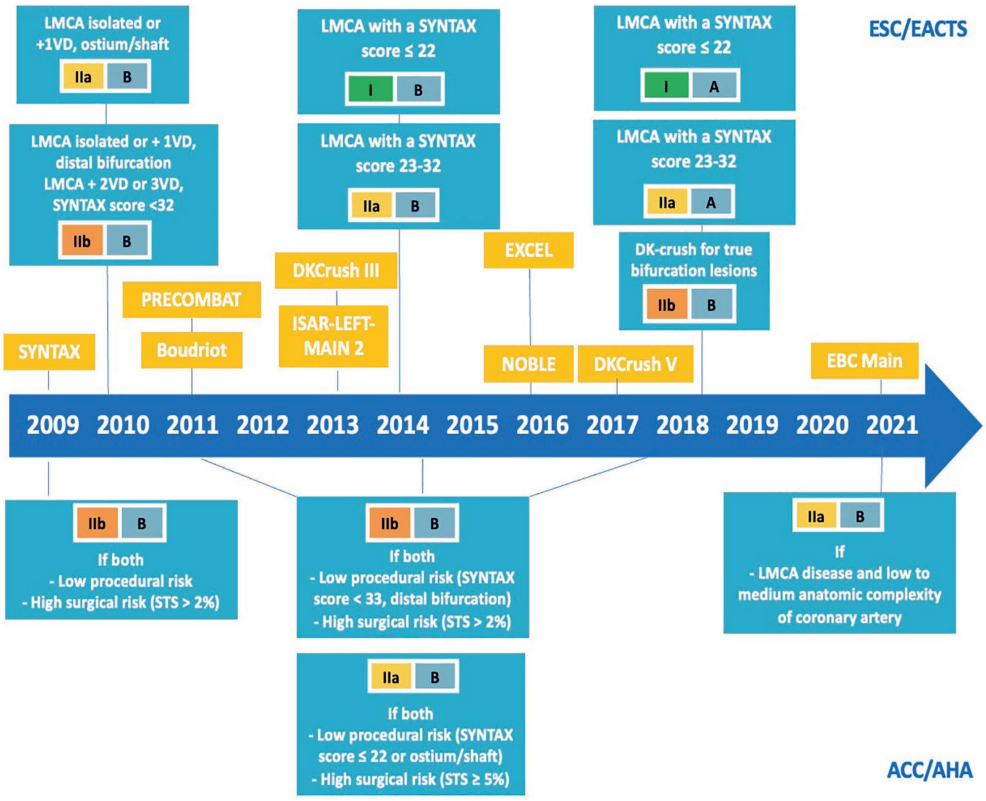


FIGURE 1 Timeline of Trials and Guidelines Over LMCA Treatment

Recommendations for LMCA PCI in patients with chronic coronary syndrome according to European and American guidelines. Landmarks RCTs comparing PCI vs CABG for LMCA disease, PCI strategies and second generation DES comparison for LMCA treatment are also displayed. DKCrush III = Double Kissing Crush III; DKCRUSH-V = Double Kissing Crush V; EACTS = European Association for Cardio-Thoracic Surgery; EBC MAIN = European Bifurcation Club Left Main Coronary Stent; ESC = European Society of Cardiology; EXCEL = Evaluation of XIENCE Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization; ISAR-LEFT-MAIN 2 = Interventional Research Incorporation Society-Left MAIN Revascularization-LEFT-MAIN 2; LMCA = left main coronary artery; NOBLE ¼ Nordic- Baltic-British Left Main Revascularization Study; PRECOMBAT = Premier of Randomized Comparison of Bypass Surgery Versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease; STS = Society of Thoracic Surgeons; SYNTAX =Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery; VD ¼ vessel disease;

SUBSEQUENT STENT IMPLANTATION RATES WITH THE PROVISIONAL TECHNIQUE DATA FROM LMCA REGISTRIES.

The latest European guidelines on myocardial revascularization recommend provisional single-stent strategy for non-LMCA bifurcation lesions.[21] Whether and when side branch

(SB) treatment is necessary during provisional treatment and, the optimal technique to select when a second stent is required, remain operator dependent. LMCA and complex bifurcation lesions add to coronary artery disease complexity per American College. of Cardiology/American Heart Association/Society for Cardiovascular Angiography and Interventions guidelines for myocardial revascularization.[22],[23] Registries have been inconsistent in reporting LMCA bifurcation complexity, PCI strategies, and the need for second stent implantation in the context of a provisional technique (Tables 1 and 2). The escalation rate from provisional to a 2-stent strategy was only 9.7% in the FAILS-2 (Failure in Left Main Study with the second generation stents) substudy, investigating second generation DES, as compared with 28% in the observational FRIEND (French multicentre registry for stenting of unprotected LMCA stenosis) registry where patients were treated with early generation DES.[28],[26]

A recent retrospective registry compared 1- and 2-stent strategies for patients with true LMCA bifurcation lesions among 4,000 LMCA bifurcation lesions (928 classified as true LMCA bifurcation lesions) in a time window from 2004 to 2015.[31] Lesion complexity was classified according to the DEFINITION (Definitions and impact of complEx biFurcation lesIons on clinical outcomes after percutaNeous coronary IntervenTIOn using drug-eluting steNts) criteria.[32] Interestingly, operators' choice of treatment with 1 or 2 stents was irrespective of the LMCA lesion complexity, reflecting the need for more clinical guidance on lesion complexity assessment, risk prediction, and stent strategy selection.[33] As in most retrospective studies, patients who received a second stent due to unplanned deterioration following provisional stenting were simply classified into the 2-stent cohort, precluding additional insights into rates of crossover and scenarios for additional stenting.

Registries have been inconsistent in reporting LMCA bifurcation complexity, the upfront PCI strategy, and need to escalate from a provisional to a 2-stent strategy.

TABLE 1 Escalation Rate From 1- to 2-Stent Strategies

Study or First Author (Year)	Design	n	LM (%)	Provisional Stenting (%)	Escalation Rate (%)	Bailout 2-Stent Technique	T or TAP Use	Culotte or Crush Used (%)	Type of Stent

							d (%)		
SMART-STRATEGY (2016)[24]	RCT Single center	258	44	100	18.2	NR	NR	NR	SES (46.9), EES (31.3), Others (21.9)
DKCRUSH-V (2017)[5]	RCT Multicenter	482	100	49.7	47.1	100	0	Xience V (60.3), Endeavor Resolute (12.4), Firebird 2 (27.3)	
EXCEL subanalysis (2018)[18]	Subanalysis of RCT	529	100	65.0	15.7	77.8	14.8	Xience (100)	
DEFINITION II (2020)[4]	RCT	653	29	49.7	22.5	64.4	35.6	Firebird-2 or Firehawk (NR), EXCEL (NR), BuMA (NR), Xience or Xience Prime (NR), Endeavour Resolute or Endeavour Integrity (NR)	
EBC MAIN (2021)[25]	RCT	467	100	49.2	22.0	64.4	11.0	Onyx (100)	
FRIEND (2011)[26]	Prospective observational study	100	100	75	28.0	NR	NR	Taxus (100)	
Burzotta et al (2012)[27]	Prospective observational study	150	15	100	8.3	100	NR	CypherSelect (50.0), Xience V (50.0)	
FAILS-2 substudy (2017)[28]	Retrospective observational study	377	100	57.3	9.7	14.3	80.2	BES (11.6), EES (79.2), ZES (7.9)	
Zimarino et al (2019)[29]	Prospective observational study	1252	23.0	79.8	5.2	69.5	13.6	NR	

Continued

Study or First Author (Year)	Study or First Author (Year)	Study or First Author (Year)	Study or First Author (Year)	Study or First Author (Year)
SMART-STRATEGY (2016)[24]	97.7	NR	NR	TVF (cardiac death, spontaneousMI, or TVR) occurred in 11.7% of the conservative group (bailout stenting for SB stenosis >75%) vs 20.8% of the aggressive group (bailout stenting for SB stenosis >50%) (P . 0.049) at 3 y.
DKCRUSH-V (2017)[5]	41.7	78.9 (provisional), 99.6 (2 stents)	99.0	TLF within 1 y occurred in 10.7% of the patients assigned to PS and in 5.0% of the patients assigned to DK crush (HR: 0.42; 95% CI: 0.21-0.85; P . 0.02).
EXCEL subanalysis (2018)[18]	76.2	54.9 (provisional), 84.3 (2HR)	NR	MACE (death, MI, or stroke) was significantly lower in patients treated with the provisional vs planned 2-stent strategy (14.1% vs 20.7%; adjusted HR: 0.55; 95% CI: 0.35-0.88; P . 0.01) at 3 y.
DEFINITION II (2020)[4]	27.7	27.8 (provisional)a, 99.3 (2HR)	90.1	TLF occurred in 11.4% and 6.1% of patients in the provisional and 2-stent groups, respectively (HR: 0.52; 95% CI: 0.30-0.90; P . 0.019) at 1 y.
EBC MAIN (2021)[25]	39.0	89.0 (provisional)b, 93.0 (2 stents)	82.5	The primary endpoint (death, MI, or TLR at 12 mo) occurred in 14.7% of the stepwise provisional group vs 17.7% of the systematic dual stent group (HR: 0.8; 95% CI: 0.5-1.3; P . 0.34).
FRIEND (2011)[26]	6.6	93.0	NR	Post-PCI myocardial ischemia was inducible in 17 (34.7%) patients of group OR vs 10 (90.9%) patients of group SR (P . 0.0007).
Burzotta et al (2012)[27]	NR	63.3	NR	Post-PCI myocardial ischemia was inducible in 17 (34.7%) patients of group OR vs 10 (90.9%) patients of group SR (P . 0.0007).
FAILS-2 substudy (2017)[28]	24.7	NR	NR	MACEs (all-cause death, MI, and TLR) were not significantly different between groups (MACE at 3 y; provisional stenting 28.1% vs elective 2-stent strategy 28.9%; adjusted P . 0.99).
Zimarino et al (2019)[29]	24.5	49.1	53.6	5.4% of MACE (cardiac death, MI excluding type 4a or ST) at 13 mo.

[a]After first stent. FKI was performed in 95.9% of the lesions treated with a second stent in the provisional group. bAfter first stent. FKI was performed in all lesions treated with a second stent in the provisional group.

BES = biolimus-eluting stent(s); DEFINITION II = Definitions and impact of complEx biFurcation lesIons on clinical outcomes after percutaNeous coronary IntervenTIOn using drug-eluting steNts; DKCRUSH-V = Double Kissing Crush V; DS = diameter stenosis; EBC MAIN = European Bifurcation Club Left Main Coronary Stent; EES = everolimus-eluting stent(s); EXCEL = Evaluation of XIENCE Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization; FAILS-2 = Failure in Left Main Study with the second generation stents; FKI = final kissing inflation; FRIEND = French multicentre RegIstry for stenting of uNprotecteD LMCA stenosis; LM = left main; MACE = major adverse cardiovascular event(s); MI = myocardial infarction; NR = not reported; OR = optimal result; PCI = percutaneous coronary intervention; POT = proximal optimization technique; PS = provisional stenting; RCT = randomized controlled trial; SB = side branch; SES = sirolimus-eluting stent(s); SMARTSTRATEGY = Smart Angioplasty Research Team-Optimal Strategy for Side

Branch Intervention in Coronary Bifurcation Lesions; SR = suboptimal result; ST = stent thrombosis; TLF = target lesion failure; TVF = target vessel failure; TVR = target vessel revascularization; ZES = zotarolimus-eluting stent(s).

TABLE 2 Overview of Different Definitions for Suboptimal LCx Result

Study or First Author (Year)	Design	n	LM (%)	True Bifurcation Lesions (%)	Stenting Strategy	Suboptimal LCx Result Requiring Any Further Intervention (%)	Modality of Assessment	Definitions of Suboptimal LCx Results
SMART-STRATEGY (2016)[24]	RCT	258	44.0	66.0	Provisional. bailout TAP Conservative vs aggressive	47.0 (whole cohort)	Angiography	DS >75% (conservative strategy) DS >50% (aggressive strategy)
DKCRUSH-V (2017)[5]	RCT	482	100	100	Provisional vs DK crush	47.0 (provisional group)	Angiography	TIMI flow grade <3 or DS >75% or dissection type >B
EXCEL subanalysis (2018)[18]	Subanalysis of RCT	529	100	34.3 (PCI group)	Provisional. bailout 2 stents (65.0) vs elective 2 stents (35.0)	22.0 (provisional group)	Angiography Intravascular ultrasound Fractional flow reserve	Dissection $grade B or TIMI <3 or DS >70% angiographic MLA #4.0 mm2 with PB >60% #0.80
DEFINITION II (2020)[4]	RCT	653	29.0	100	Provisional vs 2 stents	28.0 (provisional group)	Angiography	SB occlusion or type B/C dissection or TIMI flow grade <3
EBC MAIN (2021)[25]	RCT	467	100	100	Stepwise provisional vs elective 2 stents	22.0 (provisional group)	Angiography	TIMI flow grade <3 or severe (>90%) ostial pinching or threatened SB closure or dissection type >A

Burzotta et al (2012)[27]	Prospective observational study	150	15.0	43.0	Provisional MB stenting . bailout TAP technique	18.0 (whole cohort)	3D quantitative coronary analysis	SB lumen area <50% of SB reference area
FAILS-2 substudy (2017)[28]	Retrospective observational study	377	100	100	Provisional vs elective 2 stents	9.7 (provisional)	Angiography	Major dissections or compromised flow
Lee et al (2019)[30]	Retrospective study	83	100	0	Provisional MB stenting	16.8	Fractional flow reserve	≤0.80

DATA FROM RANDOMIZED TRIALS

In RCTs, the frequency of escalation from a 1- to a 2-stent bifurcation approach is unclear and varies from 5% up to almost 50% in true bifurcation LMCA lesions.[5,25,34] Among RCTs comparing PCI with second-generation DES vs coronary artery bypass grafting in the setting of LMCA, only the EXCEL trial reported the rate of additional stenting.[18] Among the 344 patients undergoing a planned provisional 1-stent technique, treatment of the SB was performed frequently (70.6%), and most commonly with balloon angioplasty alone. A SB stepwise stenting approach was required in 15.7% of all the provisional cases, and more frequently for LCx ostial lesion diameter stenosis ≥50% compared with diameter stenosis <50% (28.6% vs 12.1%). As expected, provisional stenting was preferably (but not exclusively) adopted for patients with noncomplex bifurcation disease. A planned 2-stent technique was preferred in cases of ostial involvement of both SBs. The adoption of provisional stenting in 42% of the cases with core laboratory–confirmed SB ostial involvement and, on the contrary, the selection of a 2-stent strategy in 23% of patients without SBs ostial involvement reflects challenges in the angiographic assessment of LMCA disease, even at experienced sites.[18]

The double kissing CRUSH-V trial compared provisional stenting with double kissing crush technique (n = 482) while EBC MAIN (European Bifurcation Club Left Main Coronary Stent) compared a stepwise provisional stenting strategy to a systematic 2-stent technique (n = 467) in true distal LMCA bifurcation stenosis.[5,34] Notably, the rate of subsequent stent implantation in the EBC MAIN was less than one-half of that in the DKCRUSH-V trial (Table 1). More extensive SB disease, lower rate of kissing balloon

inflation (KBI), and different definitions for a suboptimal LCx result in the DKCRUSH-V trial vs EBC MAIN might have determined the lower threshold for second stent placement with the provisional technique.[25],[32]

The rate of second stent implantation after provisional stenting extensively varies in RCTs, likely reflecting different selection criteria within the individual trials, discordant definitions of suboptimal SB results, and varying operator preference.

RISK FACTOR FOR SB COMPROMISE

The dynamic variability of bifurcation anatomy during the PCI procedure makes bifurcation lesion interventions technically challenging, which requires a good strategy planning and also a flexible approach. From an angiographic perspective, baseline SB diameter stenosis, diameter ratio of main branch/SB, and angulation, appear as the most relevant predictors of SB occlusion after main branch stenting for bifurcation lesions in general (Central Illustration).[35] The different angles that characterize the LMCA bifurcation and its SBs may have a profound impact on the ability to access and maintain patency with LMCA stenting.

However, the impact of pre-PCI bifurcation angle on later clinical outcomes remains controversial.[36],[37] Another debatable issue is whether the implantation of 1 or 2 stents would considerably modify the bifurcation angle and consequently affect clinical outcomes.

In a subanalysis of the SYNTAX trial, LMCA stenting caused a significant decrease in the mean angle between the LMCA and LAD (Δ = -4.5; P < 0.001) but not between the LMCA and LCx (Δ = 2.0; P = 0.064). Interestingly, in the context of a Y-shaped LMCA (with an angle between LMCA and LAD <70°), the opposite phenomenon was observed. The rates of major adverse cardiovascular events did not differ across tertiles of pre-PCI LMCA-LAD angles values (<82°, 82–106°, ≥107°; P = 0.74). However, the implantation of 2 stents resulted in lower event rates for the patients with narrower pre-PCI angles between LMCA and LAD.[37]

Provisional stenting of a distal LMCA followed by the proximal optimization technique (POT), with or without subsequent KBI, might induce geometrical changes of the SB ostium, which may visibly impress as the SB is compromised. The major geometrical

changes include straightening of the main branch with subsequent stretching of the SB and displacement of the carina toward the SB.[22,38,39] However, this angiographic SB compromise is rarely accompanied by a hemodynamically significant stenosis, as confirmed by preserved fractional flow reserve (FFR) in the SB.[40] In general, the degree of stenosis on coronary angiography poorly correlates with morphological and functional assessment by means of IVUS minimal lumen area or FFR post PCI.[41]

IVUS studies have investigated the likelihood of "escalation" from a provisional to a 2-stent strategy in distal LMCA bifurcation lesions. By IVUS analysis, the minimal lumen area of the LCx ostium decreased from 5.4 mm^2 to 4.0 mm^2 after (provisional) crossover stenting ($P < 0.001$). The smaller minimal lumen area in combination with enhanced vessel eccentricity and unchanged plaque mass suggest carina shift as the main mechanism of this acute lumen loss in the LCx.[8,39,40] KBI could correct this carina shift and restore normal bifurcation architecture. However, carina shift is a focal phenomenon and rarely associated with functional flow compromise in the LCx.[40]

When the LCx ostium is jeopardized with angiographic evidence of compromised flow (Thrombolysis In Myocardial Infarction flow grade <3) or new hemodynamically significant stenosis of the LCx ostium (with a FFR <0.80), a second stent should be placed.[42] However, the need to proceed with an additional stent for a suboptimal result at the ostium of the LCx after crossover provisional LMCA stenting is not standardized and is operator dependent (Table 2).

Upgrade from provisional to a 2-stent strategy may include T stenting/T and small protrusion stenting, culotte, or reverse crush techniques. T stenting/T and small protrusion stenting may arguably be the easiest stepwise 2-stent strategy and is favored in case of a bifurcation angle close to 90°. LCx stent implantation should be performed with minimal LMCA protrusion in order to limit neocarina formation and avoid incomplete ostium coverage. Despite limited randomized data, the culotte technique may be attractive in the context of an acute bifurcation angle and when the LCx size is comparable with distal LMCA size but requires multiple steps and creates double stent layers in the LMCA. The reverse (mini-)crush technique, depending on the level of protrusion of the SB stent into the main branch, may be applied to all bifurcation angles with a caliber mismatch.

between LMCA and LCx and also ensures complete bifurcation coverage.[43] Switching from provisional stenting to a 2-stent strategy may be challenging in the presence of proximal tortuosity, severe calcifications, and complex SB angulation.[44] Acute occlusion of the LCx, following LMCA bifurcation PCI, usually results in a large amount of ischemia and LMCA periprocedural complications that are potentially life-threatening.[33]

Angiographic predictors of escalation from provisional to 2 stent strategy are bifurcation angle, lesion complexity, and geometrical changes post-PCI. Upgrade from provisional to a 2-stent strategy may entail T stenting/T and small protrusion, culotte, or reverse crush techniques.

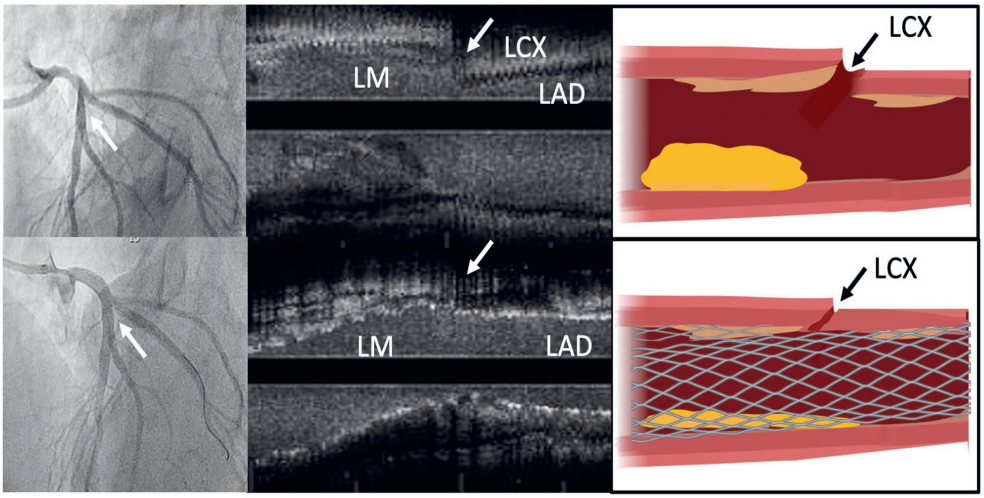


FIGURE 2 Representation of Carina Shift After Crossover Stenting

Angiographic (left) and intravascular ultrasound (right) representation of left main bifurcation prestenting (middle, top) and poststenting (middle, bottom). Carina shift after crossover stenting is indicated by the white arrows. LAD . left anterior descending artery; LCX . left circumflex artery; LM . left main artery.

PROVISIONAL VS 2-STENT OUTCOMES

Nonrandomized data consistently demonstrated worse outcomes with a 2-stent strategy in the LMCA setting.[13,41] However, the "keep it simple" 1-stent recommendation as the "standard" approach for the treatment of LMCA bifurcation lesions was challenged by recent randomized trials on 2-stent strategies for complex bifurcation lesions but

conversely was reinforced by EBC MAIN, which promoted a provisional stepwise approach.[4–6]

In the DKCRUSH-V trial, the primary endpoint of target lesion revascularization was lower for the double kissing crush vs provisional strategy at 1 year (5.0% vs 10.7%; P ¼ 0.02) and 3 years of follow-up (8.3% vs 16.9%; P ¼ 0.017).[5,34] Whether the better outcomes in the double kissing crush arm were driven by the systematic 2-stent approach per se or by the superiority of double kissing crush over T and small protrusion technique remains unanswered. Of note, the benefit of double kissing crush seemed more evident in patients who required escalation from the provisional to T stenting/T and small protrusion technique. Moreover, the unusually high reported rate of stent thrombosis in the provisional SB stenting arm (3.3% at 1 year), the extent of SB stenosis, and the involvement of selected highly experienced operators limit the generalizability of its findings in contemporary clinical practice.[34] substudy provided a different perspective on distal LMCA treatment technique, likely more reflective of an everyday clinical setting.[18]

The DEFINITION II trial randomized 653 patients with complex bifurcation lesions (including 30% LMCA bifurcations) to a routine 2-stent strategy or to a provisional stenting approach.[31] Double kissing crush and culotte techniques were highly recommended per protocol and were performed in 77.8% and 17.9% patients, respectively. The 1-year target lesion failure rate was lower in the planned 2-stent strategy cohort (6.1% vs 11.4%; P ¼ 0.019), mainly driven by fewer target vessel myocardial infarctions and clinically driven target lesion revascularizations. No differences in terms of stent thrombosis were found, and the higher rate of target vessel myocardial infarctions might be explained by a higher SB restenosis rate.

In EBC MAIN, randomizing 467 patients with true LMCA bifurcation lesions, the 1-year incidence of the primary composite endpoint of death, myocardial infarction, and target lesion revascularization occurred in 14.7% of the provisional arm vs 17.7% in the upfront 2-stent arm (HR: 0.8; 95% CI: 0.5-1.3). The upfront well-defined methodology and the adoption of different 2 stent techniques (albeit the double kissing crush technique was under-represented in the 2-stent arm) provided support for the safety of a stepwise strategy for treating selected true distal LMCA bifurcation stenosis.[25] Limited sample size

(n = 467) and lower-than-expected event rates may raise concerns over the risk of type II error for these neutral results.

It should be acknowledged that bifurcation lesion characteristics and PCI techniques vary widely among RCTs. Despite potential differences in measurement methodologies, mean SB lesion length was 16 mm in DKCRUSH-V vs 7 mm in EBC MAIN while the respective SYNTAX scores were 31 (DKCRUSH-V) vs 23 (EBC MAIN). In all the previously mentioned trials, when a 2-stent technique was performed, final kissing inflation was per protocol strongly recommended.[4–6,18,25]

Moreover, the use of the POT technique was higher in the 2-stent strategy interventions as compared with provisional stenting group in both DKCRUSH-V and DEFINITION II trials, despite strong recommendations for both treatment arms (Table 1).

Nonrandomized data have demonstrated worse outcomes with a 2-stent strategy in LMCA PCI.

In the DKCRUSH-V and DEFINITION II trials, which enrolled patients with more extensive SB disease, the double kissing crush technique yielded lower rate of target lesion revascularization than provisional strategy at short and mid-term follow-up.

The EBC MAIN trial provided support for the safety of a stepwise strategy approach for treating true distal LMCA bifurcation stenosis with less complex bifurcation features.

OPTIMAL PROVISIONAL LMCA STENTING TECHNIQUE

ANATOMY/ANGIOGRAPHY.

LMCA with nonsignificant ostial LCx stenosis of <50%, a nondominant left coronary system, or a small LCx caliber favors a 1-stent approach.

Completing provisional stenting with a POT may optimize stent apposition, restore the fractal geometry of the vessels, and facilitate SB wiring through the distal cell.[45] The stepwise layered provisional approach, as described and adopted by EBC MAIN, suggests assessment of the results with every step of the procedure.[13] After POT and in case of a suboptimal SB result (>75% diameter stenosis or TIMI flow grade <3), the SB should be rewired and KBI performed using noncompliant balloons. At this stage, re-POT is advisable in order to reduce the eccentricity index. Further stent implantation, using the T stenting/T and small protrusion or culotte technique, should be performed only in case

of SB TIMI flow grade <3, severe ostial compromise of the SB (>90%), threatened SB closure, or SB dissection >type A. Following second stent implantation, repeat KBI and re-POT are strongly recommended to restore bifurcation geometry.

Implantation of the LMCA stent across the bifurcation should be optimized by a POT to restore the fractal geometry of the bifurcation. Specific clinical and angiographic criteria have been proposed to inform the need for SB stent implantation among cases initially intended for a provisional strategy.

IVUS/OPTICAL COHERENCE TOMOGRAPHY.

Angiographic assessment of the LMCA is limited by its 2-dimensional nature. As endorsed in both European Society of Cardiology guidelines on myocardial revascularization and the American College of Cardiology/American Heart Association/Society for Cardiovascular Angiography and Interventions guideline for coronary artery revascularization, IVUS has a Class IIa recommendation for the assessment of LMCA lesion severity.[21],[23]

Intravascular imaging provides unique insights into the extent and distribution of coronary atherosclerosis, plaque composition and lesion morphology, mechanisms, and complications of stent implantation at the LMCA bifurcation (Figure 3). Both IVUS and optical coherence tomography can identify the preprocedure “spiky” carina or “eyebrow” sign at the origin of the SB as a predictor of carina shift and SB compromise after LMCA stenting (Figure 2). Based on IVUS results, plaque features are likely to have a greater influence on plaque shift than previously suggested by angiographic studies. In LMCA Stenosis with ostial LCx angiographic diameter stenosis <50%, an LCx poststenting FFR <0.80 can be predicted by a pre-PCI LCx minimal lumen area <3.7 mm^2 and a plaque burden of >56%.[39] Computer simulation of stent implantation may predict SB compromise based on plaque composition.

Calcified rather than fibrotic lesions resulted in an elliptical lumen cross-section with smaller lumen area.[46] Prestenting imaging assessment of calcium thickness and extension is pivotal in the decision-making process of plaque modification and stenting strategy. IVUS analysis of plaque distribution at LMCA bifurcation found a smaller calcium arc and calcium length index in the SB compared with the main branch.[47] The

presence of a calcified plaque and more specifically a calcium arc >60° at the minimal lumen area site in either the distal LMCA or LAD ostium was an independent predictor of poststenting LCx narrowing.[48] The underlying mechanism of SB compromise in highly calcified lesions could be explained by stent underexpansion at the side of calcification and compensatory overexpansion at the carina resulting in carina shift.[49]

Underexpansion of at least 1 of the LMCA bifurcation segments appeared more frequently in the 2-stent strategy than in the provisional stenting technique (54% vs 27%; P = 0.001), with the LCx ostium being the most common site of underexpansion (37%).[22]

A pooled retrospective analysis including 1,391 patients demonstrated a higher target lesion failure rate at 3 years in calcified unprotected left main distal bifurcation lesions as compared with noncalcified lesions (adjusted HR: 1.36; 95% CI: 1.08–1.71; P = 0.01).[50]

IVUS guidance resulted in larger stent size selection and superior stent expansion as compared with angiography guidance.[51]

In the randomized ULTIMATE (Intravascular Ultrasound Guided Drug Eluting Stents Implantation in "All-Comers" Coronary Lesions) trial, IVUS was associated with a lower 1-year and 3-year risk for target vessel failure (6.6% vs 10.7%; P = 0.01; and 2.9% vs 4.2%; P = 0.019, respectively), reporting for the first time the benefit of IVUS guidance over angiography in all-comer patients undergoing PCI with second-generation DES.[52]

Optical coherence tomography requires selective and coaxial LMCA guide catheter engagement and may make a comprehensive LMCA assessment challenging. Use of guide extensions may complement LMCA optical coherence tomography by reducing contrast spilling and allowing better LMCA visualization.

A prespecified optical coherence tomography protocol allowed adequate expansion in 86% of the patients with mid/distal LMCA stenosis enrolled in the prospective, multicenter LEMON (LEft Main Oct-guided iNterventions) trial.[53]

Imaging determinants of escalation from the provisional to 2-stent strategy are plaque distribution and plaque morphology (Central Illustration). Invasive imaging may confirm proper left main stent expansion, apposition, and geometry (Figure 4).

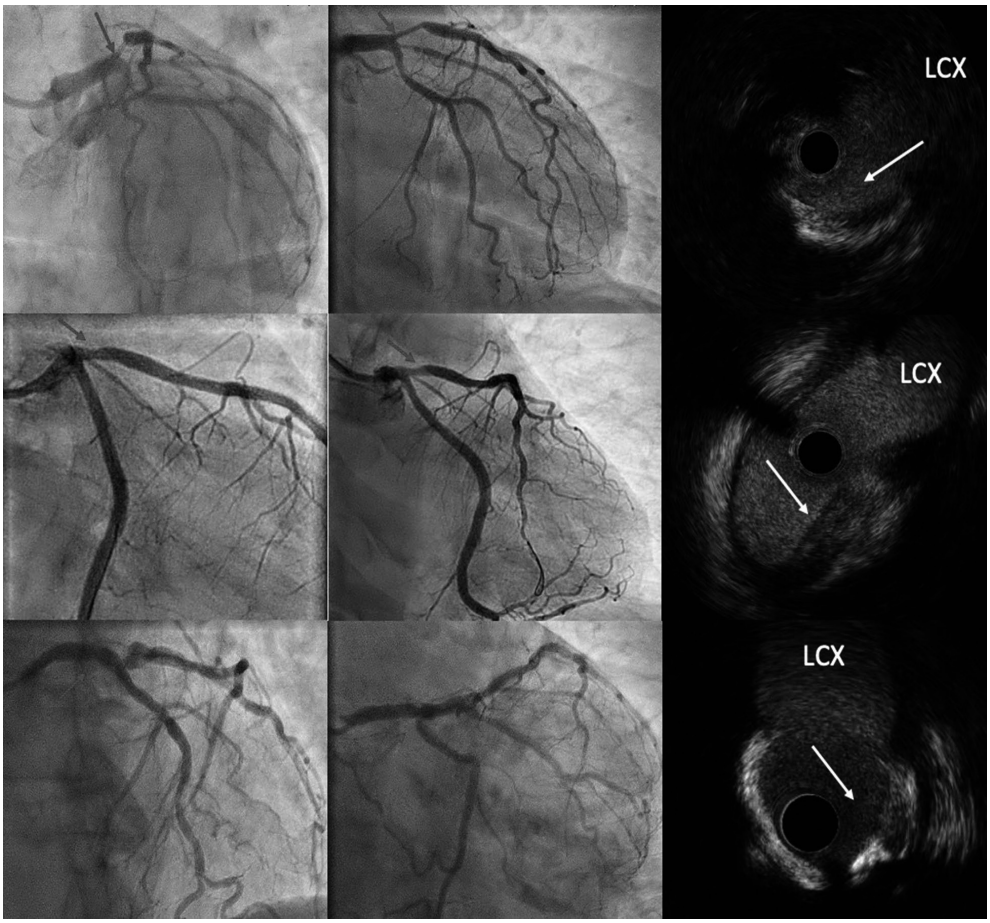
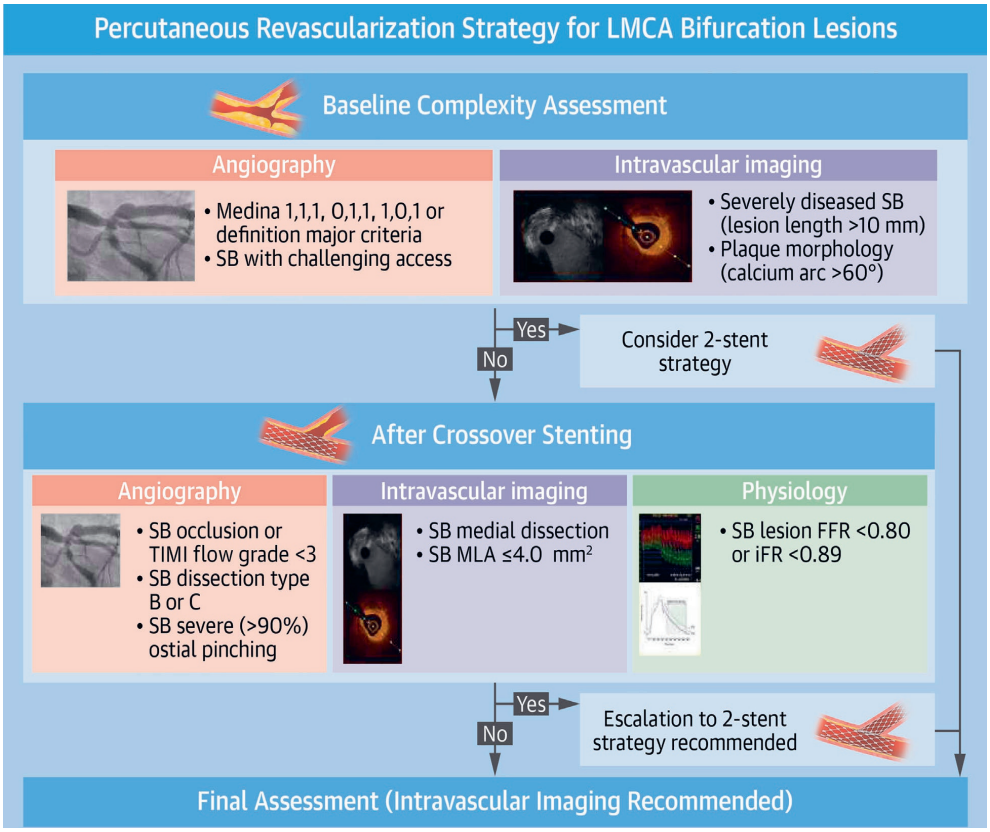


FIGURE 3 Representative Cases of IVUS Guidance in Evaluation and Treatment of LMCA Bifurcation Lesions (Top) Angiographic images of ostial LAD critical stenosis suggesting no left main coronary artery (LMCA) involvement (red arrows). Cross-sectional intravascular ultrasound (IVUS) shows ostial LAD fibrocalcific plaque extending into LMCA distal bifurcation (white arrow). (Middle) Angiographic images of ostial LAD hazy plaque

resulting in intermediate narrowing (red arrows). Cross-sectional IVUS shows soft plaque at the LAD ostium determining severe stenosis extending into LMCA (minimal lumen area: 4.88 mm2). (Bottom) Angiographic images of mildly diseased distal LMCA bifurcation. Cross-sectional IVUS shows critical and severely calcified LMCA distal bifurcation (minimal lumen area: 4.35 mm2). Abbreviations as in Figure 2.



