Asian Pacific Society of Interventional Cardiology

ICFI

Volume 10 - Number 3 - October 2024 - ISSN: 2426-3958

AsiaIntervention

Official Journal of the Asian Pacific Society of Interventional Cardiology (APSIC) and the Interventional Cardiology Foundation of India (ICFI)

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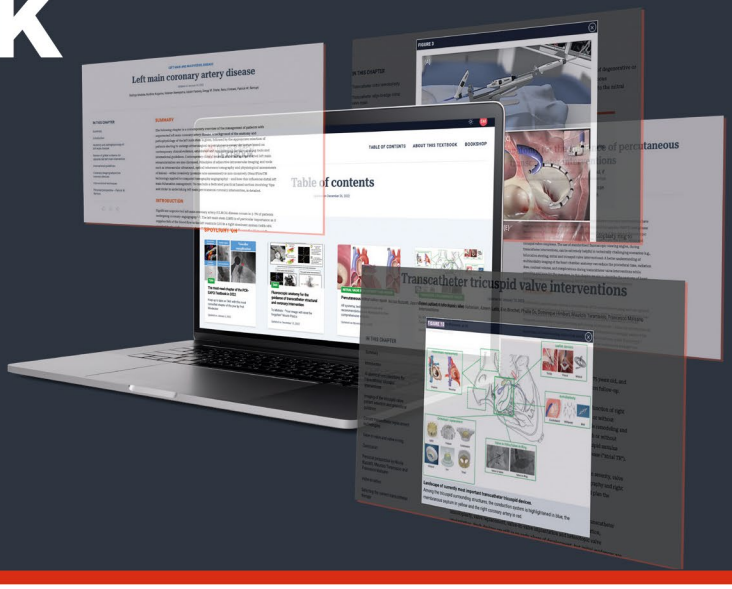

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IN THIS ISSUE OF ASIAINTERVENTION

Using physiology in managing ACS with MVD; aggressive lipid-lowering as a hospital protocol; OCT findings in acute STEMI in the young; Ultrathin-strut DES; early in-stent neoatherosclerosis and ACS; hybrid DCB/DES strategy in PCI; machine learning in predicting PCI outcomes; and much more

Upendra Kaul, *Editor-in-Chief*

Dear Colleagues,

Here we come with the promised third issue of the year 2024. The readership and the contribution from authors from all over the region, Europe and the United States is a testimony of our growing popularity. We already have enough material for the next issue slated to come early next year in 2025.

The issue begins with an expert review on the often-debated subject of interventional treatment of acute coronary syndrome (ACS) patients with multivessel disease (MVD). **Nandine Ganzorig, Vijay Kunadian et al** discuss the important issues involved in non-culprit vessels with narrowings of intermediate severity. Compelling findings show fractional flow reserve (FFR)-guided complete percutaneous coronary intervention (PCI) can reduce adverse cardiovascular events, mortality, and repeat revascularisations

in ACS and MVD patients compared to angiography-based PCI. However, FFR is limited in identifying non-flow-limiting vulnerable plaques, which can disadvantage high-risk patients. In this situation, identifying vulnerable plaques with intravascular imaging can help in decision-making and improving outcomes. Integration of these two different methods and other multimodal simplified techniques are discussed in this expert review.

Aggressive lipid-lowering in patients after intial management is always advocated; however, its overall impact on long-term outcomes and how best to deliver it still need more data. In this issue, **Sho Nakao, Toshiaki Mano et al** have, in a retrospective study, compared a hospital lipid-lowering protocol (HLP), consisting of the maximum tolerated dose of statins, ezetimibe and eicosatetraenoic acid, and compared it with the usual care group. They found that implementing HLP for ACS patients improved the 2-year clinical outcome (non-target vessel revascularisation rate) as compared to the usual care group – a finding which was expected but well documented in this study.

PCI for ST-elevation myocardial infarction (STEMI) is a standard of care in the current era. On optical coherence tomography (OCT), the morphology of the culprit vessel has shown variable pathologies like plaque erosion or plaque rupture along with varying degrees of tissue characteristics. In this Indian study by **M.P. Girish, Jamal Yusuf et al,** the authors compare these morphologies in young (<35 years) versus older individuals during PCI. OCT showed that plaque erosion and plaque rupture were the most common underlying STEMI mechanisms in young patients versus older patients, respectively, and that subjects with plaque erosion had greater evidence of subacute thrombus. These are interesting observations which need to be confirmed in larger studies.

Ultrathin-strut drug-eluting stents (DES; <70 µm) are used in a large number of cases because of their ease of use, better trackability and good long-term results. In this issue there are two articles on these stents: one of 65 µm thickness (BioMime) and another even thinner, at 50 µm thickness (Evermine). In the meriT-2 trial using the BioMime stent, **I join my colleagues Ashokkumar Thakkar et al** in an all-comers study which included treating multivessel disease, bifurcation lesions and in-stent restenosis. We report a low major adverse cardiovascular events (MACE) rate and an actuarial survival rate of 96% at 5 years, which is satisfactory.

In the article on the Evermine stent, **Sivaprasad Kunjukrishnapilla, Ashokkumar Thakkar et al** report on patients with *de novo* lesions subjected to a clinical follow-up of 2 years, who demonstrated very low MACE and mortality (<1%) rates and no stent thrombosis. A small subset underwent repeat angiography at one year. The core lab angiographic assessment showed in-segment and in-device late lumen loss of 0.12±0.31 mm and 0.17±0.31 mm, respectively, reaffirming the good angiographic and clinical results. In an editorial on the Evermine stent, **Azfar G. Zaman and Abhishek Kumar** agree with the good performance of this 50 µm DES, but have pointed out some limitations and shortcomings, such as not including left main and calcified lesions, which remain challenging in contemporary PCI. As a result, this stent may not be a workhorse stent.

The next article in this issue is by **Kazuhiro Nakao, Daiju Fukuda et al** on neoatherosclerosis, which is a well-known factor for late stent failure. The authors, by serial OCT evaluation at one year, have shown that in patients with ACS receiving new-generation DES, neoatherosclerosis sets in early as compared to non-ACS patients. These findings are contrary to the popular belief that neoatherosclerosis is always a late event. **Gian Paolo Ussia and Nino Cocco** comment in an editorial that, despite intravascular imaging, neoatherosclerosis remains an enigma and needs more explanations. This early presence in ACS patients suggests that the plaque characteristics at the time of PCI are important contributors. Prevention needs a multifactorial approach, and bioabsorbable stents without recoil and embolisation could be the way to go.

Jassie Teo, Hafidz Hadi et al, in a retrospective analysis of patients who underwent a hybrid strategy utilising DES and drug-coated balloons (DCB) in 219 lesions, report a very low rate of target lesion failure with <1% target vessel myocardial infarction and death. This again substantiates the clinical safety and efficacy of this treatment methodology which is increasingly practised. In an editorial comment on the hybrid strategy, "Less metal – the latest evolution in PCI", **Simon Eccleshall and Bruno Scheller** opine that the use of paclitaxel-eluting DCB, as an adjunct to DES or used alone, is gaining wide acceptance. They emphasise meticulous vessel preparation, with the concept that "the more you gain, the more you get". An attempt to use DCB-only should be made in complex lesions where PCI is being planned, and having DES as a backup can allow for more aggressive vessel preparation. They support the study by Teo et al as it provides more evidence in favour of the use of DCB.

This is followed by an article on a meta-analysis on machine learning (ML) to predict outcomes post-PCI. **Caitlin Fern Wee, Ching-Hui Sia et al** review a very large cohort taken from 11 studies with a total of 4,943,425 patients. ML models show promise as a useful clinical adjunct to traditional risk stratification scores in predicting outcomes post-PCI. However, significant challenges like missing data need to be addressed before ML can be integrated into clinical practice.

Finally, we have a research correspondence by **Ivan Wong, Michael Kang-Yin Lee et al** on the use of an innovative method of pacing the heart during TAVR using the SENTINEL cerebral protection device.

The editorial team has been working hard to bring this issue to you promptly. We do hope you find the journal educative and helpful in your everyday practice. Your suggestions and comments on the articles will be most appreciated.

Happy reading.

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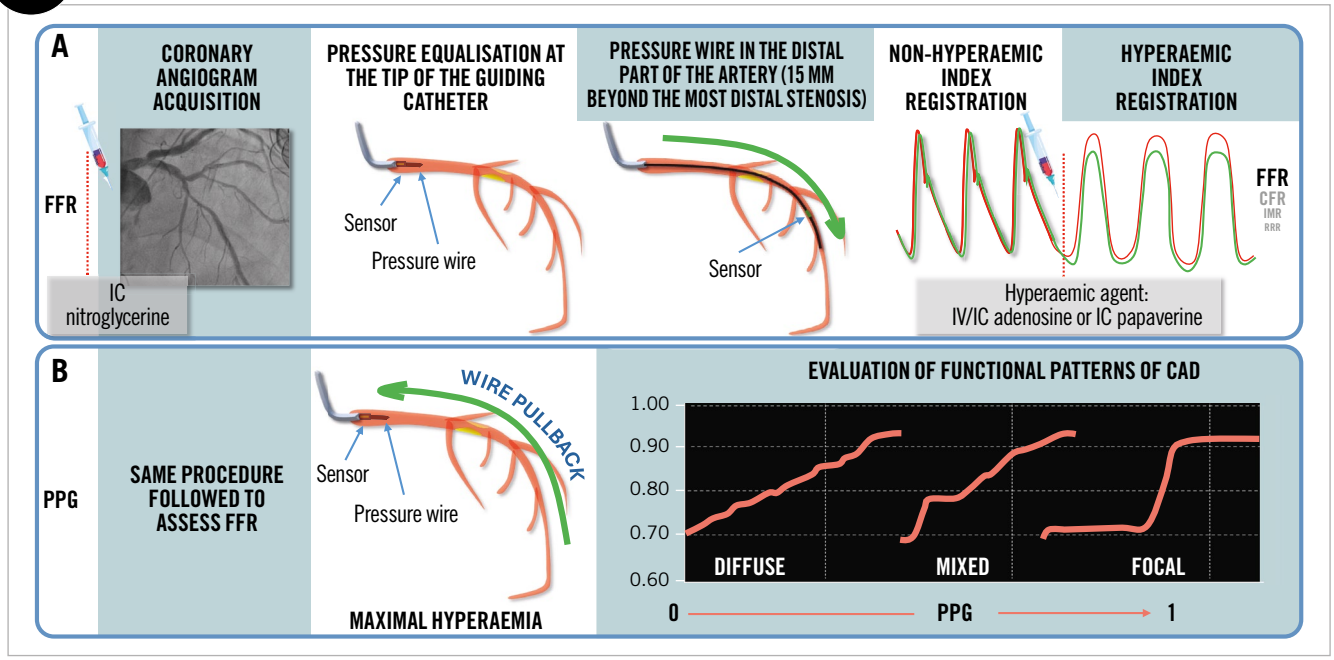

Image taken from the following paper printed in this issue:
Role of physiology in the management of multivessel disease among patients with acute coronary syndrome
Nandine Ganzorig, Vijay Kunadian
AsiaIntervention. 2024;10:157-68

Aims and scope

AsiaIntervention Journal is an international, English language, peer-reviewed journal whose aim is to create a forum of high-quality research and education in the field of percutaneous and surgical cardiovascular interventions.
It is released three times a year, in paper and electronic formats. AsiaIntervention is indexed in PubMed Central®.
AsiaIntervention is the official journal of the Asian Pacific Society of Interventional Cardiology (APSIC) and the Interventional Cardiology Foundation of India (ICFI).

Europa Digital & Publishing
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ASIAINTERVENTION
Publication : 3 numéros par an
Volume 10 - N°3 - Octobre 2024

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Graphisme et mise en page :
Groupe Composer : 2, impasse du Ramier des Catalans - CS 38503
31685 Toulouse Cedex 6 - France

Editeur :
Frédéric Doncieux
Président : Marc Doncieux.
Principal actionnaire :
FINANCIERE MF DONCIEUX ;
ISSN : 2426-3958
ISSN Online : 2491-0929

Imprimé en Inde
par Royale Press Pte Ltd.
1 Ang Mo Kio Industrial Park 2A #04-05
AMK Tech 1 - Singapore 568049

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AsiaIntervention est édité par la Société Europa Group,
SAS au capital de 1 000 000 euros,
siège social : 19, allées Jean-Jaurès, 31000 Toulouse, France ;
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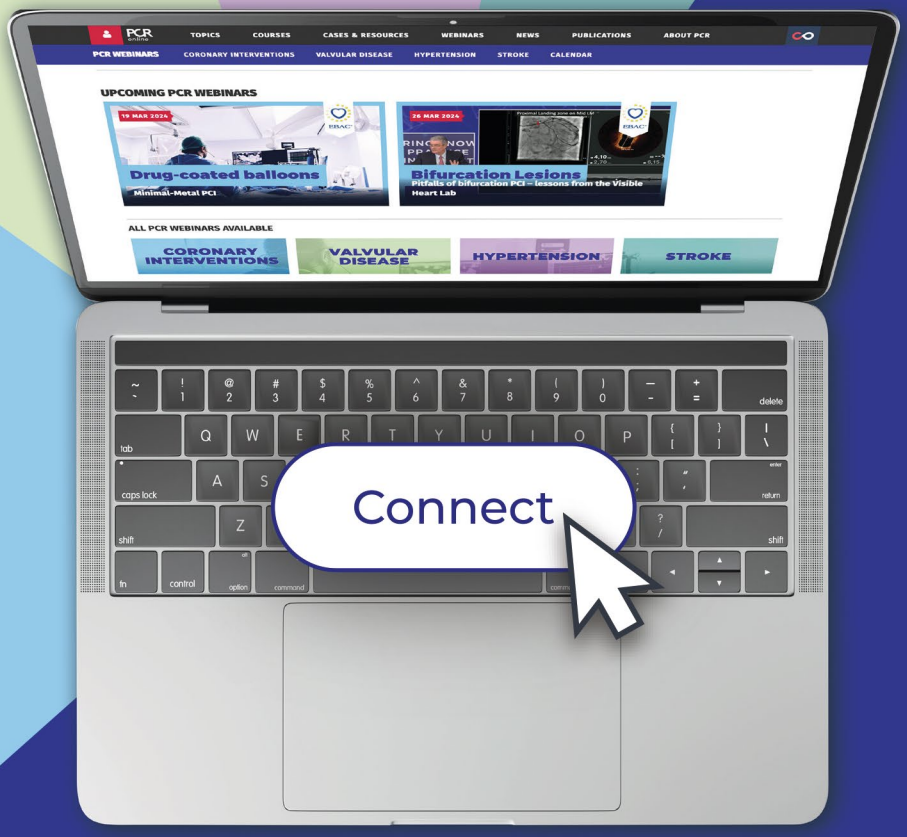

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AsiaIntervention 2024;10:151-152

Less is more: a new "thin-king" for DES?

Azfar G. Zaman[1]*, BSc, MBChB, DM; Abhishek Kumar[2], MBBS

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The quote "less is more" was made famous by the designer and architect Ludwig Mies van der Rohe and came to define the ideals of modernist design and architecture. This quote aptly describes the evolution of coronary stents. Since the first report of increased rates of stent thrombosis with first-generation drug-eluting stents (DES), technological developments in stent design, polymer and drug elution have reduced stent thrombosis rates to under 1%. Adverse clinical outcomes with the 120 µm bioabsorbable drug-eluting stent re-established the metallic platform as the mainstay of stent architecture.

Clinical outcomes with contemporary second-generation DES, though outstanding, have remained stable since their introduction several years ago. The development of ultrathin (<70 µm) stents was predicated on the hypothesis that they would cause less vascular injury and promote faster endothelialisation with reduced ischaemic events. This hypothesis was tested in a head-to-head study, which demonstrated non-inferior clinical outcomes compared to second-generation DES[1], and in meta-analyses[2,3], which showed that ultrathin-strut DES improved 1-year clinical outcomes in comparison with contemporary thicker-strut second-generation DES. The improved outcomes were in clinically meaningful areas, with a 16% reduction in target lesion failure driven by reduced myocardial infarctions[3]. Numerically lower rates of any stent thrombosis were also reported with ultrathin-strut DES; in the meta-analyses, DES strut thickness was 60 µm. The paper by Kunjukrishnapilla and colleagues[4], in this issue of AsiaIntervention, is therefore of interest to the interventional community, as the thickness of the stent strut is only 50 µm. Do the presented data support the use of an even thinner metal platform in daily clinical practice?

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Whilst the group should be congratulated for developing and testing a next-generation usable stent that continues the trend to ever thinner struts, their preliminary, but limited, data support that of a larger patient study with a 55-65 µm coronary stent[5].

The present study is a prospective, single-arm study conducted at 9 centres in India, enrolling 118 patients with *de novo* coronary lesions. Although 40% of patients had Thrombolysis in Myocardial Infarction flow 0 at the outset, it is not evident from the paper whether this was due to ST-segment elevation myocardial infarction or to chronically occluded lesions. This distinction is important as stent delivery and performance in an acute thrombus-occluded vessel is significantly different from that in a revascularised chronic occlusion. One concern interventionalists express about ultrathin stents is their performance in challenging lesion subsets – in particular calcified vessels and left main stem interventions. The absence of such lesions in this study means that the decision to use this stent as a "workhorse" in daily practice must be deferred until we have supporting data.

The undoubted strengths of the present study are the extended follow-up to 24 months and the high prevalence of patients with diabetes mellitus (39%). The absence of stent thrombosis over 2 years in patients with diabetes mellitus is encouraging and possibly lends support to the improved healing and reduced inflammation

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DOI: 10.4244/AIJ-E-24-00005

hypothesis. Taken in context with the long lesion lengths revascularised (mean stent length 26.02 mm, range 9-48 mm) and that 43% of all stents were ≤2.75 mm, the performance of the Evermine50 stent (Meril Life Sciences Pvt. Ltd.), with the absence of stent thrombosis, is noteworthy and justifies further exploration.

This paper confirms the favourable findings of previous studies with ultrathin-strut stents, and the preliminary findings with this particular stent (Evermine50) need to be supported in a larger study with more complex and challenging lesions against a competitor product powered for non-inferiority.

Nevertheless, the data are further evidence that reducing the metallic burden of an implanted stent is associated, in (non-challenging) lesions, with very low adverse outcomes and minimal late lumen loss. Favourable clinical data with use of ultrathin stents support new thinking on the transition from full metal jacket to less stent percutaneous coronary intervention (PCI) (and eventually stent-less PCI?) – less is more.

Conflict of interest statement

A. Zaman has received consulting fees from Meril Life Sciences Pvt. Ltd., SMT, Abbott, Biosensors, and Medtronic; he has received honoraria from Meril Life Sciences Pvt. Ltd., SMT, and Medtronic; support for attending meetings from SMT; and has participated on the board at SMT, Biosensors, and Medtronic. A. Kumar has received a research grant from MedAlliance (now Cordis); consulting fees from Vascular Perspectives; speaker fees from AstraZeneca, Amarin, and Novartis; and travel grants from SMT and Vascular Perspectives; he is a council member of the British Cardiovascular Interventional Society; and he is an honorary senior lecturer at Edge Hill University.

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AsiaIntervention 2024;10:153-154

In-stent neoatherosclerosis: a new problem or an opportunity to rethink the treatment of coronary disease?

Gian Paolo Ussia[1,2]*, MD; Nino Cocco[2], MD

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The risk of recurrence of cardiovascular events remains high after acute coronary syndrome (ACS)[1]. Primary percutaneous coronary intervention (PCI) has been demonstrated to decrease mortality in patients with unstable coronary disease in acute settings[2]. However, long-term mortality after myocardial infarction has not improved in the same manner as short-term mortality[3], and the reduction of the risk of long-term recurrent cardiovascular events in this setting probably represents the most important challenge in cardiology at present[1-4]. While the introduction of drug-eluting stent (DES) technology for the treatment of significant culprit lesions due to coronary artery disease (CAD) was able to markedly reduce neointimal proliferation, at the same time, a high price was paid in terms of delayed and aberrant arterial healing, due to the effects of the antiproliferative drugs eluted by the stent that impaired physiological re-endothelialisation and vascular remodelling. Still, the incidences of target lesion revascularisation and recurrent stent thrombosis (ST) due to early and late ST in ACS patients remain remarkable[5].

Stent technology evolved, but different profiles of clinical complications after stent implantation were observed. The first generation of DES were able to substantially reduce in-stent restenosis (ISR) events associated with bare metal stents (BMS) whilst increasing the incidence of in-stent thrombosis (IST). Stent restenosis was demonstrated to occur early in patients implanted with BMS, and the proliferation and migration of vascular smooth muscle cells were the prevalent mechanisms. Furthermore, newer-generation DES implants were associated with lower rates of IST than first-generation DES; however, a different type of complication known as "neoatherosclerosis" led to late stent failure. This distinct type of accelerated atherosclerosis of multifactorial aetiology develops inside of the stented segment of a coronary vessel. It is now emerging as a new problem that has yet to be solved, causing stent thrombosis and failure[6].

Although coronary stenting resolves the problem of atherosclerotic lesion-induced myocardial ischaemia, it results in a new problem of neoatherosclerosis that represents the present challenge in the context of stent failure. Understanding the mechanisms underlying the pathophysiology of neoatherosclerosis is crucial to addressing this new challenge. In this issue of AsiaIntervention, Nakao and colleagues[7], in a retrospective observational study conducted on 102 patients who had undergone percutaneous coronary intervention in both ACS and non-ACS settings, using optical coherence tomography (OCT) to investigate the presence of in-stent neoatherosclerosis, showed that neoatherosclerosis was more frequent in patients treated in an ACS setting. Optical coherence tomographic images identified a morphological abnormality and the characteristics of the tissue covering the stent struts, showing OCT to be a valid tool in this context[7]. However, the underlying causes of accelerated plaque formation after DES implantation are poorly elucidated, and there is still a substantial lack of knowledge regarding the underlying mechanisms. It occurs regardless of the stent type, and stent technology evolution is not achieving the desired results[8]. The advent of epigenetics may help us to understand the mechanisms underlying restenosis. Increasing evidence has demonstrated that epigenetics is involved in the occurrence and progression of

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DOI: 10.4244/AIJ-E-24-00006

in-stent restenosis and can provide new targets for stent failure drug development. However, epigenetic regulation takes time, especially if the drug targets the writer protein[9].

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Stettler et al demonstrated how this event is more dependent on focal triggers within the vessel involved in forming vulnerable lesions than the stent type. The finding that neoatherosclerosis is more prevalent in ACS populations compared to chronic coronary syndromes (CCS) confirms this concept and offers clinical proof that the target lesion failure is mainly related to lesion characteristics[10]. This observation highlights the marginal impact of stent evolution on the neoatherosclerotic process development, while plaque composition and stability have a significant effect. This means that the more unstable patients who are at higher risk remain those most exposed to recurrent events, still in the second-generation drug-eluting stent era, representing a warning for a profound reflection on the percutaneous treatment of coronaropathy. In light of recent observations regarding revascularisation in the context of ACS and CCS, it is necessary to begin to ask whether it is appropriate to pursue the path of technological evolution of the stent or to begin to embrace with more conviction new technologies inclined to consider cardiovascular intervention as the treatment of the artery in addition to the reopening of the stenosis and to jail the narrowing with foreign material to avoid recoil. The "leaving nothing behind" strategy is emerging as an alternative[11]. Still, the problems of recoil and embolisation need to be addressed, especially in complex scenarios and ACS, but the advent of new techniques, devices, and healthier local drugs will represent a change in the approach from opening the artery to healing the artery along with restoration of the flow.

Conflict of interest statement

The authors have no relationships relevant to the contents of this paper to disclose.

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AsiaIntervention 2024;10:155-156

Less metal – the latest evolution in PCI

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Currently, the use of a drug-coated balloon (DCB)-only approach to percutaneous coronary intervention (PCI) is expanding, as seen by the number of publications, ongoing randomised controlled trials (RCTs) and sessions at major global interventional meetings. The concept of less metal long term is one of the driving forces behind this move, as demonstrated by Shin et al in their paper reporting a reduction in events with reduced drug-eluting stents (DES) and increased DCB in multivessel procedures[1]. A closely related issue of reduced DES implantation is addressed in this edition of AsiaIntervention by Teo et al in a retrospective analysis of the hybrid approach to PCI[2]. This term describes the combination of DES and DCB within the same vessel or bifurcation. The report covers a one-year period identifying 401 patients, of whom 363 patients had 12-month follow-up data. Their results are impressive with target lesion failure (TLF) of 2.2% (target vessel myocardial infarction [TVMI] 0.83%, ischaemia-driven target lesion revascularisation [ID-TLR] 0.83% and cardiac death 0.55%). The majority of DCBs were paclitaxel-based, whilst the DES were -limus-based. Concern over mixing -limus and paclitaxel is addressed and is shown to be safe at one year. DES were bigger in diameter and length than DCBs, suggesting that more proximal lesions and the main branch (MB) of bifurcations were the intended DES recipients, with DCBs presumably used distally and in the side branch (SB). Bifurcation PCI was reported in 19% of cases. The case mix was 80.8% elective but complex with 72% type C, very long lesions, and 60% with diabetes. Intravascular imaging (IVI) was used in 30% of cases and calcium modification in 5%. This is an impressive and detailed publication from a respected high-volume centre performing complex PCI and adds to the data supporting the move away from a complete DES approach to PCI.

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One of the major concerns with this approach is the safety aspect of a proximal DES relying on a balloon-only outflow, raising the possibility of edge dissections and acute vessel closure. The excellent safety data of Teo et al[2], however, give operators reassurance that a meticulous approach to lesion preparation and assessment of the acute balloon result will allow a successful PCI. The use of IVI in 30% of cases is interesting, but it is not clear if this represents IVI use in guiding lesion preparation, DES optimisation, or assessment of DCB preparation and acute results. We would not recommend the use of IVI in a DCB-only approach for the following reasons: inexperienced operators may bailout to DES on seeing multiple luminal dissections; DCB-only PCI results are based on angiographic vessel sizing of 1:1, but IVI will increase device size and thus increase the use of bailout further; IVI tends to promote the treatment of longer lesions, whilst a DCB-only approach is more minimalist and forgiving. However, the ULTIMATE-III trial supports more aggressive lesion preparation with balloons that are 0.25 mm larger when IVUS-guided rather than angiographically guided, with less late lumen loss but a higher bailout rate[3]. Similarly, in the TRANSFORM I study, a reduction in angiographical late luminal loss was seen for the paclitaxel DCB with increasing dissection volume[4]. The old axiom of gain associated with loss seems to no longer apply, rather now, "the more you gain, the more you get" when using paclitaxel-coated DCB[5].

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DOI: 10.4244/AIJ-E-24-00004

A major deficiency of real-world cohort publications is the lack of understanding of the initially intended PCI technique, so we do not know how often the final hybrid result was the primary intention or was driven by bailout in more proximal larger vessels due to unsuccessful optimal lesion preparation or a vessel-threatening dissection. We encourage a full DCB-only approach to such long lesions where possible but in the knowledge that the hybrid approach is possible.

Bifurcation PCI is important, but we feel that in this paper it is a distraction. We suggest the simplest approach would be DCB-only for all lesions. The hybrid approach is required in only 2 situations. Firstly, when there is a planned DCB to the SB but elective or bailout DES to the MB. SB lesion preparation and DCB are performed before MB DES implantation. The stent does not then need to be recrossed (a more attractive hybrid option), but post-dilatation and potting is advised. Secondly, when MB DES is elective or bailout, but the SB was not an intended target but requires rescue after MB DES implantation. After a good balloon result is achieved, this is the only scenario in which we advocate a DCB through a newly implanted DES. Kissing and potting, as necessary, should be performed. The problems with this latter approach are increased complexity, reduced DES integrity, and the theoretical problem of drug accumulation at the ostium of the SB in the vicinity of new bare DES struts. **Figure 1** illustrates the different concepts of bifurcation treatment including DCB.

In conclusion, we congratulate Teo et al[2] on adding to the data suggesting a reduction in DES use is safe and efficacious and encourage operators to bear such data in mind in their daily practice. The results of large landmark RCTs will hopefully promote the DCB-only approach over the next few years.

Conflict of interest statement

S. Eccleshall received research grants for investigator-initiated research and lecture honoraria from B. Braun. He is a shareholder of MedAlliance and also acts as a consultant for B. Braun, Cordis, Medtronic, and MedAlliance. B. Scheller is a shareholder of InnoRa GmbH and received lecture fees and consulting honoraria from B.Braun and Medtronic.

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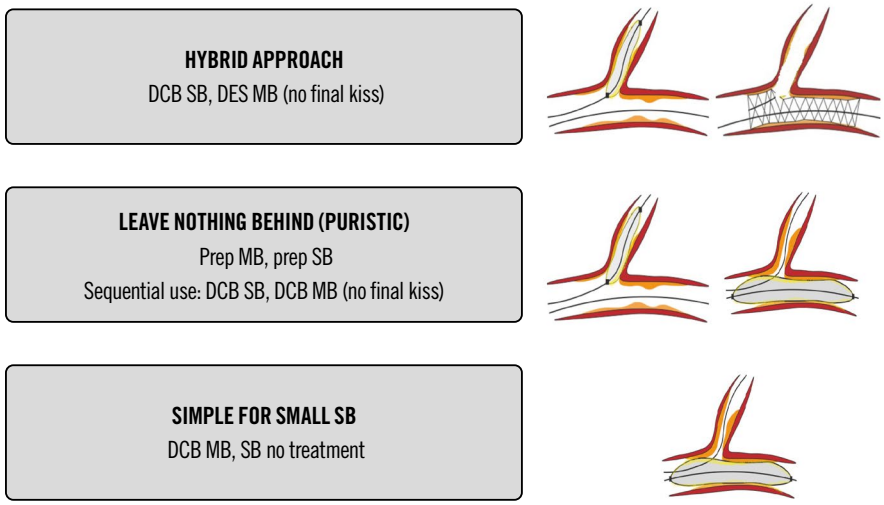

Figure 1. *Different scenarios of DCB treatment in coronary bifurcations. DCB: drug-coated balloon; DES: drug-eluting stent; MB: main branch; SB: side branch*

AsiaIntervention 2024;10:157-168

Role of physiology in the management of multivessel disease among patients with acute coronary syndrome

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KEYWORDS

- acute coronary syndrome
- coronary artery disease
- fractional flow reserve
- multiple vessel disease
- non-ST-segment elevation myocardial infarction
- ST-segment elevation myocardial infarction

Abstract

Multivessel coronary artery disease (CAD), defined as ≥50% stenosis in 2 or more epicardial arteries, is associated with a high burden of morbidity and mortality in acute coronary syndrome (ACS) patients. A salient challenge for managing this cohort is selecting the optimal revascularisation strategy, for which the use of coronary physiology has been increasingly recognised. Fractional flow reserve (FFR) is an invasive, pressure wire-based, physiological index measuring the functional significance of coronary lesions. Understanding this can help practitioners evaluate which lesions could induce myocardial ischaemia and, thus, decide which vessels require urgent revascularisation. Non-hyperaemic physiology-based indices, such as instantaneous wave-free ratio (iFR), provide valid alternatives to FFR. While FFR and iFR are recommended by international guidelines in stable CAD, there is ongoing discussion regarding the role of physiology in patients with ACS and multivessel disease (MVD); growing evidence supports FFR use in the latter. Compelling findings show FFR-guided complete percutaneous coronary intervention (PCI) can reduce adverse cardiovascular events, mortality, and repeat revascularisations in ACS and MVD patients compared to angiography-based PCI. However, FFR is limited in identifying non-flow-limiting vulnerable plaques, which can disadvantage high-risk patients. Here, integrating coronary physiology assessment with intracoronary imaging in decision-making can improve outcomes and quality of life. Further research into novel physiology-based tools in ACS and MVD is needed. This review aims to highlight the key evidence surrounding the role of FFR and other functional indices in guiding PCI strategy in ACS and MVD patients.

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SUBMITTED ON 19/07/2024 - REVISION RECEIVED ON 01/08/2024 - ACCEPTED ON 02/08/2024

DOI: 10.4244/AIJ-D-24-00051

Abbreviations

ACS	acute coronary syndrome
CAD	coronary artery disease
FFR	fractional flow reserve
FFR-CT	computed tomography-derived fractional flow reserve
IRA	infarct-related artery
iFR	instantaneous wave-free ratio
MACE	major adverse cardiovascular events
MVD	multivessel disease
non-IRA	non-infarct related artery
NSTEMI	non-ST-segment elevation myocardial infarction
NSTE-ACS	non-ST-segment elevation acute coronary syndrome
OCT	optical coherence tomography
OFR	optical coherence tomography-based fractional flow reserve
OMT	optimal medical therapy
PCI	percutaneous coronary intervention
PPG	pullback pressure gradient
QFR	quantitative flow ratio
RFR	resting full-cycle ratio
STEMI	ST-segment elevation myocardial infarction

Introduction

Multivessel coronary artery disease (CAD) is a common finding in patients with acute coronary syndrome (ACS), affecting approximately 50% of patients with ST-segment elevation myocardial infarction (STEMI)[1]. This is associated with worse prognosis, increased mortality, and higher costs compared to single-vessel disease[1,2]. Despite advancements in therapies and interventional techniques, the presence of multiple lesions continues to pose a clinical challenge for cardiologists[3], with great uncertainty regarding the optimal revascularisation strategy. The potential for physiology to guide treatment has garnered increasing interest.

Fractional flow reserve (FFR) is a coronary physiological index measured invasively to determine the potential of a lesion to impede perfusion and induce myocardial ischaemia. It is the ratio between the maximal myocardial blood flow in a stenotic coronary artery and the normal maximal myocardial blood flow in the same artery. Although currently recommended by international guidelines as one of the standard tools to assess the haemodynamic severity of non-culprit lesions (NCLs) in stable CAD[4-6], in patients with ACS concomitant with multivessel disease (MVD), the role and accuracy of FFR to guide revascularisation are less clear. This review summarises current evidence relating to the role of physiology in ACS patients with MVD.