CENTRAL ILLUSTRATION Suggested Algorithm for LMCA Bifurcation Lesion Treatment

FFR = fractional flow reserve; iFR = instantaneous wave-free ratio; LMCA = left main coronary artery; MLA = minimal lumen area; SB = side branch; TIMI = Thrombolysis In Myocardial Infarction.

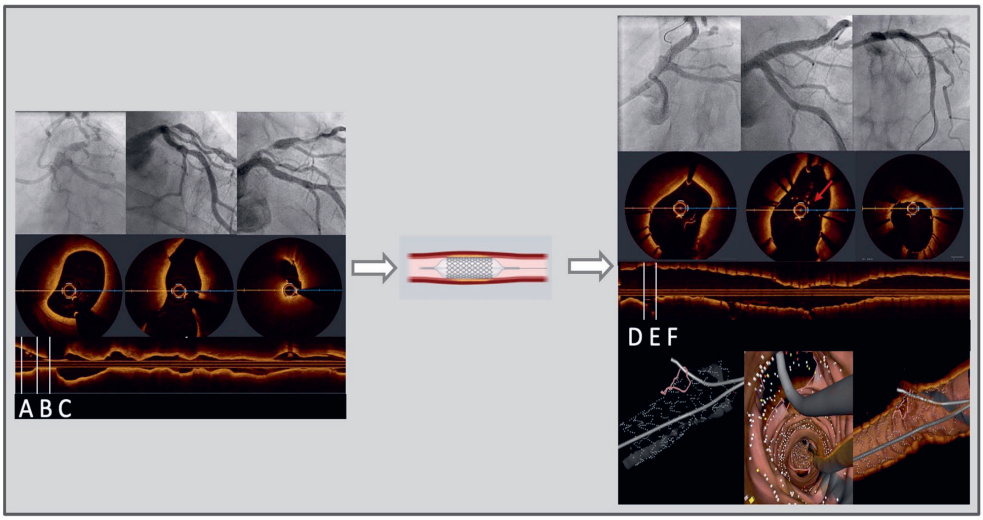


FIGURE 4 Representative Cases of Optical Coherence Tomography Guidance in Evaluation and Treatment of Ostial LAD Disease Involving LMCA Bifurcation Lesions

(Left) Cross-section A: thin-cap fibroatheroma at left main coronary artery (LMCA) shaft. Cross-section B: LMCA distal bifurcation stenosis minimal lumen area. Cross-section C: ostial left anterior descending artery (LAD) with image of intimal dissection due to predilatation. (Right) Cross-section D: strut apposition at LMCA shaft. Cross-section E: strut apposition at LMCA bifurcation toward LAD with overhanging struts in front of right coronary artery ostium (red arrow). Cross-section F: strut apposition at LAD ostium.

PHYSIOLOGY.

Physiology guidance by means of FFR or instantaneous wave-free ratio may be helpful in the evaluation of LMCA severity. However, baseline physiological assessment of daughter branches may be influenced by the presence of downstream coronary lesions.

In a small single-center study of 43 patients, LMCA crossover stenting resulted in 42% angiographic diameter stenosis >50%, 26% minimal lumen area reduction on average, and 7% poststenting positive FFR assessed at the LCx ostium.[22] The discrepancy between angiographic and imaging/physiological findings can be explained by carina shift as the main mechanism of LCx narrowing post-LMCA crossover stenting.[38] The visual-functional mismatch after LMCA-LAD stenting was also remarkable in a recent study of 83 patients (R^2 = 0.039; P = 0.071). Poststenting positive FFR was able to predict a significantly higher incidence of target lesion failure at 5 years of follow-up (33.4% in the positive FFR group vs 10.7% in the negative FFR group; P = 0.018).

Poststenting angiographic diameter stenosis ≥50% did not correlate with clinical outcomes: 5-year target lesion failure rates were 28.2% vs 9.0% in patients with diameter stenosis ≥50% and diameter stenosis <50%, respectively; HR: 2.67; 95% CI: 0.77–9.22; P = 0.12.[30] As a major limitation of the study, pre-PCI FFR was not performed.

FFR-based evaluation of the LCx in LMCA crossover stenting may shed light on ambiguous angiographic findings. However, intravascular imaging assessment can better establish the baseline involvement of the LCx and guide procedural planning in the provisional stenting approach. An outstanding uncertainty in bifurcation disease treatment relates to cases in which the SB minimal lumen area is compromised yet hemodynamic assessment is above ischemic threshold.

KBI AND POT.

The benefit of routine SB strut dilatation in the 1-stent strategy has not been fully elucidated; however, floating struts in front of an SB, when no further intervention on the SB is performed, represent local foci for increased thrombogenicity as compared with apposed struts in an in vitro model.[54]

The EBC recommends simultaneous inflation of short noncompliant balloons into LAD and LCx sized according to Murray's law (which states that the cube of the radius of a parent vessel equals the sum of the cubes of the radii of the daughters), followed by re-POT.[55] Sequential single balloon dilation in the proximal main branch, SB, and proximal main branch (POT-side-POT) is an alternative technique but may translate into higher degree of main branch stent deformation when compared with KBI. Indeed, bench tests showed the lowest percentage of malapposed and floating struts, less thrombus formation, and lower area of high shear rate and flow recirculation for the KBI technique, followed by the POT-side-POT and keep-it-open strategies.[56] Short-term follow-up results of Nordic-Baltic Bifurcation Study III confirmed a reduction of angiographic SB restenosis associated with KBI in coronary bifurcation lesions treated with the 1-stent strategy.[57] However, the composite clinical endpoints of death, myocardial infarction, and LMCA target lesion revascularization were similar at 2 years after LMCA crossover stenting irrespective of final KBI.[58] In vitro data show that floating struts in front of SB may act as loci for focal thrombogenicity. Despite a reduction in angiographic restenosis,

clinical data failed to show a benefit of systematic KBI in terms of death, myocardial infarction, and revascularization.

DUAL ANTIPLATELET THERAPY

Coronary artery bifurcation lesions may act as loci of turbulent flow and enhanced propensity for platelet aggregation, plaque rupture, and thrombosis. The fractal geometry of vascular bifurcations carries an intrinsic higher risk of periprocedural strut malapposition and underexpansion. This translates into a stent thrombosis incidence rate of 1.5% to 2% in bifurcation PCIs, which is almost twice as high as compared with nonbifurcation PCIs.[59]

European guidelines recommend a longer dual antiplatelet therapy (DAPT) duration for both stable coronary artery disease and acute coronary syndromes in complex PCI (Class IIb, Level of Evidence: B) and highlight coronary bifurcation as a risk factor for coronary ischemic events.[21]

In a patient-level pooled analysis of 5 nationwide multicenter registries on LMCA PCI, risks for target lesion failure and thrombotic adverse cardiovascular events were significantly higher in the 2-stent group than in the 1-stent group when DAPT was interrupted <1 year (HR: 2.78; 95% CI: 1.25–6.19), while it was similar in those maintaining DAPT ≥1 year (HR: 0.51; 95% CI: 0.15–1.69).[60] In a subanalysis of the KOMATE registry of 1,004 patients undergoing LMCA PCI and not experiencing major bleeding events at 1 year, the net adverse clinical events (NACE) rate at 4.5-year follow up was found to be lower in the prolonged DAPT subgroup (>12 months) vs patients with a DAPT duration <12 months (adjusted HR: 0.53; 95% CI: 0.29–0.99; P = 0.045).[13]

Therefore, the implementation of an individualized antithrombotic regimen in order to mitigate the patient's increased thrombotic risk without exposing patients to a higher risk of bleeding becomes crucial. Risk stratification based on clinical presentation, baseline bleeding risk, stenting strategy, and systematic use of intracoronary imaging are key according to the EBC consensus on antithrombotic therapy after PCI of bifurcation lesions.[61]

Whether patients at high bleeding risk would fare better with a simplified provisional approach in combination with shorter DAPT regimen requires further research. Notably,

the rate of adverse events after provisional stenting of bifurcation lesions in high-bleeding-risk patients with abbreviated DAPT duration was low.[62] Bifurcation lesions are loci for increased platelet reactivity and are considered a risk factor for coronary ischemic events.

Current evidence on DAPT in the context of LMCA PCI is scarce. Clinical presentation, baseline bleeding risk, and stenting strategy should be included in the decision-making algorithm for DAPT duration.

ADJUNCTIVE DEVICES

Most patients with angiographic coronary atheroma have a mean LMCA diameter of >4 mm.[63] Moreover, one case series found an IVUS derived mean lumen diameter >5 mm in up to 20% of the patients.[64] Percutaneous treatment of LMCA stenosis may require postdilation beyond the nominal diameter of current-generation DES, increasing the risk of polymer coating damage, strut deformation, and a significant mismatch in proximal and distal reference diameters.[65] Hence, there is potential for dedicated technologies to improve outcomes in a population of patients with a large amount of jeopardized myocardium. A retrospective registry of 139 patients undergoing IVUS-guided LMCA PCI with the Synergy Megatron DES platform (Boston Scientific) with broader overexpansion range showed no cases of longitudinal stent deformation. Study criteria for successful IVUS optimization were achieved in 74.1% of the patients.[66] The ROLEX (Revascularization Of LEft main with resolute onyX) registry similarly provided good safety and efficacy of the new-generation zotarolimus-eluting stent Resolute Onyx (Medtronic) in 450 patients with unprotected LMCA.[67] Postdilatation beyond the nominal diameter of current-generation DES and the significant mismatch in proximal and distal reference diameters catalyzed the search for dedicated stent designs to improve outcomes in patients undergoing LMCA PCI.

GAPS IN EVIDENCE: AUTHORS' PERSPECTIVES

As with other bifurcation diseases, there is no single optimal LMCA stent technique. Specific angiographic features (bifurcation angle and complexity) and intravascular imaging findings (plaque morphology and distribution) need to be carefully evaluated and

may determine stent strategy selection. In addition, the likelihood of SB closure should impact the choice of stenting strategy. Definition of an unfavorable SB mandating subsequent stent implantation in the context of a provisional 1-stent strategy remains elusive. In vitro (bench testing), ex vivo, and computational simulations offer valuable insights on the dynamics and effects of different procedural techniques (Figure 5). The selection of stent design and stent expansion capacity are pivotal in LMCA PCI.

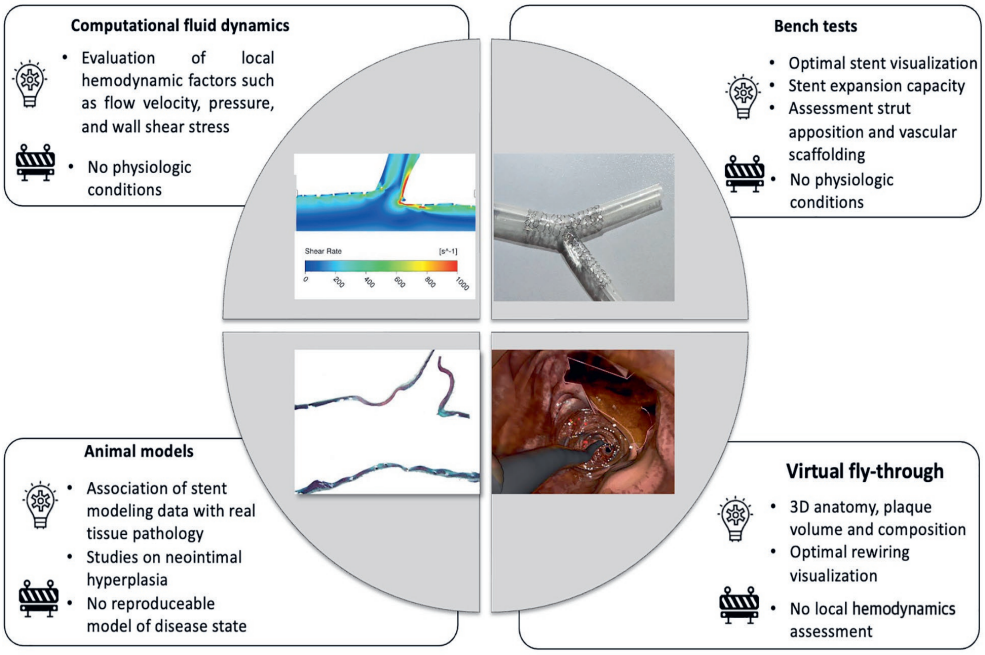


FIGURE 5 Example of Biomechanical Modeling Modalities to Improve Left Main Coronary Artery Bifurcation Stenting

3D = 3-dimensional.

CONCLUSIONS

A provisional 1-stent approach remains the most common treatment strategy for LMCA PCI. Patient selection and meticulous procedure execution including invasive imaging and stent optimization techniques are key for acute and long-term clinical success.

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Supplementary Table 1. Most used bifurcation lesions classifications

Classifications	**Medina (all bifurcations)**	**DEFINITION (LM bifurcation)**
Plaque distribution	MB prox lesion > 50% (1.-.-) MB distale lesion > 50% (-.1.-) SB lesion > 50% (-.-.1)	**Major criteria** SB DS ≥ 70% (major) SB lesion length ≥ 10 mm (major)
Others angiographic features		**Minor criteria** Moderate to severe calcification Multiple lesions Bifurcation angle < 45 º MB reference diameter < 2.5 mm Thrombus- containing lesion Multivessel lesion length > 25 mm
Definition of True (Medina) vs Complex (Definition) bifurcation lesions	MB and SB stenosis >50% (1.1.1), (0.1.1), (1.0.1)	One major and two minor DEFINITION criteria

Supplementary Table 2. Application of most relevant bifurcation lesions classifications in major RCTs on LMCA PCI

RCT	True LMCA bifurcation Medina (1.1.1), (0.1.1)	Complex LMCA bifurcation DEFINITION criteria	Main clinical outcomes in complex vs non complex LM bifurcation lesions according to DEFINITION criteria
DKCRUSH-V (2017)	100%	31.5%	Double kissing (DK) crush stenting compared to provisional stenting had similar relative reductions in the 1-year rates of target lesion failure (TLF) in both simple and complex lesions (interaction p value: 0.65), although the absolute benefit was greater for more complex lesions (11.2% vs. 4.1%)
EXCEL Sub-analysis (2018)	21.7% True bifurcation Medina (1.1.1), (0.1.1)	7% 33.9% of Medina true bifurcations	At 3 years FU, no significant differences in outcomes were observed between provisional and 2 stents technique in both complex and non complex LM lesions except for higher TVR with a planned 2-stent technique in noncomplex lesions (3.1% vs 22.8%, p: 0.02).
DEFINITION II (2020)	97.8%	92.7%	NR
EBC MAIN (2021)	100%	NR	NR

Chapter 15

Challenges and Evolving Strategies in the Treatment of In-Stent Restenosis With Drug-Coated Balloons

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Editorial

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In-stent restenosis (ISR) remains the most common cause of stent failure following percutaneous coronary intervention (PCI)[1]. Despite advancements in drug-eluting stents (DES) technology and enhanced implantation strategies—including optimized lesion preparation and intracoronary imaging (ICI) guidance—ISR still accounts for 5–10% of all PCI procedures performed in contemporary practice[1]. The predominant mechanism of ISR has shifted over time, with biological factors—particularly neoatherosclerosis—playing an increasing role over classical mechanical issues[1]. Of note, ISR is associated with a high risk of recurrent clinical events, including target lesion revascularization (TLR) as compared to de novo lesions. This poses a major treatment challenge, especially in complex scenarios such as DES-ISR, where the antiproliferative drug has already failed[1].

The 2024 guidelines for the management of chronic coronary syndromes recommend the use of DES over drug-coated balloons (DCB) in ISR[2],[3], mainly based on data from early randomized clinical trials (RCTs)[4], subsequently confirmed in the large DAEDALUS patient-level meta-analysis (10 RCTs, 1,976 patients)[5] demonstrating an increased risk of TLR at three years with DCB compared to DES (adjusted HR 1.38, 95% CI 1.05–1.82; p = 0.02)[5]. This clinical benefit of DES was evident in patients with DES-ISR but not in those with bare-metal (BMS)-ISR[5]. However, in our view, this change in recommendation should be interpreted with caution[2],[3]. Repeat stenting was associated with a numerical increase (NS) in the safety endpoint of death, myocardial infarction, and vessel thrombosis[5]. Moreover, most of the included RCTs lacked comprehensive lesion preparation and ICI guidance, the latter playing a major role (Class IIa, Level C recommendation)[3] in tackling underlying mechanical causes and optimizing DCB results. Avoiding repeat stenting is particularly attractive in patients with multiple metal layers, resistant underexpanded stents, small-vessel or diffuse ISR, and major bifurcation involvement[1]. Furthermore, the type of tissue obstructing the stent might determine the relative efficacy of different treatment strategies. The ongoing ISAR-DESIRE V RCT is

allocating patients with DES- ISR can be treated with either DCB or DES based on ICI-determined tissue patterns (homogeneous versus heterogeneous)[1].

Currently, the use of drug-coated balloons (DCB) is expanding in clinical practice worldwide[1,6]. A growing number of DCB technologies are available, but not all DCBs are equivalent, and a class effect cannot be assumed[1,3,6]. Historically, paclitaxel has been the preferred drug for DCB due to its lipophilic properties[6]. As a cytotoxic agent, paclitaxel inhibits cell division by irreversibly stabilizing microtubules, ensuring adequate retention in the vessel wall and persistent inhibition of neointimal proliferation. In contrast, sirolimus is a cytostatic agent that indirectly inhibits the cell cycle, has a wide therapeutic window, but limited lipophilicity[6]. Recent technological advancements enabling the incorporation of limus derivatives into DCBs have raised considerable expectations, given the demonstrated superiority of limus over paclitaxel in new-generation DES. Nevertheless, the relative safety and efficacy of limus- versus paclitaxel-coated balloons across different clinical and anatomical scenarios remain uncertain[1,6].

Present Study

The TIS-2 trial (Treatment of In-Stent Restenosis 2), published in this issue of the Journal, compared a sirolimus-coated balloon (SCB) using phospholipid-encapsulated sirolimus nanoparticles with a conventional iopromide paclitaxel-coated balloon (PCB) for the treatment of ISR. The study enrolled 145 patients with 158 ISR lesions.

The primary endpoint—non-inferiority of SCB versus PCB with respect to late lumen loss (LLL)—was not met (LLL: -0.024 mm; 95% CI: -0.277 to 0.229; non-inferiority margin: 0.20 mm). However, non-inferiority was observed in the BMS-ISR subgroup (-0.203 mm; 95% CI: -0.584 to 0.178). No significant differences were noted in secondary angiographic parameters, including minimal lumen diameter (MLD), percentage diameter stenosis (%DS), or binary restenosis rates (31.6% vs. 30.4%, p = 0.906), nor in 12-month cardiac event rates (31% in both groups).This study arrives just a decade after the TIS-1 RCT, also published in this Journal, comparing PCB with everolimus-DES in patients with BMS-ISR, where PCB yielded significantly lower 12-month late lumen loss (LLL) but no differences in minimal lumen diameter (MLD), percentage diameter stenosis (%DS), or binary

restenosis. The authors should be commended for their continued efforts to advance knowledge in the challenging field of ISR treatment. Nonetheless, several issues warrant further consideration.

First, the current study did not meet its primary endpoint of non-inferiority of SCB versus PCB in LLL. While LLL is an excellent mechanistic endpoint, it did not favor SCB in this trial. Other clinically meaningful angiographic outcomes—MLD, %DS, and binary restenosis—were similar and numerically favored SCB, complicating the interpretation of overall relative clinical efficacy.

Second, this is a small RCT with a wide non-inferiority margin. Pooling BMS-ISR and DES-ISR may be misleading, as these entities involve distinct mechanisms, histopathological patterns, and temporal profiles. A post-hoc sensitivity analysis in BMS-ISR suggested non-inferiority, but this should be considered hypothesis-generating. Furthermore, the study was underpowered for clinical endpoints, and the observed 1-year target lesion revascularization (TLR) rate of 26% in both groups is surprisingly high. This contrasts sharply with prior RCTs in DES-ISR patients, which reported a 3-year TLR of 15.6%, and the DAEDALUS meta-analysis, which reported a 3-year TLR of 16% following PCB treatment. Such a high early TLR rate (approximately one in four patients) remains suboptimal in a context where preventing recurrence is crucial.

Third, regarding technical considerations, the longer inflation time in the SCB arm (60 vs. 30 seconds) is difficult to maintain in practice. Coupled with the low inflation pressures used in both groups (12 atm), this may have contributed to the higher residual %DS (24% vs. 21%, $p = 0.025$) and reduced relative efficacy in the PCB arm. Prior data suggest that inflation time can impact efficacy. The observed trend toward greater acute lumen gain and the statistically significant reduction in residual stenosis with SCB was unexpected, raising concerns given the open-label design. Lesion preparation remains critical; in this study, cutting balloons were used in most patients before DCB. Notably, however, the need for bailout stenting was unusually high (23% in both groups) compared to <5% in earlier DCB trials for ISR.

Fourth, an X-ray post-processing system was used to assess mechanical causes of ISR. While pragmatic, it lacks the resolution of intracoronary imaging (ICI), which remains the gold standard for identifying stent failure mechanisms.

Final Remarks

Technological advancements in limus-coated drug-coated balloons (limus-DCB) are still evolving to match the superior pharmacokinetics of paclitaxel-coated balloons (PCB). Yet, some recent randomized controlled trials (RCTs) have failed to demonstrate non-inferiority of limus-DCB compared to PCB. The TRANSFORM I trial—also using this sirolimus-coated balloon—did not meet non-inferiority in net lumen gain versus PCB in small-vessel de novo lesions.

Moreover, a recent meta-analysis of six RCTs comparing currently available limus-DCB versus PCB demonstrated that PCB provides superior late angiographic outcomes, including late lumen loss (LLL), minimal lumen diameter (MLD), percentage diameter stenosis (%DS), binary restenosis, and late lumen enlargement. Despite these angiographic differences, clinical outcomes were similar between the two drugs. Larger studies are needed to determine whether the improved angiographic performance of PCB translates into clinically meaningful benefits.

Efficient sirolimus transfer and retention at the vessel wall remain a technical challenge. Whether novel technologies—such as biodegradable polymer microreservoirs or crystalline sirolimus bound by butylated hydroxytoluene—can enhance clinical effectiveness requires further investigation. Additionally, factors such as the type of in-stent restenosis (BMS-ISR vs DES-ISR), mechanical issues, or the underlying tissue characteristics (neointimal hyperplasia vs neoatherosclerosis) may influence DCB efficacy. These challenges present opportunities for personalized medicine, opening new avenues for the treatment of this complex clinical condition.

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Part III – Physiological Guidance in Obstructive and Non-Obstructive Coronary Disease

Chapter 16

Absolute coronary blood flow across different endotypes of ANOCA

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Abstract

BACKGROUND: Intracoronary continuous thermodilution is a novel technique to quantify absolute true coronary flow and microvascular resistance. However, few data are available in patients with angina with non-obstructive coronary arteries (ANOCA).

OBJECTIVES: This study aimed to investigate the diagnostic potential of hyperaemic absolute coronary flow (Qmax) and absolute microvascular resistance (Rμ,hyper) among different ANOCA endotypes, and to determine the correlation between continuous – and bolus – thermodilution indexes.

METHODS: A total of 222 patients were scheduled for clinically indicated coronary function testing (CFT), of whom 120 patients were included in this analysis. These patients underwent CFT including acetylcholine (ACh) provocation testing and microvascular function assessment using both bolus and continuous thermodilution.

RESULTS: CFT was negative (CFT−) in 32 (26.7%) patients. Endothelium-dependent dysfunction (ACh+) was present in 63 (52.5%) patients, and coronary microvascular dysfunction (CMD) identified at bolus thermodilution (CMD+) was present in 62 (51.7%) patients. Patients with a positive CFT (CFT+) showed significantly lower Qmax and higher Rμ,hyper values as compared to CFT−. Qmax was significantly lower in CMD+ versus CMD− patients (0.174 vs 0.222 L/min; p=0.04) but did not differ in patients with or without a positive ACh test (0.198 vs 0.219 L/ min; p=0.86).

CONCLUSIONS: The prevalence of a CFT+ is high in a selected ANOCA population. In our study, Qmax and Rμ,hyper were associated with a positive CFT. Qmax was associated with the presence of microvascular dysfunction but not with a positive acetylcholine test. The novel continuous thermodilution method can provide further insights into ANOCA endotypes.

Introduction

Angina or ischaemia with non-obstructive coronary arteries (ANOCA/INOCA) can be found in up to 25% of patients with chest pain undergoing coronary angiography[1–3]. The pathogenesis of ANOCA relies on two distinctive mechanisms (alone or in combination) which subsequently define different endotypes: coronary microvascular dysfunction (CMD) and epicardial/microvascular spasm. CMD is the consequence of structural microcirculatory remodelling, while epicardial or microvascular spasm is caused by vasomotor dysregulation and enhanced vessel reactivity[4–7]. Clinical manifestations of ANOCA comprise a wide range of symptoms which are often misdiagnosed and under- or mistreated[8,9]. The direct assessment of coronary microcirculatory responses to vasodilatory stimuli and the assessment of vasomotor disorders are pivotal to implement stratified medicine, which leads to a reduction in angina severity and better quality of life as compared with standard care[1]. Invasive coronary function testing (CFT) is currently the only diagnostic option which allows a definitive diagnosis of microvascular disorders along with characterisation of different endotypes, as recommended by current consensus guidelines[10,11]. The administration of vasoreactivity-inducing stimuli investigates the endothelium-dependent mechanisms of microvascular and epicardial vasomotor tone disorders[12]. Endothelium-independent mechanisms of CMD can be assessed using bolus thermodilution or Doppler guidewire testing[13]. However, technical challenges in acquiring a stable Doppler signal as well as the need for adenosine-induced hyperaemia for bolus thermodilution limit the widespread adoption of these diagnostic tools[14]. The diagnostic process can be implemented by using a novel technology which allows the measurement of true coronary flow and microvascular resistance[15]. Continuous thermodilution assessment of the microcirculation has been proven to be safe and reproducible and correlates with the gold standard, positron emission tomography[16]. The aim of this study was to investigate the diagnostic potential of absolute flow and microvascular resistance among different ANOCA endotypes and to assess the correlation between these continuous thermodilution-derived variables and standard physiological indices as assessed by bolus thermodilution. We further defined

a continuous thermodilution-derived range of values able to predict CMD, as diagnosed by bolus thermodilution.

Methods

STUDY DESIGN

This was a single-centre, prospective observational registry conducted at Maasstad Hospital, the Netherlands, which is a large tertiary referral centre specialising in patients with ANOCA. The study protocol conforms to the International Conference on Harmonisation/Good Clinical Practice standards and the Declaration of Helsinki. All patients gave written informed consent. Clinical characteristics including medical history, risk factors and symptoms were obtained from both the electronic patient file and an online patient questionnaire. The data were stored and pseudonymised in an online database (Castor EDC) and were only accessible to the involved researchers.

STUDY POPULATION

The study population included all consecutive suspected ANOCA patients referred to our centre for CFT from January 2019 to February 2023. Eligible patients were selected from the outpatient clinic of the cardiology department of the enrolling centre. Only patients presenting with chronic angina – defined as having symptoms of angina at least 2 times a week despite medical therapy for 3 months – were included in the final analysis. Obstructive coronary artery disease (CAD) was ruled out before CFT by anatomical imaging via coronary angiography (CAG) or coronary computed tomography angiography (CCTA) or via non-invasive ischaemia detection. Exclusion criteria were patterns of anginal symptoms other than those defined as chronic angina, contraindication to adenosine (e.g., asthma, bronchospasm, conduction disorders), significant valve disease, acute coronary syndrome presentation, left ventricular dysfunction (left ventricular ejection fraction <30%), and the inability or unwillingness to give informed consent. A description of the CFT can be found in Supplementary Appendix 1.

ENDOTYPES DEFINITION

We defined the endotypes according to the underlying pathophysiological mechanisms in patients with or without coronary spasm, as assessed with acetylcholine (ACh) vasoreactivity testing (ACh+/−), and patients with or without CMD, as measured by the bolus thermodilution method (CMD+/−) (Figure 1).

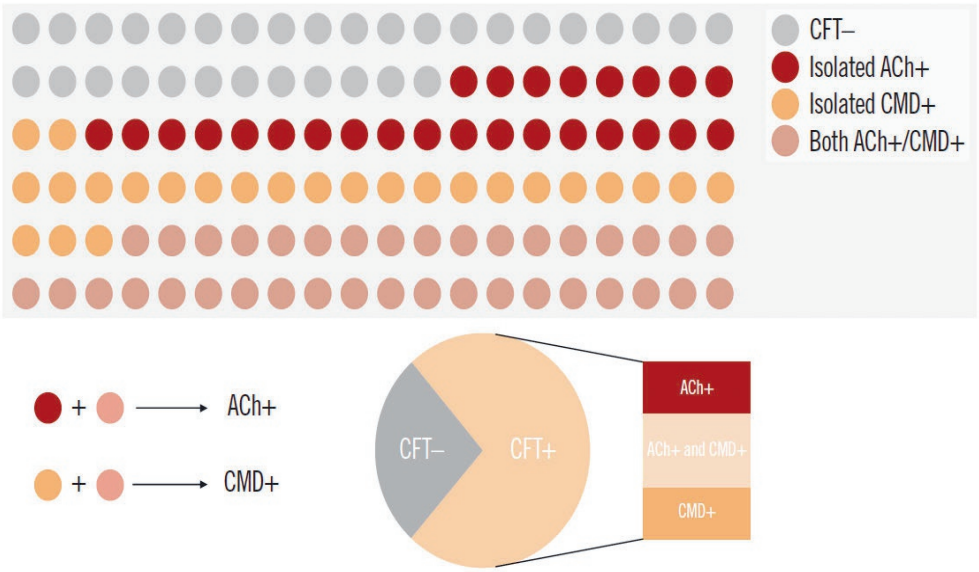


Figure 1. Prevalence of ANOCA endotypes. ACh+: patients with coronary spasm; ANOCA: angina with non-obstructive coronary arteries; CFT: coronary function testing; CMD: coronary microvascular dysfunction

The definitions of epicardial or microvascular spasm were based on contemporary international criteria as follows and are displayed in Table 1. According to the Coronary Vasomotor Disorders International Study Group (COVADIS) criteria, the ACh vasoreactivity testing was defined as abnormal in case of recognisable symptoms and ischaemic electrocardiogram (ECG) changes (i.e., ST-segment depression or ST-segment elevation of ≥0.1 mV or T-wave peaking in at least 2 contiguous leads) with either epicardial or microvascular spasm[12,17]. Epicardial coronary diameter reduction ≥90%, either focal or diffuse, in response to ACh administration was defined as vasospastic angina (VSA)[12]. Microvascular spasm was diagnosed in the absence of ≥90% epicardial diameter reduction during ACh infusion[18]. Any inconclusive result in response to ACh

administration (e.g., recognisable symptoms without ECG modifications) was considered negative. CMD was defined as the presence of an index of microvascular resistance (IMR) ≥25 and/or a coronary flow reserve (CFR) <2.5 measured with bolus thermodilution[11]. CMD was further classified as structural CMD – defined as an IMR ≥25 and CFR <2.5 – and functional CMD – defined as a CFR <2.5 with a normal IMR[19]. A positive CFT was defined by a positive response to ACh vasoreactivity testing or the presence of CMD or both.

Table 1 ANOCA endotype definitions.

	Bolus thermodilution	**Spasm provocation results**
Vasospastic angina		Angina, ischemic ECG changes and ≥90% luminal reduction
Microvascular angina		Angina and ischemic ECG changes but no or <90% luminal reduction
CMD	CFR<2.5 and/or IMR≥25	

ANOCA: angina with non-obstructive coronary arteries; CFR: coronary flow reserve; CMD: coronary microvascular dysfunction; ECG: electrocardiogram; IMR: index of microvascular resistance

STATISTICAL ANALYSIS

In this study, the continuous thermodilution parameters (hyperaemic absolute coronary flow [Qmax] and absolute microvascular resistance [Rμ,hyper]) were compared in different groups of patients CFT (+/−), CMD (+/−) and ACh (+/−), and in patients with isolated CMD+ or isolated ACh+. Normally distributed continuous variables are expressed as mean±standard deviation (SD), and categorical variables are displayed as number and percentage. Differences between groups were assessed by an unpaired Student's t-test for continuous data with a normal distribution. Otherwise, the non-parametric Mann-Whitney U test was used as appropriate. All p-values<0.05 were considered statistically significant. We used SPSS Statistics, version 29.0 (IBM) for all statistical analysis.

Results

CLINICAL CHARACTERISTICS

A total of 222 patients were scheduled for clinically indicated CFT, of whom 120 patients were included in this analysis. Reasons for exclusion were no informed consent (n=38), obstructive CAD with percutaneous coronary intervention (PCI) performed (n=5), fractional flow reserve ≤0.80 in the left anterior descending artery (n=20), clinical presentation other than chronic angina as described above (n=29), or missing parameters (n=10). Baseline and procedural characteristics are displayed in Table 2 and Table 3. Non-invasive ischaemia detection was performed in 38 (31.6%) patients, of whom 26 (21.6%) underwent exercise testing and 12 (10.0%) underwent imaging stress testing. Medications at baseline and after CFT are displayed in Table 4.

Table 2. Baseline characteristics across the whole cohort and according to ANOCA endotypes.

Characteristic	**All patients (n=120)**	**CFT− (n=32)**	**CFT+ (n=88)**	**CFT p-value**	**CMD− (n=58)**	**CMD+ (n=62)**	**CMD p-value**	**ACh− (n=57)**	**ACh+ (n=63)**	**ACh p-value**
Age, years	59.2±10.4	57.5±11.5	59.2±11.7	0.25	57.1±11.3	60.2±11.7	0.07	58.3±10.3	59.1±12.8	0.69
Female	89 (74.2)	28 (87.5)	63 (71.6)	0.07	49 (84.5)	42 (67.7)	0.03	45 (78.9)	46 (73.0)	0.44
BMI, kg/m2	27.8±4.8	28.3±5.6	27.6±4.5	0.30	27.7±4.6	27.8±4.9	0.43	27.5±5.05	28.1±4.54	0.58
History of diabetes	17 (14.2)	3 (9.4)	14 (16.3)	0.34	9 (15.8)	8 (12.9)	0.68	5 (8.7)	12 (19.6)	0.09
History of hypertension	66 (55.0)	19 (59.4)	47 (54.7)	0.64	29 (50.9)	37 (60.7)	0.28	34 (59.6)	32 (52.4)	0.43
History of hyperlipidaemia	54 (44.9)	16 (50.0)	36 (41.9)	0.43	23 (40.4)	29 (55.8)	0.43	27 (47.3)	25 (40.9)	0.48
Smoking status - Never	69 (57.3)	22 (68.8)	45 (52.9)		36 (63.2)	31 (51.7)		36 (63.1)	31 (51.6)	
Smoking status - Former	24 (20.0)	8 (25.0)	18 (21.2)	0.06	13 (22.8)	13 (21.7)	0.22	12 (21.0)	14 (23.3)	0.09
Smoking status - Current	27 (22.7)	2 (6.3)	22 (25.9)		8 (14.0)	16 (25.8)		9 (15.7)	15 (25.0)	
COPD	3 (2.5)	0 (0)	3 (6.0)	0.28	2 (2.9)	1 (1.5)	0.42	3 (5.2)	3 (4.7)	
History of AMI	22 (18.3)	7 (21.9)	15 (17.4)	0.58	9 (15.8)	13 (21.3)	0.44	10 (17.5)	12 (19.6)	0.76

Autoimmune disease	12 (10.0)	1 (3.0)	11 (12.5)	0.13	4 (6.9)	8 (12.9)	0.27	3 (5.2)	9 (14.2)	0.10
Prior CAG	76 (63.3)	20 (62.5)	56 (64.4)	0.85	35 (61.4)	41 (66.1)	0.59	35 (61.4)	41 (66.1)	0.59
Prior coronary CTA	32 (26.7)	11 (34.4)	21 (23.9)	0.25	16 (27.6)	16 (25.8)	0.82	17 (29.8)	15 (23.8)	0.46
Prior non-invasive ischaemia detection	38 (31.6)	9 (28.1)	29 (32.9)	0.78	20 (28.5)	21 (33.3)	0.25	16 (28.0)	22 (34.9)	
Exercise stress testing	26 (21.6)	6 (18.7)	20 (22.7)		14 (20.0)	12 (24.0)		12 (21.0)	14 (22.2)	0.43
Imaging stress testing	12 (10.0)	3 (9.4)	9 (10.2)		6 (8.6)	6 (12.0)		4 (7.0)	8 (12.7)	

Data are given as mean±standard deviation or n (%). ACh: acetylcholine; ACh+: patients with coronary spasm; ACh−: patients without coronary spasm; AMI: acute myocardial infarction; ANOCA: angina with non-obstructive coronary arteries; BMI: body mass index; CAG: coronary angiography; CFT: coronary function testing; CMD: coronary microvascular dysfunction; COPD: chronic obstructive pulmonary disease; CTA: computed tomography angiography

Table 3. Haemodynamic parameters across the whole cohort and according to ANOCA endotypes.

Parameter	**All patients (n=120)**	**CFT− (n=32)**	**CFT+ (n=88)**	**p-value (CFT)**	**CMD− (n=58)**	**CMD+ (n=62)**	**p-value (CMD)**	**ACh− (n=57)**	**ACh+ (n=63)**	**p-value (ACh)**
Pd/Pa	0.92±0.02	0.93±0.03	0.93±0.02	0.26	0.93±0.02	0.92±0.03	0.16	0.92±0.02	0.92±0.02	0.39
LAD FFR	0.88±0.04	0.89±0.05	0.88±0.04	0.12	0.88±0.05	0.88±0.04	0.14	0.88±0.05	0.88±0.04	0.84
LAD CFR	3.57±1.84	4.79±2.25	3.13±1.44	<0.01	4.66±1.99	2.54±0.99	<0.01	3.81±2.11	3.35±1.54	0.16
LAD CFR norm	3.70±1.58	4.86±2.37	3.34±1.61	0.05	4.32±1.64	2.89±1.08	<0.01	3.72±1.59	3.68±1.59	0.93
LAD IMR	28.77±19.90	13.78±5.90	31.77±18.63	<0.01	15.96±5.39	38.94±21.36	<0.01	24.72±18.55	33.05±20.64	0.08
LAD IMR norm	26.97±18.08	15.05±6.00	33.52±20.84	<0.01	15.41±5.67	37.79±19.01	<0.01	21.89±16.18	31.57±18.58	<0.01
LAD Qmax, L/min	0.157±0.06	0.233±0.08	0.188±0.06	0.04	0.222±0.10	0.174±0.10	0.04	0.219±0.09	0.198±0.11	0.86
LAD Rμ,hyper, WU	485.0±196.7	469.4±176.5	552.7±199.5	0.02	492.1±180.4	566.4±204.5	0.02	466.6±172.4	588.3±200.2	<0.01

Data are given as meanÅ}standard deviation. ACh: acetylcholine; ACh+: patients with coronary spasm; ACh−: patients without coronary spasm; ANOCA: angina with non-obstructive coronary arteries; CFR: coronary

flow reserve; CFT: coronary function testing; CMD: coronary microvascular dysfunction; FFR: fractional flow reserve; IMR: index of microvascular resistance; LAD: left anterior descending artery; Pa: aortic pressure; Pd: distal coronary pressure; Qmax: hyperaemic absolute coronary blood flow; Rμ,hyper: hyperaemic absolute microvascular resistance; WU: Wood units

Table 4. Medications at baseline and after CFT across the whole cohort and according to ANOCA endotypes.

Medication	Time	All patients (n=120)	CFT− (n=32)	CFT+ (n=88)	p-value (CFT)	CMD− (n=58)	CMD+ (n=62)	p-value (CMD)	ACh− (n=57)	ACh+ (n=63)	p-value (ACh)
Beta blockers	pre-CFT	42 (35.0)	13 (40.6)	29 (32.9)	0.43	23 (39.7)	19 (30.6)	0.30	22 (38.5)	20 (74.2)	0.43
Calcium channel blockers	pre-CFT	50 (41.7)	12 (37.5)	38 (43.2)	0.57	22 (37.9)	28 (56.0)	0.42	22 (38.5)	28 (44.4)	0.52
ACEi/ARBs	pre-CFT	55 (45.8)	15 (46.9)	40 (45.5)	0.89	24 (41.4)	31 (50.0)	0.34	29 (50.8)	26 (41.2)	0.29
Statins	pre-CFT	68 (56.7)	18 (56.3)	50 (56.8)	0.96	30 (51.7)	38 (61.3)	0.29	30 (52.6)	38 (60.3)	0.39
Long-acting nitrates	pre-CFT	35 (29.2)	6 (18.8)	29 (33.0)	0.13	14 (24.1)	21 (33.9)	0.24	17 (29.8)	18 (28.5)	0.88
Beta blockers	post-CFT	43 (35.8)	13 (40.6)	30 (34.1)	0.51	28 (48.3)	15 (24.0)	0.04	23 (40.3)	20 (31.7)	0.32
Calcium channel blockers	post-CFT	104 (86.7)	24 (75.0)	80 (90.9)	0.02	48 (84.2)	52 (93.6)	0.02	45 (78.9)	59 (93.6)	0.02
ACEi/ARBs	post-CFT	55 (45.8)	15 (46.9)	40 (45.5)	0.89	28 (48.3)	27 (42.8)	0.44	29 (50.8)	26 (41.2)	0.29
Statins	post-CFT	67 (55.8)	18 (56.3)	49 (55.7)	0.96	30 (51.7)	37 (59.7)	0.38	30 (52.6)	37 (58.7)	0.50
Long-acting nitrates	post-CFT	42 (35.0)	6 (18.8)	36 (40.9)	0.02	18 (31.0)	24 (38.7)	0.38	15 (26.3)	27 (42.8)	0.06

Data are presented as n (%). ACEi: angiotensin-converting enzyme inhibitors; ACh: acetylcholine; ACh+: patients with coronary spasm; ACh−: patients without coronary spasm; ANOCA: angina with non-obstructive coronary arteries; ARBs: angiotensin II receptor blockers; CFT: coronary function testing; CMD: coronary microvascular dysfunction

PREVALENCE OF ENDOTYPES

Coronary function testing was negative in 32 (26.7%) patients. Endothelium-dependent dysfunction (ACh+) was present in 63 (52.5%) patients, of whom 21 presented with VSA. In VSA patients, epicardial vasospasm >90% was diagnosed in 14 patients using a third injection of ACh (at a reduced dose of 100 μg) and in 7 patients with a third injection at the maximum dose of ACh (200 μg). Non-endothelium-dependent microvascular dysfunction identified at bolus thermodilution (CMD+) was present in 62 (51.7%) patients, of whom 35 presented with IMR ≥25 and normal CFR, 10 with CFR <2.5 and normal IMR, and 17 with both abnormal CFR and IMR. The coexistence of both ACh+ and CMD+

endotypes was detected in 37 (30.8%) patients, while isolated ACh+ and CMD+ was present in 26 (21.7%) and 25 (20.8%) patients, respectively.

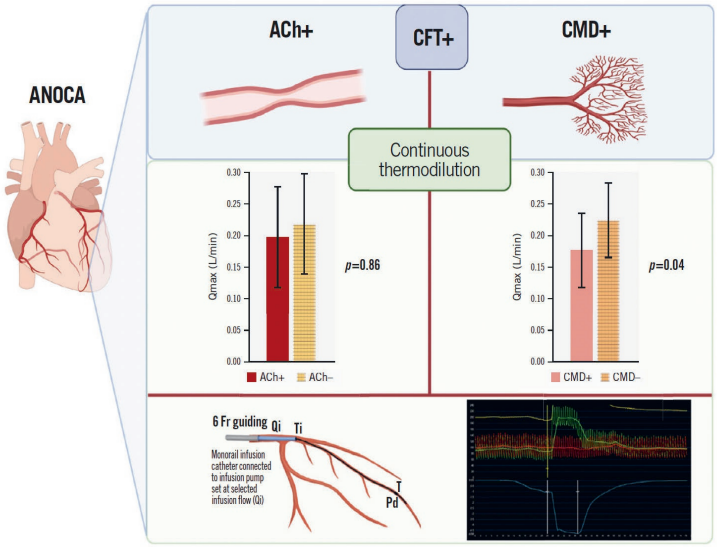
SAFETY

Procedural complications were evaluated in all patients included in the analysis. No fatal or serious adverse complications (e.g., coronary intervention, ventricular or atrial fibrillation, myocardial infarction, persistent ventricular tachycardia, sinus arrest) were observed. In 2 patients, a Type 1 Bleeding Academic Research Consortium bleeding occurred, which did not require further treatment. Eleven patients developed a transient atrioventricular (AV) block during the ACh provocation test, which is a frequent side effect of intracoronary ACh administration[20]. In all these patients, the AV block was resolved within seconds by stopping the infusion of ACh. The ACh provocation test was then continued, with the injection of ACh at a lower rate. No patients required the administration of intravenous atropine.

ABSOLUTE FLOW AND RESISTANCE ACROSS DIFFERENT ENDOTYPES

Patients exhibiting either a positive response to ACh and/or CMD (CFT+) demonstrated significantly lower Qmax and higher Rμ,hyper values compared to CFT− patients (0.188 vs 0.233 L/min; p=0.04; and 552.7 vs 469.4 Wood units [WU]; p=0.02, respectively). Patients with a positive response to acetylcholine (ACh+) exhibited no difference in terms of Qmax (0.198 vs 0.219 L/min; p=0.86) but showed significantly higher Rμ,hyper (588.3 vs 466.6 WU; p<0.01) than ACh− patients (Central illustration). Comparisons between patients with isolated positive responses to acetylcholine (ACh+) and the rest of the group revealed no differences in terms of Qmax or Rμ,hyper (0.207 vs 0.208 L/min; p=0.49; and 533.4 vs 520.1 WU; p=0.38, respectively), as depicted in Figure 2A and Figure 2B. Patients diagnosed with microvascular dysfunction (CMD+) displayed significantly lower Qmax and significantly higher Rμ,hyper values compared to CMD− patients (0.174 vs 0.222 L/min; p=0.04; and 566.4 vs 492.1 WU; p=0.02, respectively), as depicted in the Central illustration.

Absolute flow across different ANOCA endotypes.



ACh+: patients with coronary spasm; ANOCA: angina with non-obstructive coronary arteries; CFT: coronary function testing; CMD: coronary microvascular dysfunction; Fr: French; Pd: distal coronary pressure; Qi: infusion flow rate; Qmax: hyperaemic absolute coronary flow; T: blood temperature; Ti: temperature of infusion

Similarly, when patients with isolated CMD (CMD+) were compared to the remainder of the group, Qmax was significantly lower and Rμ,hyper was significantly higher (0.157 vs 0.208 L/min/m²; p=0.03; and 548.3 vs 463.1 WU; p=0.03, respectively), as shown in Figure 2C and Figure 2D. Further classification of CMD revealed significantly decreased Qmax and increased Rμ,hyper in patients with structural CMD compared to patients without structural CMD (0.194 vs 0.212 L/min; p=0.04 and 611.9 vs 500.9 WU; p<0.01, respectively), as depicted in Figure 3A. Conversely, patients with functional CMD showed no differences in Qmax or Rμ,hyper compared with patients without functional CMD (0.248 vs 0.202 L/min; p=0.12; and 481.2 vs 536.5 WU; p=0.34, respectively), as illustrated in

Figure 3B.

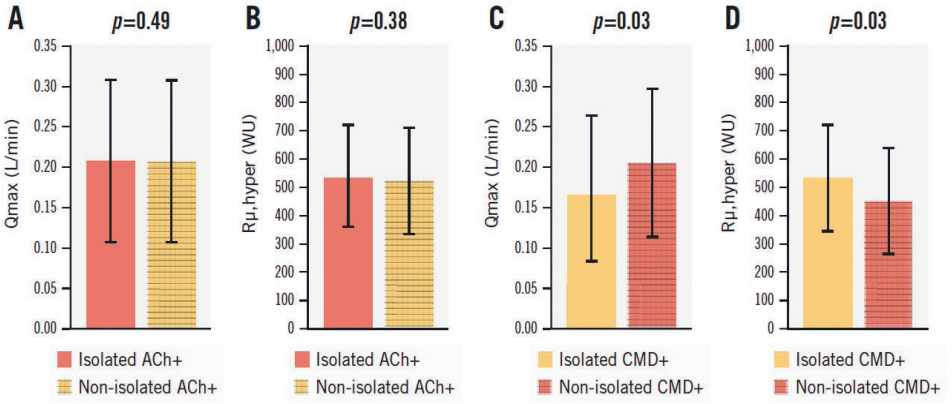


Figure 2 Qmax and Rμ,hyper according to the prevalence of isolated ACh+ and isolated CMD+. A-B) Qmax and Rμ,hyper in patients with isolated/non-isolated acetylcholine testing. C-D) Qmax and Rμ,hyper in patients with isolated/ non-isolated CMD. ACh+: patients with coronary spasm; CMD: coronary microvascular dysfunction; Qmax: hyperaemic absolute coronary flow; Rμ,hyper: absolute microvascular resistance

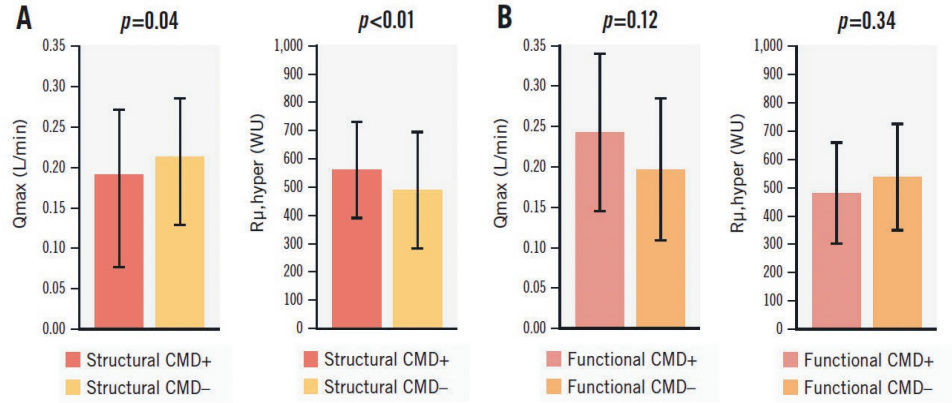


Figure 3. Qmax and Rμ,hyper according to the prevalence of structural or functional CMD. A) Structural CMD+ patients. B) Functional CMD+ patients. CMD: coronary microvascular dysfunction; Qmax: hyperaemic absolute coronary flow; Rμ,hyper: hyperaemic absolute microvascular resistance

CORRELATION BETWEEN BOLUS AND CONTINUOUS THERMODILUTION PARAMETERS

Receiver operating characteristic (ROC) analyses revealed that the optimal Rμ,hyper cutoff to predict patients with an IMR ≥25 was identified as 500 WU, with an area under the ROC curve (C-statistic) of 0.66 (95% confidence interval [CI]: 0.56 to 0.76; p=0.003). This 500 WU cutoff accurately classified patients with CMD, achieving a sensitivity of 72% and a specificity of 57%. The optimal range of Rμ,hyper values to predict patients with an IMR ≥25 was found to be between 460 and 540 WU, with a sensitivity ranging from 74% to 72%. Similarly, ROC analyses identified 0.160 L/min as the optimal Qmax cutoff to predict patients with an IMR ≥25, with an area under the ROC curve (C-statistic) of 0.71 (95% CI: 0.62 to 0.80; p<0.001). This 0.160 L/min cutoff accurately classified patients with CMD, achieving a sensitivity of 65% and a specificity of 58%. The optimal range of Qmax values to predict patients with an IMR ≥25 was found to be between 0.155 and 0.167 L/min, with a sensitivity ranging from 66% to 60% (Figure 4).

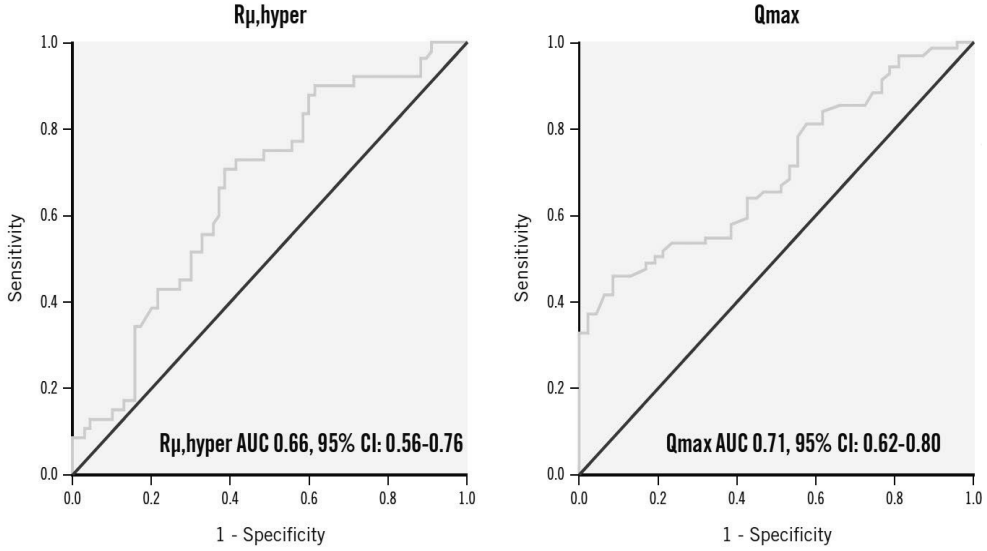


Figure 4. ROC analyses identifying Rμ,hyper and Qmax values for best predicting an IMR ≥25. AUC: area under the curve; CI: confidence interval; IMR: index of microvascular resistance; Qmax: hyperaemic absolute coronary flow; Rμ,hyper: hyperaemic absolute microvascular resistance; ROC: receiver operating characteristic

THERAPEUTIC APPROACHES FOR ANOCA PATIENTS ACROSS VARIOUS ENDOTYPES FOLLOWING CORONARY FUNCTION TESTING

Prior to coronary function testing, 42 (35%) patients were taking beta blockers (BB), 50 (41.7%) were on calcium channel blockers (CCBs), 55 (45.8%) were using angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs), 68 (56.7%) were prescribed statins, and 35 (29.2%) were using long-acting nitrates. Following coronary function testing, the percentage of patients taking CCBs and long-acting nitrates increased from 41.7% to 86.7% and from 29.2% to 35.0%, respectively. After CFT, a significantly higher percentage of patients taking CCBs was found in the CFT+ group as compared to the CFT− group (90.9% vs 75.0%; p=0.02). These results were consistent across different ANOCA endotypes (Table 4). Regarding long-acting nitrates, a higher percentage of nitrates was prescribed in CFT+ as compared to CFT− patients (40.9% vs 18.8%; p=0.02). A trend towards a higher use of nitrates was found in the ACh+ group versus the ACh− group (42.8% vs 26.3%; p=0.06). Conversely, the use of nitrates after CFT did not differ between CMD+ and CMD− groups (38.7% vs 31.0%; p=0.38).

Discussion

In this study, we assessed the continuous thermodilution-derived parameters in ANOCA patients undergoing coronary function testing. The goal of the study was to provide a better understanding of the different ANOCA endotypes using Qmax and Rμ,hyper. Moreover, we aimed to assess the correlation between bolus and continuous thermodilution parameters across different ANOCA endotypes. Up to now, few studies have investigated this novel technique in ANOCA patients, and for the first time, Qmax and Rμ,hyper have been evaluated across all ANOCA endotypes.

The main findings of our study are the following:

The prevalence of a CFT+ is high in a selected ANOCA population.

Coronary function testing significantly impacts on the use of antianginal medications across all ANOCA endotypes.

The novel continuous thermodilution method is safe in patients with ANOCA and can provide further insights into ANOCA endotypes.

The novel Qmax and Rμ,hyper are associated with a positive CFT.

Qmax is associated with microvascular dysfunction (CMD+) but not associated with a positive acetylcholine test (ACh+).

The optimal ranges of Qmax and Rμ,hyper to predict an IMR ≥25 were found to be between 0.155 and 0.167 L/min and 460 and 540 WU, respectively.

Current evidence indicates that ANOCA is not a benign condition, and these patients are at higher risk for major adverse cardiovascular events including death, non-fatal myocardial infarction, heart failure, rehospitalisation and repeated coronary angiography for recurrent angina versus reference subjects[8],[9],[21]. The social and economic burden of ANOCA is worsened by the poor awareness of this condition among treating physicians and by the lack of evidence-based recommendations, resulting in inadequate treatment in these patients[21].

The CORonary MICrovascular Angina (CorMicA) trial provided evidence that stratified therapy based on invasive diagnostic testing and addressing the underlying mechanisms of ischaemia reduces angina burden and improves quality of life in ANOCA patients[1].

A comprehensive assessment of the microcirculatory domain includes detection of both structural microcirculatory remodelling and/or functional arteriolar dysregulation[10],[11]. Haemodynamic findings associated with an impaired structural microvasculature in response to a non-endothelium-dependent vasodilator, such as adenosine, are reduced CFR and increase in minimal hyperaemic microcirculatory resistance measured by either bolus thermodilution or the Doppler technique. However, reliable Doppler measurements may be difficult to obtain in “real-world” practice due to a suboptimal Doppler signal in up to 31% of cases[14]. Bolus thermodilution measurement, based on a manual injection of saline bolus, may be hampered by intraobserver variability and by the cost and side effects of adenosine use[22].

A newly developed invasive technique – the continuous thermodilution method – has been shown to be safe, reproducible and operator independent, with no need for additional hyperaemic stimuli[14]. Continuous thermodilution was found to be associated with significantly less variability in repeated measurements than bolus thermodilution in the assessment of CMD[23]. Microvascular resistance reserve (MRR), defined as the ratio of true resting microvascular resistance and hyperaemic microvascular resistance measured by continuous thermodilution, has been found to be a suitable index to distinguish the presence or absence of CMD in patients with angina and no obstructive coronary artery disease[24],[25].

Functional arterial dysregulation is related to endothelial dysfunction, determining impaired vasorelaxation or paradoxical vasospasm in response to endothelium-dependent vasoconstricting agents. A positive ACh test indicates the presence of either epicardial or microvascular vasoconstriction.

In our study, coronary function testing was deemed safe and had a significant impact on the utilisation of antianginal medications. Subsequent to CFT, there was a marked increase in the number of patients using CCBs across all ANOCA endotypes. A positive CFT result was associated with a higher prevalence of patients using long-acting nitrates; this was particularly evident in the ACh+ subgroup. However, no significant differences were observed in patients with or without CMD. These findings may be attributed to the vasodilatory effects of long-acting nitrates on both microvascular and epicardial vasomotor disorders, while their efficacy in microvascular structural remodelling remains limited, often accompanied by side effects that restrict their benefits[26].

Konst et al. showed that Rμ,hyper was higher in patients with the endotype of microvascular dysfunction (defined as high IMR and/or low CFR) and that both Qmax and Rμ,hyper were not associated with the endotype of epicardial or microvascular spasm[27]. However, no information was provided for either of the subgroups of isolated CMD or isolated positive ACh test, nor for structural or functional CMD. In our study, we found significantly lower Qmax values in patients with CMD (CMD+), regardless of the presence of a vasomotor dysregulation. Interestingly, Qmax values were confirmed to be significantly lower in the subgroup of isolated CMD+, which validates the accuracy of this novel technology to detect the presence of microvascular (dys)function. In our study, Qmax was also not associated with a positive response to acetylcholine (ACh+), and we confirmed this finding to be valid in the subgroup of patients with isolated vasospastic disorder (isolated ACh+).

In line with the results from Konst et al., when we looked at microvascular resistance as assessed by continuous thermodilution, we found that the presence of microvascular dysfunction (CMD+) was associated with significantly higher Rμ,hyper values. These values were consistently higher in isolated CMD+ patients and were within the range of the values previously described as “abnormal”[27,28]. Patients with structural CMD showed a significantly decreased Qmax and a significantly increased Rμ,hyper, whereas the

functional CMD subgroup (CFR <2.5 with normal IMR values) did not show any differences in terms of Qmax or Rμ,hyper as compared to the rest of the study population. Structural CMD identifies patients with architectural changes in their coronary circulation, such as arteriolar obliteration, microvascular obstruction and/or capillary rarefaction. These patients can be identified by a decreased Qmax and an increased Rμ,hyper during continuous thermodilution. In contrast, functional CMD patients with diminished CFR and preserved IMR are characterised by a preserved maximum coronary blood flow and an increased resting coronary blood flow[29]. These patients can be identified by an increased resting Q (Qrest) and a decreased resting R (Rμ,rest) during continuous thermodilution (i.e., during infusion of saline at 10 mL/min), which was unfortunately not measured at the time of these analyses. The differentiation of these two CMD subgroups not only reflects different underlying pathophysiological mechanisms but also leads to different optimal treatments[19].

Both Qmax and Rμ,hyper were significantly abnormal in the whole cohort of patients with positive reaction testing (CFT+). We cannot rule out that the prevalence of 51.7% of patients with CMD (either isolated or combined) may have driven these results, leading to abnormal Qmax and Rμ,hyper values in patients with CFT+ versus CFT−.

In addition, more than one-third of the patients showed both a positive ACh test and microvascular dysfunction. Structural remodelling can also lead to an increased passive stiffness of the vessels and functional dysregulation, enhancing arteriolar sensitivity to vasoconstricting stimuli; therefore, we cannot exclude crosstalk between the two endotypes[28].

We further defined the continuous thermodilution range of values able to predict CMD, as diagnosed by bolus thermodilution. ROC analyses identified 500 WU as the optimal Rμ,hyper cutoff to predict patients with an IMR ≥25; these results are in line with those of Rivero et al.[28] Despite the easier applicability in clinical practice of a single, sharp cutoff value able to discriminate between “normal” and “diseased” patients with a very high accuracy, a range of abnormal values might better suit the purpose of identifying patients with CMD using continuous thermodilution parameters. The main reason supporting this hypothesis is the considerable variability between individual patients regarding the perfused myocardial mass. Hyperaemic flow and resistance are dependent

on the myocardial mass perfused by the supplying artery[30]. The recently developed MRR index, expressing the ratio of true resting to hyperaemic microvascular resistance, might be the best tool to identify CMD patients. At present, thermodilution methods do not possess the capability to distinguish between ANOCA endotypes, as defined by bolus thermodilution. Nevertheless, the findings of the current analysis hold promise for shedding additional light on the exploration of various endotypes. This study lays the groundwork for future investigations aimed at pinpointing optimal cutoff values capable of distinguishing between different endotypes using a more standardised and reproducible technique.

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Chapter 17

Coronary Vascular (DYS) Function and Invasive Physiology Assessment: Insights into Bolus and Continuous Thermodilution Methods

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Review

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Abstract

A considerable number of patients with angina or myocardial ischemia have no significant coronary artery disease on invasive angiography. In recent years, several steps towards a better comprehension of the pathophysiology of these conditions, angina or ischemia with non-obstructive coronary arteries (ANOCA/INOCA), have been made. Nevertheless, several gaps in knowledge

still remain. This review is intended to provide a comprehensive overview of ANOCA and INOCA, with a particular focus on pathophysiology, recent diagnostic innovations, gaps in knowledge and treatment modalities.