Technical aspects and validation of FFR measurement

During diagnostic cardiac catheterisation, a pressure-sensitive guidewire is advanced into a coronary artery to measure the pressure proximal and distal to a lesion during maximal hyperaemia. This is usually achieved by administering intravenous adenosine, or intracoronary adenosine or papaverine, resulting in vasodilation. FFR is calculated as the ratio of pressure distal to the stenosis (Pd) and pressure proximal to the stenosis (Pa) during maximal hyperaemia[7]: $FFR=Pd_{hyperaemic}/Pa_{hyperaemic}$[7]. Lesions with FFR >0.80 (negative FFR) are deemed haemodynamically non-significant, and optimal medical therapy (OMT) is recommended[8,9]. Lesions with FFR ≤0.80 (positive FFR) are considered haemodynamically significant, i.e., with the potential to cause ischaemia, and percutaneous coronary intervention (PCI) should be considered alongside OMT[9-11]. The >0.80 cutoff excludes ischaemic lesions with a positive predictive value of 95%; this threshold for guiding PCI has been validated in previous studies[7,9,12].

FFR is well established and mandated in stable CAD[4]. Several landmark trials have validated its accuracy in measuring stenosis severity and its benefit on outcomes[8,10,11]. For instance, the Fractional Flow Reserve Versus Angiography for Multivessel Evaluation (F.A.M.E.) trial found FFR-guided PCI (FFR ≤0.80) in MVD to be associated with a lower incidence of major adverse cardiovascular events (MACE) for up to 2 years, with fewer stents implanted, compared to angiographic guidance[10].

Conversely, non-hyperaemic pressure ratios (NHPRs) are valid wire-based alternatives to FFR that evaluate the functional significance of coronary lesions during the resting Pd/Pa ratio, eliminating the need for vasodilator administration. The instantaneous wave-free ratio (iFR) measures the mean Pd/Pa during the mid-diastolic wave-free period; a window starting from 25% of the way into diastole and continuing until 5 milliseconds before the start of systole[13]. This provides reliable circumstances for pressure assessment, as coronary microvascular resistance is minimal and constant[13]. Based on several trials[13-17], iFR is recommended for evaluating intermediate coronary stenoses by the European and the American guidelines for chronic CAD, indicating revascularisation if iFR ≤0.89[4,9,18]. Resting full-cycle ratio (RFR) is another NHPR, representing the smallest Pd/Pa measurement across the entire cardiac cycle[19].

Current recommendations for complete revascularisation in ACS patients with MVD

The latest 2023 European ACS guidelines recommend performing complete revascularisation for STEMI patients with MVD (Class I, Level of Evidence A), avoiding the use of functional assessment for the non-infarct related arteries (non-IRAs) during the index procedure[20]. This is based on large trials establishing its superiority over culprit-lesion-only revascularisation[21-23]. A meta-analysis of 12 randomised controlled trials (RCTs), comparing patient outcomes undergoing multivessel revascularisation or culprit-only PCI for STEMI, found that multivessel revascularisation was associated with lower rates of MACE (by 56%), angina (by 54%), and repeat PCI (by 28%) compared to culprit-only revascularisation[24]. This was supported by a separate systematic review that included 7,030 patients[25]. For haemodynamically stable patients with non-ST-segment elevation acute coronary syndrome (NSTE-ACS) and MVD, European guidelines recommend consideration of complete

revascularisation (Class IIa, Level of Evidence C)[20], and invasive physiology should be considered to assess non-IRAs[20,26].

The optimal strategy to decide which NCLs to treat remains subject to ongoing debate[20]. Visual assessment is reported to overestimate stenosis severity, particularly intermediate stenoses (50-70% diameter stenosis)[27], which may lead to overtreatment of lesions that cause neither ischaemia nor symptoms, thus exposing patients to unnecessary risks[28-31]. FFR is not frequently used in this setting partly owing to concerns of microvascular disturbance during the acute phase of a myocardial infarction (MI), which may attenuate hyperaemic response to vasodilators and, thus, impair FFR reliability[32-35]. Despite this, several trials have evaluated the application of FFR in this patient cohort, showing promising results[36,37].

FFR use in guiding PCI of non-culprit lesions for ACS patients with MVD

To date, the Complete vs Culprit-only Revascularization to Treat Multi-vessel Disease After Early PCI for STEMI (COMPLETE) trial is the largest study addressing complete revascularisation in ACS patients with MVD. Among 4,041 STEMI patients with MVD, it found that complete revascularisation of significant NCLs (n=2,016) was superior to culprit-only revascularisation (n=2,025) in reducing hard clinical endpoints over a 3-year follow-up[23]. This includes a 26% risk reduction for a composite of cardiovascular mortality or new MI in the group assigned complete revascularisation, driven by a 32% lower incidence of new MI[23]. Incidence of the co-primary composite endpoint – comprising cardiovascular death, new MI, or ischaemia-driven revascularisation – was similarly lower in the complete revascularisation group, by roughly 50%[23]. Yet, no reduction in heart failure or all-cause mortality was observed[23]. Secondary analysis of the trial also observed more angina-free individuals by the end of the study in the group assigned complete revascularisation[38]. It should be noted that in the COMPLETE trial, physiology was not used alone to guide complete revascularisation; NCLs were deemed significant if they presented with either stenosis ≥70% of vessel diameter on angiographic visual estimation or FFR ≤0.80 with 50-69% stenosis[23]. While FFR was not standardised for all patients, the positive results furthered interest into the potential benefits of an FFR-guided approach in this cohort.

Several trials have directly compared FFR-guided complete PCI to culprit-only PCI in ACS patients with MVD. Engstrøm et al randomised 627 patients with STEMI and MVD to either FFR-guided complete revascularisation or culprit-only PCI. Those assigned FFR-guided complete revascularisation had a significantly lower risk of a composite of all-cause mortality, non-fatal reinfarction, and ischaemia-driven revascularisation, compared to the culprit-only group (hazard ratio [HR] 0.56, 95% confidence interval [CI]: 0.38-0.83; p=0.004)[30]. Importantly, 31% of the patients allocated to complete revascularisation did not undergo revascularisation of NCLs, as their FFR values were >0.80[30]. This did not cause significant differences in the primary outcome rates compared to the remainder of the group assigned complete revascularisation (HR 1.54, 95% CI: 0.82-2.90; p=0.180)[30].

Similarly, the Comparison Between FFR Guided Revascularization Versus Conventional Strategy in Acute STEMI Patients With MVD (CompareAcute) trial supports the superiority of FFR-guided complete revascularisation compared to culprit-only PCI in STEMI patients with MVD. Among 885 patients, FFR-guided PCI of NCLs lowered the risk of a composite of major adverse cardiovascular and cerebrovascular events, including all-cause mortality, MI, revascularisation, and cerebrovascular events, compared to no additional invasive treatment besides primary PCI (pPCI), both at 1-year and 3-year follow-up (p<0.001)[31,39]. The primary outcomes in these 2 trials were mainly driven by fewer repeat revascularisations in patients assigned complete revascularisation[31,39], and they failed to show any differences in mortality or non-fatal MI, albeit neither trial was sufficiently powered to identify differences in hard clinical endpoints, i.e., mortality and MI[30,31,39]. From an economic standpoint, an FFR-guided approach is favourable. Cost analyses from the CompareAcute trial demonstrate a decrease in healthcare costs using an FFR-guided complete revascularisation strategy by up to 21% (at 1 year) and 22% (at 3 years), compared to culprit-only PCI[31].

Physiology use to guide PCI in older ACS patients with MVD

Over the past decades, clinical research assessing FFR-guided PCI in ACS patients with MVD largely included younger patients, with a paucity of data representing patients aged ≥75 years. However, older adults are disproportionately affected by ACS, experiencing higher rates of complications and MACE[40], and often receive suboptimal treatment[41-43]. A subanalysis of patients aged ≥75 years from the DANAMI-3-PRIMULTI trial found no significant difference in MACE with FFR-guided complete revascularisation[44]. While these findings oppose the FFR-associated prognostic benefit in the full cohort, the small sample size (n=110) prevents any reliable conclusions from being drawn[30].

A recent, large RCT addressing the effectiveness of physiology-guided PCI in older patients is the Functional Assessment in Elderly MI Patients With Multivessel Disease (FIRE) trial, wherein 1,445 patients aged ≥75 years, with MVD and either STEMI or non-STEMI (NSTEMI), were randomised to physiology-guided complete revascularisation or culprit-only PCI[45]. In the former group, 50.1% patients received revascularisation for NCLs, based on physiological assessment comprising guidewire-based methods and quantitative flow ratio (QFR)[45]. Findings show the superiority of the physiology-guided complete approach over culprit-only PCI in terms of a 27% relative risk reduction in a composite of mortality, stroke, MI, or ischaemia-driven revascularisation[45]. This was driven by a reduction in each component of the composite endpoint, excluding stroke. Safety was also assessed as a composite of contrast-associated acute kidney injury, stroke, or bleeding, for which no difference was found between the 2 groups (HR 1.11, 95% CI: 0.89-1.37; p=0.370)[45]. Hence, the demonstrated feasibility, safety, and effectiveness of physiology-guided complete PCI support the potential inclusion of this strategy into routine practice for older adults with ACS and MVD.

Recent contrasting findings

Findings from the Ffr-gUidance for compLete Non-cuLprit REVASCularization (FULL REVASC) trial are controversial. This registry-based RCT randomised 1,542 patients (mean age 65.3±10.5 years) with STEMI or very high-risk NSTEMI and MVD to undergo either FFR-guided complete or culprit-only PCI[46]. As opposed to most other trials, FULL REVASC showed that compared to culprit-only PCI, FFR-guided complete revascularisation did not cause a significant difference in the primary composite outcome – comprising all-cause death, MI, or unplanned revascularisation – at 4.8 years (HR 0.93, 95% CI: 0.74-1.17; p=0.530)[46]. When evaluating how applicable these results are and reasons for this discordance, the following should be acknowledged. The trial aimed to enrol 4,052 patients with a primary endpoint of a composite of all-cause death or MI at 1 year[46]. Based on feasibility and ethical grounds, it was terminated prematurely with 1,542 patients randomised, hence the addition of unplanned revascularisation to the primary outcome[46]. Despite the longer follow-up, the 74% statistical power achieved at 4.8 years was lower than expected[46]. Extrapolating findings to very high-risk NSTEMI patients may not be reliable, as this subgroup constituted only 8.6% of the 1,542 patients enrolled[36]. Additionally, differences in procedural characteristics could have contributed to the inconsistencies with other trials: the FIRE and COMPLETE trials randomised patients no later than 48 hours[45] and 72 hours of successful PCI of the culprit vessel[23], respectively, whereas FULL REVASC patients were randomised within 6 hours[46]. Possible microvasculature disturbance in the hyperacute phase could have overestimated stenosis severity, leading to overtreatment[35]. However, 18.8% of all the NCLs in the complete revascularisation group were treated with PCI[46] – a lower percentage than in other trials (PCI was performed in 45.5% of NCLs in the complete revascularisation arm of the FIRE trial)[45], indicating other factors could be at play. Furthermore, with the release of the conclusive COMPLETE trial findings, few patients with severe stenosis or three-vessel disease were included in the FULL REVASC trial[36,46]. Since this cohort benefits substantially from NCL revascularisation, the lack of their representation may have attenuated the overall results.

Angiography-guided PCI versus FFR-guided PCI

Another salient question is whether FFR-guided or angiography-based complete revascularisation is superior. Two major studies comparing these strategies in STEMI patients reveal contrasting results. The FLOWER-MI trial observed that, in 1,171 STEMI patients with MVD, FFR-guided complete revascularisation of NCLs was not superior to angiography-guided complete revascularisation in terms of the 1-year composite risk of death, MI, or urgent revascularisation (p=0.310)[47]. This insignificant difference was similarly observed in the 3-year follow-up extension phase[48], with fewer stents and PCI used in the FFR group. The wide confidence interval for the primary outcome prevents firm conclusion from being drawn.

Conversely, the more recent FRAME-AMI study – enrolling 562 patients with acute MI (STEMI or NSTEMI) and MVD – showed the superiority of FFR-guided PCI of non-IRAs over angiographic guidance, associated with a reduction in death, MI, or repeat revascularisation at a median 3.5-year follow-up (p=0.003)[49]. This benefit, driven by the outcomes of NSTEMI patients, was consistent regardless of non-IRA stenosis severity[49].

These findings should be interpreted cautiously for multiple reasons. Firstly, both trials had insufficient statistical power owing to a low incidence of primary outcome events (54 in FLOWER-MI; 52 at 1 year and 56 at 3 years in FRAME-AMI)[47-49]. The premature termination of FRAME-AMI might have led to exaggerated outcomes, highlighting the need for larger sample sizes. Secondly, of these 2 trials, only FRAME-AMI enrolled NSTEMI patients, making generalisations to this cohort less reliable[36,49]. Thirdly, the FLOWER-MI FFR-guided group, despite undergoing fewer interventions, had 3 times more periprocedural-related MIs than the angio-guided group, potentially explaining why the FFR group had a numerically higher incidence of non-fatal MI[47-49]. Furthermore, reliable comparisons cannot be made between the 2 trials, as the population evaluated, follow-up periods, and timing of non-IRA PCI differ.

Concerning NSTE-ACS patients with MVD, the FAMOUS NSTEMI trial supports the benefit of FFR-guided complete revascularisation compared to angiographic guidance. The former strategy resulted in fewer stents implanted and, while the rate of procedure-related MI was higher in the angiography-guided group and spontaneous MI higher in the FFR-guided group, overall health outcomes were not significantly different[50].

The impact of pattern distribution of CAD on post-PCI FFR

In patients with ACS and MVD, the role of coronary physiology may go beyond the definition of the haemodynamic lesion severity and include additional evaluation of the functional atherosclerotic pattern of NCLs. Functional patterns of CAD can be classified into focal, diffuse and mixed patterns according to the distribution of atherosclerotic plaques along the epicardial vessel; these classifications may have an impact on the final procedural results. Focal CAD is usually characterised by a higher plaque burden, mainly containing lipidic components with a high prevalence of thin-cap fibroatheroma, whereas diffuse disease has a higher prevalence of calcifications, leading to plaque stability[51]. The possibility of stratifying the pattern of CAD to predict the potential benefit of revascularisation has both clinical and prognostic implications. Previous studies have shown that PCI in patients with focal disease results in a larger FFR improvement, higher post-PCI FFR value, reduced ischaemia, and reduced angina compared to patients with diffuse disease receiving PCI[52,53]. Among patients characterised by non-invasive assessment of coronary atherosclerotic distribution, those with diffuse disease undergoing PCI have a significantly higher risk of target vessel failure compared to those with predominant focal lesions[54]. Therefore, physiology-guided classification of CAD patterns before proceeding to intervention may allow better patient selection and may improve postprocedural outcomes.

While FFR measurement is performed to establish the functional significance of haemodynamic lesions, it does not provide information on the localisation of the pressure gradient loss along the epicardial vessel. To address this limitation, an additional wire pullback has been introduced to supplement the functional assessment by providing information on the longitudinal distribution of pressure drops. The pullback pressure gradient (PPG) is an index defining different patterns of pressure loss on a continuous scale ranging from 0 (diffuse pattern) to 1 (focal pattern). From a practical perspective, PPG calculation can be incorporated into the same procedure as the FFR assessment by performing a manual pullback which takes an additional 30 seconds compared to the standard procedure **(Figure 1)**[55]. PPG is then computed using 2 pullback-derived parameters: the maximal pressure difference over 20% of the pullback time and the extent of functional disease. The prospective, large-scale, multicentre PPG Global Registry established the capacity of PPG to predict optimal procedural results and outcomes in patients with stable CAD or who had experienced ACS with MVD. Vessels with focal disease (defined by a PPG cutoff >0.62) treated with PCI achieved significantly higher final FFR values and a larger FFR increase compared to those with diffuse disease treated with PCI. PPG accurately predicted post-PCI FFR value ≥0.88 with an area under the curve (AUC) of 0.82 (95% CI: 0.79-0.84), and the optimal PPG cutoff was 0.73. Conversely, FFR alone did not predict revascularisation outcomes (AUC 0.54, 95% CI: 0.50-0.57)[56]. In addition, patients with focal disease reported greater physical limitation, worse anginal symptoms, and a lower quality of life compared to patients with diffuse disease[56]. Thus, the PPG value allows operators to identify subjects who would benefit from revascularisation and those who would incur a suboptimal post-PCI result, influencing the decision-making approach and diverting patients from PCI towards treatment with alternative strategies. This may help to avoid unnecessary invasive treatment in case of a small, expected postprocedural benefit. In the specific setting of ACS patients with MVD, medical therapy could represent the correct initial approach to adopt for the management of NCLs with a pattern of diffuse disease, switching to PCI only in case of persistent symptoms despite optimised medical treatment.

How to integrate FFR with intracoronary imaging

A physiology-based decision adopted to perform or defer PCI in NCLs is safe and effective in reducing future adverse events compared to an angiography-guided strategy[57]. However, FFR carries limitations in terms of detecting suboptimal results after stent implantation, such as edge dissection and strut underexpansion and/or malapposition. In a population stratified according to the use of an imaging-guided PCI, Ahn et al recently showed that the post-stenting FFR lost its significant prognostic value in predicting cardiac events at 5 years when optimal results were obtained using an imaging-guided strategy[58]. In addition, deferred coronary revascularisation based on FFR may be limited, because coronary physiology does not identify a functionally silent vulnerable plaque, which has been associated with a risk of recurrent cardiovascular events[59,60].

Recent evidence has raised concerns regarding deferred revascularisation based entirely on physiological assessment,

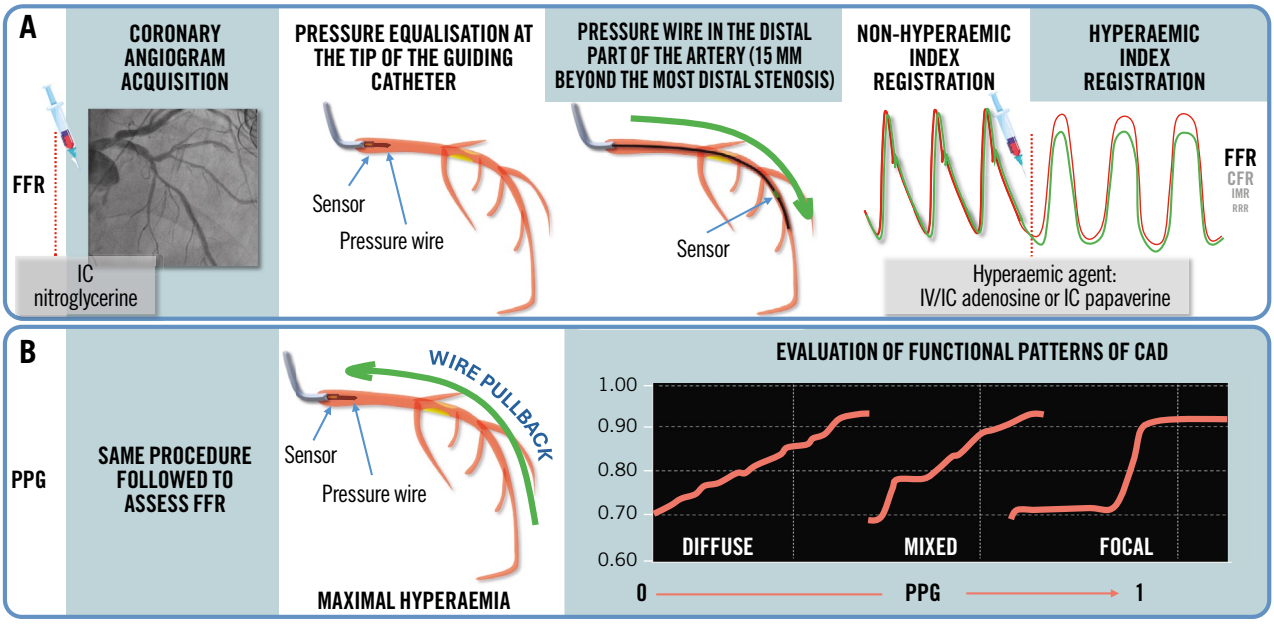


Figure 1. *Procedural steps to assess FFR and PPG indices. A) Steps to assess FFR. B) Steps to assess PPG. CAD: coronary artery disease; CFR: coronary flow reserve; FFR: fractional flow reserve; IC: intracoronary; IMR: index of microcirculatory resistance; IV: intravenous; PPG: pullback pressure gradient; RRR: resistive reserve ratio*

especially in some specific populations such as patients with diabetes mellitus, for whom ischaemia is not the only predictor of future adverse events[59]. In the PREVENT trial, treatment of non-flow-limiting (FFR >0.80) vulnerable plaques with a preventive PCI strategy reduced the composite risk of death from cardiac causes, target vessel MI, ischaemia-driven target vessel revascularisation, or hospitalisation for unstable or progressive angina at 2-year follow-up, compared with OMT alone. Preventive PCI also diminished the patient-oriented composite risk, comprising all-cause death, MI, or any repeat revascularisation[60]. The randomised FORZA trial had already investigated the use of optical coherence tomography (OCT) or FFR guidance in patients with angiographically intermediate coronary lesions and showed a borderline significant reduction (p=0.048) in the combined occurrence of MACE and residual angina in the OCT arm compared to the FFR arm[61].

FFR and intracoronary imaging complement each other, addressing different questions. Applying the use of intracoronary intravascular ultrasound or OCT to patients with non-flow-limiting plaques detected in the functional evaluation could pave the way to improving their characterisation and guidance for revascularisation, especially in cases of a borderline FFR value or ambiguous culprit lesions in the setting of NSTE-ACS. The sole application of coronary physiology in the early phase of an acute context risks underestimating the severity of the lesions since the response to hyperaemic agents may be suboptimal because of the coronary microvascular dysfunction **(Table 1)**. However, some studies investigating the diagnostic accuracy and temporal variation of FFR in NCLs demonstrated good reproducibility between the acute and subacute phases **(Table 2)**. The combined use of imaging and physiology is fundamental in high-risk categories such as diabetic patients, who benefit from early invasive treatment guided by plaque morphology as well as aggressive secondary prevention[62].

Novel computational approaches to derive FFR from intracoronary imaging have been recently proposed. The diagnostic performance of the OCT-based FFR (OFR) was evaluated by Yu et al. When compared with standard pressure wire-based FFR, OFR showed good correlation and agreement in a population with intermediate coronary stenoses[63]. The recent FUSION study is the largest multicentre study comparing OCT-derived physiology (virtual flow reserve [VFR]) with invasive FFR. VFR is obtained through a model that calculates pressure loss along the vessel with a computation time similar to conventional OCT acquisition, facilitating and diverting the choice of treatment in a substantial proportion of patients compared to angiography and imaging-guided PCI without physiology[64].

FFR versus novel physiology-based assessment tools

Limitations undermine the uptake of FFR into routine practice; these include costs, risks associated with administering pharmacological agents to induce maximal hyperaemia, and an extended procedural time. Novel physiology-based indices have emerged to help overcome these, facilitating assessments among interventional cardiologists.

Several RCTs have validated iFR, showing a diagnostic accuracy similar to FFR and non-inferior clinical outcomes of complete PCI guided by iFR ≤0.89 compared to FFR ≤0.80 for MACE at 1, 2, and 5 years[14-17,65]. A recent substudy has shown the safety of deferring revascularisation based on iFR is comparable to that based on FFR[65]. However, discrepancies between iFR and FFR occur in about 20% of cases[15,17,66]. Possible predictors of these discordances include patient sex, age, haemoglobin level, smoking, and renal insufficiency[67]. While data in ACS patients are limited, some evidence supports the diagnostic accuracy, feasibility, and safety of iFR assessment in STEMI patients with MVD[68] **(Table 2)**. Research surrounding other NHPRs remains lacking, though RFR was found to have a high diagnostic accuracy with iFR and concordance with FFR[19].

Moreover, advancements in computational flow dynamics and three-dimensional technology have enabled the development of invasive functional coronary angiography, known as angiography-derived FFR. This tool assessing coronary physiology eliminates the need for an invasive pressure wire and drug-induced

Table 1. Causes of incorrect FFR estimation and their respective mechanisms.

Cause of incorrect FFR estimation	Reason
Early phase of ACS	• Underestimation of the lesion severity due to infarct-related coronary bed dysfunction, which may blunt the maximal hyperaemic response
Aortic stenosis	• Blunted effect of adenosine to increased coronary flow, due to vasodilation at rest to avoid subendocardial ischaemia, caused by a combination of the following: - valve stenosis - myocardial hypertrophy with augmented cardiac work - potential CMD
Coronary microvascular dysfunction	• An epicardial stenosis may result in less flow limitation in case of CMD due to an increased resistance in the coronary microcirculation affecting the response of the coronary bed to adenosine • IMR ≥25 is an independent predictor of disagreement between RFR and FFR
Vasodilator tolerance	• Stimulants such as caffeine antagonise the pharmacological action of adenosine by competitively blocking adenosine receptors activity, potentially causing false-negative measurements

ACS: acute coronary syndrome; CMD: coronary microvascular dysfunction; FFR: fractional flow reserve; IMR: index of microcirculatory resistance; RFR: resting full-cycle ratio

Table 2. Studies investigating the diagnostic accuracy and temporal variation of FFR and iFR in patients with acute coronary syndrome and multivessel disease.

Study	Index used	Design	Populations and NCLs	Underestimation of lesion severity based on index	No differences in index values between acute and subacute phase	Results
Ntalianis et al 2010[80]	FFR	Prospective observational	75 STEMI 26 NSTEMI 112 NCLs	Data not applicable	Yes	FFR after pPCI vs FFR after 35±4 days: 0.77±0.13 vs 0.77±0.13; p=NS
Musto et al 2017[33]	FFR	Prospective observational	50 STEMI 66 NCLs	Data not applicable	Yes	FFR after pPCI vs FFR after 5-8 days: 0.82±0.07 vs 0.82±0.08; p=0.620
Choi et al 2018[34]	FFR	Prospective observational	34 STEMI 66 NSTEMI 128 NCLs	Data not applicable	Data not applicable	FFR in STEMI vs FFR in stable angina for 60-70% stenosis: 0.81±0.09 vs 0.70±0.12; p=0.285
Van der Hoeven et al 2019[35]	FFR	Substudy of the REDUCE-MVI RCT	73 STEMI 73 NCLs	Yes	Data not applicable	FFR after pPCI vs FFR after 1 month: 0.88±0.07 vs 0.86±0.09; p=0.001
Mejía-Rentería et al 2019[81]	FFR	Multicentric observational	49 ACS 59 NCLs	Data not applicable	Data not applicable	FFR in ACS vs FFR in stable angina: 0.79±0.11 vs 0.80±0.13; p=0.527
Musto et al 2017[33]	iFR	Prospective observational	50 STEMI 66 NCLs	Data not applicable	Yes	iFR after pPCI vs iFR after 5.9±1.5 days: 0.90±0.06 vs 0.89±0.07; p=0.640
Indolfi et al 2015[82]	iFR	Prospective observational	53 ACS 78 NCLs	Data not applicable	Data not applicable	iFR in ACS vs iFR in stable CAD: 0.94 (IQR 0.07) vs 0.96 (IQR 0.12); p=NS
Thim et al 2017[83]	iFR	Prospective observational	120 STEMI 157 NCLs	Data not applicable	Yes	iFR after pPCI vs iFR after 16 days (IQR 5-32): 0.89 (IQR 0.82-0.94) vs 0.91 (IQR 0.86-0.96); p=NS
Choi et al 2018[34]	iFR	Prospective observational	34 STEMI 66 NSTEMI 128 NCLs	Data not applicable	Data not applicable	iFR in STEMI vs iFR in stable IHD for 60-70% stenosis: 0.87±0.08 vs 0.87±0.12; p=0.990

ACS: acute coronary syndrome; FFR: fractional flow reserve; iFR: instantaneous wave-free ratio; IHD: ischaemic heart disease; IQR: interquartile range; NCL: non-culprit lesion; NS: non-significant; NSTEMI: non-ST-segment elevation myocardial infarction; pPCI: primary percutaneous coronary intervention; RCT: randomised controlled trial; REDUCE-MVI: Reducing Micro Vascular Dysfunction in Acute Myocardial Infarction by Ticagrelor; STEMI: ST-segment elevation myocardial infarction

hyperaemia, and enables online and offline estimation of FFR from angiography. QFR, based on coronary angiography reconstruction and flow velocity calculated by frame count, has shown substantial clinical evidence regarding its diagnostic accuracy and prognostic value. A patient-data meta-analysis of 819 patients and 969 vessels (inclusive of FAVOR Pilot, WIFI II, FAVOR II China, and FAVOR II Europe-Japan trials) demonstrated an overall agreement of 87% between QFR and FFR, with a diagnostic sensitivity and specificity of 84% and 88%, respectively[69]. The FAVOR III China Study established QFR-guided coronary artery revascularisation to be comparable to FFR-guided PCI[70]. The effectiveness of QFR-guided PCI is further supported by a subanalysis from the FIRE trial, which also validates the threshold QFR ≤0.80 in identifying vessels at high risk for adverse events[71]. Similarly, the AQVA trial found a significant improvement in post-PCI physiological results for QFR-guided virtual revascularisation as compared to conventional angiographic guidance[72].

The Murray law-based μQFR index enables FFR derivation using a single angiographic projection for the vessel model. Small-scale research showed that its assessment is concordant with three-dimensional QFR[73] and FFR[74]. Other angio-based parameters, such as FFR_{angio}[75] and vFFR[76], use aortic pressures to determine boundary conditions and have shown promising diagnostic performance. However, the accuracy of angio-based tools is highly dependent on projection quality, angles, and the operator's technical skills, which may hinder reproducibility[77].

Computed tomography (CT)-derived fractional flow reserve (FFR-CT) is a physiological simulation technique that models coronary vessel flow from coronary CT angiography. FFR-CT provides valuable information on the anatomy and coronary physiology of MVD patients, aiding revascularisation decision-making. The ADVANCE Registry showed that FFR-CT modified the treatment strategy in two-thirds of patients with clinically suspected CAD and atherosclerosis, with less invasive coronary angiography at 1 year for those with FFR-CT >0.80 compared to FFR-CT <0.80[78]. Complex coronary artery lesions can be more accurately assessed by FFR-CT to decide between PCI and coronary artery bypass grafting, beyond relying solely on the SYNTAX score[79].

Future perspectives

With promising evidence, there is a strong potential for FFR to assist decision-making in the management of patients with ACS

and MVD. However, its reliability may be limited in acute phase MIs, due to microvascular disturbance, as well as in identifying vulnerable plaques. This dilemma emphasises the need to supplement FFR with intracoronary imaging modalities like OCT, for which several ongoing trials will provide valuable insights. The COMPLETE-2 trial (ClinicalTrials.gov: NCT05701358) aims to enrol 5,100 patients with STEMI or NSTEMI and MVD to compare physiology-guided and angiography-guided approaches to achieve complete revascularisation, providing more definitive conclusions regarding the usefulness of FFR/RFR/iFR in ACS patients with MVD. Findings from the COMPLETE-2 OCT substudy will address the feasibility of combining FFR with intracoronary imaging and its impact on clinical outcomes.

In addition, functional angiography-based indices may overcome some limitations of FFR, particularly in deferring revascularisation in ACS patients with MVD. Ongoing trials **(Table 3)** are exploring these indices further. FFR-CT is similarly expected to play an important role in NSTE-ACS patients. Additionally, findings from ongoing trials investigating the optimal timing of complete revascularisation in ACS patients with MVD are highly anticipated **(Table 4)**.

Table 3. Ongoing studies investigating novel angiography-based physiology assessment tools.