Introduction

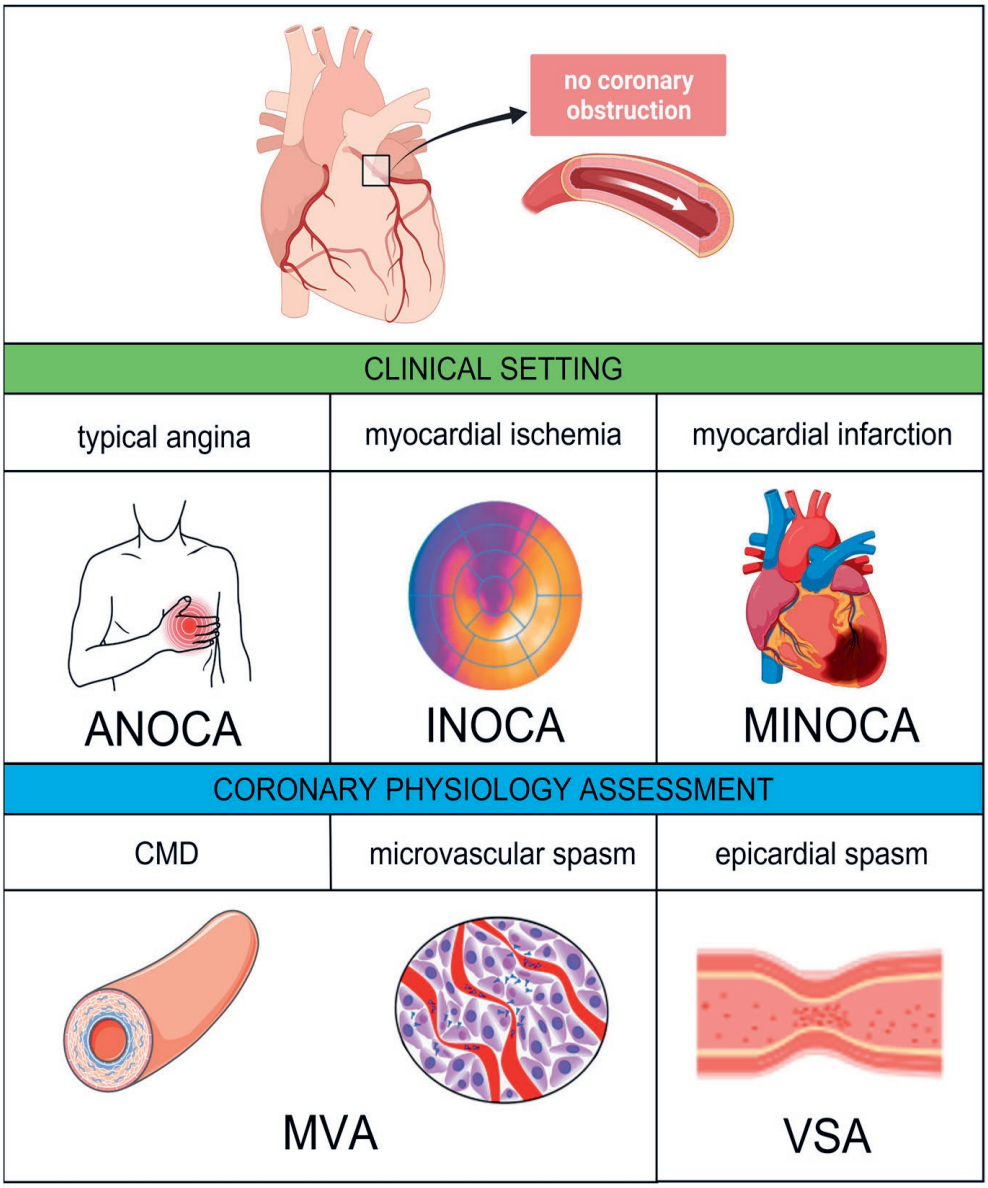
A considerable number of patients with anginal symptoms or myocardial ischemia on noninvasive testing present no significant coronary artery stenosis on coronary angiography[1]. The absence of significant coronary artery disease (CAD) often terminates the diagnostic workup for cardiac causes. In some cases, symptoms are attributed to non-cardiac conditions such as gastrointestinal or psychiatric disorders, leading to erroneous diagnoses and inappropriate treatments[2]. In recent years, the pathophysiology of angina or ischemia with non-obstructive coronary arteries (ANOCA/INOCA) have been investigated, and several steps have been made towards a better comprehension of these conditions. Nevertheless, several gaps in knowledge still remain. In this review, we aim to provide an overview of ANOCA and INOCA, with a special focus on pathogenesis, recent innovations in diagnostic modalities, evolving concepts and treatment updates.

1.Definitions

The concomitant presence of typical angina and absence of significant stenosis on coronary angiography has been historically defined as “Cardiac Syndrome X” (CSX) due to uncertainty about its mechanism[3]. The better understanding of this condition led to the replacement of the term “CSX” with microvascular angina (MVA)[4], which encompasses patients with coronary vasomotor dysfunction consisting of microvascular

spasm and/or impaired vasodilatation[5,6]. While microvascular spasm can be inferred in patients with typical angina and ischemic electrocardiogram (ECG) changes during a spasm provocative test[7], impaired vasodilator reserve due to coronary microvascular dysfunction (CMD) is characterized by a low coronary flow reserve (CFR)[5]. Differently, a transient reduction in coronary blood flow (CBF) secondary to a spasm in the epicardial coronary arteries, previously referred to as "Prinzmetal" or "variant" angina, defines the condition of vasospastic angina (VSA)[7–10]. The pathophysiological mechanisms of these conditions are addressed later in this review.

Recently, the term "ANOCA" has been coined to include all the clinical conditions determined by anginal symptoms without evidence of significant CAD on coronary angiography. When anginal symptoms are associated with documented myocardial ischemia, the term "INOCA" applies. Finally, in the presence of a universal criteria-defined myocardial infarction (MI) with no significant coronary stenosis and no other overt cause at presentation, the definition of "myocardial infarction with non-obstructive coronary artery" (MINOCA) can be used[11]. A comprehensive diagram including the abovementioned definitions is provided by Figure 1.



Abbreviations: ANOCA, angina with non-obstructive coronary arteries; CMD, coronary microvascular dysfunction: INOCA, ischemia with non-obstructive coronary arteries; MINOCA, myocardial with non-obstructive coronary arteries; MVA, microvascular angina; VSA, vasospastic angina.

Figure 1. Coronary vascular dysfunction—clinical settings and pathophysiological mechanisms. Abbreviations: ANOCA, angina with non-obstructive coronary arteries; CMD, coronary microvascular dysfunction: INOCA, ischemia with non-obstructive coronary arteries; MINOCA, myocardial with non-obstructive coronary arteries; MVA, microvascular angina; VSA, vasospastic angina.

2.Epidemiology and Prognostic Implications

The absence of significant coronary obstruction is frequent in patients experiencing angina and myocardial ischemia. With regard to ANOCA, numerous data show that its prevalence ranges from 30% to 50% among patients undergoing coronary angiography[1,12–14], with a female preponderance[14–16]. Interestingly, these percentages seem to remain stable over time despite improvements in the definition and detection of this condition[12]. Nevertheless, the correct characterization of symptoms has a central role, since the presence of typical angina is a predictor of significant CAD, while atypical symptoms are more often associated with the absence of coronary obstruction[1,13]. When a non-invasive stress test confirms the presence of significant myocardial ischemia in patients with angina, the percentage of patients without significant CAD decreases[1,17]. The prevalence of MINOCA has been reported to range between 2% and 10% of all MIs[18–22], while coronary obstruction is found in more than 90%[23]. Interestingly, women have a higher chance of a negative coronary angiography than men also in the setting of MI[18]. Notably, none of these conditions is benign. In addition to impaired quality of life, several studies reported an increased risk of adverse events in patients with ANOCA and INOCA[24–26]. The available data show a 1.3 higher risk of death and a 3–4-fold higher risk of hospitalization for cardiovascular events in ANOCA patients as compared with asymptomatic individuals[14,25], while the Women's Ischemia Syndrome Evaluation (WISE) study demonstrated a 10-year risk of all-cause death of 13% and 2.8% in patients with INOCA and in control healthy individuals, respectively[27]. In MINOCA patients, the prognosis is influenced by the underlying mechanism and the extent of myocardial dysfunction. Overall, the risk of mortality in patients with MINOCA is estimated to be about 1%, 3% and 4% in hospital, at 1 year and at 3 years, respectively[22,28,29]. Finally, the absence of significant coronary obstruction on coronary angiography may lead the treating physician to wrongly reassure patients or discontinue the medical therapy, with a potential negative impact on symptoms and quality of life.

3. Pathophysiology

Among the main pathophysiological mechanisms deemed responsible for ANOCA/INOCA and MINOCA, vascular spasm and CMD play an important role.

3.1. Epicardial and Microvascular Vasospasm

Epicardial vasospasm is a pathologic condition characterized by a transient reduction of CBF due to a spasm in the epicardial coronary arteries. This phenomenon is responsible for recurrent attacks of chest pain similar to those occurring in patients with obstructive CAD; however, these episodes often happen at rest rather than under exertion, and effort tolerance is generally preserved[30]. While initially referred to as "Prinzmetal" or "variant" angina due to its differences from classical effort angina, the exact definition of the pathophysiology of this phenomenon led to the introduction of the term "VSA".

The hyperreactivity of vascular smooth cells (VSCs) is thought to play a central role in the pathophysiology of VSA. VSCs' contraction is mediated by the phosphorylation and dephosphorylation of myosin light chains (MLCs). MLC dephosphorylation, in particular, is inhibited by rho-kinase, which has been shown to be hyper-expressed in the spastic cells[31,32]. This hypothesis is supported by preliminary studies suggesting that the use of rho-kinase inhibitors effectively prevents acetylcholine (Ach)-induced coronary spasms[33]. The occurrence of anginal symptoms at night, when the vagal tone is higher, and the induction of spasm by Ach suggest that dysregulation in the autonomic nervous system may be involved as well in the pathophysiology of VSA[8,34]. Other potential mechanisms include endothelial dysfunction with dysregulation of the nitric oxide synthases, magnesium deficiency, oxidative stress, inflammation and genetic polymorphisms[8]. Coronary spasm often occurs at the level of an atherosclerotic plaque, probably because the endothelial dysfunction, leading to an imbalance between vasodilator and vasopressor stimuli[35], can act as a trigger for local injury, ischemic damage and MI[36]. However, even healthy vessels can be affected.

Several studies suggest that a spasm can also occur at the level of the microcirculation. Mohri et al. showed that lactate was produced during a spasm provocation test in patients with angina attack and ischemic ECG changes without significant epicardial coronary obstruction[37]. Sun et al. confirmed these findings demonstrating the

occurrence of myocardial ischemia (typical angina, ischemic ECG changes and lactate production) in patients undergoing the spasm provocative test without angiographic evidence of an epicardial spasm[38]. These data support the hypothesis that, in the absence of an epicardial spasm, patients with chest pain and ECG changes during the spasm provocative test suffer from microvascular spasm. Of note, it should be considered that patients with non-diagnostic Ach-test results may be affected by CMD[7]. Finally, one of the main characteristics of both epicardial and microvascular vasospasms is the resolution of symptoms due to vasodilation in response to nitrates.

3.2. Coronary Microvascular Dysfunction

CMD is a condition that is characterized by reduced CFR either due to increased minimal microvascular resistance (MVR) or high resting flow due to the altered non-endothelial-dependent vasomotion of the coronary microvasculature (<500 μm)[39–42]. Based on the underlying mechanism, two clinical entities can be distinguished, structural and functional CMD. The main structural changes associated with CMD are the thickening of the arterioles' wall with a reduction in the lumen area, the increase in perivascular fibrous tissue and the decrease in the vascular density (capillary rarefaction), leading to high MVR. Additionally, non-endothelial-dependent mechanisms such as the impaired relaxation of VSCs, higher susceptibility of VSCs to vasoconstrictor stimuli and abnormal autonomic activity may be involved[43,44]. These abnormalities lead to an increase in the MVR and an insufficient increase in CBF under physiological stress, contributing to an imbalance between oxygen demand and supply, resulting in myocardial ischemia[5,41].

The parameter that expresses the ability of the coronary microcirculation to increase CBF under stress conditions is the CFR, defined as the ratio of the CBF during maximal vasodilation to the corresponding value at rest. Unlike other parameters used to assess the hemodynamic significance of a coronary stenosis, such as fractional flow reserve (FFR) and instantaneous wave-free ratio (iFR), CFR provides complementary information about the overall functional status of the coronary circulation. There can be a correlation between FFR, iFR and CFR in certain cases; for example, if a coronary stenosis is severe enough to limit CBF, then FFR, iFR and CFR may all be found to be altered. By contrast, other conditions, such as the presence of collateral circulation or CMD, may alter this

relationship. In the case of well-developed collaterals supplying adequate CBF to the affected territory, CFR may remain preserved even in the case of an FFR and/or iFR significant stenosis. Furthermore, an altered CFR may suggest CMD in symptomatic patients with non-hemodynamically significant coronary stenosis at FFR and/or iFR assessment[45,46].

Typically, patients with CMD due to altered microvascular architecture present with low CFR and high MVR values. However, a proportion of patients with functional CMD may exhibit low CFR/low MVR and high resting CBF values. The mechanism responsible for this specific subset of CMD is still unclear, as this might be due to either a reduced myocardial efficiency or uncoupled CBF[47]. Structural changes in the coronary microvascular have been shown to be more prevalent in patients with classical cardiovascular risk factors, including hypertension, hyperlipidemia, smoking and diabetes mellitus (DM). Moreover, they have been correlated with other conditions, including renal impairment, coronary atherosclerosis, ventricular hypertrophy, and other cardiomyopathies[5,48].

While different findings on the coronary function tests (CFTs) may suggest that coronary microvascular spasm and CMD might represent two separated entities, an anomalous vasodilatory response has been proven in patients presenting the abovementioned risk factors and predisposition for structural abnormalities[48], suggesting that both non-endothelial-dependent and endothelial-dependent alterations may coexist in patients with MVA. Importantly, the coexistence of CMD and VSA portends a worse prognosis.

4.Diagnosis

Both non-invasive and invasive tests have a role in assessing coronary vascular function. While the discussion regarding non-invasive diagnostic tests is beyond the scope of this review, in the following paragraphs, the main invasive CFTs are discussed.

4.1. Spasm Provocation Test

The spasm provocation test is executed by injecting a spasm-inducing drug in escalating doses in the coronary arteries through a guiding catheter. Ach, which binds to the muscarinic cholinergic receptors, is the most widely used drug; however, ergonovine

(ER) or methylergonovine can be employed too. There are few reports on the different responses to Ach and ER in patients with suspected VSA; however, it has been suggested that ER tends to provoke a more focal and proximal spasm, while Ach-induced spasm is more distal and diffuse[49].

Notably, Ach normally acts as a mild vasodilator on epicardial coronary arteries and dilates resistance arterioles, resulting in increases in CBF. In patients with normal endothelial function, blood flow increases >50% during low Ach doses. By contrast, the vasodilator response is attenuated at higher Ach doses in patients with VSA due to an imbalance between vasodilator and vasopressor agents, leading to vasoconstriction[50].

The spasm provocation test is performed by firstly engaging the target coronary artery. Of note, when performing the procedure via a radial artery access, the "radial cocktail" (namely Ca^{2+} channel blockers and nitrates) should be avoided. In the case of small radial arteries or marked spasm, 5F catheters are also considered a valid option to perform this assessment.

If there is no particular suspicion regarding a specific coronary segment involved in the spasm, the left coronary artery is normally the vessel of choice. During the entire duration of the test, a 12 leads ECG and the arterial blood pressure are continuously monitored. After a selective engagement of the left main, increasing doses of Ach are administered through the guiding catheter. Normally, four steps at the doses of 2, 20, 100 and 200 μg are sufficient to establish the diagnosis[51]. Ach is diluted in a 5, 10 or 20 mL syringe of 0.9% saline solution and is administered in 30–120 s based on the amount of solution used. A first cine acquisition is obtained before starting the injections; therefore, one is acquired after 20–30 s after each administration or in the case of new-onset angina or ECG changes. Intra-arterial nitrates should not be administered before starting the spasm provocation test, as they may alter the endothelial response, while they should be given at the end of the test. The test is safe, with an incidence of major complication <1%[52]. In rare cases of acute spasm refractory to nitrates, atropine can be used. According to the COVADIS group[30], VSA is diagnosed if nitrate-responsive angina is accompanied by ECG changes and coronary spasm. Typical ECG changes include ST segment elevation or depression ≥0.1 mV or new-onset negative U waves, while the constriction in the epicardial arteries should be >90%. By contrast, the induction of typical angina and ECG

changes in the absence of >90% epicardial spasm is highly suggestive of MVA due to a microvascular spasm.

Figure 2 provides an example of a positive vasospasm provocative test, while Figure 3 provides an exemplificative case of a coronary spasm that occurred at the level of a mild coronary plaque in a patient with resuscitated cardiac arrest.

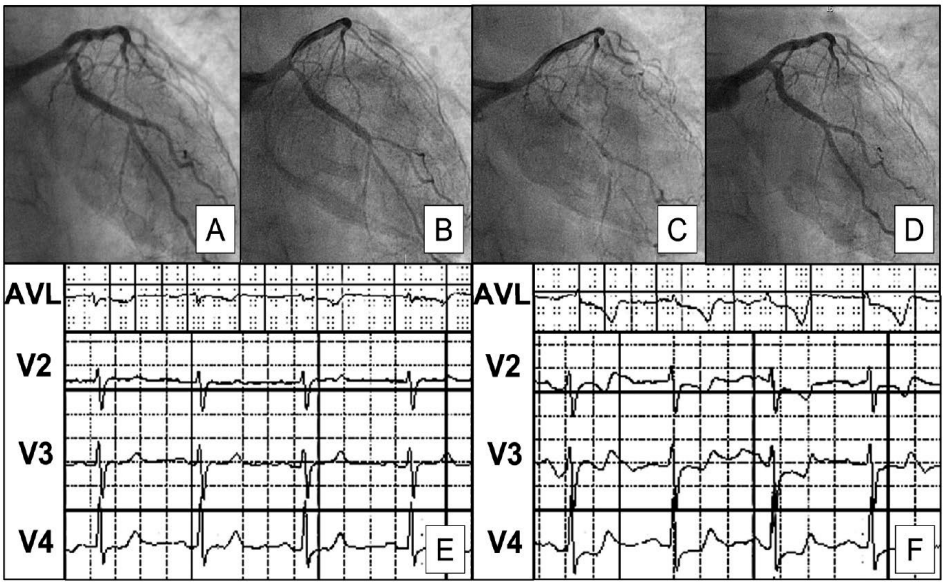


Figure 2. Spasm provocative test suggestive of vasospastic angina. (A) Baseline coronary angiography revealing no significant stenosis. (B,C) Repeated coronary angiography after administration of 2 g and 20 g of Ach showing significant spasm with >90% induced stenosis in the circumflex artery. (D) Repeated coronary angiography after administration of intracoronary nitrates revealing complete regression of coronary spasm. (E) Baseline electrocardiogram. (F) Electrocardiogram after administration of intracoronary Ach and during anginal symptoms, showing new-onset ischemic alterations in anterolateral position.

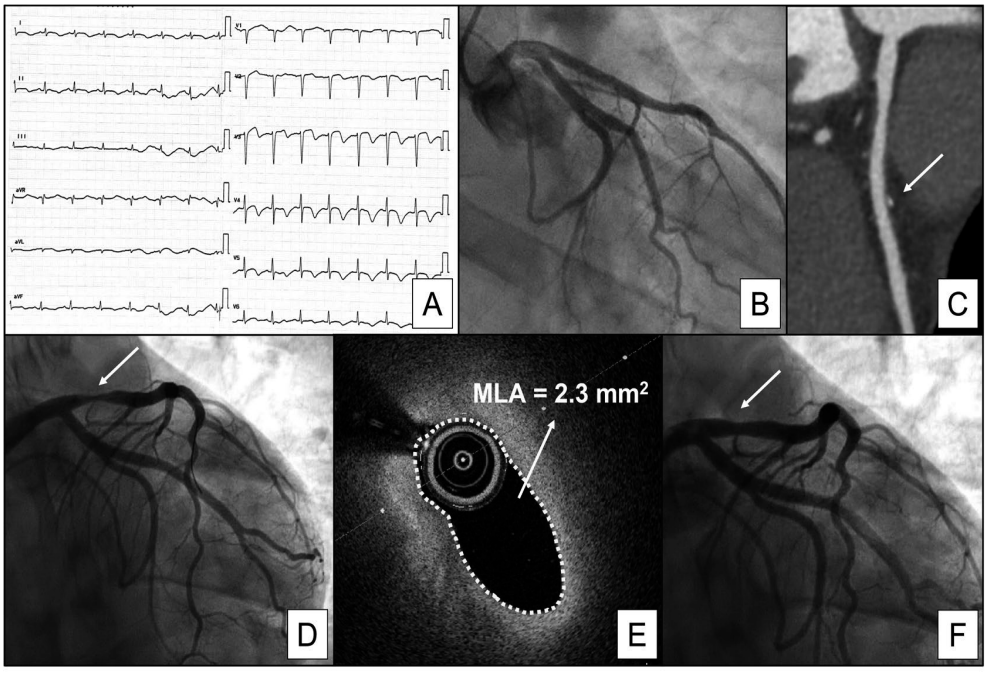


Figure 3. Representative case of coronary spasm on a mild coronary plaque in a patient presenting with out of hospital cardiac arrest. (A) Electrocardiogram at hospital presentation showing anterolateral ST segment elevation and biphasic T waves. (B) Coronary angiography revealing no significant stenosis. (C) Coronary computed tomography revealing a mild plaque with calcific core in the proximal LAD (white arrow). (D) Repeated coronary angiography showing significant spasm occurring on the proximal LAD at the passage of the OCT probe (white arrow). (E) OCT image showing coronary spasm. (F) Coronary angiography after administration of intracoronary nitrates showing the regression of the spasm (white arrow). Abbreviations: MLA, minimal lumen area.

4.2. Assessing CMD—General Concepts

In patients with suspected CMD, a comprehensive diagnostic test should include the measurement of specific indices reflecting the microvascular capacity to increase CBF under stress conditions and MVR. According to the COVADIS recommendations[7], these parameters include the CFR and the index of microvascular resistance (IMR). While CFR represents the extent to which CBF can increase above its baseline value, IMR is a dimensionless index that expresses the resistance of the microvasculature[53]. CFR reflects the status of both epicardial arteries and microcirculation, while IMR investigates the

microvascular function[54]. Both of these parameters can be derived with the bolus thermodilution method; however, recent advances in the field of coronary physiology led to the development of a new diagnostic tool, the continuous thermodilution method, introducing new indices and overcoming some of the limitations of the bolus thermodilution method.

In addition to thermodilution, CFR and MVR can be estimated by applying the Doppler technique with a dedicated velocity-measuring wire[55]. Altered values of Doppler-derived CFR assessed with the Flowire (Philips Volcano, San Diego, CA, USA) have been correlated with markers of endothelial dysfunction, such as the albumin-to-creatinine ratio[56] and subendocardial viability ratio[57], in hypertensive patients. Several studies compared the thermodilution and the Doppler techniques in assessing CMD, leading to discordant results[58],[59]. The Doppler method demonstrates lower intraobserver variability compared to thermodilution, leading to improved accuracy[59–62], and Doppler-derived CFR shows superior agreement with the gold-standard [^{15}O]-H_2O positron emission tomography[59],[60]. Notably, the bolus thermodilution method tends to overestimate Doppler-derived CFR[63], while the continuous thermodilution and the Doppler method show an excellent agreement in assessing CFR[64]. However, the Doppler method's primary drawback lies in its increased difficulty of execution and frequent constraints imposed by suboptimal signal quality[59],[65]. Therefore, despite its technical limitations, the thermodilution is currently the most widely adopted method for CMD assessment.

4.3. Bolus Thermodilution Method

A dedicated guidewire with a pressure-temperature sensitive tip is used for both the bolus and the continuous thermodilution methods (PressureWire X, Abbott Vascular, Santa Clara, CA, USA). Notably, the bolus thermodilution method is based on the assumption that CBF equals the inverse of the transit time of blood and that the epicardial volume remains constant (i.e., $Q \approx 1/Tmn$)[66].

First, the pressure sensor at the tip of the guidewire is equalized with the aortic pressure (Pa) just outside the guiding catheter, and then the wire is advanced in the coronary artery (normally to the distal left anterior descending coronary artery (LAD)). Subsequently, the temperature is zeroed to match the values in the two thermistors in the wire. The distal pressure (Pd), measured at the transition of the radiopaque part of

the guidewire, and the Pa, measured at the tip of the fluid-filled guiding catheter, are recorded simultaneously during the entire procedure. Then, the resting mean transit time (Tmn) is determined by the mean of three measurements obtained after three injections of 3 mL of saline solution in the coronary artery. To obtain reliable data, at least three injections should be performed, and transit-time values should not differ by more than 20% of each other. Operators should discard the measurements outside this range of reproducibility and continue with injections until three reliable transit time values with low variability are obtained. After determining the resting Tmn, the same procedure is repeated under hyperemia, which is generally achieved by continuous administration of adenosine through a central vein or intracoronary papaverine. A dose of adenosine 140 μg/kg/min or 12 mg of papaverine is sufficient to induce maximal hyperemia. CFR is calculated by dividing the resting Tmn by the hyperemic Tmn[67], while IMR is determined as the hyperemic Pd divided by the inverse of the hyperemic Tmn (IMR = Pdhyper × Tmnhyper)[53],[68], assuming that MVR is minimal during hyperemia (Table 1). The bolus thermodilution method further allows us to calculate the resistive reserve ratio (RRR), which is obtained by the ratio between the resting and the hyperemic MVR. This parameter is a marker of the microvasculature ability to change from baseline to minimal resistance during hyperemia[69]. According to the current recommendations, the cutoff values for normality are >2 for CFR and <25 for IMR[7],[70]. Abnormal values of CFR (<2) and/or IMR (>25) are suggestive of CMD; nonetheless, given the overestimation of CFR by bolus thermodilution, a CFR gray zone of 2.0 to 2.5 has been proposed. With respect to the RRR, this parameter has been studied in patients with myocardial infarction, where a value ≤1.7 has been associated with an increased myocardial hemorrhagic area[71], but no specific cutoff has been established for CMD yet. A representative case of CMD

assessment with the bolus thermodilution method is provided by Figure 4.

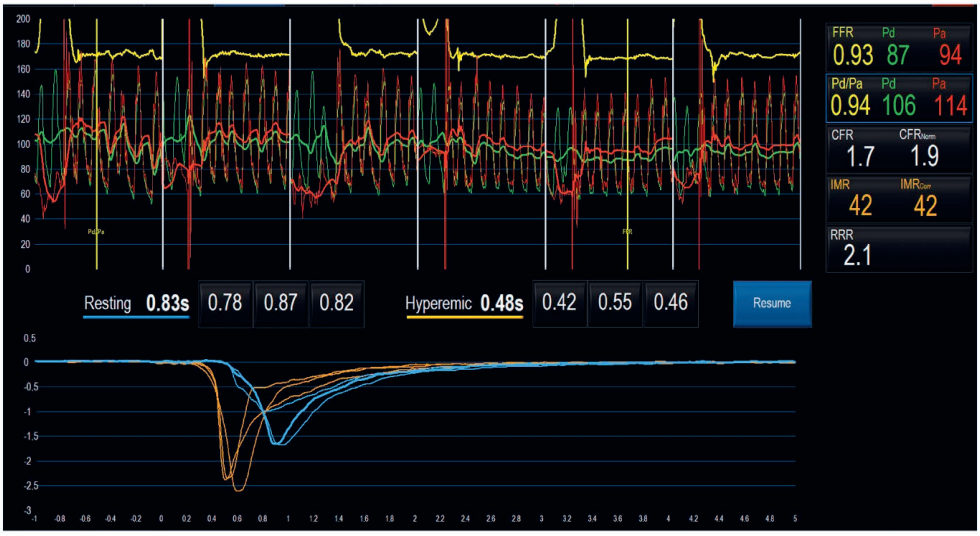


Figure 4. Microvascular assessment with the bolus thermodilution method showing high value of IMR (42 and low value of CFR (1.7), suggestive of coronary microvascular dysfunction.

Table 1. Coronary-function-testing-derived physiological parameters.

Method	Parameter	Formula	Cutoff for CMD	Meaning
Bolus thermodilution	Coronary flow reserve (CFRbolus)	CFRbolus = resting Tmn / hyperemic Tmn	<2.0 (validated)	The capacity to increase CBF from resting to stress conditions (derived from transit time).
	Index of microvascular resistance (IMR)	IMR = hyperemic Pd / hyperemic Tmn	>25 (validated)	Dimensionless index which represents MVR during stress conditions.
	Resistive reserve ratio (RRR)	RRR = (resting Pd / resting Tmn) / (hyperemic Pd / hyperemic Tmn)	Unknown	The ability of microcirculation to reduce MVR during stress conditions (derived from transit time).
Continuous thermodilution	Absolute coronary flow (Q)	Q = Ti / T * Qi * 1.08	<200 mL/min (under investigation)	Direct measurement of CBF.
	Absolute microvascular resistance (R)	R = Pd / Q	>500 UW (under investigation)	True MVR derived from CBF.
	Coronary flow reserve (CFRcontinuous)	CFRcontinuous = hyperemic Q / resting Q	<2.0–2.5 (under investigation)	The capacity to increase CBF from resting to

				stress conditions (derived from CBF).
	Microvascular resistance reserve (MRR)	MRR = CFR / (FFR * resting Pa / hyperemic Pa)	<2.1 (under investigation)	The ability of microcirculation to reduce MVR during stress conditions (derived from CBF).

4.4. Continuous Thermodilution Method

Recently, the continuous thermodilution method was validated and introduced in many centers focused on coronary physiology. This method requires the use of a dedicated monorail infusion catheter (RayFlow, Hexacath Inc., Paris, France) composed by an inner lumen for the 0.0140″ pressure–temperature guidewire and an outer lumen for saline infusion[172]. After positioning the tip of the infusion catheter at the proximal target vessel (normally the LAD) and equalizing, the guidewire is advanced about 5–6 cm distal from the catheter tip. Then, the temperature is zeroed, and saline, at room temperature, is infused at prespecified flow rates. Generally, 10 and 20 mL/min saline infusion flow rates are chosen to assess coronary physiology parameters under resting and stress conditions, respectively. Intracoronary saline infusion at 20 mL/min induces hyperemia through both vasodilation and intravascular hemolysis and has been shown to be comparable to adenosine in assessing CFR[173]. After a temperature steady state is reached, the temperature of the mixture blood/saline (T) at the temperature sensor of the guidewire is measured for about 30 s. Thereafter, the guidewire is withdrawn into the infusion catheter to obtain the temperature of the infused saline (Ti)[173],[174]. As mentioned above, the procedure is repeated two times at different saline infusion flow rates to obtain measurements under both rest and stress conditions. Alternatively, the infusion can be programmed to automatically change from 10 mL to 20 mL and 10 mL, thus obtaining all the necessary values for the calculation of Q and R with one pullback.

The absolute coronary flow (Q) is calculated as the ratio of Ti to T, multiplied by the saline infusion rate (Qi) and corrected for a constant related to the difference between heat and density of blood and saline. The absolute microvascular resistance (R) is calculated as the ratio between the distal coronary pressure (Pd) and Q (Table 1)[174]. Notably, the repetition of these measurements under rest and stress conditions allows for the calculation of both CFR and of a novel index, the microvascular resistance reserve (MRR), which is obtained

by the ratio between rest and hyperemic Q with a compensation for changes in blood pressure during hyperemic conditions and the presence of epicardial disease (Table 1). MRR is then the ratio of true resting microvascular resistance (Rμ, rest) as it would be in the hypothetical case that the epicardial artery would be completely normal, and hyperemic microvascular resistance (Rμ, hyp) expresses the capacity of the microvasculature to decrease its resistance under stress conditions[5,64]. Currently, the clinical application of Q, R and MRR is limited by the lack of validated cutoffs. However, recent studies have addressed the issue and proposed normality values. In a recent study assessing the relationship between CFR/IMR and Q and R, Konst et al. proposed a normality cutoff for Q and R, respectively, of 320 mL/min and 487 WU[62], while another study by de Vos et al. suggested that MRR values >2.7 and <2.1, respectively, exclude and confirm the presence of CMD[75]. Despite the fact that its clinical application is still limited by its relatively recent introduction, the continuous thermodilution method has been validated against the gold-standard positron emission tomography (PET), showing a strong correlation and agreement between PET- and invasive-derived CFR[76]. In addition, it has proved to be safe and highly reproducible[174]. Figure 5 provides an exemplificatory case of CMD assessment with the continuous thermodilution method.

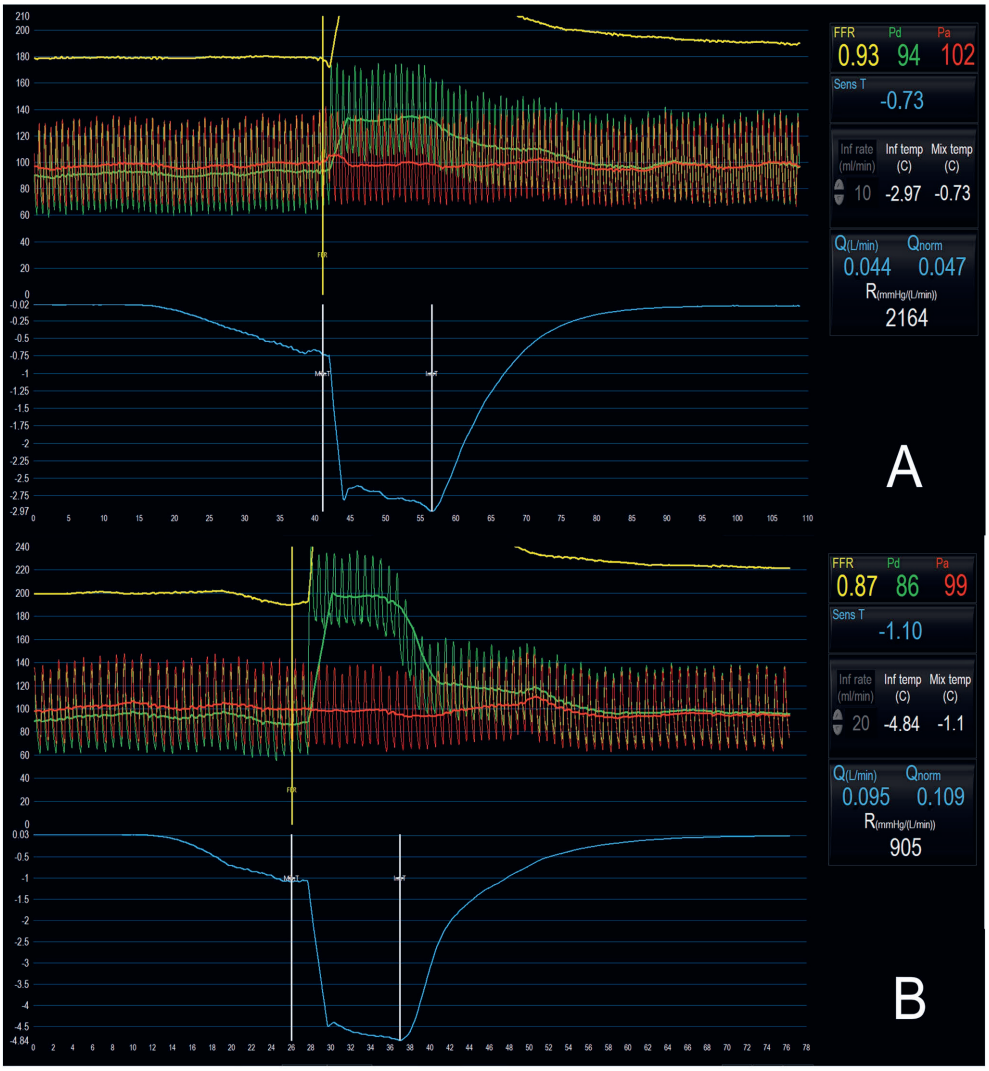


Figure 5. Microvascular assessment with the continuous thermodilution method. (A) Bolus thermodilution assessment during saline infusion reproducing resting conditions (10 mL/min). (B) Bolus thermodilution assessment during saline infusion reproducing hyperemia (20 mL/min), showing low values of Q (95 mL/min) and high value of R (905 UW) suggestive of coronary microvascular dysfunction.