Study name	Number of patients	Strategy	Comparator	Primary endpoint	Follow-up
FAVOR III Europe Japan (NCT03729739)	2,001	QFR-based diagnostic strategy	FFR-based diagnostic strategy	Composite of all-cause mortality, any MI, and any unplanned revascularisation	12 months
LIPSIASTRATEGY (NCT03497637)	1,926	vFFR	FFR-guided therapy	Composite of cardiac death, non-fatal MI, or unplanned revascularisation	12 months
FAST III (NCT04931771)	2,228	Three-dimensional angio-based vFFR-guided revascularisation	FFR-guided revascularisation	Composite of all-cause death, any MI, or any revascularisation	12 months
FLASH FFR II (NCT04575207)	2,132	caFFR	FFR-guided revascularisation	Composite of all-cause death, MI, and unplanned revascularisation	12 months
ALL-RISE (NCT05893498)	1,924	FFRangio-guided revascularisation	Pressure wire-based guided revascularisation (FFR or NHPR)	Composite of all-cause death, MI, or unplanned clinically driven revascularisation	12 months

ALL-RISE: Advancing Cath Lab Results With FFRangio Coronary Physiology Assessment; caFFR: coronary angiography-derived fractional flow reserve; FAST III: Fractional Flow Reserve or 3D-Quantitative-Coronary-Angiography Based Vessel-FFR Guided Revascularization; FAVOR III Europe Japan: Comparison of Quantitative Flow Ratio (QFR) and Conventional Pressure-wire Based Functional Evaluation for Guiding Coronary Intervention. A Randomized Clinical Non-inferiority Trial; FFR: fractional flow reserve; FFRangio: angiography-derived fractional flow reserve; FLASH FFR II: A Prospective, Multicenter, Blinded, Randomized, Noninferiority Clinical Trial of Coronary Angiography Fractional Flow Reserve (caFFR) Versus Fractional Flow Reserve (FFR) to Guide Percutaneous Coronary Intervention; LIPSIASTRATEGY: Comparison of Non-Invasive Vessel Fractional Flow Reserve Calculated From Angiographic Images Versus Fractional Flow Reserve in Patients With Intermediate Coronary Artery Stenoses; MI: myocardial infarction; NHPR: non-hyperaemic pressure ratio; QFR: quantitative flow ratio; vFFR: vessel fractional flow reserve

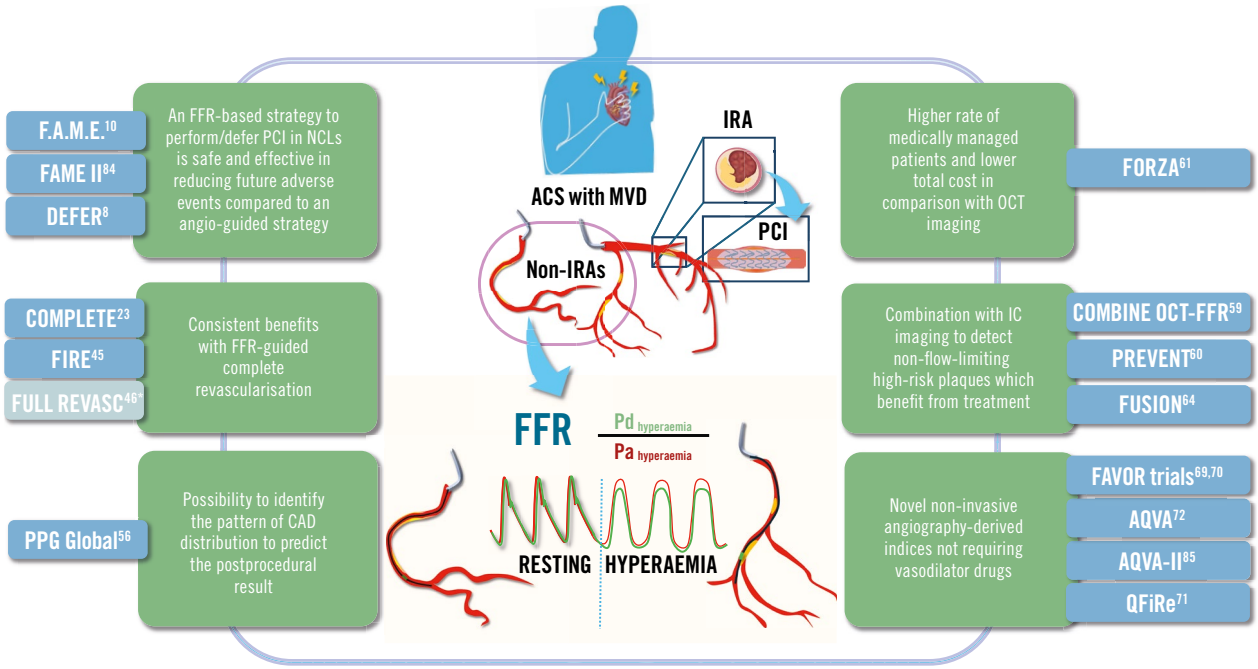
Table 4. Ongoing studies investigating the optimal timing for complete revascularisation in patients presenting with ACS and MVD.

Study name	Number of patients	Population	Strategy	Comparator	Primary endpoint	Follow-up
STAGED (NCT04918030)	1,700	STEMI and MVD	Out-of-hospital staged CR for NCLs (30±15 days)	In-hospital staged CR during the index procedure (7±3 days)	All-cause mortality	12 months
OPTION-STEMI (NCT04626882)	994	STEMI and MVD	Immediate FFR-guided CR during primary angioplasty	Staged in-hospital FFR-guided CR for NCLs	Cumulative incidence rate of all-cause death, non-fatal MI, or all unplanned revascularisation	12 months
OPTION-NSTEMI (NCT04968808)	676	NSTEMI and MVD	Immediate FFR-guided CR during index PCI	Staged in-hospital FFR-guided CR for NCLs	Cumulative incidence rate of all-cause death, non-fatal MI, or all unplanned revascularisation	12 months
TERMINAL (NCT05231226)	426	STEMI and MVD	Immediate CR	Staged CR within 45 days of index pPCI	Composite of all-cause death, ischaemia-driven revascularisation, non-fatal MI and heart failure	12 months

ACS: acute coronary syndrome; CR: complete revascularisation; FFR: fractional flow reserve; MI: myocardial infarction; MVD: multivessel disease; NCL: non-culprit lesion; NSTEMI: non-ST-segment elevation myocardial infarction; OPTION-NSTEMI: OPtimal TIming of Fractional Flow Reserve-Guided Complete RevascularizatiON in Non-ST-Segment Elevation Myocardial Infarction; OPTION-STEMI: OPtimal TIming of Fractional Flow Reserve-Guided Complete RevascularizatiON for Non-Infarct Related Artery in ST-Segment Elevation Myocardial Infarction With Multivessel Disease; pPCI: primary percutaneous coronary intervention; RCT: randomised controlled trial; STAGED: STaged Interventional Strategies for Acute ST-seGment Elevation Myocardial Infarction Patient With Multi-vessel Disease; STEMI: ST-elevation myocardial infarction; TERMINAL: Timing of Complete Revascularization in Patients With ST-segment Elevation Myocardial Infarction And Multivessel Disease-A Multi-center Randomized Controlled Trial

AsiaIntervention

CENTRAL **ILLUSTRATION** **FFR-guided revascularisation in ACS patients with multivessel disease: overview of the evidence supporting its safety and effectiveness in the assessment of non-culprit lesions.**



**The FULL-REVASC study findings are discordant to the results from other trials that compare physiology-guided complete revascularisation to culprit-only PCI in ACS patients with MVD. ACS: acute coronary syndrome; CAD: coronary artery disease; FFR: fractional flow reserve; IC: intracoronary; IRA: infarct-related artery; MVD: multivessel disease; NCL: non-culprit lesion; OCT: optical coherence tomography; Pa: aortic pressure; PCI: percutaneous coronary intervention; Pd: distal pressure*

Conclusions

Invasive physiological indices of stenosis severity can aid practitioners to optimise management approaches for coronary lesions. While strong evidence supports FFR use during PCI of ACS patients with MVD, further research should address the NSTE-ACS population and the optimal timing for invasive functional-guided PCI of NCLs. Moving forwards, there is significant potential for integrating FFR use into routine care for MVD in patients presenting with ACS, alongside intracoronary imaging and novel physiological indices **(Central illustration)**. Nonetheless, the heterogeneity of this patient cohort means that any strategy should be holistic and individualised to the patient's needs and preferences.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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AsiaIntervention 2024;10:169-176

A hospital lipid-lowering protocol improves 2-year clinical outcomes in patients with acute coronary syndrome

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This paper also includes supplementary data published online at: https://www.asiaintervention.org/doi/10.4244/AIJ-D-23-00056

KEYWORDS

- ACS/NSTE-ACS
- adjunctive pharmacotherapy
- clinical research
- drug-eluting stent

Abstract

Background: Although mortality after acute coronary syndrome (ACS) has improved in the acute phase, cardiovascular events occur at a certain frequency in the chronic phase. A hospital lipid-lowering protocol (HLP) could be effective in providing optimal lipid-lowering therapy to improve long-term clinical outcomes after ACS.

Aims: This study investigated the impact of HLP on clinical outcomes in patients with ACS.

Methods: We retrospectively analysed 1,114 ACS patients who had undergone successful percutaneous coronary intervention between November 2011 and June 2021. In December 2018, we introduced a HLP that included the prescription of the maximum tolerated dose of statin, ezetimibe, and eicosapentaenoic acid after ACS treatment. We compared 2-year clinical outcomes before (control group: 791 patients) and after the HLP's introduction (HLP group: 323 patients). The primary outcome was the non-target vessel revascularisation (non-TVR) rate. A multivariate Cox proportional hazard model and inverse probability weighting (IPW) based on the propensity score were used to evaluate the effect of HLP on the outcomes.

Results: The cumulative 2-year non-TVR incidence was significantly lower in the HLP group than in the control group (8.5% vs 13.8%; p=0.019). Multivariable analysis revealed non-TVR risk was significantly lower in the HLP group than in the control group (adjusted hazard ratio [aHR]: 0.637 [95% confidence interval {CI}: 0.416-0.975]; p=0.038). The IPW analysis confirmed a significant association between the HLP and a lower non-TVR risk (aHR: 0.544 [95% CI: 0.350-0.847]; p=0.007).

Conclusions: Implementing HLP for ACS patients improved the 2-year clinical outcome.

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SUBMITTED ON 15/10/2023 - REVISION RECEIVED ON 1st 19/03/2024 / 2nd 04/05/2024 / 3rd 31/05/2024 - ACCEPTED ON 18/07/2024

DOI: 10.4244/AIJ-D-23-00056

Abbreviations

ACS	acute coronary syndrome
HLP	hospital lipid-lowering protocol
IPW	inverse probability weighting
LDL-C	low-density lipoprotein cholesterol
MACE	major adverse cardiac events
MI	myocardial infarction
PCI	percutaneous coronary intervention
PCSK9	proprotein convertase subtilisin/kexin type 9
TLR	target lesion revascularisation
TVR	target vessel revascularisation

Introduction

Acute coronary syndrome (ACS) is a life-threatening disorder with high morbidity and mortality. Although percutaneous coronary intervention (PCI) technology has improved clinical outcomes in the acute phase, recurrence of coronary events in the chronic phase still occurs at a certain frequency, even after successful initial treatment for ACS[1-3]. These events occur at non-culprit lesions with lipid-rich plaques largely because of poor control of coronary risk factors[4,5]. Therefore, the strict control of coronary risk factors might improve long-term prognosis after ACS.

Low-density lipoprotein cholesterol (LDL-C) is a well-established causal factor for atherosclerotic cardiovascular disease. In a clinical setting, the European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) recommend an LDL-C target of <1.8 mmol/L (70 mg/dL), or a ≥50% reduction from baseline when this target cannot be reached[6]. In Japan, strong statins are recommended at the maximum tolerated dose as a class I recommendation in ACS. In high-risk patients whose LDL-C levels do not reach values below 70 mg/dL, even after administration of the maximum tolerated dose of statins, ezetimibe and a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor are considered as class IIa and class IIb recommendations, respectively. In addition, concomitant use of eicosapentaenoic acid with statins may be considered (class IIb recommendation)[7].

Despite these recommendations, mortality in the chronic phase after primary PCI for ST-elevation or non-ST-elevation myocardial infarction (MI) was reported to have reached a plateau after 2010[8]. One of the reasons might be the insufficient achievement rate of the target LDL-C level in actual clinical settings despite the guideline recommendation[9,10].

Therefore, to implement the optimal lipid-lowering therapy for patients with ACS at our hospital, we started using a hospital lipid-lowering protocol (HLP) of three lipid-lowering drugs. How HLP affects clinical practice and secondary prevention after ACS has not been determined. Thus, the objective of the present study was to elucidate the clinical impact of this HLP after the occurrence of ACS.

Methods

STUDY POPULATION

This was a single-centre retrospective observational study. We included 1,803 consecutive patients who underwent successful PCI for ACS between November 2011 and June 2021. Patients not treated with second- or third-generation drug-eluting stents (513 patients) were excluded to eliminate differences in clinical outcomes due to device performance. Patients who developed any event within 90 days (176 patients) which could largely be attributed to the treatment procedure or severity of ACS were also excluded to evaluate the impact of HLP on long-term prognosis. Among the remaining 1,114 enrolled patients, 323 and 791 were included in the HLP and control groups, respectively **(Supplementary Figure 1)**.

This study was performed in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Kansai Rosai Hospital (approval no.: 21D012g). Due to the retrospective nature of the study (observational research), written informed consent from patients was not required, in accordance with the Ethical Guidelines for Medical and Health Research Involving Human Subjects in Japan. Instead, relevant information regarding the study was made available to the public, and opportunities for individuals to refuse the inclusion of their data were ensured.

INTERVENTION PROCEDURE

Patients were eligible for inclusion if they had ACS with significant stenosis or occlusion on the initial coronary angiography and underwent PCI. PCI and post-PCI management, including antiplatelet therapy, were standardised. Intravenous heparin (5,000 IU), oral aspirin (200 mg), prasugrel (20 mg), and clopidogrel (300 mg) were administered before the PCI procedure. After PCI, all patients received prasugrel (3.75 mg) or clopidogrel (75 mg) once daily in addition to aspirin (100 mg) for the optimal duration in accordance with the relevant guidelines[11,12].

HLP FOR INTENSIVE LIPID-LOWERING THERAPY

The HLP included the prescription of the maximum tolerated dose of statins, ezetimibe (10 mg), and eicosapentaenoic acid (1,800 mg) daily after successful PCI for patients with ACS during hospitalisation. The order, timing, and initial dose of the three types of lipid-lowering agents were at the chief physician's discretion. Protocol compliance was defined as the prescription of those three drugs at discharge. If the patient's LDL-C level was >1.8 mmol/L (70 mg/dL) one month after HLP initiation, a PCSK9 inhibitor was recommended. Since HLP was only recommended, the final decision for its prescription was decided by the chief physician based on the patient's status.

OUTCOME MEASURES

We compared the 2-year clinical outcomes before (control group) and after (HLP group) the introduction of HLP for intensive lipid-lowering therapy. The primary outcome measure was the 2-year cumulative incidence of non-target vessel revascularisation (non-TVR). The secondary outcome measures were major adverse cardiac events (MACE), defined as a composite of cardiac death, MI, any repeat revascularisation, and stent thrombosis, and other clinical outcomes, including all-cause death, cardiac death,

MI, target lesion revascularisation (TLR), TVR, and definite stent thrombosis (defined in **Supplementary Appendix 1**). The achievement rate of LDL-C <1.8 mmol/L (70 mg/dL) and the change in LDL-C at 1 year were also evaluated.

STATISTICAL ANALYSES

All results are expressed as the mean±standard deviation (SD) unless otherwise stated. Continuous variables with and without homogeneity of variance were analysed using the Student's t-test and Welch's t-test, respectively. Categorical variables were analysed using Fisher's exact test for 2×2 comparisons. For more than 2×2 comparisons, nominal and ordinal variables were analysed using the chi-square test and Mann-Whitney U test, respectively. Clinical outcomes were evaluated using the Kaplan-Meier method and compared before and after HLP introduction using the log-rank test. To minimise intergroup differences in baseline characteristics, a multivariate Cox proportional hazard regression model and inverse probability weighting (IPW) based on the propensity score for the protocol were used to evaluate the effects of the protocol on the outcomes while adjusting for covariates including age, sex, left ventricular ejection fraction, hypertension, dyslipidaemia, diabetes mellitus, current smoking, chronic kidney disease, haemodialysis, chronic heart failure, stroke, atrial fibrillation, peripheral artery disease, type of ACS, ostial lesion, bifurcation, moderate-severe calcification, ACC/AHA classification, in-stent restenosis, average stent size, total stent length, lesion location, and number of stents. To confirm the robustness of these results, we performed an analysis with IPW based on the propensity score for the protocol. A logistic regression model was applied to predict the probability of the protocol using the covariates as stated for the Cox proportional hazard regression model. The results of the model were presented as adjusted hazard ratios and 95% confidence intervals (CI). All tests were two-sided with a 5% significance level. All calculations were performed using the SPSS Statistics package, version 28.0J (IBM) and R software, version 4.0.3 (R Foundation for Statistical Computing).

Table 1. Patient, lesion, and procedural characteristics.

Patient characteristics	HLP group (n=323)	Control group (n=791)	*p*-value
Male	237 (73)	595 (75)	0.57
Age, yrs	73 (62-80)	71 (62-78)	0.15
LVEF, %	58 (49-65)	61 (50-67)	0.058
Hypertension	208 (64)	614 (78)	<0.001
Dyslipidaemia	212 (66)	474 (60)	0.066
Diabetes mellitus	125 (39)	286 (36)	0.40
Current smoker	79 (24)	162 (20)	0.14
CKD	59 (18)	180 (23)	0.10
Haemodialysis	30 (9)	108 (14)	0.047
CHF	22 (7)	59 (7)	0.72
Stroke	10 (3)	46 (6)	0.061
Atrial fibrillation	27 (8)	51 (6)	0.25
Peripheral artery disease	20 (6)	78 (10)	0.051
Type of ACS on admission			0.72
STEMI	136 (42)	308 (39)	
NSTEMI	49 (15)	83 (10)	
UAP	137 (43)	400 (51)	
Lesion characteristics	**HLP group (n=378)**	**Control group (n=927)**	***p*-value**
Lesion location			0.77
Left anterior descending artery	160 (42)	365 (39)	
Left circumflex artery	73 (19)	204 (22)	
Right coronary artery	131 (35)	333 (36)	
Left main trunk	11 (3)	19 (2)	
Bypass graft	2 (1)	6 (1)	
In-stent restenosis	20 (5)	71 (8)	0.13
Ostial lesion	46 (12)	138 (15)	0.21
Bifurcation	176 (47)	360 (39)	0.009
Moderate-severe calcification	77 (20)	147 (16)	0.047
ACC/AHA classification			0.22
Type A	2 (1)	11 (1)	
Type B1	68 (18)	174 (19)	
Type B2	48 (13)	151 (16)	
Type C	259 (68)	591 (64)	

Results

BASELINE CHARACTERISTICS

The patient, lesion, and procedural characteristics are summarised in **Table 1**. In terms of coronary risk factors, hypertension (64%

Table 1. Patient, lesion, and procedural characteristics (cont'd).

Procedural characteristics	HLP group (n=378)	Control group (n=927)	*p*-value
Aspiration	146 (42)	723 (49)	0.034
Distal protection	18 (5)	191 (13)	<0.001
Predilatation	261 (69)	1671 (72)	0.25
Predilatation balloon size, mm	2.5 (2.0-3.0)	2.5 (2.25-3.0)	0.61
No. of stents	1 (1-1)	1 (1-1)	0.084
Average stent size, mm	3.0 (2.5-3.5)	3.0 (2.6-3.5)	0.62
Total stent length, mm	28 (18-38)	24 (18-38)	0.001
Post-dilatation	360 (95)	770 (83)	<0.001
Post-dilatation balloon size, mm	3.5 (3.0-4.0)	3.25 (3.0-3.5)	<0.001
Type of stent			<0.001
XIENCE[1]	145 (38)	333 (36)	
Nobori[2]	0 (0)	37 (4)	
PROMUS[3]	0 (0)	69 (7)	
Resolute[4]	10 (3)	81 (9)	
SYNERGY[3]	14 (4)	171 (18)	
Ultimaster[2]	6 (2)	129 (14)	
Orsiro[5]	95 (25)	56 (6)	
BioFreedom[6]	39 (10)	51 (6)	
COMBO Plus[7]	21 (6)	0 (0)	
Coroflex ISAR NEO[8]	47 (12)	0 (0)	

Data are presented as medians (interquartile ranges) or numbers (%). [1]By Abbott; [2]by Terumo; [3]by Boston Scientific; [4]by Medtronic; [5]by Biotronik; [6]by Biosensors; [7]by OrbusNeich; [8]by B. Braun.
ACS: acute coronary syndrome; CHF: chronic heart failure; CKD: chronic kidney disease; DCB: drug-coated balloon; HLP: hospital lipid-lowering protocol; LVEF: left ventricular ejection fraction; NSTEMI: non-ST-elevation myocardial infarction; STEMI: ST-elevation myocardial infarction; UAP: unstable angina pectoris

vs 78%; p<0.001) and haemodialysis (9% vs 14%; p=0.047) were more frequent in the control group. Lesion complexities, including bifurcation (47% vs 39%; p=0.009) and moderate-severe calcification (20% vs 16%; p=0.047), were more severe in the HLP group than in the control group.

CLINICAL OUTCOMES

The **Central illustration** and **Figure 1** show the cumulative incidence of each outcome and its Kaplan-Meier curve. After adjusting for covariates using a multivariate Cox proportional hazard regression model, the cumulative incidences of non-TVR (adjusted hazard ratio 0.637, 95% CI: 0.416-0.975; p=0.038), as well as those of TLR and TVR, were still significantly lower in the HLP group **(Table 2)**. The IPW analysis consistently showed a significantly lower risk of non-TVR in the HLP group (adjusted hazard ratio 0.544, 95% CI: 0.350-0.847; p=0.007).

To demonstrate the efficacy of protocol compliance, we further analysed whether HLP compliance had an impact on clinical outcomes. Compared to the protocol non-compliance group, non-TVR (5.4% vs 13.1%; p=0.033) was significantly lower in the protocol compliance group **(Figure 2)**.

LIPID PROFILES

The patients' lipid profiles at the index PCI and 1 year afterwards are provided in **Supplementary Table 1**. The 1-year achievement rate of LDL-C <1.8 mmol/L (70 mg/dL) reached 61% in the HLP group, which was significantly higher than that in the control group (27%; p<0.001). Details of the prescription of lipid-lowering drugs, including the type and dose of statins, and side effects are provided in **Supplementary Table 2** and **Supplementary Table 3**.

Discussion

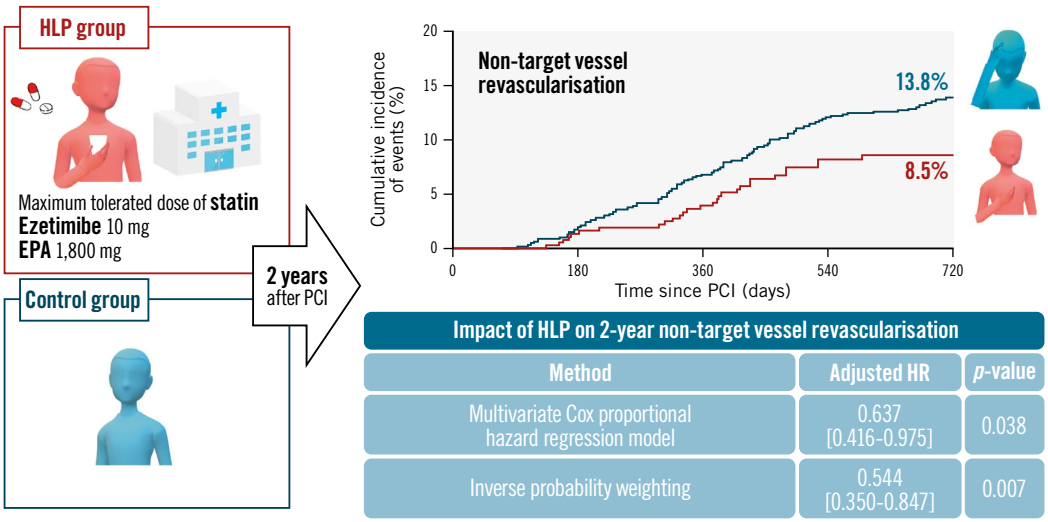
The results of our retrospective analyses of more than 1,100 patients who underwent successful PCI for ACS at our hospital demonstrated that the cumulative incidence rates of non-TVR, TLR, and TVR at 2 years were significantly lower after HLP introduction according to multivariate analyses. The IPW analysis confirmed the effectiveness of HLP in non-TVR events.

HLP AND CARDIOVASCULAR EVENTS

Non-TVR events occasionally occur, even after successful PCI for non-culprit stenotic lesions in patients with ACS. The results of the FLOWER-MI study suggest that the plaque in non-culprit lesions is highly unstable, and revascularisation by functional ischaemia evaluation alone is insufficient to prevent cardiovascular events after ACS treatment[13]. Therefore, stabilising unstable lipid plaques in lesions not responsible for ACS by strict lipid-lowering therapy is especially important in preventing non-TVR events. High-potency statins at the maximum tolerable dose have been recommended as the cornerstone lipid-lowering therapy and were reported to significantly reduce the plaque volumes of non-culprit lesions in patients with ACS[14]. In addition, the combination of statin plus ezetimibe or eicosapentaenoic acid showed greater coronary plaque regression compared to standard statin monotherapy[15-17]. Furthermore, alirocumab, a PCSK9 inhibitor, made the fibrous

AsiaIntervention

CENTRAL ILLUSTRATION A hospital lipid-lowering protocol (HLP) improves 2-year clinical outcomes in patients with acute coronary syndrome.



Impact of HLP on 2-year non-target vessel revascularisation		
Method	Adjusted HR	*p*-value
Multivariate Cox proportional hazard regression model	0.637 [0.416-0.975]	0.038
Inverse probability weighting	0.544 [0.350-0.847]	0.007

A hospital lipid-lowering protocol improved the cumulative 2-year incidence of non-target vessel revascularisation in patients with acute coronary syndrome. EPA: eicosapentaenoic acid; HR: hazard ratio; PCI: percutaneous coronary intervention

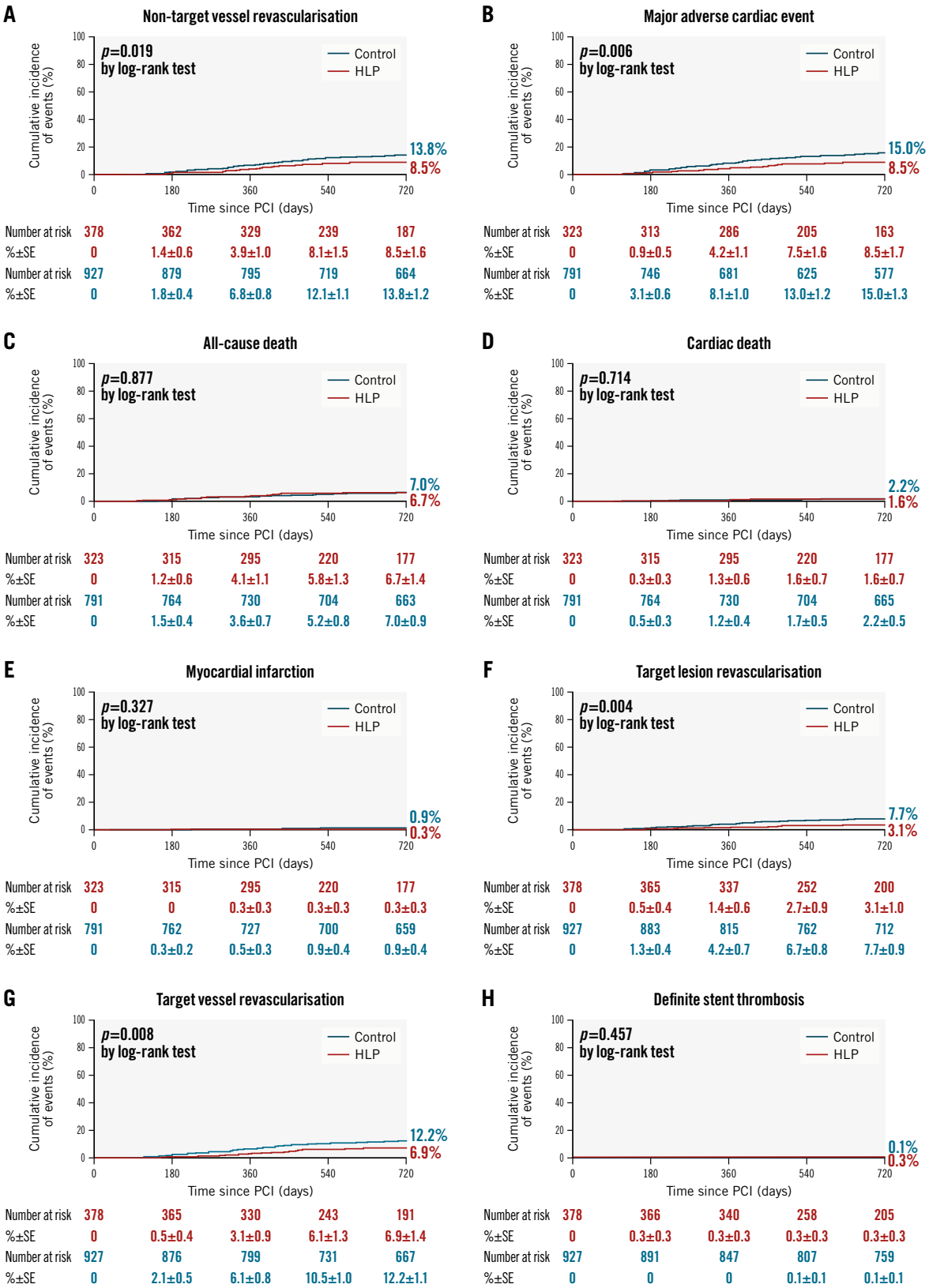


Figure 1. *Cumulative incidence rates of 2-year clinical outcomes. A) Non-target vessel revascularisation: hospital lipid-lowering protocol (HLP) 8.5%, control 13.8% (p=0.019). B) Major adverse cardiac events: HLP 8.5%, control 15.0% (p=0.006). C) All-cause death: HLP 6.7%, control 7.0% (p=0.877). D) Cardiac death: HLP 1.6%, control 2.2% (p=0.714). E) Myocardial infarction: HLP 0.3%, control 0.9% (p=0.327). F) Target lesion revascularisation: HLP 3.1%, control 7.7% (p=0.004). G) Target vessel revascularisation: HLP 6.9%, control 12.2% (p=0.008). H) Definite stent thrombosis: HLP 0.3%, control 0.1% (p=0.457). PCI: percutaneous coronary intervention; SE: standard error*

Table 2. Cumulative incidence of each clinical outcome after adjusting for covariates by a multivariate Cox proportional hazard regression model and IPW.

	Crude		Multivariate		IPW	
	HR	*p*-value	HR	*p*-value	HR	*p*-value
Non-TVR	0.614 [0.406-0.927]	**0.019**	0.637 [0.416-0.975]	**0.038**	0.544 [0.350-0.847]	**0.007**
MACE	0.544 [0.350-0.845]	**0.006**	0.721 [0.508-1.024]	0.068	0.795 [0.540-1.171]	0.246
All-cause death	0.959 [0.568-1.622]	0.742	0.960 [0.536-1.722]	0.892	1.00 [0.577-1.737]	0.998
Cardiac death	0.829 [0.303-2.266]	0.714	0.567 [0.177-1.813]	0.339	1.01 [0.348-2.944]	0.982
MI	0.366 [0.045-2.974]	0.327	0.086 [0.003-2.153]	0.135	0.870 [0.111-6.843]	0.894
TLR	0.389 [0.200-0.756]	**0.004**	0.441 [0.223-0.873]	**0.019**	0.720 [0.324-1.600]	0.419
TVR	0.542 [0.342-0.858]	**0.008**	0.623 [0.389-0.997]	**0.049**	0.829 [0.486-1.413]	0.490
ST	2.745 [0.171-44.071]	0.457	2.220 [0.000-1.328]	0.988	1.504 [0.106-21.290]	0.763

P-values in bold indicate statistical significance. HR: hazard ratio; IPW: inverse probability weighting; MACE: major adverse cardiac events; MI: myocardial infarction; non-TVR: non-target vessel revascularisation; ST: stent thrombosis; TLR: target lesion revascularisation; TVR: target vessel revascularisation

cap thicker, the lipid plaque angle smaller, and the atheroma volume smaller as evaluated by intravascular imaging compared to placebo, which were significant effects[18]. Regarding the timing of the introduction of these drugs, early aggressive lipid-lowering therapy after ACS significantly reduced the plaque volume of non-culprit lesions in patients with ACS[19]. Due to these plaque-stabilising effects of lipid-lowering drugs, early lipid-lowering therapy with statins decreases not only short-term mortality but also recurrent cardiovascular events[20,21]. Our present analyses revealed that after HLP introduction, prescription rates of high-potency statins, ezetimibe, and eicosapentaenoic acid at discharge increased to 90%, 63%, and 41%, respectively. HLP helped accomplish the early introduction of intensive lipid-lowering therapy including the maximum tolerated dose of higher-potency statins, concomitantly used with ezetimibe and eicosapentaenoic acid. These factors have contributed to increasing the achievement rate of LDL-C <1.8 mmol/L (70 mg/dL) to 61%, resulting in reduced non-TVR rates. A subanalysis confirmed the effectiveness of our HLP **(Figure 2)**.

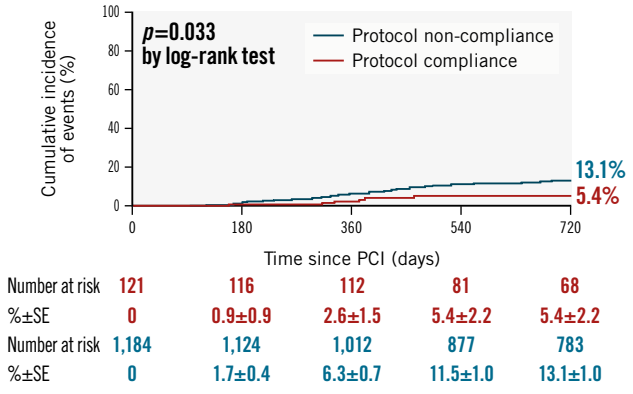


Figure 2. *Cumulative incidence of 2-year clinical outcomes stratified by hospital lipid-lowering protocol compliance. Non-target vessel revascularisation: protocol compliance group 5.4%, protocol non-compliance group 13.1% (p=0.033). PCI: percutaneous coronary intervention; SE: standard error*

IMPROVEMENT OF 2-YEAR CLINICAL OUTCOMES

Previously, we reported 1-year results after the introduction of HLP showing that HLP did not decrease clinical adverse events, while the achievement rate of the target LDL-C level significantly improved[22]. The Kaplan-Meier curves of previous studies, in which lipid-lowering drugs improved clinical outcomes, demonstrate that the difference in event rates between the HLP group and the control group increases after 1 year[20,23,24]. Therefore, long-term follow-up is necessary to demonstrate the efficacy of lipid-lowering therapy, and it is considered that at least 2 years are necessary for our HLP to improve clinical outcomes. To the best of our knowledge, this is the first study to systematically demonstrate the efficacy of HLP for intensive lipid-lowering therapy to achieve the target LDL-C level and improve real-world clinical outcomes.

Limitations

This study has several limitations. First, it was a single-centre retrospective observational study, and the two groups showed heterogeneity in both baseline demographic and procedural variables; however, we matched the baseline characteristics with multivariate Cox regression analysis, as well as IPW analysis based on propensity scores. Second, the proportion of HLP-compliant patients was low, at 32%, possibly because the introduction of lipid-lowering drugs depended on the physician, and higher age and unstable angina were considered independent predictors of poor HLP compliance as previously reported[22]. However, HLP-compliant patients showed better clinical outcomes **(Figure 2)**, and the clinical improvement is still recognised even though the HLP compliance rate is relatively low. Therefore, further improvement in clinical results can be expected by increasing the HLP compliance rate. Third, there might be a difference in the frequency of follow-up angiography and non-clinically driven revascularisation because no clinical benefits were observed for routine follow-up coronary angiography after PCI. However, patients who underwent follow-up coronary angiography for any reason accounted for 43% (343/791) before and 43% (138/323)

after HLP introduction, which showed no significant difference. Fourth, 2-year data about LDL-C values and prescribed lipid-lowering drugs are rare, and we could not demonstrate a direct relationship between LDL-C values and clinical outcomes. Furthermore, we could not evaluate the patients' medication compliance, and medication use may have been overestimated. Finally, TLR and TVR rates were not significantly different in the IPW analysis, in contrast to the multivariate analysis. The relatively low number of events might be the reason, and the longer follow-up and higher number of events might have made a difference in the IPW analysis.

Conclusions

Implementing HLP for patients with ACS who underwent successful PCI improved the 2-year clinical outcomes including non-TVR in multivariate analyses, and the IPW analysis confirmed the effectiveness of HLP for non-TVR.

Impact on daily practice

A hospital lipid-lowering protocol (HLP) that includes the prescription of the maximum tolerated dose of statin, ezetimibe, and eicosapentaenoic acid could increase the achievement rate of the guideline-directed low-density lipoprotein cholesterol level and reduce 2-year cardiovascular events for patients with acute coronary syndrome (ACS). It is strongly recommended to implement an in-hospital protocol for lipid-lowering therapy after ACS. Since the proportion of HLP compliance was still low, further improvement of clinical results can be expected by striving to increase the HLP compliance rate. In addition, longer-term follow-up is necessary to confirm the effectiveness of HLP.

Acknowledgements

We wish to thank Ms Saori Kashu for her expertise in data aggregation.

Conflict of interest statement

T. Ishihara received lecture fees from Nipro and Kaneka. O. Iida received remuneration from Boston Scientific Japan, W. L. Gore & Associates G.K., BD, and Terumo. T. Mano received a research grant from Abbott Vascular Japan. The other authors have no conflicts of interest to declare.

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Supplementary data

Supplementary Appendix 1. Definitions.

Supplementary Table 1. Lipid profiles.

Supplementary Table 2. Prescription of lipid-lowering drugs.

Supplementary Table 3. Side effects of lipid-lowering drugs.

Supplementary Figure 1. Study flowchart.

The supplementary data are published online at: https://www.asiaintervention.org/ doi/10.4244/AIJ-D-23-00056

AsiaIntervention 2024;10:177-185

OCT-based comparative evaluation of culprit lesion morphology in very young versus older adult patients with STEMI

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This paper also includes supplementary data published online at: https://www.asiaintervention.org/doi/10.4244/AIJ-D-24-00013

KEYWORDS

- optical coherence tomography
- plaque rupture
- STEMI
- thrombus-containing lesion

Abstract

Background: The clinical and pathophysiological characteristics of coronary artery disease in very young adults are poorly described.

Aims: Using optical coherence tomography (OCT), we compared culprit lesion morphology in very young adult patients (≤35 years) versus older adult patients (>60 years) with ST-segment elevation myocardial infarction (STEMI).

Methods: Culprit lesion morphology was classified as plaque rupture, plaque erosion, or calcified nodule. Thrombus age was subclassified into acute (intraluminal thrombus with surface irregularity) or subacute (mostly mural thrombus with a smooth surface).

Results: A total of 61 patients who underwent thrombolysis within 24 hours from symptom onset were included, with 38 (59.7%) subjects ≤35 years and 23 (40.3%) subjects >60 years of age. As an underlying mechanism of STEMI thrombosis, plaque erosion was more common in very young patients (52.6% vs 21.7%; p=0.02) while plaque rupture was more common in elderly patients (65.2% vs 36.8%; p=0.03). Acute or subacute thrombus was identified in 68.9% (42/61) of patients, with red thrombus being more frequent in very young patients. In the entire patient cohort, acute thrombus was more frequent in plaque rupture compared with plaque erosion (62.0% vs 28.0%; p=0.01), whereas subacute thrombus was more common in plaque erosion versus plaque rupture (52.0% vs 10.3%; p=0.0008).

Conclusions: OCT showed that plaque erosion and plaque rupture were the most common underlying STEMI mechanisms in very young patients and older patients, respectively, and that subjects with plaque erosion had greater evidence of subacute thrombus.

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SUBMITTED ON 11/03/2024 - REVISION RECEIVED ON 25/06/2024 - ACCEPTED ON 24/07/2024

DOI: 10.4244/AIJ-D-24-00013

Abbreviations

ACS	acute coronary syndrome
CAD	coronary artery disease
OCT	optical coherence tomography
PCI	percutaneous coronary intervention
STEMI	ST-segment elevation myocardial infarction
TCFA	thin-cap fibroatheroma
TIMI	Thrombolysis in Myocardial Infarction

Introduction

The prevalence of cardiovascular diseases among younger adults is increasing[1]. Adults who experience acute coronary syndrome (ACS) at a younger age are reported to have a different pathophysiology compared to older adult patients[1]. Optical coherence tomography (OCT), a high-resolution intracoronary imaging technique, facilitates a thorough assessment of plaque morphology in ACS patients[2]. The major mechanisms for ST-segment elevation myocardial infarction (STEMI) include plaque rupture, plaque erosion, and calcified nodules – all of which may be readily visualised by intravascular imaging[2,3]. Additionally, OCT can evaluate the healing process of plaque rupture or erosion along with thrombus detection, which may help in understanding the underlying disease mechanism[4,5].

There are conflicting data on the morphological characteristics of culprit plaques in different age groups. One European multicentre OCT registry has shown that young patients (age ≤50 years) with STEMI are more likely to have a higher prevalence of culprit plaque rupture, a thinner cap, and fewer fibrotic or fibrocalcific components as compared to the elderly[6]. On the contrary, a Chinese OCT registry[7] suggested that younger patients (age <50 years) with STEMI had more plaque erosions and fewer thin-cap fibroatheromas (TCFAs).

The present study aimed to investigate the morphological characteristics of culprit plaque and thrombus in very young adult (≤35 years) versus older adult STEMI patients (>60 years).

Methods

STUDY DESIGN AND POPULATION

This was a prospective, single-centre, investigator-initiated study using OCT to examine culprit lesion morphology in very young adult patients (≤35 years) compared with older adult patients (>60 years) with STEMI **(Central illustration)**. The diagnosis of STEMI was based on the Fourth Universal Definition of Myocardial Infarction (MI)[8]. Patients with STEMI who underwent thrombolysis within 48 hours from symptom onset at peripheral hospitals and were then transferred to a tertiary care centre for further evaluation and treatment were screened, consecutively. Patients with left ventricular ejection fraction ≥35% who agreed to comply with all specified study requirements were included. Exclusion criteria were acute heart failure or shock, renal failure, prior coronary bypass surgery, allergy to contrast media, life expectancy of <1 year, and pregnancy. Angiographic exclusion criteria were left main disease, chronic total occlusion, tortuous or calcified vessels through which OCT contrast medium was not expected to pass, or stent thrombosis. At the beginning of the study, only very

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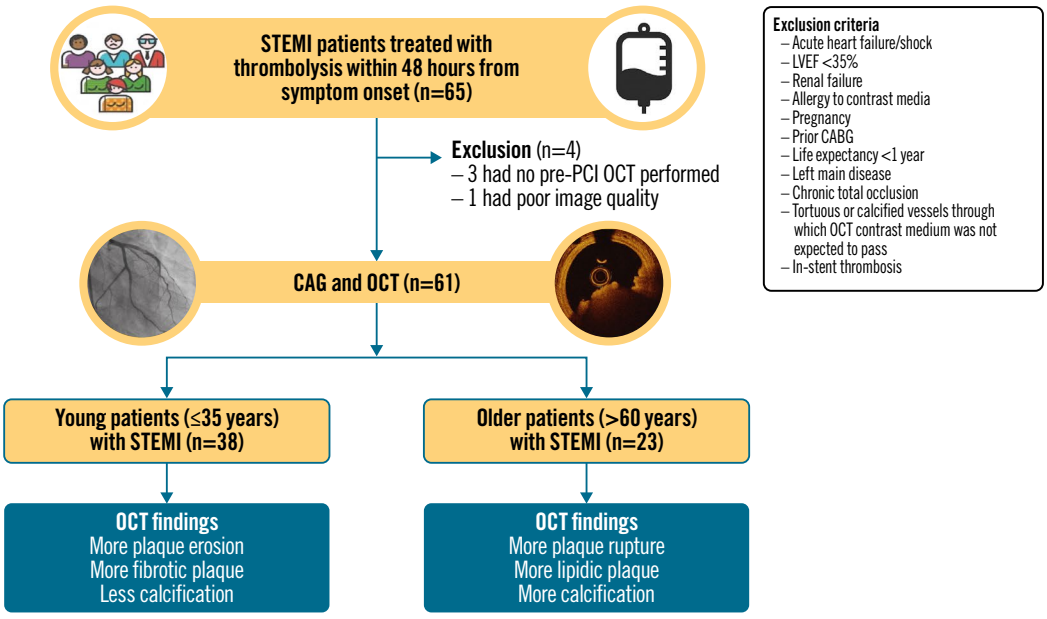
CENTRAL **ILLUSTRATION** Study flowchart.



CABG: coronary artery bypass grafting; CAG: coronary angiography; LVEF: left ventricular ejection fraction; OCT: optical coherence tomography; PCI: percutaneous coronary intervention; STEMI: ST-segment elevation myocardial infarction

young patients (≤35 years) were enrolled. Culprit lesions were identified through localising findings from electrocardiograms, echocardiograms, and coronary angiograms.

The present study was approved by the institutional ethics committee and was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice and local regulations. All enrolled patients provided written informed consent for the study.

CORONARY ANGIOGRAPHY ANALYSIS

Quantitative coronary angiographic analysis was performed using QAngio XA, version 7.2 (Medis Medical Imaging Systems) by independent cardiologists blinded to the clinical data[9].

OCT IMAGE ACQUISITION AND ANALYSIS

All enrolled patients underwent coronary angiography followed by OCT using standard techniques. After administration of intracoronary nitroglycerine (200 µg), OCT images were acquired using a frequency domain OCT system (ILUMIEN OPTIS) and a Dragonfly OPTIS OCT catheter (both Abbott). A 1.5 mm compliant balloon was inflated at nominal pressure to predilate the lesion if the OCT catheter was unable to pass beyond the lesion. Automated pullback was triggered with intracoronary contrast injection (3-4 ml/s, 12-14 ml total) with a motorised pullback speed of up to 25 mm/s and a frame rate of 100/s. All OCT images were analysed offline using proprietary software (OPTIS Offline Review Workstation software, version E.4.1 [Abbott]) by an OCT core laboratory blinded to the clinical data (Cardiovascular Research Foundation, New York, NY, USA).

OCT morphologies were classified according to established OCT reporting standards[10,11]. Briefly, plaque rupture was defined as disruption of a fibrous cap overlaying lipidic plaque **(Figure 1A)**. Plaque erosion was defined as the presence of an intact fibrous cap with attached thrombus, irregularity of the lumen of the culprit lesion in the absence of thrombus, or lesions with underlying plaque attenuated by thrombus without superficial lipid or calcium immediately proximal or distal to the site of thrombus **(Figure 1B)**. A calcified nodule was defined as an accumulation of small calcium fragments protruding into the lumen with strong attenuation **(Figure 1C)**. Thrombus was defined as an irregular intraluminal mass (>250 µm) which was either attached to the vessel wall or free-floating in the lumen and was subclassified into red (high backscatter with high attenuation) or white thrombus (low backscatter with low attenuation). Additionally, thrombus age was subclassified into acute (intraluminal thrombus with surface irregularity) or subacute (mostly comprised of mural thrombus with a smooth surface with some findings of acute thrombus) **(Figure 1D)**. If the surface tissue of the culprit lesion had a smooth layer demarcated with underlying plaque, it was considered as late thrombus and/or healed plaque **(Figure 1E)**[5,12]. Multiple intraluminal communicating channels separated by septa (honeycomb pattern) were considered to represent late thrombus **(Figure 1F)**. If the culprit lesion had evidence of ruptured cavity (i.e., intraplaque haemorrhage defined as a low intensity region without attenuation), overlaying late thrombus and/or healed plaque adjacent to lipidic plaque, it was categorised as plaque rupture[12-14]. If the culprit lesion had only late thrombus and/or healed plaque overlaying fibrous plaque without adjacent lipidic plaque, it was categorised as plaque erosion[5]. When none of the above findings were observed, it was considered indeterminate. Lipidic plaque was defined as a region with strong signal attenuation with poorly delineated borders that was covered by a fibrous cap. Fibrous cap thickness was measured three times at the thinnest part, and the average value was calculated. TCFA was defined as lipidic plaque >90° with a fibrous cap thickness <65 µm. Fibrous plaque was homogeneous plaque with high backscatter. Calcified plaque was a signal-poor or heterogeneous region with a sharply delineated border.

STATISTICAL ANALYSIS

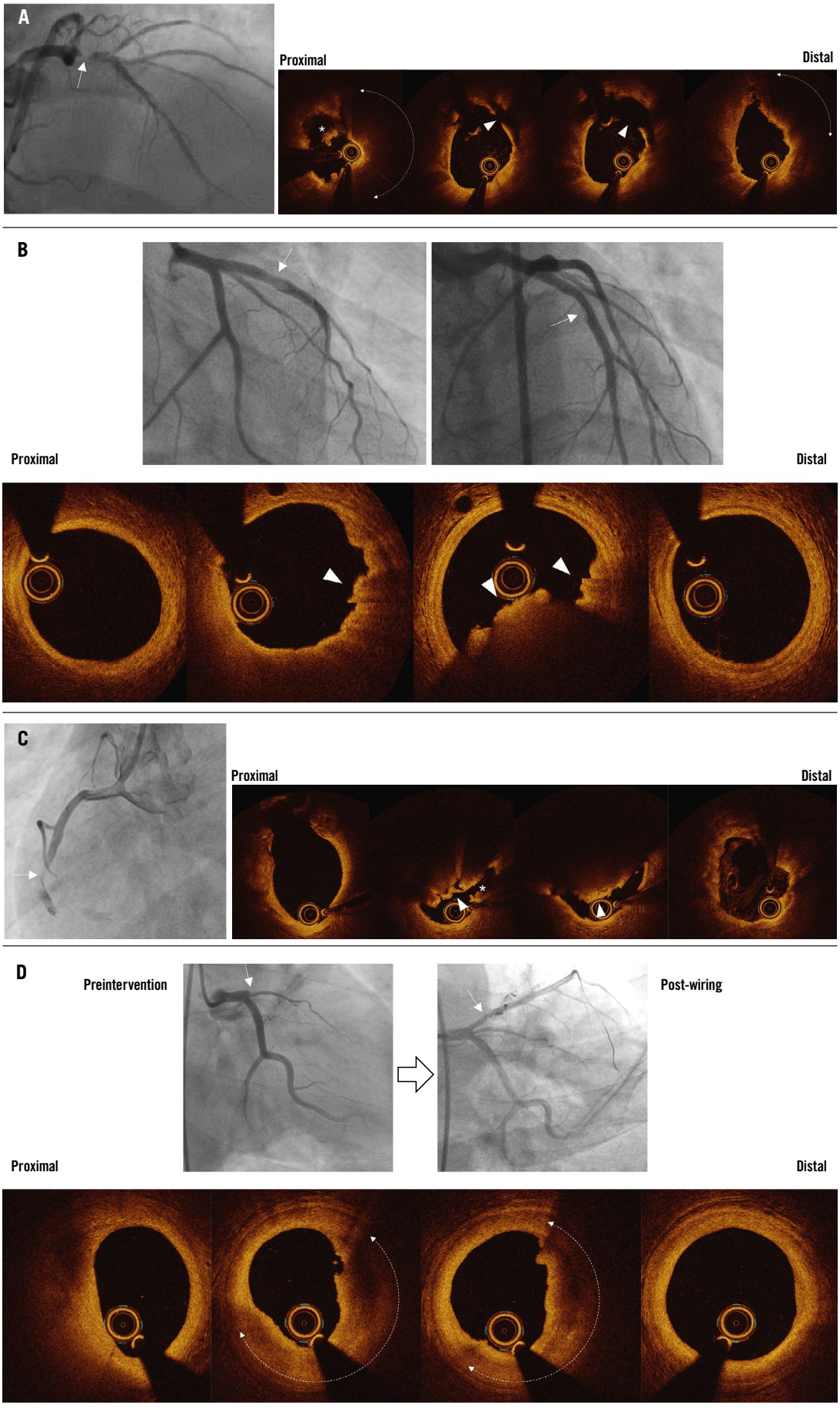
Normally distributed continuous data are expressed as mean±standard deviation and were compared using an unpaired Student's t-test. Non-normally distributed continuous data are shown as median (first quartile, third quartile) and were compared using the Mann-Whitney U test. Categorical data are represented as proportions and were compared using the chi-square or Fisher's exact test, as appropriate. A 2-sided p-value<0.05 was considered statistically significant. SPSS Statistics, version 24.0 (IBM) and Prism, version 8.0.0 (GraphPad Software) software were used for statistical analysis.

Results

Between January 2020 and January 2022, a total of 65 STEMI patients were enrolled. After exclusion of 4 patients with no pre-stent OCT or poor-quality OCT images (2 in each group), 61 patients were included in the final analysis. The time from symptom onset to thrombolysis was similar in young versus older patients (6.1±2.4 hours vs 6.6±2.1 hours; p=0.36) **(Table 1)**. The time from symptom onset to OCT was also comparable in young versus older patients (5.5±3.7 days vs 4.0±3.9 days; p=0.21).

BASELINE CHARACTERISTICS, ANGIOGRAPHIC FINDINGS, AND TREATMENT

Data are presented in **Table 1**. The mean age of patients in the ≤35 years age group was 29.9±4.2 years, while the mean age of the patients in the >60 years age group was 64.5±4.2 years. Most patients in the two groups were males (94.7% vs 86.9%; p=0.29). A history of smoking was more prevalent in very young patients compared with older patients (63.2% vs 34.8%; p=0.03), whereas hypertension was less common (5.3% vs 69.6%; p<0.0001) in very young patients. The left anterior descending artery was the most likely culprit vessel, followed by the right coronary artery. Angiographic stenosis was less severe and lesion length was shorter in very young patients compared with older patients.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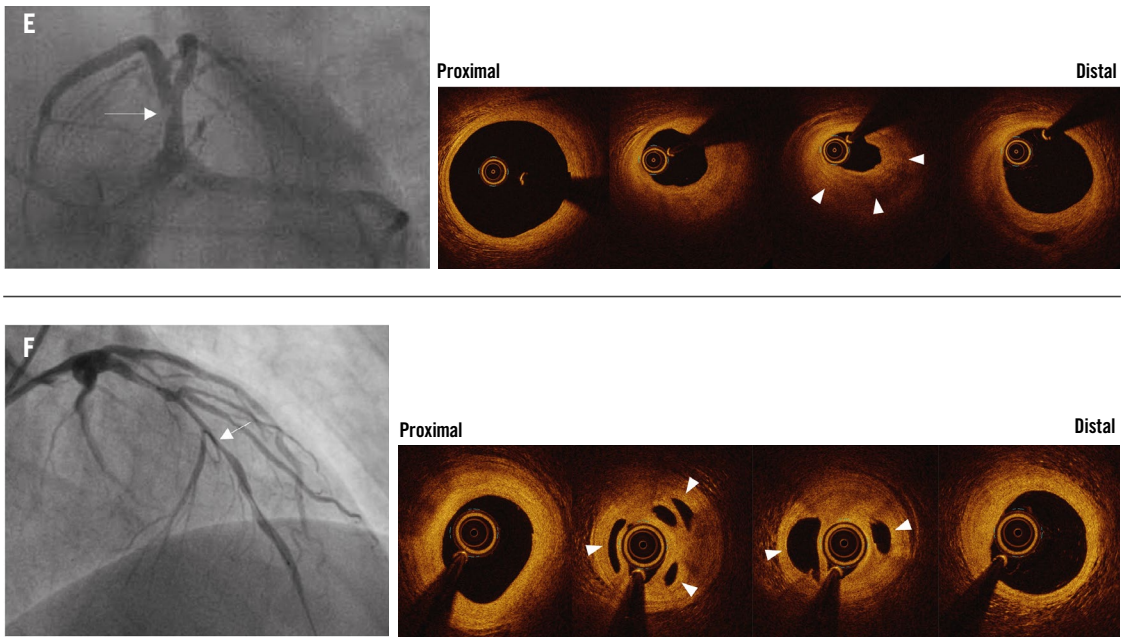

Figure 1. *Representative cases. For each case, the first image(s) is the coronary angiogram (with white arrows indicating the location of the optical coherence tomography [OCT] images), and the subsequent images are from OCT. A) Plaque rupture with acute thrombus. This coronary angiogram from a 68-year-old male with ST-segment elevation myocardial infarction (STEMI) shows severe luminal narrowing in the proximal left anterior descending artery (LAD). The OCT images show plaque rupture (arrowheads) with acute thrombus formation (asterisk) overlying lipidic plaque (dotted line with double arrowheads). B) Plaque erosion with acute thrombus. This coronary angiogram from a young 26-year-old male with STEMI shows haziness in the proximal LAD. The OCT images show plaque erosion with acute thrombus formation (arrowheads). C) Eruptive calcified nodule with acute thrombus. This coronary angiogram from a 68-year-old male with STEMI shows the presence of thrombus with luminal narrowing in the proximal and mid right coronary artery (RCA). The OCT images show an eruptive calcified nodule with overlaying acute thrombus (asterisk). D) Plaque erosion with subacute thrombus. This preinterventional coronary angiogram from a 35-year-old male with STEMI shows a total occlusion in the proximal LAD. After wiring, the lesion showed mild narrowing. The OCT images show plaque erosion with subacute thrombus formation (dotted lines with double arrowheads). E) Plaque erosion with late thrombus and/or healed plaque. This coronary angiogram from a 28-year-old male with STEMI shows a filling defect in the proximal LAD. The OCT images show plaque erosion with late thrombus and/or healed plaque formation (arrowheads). F) Plaque erosion with honeycomb pattern of late thrombus. This coronary angiogram from a 35-year-old male with STEMI shows diffuse narrowing in the LAD. The OCT images show plaque erosion with multiple intraluminal communicating channels separated by septa (arrowheads), which are considered to represent recanalised late thrombus.*

OCT FINDINGS

Plaque erosion as the underlying mechanism of STEMI was more common in very young versus older patients (52.6% vs 21.7%; p=0.02) **(Figure 2A)**. Plaque rupture was more common in older patients compared with very young patients (65.2% vs 36.8%; p=0.03). Calcified nodules were only present in 2 older patients. There were 5 patients whose culprit lesions were considered indeterminate; all of them had no thrombus or no late thrombus, and/or healed plaque within an entirely normal artery in 2 young patients, mild focal stenosis in 1 young patient, and diffuse stenosis in 1 older patient. When compared to very young patients, older patients showed a higher proportion of lipidic plaque (73.9% vs 42.1%; p=0.02) **(Table 2)**. Fibrous plaques were more common in very young patients (52.6% vs 17.4%; p=0.008).

Acute or subacute thrombus was identified in 68.9% (42/61) of patients **(Table 2)**. Red thrombus was more frequent in very young patients, but there were no statistically significant differences in the rates of acute or subacute thrombus. When we combined all patients and compared thrombus age between plaque rupture versus plaque erosion, acute thrombus was more frequent in plaque rupture compared with plaque erosion (62.0% vs 28.0%; p=0.01), whereas subacute thrombus was more common in plaque erosion versus plaque rupture (52.0% vs 10.3%; p=0.0008) **(Figure 2B)**.

TREATMENT

All patients underwent thrombolysis within 24 hours from symptom onset. All older patients underwent percutaneous coronary intervention (PCI), whereas 55.3% of younger patients underwent PCI, and the rest were treated medically.

FOLLOW-UP

Six-month outcomes were confirmed for all 61 patients. There were no revascularisations in either group. One patient in the older age group was hospitalised because of heart failure with reduced ejection fraction at 28 days after STEMI. One patient in the very young age group died because of an out-of-hospital sudden cardiac

Table 1. Baseline patient characteristics, angiographic findings, and treatment.

	≤35 years (n=38)	>60 years (n=23)	*p*-value
Baseline patient characteristics			
Age, years	29.9±4.2	64.5±4.2	<0.0001
Male	36 (94.7)	20 (86.9)	0.29
Current or former smoker	24 (63.2)	8 (34.8)	0.03
Diabetes mellitus	3 (7.9)	2 (8.7)	0.91
Hypertension	2 (5.3)	16 (69.6)	<0.0001
Family history of coronary artery disease	3 (7.9)	0 (0)	0.17
Prior percutaneous coronary intervention	0 (0)	1 (4.3)	0.20
Symptom onset to thrombolysis, hours	6.1±2.4	6.6±2.1	0.36
Symptom onset to OCT, days	5.5±3.7	4.0±3.9	0.21
Angiographic findings			
Culprit vessel			
Left anterior descending artery	29 (76.3)	17 (73.9)	0.83
Diagonal branch	2 (5.3)	0 (0)	0.27
Left circumflex artery	0 (0)	4 (17.4)	0.008
Right coronary artery	7 (18.4)	2 (8.7)	0.30
Reference vessel diameter, mm	2.44±0.86	2.13±0.62	0.15
Minimal lumen diameter, mm	1.52±0.65	1.07±0.28	0.007
Diameter stenosis, %	34.4±13.2	47.0±15.0	0.001
Lesion length, mm	26.2±11.5	32.0±11.5	0.06
Treatment			
Medical therapy	17 (44.7)	0 (0)	0.0002
PCI	21 (55.3)	23 (100)	<0.0001
Stent length, mm	32.8±13.3	32.8±9.5	1.0
Stent diameter, mm	3.3±0.5	3.0±0.4	0.01
Medications at discharge			
Aspirin	38 (100)	23 (100)	--
$P2Y_{12}$ inhibitors	36 (94.7)	23 (100)	0.26
Statins	38 (100)	21 (91.3)	0.06
ACEi/ARBs	35 (92.1)	18 (78.2)	0.12
Beta blockers	38 (100)	15 (65.3)	0.0001

Values are mean±standard deviation or n (%). ACEi: angiotensin-converting enzyme inhibitors; ARB: angiotensin receptor blockers; OCT: optical coherence tomography; PCI: percutaneous coronary intervention

arrest at 98 days after STEMI. Another patient in the older age group died due to an out-of-hospital sudden cardiac arrest at 124 days after STEMI.

Discussion

To the best of our knowledge, this is the first study to use OCT to show underlying culprit lesion pathophysiology in very young (≤35 years) adult STEMI patients. We report the following important findings. First, OCT imaging revealed that the mechanisms for STEMI in young and older adult patients were different. Plaque erosion was common in very young adult patients, while plaque rupture was seen in a greater proportion of older adult patients. Additionally, the typical findings of a vulnerable plaque were less likely to be observed in very young STEMI patients. Second, plaque rupture was associated with more acute thrombi, while plaque erosion had a higher frequency of subacute thrombi.

STEMI IN YOUNGER AND OLDER PATIENTS – INSIGHTS AND MECHANISMS

Yahagi et al[15] showed in 236 sudden death autopsy cases with acute thrombi, plaque erosion was more prevalent in younger than older bodies (36.2% in <50 years vs 22.4% in ≥50 years). Among younger bodies, females suffered plaque erosion four times more often compared with males. Similarly, a large STEMI-OCT registry showed that the associated clinical factors for plaque erosion were younger age (<50 years) and current smoking[16], which is consistent with our findings. Similar findings were reported by Fang and colleagues wherein younger STEMI patients (<50 years) were more likely to be current smokers with a greater frequency

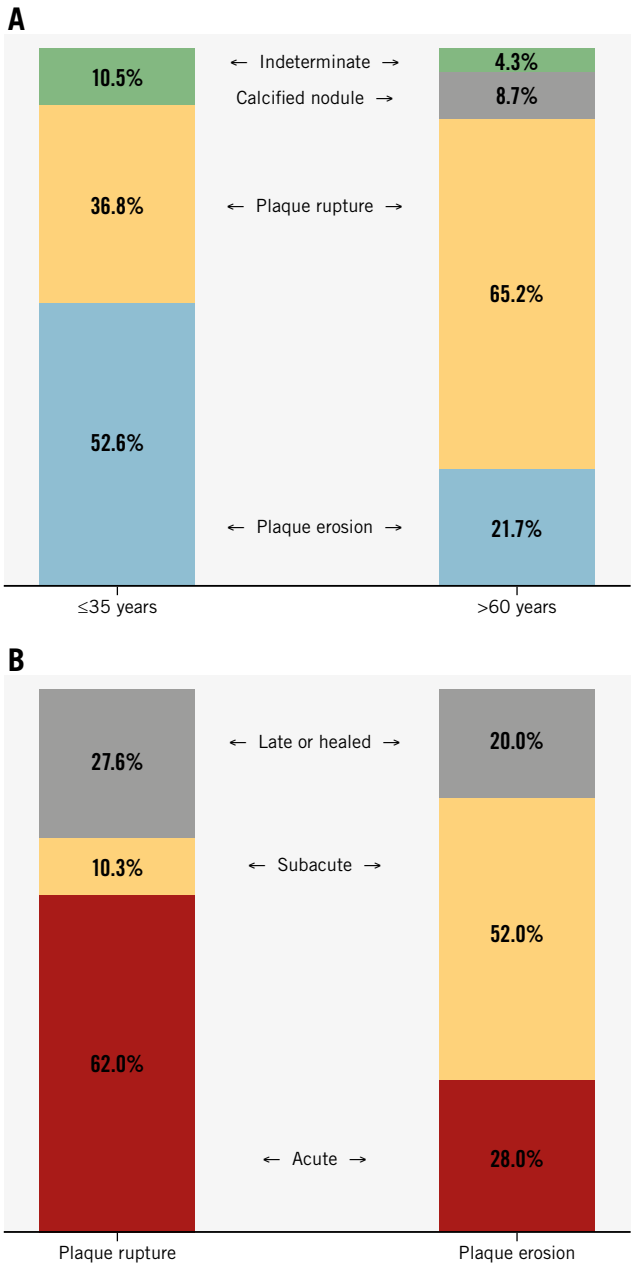

Figure 2. *OCT features of the two groups. A) Underlying plaque types between very young versus older patients. B) Thrombus age between plaque rupture versus plaque erosion. OCT: optical coherence tomography*

of dyslipidaemia **(Supplementary Table 1)**[7]. Smoking is a potent trigger for acute coronary thrombosis by altering endothelial function, platelet activation, and other homeostatic processes. It has been shown to be an important cause of plaque erosion and coronary thrombosis, especially in young men and premenopausal women[17]. In young patients with STEMI with minimal luminal narrowing, plaque erosion often leads to subclinical thrombosis, resulting in layered pattern plaques[5,13]. Four-year outcomes from the Effective Anti-Thrombotic Therapy Without Stenting: Intravscular Optical Coherence Tomography-Based Management in Plaque Erosion (EROSION) study showed that among 52 STEMI patients with plaque erosion and deferred stenting,

Table 2. Optical coherence tomography findings.

	≤35 years (n=38)	>60 years (n=23)	*p*-value
Minimum lumen area, mm²	1.9 [1.3-3.8]	0.9 [0.8-1.2]	0.0005
Lumen area stenosis, %	68.6 [57.0-85.0]	75.0 [64.0-80.1]	0.72
Proximal reference lumen area, mm²	3.6 [3.1-4.0]	3.1 [2.9-3.4]	0.07
Distal reference lumen area, mm²	2.9 [2.5-3.3]	2.5 [2.2-2.7]	0.001
Lipidic plaque	16 (42.1)	17 (73.9)	0.02
Thin-cap fibroatheroma	10 (26.3)	9 (39.1)	0.29
Fibrous plaque	20 (52.6)	4 (17.4)	0.008
Calcified plaque	0 (0)	2 (8.7)	0.14
Normal artery	2 (5.3)	0 (0)	0.52
Any thrombus*	28 (73.7)	14 (60.9)	0.29
Thrombus type			
Red thrombus	8 (21.1)	0 (0)	0.01
White thrombus	20 (52.6)	14 (60.9)	0.53
Thrombus age			
Acute	15 (39.5)	11 (47.8)	0.52
Subacute	13 (34.2)	3 (13.0)	0.08
Late thrombus and/or healed plaque	6 (15.8)	8 (34.8)	0.09

Values are median [1st quartile-3rd quartile] or n (%). *Not including late thrombus and/or healed plaque.

5 patients underwent target lesion revascularisation within 1 year, and an additional 6 patients were stented between 1 and 4 years after diagnosis[18,19]. In young STEMI patients with plaque erosion and without significant luminal stenosis (residual diameter stenosis <70% on coronary angiography), effective antithrombotic therapy without stent implantation may be a definitive treatment option.