4.5. Bolus vs. Continuous Thermodilution Method to Assess CMD

Whether the bolus or the continuous thermodilution should be the method of choice in assessing CMD is a current matter of debate. Despite its recent introduction and the lack of validated cutoffs, the increasing uptake of the continuous thermodilution method in the catheterization laboratories opens a new window to a better understanding of microvascular dysfunction and to differentiate among different endotypes. Moreover, several aspects of this technique make it particularly interesting and potentially able to overcome some of the inherent limitations of the bolus thermodilution method. First, since adenosine is not required, assessing the microvascular function with the continuous thermodilution method represents a more tolerable procedure because unpleasant side effects, including tachycardia, chest oppression, and dyspnea, are eliminated. Second, adenosine is contraindicated in patients with bronchoconstrictive lung disease, asthma and second- or third-degree atrioventricular block, limiting the spectrum of patients eligible for the bolus thermodilution. Moreover, while the bolus thermodilution requires the physician to discard measurements with poor-quality curves or that are highly discordant, the continuous method is less operator dependent. Finally, the bolus thermodilution method is based on the assumption that CBF corresponds to the inverse of Tmn of the saline injection, while continuous-thermodilution-derived Q and R come from a direct measurement of true CBF[172]. Nonetheless, continuous thermodilution is more costly and requires an infusion pump that is able to be programed for the infusion of saline in mL/min.

In addition to the inherent diversities related to procedural factors, other aspects have been highlighted by recent studies comparing reproducibility, variability and symptoms prediction capacity of these two modalities. Gallinoro et al. showed that the variability of continuous-derived CFR and MRR is significantly smaller than of the bolus-derived CFR, IMR and RRR (12.8% vs. 31.3% for CFR_cont and CFR_bolus; and 12.4% vs. 23.2% vs. 31.8% for MRR, IMR and RRR, respectively)[77]. Similar findings come from a recent study by Jansen et al. in which 73 patients underwent baseline and follow-up CFTs after 6 weeks. In this study, the authors showed that continuous-derived Q and R at 6 weeks significantly correlated with their baseline measurements, while bolus-derived CFR and IMR values did not[78]. The variability of bolus-derived CFR between baseline and follow-

up might be explained by different resting flow values between the first and the second measurement. By contrast, the variability of the IMR values might be related to the intra-observer inconsistency of bolus transit times within different procedures.

With respect to their clinical relevance, deVos et al. found that continuous-thermodilution-derived CFR and MRR were significantly associated with quality of life and angina domains, while the corresponding bolus-thermodilution-derived parameters were not. Notably, the correlation between symptoms and continuous-derived CFR and MRR further improved after excluding patients with spasm[79]. Another study by Konst et al. similarly showed that high values of continuous-thermodilution-derived R and/or low Q were more frequent in patients with severe angina, while bolus-thermodilution-derived CFR and IMR did not correlate with symptoms[62]. These results suggest that continuous- rather than bolus-thermodilution-derived parameters relate better to anginal symptoms.

The available data seem to suggest that the continuous thermodilution represents a more reliable and operator-independent method to evaluate the microvascular function. However, more validation studies are needed before this becomes the reference method to assess CMD.

5.Treatment

The management of patients with ANOCA/INOCA should be based on multidisciplinary counselling evaluating lifestyle and risk factors. The main cardiovascular risk factors, such as obesity, hypertension, dyslipidemia, DM and smoking, may be involved in the pathophysiology of CMD and epicardial or microvascular spasm. Therefore, lifestyle changes and risk factors' control are the first-line recommendations in this category of patients[70]. Additionally, it is well known that physical exercise is associated with improvement in the endothelial function through nitric oxide (NO) formation and endothelium-dependent vasodilation[80]. The anti-inflammatory properties of statins and their effects on the endothelial function might be beneficial in patients without significant CAD[81]. Moreover, previous studies evaluating the efficacy of statins on CMD showed a significant improvement of CFR values in patients treated with atorvastatin[82]

or rosuvastatin[83],[84]. Hypertension is often associated with CMD, and angiotensin-converting enzyme inhibitors have been proven to ameliorate exercise tolerance and angina symptoms in patients with MVA[85]. Notably, patients treated with long-term enalapril showed an improvement of coronary microvasculature function and myocardial ischemia due to an increased bioavailability of endothelial NO[86]. In addition, the WISE study showed an increase of CFR values in women with CMD treated with quinalapril[87]. The Coronary Microvascular Angina (CorMicA) trial first demonstrated an improvement of angina symptoms and quality of life at 6 months and 1 year in patients treated with stratified medical therapy guided by invasive CFTs[88],[89]. To simplify, a proper diagnosis between different ANOCA endotypes allows for a specific and distinct treatment which has been proven to improve the clinical outcome[90].

Therapy of ANOCA

Beta-blockers may reduce ischemia symptoms in patients with MVA by reducing myocardial oxygen consumption and represent the first-line therapy recommended by the European Society of Cardiology[91]. However, only a few data are available about the effect of beta-blockers on microvascular function. Atenolol and propranolol have been shown to reduce ischemic episodes in patients with MVA[92],[93], while intracoronary nebivolol administration showed a significant improvement in CFR values due to its vasodilatory effect[94]. Calcium channel blockers (CCBs) may be considered second-line therapy if beta-blockers are not tolerated, or as first-line therapy in patients with response to Ach testing suggestive of microvascular spasm[91]. Moreover, dihydropyridine CCBs such as amlodipine may be added to beta-blockers if blood-pressure values permit it[90]. As far as it is known about non-dihydropyridine CCBs and microvascular function, diltiazem failed to improve CFR values in patients with MVA[95]. Data about the effect of nitrates on coronary microcirculation are limited, and long-acting nitrates seemed ineffective, poorly tolerated or even detrimental in patients with MVA[96],[97]. Nicorandil is a potassium-channel activator with a coronary microvascular dilatory effect and may be considered antianginal therapy[90]. Ranolazine is an antianginal drug that improves myocardial perfusion; however, data about its impact on coronary microcirculation are

scarce. A randomized placebo-controlled trial showed that ranolazine therapy did not improve symptoms or myocardial perfusion in patients with no-obstructive CAD and CMD but improved myocardial perfusion in a subgroup of patients with low CFR values[98]. Finally, ivabradine may reduce angina symptoms by decreasing heart rate at rest and during exercise. However, studies evaluating the effect of ivabradine on microvascular function showed conflicting results[99],[100]. Importantly, patients with CMD due to low CFR/low MVR and high resting CBF are unlikely to benefit from vasodilating drugs, while it could be theoretically more appropriate to specifically act on myocardial efficiency or uncoupled CBF[47].

CCBs should be considered first-line therapy and are effective in treating the majority of patients with epicardial vasospasm[101]. In some patients, high-dose CCBs or even a combination of non-dihydropyridine and dihydropyridine CCBs, such as diltiazem and amlodipine, is needed[70],[102]. Despite the fact that long-acting nitrates are not suggested in patients with MVA, they showed a good efficacy in the treatment of VSA[103] and may be added in some patients. On the contrary, beta blockers are not recommended, as they might favor spasm by reducing the beta-mediated vasodilation, which opposes the alpha-mediated vasoconstriction[104].

6.Gaps in Knowledge

In the last decades, there has been a growing interest in coronary physiology assessments for a proper diagnosis of ANOCA and INOCA patients. Many studies investigated the diagnostic accuracy of invasive CFTs and their impact on clinical outcomes. However, some aspects of these techniques are still a matter of debate.

Previous studies revealed a modest correlation between Doppler-derived and bolus-thermodilution-derived CFR and a trend towards CFR overestimation with the bolus thermodilution method[59],[63]. For this reason, some authors suggested a CFR threshold of 2.5 when measured with the bolus thermodilution method for better diagnostic accuracy of CMD[63]. Accordingly, a recent study by Gallinoro et al. found higher values of CFR when derived from bolus thermodilution than from continuous thermodilution[77]. Thus, further investigations are needed to confirm the better accuracy of higher cutoff values for bolus-thermodilution-derived CFR for the diagnosis of CMD.

One of the main limitations of these tests is still the uncertainty regarding their prognostic implications. Previous data demonstrated that a low CFR is associated with the worst clinical outcomes[105–107], while the clinical impact of high MVR values is still unclear. In a recent study, Boerhout et al. showed that the risk of MACE was higher in patients with an abnormal CFR regardless of normal or abnormal MVR[108]. Therefore further studies evaluating the long-term follow-up of patients affected by CMD will shed light on the clinical impact of augmented MVR. Moreover, further evidence is needed to clarify the clinical implications of an abnormal MRR index.

Due to its wide myocardial perfusion territory, the LAD is typically the target vessel in which coronary physiology measurements are performed. CFTs can be performed in the left circumflex or right coronary artery in the case of technical issues in testing the LAD, or in addition to the LAD assessment in the case of negative results but a high clinical suspicion of CMD[70]. However, solid data about the comparison between CFR and MVR values measured in different myocardial territories are not available. In addition, it is unclear whether INOCA patients with a defined regionality of myocardial ischemia might present different coronary physiology features between the ischemic and the nonischemic territories.

As mentioned above, recent data suggested the superiority of the continuous thermodilution over the bolus thermodilution method in assessing the microvascular function, mainly due to its better reproducibility, precision, and correlation with symptoms. As a consequence, it has to be investigated whether the continuous thermodilution method would increase the diagnostic accuracy of different CMD endotypes, such as coronary microvascular function presenting an isolated increase of MVR with normal CFR on bolus thermodilution, and, therefore, it is necessary to identify those patients who may benefit from specific and individualized therapies. In this context, the Netherlands registry of invasive Coronary vasomotor Function Testing was initiated with the aim of collecting baseline, procedural and follow-up data in patients with suspected and/or established ANOCA and INOCA. This registry will provide more insight into the pathophysiology, diagnostic process, and treatment of these patients, with potential implications from both scientific and clinical perspectives[6].

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Chapter 18

Coronary microvascular dysfunction: Focus on pathophysiological mechanisms and recent diagnostic techniques.

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Review

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Abstract

In interventional cardiology, our efforts have traditionally centered on treating lesions in the epicardial coronary arter-ies, which can be visualized on coronary angiography. However, a significant proportion of patients experience similar symptoms to those with epicardial coronary artery lesions, yet without any angiographically visible coronary artery disease. These cases fall under the spectrum of coronary microvascular dysfunction. In this review, we will explore the disease's pathophysiology and focus on new frontiers in terms of diagnostic approaches and therapeutic strategies according to different endotypes.

Introduction

1.1. Definition of coronary microvascular dysfunction (CMD)

Coronary microvascular dysfunction (CMD), is characterized by reduced Coronary Flow Reserve (CFR) and/or increased microvascular resistance (IMR) despite the absence of obstructive epicardial disease[1]. This condition can clinically manifest in various scenarios, all of which are associated with the absence of documented epicardial coronary artery disease (CAD). These include conditions such as angina without coronary artery obstruction (ANOCA), documented myocardial ischemia in absence of obstructive coronary artery disease (INOCA), and myocardial infarction, according to the universal definition of infarction, without obstructive coronary disease (MINOCA)[2]. The pathophysiological cause of these conditions is heterogeneous, and can be attributed to two main factors: CMD or the presence of coronary abnormal vasomotion either at epicardial or microcirculatory level[3].

1.2. Epidemiology and prevalence

A significant number of patients (up to 70 %) who undergo coronary angiography for anginal symptoms do not have obstructive coronary arteries despite showing measurable ischemia[4]. Research over the last two decades has highlighted that CMD and vascular dysfunction are key additional mechanisms of ischemic heart disease (IHD)[1]. Although some data initially suggested a gender difference in the distribution of non-obstructive coronary artery disease, conflicting evidence exists. The Women's Ischemia Syndrome Evaluation (WISE) study found that 47 % of women with chest pain but normal or

minimally irregular coronary arteries had abnormal coronary microcirculation, as shown by intracoronary reactivity tests[5,6]. However, another large cohort study found that 64 % of patients without obstructive CAD had CMD based on vasoreactivity tests, with similar prevalence rates between men and women (60 % vs. 66 %)[7]. This suggests that the gender difference in non-obstructive coronary artery disease might not be as significant as initially thought[8,9].

2. Anatomy and physiology of coronary microvasculature

2.1. Structure of coronary microvasculature

The coronary vasculature is structured into three continuous compartments, each with distinct functions and decreasing size (Fig. 1).

1) The proximal compartment consists of large epicardial arteries, which have a diameter ranging from 5.0 to 0.5 mm and a three-layered wall. These arteries serve a capacitance function and offer minimal resistance to coronary blood flow (CBF) when there is no significant stenosis.

2) The intermediate compartment includes pre-arteriolar vessels with diameters between 100 and 500 μm. This compartment is further divided into two territories: the proximal pre-arterioles (500 to 150 μm), which are more responsive to changes in blood flow, and the distal pre-arterioles (150 to 100 μm), which are more sensitive to pressure variations. These vessels contribute significantly to the resistance of blood flow, causing a measurable pressure drop along their length. Their vasomotor actions are generally not directly influenced by diffusible myocardial metabolites.

3) The distal compartment is made up of intramural arterioles with diameters <100 μm. These arterioles are crucial for matching myocardial blood supply with oxygen consumption and contribute to >50 % of the total coronary vascular resistance.

4) Capillaries, with diameters under 10 μm, act as exchange sites due to their extensive surface area and high permeability.

In healthy hearts, CBF and myocardial perfusion are controlled by the tone of coronary arterioles. The CBF stays consistent across various perfusion pressures by dynamically adjusting the resistance of these vessels. This regulation is influenced by adrenergic signals, changes in local oxygen levels, and variations in transmural pressure[10,11]. These

interconnected control mechanisms help prevent myocardial ischemia as atherosclerosis develops in the epicardial arteries (Fig. 1).

3. Pathophysiology

In healthy coronary vessels, blood flow remains stable across various perfusion pressures through a process called autoregulation, which involves changes in arteriolar tone. In the context of non-obstructive CAD, the pathophysiological bases can be found either in CMD, which can disrupt this regulation through structural and functional abnormalities[112], or in vasospastic mechanisms, where coronary spasm may affect both the epicardial coronary arteries and/or the coronary microcirculation.

3.1. Structural CMD

This condition involves physical changes such as luminal obstruction, capillary loss, and fibrosis, which increase vessel resistance. These changes are often linked to cardiovascular risk factors like hypertension, smoking, diabetes, as well as conditions like infiltrative disease and hypertrophic cardiomyopathy[1314]. Structural remodeling includes inward changes in arterioles, increased wall-to-lumen ratios, and reduced capillary density (capillary rarefaction) hampering the ability of microcirculatory system to dilate, limiting oxygen delivery and making vessels more reactive to constricting stimuli. Consequently, CFR is reduced, and minimal microcirculatory resistance is increased[15].

3.2. Functional CMD

A subset of patients present with low CFR, low or normal microvascular resistance (MVR), and high resting coronary blood flow (CBF). This phenomenon is thought to be associated with an increased myocardial oxygen demand or impaired coronary autoregulation, resulting in elevated resting coronary flow despite normal microcirculation and myocardial workload under maximally vasodilated conditions. The exact mechanism underlying this specific form of CMD remains unclear, potentially involving either reduced myocardial efficiency or uncoupled CBF[16].

3.3. Vasomotor dysfunction

The administration of vasoreactivity-inducing stimuli investigates the endothelium-dependent mechanisms of microvascular and epicardial vasomotor tone disorders.

Functional arteriolar dysregulation is associated to endothelial dysfunction, leading to impaired vasorelaxation or paradoxical vasoconstriction of medium and large arterioles in response to endothelium-dependent vasodilators, as well as increased sensitivity to vasoconstricting agents. Microvascular spasm is diagnosed during acetylcholine provocation testing when myocardial ischemia (anginal symptoms, EKG changes) can be induced in the absence of angiographically evident spasm (<90 % diameter reduction) in the epicardial coronary arteries[17]. Epicardial coronary artery spasm is a vasomotor disorder originating mainly from vascular smooth muscle hyperreactivity (VSMCs), with endothelial cells dysfunction playing a lesser role than at an arteriolar level. These cells contract through the phosphorylation and dephosphorylation of myosin light chains (MLCs), with rho-kinase, which is overexpressed in spastic cells, inhibiting MLC dephosphorylation[18][19]. Coronary spasms may occur at sites of atherosclerotic plaques due to endothelial dysfunction, which causes an imbalance between vasodilatory and vasoconstrictor signals, potentially triggering local injury and myocardial infarction[20]. Coronary spasm at both epicardial and microvascular level can lead to conditions such as MINOCA, ANOCA, and INOCA.

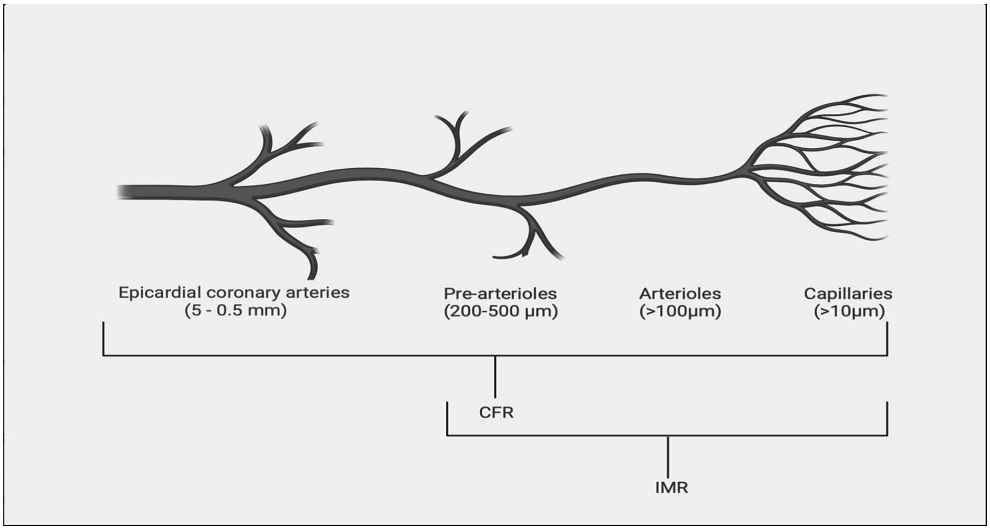


Fig. 1. Coronary vessel anatomy. CFR, coronary flow reserve; IMR, index of microcirculatory resistance.

4. Diagnosis

4.1. Non-invasive testing methods

Several non-invasive techniques are available for diagnosing CMD. While these non-invasive methods do not directly assess vasospasm, they are crucial for evaluating the vasodilatory capacity of VSMC, which can indicate impaired microcirculatory function.

4.1.1. Transthoracic Doppler echocardiography (TTDE)

Transthoracic Doppler echocardiography (TTDE) is a technique for evaluating CMD. It measures coronary flow velocity reserve (CFVR) by assessing the peak diastolic flow in the epicardial arteries both at rest and during stress induced by agents like adenosine, dipyridamole, or regadenoson[21]. CFVR is calculated as the ratio of diastolic CBF velocity at rest compared to during stress. A CFVR value of ≤2–2.5 is commonly used to indicate impaired microvascular function[22].

TTDE is advantageous for several reasons: it is relatively cost-effective, non-invasive, and does not expose patients to radiation. However, its effectiveness is highly dependent on the operator's expertise and experience, and it presents technical challenges, particularly in obtaining clear images of the coronary arteries. Overall, TTDE remains a valuable, non-invasive tool for assessing coronary microvascular function, offering practical benefits despite its limitations and dependence on operator skill.

4.1.2. Positron emission tomography (PET)

Positron emission tomography-myocardial perfusion imaging (PET-MPI) is a highly accurate non-invasive technique used to assess CMD by CFR assessment. This is achieved by calculating the rate of radioactive tracer uptake in the left ventricular myocardium both at rest and during peak vasodilator stress. The most commonly used tracers in PET-MPI include rubidium-82 labeled rubidium chloride, nitrogen-13 labeled ammonia, and oxygen-15-labeled water[23]. Oxygen-15-labeled water is particularly noted for its high first-pass extraction and strong correlation with myocardial blood flow (MBF), making it a preferred choice in some studies.

PET-MPI is considered the gold standard for non-invasive CMD testing due to its ability to accurately measure myocardial perfusion reserve (MPR, which threshold is <2)[24] across all coronary territories simultaneously. Despite its clinical value, the widespread use of PET-MPI is constrained by its high cost, limited availability, and associated radiation exposure. Nonetheless, PET remains the most validated and precise method for

assessing coronary vasomotor dysfunction, making it an essential tool in the diagnosis and management of CMD.

4.1.3. Cardiac magnetic resonance (CMR)

Cardiac Magnetic Resonance (CMR) imaging has become a valuable tool for assessing myocardial ischemia, particularly in patients with suspected CAD or CMD. CMR stress perfusion imaging works by evaluating myocardial perfusion based on changes in signal intensity following the administration of a gadolinium-based contrast agent. This method allows for the assessment of MBF both at rest and during stress induced by vasodilatory agents.

CMR can calculate MPR by measuring the ratio of MBF at peak hyperemia compared to rest, providing a quantitative assessment of coronary vasomotor function[25]. This capability is particularly useful in diagnosing CMD, especially in cases where patients present with symptoms of myocardial ischemia but do not have obstructive coronary artery disease.

CMR offers significant advantages, including high spatial resolution and the ability to assess all coronary territories without ionizing radiation. However, similar to PET, the widespread use of CMR is limited by its high cost and the technical demands of post-processing the images. Despite these challenges, CMR remains a critical tool in the non-invasive evaluation of myocardial perfusion and the diagnosis of CMD.

4.1.4. Dynamic myocardial perfusion CT

Dynamic myocardial perfusion computed tomography (CT) is an emerging technique for evaluating MBF and MPR. This method involves capturing the first pass of an iodinated contrast agent through the heart using CT imaging, which facilitates the estimation of MBF[26]. A significant advantage of dynamic CT is its high spatial resolution, enabling a detailed analysis of both coronary arteries and myocardial tissue in a single scan[27].

Despite its benefits, dynamic CT has some limitations. It involves higher radiation exposure compared to other imaging modalities, which can be a concern, especially for younger or radiation-sensitive patients. Nonetheless, the ability to integrate coronary computed tomography angiography (CTCA) with myocardial perfusion assessment in one examination makes dynamic CT a promising tool for comprehensive evaluation. This dual

capability allows for the simultaneous assessment of both epicardial CAD and coronary microvascular dysfunction CMD.

While the application of dynamic myocardial perfusion CT for CMD assessment is still limited and less studied compared to CMR, it represents a significant advancement. Its potential to combine anatomical and functional evaluation in a single diagnostic session makes it an attractive option for detailed cardiovascular assessment (Table 1).

4.2. Invasive testing methods

4.2.1. Coronary angiography

Coronary angiography is an invasive procedure primarily utilized to exclude the presence of CAD. However, beyond its role in assessing epicardial vessels, it also provides insights into coronary microcirculation. During angiography, the dynamic passage of contrast through the coronary arteries can reveal microvascular abnormalities, such as the "coronary slow-flow phenomenon." This phenomenon is characterized by delayed opacification of the distal coronary vasculature despite the absence of significant obstructive CAD, serving as significant indicator of CMD. Various studies have used different criteria to define slow-flow, including the Thrombolysis In Myocardial Infarction (TIMI-2) flow or a corrected TIMI frame count (CTFC) of over 25 frames[22].

Emerging angiography-derived indices, such as IMRangio derived from FFR, have shown good correlation with traditional IMR in assessing CMD. NH-IMRangio is a non-hyperemic variant validated to predict outcomes, such as mortality and heart failure, over a long-term follow-up. caIMR integrates TIMI frame counts and has demonstrated robust prognostic value, predicting adverse outcomes with greater accuracy. These computational tools use angiographic images and mathematical modeling to estimate coronary microvascular resistance, eliminating the need for pressure wires and hyperemia induction[28].

4.2.2. Functional evaluation

During coronary function testing, the left anterior descending (LAD) coronary artery is often the preferred target vessel due to its myocardial mass and coronary dominance. If initial tests are negative and clinical suspicion remains high, other coronary arteries may be evaluated. Heparin is administered intravenously to achieve therapeutic anticoagulation, with an activated clotting time of approximately 250 s. The testing can

be performed using a pressure–temperature sensor guidewire (such as the PressureWire XTM Abbott Vascular, Santa Clara, CA, USA) or a Doppler guidewire (such as the ComboWire XT or Flowire, Philips Volcano Corporation, San Diego, CA, USA)[29]. According to the COVADIS[22] recommendations, key parameters for assessing coronary microvascular function include Coronary Flow Reserve (CFR) and the Index of Microvascular Resistance (IMR). CFR measures how much the CBF can increase above its baseline during stress conditions, reflecting both epicardial and microvascular system, while IMR specifically assesses microvascular resistance[30]. Both parameters can be measured using the bolus thermodilution method, though advances have led to the continuous thermodilution method, which introduces new indices and overcomes some limitations of the bolus method[16]. CFR and microvascular resistance can also be measured using the Doppler technique with a coronary flow velocity-measuring guide wire but is technically challenging and often limited by signal quality issues[29]. Thermodilution remains the most widely used method for assessing CMD due to its practicality.

4.2.3. Bolus thermodilution

The bolus thermodilution method assumes that the CBF is inversely proportional to blood transit time in the coronary artery, with constant epicardial volume ($Q \approx 1/Tmn$)[31]. The process begins by equalizing the guidewire's pressure sensor with the aortic pressure (Pa) outside the guiding catheter. The wire is then advanced into the coronary artery, and temperature calibration is performed to match the values at the wire's thermistors. Throughout, distal pressure (Pd) and Pa are recorded simultaneously, resting mean transit time (Tmn) is determined by averaging three resting transit time measurements obtained after three intracoronary saline injections, ensuring consistent transit time values with <20 % variability. This process is repeated under hyperemia, induced by adenosine or papaverine administration[16]. CFR is calculated by dividing resting Tmn by hyperemic Tmn, while the Index of Microvascular Resistance (IMR) is calculated as hyperemic Pd multiplied by hyperemic Tmn, assuming minimal microvascular resistance (MVR) during hyperemia[32]. Additionally, the bolus thermodilution method allows calculation of the resistive reserve ratio (RRR), which reflects the microvasculature's ability to adjust resistance during hyperemia.

4.2.4. Continuous thermodilution

The continuous thermodilution method has been recently investigated and adopted in many centers specializing in coronary physiology[33]. This method involves advancing a pressure-temperature sensitive guidewire into the coronary artery, and infusing intracoronary saline via a monorail infusion catheter (RayFlow Hexacath Inc., Paris, France) at specific rates (10 or 6–7–8 mL/min to 20 mL/min) through the monorail catheter to assess coronary physiology under both resting and stress conditions. Saline infusion at 20 mL/min induces hyperemia[34], allowing for the assessment of Coronary Flow Reserve (CFR). Key measurements include absolute coronary flow (Q) and microvascular resistance (R), with the latter being derived from the distal coronary pressure and flow rate[35]. Additionally, a novel index, Microvascular Resistance Reserve (MRR), evaluates the microvasculature's ability to reduce resistance during stress. While the clinical application of these measurements is still limited due to the lack of widely accepted cutoffs, recent studies have proposed normal ranges for Q, R, and MRR[16].

4.2.5. Acetylcholine testing

Intracoronary acetylcholine (ACH) testing is used to evaluate coronary (epicardial and microvascular) vasospasm, it induces vasospasm through muscarinic receptors, and a positive test is indicated by ischemic ST-segment changes and symptom reproduction without significant epicardial constriction (<90 %). This test helps identify endothelial-dependent mechanisms of CMD[36].

Table 1 Non-invasive imaging methods and thresholds CFRV, coronary flow reserve veloc-ity; MPR, myocardial perfusion reserve; MPRI, myocardial perfusion reserve index. TTDE, Transthoracic Doppler echocardiography; PET, positron emission tomogra-phy; CMR, Cardiac magnetic resonance, DMPCT, dynamic myocardial perfusion computed tomography.

Methods	Contrast used	Threshold
TTDE	Adenosine/dipyridamole/regadenoson	CFRV<2
PET	^{13}Nammonia; ^{82}Rubidium	MPR < 2
CMR	Gadolinium	MPRI<2
DMPCT	Iodine-based contrast	MPR < 2

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Chapter 19

Coronary microvascular dysfunction: Phenotype-specific targeted therapies.

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Review

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Abstract

Coronary microvascular dysfunction remains an underdiagnosed clinical entity with historically limited therapeutic options. In this review, we aim to provide a comprehensive overview of its pathophysiology, linking it to the specific clinical syndromes with which it is frequently associated. Based on these mechanistic and phenotypic correlations, we propose tailored diagnostic approaches and therapeutic strategies to support more precise and effective clinical management.

1. Special Populations

1.1. CMD in Acute Coronary Syndromes

In the setting of acute coronary syndromes (ACS), impaired coronary microvascular reperfusion downstream of the culprit lesion can be identified in 5–65% of patients undergoing primary percutaneous coronary intervention (PCI) and is strongly associated with adverse outcomes[1,2]. The underlying mechanisms are multifactorial and include ischemic injury, ischemia–reperfusion injury, and distal embolization[3,4]. Individual susceptibility—shaped by genetic factors and pre-existing conditions such as diabetes and hypertension—also contributes to coronary microvascular obstruction and dysfunction (CMVO).

A coronary flow reserve (CFR) < 2 measured after revascularization, both in infarct-related and remote territories, predicts left ventricular remodeling and portends a worse prognosis[5]. Similarly, an index of microcirculatory resistance (IMR) > 40 measured immediately post-PCI has been consistently associated with higher rates of adverse clinical events, including death and heart-failure–related rehospitalization[6]. Finally, an RRR ≤ 1.7 in patients with ACS appears to correlate with increased myocardial hemorrhage, reflecting a more severe degree of microvascular injury[7].

1.2. CMD in HFpEF

Coronary microvascular dysfunction plays a central role in the pathogenesis of heart failure with preserved ejection fraction (HFpEF), with growing evidence suggesting that CMD and microvascular angina represent phenotypic expressions along the same disease spectrum[8,9]. The close anatomical and functional relationship between cardiomyocytes and endothelial cells facilitates bidirectional signaling that governs myocardial perfusion

and the release of vasoactive mediators such as nitric oxide (NO) and natriuretic peptides.

CMD in HFpEF is frequently driven by systemic inflammation, triggered by cardiovascular risk factors including hypertension, diabetes, obesity, and chronic inflammatory states. This inflammatory milieu reduces NO bioavailability and promotes myocardial fibrosis and hypertrophy, leading to left ventricular (LV) diastolic dysfunction[10].

HFpEF is characterized by diastolic dysfunction and concentric LV hypertrophy, in contrast to heart failure with reduced ejection fraction (HFrEF), which is marked by cardiomyocyte loss and LV dilation. Biomarkers of inflammation are typically higher in HFpEF, whereas markers of cardiomyocyte injury are more prominent in HFrEF. Moreover, the systemic multiorgan inflammation and microvascular dysfunction characteristic of HFpEF may contribute to extracardiac complications, underscoring the syndrome's systemic nature.

Recent studies, including the PROMIS-HFpEF study, have shown a high prevalence of CMD in HFpEF patients, linking CMD to worse cardiovascular outcomes and increased hospitalizations[11,12]. The exact role of CMD in HFpEF progression remains debated, but its association with diastolic dysfunction and systemic inflammation underscores its significance in HFpEF pathophysiology.

A recent study by Paolisso et al.[13] investigated CMD in patients with both HFpEF and HFrEF. CMD was documented in approximately 50% of the analyzed population. Using continuous thermodilution measurements, the study identified distinct CMD patterns in the two phenotypes.

Patients with HFpEF exhibited a structural CMD phenotype, characterized by increased microvascular resistance and reduced coronary flow, likely secondary to an underlying inflammatory and fibrotic profile. In contrast, HFrEF patients presented a functional CMD phenotype, with increased basal coronary flow and reduced microvascular resistance. This dysfunction is linked to neurohormonal activation and catecholaminergic drive, which increases myocardial oxygen demand at rest.

1.3. CMD in Aortic Stenosis

In approximately 40% of patients with aortic valve stenosis (AS), angina occurs despite the absence of coronary artery blockages due to CMD[14]. AS patients develop left ventricular hypertrophy (LVH) as an adaptive response to reduce wall stress. However, this hypertrophy, combined with the pressure gradient across the aortic valve, negatively affects coronary circulation.

This results in reduced CFR due to mechanisms such as shorter diastolic coronary filling time, elevated LV filling pressure, and impaired subendocardial perfusion[15]. Although myocardial blood flow increases to meet the higher oxygen demand of the hypertrophied LV, the microcirculation cannot further augment flow, limiting CFR[16]. Severity of AS, hemodynamic load, and reduced diastolic perfusion time are more critical for CFR reduction than LV mass alone. Importantly, low CFR is an independent predictor of future cardiovascular events in AS patients. Surgical or transcatheter aortic valve replacement (TAVR) is the only effective treatment once symptoms appear, as it restores myocardial perfusion and microcirculatory function by reducing LV wall stress[17].

Fig. 1. Central Illustration: functional evaluation in specific subsets; CFR, coronary flow reserve; IMR, index of microcirculatory resistance; Qbasal, resting flow; Qhyper, hyperemic flow; R, microvascular resistance.