THROMBUS AGE ON OCT

In the majority of STEMI cases, occlusive luminal thrombosis is the predominant mechanism of ACS with >75% of patients with fatal ACS having thrombotic occlusion secondary to atherosclerotic plaque rupture[13,20]. Systemic thrombolysis was used in our study as a part of the pharmacoinvasive procedure, as the majority of patients initially presented to a non-PCI centre. Earlier studies have highlighted the role of systemic thrombolysis in mortality reduction in STEMI[21]. Subjects with an occluded infarct-related artery having Thrombolysis in Myocardial Infarction (TIMI) grade 0 or 1 flow at 90 minutes post-thrombolysis were associated with an 8.9% 30-day mortality rate; subjects with TIMI grade 2 had a 7.4% mortality rate, and those with TIMI grade 3 flow (i.e., normal perfusion) had a 4.0% mortality rate. Previously, age of thrombus has been evaluated either on autopsy specimens[13] or on the histopathology of the aspirated thrombus from the coronaries[22]. Kramer et al[13], in their histopathological evaluation of coronary arteries in sudden cardiac death, reported that subjects with plaque

rupture had a significantly greater degree of acute thrombus, while subacute and chronic thrombus was seen in those with plaque erosion, consistent with our study. The current study suggests that real-time identification of the age of thrombus based on OCT could potentially help in identifying the disease pathophysiology, determining treatment options, and improving outcomes.

CLINICAL IMPLICATIONS

Considering the distinct demographic characteristics and OCT pathologies of plaque rupture and plaque erosion in STEMI patients, individualised STEMI treatment strategies are of vital importance. Young STEMI patients with plaque erosion, <70% diameter stenosis, and TIMI 3 flow may be effectively managed with dual antiplatelet therapy alone as in the EROSION study. STEMI patients with plaque erosion on OCT often tend to have a better prognosis compared to those with plaque rupture[23]. Subjects with plaque erosion on OCT may be stabilised with medical therapy without stent implantation. This shift in the policy of management of STEMI patients with plaque erosion to antithrombotic therapies rather than PCI deserves consideration, especially in resource-limited countries such as India. This shall not only help in reducing procedure-related risks such as stent failure but also lead to a reduction in healthcare costs.

Limitations

The major limitation of the present study is the small sample size and single-centre design. Also, females were underrepresented in this study. OCT is hampered in the presence of large thrombus. The study patients were all from India; hence, extrapolation of the results of this study to various ethnic groups and larger populations is not possible. However, the South Asian population including Indians are known to suffer from ischaemic heart disease a decade earlier than other populations[24].

Conclusions

Very young adult patients with STEMI treated with thrombolysis are characterised by a predominant fibrous plaque phenotype and erosion as the primary mechanism of STEMI with more subacute and chronic thrombus.

Impact on daily practice

Plaque erosion is the dominant underlying pathophysiology in very young patients with ST-segment elevation myocardial infarction. Patients with minimal residual stenosis and Thrombolysis in Myocardial Infarction 3 flow may be considered for medical therapy without immediate percutaneous coronary intervention.

Conflict of interest statement

A. Maehara reports consultant fees for Abbott, Boston Scientific, Philips, and SpectraWAVE; and speaker honoraria from Nipro. M. Matsumura reports consultant fees from Boston Scientific and Terumo. A. Qamar reports receiving institutional grant support from Novo Nordisk and NorthShore Auxiliary Research Scholar Fund; and fees for educational activities from the American College of Cardiology, Society for Vascular Medicine, Society for Cardiovascular Angiography and Interventions, Johnson & Johnson, Pfizer, Medscape, and Clinical Exercise Physiology Association. G.S. Mintz reports honoraria from Boston Scientific, Philips, Abbott, SpectraWAVE, and Gentuity. Z.A. Ali reports institutional grant support from Abbott, Abiomed, Acist Medical Systems, Amgen, Boston Scientific, CathWorks, Canon, Conavi, HeartFlow, Inari, Medtronic, National Institute of Health, Nipro, Opsens Medical, Medis, Philips, Shockwave Medical, Siemens, SpectraWAVE, and Teleflex Inc; consultant honoraria from Abiomed, AstraZeneca, Boston Scientific, CathWorks, Opsens Medical, Philips, and Shockwave Medical; and equity in Elucid, Lifelink, SpectraWAVE, Shockwave Medical, and VitalConnect. The other authors have no conflicts of interest to declare.

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Supplementary data

Supplementary Table 1. Comparison between a Chinese study (Fang et al) and an Indian study (Girish et al).

The supplementary data are published online at: https://www.asiaintervention.org/
doi/10.4244/AIJ-D-24-00013

AsiaIntervention 2024;10:186-194

Real-world evidence of BioMime sirolimus-eluting stent in obstructive coronary artery disease: the meriT-2 trial

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KEYWORDS

- clinical trial
- drug-eluting stent
- miscellaneous
- stent thrombosis

Abstract

Background: The efficacy and safety of the ultrathin BioMime sirolimus-eluting coronary stent (SES) system in treating single or multiple *de novo* native coronary lesions, in-stent restenosis, and bifurcation lesions have been evidenced at 1 year.

Aims: We sought to investigate the long-term safety and efficacy of the BioMime SES in a real-world population with obstructive coronary artery disease (CAD).

Methods: The prospective, single-arm, multicentre meriT-2 trial enrolled 250 patients from 11 sites across India. The safety endpoint was the cumulative frequency of major adverse cardiovascular events (MACE) at 5 years, defined as a composite of cardiac death, myocardial infarction (MI), emergent coronary artery bypass grafting or clinically indicated target lesion revascularisation (CI-TLR). Stent thrombosis (ST) was evaluated according to the Academic Research Consortium definitions.

Results: A total of 214 (85.6%) subjects completed the 5-year follow-up. The mean age of patients was 57.44±10.75 years, and 82.71% were males. A total of 308 lesions were treated with BioMime SES. Most of the lesions were localised in the left anterior descending artery (45.46%) and were type B2 lesions (44.81%). The cumulative MACE rate at 5 years was 8.9% (n=19), including 0.9% cardiac deaths, 1.9% MI and 6.1% CI-TLR. The rate of ST was only 0.5%. The Kaplan-Meier survivor analysis revealed actuarial survivorship of 95.6% for the intention-to-treat population (n=250) over 5 years.

Conclusions: The long-term clinical outcomes of the meriT-2 trial established the safety and efficacy of the ultrathin-strut biodegradable-polymer-based BioMime SES with satisfactory clinical outcomes at 5 years.

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SUBMITTED ON 27/01/24 - REVISION RECEIVED ON 1st 22/03/24 / 2nd 04/05/24 / 3rd 12/06/24 / 4th 29/06/24 - ACCEPTED ON 16/07/24

DOI: 10.4244/AIJ-D-24-00007

Abbreviations

ARC	Academic Research Consortium
CABG	coronary artery bypass grafting
CAD	coronary artery disease
CI-TLR	clinically indicated target lesion revascularisation
CTO	chronic total occlusion
CVA	cerebrovascular accident
ID-TLR	ischaemia-driven target lesion revascularisation
ID-TVR	ischaemia-driven target vessel revascularisation
IHD	ischaemic heart disease
ITT	intention-to-treat
LAD	left anterior descending artery
LCx	left circumflex artery
LLL	late lumen loss
MACE	major adverse cardiovascular events
MI	myocardial infarction
MLD	minimum lumen diameter
PCI	percutaneous coronary intervention
PLGA	poly-DL-lactide-co-glycolide
PLLA	poly-L-lactide
PTCA	percutaneous transluminal coronary angioplasty
RCA	right coronary artery
SES	sirolimus-eluting stent
ST	stent thrombosis
TIA	transient ischaemic attack
TIMI	Thrombolysis in Myocardial Infarction
TLR	target lesion revascularisation
TVMI	target vessel-related myocardial infarction
TVR	target vessel revascularisation

Introduction

Obstructive coronary arteries are the predominant cause of coronary artery disease (CAD), which is a major contributor of cardiac mortality and morbidity globally[1]. Stable angina, acute coronary syndromes, and silent myocardial ischaemia are the different types of CAD or ischaemic heart disease[1,2]. In the event of severe CAD symptoms, percutaneous coronary intervention (PCI) is considered as a suitable, minimally invasive treatment choice that treats the narrowing coronary arteries and enhances the supply of oxygenated blood to the coronary arteries. PCI with coronary angioplasty has undergone a paradigm shift from the times of plain old balloon angioplasty to the introduction of stents. Since bare metal stents were deemed less durable in the long term, the use of drug-eluting stents (DES) became widely accepted. Percutaneous transluminal coronary angioplasty (PTCA) with DES implantation has shown great success in the last decade for the treatment of different coronary lesions with or without calcification. However, the rates for procedural outcomes, such as in-stent restenosis (ISR) or lumen loss, and clinical outcomes, such as cardiovascular mortality and bleeding, reported in the current literature show that challenges remain in the current practice of interventional cardiology[3,4]. Therefore, presenting the advancements in stenting devices is warranted.

Noteworthily, a DES is well known for its abilities to control the development of neointimal hyperplasia and to contribute to neoendothelialisation following stent implantation[4,5]. Newer-generation stents with thinner struts, especially sirolimus-eluting stents (SES), have proven their efficacy in combatting the development of restenosis and late stent thrombosis (ST), which are linked to adverse prognostic implications and worsening CAD. The recent evidence on DES shows a marked reduction in the burden of mortality and improvement in the quality of life for patients undergoing PCI. With time, the new-generation thinner-strut stents have become the preference for ensuring successful PCI for various lesion types in the main coronaries as well as in the distal branches[6-8]. BioMime SES (Meril Life Sciences Pvt. Ltd., India) is one of the newer-generation SES platforms, with an ultrathin (65 µm) strut and a cobalt-chromium construction[8,9]. This next-generation SES has a novel hybrid design with closed (on the proximal and distal ends of the stent) and open cells (in the middle), which facilitate morphology-mediated expansion for adequate conformability, flexibility, and radial strength, with less chance of edge dissections[9].

The series of publications of the meriT trials provide evidence on the efficacy and safety of the ultrathin BioMime SES in treating single or multiple *de novo* native coronary lesions, ISR, and bifurcation lesions. They report excellent procedural (100% in meriT-1 and meriT-3, 99.2% in meriT-2) and device success rates (99.41% in meriT-V), low rates of major adverse cardiovascular events (MACE; 0% in meriT-1, 6% in meriT-2, 2.35% in meriT-3, and 2.98% in meriT-V trials), and relatively low rates of in-stent late lumen loss (LLL) at the 8-month angiographic follow-up (median 0.15 mm [interquartile range {IQR} 0.09-0.33] in meriT-1 and 0.12 mm [IQR 0.04-0.30] in meriT-2 trials)[8-12]. The 12-month clinical outcomes from the meriT-2 trial, along with 8-month angiographic follow-up data, showed high procedural and safety success rates, with notably low LLL[10]. In the meriT-V trial, the clinical performance of BioMime SES was investigated in comparison to the XIENCE V/Prime/Xpedition everolimus-eluting coronary stent systems (EECSS; Abbott)[12]. Abizaid et al reported similar rates of in-stent LLL at the 9-month angiographic follow-up (BioMime SES vs XIENCE EECSS: 0.15±0.27 mm vs 0.15±0.29 mm)[12].

In continuation of the previous publication of 1-year outcomes of the meriT-2 trial, we report the clinical outcomes of patients who completed the 5-year follow-up after undergoing PCI with the implantation of BioMime SES.

Methods

STUDY POPULATION

The meriT-2 trial was a prospective, long-term, non-randomised, single-arm, multicentre study enrolling 250 patients at 11 investigational sites across India. The objective of this clinical study was to evaluate the safety, efficacy, and overall clinical performance of the BioMime SES system in the treatment of coronary lesions in CAD patients over a period of 5 years. The

following inclusion criteria were applied for patient enrolment: patients aged ≥18 years, those eligible for PTCA with stenting, patients with symptomatic ischaemic heart disease, and those with obstructive CAD with Thrombolysis in Myocardial Infarction (TIMI) coronary flow grade ≥2. Patients in whom PTCA with stenting for chronic total occlusion (CTO) and bifurcation lesions was also permitted were included if they had *de novo* lesions and lesion lengths ≤35 mm that could be treated with a single stent (13 mm to 40 mm lengths) without the need for overlapping stents.

STUDY OUTCOME MEASURES

In continuation of the previous publication of the 12-month follow-up data of the meriT-2 trial, this publication is intended to present the long-term clinical follow-up data of the meriT-2 trial including MACE (comprising cardiac death, myocardial infarction [MI], emergent coronary artery bypass grafting [CABG], and clinically indicated target lesion revascularisation [CI-TLR], i.e., repeat PCI or CABG)[10]. ST was evaluated as per the Academic Research Consortium (ARC) definitions[13].

The study was approved by the local ethics committees of all the participating centres, and the trial was performed under the principles stated in the Declaration of Helsinki. Written informed consent was provided by the enrolled patients before the index procedure. The meriT-2 trial was registered at the National Institute of Medical Statistics, Indian Council of Medical Research (Clinical Trials Registry – India, CTRI; www.ctri.nic.in/Clinicaltrials: CTRI/2016/11/007440) and at the US National Institute of Health (ClinicalTrials.gov: NCT02406326).

FOLLOW-UP

The follow-up dates were preplanned (5 years) from the date of the individual's index procedure. In this article, the clinical outcomes data from 3- and 5-year follow-up visits are reported. The patients were assessed thoroughly for any symptoms of late ST or ISR as well as the need for CI-TLR through PCI or CABG surgery. The PCI procedures were performed in accordance with the standard American Heart Association (AHA) guidelines[14].

STATISTICAL ANALYSIS

All data were recorded on case report forms. Categorical variables have been described as counts and percentages. Continuous variables have been described as mean±standard deviation (SD) in case of normal distribution and median with IQR (25-75%) in case of non-normal distribution of data. The safety and efficacy analyses were conducted on the basis of the intention-to-treat (ITT) principle. In this article, we are reporting the per-protocol analysis of the enrolled study population, whereas the ITT analysis was described in the previous publication of the same trial[10]. The ITT population included all patients meeting the eligibility criteria and undergoing the index PCI with the study device. The ITT analysis of 250 patients including the 12-month follow-up data has been reported earlier[10]. In this article, we report the per-protocol analysis of the 214 patients who completed the 5-year follow-up, including the Kaplan-Meier survival analysis of this study population, which was conducted to establish the MACE-free survival over 5 years. Comparisons between groups using 2-sided p-values were obtained using Fisher's exact test or the χ^2 test. The time-to-event analysis and overall survival analysis was performed using the Kaplan-Meier method; p-values were derived using the log-rank t-test. The lost-to-follow-up and withdrawn cases were censored when the survival analysis was performed. SPSS, version 20 (IBM) was used for all statistical analyses.

Results

The data of the 214 patients (85.6% of the 250 enrolled patients) who completed the 5-year follow-up visits were analysed. **Figure 1** presents the CONSORT patient flow diagram of the trial. The baseline characteristics of these patients are presented in **Table 1**. Briefly, the patient population had a mean age of 57.44±10.75 years and a mean body mass index of 25.11±3.52 kg/m^2. A total of 82.71% of patients were males. Common cardiac risk factors such as diabetes and hypertension were present in 32.71% and 50.00% patients, respectively. The cardiac history evaluation revealed that 30.84% of patients had experienced a past (≥30 days) MI, while 24.76% had a recent MI (<30 days).

A total of 308 lesions were identified and treated with BioMime SES. Most of the treated lesions were in the left anterior descending artery (n=140, 45.46%), followed by the right coronary artery (n=101, 32.79%), and left circumflex artery (n=67, 21.75%). Type B2 lesions (n=138) were predominantly (44.81%) present, while 106 were type B1 lesions (34.42%), 52 were type C lesions (16.88%), and 12 lesions (3.89%) were of type A morphology **(Table 2)**. The mean lesion length was 14.52±8.15 mm. The entire patient sample of the meriT-2 trial did not have any cases of CTO; however, 5.1% (n=18) of treated lesions were bifurcation lesions. In terms of clinical presentation, 10.74% patients presented with silent ischaemia, while 34.57% and 29.43% had stable and unstable angina, respectively. Preprocedural TIMI flow grade of 0 or 1 was present in 33.44% patients, while postprocedural TIMI flow grade 3 was achieved in the majority of the patients (98.7%).

Antiplatelet therapy was prescribed as per the investigator's discretion and included aspirin (98.6%), clopidogrel (97.7%), prasugrel (0.47%), persantin (0.47%) and tirofiban (0.47%).

CLINICAL OUTCOMES UP TO 3 YEARS

A total of 242 patients completed the 3-year follow-up. The MACE rate was 7.9% (cardiac death in 0.8%, MI in 1.7%, and CI-TLR in 5.4% of the patients). Definite/probable ST had occurred in 1 patient (0.4%) at 6-month follow-up, and no new cases of ST were reported during the 3-year follow-up **(Table 3, Figure 2)**. The cumulative frequency of all-cause death was 3.7%, including 2 cardiac and 7 non-cardiac deaths, at 3 years. Repeat revascularisation was required in 13 patients (5.4%), including 1 patient who underwent CABG **(Table 3)**.

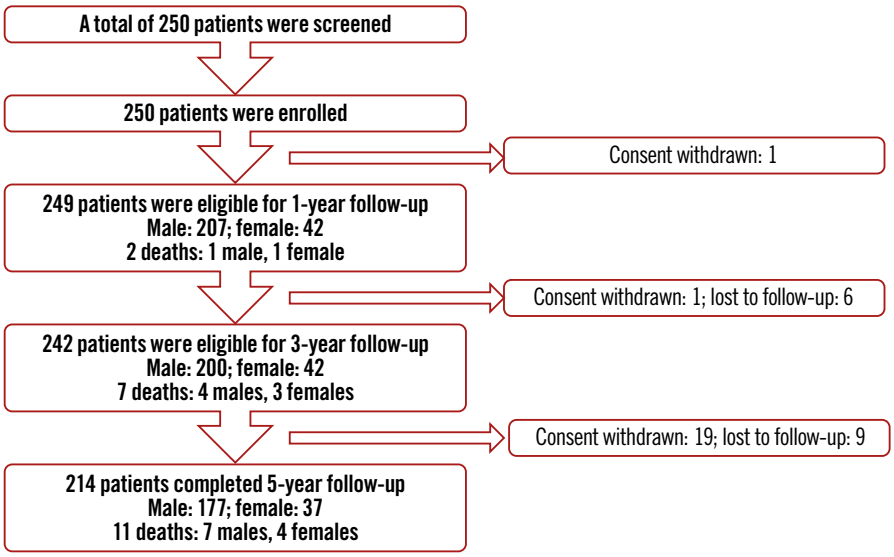


Figure 1. *CONSORT flow diagram over the 5-year follow-up period. Index procedure performed on 249 patients.*

Table 1. Baseline characteristics of the study population who completed 5-year follow-up.

Variables	Enrolled study population (N=250)	Study population at 5-year follow-up (N=214)
Age, years	56.8±10.6	57.44±10.75
Sex		
Female	42 (16.8)	37 (17.29)
Male	208 (83.2)	177 (82.71)
Diabetes mellitus	91 (36.4)	70 (32.71)
Hypertension	123 (49.2)	107 (50.00)
Dyslipidaemia	26 (10.4)	-
Prior MI (≥30 days)	80 (32.0)	66 (30.84)
Prior PCI	15 (6.0)	11 (5.14)
Prior CABG	4 (1.6)	3 (1.40)
Prior stroke/TIA/CVA	2 (0.8)	2 (0.93)
History of CHF	5 (2.0)	3 (1.40)
Clinical presentation		
Asymptomatic/silent ischaemia	28 (11.2)	23 (10.74)
Stable angina	94 (37.6)	74 (34.57)
Unstable angina	68 (27.2)	63 (29.43)
Recent MI (<30 days)	59 (23.6)	53 (24.76)

Values are mean±standard deviation or n (%). CABG: coronary artery bypass grafting; CHF: congestive heart failure; CVA: cerebrovascular accident; MI: myocardial infarction; PCI: percutaneous coronary intervention; TIA: transient ischaemic attack

Table 2. Lesion characteristics of the patients with 5-year follow-up.

Variable	Total no. of lesions (n=308)
Target coronary vessel	
LAD	140 (45.46)
LCx	67 (21.75)
RCA	101 (32.79)
Lesion class#	
A	12 (3.89)
B1	106 (34.42)
B2	138 (44.81)
C	52 (16.88)

Values are presented as n (%). #According to the modified American College of Cardiology/American Heart Association classification criteria. LAD: left anterior descending artery; LCx: left circumflex artery; RCA: right coronary artery

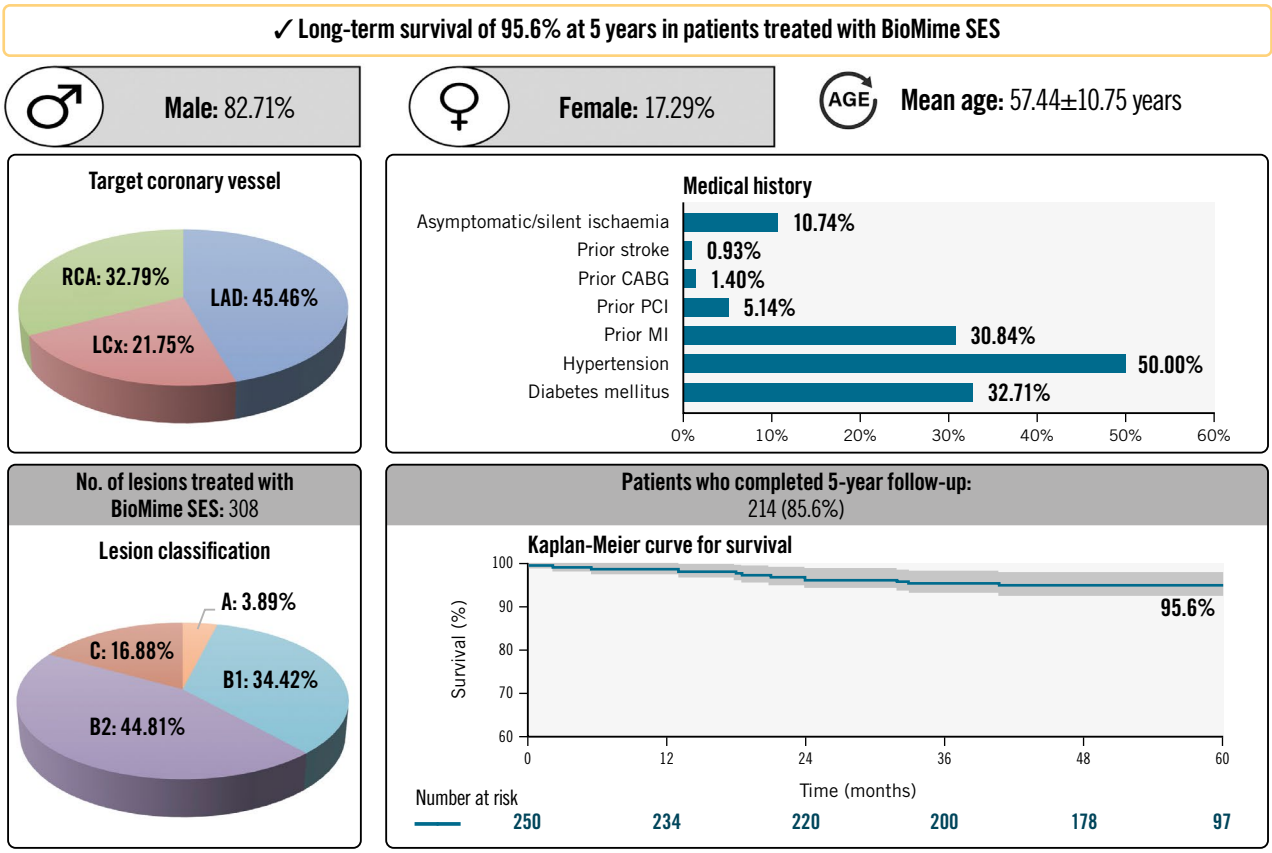
CLINICAL OUTCOMES UP TO 5 YEARS

A total of 214 patients completed the 5-year follow-up. MACE was reported in 8.9% of patients (cardiac death in 0.9%, MI in 1.9%, and CI-TLR in 6.1% of the patients) **(Figure 2)**. The rates of possible ST and definite/probable ST were considerably low, and no new cases were observed during the 5-year follow-up period **(Table 3)**. Between the 3-year and 5-year follow-ups, no other all-cause mortality events had occurred in female patients, while 2 more males died. Hence, a total of 7 men and 4 women died during 5-year follow-up. The actuarial MACE-free survival obtained with the Kaplan-Meier analysis was 95.6% over the 5-year study period for the ITT population **(Central illustration)**.

Discussion

In this report, we discuss the long-term data of 214 patients who completed the 5-year follow-up after undergoing PCI with the implantation of BioMime SES. The first key finding of the meriT-2 trial is that the cumulative frequency of late ST (definite or probable) at the 5-year follow-up was quite low (0.5%). Secondly, no cardiac deaths were reported in the 5-year study period

CENTRAL **ILLUSTRATION** **Long-term follow-up data of the meriT-2 trial reveal the safety and efficacy of the BioMime SES.**



CABG: coronary artery bypass grafting; LAD: left anterior descending artery; LCx: left circumflex artery; MI: myocardial infarction; PCI: percutaneous coronary intervention; RCA: right coronary artery; SES: sirolimus-eluting stent

Table 3. Cumulative data of the clinical outcomes of the study population at 3- and 5-year follow-up.

	3-year follow-up (N=242)	5-year follow-up (N=214)	*p*-value
MACE	19 (7.9)	19 (8.9)	0.8209
Cardiac death	2 (0.8)	2 (0.9)	1.0000
MI	4 (1.7)	4 (1.9)	1.0000
Clinically indicated TLR	13 (5.4)	13 (6.1)	0.9039
PCI	12 (5.0)	12 (5.6)	0.9207
CABG	1 (0.4)	1 (0.5)	1.0000
Non-cardiac death	7 (2.9)	9 (4.2)	0.6132
Stent thrombosis*	1 (0.4)	1 (0.5)	1.0000
Definite/probable	1 (0.4)	1 (0.5)	1.0000
Possible	0	0	-

Values are n (%). *According to the ARC definitions. ARC: Academic Research Consortium; CABG: coronary artery bypass grafting; MACE: major adverse cardiovascular events; MI: myocardial infarction; PCI: percutaneous coronary intervention; TLR: target lesion revascularisation

(cumulative MACE rate at 5 years: 8.9%), which is noteworthy, given the study sample's significant comorbidity burden and history of acute coronary events. With the 5-year clinical outcome data available for the study, we affirm that the meriT-2 trial reports satisfactory levels of long-term efficacy and safety of the BioMime SES for the treatment of *de novo* lesions in patients with obstructive CAD. In this study, the actuarial MACE-free survival at 5 years was 95.6% based on Kaplan-Meier analysis.

The first-in-human evaluation of the BioMime SES was conducted in the meriT-1 study, which reported 0% MACE (composite of MI, cardiac death, TLR) and ST rates. The overall results from the meriT-1 trial demonstrated excellent performance and safety outcomes at the 12-month follow-up with high procedural success and a low median in-stent LLL (0.15 mm [IQR 0.09-0.33]) at the 8-month angiographic follow-up[9]. The results of the meriT-2 trial reiterate the competency of the BioMime SES based on the previously reported 1-year data reported by Seth et al (2016)[10]. It was shown that the cumulative MACE rate was 6%, including 0.4% MI, 4.8% CI-TLR, and 0.8% cardiac death. The reported meriT-2 trial data highlight the feasibility of implanting

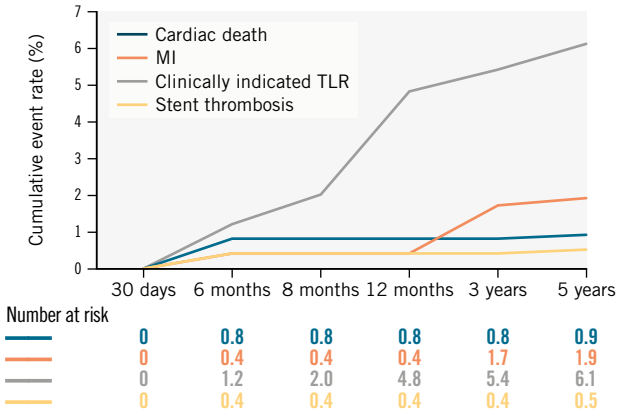


Figure 2. *Cumulative clinical outcomes of the meriT-2 trial up to 5-year follow-up. MI: myocardial infarction; TLR: target lesion revascularisation*

the BioMime SES, as 99.2% angiographic and procedural success was achieved[10]. Furthermore, Seth et al reported that at the 8-month angiographic follow-up, the median in-stent LLL was 0.12 mm (IQR 0.04-0.30), suggesting the considerable ability of the study device in inhibiting neointimal hyperplasia and preventing restenosis[10]. The low rate of ST and high MACE-free survival rate achieved in the study population at 5 years corroborate data regarding the efficacy of the BioMime SES. In continuation of the meriT series, the meriT-V trial has demonstrated remarkable efficacy in not only achieving low in-segment LLL (0.12±0.26 mm) and in-stent LLL (0.15±0.27 mm) at 9 months post-PCI, as reported by Abizaid et al (2018), but also in reducing long-term adverse events including MACE, ischaemia-driven target lesion revascularisation (ID-TLR), ischaemia-driven target vessel revascularisation (ID-TVR), cardiac death, and late ST[12]. The meriT-V trial demonstrated good efficacy of the BioMime SES in terms of lowering the repeat revascularisation rates during the 2-year follow-up[15]. The quantitative coronary angiographic analysis of the meriT-V trial at the 9-month angiographic follow-up showed the non-inferiority of the BioMime SES in comparison to XIENCE V/Prime/Xpedition EECSS in terms of the primary endpoint data, as similar in-stent LLL rates were observed with both the devices (BioMime SES vs XIENCE EECSS: 0.15±0.27 mm vs 0.15±0.29 mm) at the 9-month angiographic follow-up[12]. In addition, neither of the groups had any significant difference in the percentage of diameter stenosis (BioMime SES vs XIENCE EECSS: 16.82±11.90% vs 16.57±11.71%) at the 9-month follow-up[12].

Furthermore, the clinical outcomes of the meriT-2 trial are comparable to those reported from the DESSOLVE III trial **(Table 4)**[16]. The role of a DES in the treatment of ISR or *de novo* coronary lesions involves multiple mechanisms that contribute to re-endothelisation and suppression of vascular remodelling. Inhibition of stenotic vascular remodelling is based on the action of the antiproliferative drug (sirolimus), which inhibits the growth and proliferative activity of vascular smooth muscle cells that migrate and proliferate into the intimal or medial layers of the arterial wall and cause stiffening. The rapid re-endothelisation promoted by the action of sirolimus over a span of 30 days by a sustained or extended release causes a stark decrease in the risk of ISR[10,17].

The study device, BioMime SES, is known for its excellent conformability to the arterial lumen. The fusion of open and closed cells into a hybrid structure enables a better vessel conformity and offers a higher efficiency in-stent deployment owing to the presence of the ultrathin 65 µm struts. Other stents with an ultrathin construction have also shown similar results **(Table 5)**. The device is known for its abilities to reduce balloon-related vascular edge injuries and offer complete resorption of the biopolymeric coating within 30 days[18]. From the outcomes of the meriT-2 trial, the advantages of the ultrathin-strut design of the BioMime SES are demonstrated as early and late safety events, which were lower than those reported in contemporary studies **(Table 5)**. However, consolidated meta-analyses of the data in future investigations are warranted to fully ascertain the clinical equivalence of the study device with the other commercially available devices.

Nevertheless, we believe that these improved outcomes may be attributed to the presence of a highly biocompatible and biodegradable polymer composite comprising two biodegradable polymers – poly-L-lactide (PLLA) and poly-DL-lactide-co-glycolide (PLGA). In comparison with contemporary studies on ultrathin-strut SES designs, the meriT-2 trial presents considerable evidence on the BioMime SES in terms of low cardiac deaths and CI-TLR, which ultimately reduce the MACE rates. The MACE rates reported in this study (8.9%) are comparable to the rates of device-oriented composite endpoints or MACE shown for the PROMUS everolimus-eluting stent (Boston Scientific), MiStent SES (Micell Technologies) and XIENCE EECSS **(Table 5)**[16,19].

The long-term outcomes data of the meriT-2 trial present satisfactory PCI outcomes up to 5 years, which validate the performance of the BioMime SES in patients with obstructive CAD. The repeat revascularisation rate with PCI (n=12, 5.6%) and CABG (n=1, 0.5%) during the 5-year follow-up was relatively low. Furthermore, we noted that the revascularisation rate was comparable to that observed in the LEADERS FREE III study **(Table 5)**[20]. An independent patient-data meta-analysis compared 5 randomised controlled trials, BIOFLOW-II, BIOFLOW-IV, BIOFLOW-V, BIOSCIENCE and BIOSTEMI, to evaluate the safety and efficacy of ultrathin-strut biodegradable-polymer sirolimus-eluting stents (BP-SES) and thin-strut durable-polymer everolimus-eluting stents (DP-EES). Among both the groups, there were no significant differences between BP-SES and DP-EES with regard to cardiac death (3.4% vs 4.1%), all-cause mortality (6.4% vs 6.4%) or revascularisation (11.8% vs 12.5%). These 5 randomised controlled trials demonstrated a similar risk of TLF among patients undergoing PCI with BP-SES compared to those undergoing PCI with DP-EES[21]. Thus, the data from the meriT-2 trial provide evidence of satisfactory clinical outcomes at

Table 4. Recently published clinical studies from contemporary devices conducted with thin-strut DES.

Study names	Study design	Study device
DESSOLVE III trial[16]	Prospective, multicentre, single-blinded, all-comers, randomised controlled trial	MiStent SES (64 µm)[a] and XIENCE EECSS (strut thickness of 81 µm)[b]
Genoss DES Prospective Multicenter Registry[22]	Prospective, single-arm observational, multicentre registry	GENOSS DES SES (70 µm)[c]
Historical cohort study[19]	Retrospective, historical cohort study	PROMUS[d]/Resolute[e]/ XIENCE[b] (PRX) and BioMime[f]
BIOFLOW-VII[23]	Prospective, multicentre, single-arm US post-marketing approval study	Orsiro SES (60 µm)[g]
Thailand Orsiro Registry[24]	Prospective, non-randomised, multicentre, observational study	Orsiro SES (60 µm)[g]
Leaders Free III study[20]	Prospective, international, multicentre, single-arm study	BioFreedom biolimus-A9-eluting stent (84-88 µm)[h]
FlexyRap DES study[25]	Retrospective, single-arm, multicentre, post-marketing study	FlexyRap cobalt-chromium rapamycin-eluting stent (60 µm)[i]

[a]By Micell Technologies; [b]by Abbott; [c]by Genoss; [d]by Boston Scientific; [e]by Medtronic; [f]by Meril Life Sciences; [g]by Biotronik; [h]by Biosensors International; [i]by SLTL Medical. DES: drug-eluting stent; EECSS: everolimus-eluting coronary stent system; SES: sirolimus-eluting stent

Table 5. Recently published clinical outcomes from contemporary studies conducted with thin-strut DES.

Study names	No. of patients and follow-up	Cardiac death	Any TLR/ CD-TLR/ CI-TLR	Any TVR/ CD-TVR/ non-CD-TVR	MI	TVMI	Late ST	ST
DESSOLVE III trial[16]	N=1398 3 years	MiStent[a] vs XIENCE EECSS[b]: 3.9% vs 3.8%	MiStent vs XIENCE EECSS (CD-TLR): 5.2% vs 6.5%	MiStent vs XIENCE EECSS (any TVR): 8.7% vs 10.2%	MiStent vs XIENCE EECSS (any MI): 3.5% vs 3.2%	MiStent vs XIENCE EECSS: 3.2% vs 2.5%	MiStent vs XIENCE EECSS: 0.4% vs 0.6%	MiStent vs XIENCE EECSS (definite ST): 0.6% vs 1.2%
Genoss DES Prospective Multicenter Registry[22]	N=622 1 year	0.2%	0.5%	0.8%	Any MI: 0.6%	0.2%	0.5%	Definite ST: 0.5% Probable ST: 0.6%
Historical cohort study[19]	N=1709 1 year	PRX vs BioMime SES[e] group vs overlap (1.5% vs 2.4% vs 1.1%)	PRX vs BioMime SES group vs overlap (1.6% vs 0.8% vs 1.9%)	PRX vs BioMime SES group vs overlap (2.8% vs 1.6% vs 3.2%)	-	-	-	-
BIOFLOW-VII[23]	N=556 1 year	0%	0.9	2.3%	Any MI: 1.7%	1.3%	-	Definite ST: 0.4% Probable ST: 0%
Thailand Orsiro Registry[24]	N=150 1 year	5.3%	-	0.7%	Any MI: 1.3%	0%	-	Definite ST: 0.7% Probable ST: 0.7%
Leaders Free III study[20]	N=401 1 year	3.7%	4.2%	5.0%	4.4%	-	-	Definite/ probable ST: 1.0%
FlexyRap DES study[25]	N=500 5 years	0%	0%	0%	-	0.2%	Late ST: 0% Very late ST: 0%	-

[a]By Micell Technologies; [b]by Abbott; [c]by Boston Scientific; [d]by Medtronic; [e]by Meril Life Sciences. CD-TLR: clinically driven TLR; CD-TVR: clinically driven TVR; CI-TLR: clinically indicated TLR; DES: drug-eluting stent; EECSS: everolimus-eluting coronary stent system; MI: myocardial infarction; PRX: PROMUS[c]/Resolute[d]/XIENCE[b]; SES: sirolimus-eluting stent; ST: stent thrombosis; TLR: target lesion revascularisation; TVMI: target vessel myocardial infarction; TVR: target vessel revascularisation

long-term follow-up. It is noteworthy that there were no restrictions on the inclusion of females in the study, which helped assimilate the outcomes for female patients in a middle-income nation as well. The infrastructural developments and improvements in socioeconomic factors helped assess the PCI outcomes across both sexes and across multiple age groups.

Limitations

We noted that the stringent exclusion criteria limited the inclusion of real-world patients, and the lack of a heterogeneous ethnic population in this study may limit its generalisability for the larger proportion of PCI patients in real-world practice. The absence of a comparative arm in the meriT-2 trial needs to be acknowledged.

Moreover, long-term coronary angiographic data would be necessary to ascertain the durability of the biodegradable-polymer-based cobalt-chromium stent, BioMime SES. In the current era of PCI, the need for late angiographic follow-up has been reduced owing to the consistent decrease in ST events. In selected cases, angiographic follow-up may be conducted when the clinical findings indicate the need for an invasive examination.

Conclusions

Long-term follow-up data of the meriT-2 trial reveal the safety and efficacy of the BioMime SES in the treatment of obstructive CAD with the absence of late ST and low frequency of MACE over the 5-year study period. Long-term survivorship of 95.6% at 5 years was demonstrated in patients treated with the BioMime SES, despite these patients having multiple comorbidities.

Impact on daily practice

These real-world long-term outcomes at 5 years with the BioMime sirolimus-eluting stent will impact the daily practices of interventional cardiologists in optimising their treatment of patients with obstructive coronary artery disease. For researchers, the antiproliferative activity of sirolimus on the stent which, due to rapid re-endothelisation, reduces in-stent restenosis, in turn, improving long-term outcomes, would be of interest.

Data availability statement

The study data are available from the corresponding author upon reasonable request.

Acknowledgements

We would like to thank the biostatisticians, Mr Sayyed Israr Ahamad, Ms Rutuja D. Sadekar, and Mr Vishal Jagadale, at Meril Life Sciences Pvt. Ltd., India, for their tireless efforts and support throughout data analysis and in obtaining survival analysis data. We also extend our gratitude to Ms Vibhuti S. Bhatt, Ms Mahasweta G. Pal, and Dr Latheef Kasala for their assistance in finalising the manuscript.

Guest Editor

This paper was guest edited by Davide Capodanno, MD, PhD; *A.O.U. Policlinico "G. Rodolico-San Marco", University of Catania, Catania, Italy*

Funding

The meriT-2 trial was funded by Meril Life Sciences Pvt. Ltd., Gujarat, India.

Conflict of interest statement

A. Thakkar and U. Chandra are full-time employees of Meril Life Sciences Pvt. Ltd. U. Kaul is the Editor-in-Chief of AsiaIntervention. The other authors have no conflicts of interest to declare. The Guest Editor has no relevant conflicts of interest to declare.

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Clinical safety and performance of the world's thinnest-strut Evermine50 everolimus-eluting stent: a 24-month follow-up of the Evermine50 EES–1 study

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KEYWORDS

- ACS/NSTE-ACS
- chronic coronary total occlusion
- diffuse disease
- drug-eluting stent

Abstract

Background: Ultrathin-strut stents are considered the future of percutaneous coronary intervention for treating coronary artery disease (CAD). These drug-eluting stents with biodegradable-polymer technology have the potential to improve clinical outcomes in CAD patients.

Aims: This study aimed to evaluate the safety and performance of newer-generation ultrathin-strut (50 µm) Evermine50 everolimus-eluting stents (EES) in patients with single or multiple long lesions.

Methods: This is a prospective, single-arm, multicentre study conducted in India that enrolled 118 patients with *de novo* coronary lesions. The endpoints were defined based on the major adverse cardiac events (MACE; composite of cardiac death, myocardial infarction [MI] and clinically driven target lesion revascularisation) up to 24-month follow-up. A subset of patients (n=21) underwent angiographic follow-up for a mean follow-up period of 12 months.

Results: A total of 138 lesions were successfully treated in 118 patients, the majority of whom were males (80.51%). The average stent length and diameter deployed were 26.02±9.24 mm and 2.97±0.36 mm, respectively. The results exhibited low MACE at 24-month follow-up (0.87%) with no stent thrombosis and 1 death (0.87%, which was cardiac). The core lab angiographic assessment showed in-segment and in-device late lumen loss of 0.12±0.31 mm and 0.17±0.31 mm, respectively, at a mean follow-up of 12 months, with clinically acceptable outcomes.

Conclusions: The Evermine50 EES showed satisfactory primary clinical as well as angiographic outcomes, reaffirming the safety and performance of the world's thinnest-strut stent by exhibiting low rates of MACE at 24-month follow-up with an absence of any stent thrombosis and MI. Clinical Trials Registry-India (CTRI) number: CTRI/2017/02/007781.

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SUBMITTED ON 05/02/2024 - REVISION RECEIVED ON 1st 03/05/2024 / 2nd 18/06/2024 - ACCEPTED ON 21/06/2024

DOI: 10.4244/AIJ-D-24-00009

Abbreviations

BP	biodegradable polymer
CAD	coronary artery disease
CD-TLR	clinically driven target lesion revascularisation
DES	drug-eluting stent
DP	durable polymer
EES	everolimus-eluting stent
ID-TLR	ischaemia-driven target lesion revascularisation
ID-TVR	ischaemia-driven target vessel revascularisation
LLL	late lumen loss
MACE	major adverse cardiac events
MI	myocardial infarction
MLD	minimal lumen diameter
PCI	percutaneous coronary intervention
SES	sirolimus-eluting stent
ST	stent thrombosis
TIMI	Thrombolysis in Myocardial Infarction
TLR	target lesion revascularisation
TVMI	target vessel myocardial infarction
TVR	target vessel revascularisation

Introduction

Lifestyle changes have escalated the prevalence of coronary artery disease (CAD) widely, especially in middle-aged and elderly patients. Percutaneous coronary intervention (PCI) has been considered the gold standard for coronary artery revascularisation for the last five decades[1]. There have been various approaches to treat obstructive lesions in coronary arteries, which are characterised by the deposition of plaque in the lumen of these vessels, in turn, restricting the myocardial blood flow. Tremendous advances in PCI technologies have taken place over decades from transluminal-only coronary balloon angioplasty to recent drug-eluting stents (DES) with bioresorbable polymers[1]. Stent platform technology has grown from bare metal stents (BMS) to series of newer-generation DES. The first-generation DES aimed to reduce the risk of stent thrombosis (ST) along with the repeated revascularisation and restenosis rates[2]. The second-generation DES further addressed these issues. However, the second-generation DES were also associated with a higher risk of major adverse cardiac events (MACE), ST and late restenosis in some cases, and the plausible reason was often ascribed to the thicker strut size. This has thus fuelled the need for thinner struts and advanced generations of DES[1,2]. Research has showed that by reducing the strut thickness to a minimum, the rate of MACE and ST can fall to near zero[3]. Also, replacing the durable polymer with biodegradable polymers like poly lactic-co-glycolic acid (PLGA) and poly-L-lactic acid (PLLA) may reduce stimulation of the inflammatory response[4]. This led to the conceptualisation of Evermine50 everolimus-eluting stent (EES; Meril Life Sciences Pvt. Ltd). It is the world's thinnest-strut (50 µm) EES with a biodegradable-polymer coating. It has potential advantages over thicker struts, because it causes less vessel injury, inflammation, and thrombus formation, and enables faster endothelialisation and early vascular healing, with a lower risk of malapposed struts being observed[4,5]. Clinical outcomes from various studies showed that Evermine50 EES was a safer and more reliable stent to treat long and multiple lesions[3-5].

A single-centre retrospective study in 171 patients showed no procedural complications and no definite or probable ST with a relatively low all-cause mortality-to-survivorship ratio[4]. On the other hand, a prospective study in 711 subjects treated with >40 mm Evermine50 EES revealed a lower rate of the device-oriented composite endpoint (6.6%), which was a composite of cardiac death, target vessel myocardial infarction (TVMI) and clinically driven target lesion revascularisation (CD-TLR) at 12 months, and further showed a lower rate of definite and probable ST of 1.1% and 0.8%, respectively, in patients with unduly long lesions at 12-month follow-up[6].

In this present prospective, single-arm, post-marketing multicentre study, we report our experience on the safety and performance of the ultrathin-strut Evermine50 EES in patients suffering from *de novo* coronary artery lesions.

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Methods

STUDY DESIGN AND POPULATION

This prospective, single-arm, multicentre (9 centres), post-marketing study conducted over a 24-month period evaluated the safety and performance of Evermine50 EES implanted in patients suffering from *de novo* coronary artery lesions. Patients above 18 years of age were enrolled in the study. Patients with hypersensitivity to heparin, cobalt-chromium (CoCr) metal alloy, everolimus, polymer lactide, glycolide, and antiplatelet drugs, like prasugrel, clopidogrel etc., and those who did not provide written informed consent were not included in the study.

DEVICE DESCRIPTION AND PROCEDURAL DETAILS

The Evermine50 EES is the world's thinnest (50 µm) everolimus-eluting stent. It has a biodegradable polymer, PLGA- and PLLA-coated EES system, developed on the CoCr platform. The device is European Conformity (CE)-marked and commercially available in varied lengths and diameters[7].

PROCEDURAL AND POSTINTERVENTIONAL MEDICATIONS

The PCI procedure was performed as per the American College of Cardiology/American Heart Association guidelines[8]. Preprocedure, all the patients were given 75-100 mg aspirin and 300 mg of clopidogrel or as per the investigators' discretion. Heparin (70-100 units/kg) was used to maintain an activated coagulation time >250 seconds as per the requirements of the PCI procedure.

STUDY ENDPOINTS

The safety endpoint was MACE (which was a composite of cardiac death, myocardial infarction [MI], and CD-TLR) and stent thrombosis at 1-, 6-, 12- and 24-month follow-up. The performance endpoint comprised ischaemia-driven target lesion revascularisation (ID-TLR), ischaemia-driven target vessel revascularisation (ID-TVR) up to 24 months, and procedural (within 24 hours) and

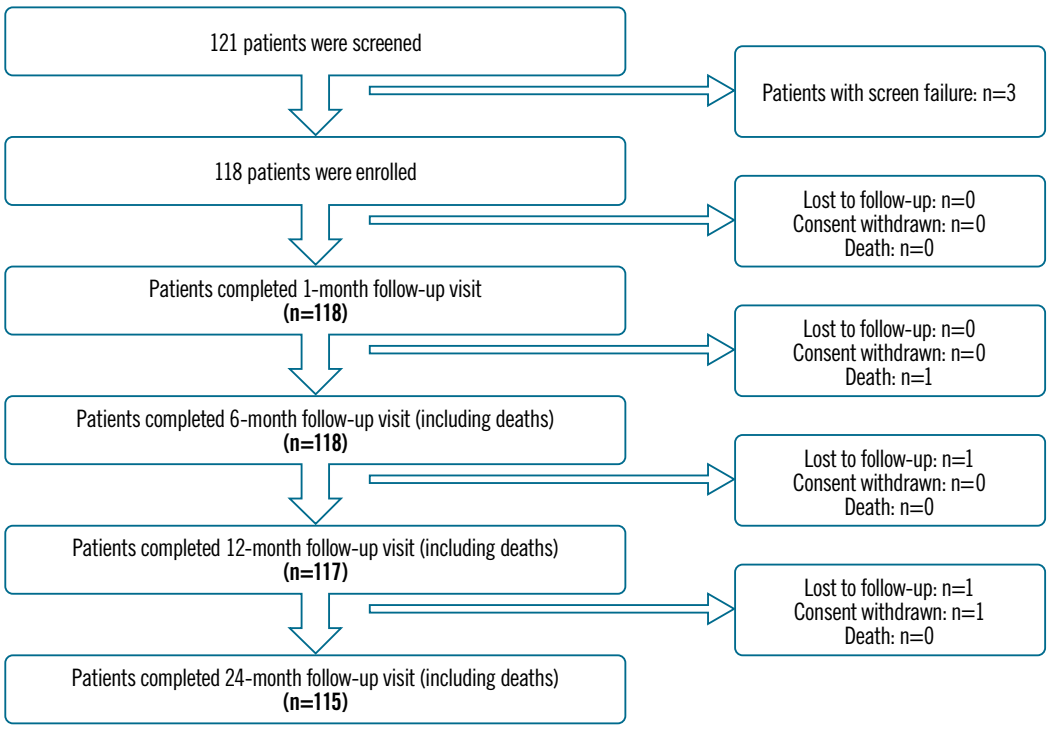


Figure 1. *CONSORT flow diagram for 24-month follow-up.*

device success (post-procedure). In-stent and in-segment minimal lumen diameter (MLD) and late lumen loss (LLL) at 12-month follow-up were compared to pre- and post-PCI by quantitative coronary angiography (QCA) as assessed at an independent core lab (CBCC Global Research LLP, Ahmedabad, India).

STATISTICAL ANALYSIS

The demographic and baseline characteristics are summarised using descriptive statistics. Categorical variables are described as counts and percentages and were compared using Pearson's chi-square test or Fisher's exact test. Continuous variables are described as means±standard deviation (SD) and were compared using the t-test or Mann-Whitney U test, as appropriate. A 2-sided p-value of less than 0.05 was considered to indicate statistical significance. All statistical analyses were performed using Statistical Package for the Social Sciences software, version 22 (IBM).

Results

BASELINE DEMOGRAPHIC CHARACTERISTICS

A total of 121 patients were screened, of whom 3 failed the screening test and 118 were enrolled in the study **(Figure 1)**. The mean age of the patients was 58.16±10.73 years, and the majority were males (80.51%) **(Table 1)**. Out of the 118 patients, 64 (54.24%) had single-vessel disease, followed by 39 (33.05%) and 15 (12.71%) patients with double- and triple-vessel disease, respectively **(Figure 2)**. The medical histories of the 118 enrolled patients were studied; 38.98% had diabetes, 47.46% were suffering from hypertension, and 36.44% were smokers **(Figure 3)**.

Table 1. Baseline characteristics and demographic details.

Variables	n=118 patients
Age, years	58.16±10.73
Sex	
Male	95 (80.51)
Female	23 (19.49)
BMI*, kg/m^2	24.90±3.70
Heart rate, bpm	77.58±11.04
DBP, mmHg	80.21±11.64
SBP, mmHg	127.25±18.34

Values are mean±standard deviation or n (%). *n=116. BMI: body mass index; bpm: beats per minute; DBP: diastolic blood pressure; SBP: systolic blood pressure

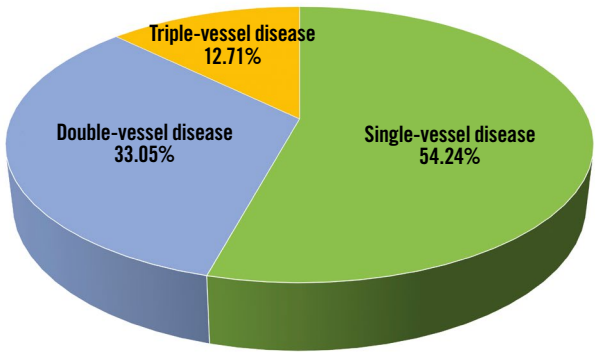


Figure 2. *Distribution of the diseased vessels.*

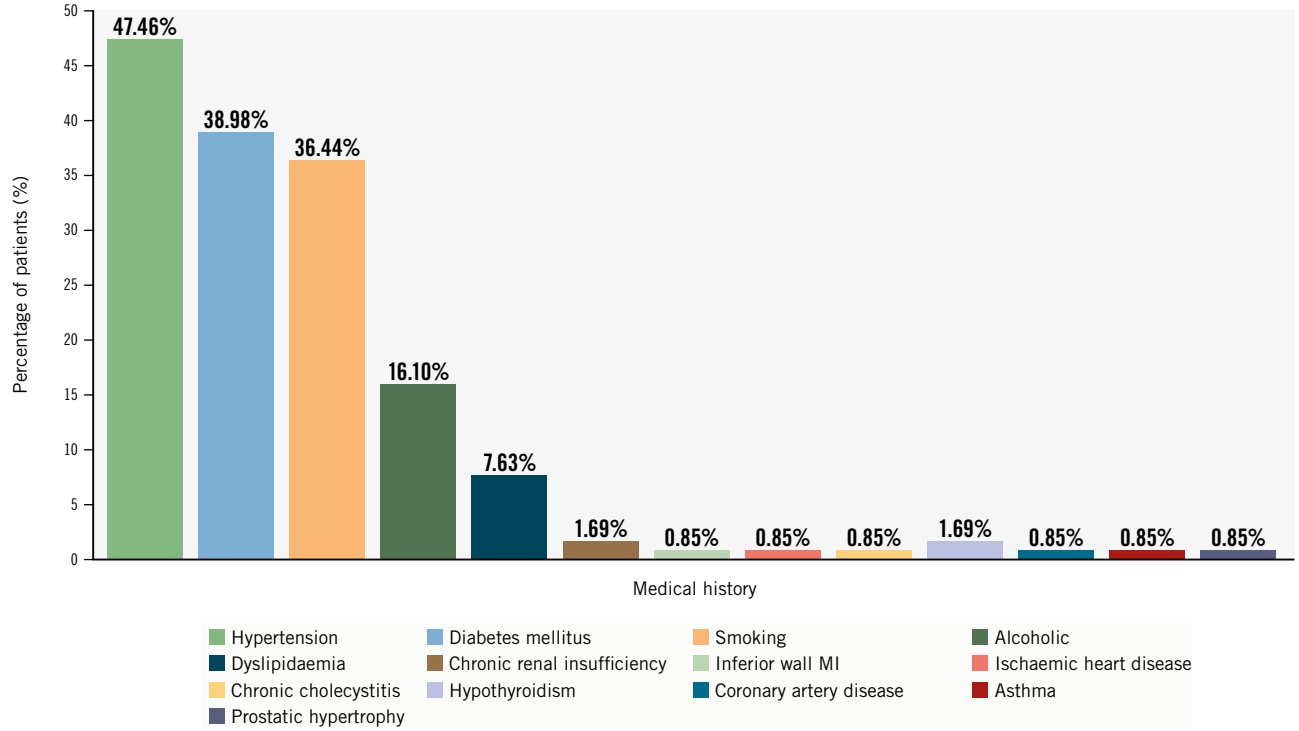


Figure 3. *Medical and cardiac history of the patients. MI: myocardial infarction*

LESION CHARACTERISTICS

A total of 138 lesions were treated in 118 patients. The most common target vessel treated was the left anterior descending artery, in 63 (45.65%) patients, followed by the right coronary artery, in 46 (33.33%) patients, and the left circumflex artery, in 19 (13.77%) patients **(Table 2)**. Predilatation was performed in 66.19% of patients, while post-dilatation was performed in 77.70% of patients. The average diameter and length of the implanted Evermine50 EES were 2.97±0.36 mm (range: 2.25-3.50 mm) and 26.02±9.24 mm (range: 13-48 mm), respectively. In 34.75% of the patients, the right femoral artery was the access point; in the remaining patients, the right or left radial artery was used as the access site **(Table 2)**. A large proportion of patients (40.29%) had preprocedural Thrombolysis in Myocardial Infarction (TIMI) flow grade 0, which improved post-procedure to TIMI flow grade 3 in 99.28% of patients **(Table 2)**. Acute procedural success, defined as TIMI flow grade 3, and device success, defined as successful implantation of the device, were found to be 100%, with no MACE nor any adverse events during the index procedure **(Table 2)**.

CLINICAL OUTCOMES

At the end of the 24-month follow-up period, 1 (0.87%) patient experienced MACE. None of the patients exhibited MI, ID-TLR, ID-TVR, CD-TLR or ST during the 24 months of follow-up. There was 1 all-cause death reported during the 6-month follow-up period, which was a cardiac death (due to cardiorespiratory arrest). Detailed clinical outcomes are shown in **Table 3**. Myocardial reperfusion was re-established to TIMI flow grade 3 in 99.28% of patients post-PCI, while TIMI flow grade 2 was achieved in 0.72% of patients **(Table 3)**.

ANGIOGRAPHIC OUTCOMES

Of 118 patients enrolled in the study, angiographic follow-up was carried out in a subset of patients (n=21) at a mean follow-up of 12 months. An independent core laboratory (CBCC Global Research LLP, Ahmedabad, India), assessed the coronary angiograms preprocedure, post-procedure and at a mean follow-up of 12 months. As per the independent core laboratory's assessment, the in-device MLD post-procedure and at follow-up were 2.54±0.34 mm and 2.37±0.32 mm, respectively, and the in-segment MLD were 2.41±0.37 mm and 2.28±0.37 mm, respectively, with a p-value<0.0001, as mentioned in **Table 4**. In-device and in-segment LLL at the mean follow-up (12 months) were 0.17±0.31 mm and 0.12±0.31 mm, respectively. An overview of the Evermine50 EES-1 study is shown in the **Central illustration**.

Discussion

The results obtained from this study can be reported as satisfactory for all the patients in terms of the safety and performance of the Evermine50 EES. Across the demographics and varied medical history of patients, it was observed that there was 100% procedural and device success.

Given that ST − occurring for various reasons such as delayed endothelialisation, hypersensitivity reactions, chronic inflammation of arteries, etc. − has been a major cause of rehospitalisation, this study focused on minimising ST and attained 100% clinical

Table 2. Lesion and procedural characteristics.

Variables	118 patients/ 138 lesions
Lesion characteristics	
Total number of lesions treated with study device	138
Total number of study stents deployed	139*
Number of lesions per patient	1.17
Lesion location	
RCA	46 (33.33)
LAD	63 (45.65)
LCx	19 (13.77)
OM1	7 (5.07)
LPDA	1 (0.72)
Ramus	1 (0.72)
LMCA	1 (0.72)
ACC/AHA lesion types	n=125
Type A	49 (39.2)
Type B1	42 (33.6)
Type B2	5 (4.0)
Type C	29 (23.2)
Average stent length, mm	26.02±9.24
Average stent diameter, mm	2.97±0.36
Diameter, mm	
2.25	2 (1.44)
2.50	23 (16.55)
2.75	36 (25.90)
3.00	41 (29.50)
3.50	37 (26.62)
Length, mm	
13	9 (6.47)
16	22 (15.83)
19	21 (15.11)
24	29 (20.86)
29	14 (10.07)
32	16 (11.51)
37	7 (5.04)
40	15 (10.79)
44	3 (2.16)
48	3 (2.16)
TIMI flow preprocedure	
0	56 (40.29)
1	28 (20.14)
2	55 (39.57)
3	0 (0)
TIMI flow post-procedure	
0	0 (0)
1	0 (0)
2	1 (0.72)
3	138 (99.28)
Predilatation	92 (66.19)
Post-dilatation	108 (77.70)
LVEF, %	50.06±9.65
Diameter stenosis, %	87.43±11.38
Procedure access site	
Femoral – right	41 (34.75)
Radial – right	75 (63.56)
Radial – left	2 (1.69)
Contrast media used	
Ionic	20 (16.95)
Non-ionic	98 (83.05)
Procedural success	118 (100)
Device success	118 (100)

Values are n, n (%) or mean±standard deviation. *One lesion was treated with two Evermine50 EES (Meril Life Sciences Pvt. Ltd). ACC: American College of Cardiology; AHA: American Heart Association; EES: everolimus-eluting stent; LAD: left anterior descending artery; LCx: left circumflex artery; LMCA: left main coronary artery; LPDA: left posterior descending artery; LVEF: left ventricular ejection fraction; OM1: first obtuse marginal; RCA: right coronary artery; TIMI: Thrombolysis in Myocardial Infarction

success in preventing ST. ST has always been reported in a higher number of patients implanted with an early-generation DES as compared to BMS. Evermine50 EES, in contrast, has the thinnest strut thickness (50 µm) of currently available devices, which allows streamlining of the flow of blood, minimising platelet aggregation around the stent, and thus reducing the chances of ST[5].

In a retrospective study on the treatment of very long coronary artery stenoses (>30 mm) by Patra et al 2020, the Evermine50 EES was compared with the Tetrilimus (Sahajanand Medical Technologies Limited), and it was observed that the results reported for the Evermine50 EES were comparable to those with the Tetrilimus in terms of MACE, MI, ST, and target lesion revascularisation (TLR), and all-cause mortality was approximately 3% in both groups, with zero reports of MI, ST and TLR[5].

Shiomi et al 2019 reported the outcomes of the RESET trial, where they compared outcomes of CYPHER SELECT Plus (Cordis), a first-generation sirolimus-eluting stent (SES), with those of XIENCE V (Abbott), a second-generation EES, up to 7 years[9]. Although target vessel revascularisation (TVR) was not significantly different between the two groups (11.7% for SES and 10.2% for EES), the second-generation EES provided a lower risk of ST than the first-generation SES. The authors concluded that the second-generation EES could provide longer-term improved safety compared to the first-generation SES. Moreover, Panoulas et al 2015 analysed the inception and evolution of various EES platforms and emphasised the superior efficacy and safety of EES over BMS and DES such as paclitaxel-eluting stents and SES[10].

Picard et al 2019, in a systematic review and meta-analysis, examined and compared the safety and efficacy of

Table 3. Cumulative clinical events up to 24-month follow-up.

Clinical events	Post-procedure	1 month	6 months	12 months[#]	24 months[$@]
	n=118	n=118	n=118	n=117	n=115
All-cause death	0 (0)	0 (0)	1 (0.85)	1 (0.85)	1 (0.87)
Cardiac death	0 (0)	0 (0)	1 (0.85)	1 (0.85)	1 (0.87)
Non-cardiac death	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
MI	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
CD-TLR	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
ID-TLR	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
ID-TVR	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
ST	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
MACE	0 (0)	0 (0)	1 (0.85)	1 (0.85)	1 (0.87)

Values are n (%). [#]1 patient was lost to follow-up at 12 months; [$]1 additional patient was lost to follow-up at 24 months; [@]1 patient withdrew consent at 24-month follow-up. CD-TLR: clinically driven target lesion revascularisation; ID-TLR: ischaemia-driven target lesion revascularisation; ID-TVR: ischaemia-driven target vessel revascularisation; MACE: major adverse cardiac events; MI: myocardial infarction; ST: stent thrombosis

Table 4. Quantitative coronary angiography analysis by an independent core lab at a mean follow-up of 12 months.

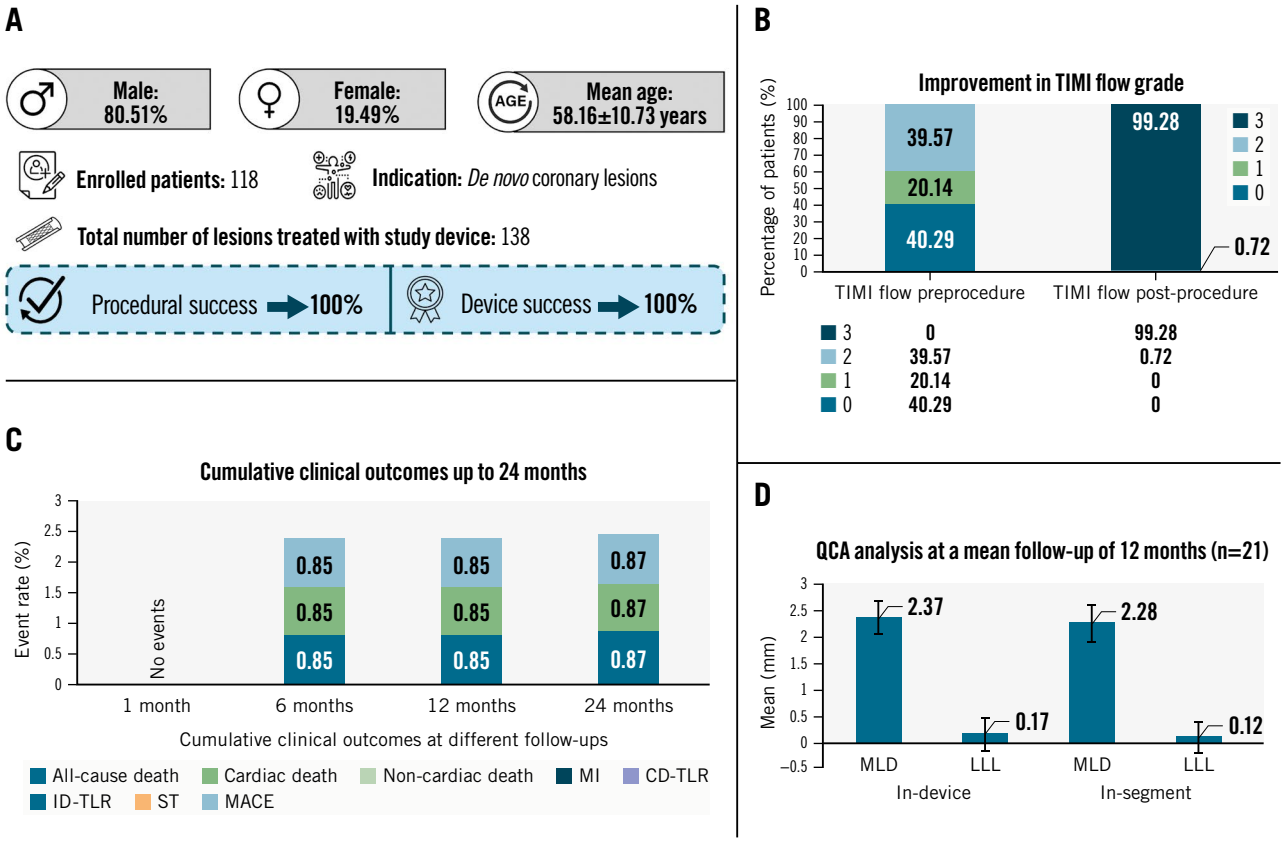
Parameters	Preprocedure (n=21)	Post-procedure (n=21)	12-month mean follow-up (n=21)	*p*-value (preprocedure vs 12-month follow-up)
In-device				
MLD (mm)	0.50±0.43	2.54±0.34	2.37±0.32	<0.0001
LLL (mm)	-	-	0.17±0.31	-
In-segment				
MLD (mm)	0.50±0.43	2.41±0.37	2.28±0.37	<0.0001
LLL (mm)	-	-	0.12±0.31	-

Values are mean±SD. LLL: late lumen loss; MLD: minimal lumen diameter; SD: standard deviation

biodegradable-polymer EES with durable-polymer DES[11]. A total of 4,631 patients were included in the analysis, of whom 2,315 patients were included in the biodegradable-polymer EES group and 2,316 patients in the durable-polymer DES group (1,143 patients were treated with an EES and 1,173 patients were treated with a zotarolimus-eluting stent). The baseline characteristics of the patients were similar in both groups except for the higher prevalence of prior MI in the durable-polymer DES group than the biodegradable-polymer EES group (25.7% vs 22.5%; p=0.001). Similarly, the procedural characteristics were also comparable except for the slightly longer lesion length in the biodegradable-polymer EES group compared to the durable-polymer DES group (15.1 mm vs 14.9 mm; p=0.04). No other significant differences were observed in clinical outcomes – cardiac mortality, MI, any TLR, ST or any MACE. The TALENT trial enrolled 1,435 patients to compare the safety and efficacy of Supraflex (an SES with ultrathin struts; Sahajanand Medical Technologies Ltd.) with XIENCE up to 3-year follow-up[12]. The study confirmed the safety and efficacy of the Supraflex stent as equal to those of the XIENCE stent. On the other hand, the CASTLE trial was conducted to compare an ultrathin biodegradable-polymer SES (BP-SES) with a thin durable-polymer EES (DP-EES) for a 1-year follow-up period[13]. The study demonstrated that DP-EES was non-inferior to BP-SES based on target lesion failure, and the strut thickness differences among DES have a minimal effect on clinical outcomes.