2. Management and Treatment

2.1. Lifestyle Modifications

Lifestyle modification therapy is essential for managing CMD and improving cardiovascular health. Key strategies include:

Physical Exercise: Regular exercise enhances cardiorespiratory fitness, improves CFR, and reduces angina symptoms while supporting weight management and lowering blood pressure[18,19].

Smoking Cessation: Quitting smoking improves vascular function and reduces cardiovascular risk, including CMD[20].

Weight Management: Losing excess weight helps control blood pressure and cholesterol levels, reducing CMD risk and improving overall heart health[21].

Dietary Changes: A heart-healthy diet rich in fruits, vegetables, and whole grains, while low in saturated fats and cholesterol, supports better vascular health and metabolic control.

Environmental Factors: Reducing exposure to air pollution can further alleviate CMD symptoms and improve cardiovascular outcomes[22].

2.2. Pharmacological Treatments

The CorMicA trial confirmed that personalized, stratification-based therapy, including ACE inhibitors, improved angina control and quality of life in patients with non-obstructive CAD[23] (Fig. 2).

2.3. Anti-Anginal Medication

Beta-blockers:

Third-generation beta-blockers with vasodilatory effects, such as nebivolol and carvedilol[24,25,26], have shown promise in addressing CMD pathophysiology by improving endothelial function, reducing myocardial oxygen demand, and increasing diastolic perfusion time[27]. Despite these benefits, beta-blockers are generally avoided in patients with vasospastic microvascular disease due to the risk of potentially unopposed alpha-stimulation.

Calcium Channel Blockers:

In severe vasospastic angina (VSA), high doses of calcium channel blockers may be required, such as 200 mg of diltiazem twice daily, or combinations of non-dihydropyridine (e.g., diltiazem) with dihydropyridine agents (e.g., amlodipine). Non-dihydropyridine calcium channel blockers are preferred in vasospasm-mediated CMD due to their effectiveness[28,29].

Nitrates:

Nitrates primarily exert anti-anginal effects via venodilation, which reduces preload, and may also cause some coronary vasodilation. In microvascular angina (MVA), long-acting nitrates are often ineffective, poorly tolerated, and may worsen symptoms due to a coronary “steal” phenomenon, where blood flow is diverted from the already compromised microcirculation[30].

Ranolazine:

Ranolazine, an anti-anginal agent, has been extensively studied in small randomized clinical trials with mixed results regarding its efficacy on CFR, symptoms, and stress test outcomes[31,32], with other trials reporting conflicting findings on symptom improvement[33,34].

2.4. Anti-Atherosclerosis Medications

ACE Inhibitors:

ACE inhibitors are effective in managing MVA and CMD, particularly in hypertensive patients[35]. They improve myocardial blood flow, enhance CFR, and reduce angina symptoms.

Statins:

Statins reduce plaque lipid-rich cores, inflammation, macrophage and foam cell formation, while promoting fibrous cap thickening and reducing platelet reactivity[36]. When combined with ACE inhibitors, these benefits may be amplified[37]. Beyond lipid lowering, statins have antiatherosclerotic and anti-inflammatory effects, supporting their use in improving CFR[38]. Studies show that fluvastatin improves CFR, with even greater benefits when combined with diltiazem[39]. Small pilot studies also demonstrated that atorvastatin improved CFR after 2 and 6 months of treatment[40,41].

2.5. Emerging Therapies

Devices:

Enhanced external counterpulsation (EECP), which uses pneumatic cuffs on the patient's legs, can be considered as an adjunctive treatment for INOCA in patients with chronic coronary syndrome (CCS) who do not respond to traditional anti-anginal medications[42,43].

The Coronary Sinus Reducer (Neovasc Medical, Inc., Or Yehuda, Israel) is an endoluminal, balloon-expandable device made of hourglass-shaped stainless steel, implantable via a percutaneous approach. Its goal is to increase hydrostatic pressure within the coronary sinus—the final drainage pathway of the coronary venous system—leading to redistribution of coronary blood flow from non-ischemic to ischemic areas, thereby reducing myocardial ischemia.

CD34+ Cell Therapy:

CD34+ cell therapy has emerged as a promising treatment for these patients by promoting vascular repair and enhancing angiogenesis, improving coronary microvascular function and myocardial tissue perfusion. Intracoronary infusion of CD34+ cells has been shown to improve coronary flow reserve, resulting in reduced angina severity and better quality of life at 6 months[44].

3. Conclusion

Coronary microvascular dysfunction is associated with a wide range of clinical conditions and presents a heterogeneous profile. It is an often-overlooked entity, despite evidence showing its high prevalence in the general population and its association with both cardiac and extracardiac conditions. Recognizing CMD requires moving beyond an epicardiocentric perspective.

Currently, clinicians have access to comprehensive diagnostic strategies for CMD and can offer tailored therapeutic interventions. However, there remains a need for targeted pharmacological and interventional treatments, which will require validation through future randomized clinical trials.

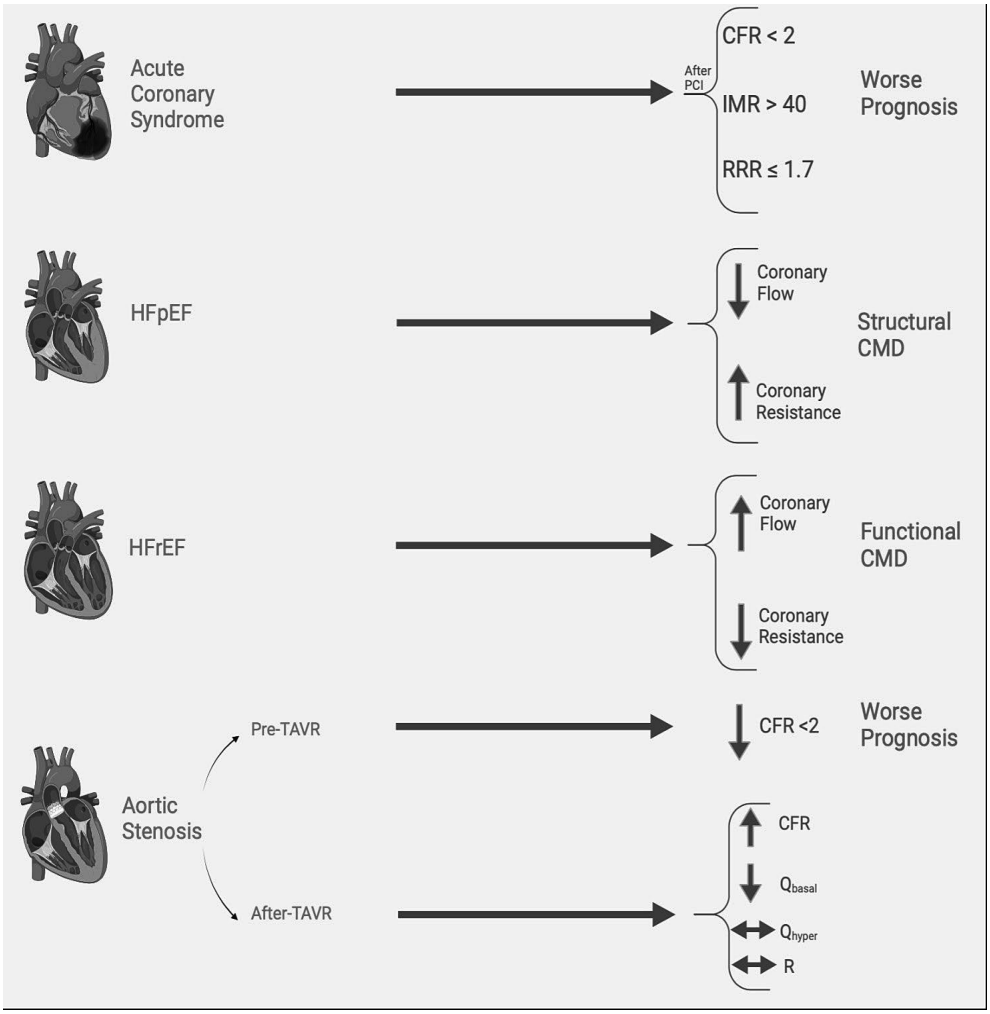


Fig. 1. Central Illustration, functional evaluation in specific subsets; CFR coronary flow reserve; IMR, index of microcirculatory resistance.; Qbasal, resting flow; Qhyper, Hyperaemic flow; R, microvascular resistance.

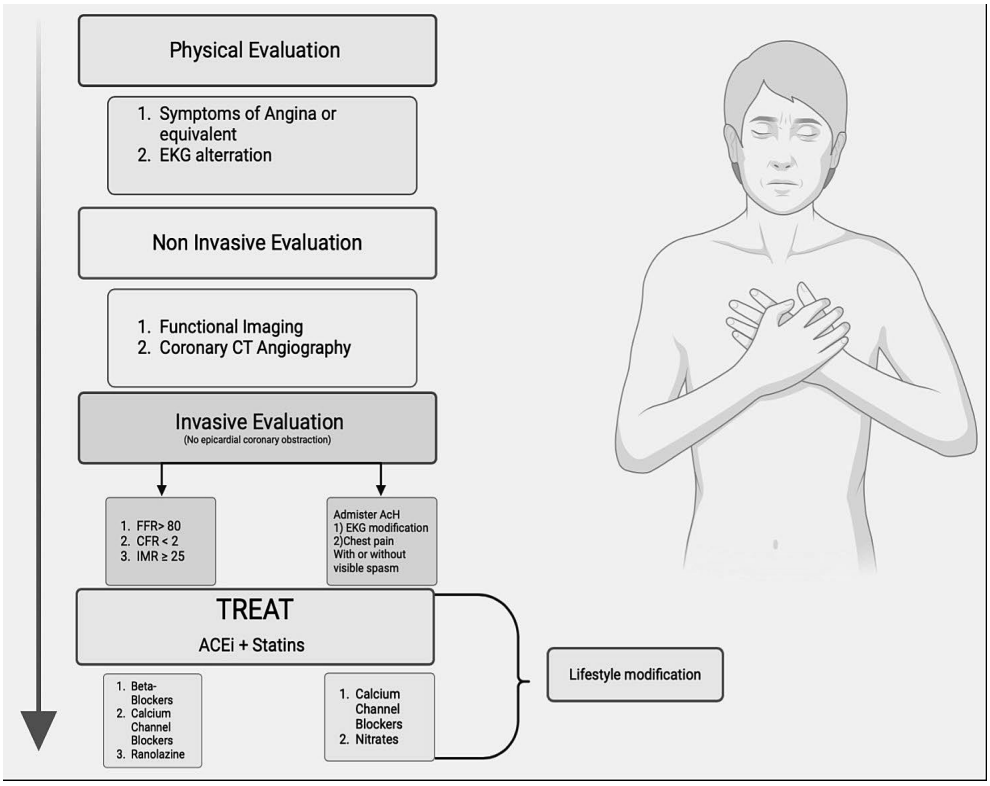


Fig. 2. Diagnostic and therapeutic algorithm. CT, computed tomography; FFR, fractional flow reserve; CFR, coronary flow reserve; IMR, index of microcirculatory resistance; ACEi, angiotensin-converting enzyme inhibitors; AcH, acetylcholine.

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Chapter 20

The Influence of Hydrostatic Pressure on Physiological Indexes.

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Editorial

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“Gravity is one variable in a lot of scientific processes. If you can remove gravity or minimize its effect, then you can understand the other processes that are going on.”
—Laurel Clark, NASA astronaut and medical doctor

Fractional flow reserve (FFR) is the gold standard for invasive assessment of hemodynamic severity of a coronary stenosis and has been shown to improve clinical outcomes in randomized clinical trials[1]. Acknowledged pitfalls of FFR may originate from calibration, equalization, submaximal hyperemia, drifting, whipping, and wedging. Hydrostatic pressure is also a factor contributing to FFR imprecision, but relies instead on a physical principle of coronary anatomy. Normal coronary arteries lie in different vertical planes. The position of the pressure wire sensor during FFR measurement is rarely at the same level as the coronary ostium where equalization is performed. As a consequence, FFR values may under- or overestimate the functional severity of a stenosis depending on the coronary artery examined and its anatomical course.

The concept of hydrostatic error has been poorly investigated so far, and is not recognized in clinical practice. Al-Janabi et al. used computed tomography angiography (CTA) to measure height differences between the coronary ostia and varying points in the coronary tree, demonstrating a statistically significant height variation between the proximal and distal vessel[2]. However, CTA may fail to identify the most distal parts of the coronary vessels, resulting in an underestimation of height differences[2].

In vitro measurements, performed by Härle et al., using a dynamic pressure simulator, showed a significant correlation between absolute pressure differences and height differences ($r = 0.993$; $p < 0.0001$) with a slope of 0.77 mmHg/cm[3]. Resting Pd/Pa and FFR values from in vivo measurements in supine and prone positions were found by Kawaguchi et al. to differ significantly between anterior and posterior coronary territories. FFR values, corrected by adding the hydrostatic pressure factor, showed good correlation between measurements in both positions (R^2: 0.948 in the left anterior descending [LAD]; R^2: 0.942 in the left circumflex [LCx]; and R^2: 0.928 in the right coronary artery [RCA])[4]. Üveges et al. investigated the effect of hydrostatic pressure on 41 measurements of FFR between 0.7 and 0.9, using a 3D reconstruction model. Correction of hemodynamic indexes by the hydrostatic pressure factor led to a

reclassification of FFR and resting Pd/Pa values in 5 (12%) and 11 (27%) measurements, respectively[5]. Limitations of in vivo studies using computer simulation and 3D reconstruction to investigate hydrostatic pressure are related to assumptions of standard mass density, motion of coronary arteries during the cardiac cycle, and accuracy of frame selection, as well as the influence on artery heights of comorbidities (obesity, emphysema, aortic stenosis).

Wirecath® (Cavis Technologies AB, Uppsala, Sweden) overcomes the hydrostatic error by using "open wire technology," with a water-filled interior and an external pressure transducer for hemodynamic measurements. We performed simultaneous measurements of stenosis severity with a conventional sensor-tipped FFR wire and Wirecath technology in a patient presenting with chronic coronary syndrome and multivessel disease (Figure). Given the dichotomous interpretation of FFR measurements, the use of Wirecath determined the reclassification of the RCA stenosis from non-ischemic to ischemic. The hydrostatic error has a greater impact on resting indices as compared to FFR[4] (Fig. 1). In clinical practice, hydrostatic pressure accounts for hemodynamic index values >1.00 most commonly in posterior territories and values lower than 1.00 in anterior territories. The hydrostatic pressure phenomenon may affect the interpretation of physiological indexes. When a binary cut-off for hemodynamic assessment is used, a small change in FFR values may reclassify the stenosis from ischemic to non-ischemic, or steer the indication from coronary artery bypass grafting (CABG) to percutaneous coronary intervention (PCI), and vice versa. Future research is needed to understand the clinical relevance of hydrostatic error in guiding functional assessment of lesion severity.

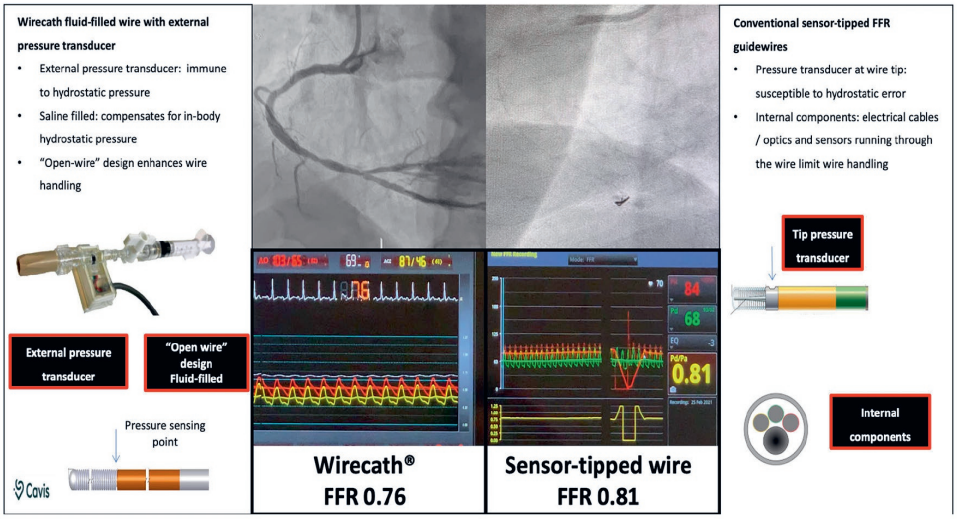


Fig. 1. Central figure upper panel. RCA coronary angiography froman LAO 40° (left) and an LAO67° (right) view. Lower panel. FFR valuewithWirecath 0.76 (left) and a sensor-tippedwire 0.81 (right) in the RCA. Right panel CAVISWirecath. Left panel Sensor-tipped wire.

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Chapter 21

Physiology Guidance for Intermediate Coronary Artery Stenosis: What Do We Leave Behind if We Shift Back From Physiological to Anatomical Assessment?

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Editorial

Published in Cardiovascular Revascularization Medicine Journal

The adoption of physiology in clinical practice remains low (10–20 %), due to costs, longer procedural time, and limitations related to the use of hyperemia-inducing agents[1].

Leor et al. provide important insight into fractional flow reserve (FFR) adoption rates, reclassification of CAD severity, mode of intervention, and outcomes from a large contemporaneous real-world cohort of patients with intermediate coronary stenosis undergoing physiological assessment[2].

In line with previous randomized data, the Spanish Pressure Wire Registry (REGIPRES) study showed that the use of intracoronary pressure wire is safe and leads to reclassification of the extent of CAD[3].

Previously published data also suggest that intermediate lesions in angiographic multivessel disease benefit most when physiological assessment is performed and tend to decrease the need for revascularization[4].

Recent results of the International Study of Comparative Health Effectiveness With Medical and Invasive Approaches (ISCHEMIA) trial have shifted back the focus from physiology to anatomy in stable coronary artery disease[5]. Previous studies investigating patients who underwent coronary computed tomographic angiography (CCTA) have demonstrated that more extensive and severe CAD is associated with worse prognosis[6]. ISCHEMIA demonstrated a graded association between CAD severity and adverse outcomes in a large cohort of patients with extensive CAD on CCTA (79 % with multivessel disease). Of note, the level of ischemia on functional tests was not associated with increased risk of adverse outcomes after adjustment for CAD severity[5,7].

What do we leave behind if we shift back from physiological to anatomical assessment of coronary artery stenosis?

In this real-world REGIPRES registry, less than 25 % of patients had more than one vessel measured, reflecting low CAD severity. Nevertheless, mild coronary artery stenosis may have functional significance with prognostic impact, especially when considering that in half of these patients the left anterior descending coronary artery was the investigated vessel[2]. In a modest percentage of patients excluded from ISCHEMIA because they did not present obstructive coronary artery disease, debilitating symptoms and stress-induced cardiac dysfunction persisted at 1-year follow-up[8]. A physiology-guided

approach integrates both epicardial and microcirculatory determinants, going beyond epicardial lesion severity.

The use of physiology in this large registry led to an increase of patients treated conservatively (from 27 % to 52.8 %) without differences in 12-month follow-up MACE between patients with a change in treatment strategy versus those with no change (6.0 % vs 4.9 %, respectively; p = 0.42). Moreover, in the subgroup of patients with PCI as the initial treatment, the change in strategy was associated with a lower rate of 1-year MACE compared to the whole cohort (4.6 % vs 8.2 %, p = 0.034)[2]. However, these outcome results should be analyzed with caution as they reflect a selected population in which physiological guidance was used rather than the entire all-comers population.

Of note, almost half of the patients had an acute coronary syndrome (ACS) presentation. Besides different baseline clinical characteristics, acute or chronic presentation neither resulted in different rates of treatment changes nor in different outcomes. The evidence supporting the use of physiology in ACS is less robust than for stable patients.

An important distinction between NSTEMI and STEMI in the use of physiological indexes is mandatory.

FFR measurement of non-culprit lesions has been extensively and safely used in large randomized controlled trials to guide complete revascularization in the STEMI setting, resulting in lower acute and repeat revascularization rates compared to initial culprit-only or complete angiography-guided revascularization strategies[9],[10]. However, transient physiological changes in the acute setting may moderately impact non-culprit lesion severity assessment in acute STEMI[11].

Physiology guidance for both culprit and non-culprit lesion revascularization in NSTEMI patients is based on limited data. Different mechanisms such as distal embolization, increased left end-diastolic pressure, watershed edema, and increased vasomotor tone are some of the factors that may lead to a blunted response to hyperemia in ACS patients. Uncertainty remains around the best timing to assess both culprit and non-culprit lesions in NSTEMI.

Both FAMOUS-NSTEMI (n = 350) and the ACS subgroup of the FAME trial (n = 328) were not powered to assess the superiority of FFR-guided over angiography-guided revascularization in terms of clinical outcomes[12],[13].

In the REGIPRESS registry, a total of 26.8 % of evaluated lesions were regarded as the culprit lesion and 37.6 % as a non-culprit lesion, while in 35.6 % of cases the culprit or non-culprit status of the lesion could not be established[2]. These results confirm previous findings about the challenging identification of the culprit lesion in more than 40 % of NSTEMI patients[14].

In recent years, instantaneous wave-free ratio (iFR) has proven to be non-inferior compared with FFR in guiding myocardial revascularization at mid-term follow-up[15]. Limited data are available for non-hyperemic indexes in ACS patients. The pooled analysis of DEFINE-FLAIR and iFR SWEDEHEART randomized trials showed similar safety in deferring revascularization with both iFR and FFR, despite the higher rate of deferral associated with non-hyperemic indexes[16]. The REGIPRESS registry found a trend toward a greater deferral rate with non-hyperemic indexes.

To conclude, the REGIPRESS registry confirmed the role of physiological indexes in the reclassification of angiographic intermediate coronary artery stenosis, leading to a lower revascularization rate and a decrease in clinical events at one year of follow-up for those patients initially planned for PCI.

After ISCHEMIA, are we really ready to leave this informative tool behind?

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Chapter 22

Applied coronary physiology for planning and guidance of percutaneous coronary interventions. A clinical consensus statement from the European Association of Percutaneous Cardiovascular Interventions (EAPCI) of the European Society of Cardiology

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Abstract

The clinical value of fractional flow reserve and non-hyperaemic pressure ratios are well established in determining an indication for percutaneous coronary intervention (PCI) in patients with coronary artery disease (CAD). In addition, over the last 5 years we have witnessed a shift towards the use of physiology to enhance procedural planning, assess post-PCI functional results, and guide PCI optimisation. In this regard, clinical studies have reported compelling data supporting the use of longitudinal vessel analysis, obtained with pressure guidewire pullbacks, to better understand how obstructive CAD contributes to myocardial ischaemia, to establish the likelihood of functionally successful PCI, to identify the presence and location of residual flow-limiting stenoses and to predict long-term outcomes. The introduction of new functional coronary angiography tools, which merge angiographic information with fluid dynamic equations to deliver information equivalent to intracoronary pressure measurements, are now available and potentially also applicable to these endeavours. Furthermore, the ability of longitudinal vessel analysis to predict the functional results of stenting has played an integral role in the evolving field of simulated PCI. Nevertheless, it is important to have an awareness of the value and challenges of physiology-guided PCI in specific clinical and anatomical contexts. The main aim of this European Association of Percutaneous Cardiovascular Interventions clinical consensus statement is to offer up-to-date evidence and expert opinion on the use of applied coronary physiology for procedural PCI planning, disease pattern recognition and post-PCI optimisation.

Introduction

Intracoronary Physiological Assessment for PCI Planning and Optimization

Intracoronary physiological assessment is recognized as a valuable strategy to identify the presence of flow-limiting epicardial stenoses in patients with chronic coronary syndromes (CCS) and to determine indications for percutaneous coronary intervention (PCI)[1]. However, its role in procedural planning and in assessing the functional results of PCI remains less well defined.

Traditionally, it was assumed that once the presence of flow-limiting disease was confirmed by a single pressure guidewire measurement, angiography-guided PCI would restore vessel conductance effectively. Yet, studies utilizing physiological post-PCI evaluation based on fractional flow reserve (FFR) and non-hyperaemic pressure ratios (NHPR) demonstrate that this assumption is not always correct. Relying solely on angiographic guidance can result in suboptimal functional outcomes post-PCI in a significant proportion of cases[2–4].

This document reviews the use of coronary physiology for planning and guiding PCI, providing evidence from the literature and expert operator consensus. It includes practical recommendations on the use of commercially available physiology tools. The European Society of Cardiology (ESC) Clinical Guidelines Committee has reviewed and approved this document to ensure consistency with existing guideline recommendations.

Many topics discussed herein focus on intracoronary pressure guidewires, which remain the most widely used devices for physiological assessment in the catheterization laboratory. Functional coronary angiography (FCA) tools, which combine angiographic data with fluid dynamic calculations to provide equivalent information to invasive pressure measurements, are also considered as valuable alternatives for planning coronary revascularization. An updated overview of NHPR and FFR use in various clinical scenarios is provided in Supplementary Appendix 1.

From Confirming the Indication to Planning and Guiding PCI

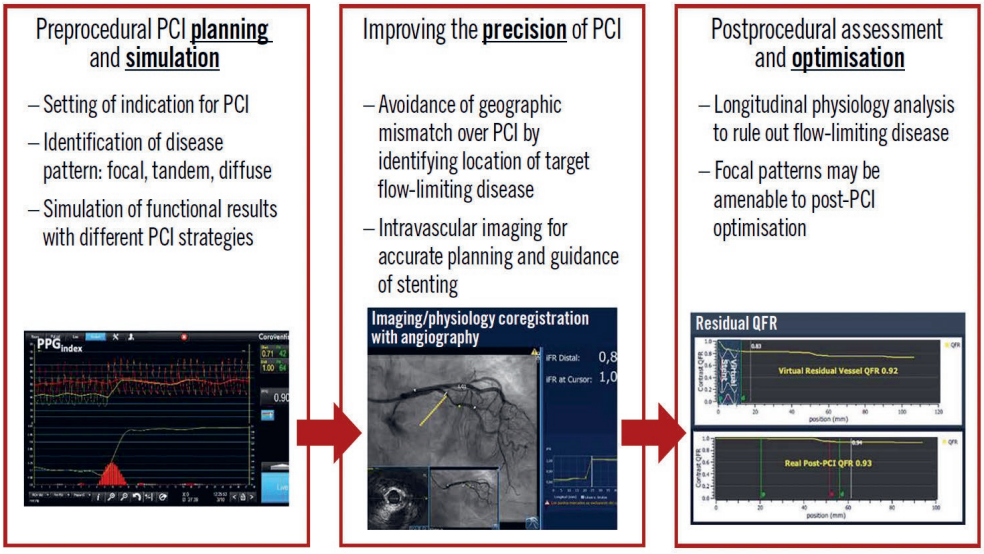
The limitations of coronary angiography in accurately characterizing the flow-limiting effects of coronary stenoses can be overcome by adjunctive noninvasive or invasive physiological assessments of coronary artery disease (CAD), whose utility is supported by evidence-based guidelines[5]. In the absence of prior evidence of myocardial ischemia, FFR or instantaneous wave-free ratio (iFR) are recommended to assess the hemodynamic significance of intermediate-grade coronary stenoses. FFR may also be considered in patients with multivessel disease undergoing PCI[5].

Criticism of angiography-guided decision-making has extended to the evaluation of whether an optimal functional result has been achieved post-PCI. Suboptimal functional results despite satisfactory angiographic PCI outcomes have been documented[2,3] and carry prognostic relevance (Supplementary Table 1)[4,6–25].

Physiological guidance may improve PCI outcomes in at least three ways:

1. Preprocedural planning and simulation – using physiology to identify all flow-limiting lesions before intervention.
2. Intraprocedural precision – guiding PCI to optimally address functionally significant stenoses.
3. Procedural optimization – identifying suboptimal PCI results and guiding additional interventions to achieve functional success (Central illustration).

Despite the limited number of studies specifically evaluating physiological guidance for PCI optimization, current evidence provides a rationale for integrating physiological tools into PCI strategies. Such tools aim to remove all flow-limiting stenoses, verify the functional success of interventions, and guide procedural optimization. Table 1 summarizes key principles of physiological guidance in PCI.



CENTRAL ILLUSTRATION Applications of physiology in planning and guiding PCI procedures.

iFR: instantaneous wave-free ratio; PCI: percutaneous coronary intervention; PPG: pullback pressure gradient; QFR: quantitative flow ratio

Table 1. Objectives of physiological planning and guidance of PCI.

Pre-PCI physiological assessment		
Objective	Technique	Benefit
Determining the indication for PCI	Pressure wire or FCA to identify presence of flow-limiting disease	Management of significant stenoses may confer prognostic or symptom benefit; Deferral of non-flow-limiting disease avoids unnecessary PCI
Identifying patterns of flow-limiting disease	Longitudinal physiological vessel analysis to identify focal, tandem, and diffuse patterns	Assists in gauging effectiveness of PCI; Aids with planning the length of stent and/or number of stents; Reconsider PCI when a suboptimal result is anticipated
Simulate impact of stenting in specific locations	NHPR and imaging-based functional assessments to simulate relief of stenosis virtually	Plan effectiveness of PCI before stent deployment; Allows for several simulations prior to PCI
Facilitating precision stent deployment	Correlating physiology and angiography using coregistration technologies or visual assessment, use of concomitant intracoronary imaging	Avoidance of geographical miss during stenting, missing flow-limiting lesions; Accurate sizing of balloons and stents
Post-PCI physiological assessment		
Ensuring an optimal functional result of PCI	Physiological measurements in PCI target vessel after satisfactory angiographic result, jailed side-branch interrogation	Early identification of residual flow-limiting disease in the PCI target vessel after the intervention
Identifying potential targets of functional optimisation of PCI	Post-PCI longitudinal vessel analysis	Establishing the cause of suboptimal functional PCI results; Establishing the feasibility and mode of PCI optimisation
Assessing the impact of PCI optimisation	Repeat physiological measurements after physiology-based optimisation	Residual disease not amenable to PCI may identify need for directed medical therapy or surgical revascularisation

FCA: functional coronary angiography; NHPR: non-hyperaemic pressure ratio; PCI: percutaneous coronary intervention

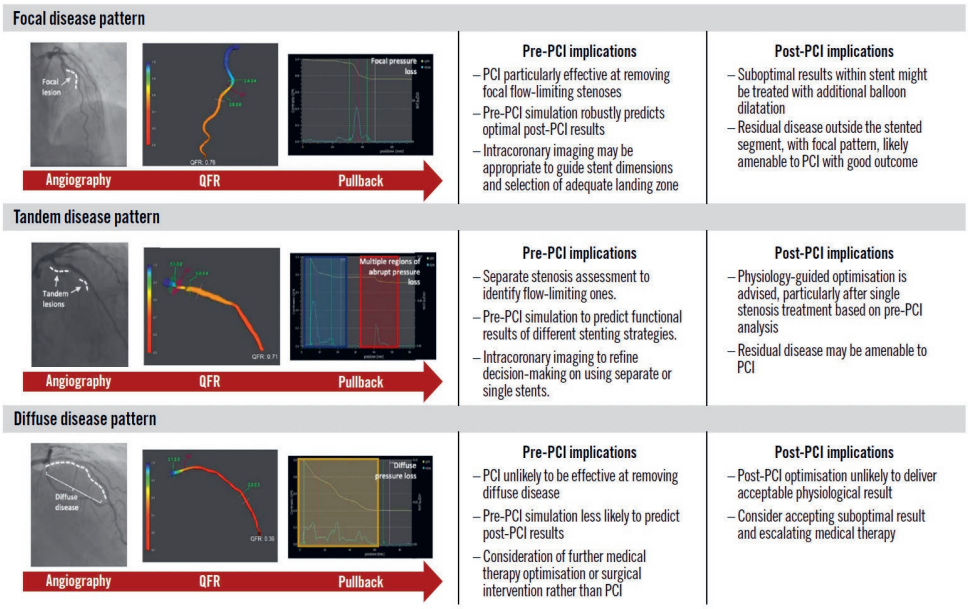


Figure 1. Patterns of flow-limiting disease identified in longitudinal vessel analysis before and after PCI. PCI: percutaneous coronary intervention; QFR: quantitative flow ratio

Technological Developments in Applied Coronary Physiology in PCI

Hyperaemic and Non-Hyperaemic Pressure Indices

Fractional flow reserve (FFR) remains the most widely used intracoronary tool to define flow-limiting epicardial stenoses, with randomized trials and observational studies supporting both deferral[26–28] and performance[26,29] of revascularization based on FFR values, predominantly in patients with chronic coronary syndromes (CCS). Contrast-based FFR, which induces submaximal myocardial hyperaemia via iodinated contrast, has been proposed as an adenosine-free alternative[30].

Non-hyperaemic pressure ratios (NHPR) are increasingly utilized in clinical practice due to a more favorable side-effect profile, lower cost, shorter procedure time, and ease of use compared with pharmacological hyperaemia. These advantages facilitate multiple intraprocedural measurements across different vessels or stages of PCI. Guidance by instantaneous wave-free ratio (iFR), a widely used NHPR, has been shown to be non-inferior to FFR in guiding revascularization for major adverse cardiac events (MACE) at both 1-year[31,32] and 5-year follow-ups[33]. Other diastolic NHPR correlate closely with iFR

and share a similar ischemic cut-off of ≤0.89[34]. Importantly, all NHPR demonstrate significant associations with 2-year vessel-oriented composite endpoints[35].

In the context of planning and guiding PCI, pressure guidewire use can encounter specific caveats related to physiological assessment in complex clinical or anatomical scenarios (Table 2). Supplementary Appendix 1 provides detailed information on potential pitfalls and considerations regarding guide catheter, guide catheter extension, and microcatheter use.

Functional Coronary Angiography

The demonstrated success of FFR and NHPR in estimating functional stenosis severity has driven the development of functional coronary angiography (FCA) technologies. FCA can derive physiological information from invasive coronary angiography or non-invasive computed tomography coronary angiography (CTCA), with both approaches correlating well with wire-based FFR.