The BIOSCIENCE randomised trial was conducted to compare the ultrathin (60 µm) BP-SES (Orsiro) and the DP-EES (XIENCE Prime/Xpedition [Abbott]) and reported all-cause mortality for the SES and EES to be 14.1% and 10.3%, respectively. Hence, results were found to be better for ultrathin BP-SES[14]. In another study, Jiménez et al compared the 80 µm biodegradable-polymer Ultimaster SES (Terumo) with a XIENCE EES, and they found no significant differences between the two devices in terms of cardiac death, ST and MI[15]. Similar results are reported in the present study, where the absence of ST, MI, CD-TLR, ID-TLR and ID-TVR was observed. This implies that newer stents with thinner struts improve clinical outcomes in patients suffering from multiple and complex lesions. Moreover, Evermine50 EES showed an absence of MI, CD-TLR and a lower rate of cardiac death, which thereby resulted in a lower MACE rate, compared to previous studies on other devices, proving the safety and performance of the ultrathin-strut EES stent. There was significant improvement in MLD from preprocedure to mean follow-up (in device: 0.50±0.43 mm vs 2.37±0.32 mm) with an acceptable range of LLL.

CENTRAL **ILLUSTRATION** **Evermine50 EES-1 study: results from the 24-month follow-up.**



Over 24 months, satisfactory results were obtained for all patients in terms of safety and performance of the ultrathin Evermine50 EES with a low MACE rate and absence of MI, CD-TLR, ID-TLR, ID-TVR and ST events. A) Demographic and procedural details; B) pre- and postprocedural TIMI flow grades; C) clinical outcomes up to 24-month follow-up; D) QCA analysis at a mean follow-up of 12 months. CD-TLR: clinically driven target lesion revascularisation; EES: everolimus-eluting stent; ID-TLR: ischemia-driven target lesion revascularisation; ID-TVR: ischemia-driven target vessel revascularisation; LLL: late lumen loss; MACE: major adverse cardiac events; MI: myocardial infarction; MLD: minimal lumen diameter; QCA: quantitative coronary angiography; ST: stent thrombosis; TIMI: Thrombolysis in Myocardial Infarction

Limitations

Our study has a few limitations; the first is the lack of optical coherence tomography analysis data for all patients due to a small patient pool at the sites. However, QCA was performed at a mean follow-up of 12 months in order to assess the LLL. Secondly, this is a single-arm study with 24 months of follow-up. Further long-term randomised controlled trials including a larger patient population with complex lesion types are needed to compare the Evermine50 EES with other contemporary DES in real-world populations.

Conclusions

This long-term (24-month) follow-up study reiterates that the Evermine50 EES has favourable safety and performance in treating real-world CAD patients suffering from long and multiple lesions, showing improved TIMI flow and low MACE with an absence of ST, ID-TLR, ID-TVR and CD-TLR.

Impact on daily practice

The second-generation drug-eluting stents (DES) were associated with a higher risk of major adverse cardiac events, stent thrombosis and late restenosis in some cases, and the possible reason was often ascribed to the thicker strut size. Thus emerged the need for thinner struts and an advanced generation of DES. Research showed that reducing the strut thickness to a minimum can minimise the adverse outcomes. The midterm outcomes of this everolimus-eluting stent will impact the practice of cardiologists in treating long and multiple *de novo* coronary artery lesions.

Funding

The Evermine50 EES-1 study was funded by Meril Life Sciences Pvt. Ltd, Gujarat, India.

Conflict of interest statement

A. Thakkar is a full-time employee of Meril Life Sciences Pvt. Ltd. The other authors have no conflicts of interest to declare.

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AsiaIntervention 2024;10:203-211

Impact of acute coronary syndrome on early in-stent neoatherosclerosis as shown by optical coherence tomography

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KEYWORDS

- ACS/NSTE-ACS
- drug-eluting stent
- optical coherence tomography
- stable angina

Abstract

Background: Patients with acute coronary syndrome (ACS) have a higher risk of requiring target vessel revascularisation after percutaneous coronary intervention (PCI) than patients with stable angina. Neoatherosclerosis is a significant risk factor for very late stent thrombosis, and the presence of neoatherosclerosis is independently associated with major adverse cardiac events.

Aims: In this study, we used optical coherence tomography (OCT) to investigate the impact of ACS on neoatherosclerosis within 1 year after PCI.

Methods: We investigated 102 patients (122 lesions) who had undergone PCI using a second-generation drug-eluting stent (DES) from March 2017 to November 2020 and were followed up with OCT within 1 year. The patients were categorised into the ACS group or non-ACS group according to their clinical findings at the time of target lesion treatment. We used OCT to investigate the presence of neoatherosclerosis.

Results: The ACS group comprised 23 (22.5%) patients. There were no differences in the patients' clinical characteristics between the groups. The total stent length tended to be shorter in the ACS group than in the non-ACS group (24 mm vs 32 mm, respectively; p=0.09), but this difference was not statistically significant. The median duration from PCI was 290 days. Neoatherosclerosis was more frequent in ACS lesions (39% vs 4%; p<0.01), and implantation of a DES in ACS lesions was an independent predictor of neoatherosclerosis occurrence (odds ratio 9.70; p<0.01).

Conclusions: This observational study using OCT indicates that stenting for ACS lesions is associated with early in-stent neoatherosclerosis.

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SUBMITTED ON 09/04/2024 - REVISION RECEIVED ON 07/05/2024 - ACCEPTED ON 15/05/2024

DOI: 10.4244/AIJ-D-24-00021

Abbreviations

ACS	acute coronary syndrome
BMS	bare metal stent
DES	drug-eluting stent
ISR	in-stent restenosis
IVUS	intravascular ultrasound
LDL	low-density lipoprotein
NA	neoatherosclerosis
OCT	optical coherence tomography
PCI	percutaneous coronary intervention
PCSK9	proprotein convertase subtilisin/kexin type 9
RAS	renin-angiotensin system

Introduction

Patients with acute coronary syndrome (ACS) generally have a higher risk of revascularisation after percutaneous coronary intervention (PCI) and a worse long-term prognosis than patients with stable angina[1]. The incidence of cardiovascular events in the PACIFIC study, a prospective multicentre ACS registry in Japan, was more than twice the incidence in all patients with coronary artery disease (>35/1,000 vs 4.5-15/1,000 per year, respectively) within 1 year after ACS onset[2,3].

Drug-eluting stents (DES) are frequently used regardless of the presence of ACS[3]. Although a DES can more effectively reduce the risk of in-stent restenosis (ISR) than a bare metal stent (BMS), DES are associated with specific complications, such as delayed thrombosis after DES implantation (late or very late stent thrombosis). Neoatherosclerosis (NA), the development of new atherosclerotic lesions at the site of stent implantation[4], is thought to be one of the causes of thrombosis in these cases. Optical coherence tomography (OCT) is one of the most effective imaging modalities with which to detect atherosclerotic changes within the neointima[5]. Researchers who observed ISR lesions using OCT reported that significantly unstable lesions (thin-cap fibroatheroma-containing neointima, neointimal rupture, and thrombi) were observed in patients with unstable angina after DES implantation[5]. We hypothesised that because DES implantation in unstable lesions causes early NA, patients with ACS may have a higher adverse event rate after PCI. However, most studies to date have focused on OCT observation of ISR lesions, involved a long period of time from stent implantation to in-stent evaluation, and utilised first-generation DES.

In this study, we used OCT to compare the in-stent findings at 1 year in patients with and without ACS treated with a second-generation DES.

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Methods

STUDY POPULATION

In total, 703 patients who underwent PCI at our institution from March 2017 to November 2020 were retrospectively identified. Among them, 359 patients (484 lesions) were selected for this study after excluding patients without newly stented lesions. Of these, 102 patients (122 lesions) who were followed up with in-stent observation using OCT were enrolled. Patients who had undergone PCI <90 or >366 days prior to in-stent OCT observation were excluded. Patients who underwent in-stent observation using intravascular ultrasound (IVUS) were also excluded **(Figure 1)**. If a patient had 2 or more lesions, only the first lesion treated was included in the lesion analysis. This study was approved by the Ethics Committee of Osaka Metropolitan University Graduate School of Medicine, Osaka, Japan (approval number: 2020-271) and performed in accordance with the Declaration of Helsinki.

INTRAVASCULAR ULTRASOUND/OPTICAL COHERENCE TOMOGRAPHY IMAGE ACQUISITION

IVUS images were acquired using an AltaView imaging catheter (Terumo) or OptiCross imaging catheter (Boston Scientific). OCT image acquisition was performed using a FastView catheter (Terumo) with the Lunawave optical frequency domain imaging system (Terumo) or a Dragonfly JP catheter (Abbott) with the ILUMIEN OPTIS imaging system (Abbott). The OCT catheter was pulled back at a rate of 20 mm/s. Contrast medium was continuously flushed through a guiding catheter at a rate of 3 mL/s for a duration of 4 to 5 seconds. Continuous images were acquired and stored digitally for analysis.

OPTICAL COHERENCE TOMOGRAPHY IMAGING ANALYSIS

The criteria for the diagnosis of NA were lesions with lipid-laden neointima, neointima with calcification, a thin-cap fibroatheroma-like neointima, or neointimal rupture. Lipid-laden neointima was defined as a signal-poor region with diffuse borders, and neointima with calcification was defined as a well-delineated, signal-poor region with sharp borders **(Figure 2)**. The lipid arc was measured at every 1 mm interval, and the plaque length was measured. The lipid volume index was then calculated as the mean lipid arc multiplied by the lipid core length, with the length being

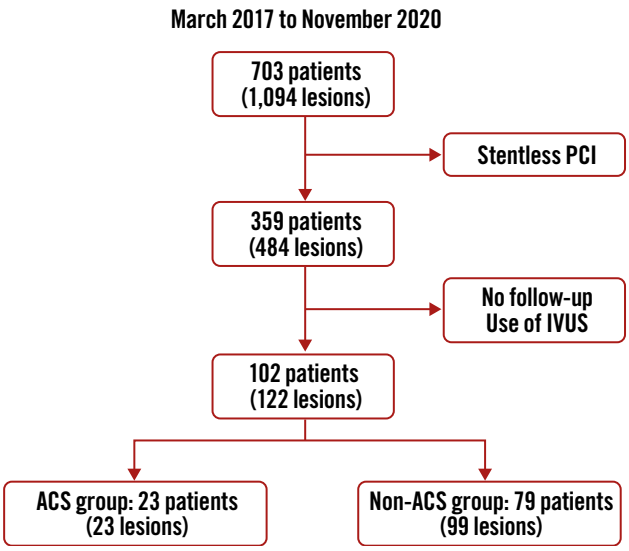

Figure 1. *Study flow diagram. ACS: acute coronary syndrome; IVUS: intravascular ultrasound; PCI: percutaneous coronary intervention*

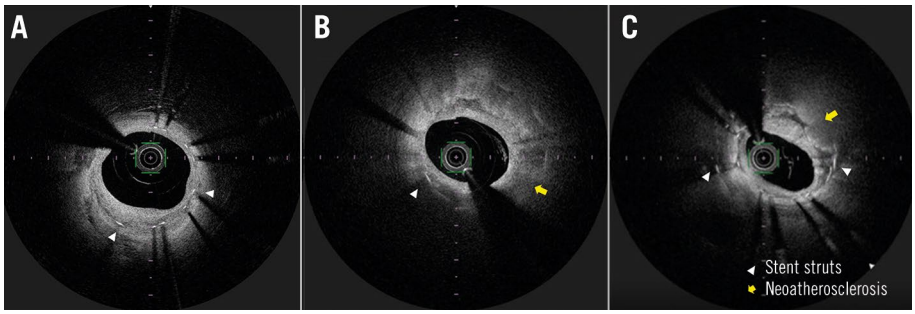

Figure 2. *Representative optical coherence tomography images of neointima and neoatherosclerosis. A) Image of normal neointima. Homogeneous tissue deposits are present inside the stent struts. B) Image of lipid neoatherosclerosis. Heterogeneous tissue deposits with posterior attenuation (yellow arrow) are present. C) Image of calcified neoatherosclerosis. Bright protruding tissue with an irregular surface (yellow arrow) is present.*

defined as that containing >90 degrees of lipid[6]. The localisation and properties of NA were examined by 3 investigators (K. Nakao, T. Yamaguchi, and T. Yamazaki), and lipid NA was analysed by three investigators (N. Fujisawa, K. Otsuka, and T. Yamazaki).

STATISTICAL ANALYSIS

The data are expressed as median (interquartile range). Comparisons between the 2 groups were performed with the Mann-Whitney U test or Fisher's exact probability test, and differences in means were tested at the critical level of ≤5%. Multivariate analysis was performed with logistic regression. All data were analysed using SPSS software, version 27.0.1.0 (IBM).

Results

This retrospective cross-sectional study conducted at a median of 290 days after DES implantation revealed that NA occurred significantly more often with stents placed in ACS lesions (39% vs 6%; p<0.01) **(Table 1)**. NA was observed in 12 patients, including 3 (4%) in the non-ACS group and 9 (39%) in the ACS group **(Central illustration)**.

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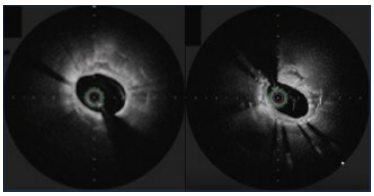
CENTRAL **ILLUSTRATION** **ACS is an independent predictor of neoatherosclerosis one year after 2nd-generation DES implantation.**



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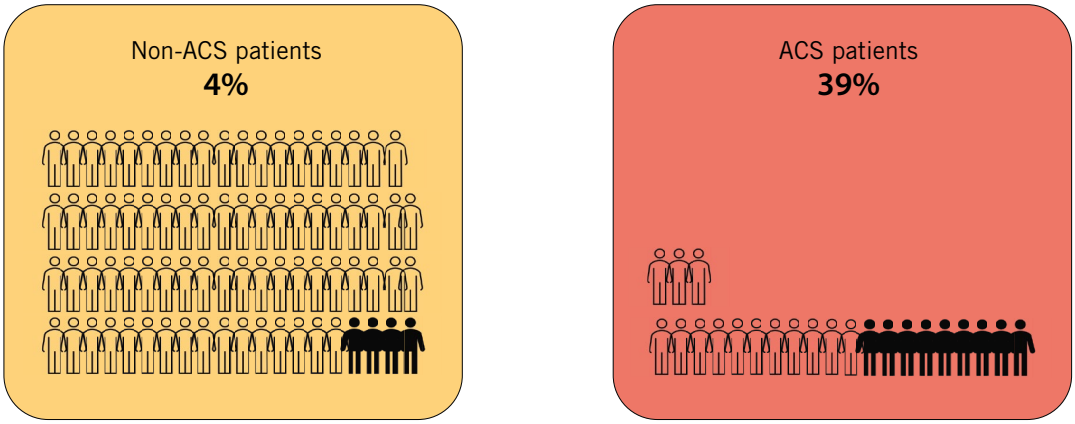

ACS: acute coronary syndrome; DES: drug-eluting stent; OR: odds ratio

In this study, we surveyed 102 patients (23 with ACS and 79 without ACS). All patients had been receiving dual antiplatelet therapy with 2 oral antiplatelet agents for at least 6 months after PCI. The patients' profiles and main laboratory data are summarised in **Table 2**. There was no significant difference in the history of PCI, but significantly more patients in the ACS than non-ACS group had a history of ACS (39% vs 11%, respectively; p<0.01).

Table 3 shows the medication and laboratory data at follow-up. Overall, control of the low-density lipoprotein (LDL) cholesterol level was good in both groups. The ACS group received significantly more proprotein convertase subtilisin/kexin type 9

Table 1. Lesion characteristics.

	Total (n=102)	Non-ACS (n=79)	ACS (n=23)	*p*-value
Baseline				
Lesion location				
LAD	65 (64)	52 (66)	13 (57)	0.46
LCx	14 (14)	12 (15)	2 (9)	0.73
RCA	20 (20)	12 (15)	8 (35)	0.07
Including LMCA	5 (5)	5 (6)	0	0.59
Lesion type				
Type A	0 (0)	0 (0)	0 (0)	
Type B1	4 (4)	3 (4)	1 (4)	1
Type B2	32 (31)	24 (30)	8 (35)	0.8
Type C	66 (65)	52 (66)	14 (61)	0.81
Chronic total occlusion	7 (7)	6 (8)	1 (4)	1
Debulking				
Rotablator	26 (26)	20 (25)	6 (26)	1
OAS	4 (4)	4 (5)	0 (0)	0.57
DCA	2 (2)	2 (3)	0 (0)	1
Type of stent				
Stent material and drug agent				
CoCr everolimus-eluting stent	24 (24)	20 (25)	4 (17)	0.58
Sirolimus-eluting stent	23 (23)	19 (24)	4 (17)	0.58
PtCr everolimus-eluting stent	43 (42)	34 (43)	9 (42)	0.81
Zotarolimus-eluting stent	8 (8)	4 (6)	4 (17)	0.07
Other	4 (4)	2 (3)	2 (9)	0.22
Drug delivery technology				
DP-DES	32 (31)	24 (30)	8 (35)	0.8
BP-DES	68 (67)	55 (70)	13 (57)	0.31
Other	2 (2)	0 (0)	2 (9)	<0.05
Stent size				
Stent diameter, mm	3.00 (2.75-3.50)	3.00 (2.75-3.50)	3.00 (3.00-3.50)	0.06
Stent length, mm	24 (20-33)	28 (20-34)	23 (18-24)	0.06
Number of stents	1 (1-1)	1 (1-1)	1 (1-1)	0.82
Total stent length, mm	28 (23-38)	32 (23-32)	24 (20-35)	0.09
PCI imaging				
IVUS	44 (44)	31 (39)	13 (57)	0.49
OCT/OFDI	57 (56)	48 (60)	10 (43)	0.49
Follow-up				
Duration, days	294 (257-337)	301 (260-339)	287 (254-321)	0.41
Neoatherosclerosis	12 (12)	3 (4)	9 (39)	<0.01

Values are presented as n (%) or median with interquartile range (25%-75%). BP-DES: bioabsorbable-polymer drug-eluting stent; CoCr: cobalt-chromium; DCA: directional coronary atherectomy; DP-DES: durable-polymer drug-eluting stent; IVUS: intravascular ultrasound; LAD: left anterior descending artery; LCx: left circumflex artery; LMCA: left main coronary artery; OAS: orbital atherectomy system; OCT: optical coherence tomography; OFDI: optical frequency domain imaging; PCI: percutaneous coronary intervention; PtCr: platinum-chromium; RCA: right coronary artery

(PCSK9) inhibitor therapy (p=0.01) and tended to have higher high-sensitivity C-reactive protein levels (p=0.05).

Table 1 shows the target lesion characteristics. The median duration from PCI to follow-up was 287 days in the ACS group and 301 days in the non-ACS group. The ACS group had a higher percentage of patients in whom the right coronary artery was the culprit vessel, but there were no significant differences in lesion characteristics at the time of PCI or during the post-stenting imaging evaluation. **Table 4** shows the measurable post-intervention quantitative intravascular imaging data. The distal reference lumen area was significantly lower in the non-ACS group, and the minimum stent area (MSA) tended to be higher in

Table 2. Baseline clinical characteristics.

	Total (n=102)	Non-ACS (n=79)	ACS (n=23)	*p*-value
Age, years	71 (65-78)	71 (65-77)	74 (69-80)	0.19
Male	79 (77)	64 (81)	15 (65)	0.16
Hypertension	75 (74)	60 (76)	15 (65)	0.42
Hypercholesterolaemia	74 (73)	58 (73)	16 (70)	0.79
Diabetes mellitus	41 (40)	34 (43)	7 (30)	0.34
Haemodialysis	6 (6)	3 (4)	3 (13)	0.13
Previous coronary angioplasty	31 (30)	25 (30)	6 (30)	0.8
Previous coronary artery bypass	2 (2)	1 (1)	1 (4)	0.4
Previous ACS	18 (17)	9 (11)	9 (39)	<0.01
CPA	3 (3)	2 (3)	1 (4)	0.54
Medication				
Statin	56 (55)	46 (58)	10 (43)	0.24
ACEi or ARB	49 (48)	40 (51)	9 (39)	0.35
PCSK9 inhibitor	2 (2)	0 (0)	2 (9)	0.05
Angina status				
Stable	79 (77)			
Acute coronary syndrome	23 (21)		23 (100)	
STEMI	8 (8)		8 (35)	
NSTEMI or UAP	15 (15)		15 (65)	
Laboratory data				
WBC, /μL	6,671 (5,200-7,400)	6,300 (5,200-7,500)	5,900 (5,000-7,200)	0.72
Hb, g/dL	13.4 (12.5-14.7)	13.7 (12.6-15.0)	12.7 (11.6-14.3)	0.22
hs-CRP, mg/dL	0.11 (0.05-0.29)	0.11 (0.05-0.29)	0.07 (0.04-0.57)	0.73
BUN, mg/dL	17.5 (14-23)	18 (14-23)	17 (14-29)	0.9
Creatinine, mg/dL	0.9 (0.8-1.1)	0.9 (0.76-1.09)	0.87 (0.75-1.23)	0.95
eGFR, ml/min/1.73m^2	61 (48-74)	61 (49-74)	58 (32-69)	0.42
UA, mg/dL	5.8 (4.8-6.7)	5.9 (4.9-6.8)	5.0 (4.2-6.1)	0.37
Triglyceride, mg/dL	110 (86-174)	110 (87-184)	125 (62-164)	0.67
Total cholesterol, mg/dL	164 (136-188)	162 (136-180)	178 (146-208)	0.24
HDL cholesterol, mg/dL	49 (39-59)	47 (38-57)	51 (42-60)	0.7
LDL cholesterol, mg/dL	88 (73-117)	88 (70-114)	100 (75-125)	0.24
Non-HDL cholesterol, mg/dL	114 (91-142)	109 (90-132)	125 (97-152)	0.13
FBS, mg/dL	103 (94-129)	101 (94-125)	110 (93-136)	0.18
HbA1c, %	6.0 (5.7-6.6)	6.0 (5.7-6.4)	6.1 (5.6-7.0)	0.2
hs-cTnT, ng/mL	15 (8-30)	10 (8-16)	19 (8-39)	0.2
BNP, pg/mL	46 (21-120)	44 (17-92)	51 (25-51)	0.17
Lp(a), mg/dL	11 (5-15)	11 (5-14)	15 (7-39)	0.11

Values are presented as n (%) or median with interquartile range (25%-75%). ACEi: angiotensin-converting enzyme inhibitor; ACS: acute coronary syndrome; ARB: angiotensin II receptor blocker; BNP: brain natriuretic peptide; BUN: blood urea nitrogen; CPA: cardiopulmonary arrest; eGFR: estimated glomerular filtration rate; FBS: fasting blood sugar; Hb: haemoglobin; HbA1c: haemoglobin A1c; HDL: high-density lipoprotein; hs-CRP: high-sensitivity C-reactive protein; hs-cTnT: high-sensitivity cardiac troponin T; LDL: low-density lipoprotein; Lp: lipoprotein; PCSK9: proprotein convertase subtilisin/kexin type 9; NSTEMI: non-ST-segment elevation myocardial infarction; STEMI: ST-segment elevation myocardial infarction; UA: uric acid; UAP: unstable angina pectoris; WBC: white blood cells

Table 3. Medication and laboratory data at follow-up.

	Total (n=102)	Non-ACS (n=79)	ACS (n=23)	*p*-value
Medication				
Statin	94 (92)	74 (94)	20 (87)	0.38
ACEi/ARB	60 (59)	49 (62)	11 (48)	0.24
PCSK9 inhibitor	8 (8)	3 (4)	5 (22)	0.01
Laboratory data				
WBC, /μL	6,000 (5,075-7,000)	6,000 (5,100-7,075)	5,650 (4,275-6,300)	0.43
Hb, g/dL	13.5 (12.2-14.5)	13.5 (12.2-14.6)	12.9 (12.2-14.5)	0.58
hs-CRP, mg/dL	0.07 (0.03-0.16)	0.06 (0.03-0.110)	0.11 (0.04-0.55)	0.05
BUN, mg/dL	18 (15-22)	18 (15-22)	22 (18- 26)	0.72
Creatinine, mg/dL	0.9 (0.8-1.1)	0.9 (0.7-1.1)	0.9 (0.7-4.5)	0.9
eGFR, ml/min/1.73 m^2	62 (48-73)	60 (50-73)	55 (15-76)	0.41
UA, mg/dL	5.4 (4.4-6.4)	5.2 (4.5-6.6)	4.8 (3.8-6.0)	0.1
Triglyceride, mg/dL	109 (79-168)	103 (80-171)	118 (88-178)	0.84
Total cholesterol, mg/dL	144 (126-163)	138 (123-156)	145 (135-167)	0.31
HDL cholesterol, mg/dL	52 (40-60)	51 (39-59)	53 (44-62)	0.45
LDL cholesterol, mg/dL	67 (55-82)	66 (52-80)	67 (61-86)	0.61
Non-HDL cholesterol, mg/dL	95 (79-106)	93 (73-104)	98 (85-104)	0.52
FBS, mg/dL	103 (92-122)	104 (90-121)	126 (92-134)	0.74
HbA1c, %	6.1 (5.8-6.7)	6.1 (5.8-6.8)	6.3 (5.7-7.4)	0.79
BNP, pg/mL	32 (15-65)	39 (13-76)	31 (16-134)	0.46
Lp(a), mg/dL	11 (5-20)	10 (4-20)	18 (6-44)	0.14

Values are presented as n (%) or median with interquartile range (25%-75%). ACEi: angiotensin-converting enzyme inhibitor; ACS: acute coronary syndrome; ARB: angiotensin II receptor blocker; BNP: brain natriuretic peptide; BUN: blood urea nitrogen; eGFR: estimated glomerular filtration rate; FBS: fasting blood sugar; Hb: haemoglobin; HbA1c: haemoglobin A1c; HDL: high-density lipoprotein; hs-CRP: high-sensitivity C-reactive protein; LDL: low-density lipoprotein; Lp: lipoprotein; NSTEMI: non-ST-segment elevation myocardial infarction; PCSK9: proprotein convertase subtilisin/kexin type 9; STEMI: ST-segment elevation myocardial infarction; UA: uric acid; WBC: white blood cells

Table 4. Post-intervention quantitative intravascular imaging data.

	Total (n=97)	Non-ACS (n=77)	ACS (n=20)	*p*-value
Distal reference lumen area, mm^2	5.71 (4.37-7.78)	5.41 (4.08-7.18)	6.57 (4.93-8.85)	0.04
Proximal reference lumen area, mm^2	8.23 (6.35-9.70)	8.26 (6.35-9.78)	7.67 (5.98-9.23)	0.74
MSA, mm^2	5.40 (3.84-6.22)	5.12 (3.71-6.07)	5.80 (4.65-7.94)	0.06
Conventional stent expansion, %	75.5 (64.7-85.4)	75.1 (64.0-84.5)	82.3 (70.0-90.3)	0.58
MSA by distal reference lumen area, %	93.9 (79.6-102.9)	93.9 (80.8-104.2)	94.8 (78.5-100.2)	0.1
Malapposition	21 (22)	17 (22)	4 (20)	0.19
Protrusion	21 (22)	14 (18)	7 (35)	0.79
Landing zone disease				
Edge dissection	20 (21)	18 (23)	2 (10)	0.73
On the calcified lesion	20 (21)	12 (16)	8 (40)	0.6

Values are presented as n (%) or median with interquartile range (25%-75%). Conventional stent expansion is calculated as follows: MSA/average reference lumen area×100 (with the average reference lumen area calculated as follows: 1/2 [proximal reference lumen area+distal reference lumen area]). MSA by distal reference lumen area is calculated as MSA/distal reference lumen area×100. ACS: acute coronary syndrome; MSA: minimum stent area

the ACS group. No significant differences were observed in stent expansion or stent landing zone.

We performed univariate and multivariate analyses of factors predicting the occurrence of NA, dividing them into patient background factors and lesion characteristics **(Table 5)**. Both analyses showed a high odds ratio (OR) for stent implantation in patients with ACS. No trends were observed in terms of stent material or drugs.

Regarding the NA characteristics observed on OCT, 10 lesions contained lipid and 2 had calcification. We compared the properties of lipid NA between the ACS and non-ACS groups, but no significant differences were observed **(Table 6)**.

Table 5. Univariate and multivariate analyses to predict neoatherosclerosis based on patient and lesion characteristics at follow-up.

	Univariate			Multivariate model 1			Multivariate model 2			Multivariate model 3		
	OR	95% CI	*p*-value	OR	95% CI	*p*-value	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Stent implantation for ACS	16.29	3.92-67.75	<0.01	17.11	4.03-72.64	<0.01	12.62	2.89-54.99	<0.01	15.12	3.53-64.78	<0.01
Age	1	0.94-1.06	0.87	0.98	0.92-1.05	0.56						
LDL cholesterol	1.02	0.99-1.04	0.24									
Statin	0.36	0.06-2.01	0.24									
PCSK9 inhibitor	8.09	0.47-138.72	0.15									
hs-CRP	3.51	1.18-10.44	0.02				2.24	0.70-7.52	0.18			
eGFR	0.97	0.95-1.00	0.03							0.98	0.95-1.01	0.1
Stent diameter	0.7	0.19-2.55	0.58									
Stent length	0.98	0.91-1.05	0.55									
Total stent length	0.98	0.94-1.03	0.46									
RCA lesion	0.8	0.16-3.98	0.79									
Duration of follow-up	1	0.99-1.01	0.88									
DP-DES	1.11	0.31-3.98	0.88									
BP-DES	1	0.28-3.59	1									
Zotarolimus-eluting stent	1.08	0.12-9.61	0.95									
Distal reference lumen area	1	0.77-1.28	0.98									
MSA	0.93	0.68-1.29	0.68									

ACS: acute coronary syndrome; BP-DES: bioabsorbable-polymer drug-eluting stent; CI: confidence interval; DP-DES: durable-polymer drug-eluting stent; eGFR: estimated glomerular filtration rate; hs-CRP: high-sensitivity C-reactive protein; LDL: low-density lipoprotein; MSA: minimum stent area; OR: odds ratio; PCSK9: proprotein convertase subtilisin/kexin type 9; RCA: right coronary artery

Table 6. OCT/OFDI analyses of lipid neoatherosclerosis.

	Total (n=10)	Non-ACS (n=3)	ACS (n=7)	*p*-value
Max lipid arc, °	138	108	152	0.52
Lipid core length, mm	5.6	5.8	5.3	0.83
Lipid volume index	448	422	475	1

Values are presented as median. ACS: acute coronary syndrome; OCT: optical coherence tomography; OFDI: optical frequency domain imaging

Five of the 12 patients with NA observed during follow-up OCT underwent PCI, but they remained event-free for 3 years.

Discussion

This study showed that NA occurred more frequently in ACS lesions than in non-ACS lesions at approximately 1 year of follow-up.

This retrospective cross-sectional study used the occurrence of NA as an outcome. By contrast, other stent follow-up OCT observational studies used clinically driven target lesion revascularisation or clinically driven target vessel revascularisation as an outcome. The results of the present study are considered useful for understanding the process of intimal repair after DES implantation.

In approximately 64% of cases, ACS is caused by thrombosis due to plaque rupture and subsequent platelet aggregation, and this is followed by plaque erosion in 25% of cases. ACS caused by calcified nodules has also recently received attention. In any case, the characteristics of the lesions that cause ACS are different from the characteristics of stable coronary artery lesions[6].