Computed tomography-derived FFR (FFRCT) integrates a three-dimensional (3D) reconstruction of coronary vessels from CTCA with computational fluid dynamics[36], providing reliable estimates of invasive FFR[37]. Similarly, several FFR-equivalent measurements can be obtained from invasive coronary angiograms[38–41]. Quantitative flow ratio (QFR) is the only angiography-based physiological index prospectively validated to date, and its use in guiding coronary revascularization has been associated with improved clinical outcomes compared with conventional angiography[42].

A major advantage of FCA modalities is longitudinal vessel analysis, which enables accurate length measurements and precise localization of flow-limiting disease. Potential limitations of imaging-based functional coronary analysis are summarized in Supplementary Table 2.

Longitudinal Physiological Vessel Analysis

Traditionally, coronary physiology indices have been reported as a single distal value, reflecting cumulative pressure losses along the epicardial vessel. Longitudinal assessment using pressure wire pullback adds a valuable dimension by mapping pressure changes along the vessel length. Pullback maneuvers can be performed manually[34] with

FFR or NHPR[44],[45], with millimeter-level precision achievable via motorized pullback[46] or software that tracks the radiopaque wire tip[47]. Dedicated software generates stable pullback curves (FFR, iFR, or resting full-cycle ratio [RFR]) free from fluctuations caused by the Venturi effect (Supplementary Figure 1).

Pre-PCI longitudinal vessel assessment identifies the distribution of pressure losses along the epicardial vessel and differentiates focal versus diffuse flow-limiting disease (Figure 1). Differentiation can be performed visually or using objective indices such as the pressure pullback gradient (PPGindex)[45], which demonstrates high inter- and intra-operator reproducibility[48]. Automated algorithms, such as dFFR(t)/dt, analyze instantaneous FFR gradients over time, with both PPGindex and dFFR(t)/dt applicable to QFR. Their prognostic relevance for post-PCI outcomes has been documented[49],[50]. Criteria for defining focal, tandem, and diffuse patterns, along with supporting studies, are summarized in Table 3 and Supplementary Table 3[2],[3],[45],[50–61].

Discriminating between focal and diffuse CAD has immediate clinical implications. Focal patterns are associated with optimal physiological results post-PCI, favorable prognosis, and angina relief. In contrast, diffuse patterns often result in suboptimal post-PCI outcomes, poorer prognosis, and persistent anginal symptoms[62].

Post-PCI, longitudinal physiological assessment can identify residual focal pressure gradients, either within or adjacent to stents, potentially amenable to additional stent optimization or PCI[2]. Conversely, diffuse residual disease may advise against further instrumentation, highlighting the utility of physiological guidance in tailoring PCI strategies.

Table 2. Challenges and pitfalls related to physiological assessment.

Patient factors		
Challenges and pitfalls	**Comment**	**Solution**
Presence of significant ostial CAD	Identified with ventricularisation or "damping" pressure waveform on engagement, not assessable with some FCA modalities	Reposition guide catheter to a more proximal position, ensure coaxiality, consider downsizing guide catheter, use an additional guidewire or septal wire to control catheter tip position
Haemodynamic crosstalk in presence of tandem lesions	Sequential lesions along a vessel invariably physiologically	Consider simulated planning prior to undertaking PCI on 1 or 2 stenoses based on longitudinal

	influence the other lesions in the vessel	vessel analysis obtained with functional coronary angiography, NHPR, or FFR
Procedura factors		
Challenges and pitfalls	**Comment**	**Solution**
Pressure wire drift	Offset of pressure reading during the procedure	Repeat procedure, use drift correction/re-normalise, or use image-based technique
Pseudostenosis caused by intracoronary wires	Straightening of tortuous vessels by intra-coronary wire may generate introsusceptions with haemodynamic relevance	Consider FCA as an alternative to intracoronary pressure guidewires
Ventricularisation/damping of aortic pressure	Guiding catheter engaged abutting the vascular lumen or in significant ostial lesions	Reposition guide catheter, ensure coaxiality, consider downsizing guide catheter, equalisation of pressure guidewire is advised
Use of guide catheter with side holes	False estimate of Pa at the tip of the guiding catheter	Advise not to use catheter with side holes for intracoronary assessment. If needed for clinical reasons, ensure catheter disengagement and use of IV adenosine.
Use of guide catheter extensions	May cause ventricularisation of Pa, if introduced after pressure equalisation, may modify Pa and affect measurements	Perform pressure equalisation with extension within guide catheter, withdraw guide extension at the time of physiological assessment
Use of coronary microcatheters	If used after pressure equalisation, may modify Pa and affect measurements	Perform pressure equalisation with microcatheter within guide catheter before measurements
Wire whipping	Pressure wire signal degrading through contact with vascular lumen	Repositioning of the pressure wire often resolves this issue
Transient microvascular dysfunction associated with the procedure	Rotational atherectomy and PCI tools generating microparticles may cause transient microvascular dysfunction, affecting pressure indices	Consider FCA as an alternative to intracoronary assessment if transient microvascular dysfunction is assumed or suspected
FFR measurement in region without stable hyperaemia	Whilst the software reports the lowest physiological reading, these might not be in stable hyperaemia and therefore overestimate lesion severity	Measure FFR in stable hyperaemia, and if needed adjust measurement points manually

CAD: coronary artery disease; IV: intravenous; FCA: functional coronary angiography; FFR: fractional flow reserve; NHPR: non-hyperaemic pressure ratio; Pa: aortic pressure; PCI: percutaneous coronary intervention

Table 3. Criteria used to define focal, tandem and diffuse patterns of obstructive coronary disease

Pre-PCI physiology assessments			
Pattern	FFR	NHPR (iFR/RFR/DFR)	FCA (QFR/vFFR/FFRCT)

Focal	FFR ≤0.80 at distal segment, abrupt single point of pressure loss	iFR/RFR/DFR ≤0.89 at distal segment, with abrupt single point of ≥0.03 index units over ≤15 mm segment	QFR/vFFR/FFRCT ≤0.80 at distal segment, with single region of pressure loss of >0.05 in <10 mm segment
Tandem	FFR ≤0.80 at distal segment, presence of ≥2 abrupt change of FFR values	iFR/RFR/DFR ≤0.89, at distal segment, with presence of ≥2 abrupt changes of index values	QFR/vFFR/FFRCT ≤0.80 at distal vessel with presence of ≥2 abrupt changes of pressure loss
Diffuse*	FFR ≤0.80 at distal segment with progressive and linear loss in FFR values over length of vessel	iFR/RFR/DFR ≤0.89 at distal segment, with progressive and linear loss in pressure over length of vessel during iFR pullback	Progressive and linear loss in QFR/vFFR/FFRCT values over length of vessel during longitudinal analysis
Post-PCI physiology assessments			
Focal	FFR with abrupt pressure loss at the stented site or elsewhere within the treated vessel	Abrupt drop of iFR/RFR/DFR values at the stented site or elsewhere within the treated vessel	Abrupt drop of QFR/vFFR values at the stented site or elsewhere within the treated vessel
Tandem	Abrupt drop of FFR values at the level of an untreated tandem stenosis	Abrupt drop of iFR/RFR/DFR values at the level of an untreated tandem stenosis	Abrupt drop of QFR/vFFR values at the level of an untreated tandem stenosis
Diffuse*	Progressive and linear loss in FFR values over length of stented vessel during pullback	Progressive and linear loss in iFR/RFR/DFR values over length of stented vessel during pullback	Progressive and linear loss in QFR/vFFR values over length of stented vessel

*These criteria are clinical consensus statements and further validation is warranted. DFR: diastolic hyperaemia-free ratio; FCA: functional coronary angiography; FFR: fractional flow reserve; FFRCT: computed tomography-derived FFR; iFR: instantaneous wave-free ratio; NHPR: non-hyperaemic pressure ratio; PCI: percutaneous coronary intervention; QFR: quantitative flow ratio; RFR: resting full-cycle ratio; vFFR: virtual FFR

COREGISTRATION WITH ANGIOGRAPHY

Merging longitudinal vessel physiology with the coronary angiogram allows for accurate localisation of flow-limiting atherosclerotic disease and facilitates procedural planning[47]. The coregistered map provides signposts with a clear distribution of regions of pressure loss, enabling optimal localisation of specific target lesions that might benefit from PCI, and the implementation of length measurements (Supplementary Figure 2). This technology can be used in conjunction with iFR and is particularly useful when forming strategies for intervention on tandem lesions and interrogating areas of diffuse disease.

SIMULATION OF FUNCTIONAL PCI RESULTS

Despite consistent evidence showing that suboptimal values of physiological indices after PCI are associated with poorer outcomes, there is a relative paucity of evidence

regarding whether they can be used to guide PCI optimisation and, ultimately, to improve patient outcomes. Since the aim of PCI is the elimination of ischaemia-generating lesions, predicting the haemodynamic results of a given strategy before embarking on stenting appears to be a rational approach to avoid suboptimal results of the intervention. The concept of in silico simulation of PCI to predict functional results of an intervention is appealing, as it allows for both procedural planning and modelling of post-PCI physiology prior to undertaking the procedure.

There are different approaches to simulate functional PCI results from baseline longitudinal vessel analysis (Figure 2). A simple mathematical approach to estimate the impact of PCI based on pullback curves can be followed: predicted NHPR (NHPRpred)=pre-PCI NHPR (lowest value) + Σintention-to-treat NHPR gradient(s). Pioneering studies with iFR pullback have demonstrated its ability to predict post-PCI results[63]. Subsequently, this has also been confirmed for other NHPR such as the RFR and diastolic pressure ratio[61]. Subtraction of the flow-limiting effect of one or more coronary stenoses can be readily performed with current software versions of iFR coregistration with angiography[31]. From the perspective of FCA, a dedicated virtual stenting tool has been developed for FFRCT[64]. The FFRCT Planner (HeartFlow) has been shown to be accurate and precise at predicting post-PCI FFR[65]. Analysis with QFR and virtual FFR (vFFR) provides an estimate of post-PCI values after treatment of a given stenosis (residual QFR and vFFR), which has been shown to predict post-PCI FFR[25],[66],[67]. Figure 3 shows a pullback curve analysis performed with iFR and coregistration, including simulated stenting at a specific location.

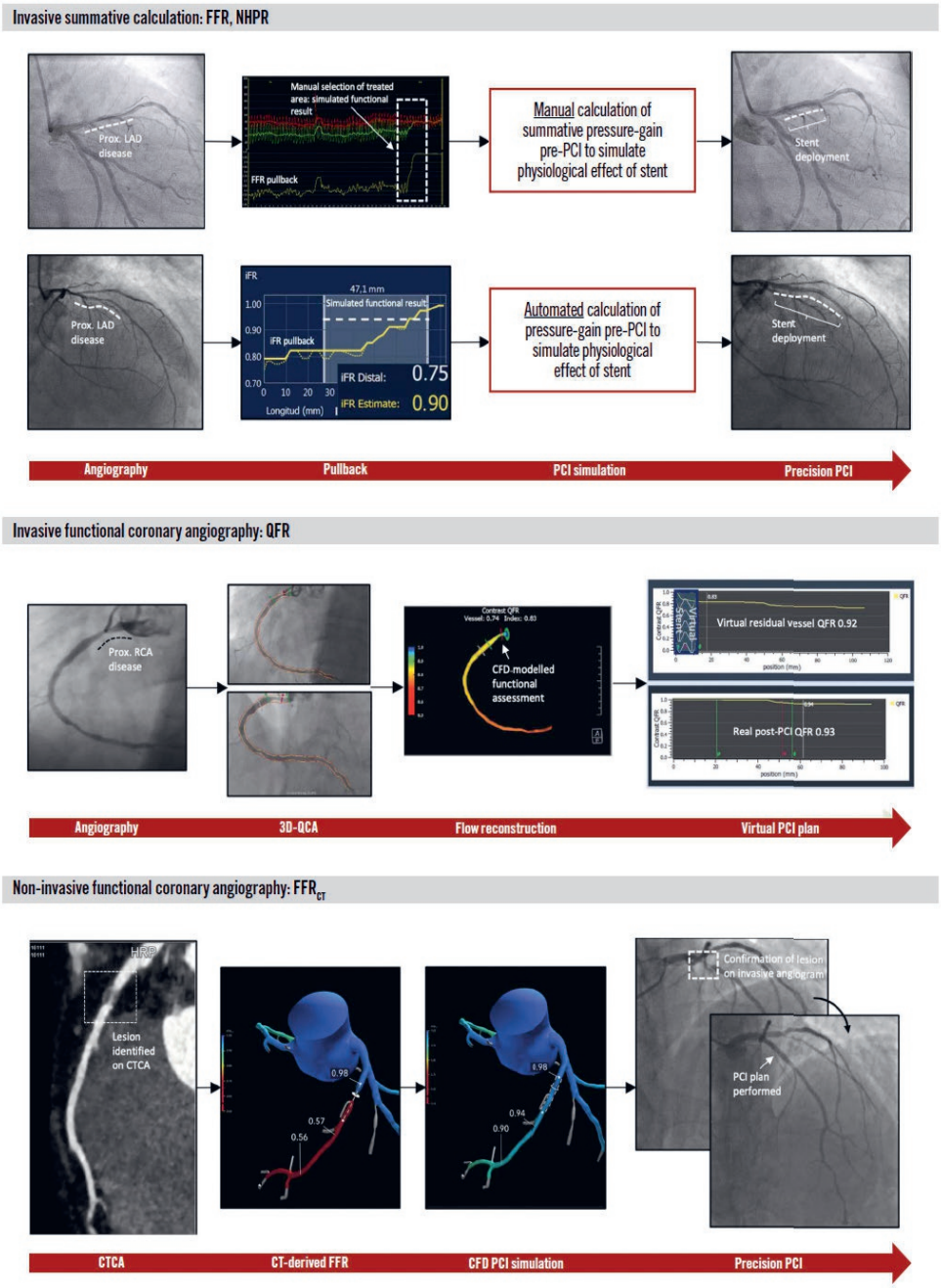


Figure 2. Approaches for simulating functional PCI results based on longitudinal vessel analysis. 3D-QCA: three-dimensional quantitative coronary angiography; CFD: computational fluid dynamics; CTCA: computed tomography coronary angiography; FFR: fractional flow reserve; FFRCT: computed tomography-derived FFR;

iFR: instantaneous wave-free ratio; LAD: left anterior descending artery; NHPR: non-hyperaemic pressure ratio; PCI: percutaneous coronary intervention; QFR: quantitative flow ratio; RCA: right coronary artery

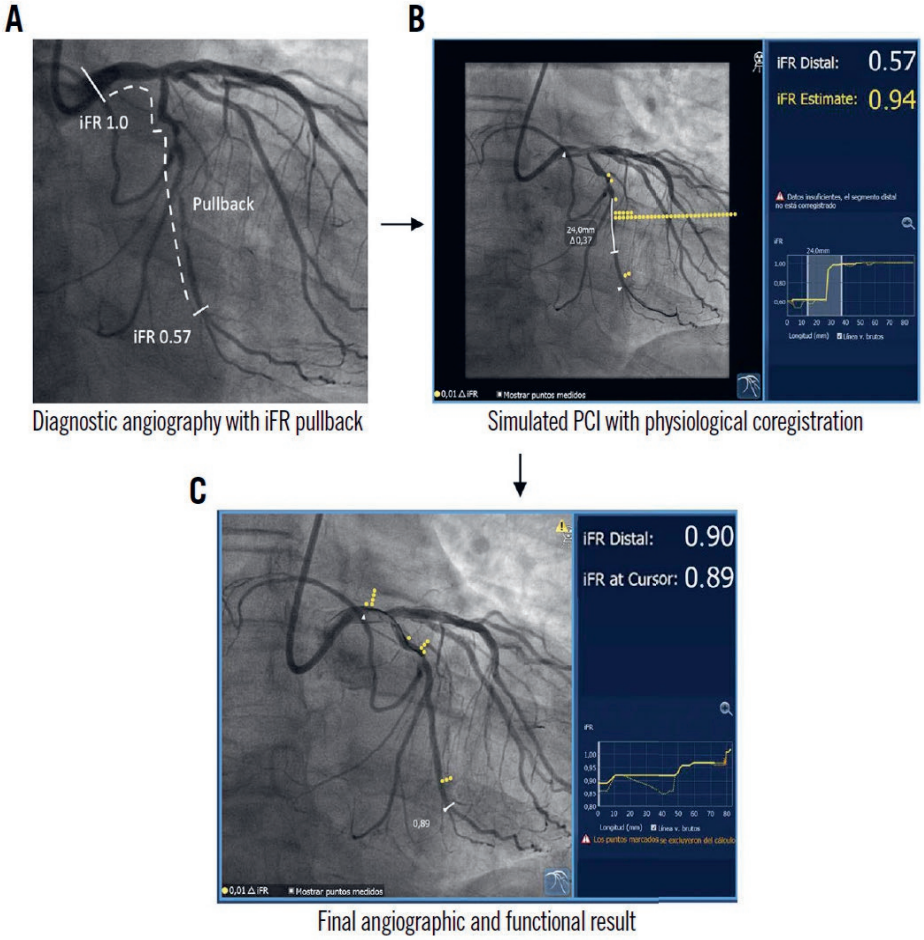


Figure 3. Simulation of functional PCI results using coregistration of physiology and the coronary angiogram. A) Angiography of the left circumflex artery interrogated with longitudinal physiological assessment. B) The presence of flow-limiting disease in the vessel is demonstrated by a distal iFR of 0.57. Longitudinal vessel analysis revealed a focal disease phenotype. iFR coregistration with angiography allows accurate localisation of flow-limiting disease in the coronary anatomy. The PCI simulation suggests adequate functional results of the

intervention, with a predicted post-PCI iFR of 0.94. C) Final co-registered angiographic-physiology result shown, with final iFR of 0.90. iFR: instantaneous wave-free ratio; PCI: percutaneous coronary intervention

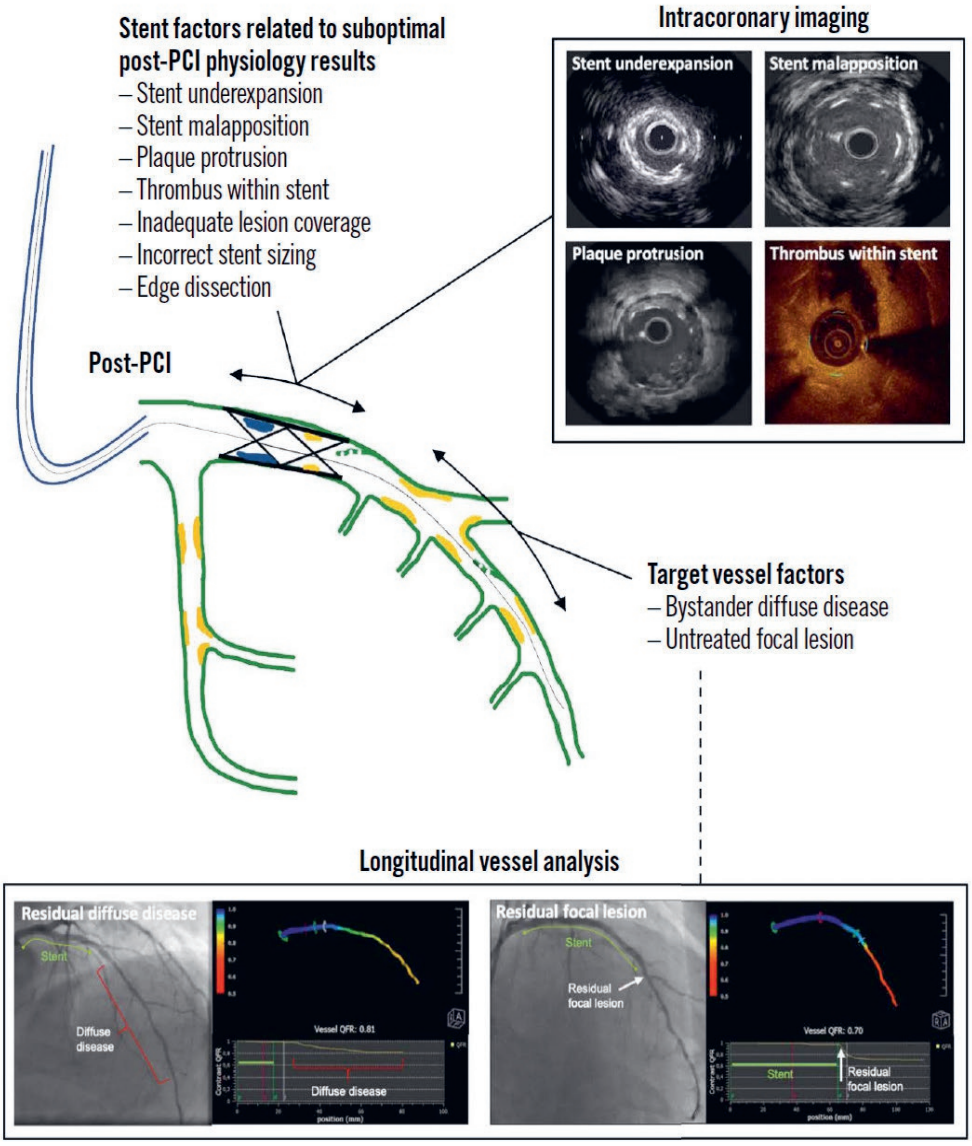


Figure 4. Mechanisms of suboptimal post-PCI physiological results. PCI: percutaneous coronary intervention; QFR: quantitative flow ratio

CORONARY PRESSURE WIRES AND MEASURING TOOLS

Continued improvement in pressure guidewire technology has facilitated the accurate interrogation and measurement of complex coronary anatomies. Contemporary guidewire-based pressure indices are fitted with sensors that use either electrical or fibreoptic signal transmission. Advances in manufacturing processes have resulted in an improved accuracy and stability of the sensor, thus, minimising the drift phenomenon with workhorse guidewire-like characteristics, resulting in optimised torque control and manoeuvrability. The latter is critical for the safe wiring of the target vessel prior to the measurement of pressure loss and PCI. Microcatheter-based pressure measurement technology requires a 0.014" guidewire, according to anatomy or operator preference, but requires a 0.020" shaft profile for the microcatheter, which may interfere with measurements, especially in small vessels or severe stenoses, and can be difficult to navigate around tight angulations. The currently available and pending devices for invasive functional assessments are shown in Supplementary Table 4.

Physiological assessment of post-PCI results

Post-PCI intracoronary pressure measurements can identify residual flow-limiting disease, differentiate residual focal lesions from diffuse disease and provide prognostic information. Whilst a higher post-PCI FFR is associated with a lower incidence of adverse clinical outcomes, the cut-off point for an optimal PCI result is still debated[68]. A post-PCI FFR ≥0.90 has been associated with a significantly lower risk of repeat PCI and MACE in a systematic review of 7,470 patients[69]. The most robust recent data, obtained in a patient-level meta-analysis of 5,869 vessels treated with modern drug-eluting stents, reported optimal post-PCI FFR cut-off values of 0.86 for target vessel failure and 0.80 for the composite of cardiac death or target vessel myocardial infarction[70]. For NHPR, a post-PCI iFR ≥0.95 was associated with improved patient outcomes in the DEFINE PCI study[3]. An optimal cut-off for post-PCI distal coronary pressure/aortic pressure (Pd/Pa) ratio of >0.96 has also been proposed[23].

Contemporary reports indicate that post-PCI physiology results might remain below the clinical revascularisation thresholds of ≤0.80 for FFR and <0.90 for NHPR in approximately 24-36% of cases[2,3,71]. Potential mechanisms of suboptimal post-PCI

physiology results are outlined in Figure 4. Additional interventions guided by post-PCI coronary physiology assessments can improve the final result[2,10,71]. Caution should be exerted to avoid overtreatment, for example when the identified cause of suboptimal functional results entails treatment of long coronary segments or aggressive lesion manipulation. Intracoronary imaging may contribute to a better understanding of the cause of suboptimal functional results and to safer decision-making. Furthermore, it has to be kept in mind that cardiovascular risk may differ between patients despite having achieved an optimal functional result; this is largely dictated by the extension and characteristics of underlying atherosclerosis.

While functionally suboptimal PCI results are associated with adverse clinical outcomes and can be related to residual treatable disease, they may more frequently be an epiphenomenon of diffuse atherosclerosis that cannot be adequately addressed with revascularisation. This may explain why larger relative increases in FFR after stenting (typically achieved through treatment of focal, physiologically severe lesions) are associated with lower rates of target vessel failure, reduced incidence of angina and improved quality of life[14,21,72]. As not all residual flow-limiting disease is amenable to treatment with PCI, achieving optimal post-PCI FFR or NHPR target values can be challenging, or frequently impossible, in many patients[73]. Beyond the pattern of coronary artery disease, there are additional anatomical factors that may contribute to lower pressure-based indices. Evolving evidence suggests that post-PCI FFR values are consistently lower in left anterior descending (LAD) versus non-LAD vessels and might require vessel-specific optimal thresholds, adding a further level of complexity[2,22]. The lower LAD values likely occur because of the interplay of several factors, including the higher prevalence of intramuscular coronary tracts observed in the LAD (Supplementary Figure 3), the impact of hydrostatic effects relating to coronary anatomy and the resultant height of the pressure wire sensor above or below the aortic pressure transducer (typically causing a hydrostatic offset of around 3.6 mmHg)[74], and higher coronary flow rates due to the larger myocardial mass subtended by the LAD (high flow across long segments of mild residual diffuse atheroma can generate an appreciable pressure gradient). Based on this, normal FFR values for the LAD have recently been shown to be 0.92, compared to 0.96 in non-LAD vessels[75]. Finally, in all anatomical

locations, when NHPR are used, residual reactive hyperaemia induced by intervention-related vessel manipulation may render false positive measurements if performed immediately after stent implantation or contrast/saline injections.

Complementary role of combined imaging and physiology in PCI planning and guidance

Whilst the objective of PCI is the removal of flow-limiting disease, long-term results of interventions are strongly influenced by procedural factors that are better addressed with intracoronary imaging techniques, such as intravascular ultrasound (IVUS) and optical coherence tomography (OCT) – both of which provide detail on CAD patterns and guidance for PCI. A detailed description of these techniques and on their use in planning, guiding and optimising PCI is available elsewhere[76]. The results of comprehensive vessel imaging post-PCI compared with FFR and its effect on long-term outcomes have been reported[77]. In addition, there is growing interest in whether the presence of vulnerable atheroma in non-flow-limiting lesions might be associated with a higher risk of future events[78]. Merging information based on the presence and location of flow-limiting stenoses provided by physiology, with information on plaque characteristics and distribution, and vessel dimensions derived from imaging might aid in the selection of PCI devices and strategies in terms of lesion preparation, plaque-free landing zone for PCI, and the selection of stent diameter and length, all important aspects which ultimately improve long-term procedural results. Triregistration, with physiology and intracoronary imaging in conjunction with angiography, is currently available for IVUS and iFR. Coregistration with angiography is also feasible with OCT. Intracoronary imaging-derived physiology, such as OCT-derived FFR, currently lacks validation and is not available for clinical use. In addition, there is extensive evidence suggesting that PCI optimisation with intravascular imaging improves long-term procedural outcomes[2,76,79-84]. This benefit is independent of the modest increase in FFR values noted in image-based PCI optimisation studies[79,85,86]. The synergistic use of intracoronary imaging and post-PCI longitudinal vessel pullback can be used to investigate causes of focal pressure loss after PCI and assist with decisions on how they could be rectified[86]. Imaging may also

highlight the existence of high-risk morphological features of coronary disease – both at baseline and post-PCI – with prognostic implications, even when these are not ischaemia-generating[87], such as in instances of malapposition or significant edge dissection.

Integrating available tools and knowledge into algorithms for physiology-based planning and optimisation

The points discussed thus far can be tentatively integrated into algorithms for PCI planning and post-PCI evaluation. It is suggested that a comprehensive virtual analysis of the target vessel be performed prior to PCI, to support the indication for PCI and to assist in procedural planning and strategising, with the support of simulation if available. Following PCI, the result should be interrogated using a combination of physiology and/or imaging techniques, with post-PCI optimisation carried out when residual focal or tandem pressure loss remains. Suggested algorithms for comprehensive lesion assessment using pre- and post-PCI physiology are shown in Figure 5 and Figure 6.

Applied coronary physiology in specific PCI scenarios

In addition to the general principles discussed above, the use of physiology to plan and guide PCI in specific scenarios is deserving of a separate discussion. Supplementary Appendix 2 outlines applied coronary physiology for the following contexts: multivessel coronary artery disease, vessels with tandem lesions or diffusely diseased vessels, lesions in vessels providing collaterals to chronically occluded arteries, patients with acute coronary syndromes, bifurcation lesions and jailed side branches, left main stem stenosis, coronary lesions in patients with aortic stenosis, native vessel or surgical graft stenosis in patients with prior coronary artery bypass graft, and in vessels with myocardial bridge – all in greater detail.

Future directions and outlook

The use of physiology in procedural planning and simulation of PCI is an area of growing interest, though, as yet, supported only by a relatively small evidence base. Upcoming trials in the field will provide valuable evidence on the use of invasive physiology and FCA

for this purpose. Whilst it is generally accepted that PCI is an appropriate therapy for patients with focal CAD, the optimal treatment strategy for patients with haemodynamically significant lesions in the presence of diffuse disease is a subject of ongoing investigation.

Prospective studies are also being conducted to assess the use of coregistration technology on stent deployment and patient outcomes. The DEFINE GPS (Distal Evaluation of Functional Performance With Intravascular Sensors to Assess the Narrowing Effect: Guided Physiologic Stenting; ClinicalTrials.gov: NCT04451044) and iLARDI (Usefulness of the Use of Co-registration Strategy With iFR in Long and/or Diffuse Coronary Lesions; ClinicalTrials.gov: NCT04283734) investigators aim to assess the impact of iFR coregistration (SyncVision; Philips) on guiding PCI and influencing the number and lengths of implanted stents, and in DEFINE GPS, whether this might influence the rate of MACE. The PPG Global Registry involves a prospective evaluation of the impact of the PPG index on clinical decision-making for PCI (or not) and related outcomes (ClinicalTrials.gov: NCT04789317). Future studies should better define the role of microvascular dysfunction in relation to PCI outcomes. Collectively, these studies will add significant value in objectively assessing the utility of pre-PCI simulation and planning using physiological indices.

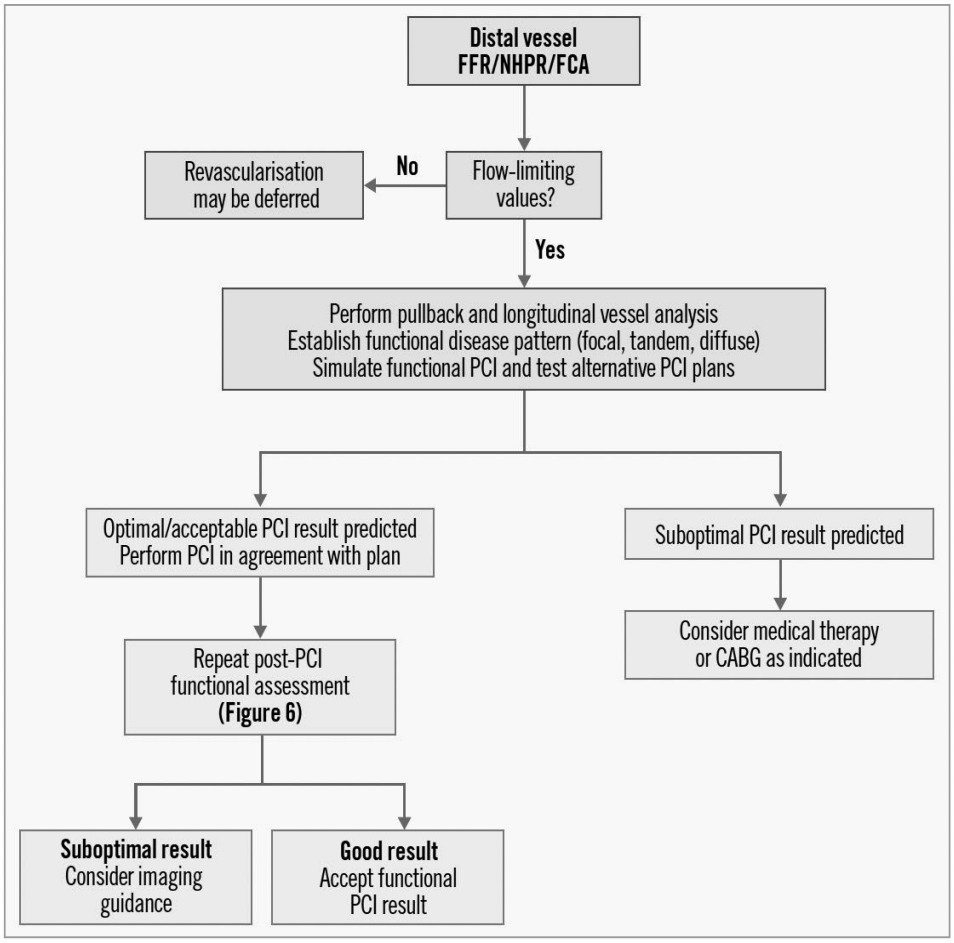


Figure 5. Proposed algorithm for pre-PCI physiology assessment and planning of PCI based on physiological interrogation. CABG: coronary artery bypass graft; FCA: functional coronary angiography; FFR: fractional flow reserve; NHPR: non-hyperaemic pressure ratio; PCI: percutaneous coronary intervention

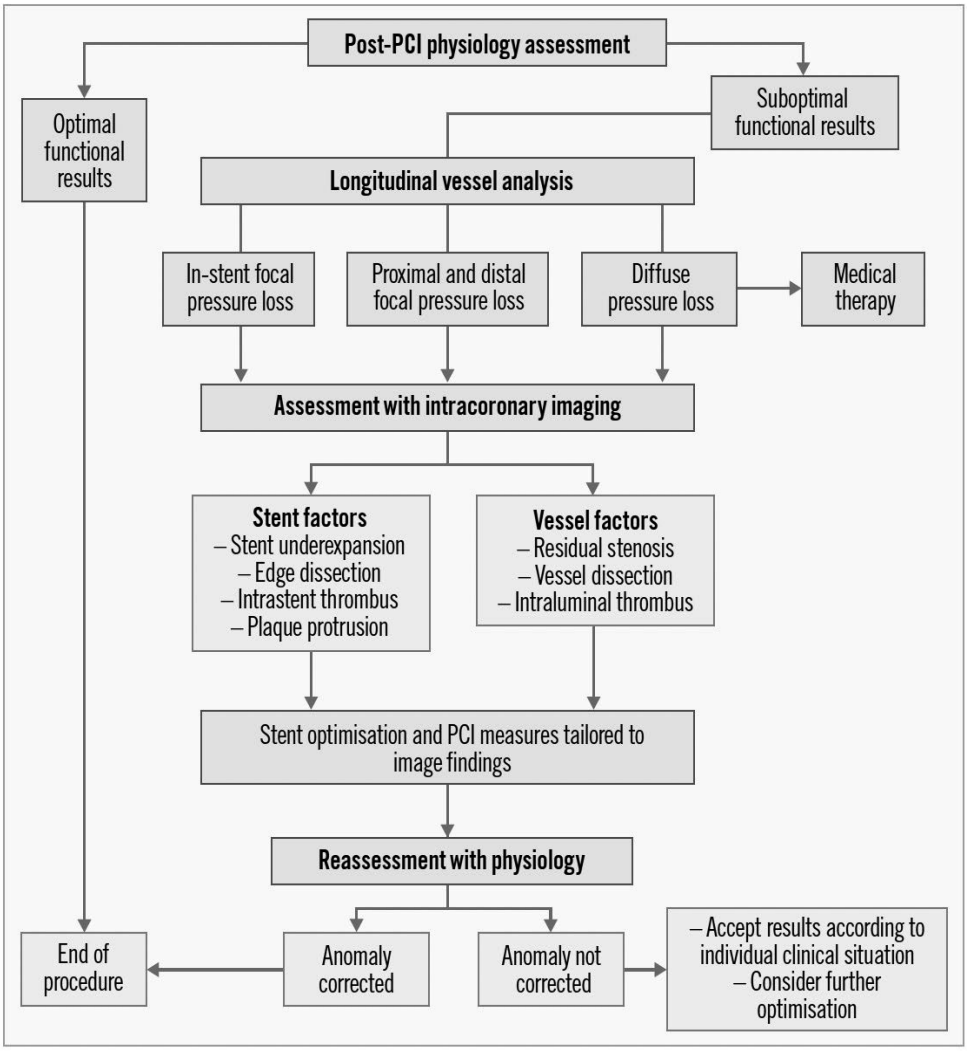


Figure 6. Proposed algorithm for postprocedural assessment and optimisation of functional PCI results based on physiological interrogation. PCI: percutaneous coronary intervention

Conclusions

The raison d'être of PCI is to abolish flow-limiting stenoses and ischaemia in order to improve patient symptoms and/or prognosis. In conjunction with angiographic findings, physiology determined by FFR, NHPR and FCA assists in weighing important decisions in

procedural planning. Emerging studies hint at the application of in silico PCI simulation prior to intervening on a patient. This offers a novel perspective on planning the effectiveness of an intervention and could enable the adoption of revascularisation strategies associated with the highest physiological gain. Furthermore, identifying patients with little physiological gain after PCI, despite optimisation, is highly important, as they are at high risk of premature stent failure.

Physiology in the post-PCI setting facilitates procedural optimisation through descriptive longitudinal vessel analyses of stented segments, offering clarity on the presence of residual flow-limiting disease. These technologies, in combination with the ability to coregister anatomy with physiology and intravascular imaging, which allows for the identification of different disease phenotypes, have revolutionised PCI in the modern era. Clinical trials assessing the effectiveness of these tools on clinical outcomes are eagerly awaited.

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PhD portfolio

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Acknowledgements

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Chapter 23

Summary and conclusion

Part I: Procedural and Pharmacological Optimization in ACS Patients

This section addresses key advancements in the management of acute coronary syndrome (ACS), with a particular focus on patients with multivessel disease (MVD). The introduction of newer-generation drug-eluting stents (DES), characterized by thinner struts, bioresorbable polymers, and enhanced endothelial healing properties, has substantially reduced thrombotic complications.1 These technological innovations have also raised the possibility of safely shortening dual antiplatelet therapy (DAPT) duration in selected patient populations.

While shorter DAPT strategies have been extensively studied in patients with chronic coronary syndrome (CCS), translating this approach to ACS patients has proven more challenging due to the heightened risk of recurrent ischemic events.2 Nonetheless, recent randomized trials have explored abbreviated DAPT regimens—often involving early aspirin discontinuation followed by P2Y12 inhibitor monotherapy—and have shown encouraging results.3,4 These studies have included high bleeding risk patients, unselected ACS cohorts, and Asian populations.3-7 However, to date, no randomized trial has specifically investigated early aspirin withdrawal in patients presenting with acute myocardial infarction (MI) who undergo complete revascularization using guideline-recommended strategies and contemporary DES.

The large-scale, multicenter TARGET FIRST trial (n=2246) provided important insights by demonstrating that early transition to P2Y12 inhibitor monotherapy was non-inferior to continued DAPT in preventing net adverse clinical and cerebral events (NACCE)—a composite of all-cause mortality, MI, stent thrombosis, stroke, or BARC type 3 or 5 bleeding. Notably, monotherapy resulted in a 54% relative reduction in bleeding events (BARC type 2, 3, or 5), underscoring its potential safety benefit.8

Building on these findings, the COMPARE STEMI ONE trial is designed to take a further step by focusing specifically on ST-elevation myocardial infarction (STEMI) patients. This randomized trial will investigate the combination of a shortened DAPT regimen with Prasugrel monotherapy, alongside OCT-guided revascularization of non-culprit lesions, in patients with multivessel disease. This dual approach aims to assess whether procedural optimization using intracoronary imaging, together with tailored antithrombotic therapy, can enhance both ischemic and bleeding outcomes in this high-risk cohort.9

While the role of intracoronary imaging—particularly IVUS and OCT—in optimizing PCI has been well established, its utility in identifying vulnerable plaques which deserves preventive PCI remains an evolving area.10-12 Imaging may offer additional insights into plaque morphology and features associated with thrombogenic potential.13,14 However, the clinical relevance of identifying morphologically high-risk plaques has been questioned, given that these lesions may persist for years without precipitating events. Further research is needed to determine whether certain NCLs would benefit from preventive interventions based on imaging-defined vulnerability.

An important and often under-recognized dimension of ACS management is the role of sex-based differences in clinical presentation, response to therapy, and outcomes.15 Significant gaps remain in our understanding of how biological sex influences thrombotic and bleeding risks, as well as pharmacologic response to antithrombotic therapies. There is a pressing need for the development and implementation of sex-specific clinical recommendations. The current EAPCI clinical consensus statement on this topic emphasizes the importance of tailoring antithrombotic therapy in women and highlights the need to address systemic barriers to female enrollment in cardiovascular clinical trials.16,17

Overall, the studies presented in this section aim to support a more individualized approach to ACS management, integrating procedural precision, imaging guidance, and patient-specific characteristics—such as bleeding risk, sex, and plaque morphology—to optimize both safety and efficacy of therapy.

Part II: Technological Advancements and Imaging in Complex PCI

Recent advancements in stent technology, particularly the development of newer-generation drug-eluting stents (DES) with thinner struts and bioresorbable polymers, have led to significant improvements in PCI outcomes.18,19 These innovations are associated with reduced flow disturbance, less vascular inflammation, and accelerated endothelial healing—all of which contribute to lower thrombotic risk.20 As a result, thinner and ultrathin strut DES are particularly attractive in high bleeding risk (HBR) patients, where minimizing the duration of dual antiplatelet therapy (DAPT) is crucial.
The COMPARE 60/80 HBR trial provides pivotal evidence in this regard. In this randomized study, the ultrathin-strut biodegradable-polymer sirolimus-eluting Supraflex Cruz stent was found to be noninferior to the thin-strut biodegradable-polymer sirolimus-eluting Ultimaster Tansei stent for net adverse clinical events (NACE) at 12 months in an HBR population undergoing short DAPT post-PCI.21,22 This finding supports the clinical safety and efficacy of the Supraflex Cruz stent in this vulnerable group and underscores a broader implication: in the evolving landscape of personalized antithrombotic strategies, the choice of stent matters. Devices proven safe and effective in settings of abbreviated DAPT should be preferentially considered for HBR patients.

In parallel, intravascular imaging has emerged as a cornerstone of modern PCI, particularly in complex anatomical settings. The latest ESC guidelines for chronic coronary syndromes grant a Class I recommendation for imaging-guided PCI of complex lesions.23 Among the most challenging lesion subsets are calcified coronary lesions, which can hinder device deliverability and adequate stent expansion—two key predictors of adverse outcomes. Calcification contributes to increased rates of restenosis and thrombosis, particularly when stent underexpansion occurs.24,25 Strut thickness plays a crucial role in device performance in this context, influencing deliverability, radial strength, and healing response.26 However, comparative data on different strut thicknesses in calcified lesions remain limited—especially when assessed using intravascular imaging modalities like IVUS or OCT to quantify calcium burden and stent

expansion. Further research is needed to define optimal stent selection and procedural techniques for calcified lesions, particularly in the era of precision PCI.

Another complex anatomical subset is bifurcation lesions, which carry an inherently higher risk of adverse events, especially when involving the left main coronary artery (LMCA). Disease in this territory affects a substantial myocardial territory and increases the risk of major adverse cardiovascular events. The traditional strategy of provisional stenting has been widely adopted for most bifurcations; however, recent evidence has challenged the "one-size-fits-all" approach, particularly in the setting of true LMCA bifurcation lesions.27,28 These lesions are often more complex and may warrant an early escalation to a two-stent technique. Intravascular imaging plays a central role in the procedural planning and execution of LMCA PCI. Beyond angiography, imaging allows accurate assessment of plaque composition, lesion morphology, and vessel size. It helps guide both the decision-making between single- versus dual-stent strategy and the optimization of stent expansion, apposition, and final geometry. Importantly, imaging can detect complications and confirm the adequacy of PCI results, especially at bifurcation sites, contributing to improved procedural and long-term outcomes.29

Finally, in-stent restenosis (ISR) remains one of the leading causes of long-term stent failure.30 While early cases of ISR were largely mechanical in origin (e.g., stent underexpansion or fracture), there has been a shift toward biological mechanisms, particularly neoatherosclerosis, in the current DES era.30 This presents a unique therapeutic challenge, especially in cases of DES-ISR, where the antiproliferative drug has already failed once. In this context, drug-coated balloons (DCBs) may be a valid non-stent-based alternative, allowing antiproliferative drug delivery without adding a new layer of metal. Their use is expanding globally.31 However, it is important to recognize that not all DCBs are equal, and a class effect cannot be assumed.30,31 While paclitaxel-coated balloons currently dominate the clinical landscape and have demonstrated favorable angiographic outcomes, newer limus-based DCBs are still evolving, aiming to match or surpass paclitaxel in terms of pharmacokinetics and clinical efficacy. Ongoing and future large-scale randomized trials will be critical in determining whether the

observed angiographic benefits of paclitaxel-based DCBs translate into clinically meaningful differences in outcomes, and whether limus-based DCBs can offer comparable or superior results—especially in complex subsets like DES-ISR.32

Part III: Evolving Concepts in Coronary Physiology: Diagnostic and Therapeutic Implications for Obstructive and Non-Obstructive Disease

The final section of this thesis explores a clinically significant and increasingly recognized subset of patients: those with angina or ischemia but no obstructive coronary artery disease (ANOCA). This group, which may comprise up to 25% of patients undergoing coronary angiography, often remains symptomatic despite the absence of epicardial obstruction, with persistently impaired quality of life and elevated cardiovascular risk.33 A key step in managing these patients lies in distinguishing between coronary microvascular dysfunction (CMD) and vasomotor disorders such as coronary spasm—each requiring distinct diagnostic approaches and tailored therapies. Invasive coronary function testing (CFT) remains the gold standard, yet its widespread implementation is limited by technical complexity and low availability.34-36 The advent of continuous thermodilution offers a promising alternative, enabling more reproducible, operator-independent assessment of coronary physiology without the need for hyperaemic agents.37

In our study, we evaluated continuous thermodilution-derived parameters—Qmax and Rμ,hyper—in ANOCA patients undergoing CFT. We aimed to enhance the characterization of ANOCA endotypes and to examine the correlation between continuous and bolus thermodilution-derived metrics across these subgroups.38 Ongoing research is expected to clarify the diagnostic accuracy, reproducibility, and potential clinical integration of these newer physiological indices compared to traditional methods.

The persistent underdiagnosis and undertreatment of CMD underscore the need for standardized diagnostic pathways and evidence-based therapies. The expert reviews and consensus documents presented in this thesis highlight CMD as a heterogeneous and often overlooked condition, commonly associated with both cardiac and extracardiac

syndromes. These documents advocate for a syndrome-specific approach, emphasizing individualized diagnosis and treatment, while calling for targeted pharmacological and interventional strategies validated through future randomized trials.39,40

CMD challenges the traditional epicardiocentric paradigm of ischemic heart disease. While diagnostic tools to detect CMD are now available and increasingly refined, therapeutic options remain limited. Bridging this gap will require both expanded clinical awareness and dedicated clinical trials to identify effective, personalized treatment pathways.

In parallel, the application of coronary physiology to PCI planning—as recommended by the latest EAPCI clinical consensus—marks a key shift toward precision medicine in interventional cardiology. While indices like fractional flow reserve (FFR) and non-hyperaemic pressure ratios have become standard in guiding the indication for PCI, their role has expanded over the past five years to include pre-procedural planning, post-PCI assessment, and identification of residual ischemia. Emerging techniques such as pressure-wire pullback-derived vessel analysis offer valuable insights into the distribution of ischemia, help predict PCI success, and aid in identifying residual flow-limiting stenoses. Additionally, novel functional coronary angiography tools, which integrate angiographic imaging with computational fluid dynamics, now allow for physiology-based assessment without the need for pressure wires—potentially broadening the applicability of physiology-guided PCI.41

In summary, this section emphasizes the need for expanding the role of coronary physiology beyond lesion assessment, into procedural planning, disease pattern recognition, and post-intervention optimization. The ultimate goal remains to integrate these tools into routine practice to improve outcomes for both obstructive and non-obstructive forms of ischemic heart disease.

Conclusions

In this thesis, we highlighted how advances in technology, intracoronary imaging, and applied coronary physiology are transforming the management of both obstructive and non-obstructive coronary syndromes. Tailored strategies—guided by patient-specific

factors such as bleeding risk, anatomical complexity, and coronary function—are essential to optimizing outcomes. Moving forward, the continued integration of innovative technologies with physiological, imaging, and mechanistic insights will be key to delivering more personalized and effective coronary interventions.

Samenvatting en conclusies

Deel I: Procedurele en farmacologische optimalisatie bij ACS-patiënten

Dit deel behandelt belangrijke vooruitgangen in de behandeling van acuut coronair syndroom (ACS), met bijzondere aandacht voor patiënten met multivaatlijden (MVD). De introductie van nieuwe generatie drug-eluting stents (DES), gekenmerkt door dunnere struts, bioresorbeerbare polymeren en verbeterde endothelialisatie, heeft trombotische complicaties aanzienlijk verminderd. 1 Deze technologische innovaties hebben tevens de mogelijkheid geopend om de duur van duale plaatjesremming (DAPT) veilig te verkorten bij geselecteerde patiëntengroepen.

Hoewel verkorte DAPT-strategieën uitgebreid zijn onderzocht bij patiënten met chronisch coronair syndroom (CCS), blijkt de toepassing bij ACS-patiënten uitdagender vanwege het verhoogde risico op recidiverende ischemische events. 2 Desondanks hebben recente gerandomiseerde studies verkorte DAPT-schema's onderzocht—vaak met vroege stopzetting van aspirine gevolgd door P2Y12-remmer monotherapie—met bemoedigende resultaten. 3,4 Deze studies omvatten onder andere patiënten met een hoog bloedingsrisico, niet-geselecteerde ACS-populaties en Aziatische cohorten. 3-7 Tot op heden heeft echter geen enkele gerandomiseerde studie specifiek vroege aspirinestop onderzocht bij patiënten met een acuut myocardinfarct (MI) die complete revascularisatie ondergaan volgens richtlijnen en met gebruik van moderne DES.

De grootschalige multicenter TARGET FIRST-studie (n=2246) leverde belangrijke inzichten door aan te tonen dat vroege overgang naar P2Y12-remmer monotherapie niet inferieur was aan voortgezette DAPT voor het voorkomen van netto nadelige klinische en cerebrale events (NACCE). Opvallend was een relatieve reductie van 54% in bloedingen (BARC type 2, 3 of 5), wat het potentiële veiligheidsvoordeel onderstreept. 8

Voortbouwend op deze bevindingen is de COMPARE STEMI ONE-studie ontworpen, specifiek gericht op patiënten met ST-elevatie myocardinfarct (STEMI). Deze gerandomiseerde studie onderzoekt een combinatie van verkorte DAPT met prasugrel

monotherapie, samen met OCT-geleide revascularisatie van niet-culprit laesies bij patiënten met multivaatlijden. Deze gecombineerde aanpak beoogt te evalueren of procedurele optimalisatie met intracoronaire beeldvorming en gepersonaliseerde antitrombotische therapie zowel ischemische als bloedingsuitkomsten kan verbeteren. 9 Hoewel intracoronaire beeldvorming—met name IVUS en OCT—in het optimaliseren van PCI goed is onderbouwd, blijft de waarde voor het identificeren van kwetsbare plaques die preventieve PCI rechtvaardigen onderwerp van onderzoek. 10-12 Beeldvorming kan extra inzicht bieden in plaquemorfologie en kenmerken geassocieerd met trombogene potentie. 13,14 De klinische relevantie hiervan blijft echter onzeker, aangezien dergelijke plaques jarenlang stabiel kunnen blijven zonder events te veroorzaken. Verdere studies zijn nodig om te bepalen welke niet-culprit laesies baat hebben bij preventieve interventie.

Een belangrijke en vaak onderbelichte dimensie binnen ACS is het verschil tussen mannen en vrouwen in presentatie, therapierespons en uitkomsten. 15 Er bestaan nog aanzienlijke kennishiaten over hoe biologisch geslacht trombotisch en bloedingsrisico beïnvloedt, evenals de farmacologische respons op antitrombotische therapieën. Er is daarom dringend behoefte aan geslachtsspecifieke aanbevelingen. Recente EAPCI-consensusdocumenten benadrukken het belang van gepersonaliseerde antitrombotische therapie bij vrouwen en het aanpakken van systemische barrières voor inclusie van vrouwen in klinische studies. 16,17

Samengevat ondersteunen de studies in dit deel een meer geïndividualiseerde benadering van ACS, waarbij procedurele precisie, beeldvorming en patiëntkarakteristieken—zoals bloedingsrisico, geslacht en plaquemorfologie—worden geïntegreerd om veiligheid en effectiviteit te optimaliseren.

Deel II: Technologische vooruitgang en beeldvorming bij complexe PCI

Recente ontwikkelingen in stenttechnologie, met name nieuwe generatie DES met dunnere struts en bioresorbeerbare polymeren, hebben geleid tot significante verbeteringen in PCI-uitkomsten. 18,19 Deze innovaties verminderen stromingsverstoring, vaatwandontsteking en bevorderen snellere endothelialisatie, wat

resulteert in een lager tromboserisico. 20 Hierdoor zijn dunne en ultradunne strut DES bijzonder aantrekkelijk bij patiënten met een hoog bloedingsrisico (HBR), waar verkorting van DAPT essentieel is.

De COMPARE 60/80 HBR-studie levert belangrijk bewijs: de ultradunne Supraflex Cruz-stent bleek niet inferieur aan de Ultimaster Tansei-stent voor klinische eindpunten (NACE) na 12 maanden bij HBR-patiënten met verkorte DAPT. 21,22 Dit ondersteunt het belang van stentkeuze binnen gepersonaliseerde therapie.

Tegelijkertijd is intracoronaire beeldvorming een hoeksteen geworden van moderne PCI, vooral bij complexe anatomie. De nieuwste ESC-richtlijnen geven een klasse I aanbeveling voor beeldvorming-geleide PCI bij complexe laesies. 23 Verkalkte laesies vormen hierbij een grote uitdaging vanwege verminderde deliverability en stentexpansie, wat geassocieerd is met slechtere uitkomsten. Calcificatie draagt bij aan hogere restenose- en tromboserisico's, vooral bij onderexpansie. 24,25 Strutdikte speelt hierin een belangrijke rol, maar vergelijkende data blijven beperkt. 26 Verdere studies zijn nodig om optimale strategieën te definiëren.

Bifurcatielaesies vormen een andere complexe categorie, vooral bij betrokkenheid van de linker hoofdstam. Hoewel de voorlopige stentstrategie vaak wordt toegepast, suggereren recente data dat een tweestentstrategie in sommige gevallen beter is. 27,28 Intracoronaire beeldvorming is essentieel voor planning, uitvoering en optimalisatie van deze procedures en verbetert zowel procedurele als lange-termijn uitkomsten. 29

Ten slotte blijft in-stent restenose (ISR) een belangrijke oorzaak van falen op lange termijn. 30 Waar dit vroeger vooral mechanisch was, speelt tegenwoordig neoatherosclerose een grotere rol. Drug-coated balloons (DCB) vormen een aantrekkelijk alternatief zonder extra metaalimplantatie en worden steeds vaker toegepast. 31 Niet alle DCB's zijn echter gelijk, en verdere studies zijn nodig om verschillen tussen technologieën te verduidelijken en klinische relevantie aan te tonen. 30-32

Deel III: Nieuwe inzichten in coronaire fysiologie

Het laatste deel richt zich op patiënten met angina of ischemie zonder obstructief coronairlijden (ANOCA). Deze groep, die tot 25% van de patiënten omvat, blijft vaak

symptomatisch met verminderde kwaliteit van leven en verhoogd cardiovasculair risico. 33

Een cruciale stap is het onderscheiden van coronaire microvasculaire dysfunctie (CMD) en vasomotorische stoornissen, aangezien deze verschillende behandelingen vereisen. Invasieve functietesten blijven de gouden standaard, maar worden beperkt toegepast. 34-36 Continue thermodilutie biedt een veelbelovend alternatief met betere reproduceerbaarheid en minder afhankelijkheid van de operator. 37

In onze studie onderzochten wij parameters zoals Qmax en Rμ,hyper om ANOCA-subtypes beter te karakteriseren en correlaties met traditionele methoden te evalueren. 38 Verdere studies moeten de klinische waarde hiervan bevestigen.

CMD wordt nog vaak ondergediagnosticeerd en onderbehandeld. Consensus documenten pleiten voor een syndroom-specifieke aanpak en meer onderzoek naar gerichte therapieën. 39,40

Daarnaast speelt coronaire fysiologie een steeds grotere rol in PCI-planning. Nieuwe technieken maken een meer gepersonaliseerde benadering mogelijk en kunnen ischemie beter karakteriseren en behandelingen sturen. 41

Samengevat benadrukt dit deel het belang van uitbreiding van coronaire fysiologie naar diagnostiek, planning en evaluatie van PCI om uitkomsten te verbeteren.

Conclusies

In deze thesis tonen we aan dat technologische innovaties, intracoronaire beeldvorming en toegepaste coronaire fysiologie de behandeling van zowel obstructieve als niet-obstructieve coronairlijden transformeren. Gepersonaliseerde strategieën—gebaseerd op bloedingsrisico, anatomie en coronaire functie—zijn essentieel voor optimale uitkomsten.

De verdere integratie van technologie, beeldvorming en fysiologie zal cruciaal zijn voor meer gepersonaliseerde en effectieve coronaire interventies in de toekomst.

Chapter 24

PhD portfolio

*Education – Core/general skills			
	Name course	**Planned in year**	**EC**
1.	eBROK (*mandatory when applicable*)	**x**1 □2 □3 **x** 4	1.5
***Education – Scientific knowledge**			
1.	Online medical statistics course Stanford University	**x** 1 □2 □3 □4	6.0
2.	Advanced Clinical Trials [EL013]	□1 **x** 2 □3 □4	1.9
***Education – Seminars, webinars, conferences, network meetings**			
	Name	**Planned in (month/ year)**	**EC**
1.	European Society of Cardiology Conference 2021 Invited Faculty. Title Lecture: *Management of CAD Patients by the Heart Team*	27-30 august 2021	1.2
2.	European Society of Cardiology Conference 2023 Invited Faculty. Title Lecture: *Shortening Dual Antiplatelet Therapy Duration: How, When, and Why?*	25-28 august 2023	1.2
3.	European Society of Cardiology Conference 2024 Invited Faculty. HOT LINE 11 Discussant. Review of the Late-Breaking Trial *REC-CAGEFREE I.*	30august-2 september 2024	1.2
4.	TCT 2022 Invited Faculty and Abstract Grader	16-19 september 2022	1.2
5.	TCT 2023 Invited Faculty and Abstract Grader	23-26 october 2023	1.2
6.	TCT 2024 Invited Faculty and Abstract Grader	27-30 october 2024	1.2
7.	TIO MCS Title Lecture: *Continuous or Pulsatile MCS for High-Risk PCI/Shock Patients.*	14 december 2023	0.5
8.	EuroPCR 2022 Invited Faculty, Abstract Grader, Programma Committee Member	17-20 May 2022	1.2
8.	EuroPCR 2023 Invited Faculty, Abstract Grader, Programma Committee Member	16-19 May 2023	1.2
8.	EuroPCR 2024 Invited Faculty, Abstract Grader, Programma Committee Member	14-17 May 2024	1.2
9.	JIM Conference 2022: Invited Speaker	19-21 June 2022	0.9
10.	JIM-GISE Conference 2023: Invited Speaker	9-11 February 2023	0.9

11.	JIM-GISE Conference 2024: Invited Speaker	21-23 March 2024	0.9
12.	JIM-GISE Conference 2025: Invited Speaker	20-22 February 2025	0.9
13.	DRES 2021 Invited live operator	12 June 2021	0.5
14.	DRES 2024 Invited faculty	13-14 June 2024	1
15.	Radboud University, Nijmegen, The Netherlands (2022): Invited Speaker. Single antiplatelet therapy after PCI	13 june 2022	0.5
16.	A two-decade journey in Randomized Trials and Percutaneous Coronary Intervention. Organizing Committee	19 January 2024	0.5
17.	SCAI Bifurcation Club. Invited lecture Suggested algorithm for Left Main Bifurcation Treatment	27 April 2023	0.5
18.	ACC 2021 Invited speaker Complications: Prevention and Management Mindset	18 dec 2021	0.5
Education – teaching tasks (*e.g. practical guidance/supervision of students, lecturing*)			
	Subject of teaching/Task description	Estimated time	EC
1.	PCR fellow course 2022	16 May 2022	0.5
2.	PCR fellow course 2023	15 May 2023	0.5
3.	PCR fellow course 2024	13 May 2024	0.5
4.	AGIK German Society of Cardiology Conference, Düsseldorf: Invited Trainer as EAPCI Representative (2024)	26 October 2024	0.5
5.	OCC Summit, Istanbul: Invited Trainer as PCR Representative 2023	11-12 October 2023	1
6.	OCC Summit, Istanbul: Invited Trainer as PCR Representative 2024	30 september-1 october 2024	1
7.	JIM-GISE Fellow course	19 February 2025	0.5
Other tasks during PhD project (*together other tasks, e.g. clinical tasks, supervision, teaching, should on average not take more than 20% of the appointment*)			
	Task description	**Estimated time**	**EC**
1.	II Level Master: Interventional Treatment of Structural Heart Disease with Multimodality Imaging (University of Padua, 2021).	2021-2022	10
2.	EAPCI Gender and Disparities Committee Chair 2022-2024	September 2022-September 2024	2
3.	ESC CPC Committee member term 2024-2026	September 2024-current	2
4.	EAPCI Congress Committee Chair term 2024-2026	September 2024-current	2
		Total EC	**49.8**

Chapter 25

List of publications

1. Paradies G, Petrosillo G, **Paradies V**, Ruggiero FM. Role of cardiolipin peroxidation and Ca2+ in mitochondrial dysfunction and disease. Cell Calcium. 2009 Jun;45(6):643-50.
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6. Paradies G, **Paradies V**, Ruggiero FM, Petrosillo G. Changes in the mitochondrial permeability transition pore in aging and age-associated diseases. Mech Ageing Dev. 2013 Jan-Feb;134(1-2):1-9.
7. Paradies G, **Paradies V**, Ruggiero FM, Petrosillo G. Cardiolipin and mitochondrial function in health and disease. Antioxid Redox Signal. 2014 Apr 20;20(12):1925-53
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12. Marchese A., **Paradies V.,** Sirbu V., Musumeci G., Tavazzi L. Regression of severe bare metal stent restenosis: IVUS and OCT findings. Int J Cardiol. 2015 Apr 15;185:78-80
13. Pepe M., **Paradies V.**, Resta R., Cafaro A., Bartolomucci F., Masi F., Quagliara D., Favale S. Functional mitral regurgitation: if the myocardium is guilty do we also need to 'rehabilitate' the valve? EMJ Cardiol. 2015;3[1]:38-47
14. M. Iacoviello , A. Doronzo, **V. Paradies**, V. Antoncecchi, F. Monitillo, G. Citarelli, M. Leone, A. Puzzovivo, L. Gesualdo, M. M. Ciccone The independent association between altered renal arterial resistance and loop diuretic dose in chronic heart failure outpatients. IJC Heart & Vasculature May;28(3):263-265.
15. Marchese A., Rossini R., Basile M., Bedogni F., Danzi GB., Musumeci G., **Paradies V.,** Piccaluga E., Sardella G., Varbella F., Giordano A., Berti S. La posizione della Società Italiana di Cardiologia Invasiva (SICI-GISE) sulle indicazioni alla coronarografia nel paziente con angina stabile. G Ital Cardiol (Rome). 2015 Oct;16(10):582-9.
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Chapter 26

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You are a remarkable example of a hardworking and dedicated professional, with an exceptional sense of responsibility and commitment to your work. Your approach has been both inspiring and motivating throughout my PhD journey.
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e di lucidità pragmatica, sempre pronta ad offrire consigli concreti, efficaci e profondamente saggi.

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About the cover

I would like to thank Antonello Gurrado for realizing this outstanding cover. He is a remarkable artist who generously dedicated part of his valuable time to help me create it. A significant part of his work is devoted to tree collections, which has beautifully shaped the artistic concept behind this cover.

As many of you may know, I come from Bari in Puglia, a region renowned for its ancient and majestic olive trees. Olive trees carry rich symbolism across Mediterranean and classical traditions. They are most commonly associated with peace and reconciliation, rooted in ancient Greek culture. At the same time, they also represent wisdom and endurance. Living for hundreds to thousands of years and often thriving under harsh conditions, olive trees have become a powerful symbol of resilience, patience, and longevity.

In Mediterranean regions such as Puglia, they are also deeply connected to identity and heritage, reflecting continuity between generations and the enduring bond between people, land, and time.

Beyond their cultural and personal significance, olive trees also hold a striking biological resonance. Their branching architecture closely mirrors the bifurcation patterns of coronary arteries. Because of this structure, they are often seen as symbols of life networks and interconnectedness—an analogy that aligns naturally with vascular anatomy and cardiovascular science.

Chapter 27

Curriculum vitae



Personal Information

Date of Birth: 05 July 1984
Place of Birth: Bari, Italy
Nationality: Italian
Current Residence: Rotterdam, The Netherlands

Education and Academic Training

2003 – Secondary School Diploma (100/100)
E. Fermi High School, Bari, Italy

2006 – International Internship (Internal Medicine)
University of Murcia, Faculty of Medical Sciences, Spain
Reina Sofia Hospital (1-month internship program)

2009 – International Research Exchange (Cardiovascular Surgery)
University of Porto, Faculty of Medical Sciences, Portugal
Hospital São João – Prof. Adelino Leite Moreira (1-month research exchange)

2009 – MD, Medicine and Surgery (110/110 *cum laude*)
University of Bari, Italy

2009 – Italian Medical Licensure Examination (Passed)

2015 – Specialization in Cardiology (70/70 *cum laude*)
University of Bari, Italy

2018 – Dutch Registration as Interventional Cardiologist

2018 – CMR Level II Certification
American Society of Cardiovascular Magnetic Resonance

2021 – Medical Statistics Course
Stanford University

2021 – II Level Master: Interventional Treatment of Structural Heart Disease with Multimodality Imaging
University of Padua, Italy

2021–2026 – PhD Candidate
Erasmus Medical Center, Rotterdam, The Netherlands
PhD defense scheduled: 07 July 2026

Professional Experience

2009–2015 – Cardiology Resident
University of Bari, Italy

2014–2015 – Medical Doctor, Interventional Cardiology Lab
Anthea Hospital, Bari, Italy

2016–2017 – Interventional Cardiology Fellow
Maasstad Hospital, Rotterdam, The Netherlands

2017–2018 – Clinical Research Fellow
National Heart Centre Singapore – Duke-NUS

2018–2019 – Interventional Cardiologist
San Paolo Hospital, Bari, Italy

2019–2026 (September) – Consultant Interventional Cardiologist
Maasstad Hospital, Rotterdam, The Netherlands

- CEO, Partnership Cardiologen Rotterdam Zuid
- CEO, Research Maatschap Cardiologen Rotterdam Zuid
- Head of Research, Department of Cardiology, Maasstad Hospital
- Co-Director, Cardiac Catheterization Laboratory, Maasstad Hospital

2023–Present – Associate Professor Qualification (Italy, Second Tier)

October 2026 – Consultant Interventional Cardiologist Erasmus Medical Centre Rotterdam, The Netherlands

Scientific Societies and Leadership Roles

- EAPCI Congress Committee –Chair (2024–2026)
- EAPCI ESC Congress Committee Programme Member (2024–2026)
- Current board member of the WIC (werk interventie groep Nederland)
- Current board member of the DRES organization (Dutch interventional cardiology congress)