Regarding lipid management, effective control of LDL cholesterol using potent statin therapy is recommended for secondary prevention after PCI[3,7,8]. In the present study, PCI was performed with an LDL cholesterol level of 88 mg/dL and well-controlled lipids. At follow-up, the LDL cholesterol level was controlled at <70 mg/dL in both groups, and PCSK9 inhibitors were also aggressively administered in high-risk patients. Although there is no clear evidence that the LDL cholesterol level is involved in the development of NA, a high LDL cholesterol level has been reported to be an independent predictor of NA incidence and plaque vulnerability in patients with late ISR[9], and LDL cholesterol management is important after PCI. In LDL cholesterol management, a 50% reduction is recommended for secondary prevention of atherosclerotic cardiovascular disease in the USA[7], and a level of <50 mg/dL is recommended in Europe[8]. In the present study, the median LDL cholesterol level was 67 mg/dL (interquartile range [IQR] 55-82 mg/dL), and the reduction rate was 22% (IQR 0-43%), which may have left room for further

therapeutic intervention; however, no correlation was found with the occurrence of NA.

OCT is one of the best intravascular imaging techniques for the diagnosis of NA because of its very high resolution and excellent assessment of lesion characteristics[5]. Gonzalo et al[10] initially classified OCT images with different ISR patterns as layered, homogeneous, and heterogeneous, and Yamamoto et al[11] further classified them into 6 categories. In one study, OCT images of ISR showed more layered and heterogeneous patterns in DES and more homogeneous patterns in BMS[12], suggesting that the neointima of DES and BMS are pathologically different. In a pathological study, Nakazawa et al[13] suggested that DES implantation is strongly associated with the development of NA, whereas patients with BMS implantation rarely develop NA <3 years after implantation but often develop NA >6 years later. NA progression is accelerated in patients who undergo DES implantation <2 years after PCI[8,13], and this may be a cause of thrombosis. An observational OCT study of ISR lesions by Nakamura et al[14] also showed that ISR of DES, including first-generation DES, was an independent predictor of NA. With regard to second-generation DES, a study comparing the lesion characteristics of early (<1 year) and late (>1 year) restenosis showed a higher frequency of uniform neointima in the early group and a significantly higher frequency of lipid-laden thin-cap fibroatheroma, neovascularisation, and macrophage infiltration in the late group[15]. These changes were thought to be due to the delayed arterial healing associated with DES implantation, even with second-generation DES implantation. Most of these previous studies involved lesions that had undergone stenting followed by either clinically driven target lesion revascularisation or clinically driven target vessel revascularisation. However, ours was a cross-sectional study involving the evaluation of lesions at 1 year after implantation of new-generation DES, and our findings may help to elucidate the mechanisms underlying the intimal repair process after DES implantation in ACS lesions.

A similar observational OCT study was performed 1 year after durable-polymer DES and bioabsorbable-polymer DES implantation. The study showed no statistically significant differences between the 2 types of DES, but treatment with renin-angiotensin system (RAS) inhibitors reduced the risk of NA[16]. Additionally, the study did not show that unstable angina or myocardial infarction were predictive factors for the incidence of NA, but this may have been due to differences in the patients' backgrounds and the study design. Regarding the effect of RAS inhibitors on the incidence of NA, the present study showed the opposite trend (OR 2.39; p=0.18). This trend might be explained by our very high-risk patient population or a possible residual risk of NA occurrence that cannot be prevented with RAS inhibitors.

The finding that NA can occur 1 year after DES implantation, even with thorough secondary prevention, indicates that there are still unknown residual risk factors in patients with ACS. Thus, further stent drug delivery technologies need to be developed for ACS lesions.

Limitations

This study had several limitations. First, it was a retrospective, single-centre, observational study. Second, the number of patients with ACS was small. Third, because IVUS was included as an intravascular imaging technique at the time of PCI, measurement errors between OCT and IVUS may have occurred in the assessment of stent malapposition and protrusion immediately after treatment. Fourth, not all post-PCI patients were followed up, resulting in a possible selection bias.

Conclusions

The results of this observational study of OCT follow-up examination after second-generation DES implantation showed that ACS lesions were associated with the development of early NA.

Impact on daily practice

Stent thrombosis due to early neoatherosclerosis is a concern even with the latest generation of drug-eluting stents. The results of this study suggest that stent implantation for acute coronary syndrome lesions is a risk factor for early neoatherosclerosis occurrence. These results may inform future strategies for percutaneous coronary intervention and the development of stents tailored to acute coronary syndrome.

Acknowledgements

We thank Edanz for editing a draft of this manuscript.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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AsiaIntervention 2024;10:212-218

Hybrid strategy of drug-eluting stent and drug-coated balloon in the treatment of *de novo* coronary artery disease: 1-year clinical outcomes

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This paper also includes supplementary data published online at: https://www.asiaintervention.org/doi/10.4244/AIJ-D-23-00066

KEYWORDS

- bifurcation
- diffuse disease
- drug-coated balloon
- drug-eluting stent
- hybrid revascularisation

Abstract

Background: The hybrid strategy of drug-eluting stent (DES) and drug-coated balloon (DCB) has been increasingly accepted for the treatment of *de novo* coronary artery disease. However, data regarding the clinical outcome of this practice in a Southeast Asian population are limited.

Aims: We aimed to investigate the safety and clinical outcome of this hybrid strategy (DES and DCB) in the treatment of *de novo* coronary artery disease. The primary endpoint was target lesion failure (TLF) in the DES/DCB-treated segment at 12 months. TLF is defined as the composite of cardiac death, target vessel myocardial infarction (TVMI) and ischaemia-driven target lesion revascularisation (ID-TLR) in the DES- and/or DCB-treated segment.

Methods: A total of 401 patients with 458 lesions were treated with the hybrid strategy at the National Heart Institute (IJN), Kuala Lumpur, Malaysia, from 1 July 2021 to 30 June 2022, were retrospectively enrolled in the study. A total of 38 patients (9.5%) were lost to subsequent follow-up, and the remaining 363 patients (90.5%) were included in the outcome analysis. Clinical outcomes at 1 year were analysed.

Results: In all, 219 lesions (47.8%) involved the left anterior descending artery, 146 lesions (31.9%) involved the right coronary artery, and 57 lesions (12.4%) involved the left circumflex artery. In all, 87 lesions (19%) were bifurcation lesions. A total of 8 patients (2.2%) had TLF, of whom 3 patients (0.83%) had TVMI, 3 patients (0.83%) had ID-TLR, and 2 patients (0.6%) experienced cardiac death. Four patients died of a non-cardiac cause at 1-year follow-up.

Conclusions: A hybrid strategy of DES and DCB for the treatment of *de novo* coronary artery lesions appears to be feasible and clinically safe according to the 1-year outcomes.

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SUBMITTED ON 29/11/2023 - REVISION RECEIVED ON 1st 25/04/2024 / 2nd 13/06/2024 - ACCEPTED ON 14/06/2024

DOI: 10.4244/AIJ-D-23-00066

Abbreviations

DAPT	dual antiplatelet therapy
DCB	drug-coated balloon
DES	drug-eluting stent
ID-TLR	ischaemia-driven target lesion revascularisation
ISR	in-stent restenosis
IVUS	intravascular ultrasound
LAD	left anterior descending artery
LCx	left circumflex artery
LM	left main artery
MACE	major adverse cardiovascular events
MB	main branch
MI	myocardial infarction
MV	main vessel
MV-MB	main vessel-main branch
Non-LM	non-left main artery
OCT	optical coherence tomography
PCI	percutaneous coronary intervention
POT	proximal optimisation technique
RCA	right coronary artery
SB	side branch
TIMI	Thrombolysis in Myocardial Infarction
TLF	target lesion failure
TVMI	target vessel myocardial infarction

Introduction

Drug-eluting stents (DES) have revolutionised interventional cardiology and have long been established as the standard treatment for percutaneous coronary intervention (PCI). However, concerns remain regarding late adverse events, such as late or very late in-stent restenosis (ISR), even with the new generation of DES. Stent length, stent diameter and overlapping stents are known to be independent predictors of ISR and stent thrombosis[1,2,3].

The use of drug-coated balloons (DCBs) has been gaining acceptance with the concept of "leave nothing behind"[4]. The safety and efficacy of DCBs in *de novo* small and diffuse lesions have been recently shown to be non-inferior to DES[5]. Their benefits are also proven in *de novo* lesions in diabetic and high bleeding risk patients[6].

The option of a hybrid strategy combining a DES and DCB has been gaining increasing acceptance among interventional cardiologists. This strategy is often adopted in complex PCI involving long diffuse lesions or bifurcation lesions. Data regarding clinical outcomes for this practice are still very limited especially among the Southeast Asian population.

The aim of this study is to assess the safety and clinical outcome of the hybrid strategy (DES and DCB) in the treatment of *de novo* coronary artery disease. The primary endpoint was target lesion failure (TLF) in the DES/DCB-treated segment at 12 months. TLF is defined as the composite of cardiac death, target vessel myocardial infarction (TVMI) and ischaemia-driven target lesion revascularisation (ID-TLR) in the DES- and/or DCB-treated segment. The secondary endpoint was all-cause mortality, major adverse cardiovascular events (MACE) and TLF predischarge or within 30 days of the procedure. MACE included acute myocardial infarction, stroke and cardiac death. TLF is defined as the composite of cardiac death, TVMI (excluding periprocedural myocardial infarction) and ID-TLR in the DES- and/or DCB-treated segment.

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Methods

STUDY DESIGN

This is a retrospective, single-centre, observational study of patients who were admitted to the National Heart Institute (IJN), Kuala Lumpur from 1 July 2021 to 30 June 2022 (12 months) for chronic or acute coronary syndrome (ACS). All patients who underwent PCI treatment were screened. Patients who were treated using a hybrid strategy of DES and DCB for *de novo* coronary artery disease were enrolled in the study.

Exclusion criteria were as follows:

1. Patients aged 18 and below.
2. Patients whose PCI was done to treat a segment with ISR.

In our study, the hybrid strategy is defined as a slight overlap of a new-generation DES (usually larger in diameter and located proximally) and a DCB (usually smaller in diameter and located distally) in a single coronary vessel. Bifurcation lesions that were treated with the hybrid strategy, i.e., the main branch was treated with a DES and the side branch was treated with a DCB, were also enrolled in the study.

The recruited subjects were followed up for a year after PCI. Patients lost to follow-up were excluded from the outcome analysis. The study was reviewed by the Clinical Research Department of the Institut Jantung Negara (National Heart Institute) and was approved by the ethics department.

DATA COLLECTION AND STATISTICS

Patients' clinical data were collected from a registry database, patient medical records, electronic medical information system and phone calls. All clinic visits and hospital admissions were reviewed. The indication for PCI was recorded and analysed. All statistics are descriptive. Categorical variables are presented as percentages. Continuous data are presented as mean±standard deviation (SD).

DRUG THERAPY

All patients undergoing PCI were pretreated with a loading dose of dual antiplatelet therapy (DAPT). This consisted of a loading dose of aspirin 300 mg in combination with a $P2Y_{12}$ inhibitor (clopidogrel 300 mg or ticagrelor 180 mg) for patients who were antiplatelet naïve. Patients who were already on these medications continued with their regular doses.

Following the procedure, patients were prescribed 12 months of DAPT with the exception of patients in the high bleeding risk group. In such cases, the duration of DAPT was permitted to be reduced based on the clinical judgement of the treating physician[7]. Additionally, all study patients received standard medical therapy post-procedure including statins, beta blockers and angiotensin receptor blockers.

PCI PROCEDURE

Diagnostic angiography evaluation

All patients who underwent diagnostic coronary angiography were evaluated for coronary artery disease. If PCI was indicated, the decision for treatment with DES only, DCB only or the hybrid strategy was made at the discretion of the operator.

Lesion preparation

Optimal lesion preparation is mandatory for all PCIs. The balloons used included semicompliant, non-compliant and scoring balloons. Intracoronary imaging modalities such as intravascular ultrasound (IVUS) and intracoronary optical coherence tomography (OCT) were employed for further vessel evaluation at the operator's discretion. Additionally, atherectomy techniques, such as rotablation, orbital atherectomy, or intracoronary lithotripsy, were utilised for heavily calcified lesions.

For segments treated with a DCB, vessel preparation adhered to current international recommendations, with a balloon-to-vessel ratio of 0.8-1.0. Following predilation, the DCB segment was assessed, and if residual diameter stenosis was ≤30% and Thrombolysis in Myocardial Infarction (TIMI) 3 flow without flow-limiting dissection was achieved, DCB application ensued[6]. The inflation time for the DCB was set at 30-60 seconds, with a preference for 60 seconds, unless the patient experienced angina or haemodynamic instability due to prolonged ischaemia.

Drug-eluting stents and drug-coated balloons

The selection of the type of new-generation DES and DCB was left to the discretion of the operator. The specific DES and DCBs utilised in our study are listed below:

DRUG-ELUTING STENTS

Everolimus-eluting stents: SYNERGY (Boston Scientific); SYNERGY MEGATRON (Boston Scientific); XIENCE Expedition (Abbott); XIENCE Alpine (Abbott); XIENCE Sierra (Abbott)

Sirolimus-eluting stents: COMBO Plus (OrbusNeich); Cre8 EVO (Alvimedica); Orsiro (Biotronik); Ultimaster (Terumo); Ultimaster Tansei (Terumo)

Zotarolimus-eluting stents: Resolute Onyx (Medtronic)

Biolimus-eluting stents: BioFreedom (Biosensors); BioFreedom Ultra (Biosensors)

DRUG-COATED BALLOONS

Paclitaxel-coated balloons: AGENT (Boston Scientific); RESTORE (Cardionovum); SeQuent Please NEO (B. Braun); Panthera Lux (Biotronik)

Sirolimus-coated balloons: MagicTouch (Concept Medical); SELUTION SLR (MedAlliance)

Post-dilation

Stented segments were postdilated with non-compliant balloons for optimal approximation of the stent.

Bifurcation percutaneous coronary intervention

For bifurcation lesion PCIs, DCBs were designated to address the side branch (SB), while DES were used for the main vessel (MV) and main branch (MB). Following the separate advancement of guidewires into both branches, adequate predilation was performed on each segment before the introduction of the DES and DCB.

After adequate predilation, the SB segment was assessed for residual diameter stenosis ≤30% and TIMI 3 flow without flow-limiting dissection. If these criteria were met, the DCB was introduced into the SB with a slight protrusion into the main branch, followed by inflation for 30-60 seconds (preferably 60 seconds, unless the patient experienced angina or haemodynamic instability due to prolonged ischaemia).

Following DCB inflation in the SB, the procedure continued with stenting of the MV-MB using a new-generation DES. The sequence of deploying the DES into the MV-MB and the DCB into the SB was at the discretion of the operator.

After deploying the DES and DCB, the DES segment was subsequently postdilated using non-compliant balloons to ensure optimal stent apposition. The decision to proceed with further interventions, such as kissing balloon inflation and proximal optimisation technique (POT) together with the sequence of these and repetition, if necessary, was also left to the discretion of the operator. Procedural steps of the bifurcation PCIs (left main [LM] bifurcation and non-LM bifurcation) done with the hybrid strategy were documented. Out of the 87 bifurcation PCIs performed with the hybrid strategy, 84 PCIs were done with the DCB deployed first. Procedural steps and the sequence after DCB and DES deployment are summarised in **Table 1** according to LM and non-LM bifurcation PCI.

The percutaneous coronary intervention was deemed successful if both the MB and SB achieved TIMI 3 flow, with no residual diameter stenosis exceeding 30% at the DCB segment upon final assessment.

Table 1. Procedural steps after implantation of DCB and DES in a hybrid strategy for bifurcation PCI.

Procedural steps	Number of PCI
LM bifurcation PCI	**N=30**
Post-dilate DES segment plus POT	14 (46.7)
Post-dilate DES segment plus KBI	8 (26.7)
Post-dilate DES segment plus KBI-POT	5 (16.6)
Post-dilate DES segment plus POT-KBI-POT	3 (10.0)
Non-LM bifurcation PCI	**N=57**
Post-dilate DES segment only	25 (43.9)
Post-dilate DES segment plus POT	13 (22.8)
Post-dilate DES segment plus KBI	11 (19.2)
Post-dilate DES plus KBI-POT	8 (14.1)

Data are given as n (%). DCB: drug-coated balloon; DES: drug-eluting stent; KBI: kissing balloon inflation; LM: left main artery; PCI: percutaneous coronary intervention; POT: proximal optimisation technique

Results

A total of 401 patients with 458 lesions were included in this study, of whom 38 patients (9.5%) were lost to follow-up. The remaining 363 patients (90.5%) were included in the outcome analysis at 1 year **(Figure 1)**.

BASELINE CHARACTERISTICS

The mean age was 59.7±11.9 years, and 80.5% of the patients were male. In all, 287 patients (71.6%) were hypertensive, 243 patients (60.6%) were diabetic, 224 patients (55.4%) had dyslipidaemia, 78 patients (19.5%) had a history of myocardial infarction, and 93 patients (23.2%) had previously undergone PCI **(Table 2)**.

LESION CHARACTERISTICS

Most of the lesions were complex type C lesions (332 lesions [72.5%]). A total of 125 lesions (26.3%) were type B lesions, of which 100 lesions (21.8%) were B1 and 25 lesions (5.5%) were B2. Only one lesion (0.2%) was type A.

The left anterior descending artery (LAD) was the most commonly treated with the hybrid strategy, with 219 lesions (47.8%). This was followed by the right coronary artery (RCA) with 146 lesions (31.9%) and the left circumflex artery (LCx) with 57 lesions (12.4%).

A total of 35 lesions (7.6%) involved the left main stem (LMS); 33 lesions (7.3%) were LM-LAD lesions where a DES was inserted at the LM-proximal LAD segment and a DCB was used distal to the DES in the LAD, 2 lesions (0.3%) were LM-LCx lesions, and 1 (0.2%) was a saphenous vein graft-obtuse marginal artery lesion.

Overall, 87 lesions (19.0%) were bifurcation lesions, with 43 lesions (9.4%) involving LAD-diagonal bifurcations, 13 lesions (2.8%) involving LCx-obtuse marginal artery bifurcations, and 1 lesion (0.2%) involving the right posterior descending artery-posterior left ventricular artery bifurcation. Thirty lesions (6.6%) were LMS-LAD-LCx bifurcation lesions **(Table 3)**.

PROCEDURE DESCRIPTION

A total of 324 patients (80.8%) were admitted electively, while 77 patients were admitted for ACS, of whom 46 patients (11.5%) had non-ST-segment elevation myocardial infarction or unstable angina, and 31 patients (7.7%) had ST-segment elevation myocardial

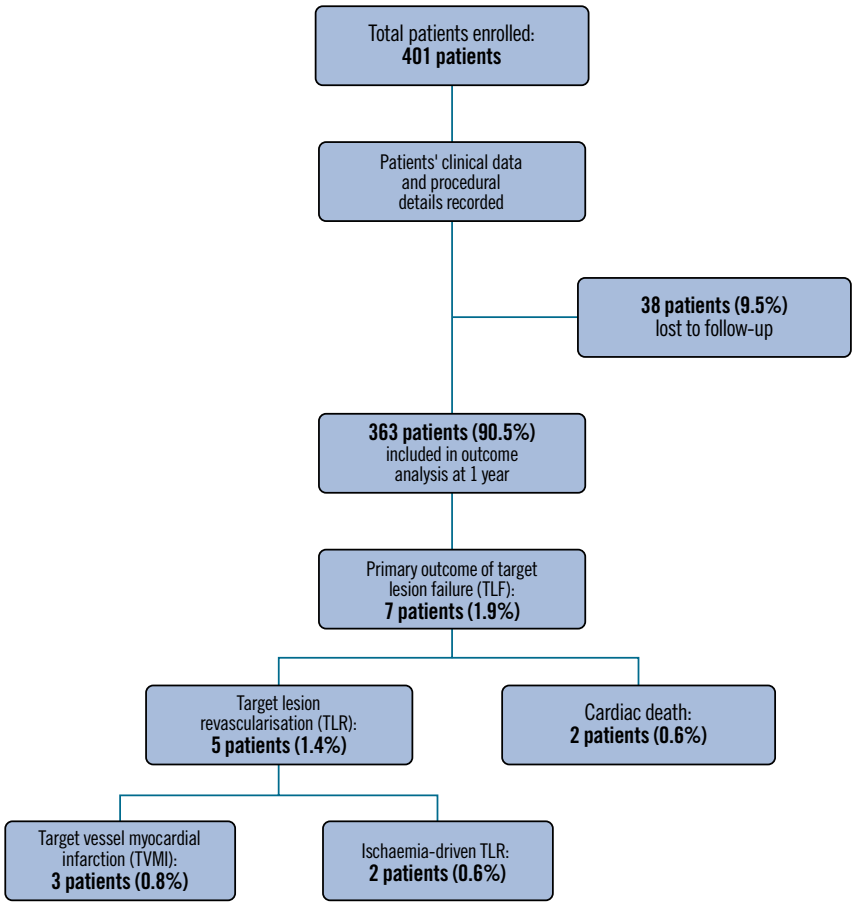

Figure 1. *Study flowchart and results. A total of 401 patients were enrolled into the study. All patients' clinical data and procedural details were recorded. In all, 38 patients (9.5%) were lost to follow-up and were excluded from the outcome analysis. A total of 363 patients (90.5%) completed the 1-year study and were included in the outcome analysis. The primary outcome of TLF occurred in 7 patients (1.9%), out of whom 5 patients (1.4%) needed TLR, and 2 patients (0.55%) died of a cardiac cause. Of the 5 patients who needed TLR, 3 patients (0.8%) had TVMI, and 2 patients (0.6%) had ischaemia-driven TLR.*

Table 2. Baseline characteristics and demographics.

Baseline characteristics	(n=401)
Age, years	59.7±11.9
Sex	
Male	323 (80.5)
Female	78 (19.5)
Ethnicity	
Malay	254 (63.3)
Chinese	53 (13.2)
Indian	83 (20.7)
Other	11 (2.6)
Smoking	41 (10.2)
Dyslipidaemia	224 (55.4)
Hypertension	287 (71.6)
Diabetes	243 (60.6)
History of MI	78 (19.5)
History of cerebrovascular accident	9 (2.2)
History of peripheral vascular disease	3 (0.7)
History of chronic renal failure	24 (6.0)
Previous PCI	93 (23.2)
Previous CABG	6 (1.5)

Data are presented as mean±standard deviation or n (%).
CABG: coronary artery bypass graft; MI: myocardial infarction; PCI: percutaneous coronary intervention

Table 3. Lesion characteristics.

Lesion characteristics		(n=458)
Coronary lesion		
De novo		458 (100)
Lesion type		
A		1 (0.2)
B1		100 (21.8)
B2		25 (5.5)
C		332 (72.5)
Coronary artery		
LAD		219 (47.8)
LCx		57 (12.4)
RCA		146 (31.9)
LMS-LAD		33 (7.3)
LMS-LCx		2 (0.4)
SVG-OM		1 (0.2)
Bifurcation lesion		87 (19.0)
LMS	LMS-LAD-LCx	30 (6.6)
LAD	LAD-diagonal	43 (9.4)
LCx	LCx-OM	13 (2.8)
RCA	RPDA-PLV	1 (0.2)

Data are presented as n (%). LAD: left anterior descending artery; LCx: left circumflex artery; LMS: left main stem; OM: obtuse marginal artery; PLV: posterior left ventricular artery; RCA: right coronary artery; RPDA: right posterior descending artery; SVG: saphenous vein graft

Table 4. Procedure description.

Procedure characteristics	N=401
PCI status	
Elective	324 (80.8)
NSTEMI/UA	46 (11.5)
STEMI	31 (7.7)
Approach	
Radial	345 (86.3)
Femoral	55 (13.7)
Intracoronary imaging	123 (30.6)
IVUS	114 (28.4)
OCT	9 (2.2)
Atherectomy	21 (5.2)
Rotablation	6 (1.5)
Orbital atherectomy	10 (2.5)
Intracoronary lithotripsy	5 (1.2)

Data are presented as n (%). IVUS: intravascular ultrasound; NSTEMI: non-ST-segment elevation myocardial infarction; OCT: optical coherence tomography; PCI: percutaneous coronary intervention; STEMI: ST-segment elevation myocardial infarction; UA: unstable angina

infarction. The radial approach was used in 345 patients (86.3%), while the femoral approach was used in 55 patients (13.7%). Intracoronary imaging-guided PCI was performed in 123 patients (30.6%): 114 patients (28.4%) with IVUS and 9 patients (2.2%) with OCT.

Atherectomy was used for heavily calcified lesions in 21 patients (5.2%), of whom 6 patients (1.5%) had rotablation, 10 patients (2.5%) had orbital atherectomy, and 5 patients (1.2%) had intracoronary lithotripsy **(Table 4)**.

DRUG-ELUTING STENT AND DRUG-COATED BALLOON DESCRIPTION

The estimated mean lesion length (DES+DCB) was 44.6±23.3 mm, with a mean DES length of 28.7±9.1 mm and a mean DCB segment length of 25.5±8.1 mm. The mean number of DES implanted per lesion was 1.3±0.6, and the mean number of DCBs per lesion was 1.1±0.3. The mean DES diameter was 3.0±0.4 mm, and the mean DCB diameter was 2.5±0.3 mm **(Table 5)**.

The most common combination of antiproliferative drugs for the DES and DCB strategy was everolimus (DES) plus paclitaxel (DCB), in 202 (50.4%) PCIs, followed by zotarolimus (DES) plus paclitaxel (DCB) in 116 (28.9%) PCIs. Paclitaxel-eluting balloons accounted for 99% of DCBs used **(Table 5)**.

ANTIPLATELET TREATMENT

Twelve-month DAPT was prescribed in 339 patients (84.5%). Two patients (0.5%) had 1-month DAPT, 1 patient (0.2%) had 3-month DAPT, and 2 patients (0.5%) had 6-month DAPT. A total of 38 patients (9.5%) were lost to follow-up and were excluded from analysis. The reasons for a short DAPT duration were gastrointestinal bleed in 2 patients and plans for a non-cardiac operation in 3 patients.

CLINICAL OUTCOMES

No TLF events happened in the hospital. All patients were discharged well, with no incidents of repeat angiography needed within 30 days. All patients were monitored and followed up for 12 months. Out of the 401 patients enrolled, 38 patients (9.5%) were lost to subsequent follow-up.

Of the 363 patients who completed the study, the primary outcome of TLF occurred in 7 patients (1.9%). Two patients (0.6%) experienced cardiac death, and 5 patients (1.4%) had target lesion revascularisation (TLR), of whom 3 patients (0.8%) had TVMI and 2 patients (0.6%) had ID-TLR **(Table 6)**. TLF occurred at the DES segment in 3 patients and at the DCB segment in 2 patients. All patients were still on DAPT during the TLF events. The primary outcome patients' profiles and details of the revascularisation procedure are summarised in **Supplementary Table 1**.

Four patients died of a non-cardiac cause at 1-year follow-up (1 patient died of haemorrhagic stroke, 2 patients died due to malignancy, 1 patient due to infection) **(Figure 1, Table 6)**.

Discussion

HYBRID STRATEGY IN LONG DIFFUSE LESIONS

The safety and efficacy of new-generation DES have been well established. However, the limitations of DES implantation, such as late and very late stent thrombosis, still remain the Achilles heel of interventional cardiology[8]. Stent length, overlapping stents and stent diameter are known to be consistent predictors of stent thrombosis[3,9,10]. Currently, DCB treatment is the recommended treatment for ISR and received a class Ia recommendation from the European Society of Cardiology[11]. Multiple studies on the use of DCB in the treatment of *de novo* complex lesions showed promising results[12]. The option of a hybrid strategy combining DES and DCBs offers the advantage of avoiding a long stent length, overlapping of DES and the implantation of DES in small diameter vessels.

In our study, the estimated mean lesion length (DES+DCB) for each treated vessel was 44.6±23.3 mm. With the implementation of the hybrid strategy, the mean DES length was reduced to 28.7±9.1 mm. The remaining lesion length was complemented with a DCB, and the mean segment length of the DCB for each treated vessel was 25.5±8.1 mm. And with the use of DCBs, there were no overlapping stents.

Another strong predictor of stent thrombosis is a reference diameter of <2.6 mm[10]. In this study, the mean DES diameter was 3.0±0.4 mm, and the mean DCB diameter was 2.5±0.3 mm. With the use of the hybrid strategy, we were able to reduce stent implantation of stents with a small diameter <2.5 mm, thus reducing the risk of ISR and need for revascularisation.

HYBRID STRATEGY IN BIFURCATION DISEASE

Coronary bifurcation lesions, which constitute about 20% of PCI procedures[13], represent a unique subset of coronary artery lesions in clinical practice. True bifurcation lesions often present as complex PCI, and 2-stent strategies in these lesions are associated with higher procedural risk and complexity[14]. Side branch ostia seem to be particularly prone to restenosis: abnormalities in shear stress and the presence of multiple layers of struts contribute to this[15].

A provisional strategy in bifurcation PCI is the first-line recommendation in most cases; however, side branch modification is commonly done during POT and kissing balloon inflation, mainly using a plain uncoated balloon, inevitably causing endothelial trauma. The notion of treating a side branch with an antiproliferative agent to prevent further stenosis in a 1-stent strategy is an attractive

Table 5. Description of DES & DCB.

DES & DCB characteristics	Results
Estimated lesion length (DES+DCB), mm	44.6±23.3
Total number of DES	1.3±0.6 (1-4)
Total number of DCB	1.1±0.3 (1-3)
DCB length, mm	25.5±8.1 (12-48)
DCB diameter, mm	2.5±0.3 (2.0-4.0)
DES length, mm	28.7±9.1 (10-48)
DES diameter, mm	3.0±0.4 (2.0-5.0)
Antiproliferative drug combination of DES and DCB	Total=401
Everolimus+Paclitaxel	202 (50.4)
Zotarolimus+Paclitaxel	116 (28.9)
Sirolimus+Paclitaxel	41 (10.2)
Biolimus+Paclitaxel	9 (2.2)
(Everolimus+Zotarolimus)*+Paclitaxel	13 (3.2)
(Everolimus+Sirolimus)*+Paclitaxel	10 (2.5)
(Zotarolimus+Sirolimus)*+Paclitaxel	5 (1.2)
(Biolimus +Sirolimus)*+Paclitaxel	1 (0.2)
Everolimus+Sirolimus	2 (0.5)
Sirolimus+Sirolimus	1 (0.2)
Zotarolimus+Sirolimus	1 (0.2)

Data are presented as mean±SD, range (min-max) or n (%). *2 DES inserted. DCB: drug-coated balloon; DES: drug-eluting stent; SD: standard deviation

Table 6. Primary and secondary outcomes.

Outcomes	N
Primary outcome (1 year)	n=363*
Lost to follow-up	38 (9.5)
Target lesion failure	7 (1.9)
Cardiac death	2 (0.6)
Target vessel revascularisation	5 (1.4)
Target vessel MI	3 (0.8)
Ischaemia-driven target vessel revascularisation	2 (0.6)
Secondary outcome (in-hospital and 30 days)	n=401
Alive	401 (100)
In-hospital death	0
30-day target lesion failure	0
MACE at 1 year	
Cardiac death	2 (0.6)
MI	5 (1.4)
Stroke	1 (0.3)
All-cause mortality	6 (1.7)

Data are given as n (%). *Outcome analysis excluding patients lost to follow-up. MACE: major adverse cardiovascular events; MI: myocardial infarction

one. Results from BIOLUX RCT, which evaluated the feasibility of provisional stenting with DES in the MB and DCB in the SB, showed that this notion appears to be safe and effective[16]. This strategy resonates well with the European Bifurcation Club's recommendation to perform the bifurcation procedure with just 1 stent[17]. However, this study of DCB in SB treatment was limited by low power due to the small number of patients studied[18]. More data are needed in terms of the technicality involved and long-term outcomes of this strategy in bifurcation PCI.

Limitations

This is a retrospective study, and we were not able to randomise patients into control and intervention arms. All enrolled subjects were from a single centre and, thus, may not represent patients from other regions.

As a national tertiary referral centre, patients returned to their local health facilities for subsequent follow-up after PCI. Thus, we were not able to track and record events or clinical outcomes of all of our patients. Subsequently, 38 patients (9.5%) were lost to follow-up.

Conclusions

The hybrid strategy of DES and DCB treatment for *de novo* coronary artery disease is clinically feasible and safe based on our preliminary study. Further randomised and high-powered studies are warranted to study the long-term benefits and safety outcomes of this strategy in percutaneous coronary interventions.

Impact on daily practice

The hybrid strategy of combining drug-eluting stents and drug-coated balloons in percutaneous coronary intervention presents a novel approach for treating complex coronary artery lesions. This method provides an effective solution for minimising stent length and reducing overlapping segments in long diffuse lesions and bifurcation lesions. Further data from randomised controlled trials and large-scale studies are anticipated to evaluate the long-term benefits and safety outcomes of this strategy.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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Supplementary data

Supplementary Table 1. Primary outcome patients' profiles and revascularisation procedure summary.

The supplementary data are published online at: https://www.asiaintervention.org/ doi/10.4244/AIJ-D-23-00066

AsiaIntervention 2024;10:219-232

Accuracy of machine learning in predicting outcomes post-percutaneous coronary intervention: a systematic review

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This paper also includes supplementary data published online at: https://www.asiaintervention.org/doi/10.4244/AIJ-D-23-00023

KEYWORDS

- coronary artery disease
- prior PCI
- risk stratification

Abstract

Background: Recent studies have shown potential in introducing machine learning (ML) algorithms to predict outcomes post-percutaneous coronary intervention (PCI).

Aims: We aimed to critically appraise current ML models' effectiveness as clinical tools to predict outcomes post-PCI.

Methods: Searches of four databases were conducted for articles published from the database inception date to 29 May 2021. Studies using ML to predict outcomes post-PCI were included. For individual post-PCI outcomes, measures of diagnostic accuracy were extracted. An adapted checklist comprising existing frameworks for new risk markers, diagnostic accuracy, prognostic tools and ML was used to critically appraise the included studies along the stages of the translational pathway: development, validation, and impact. Quality of training data and methods of dealing with missing data were evaluated.

Results: Twelve cohorts from 11 studies were included with a total of 4,943,425 patients. ML models performed with high diagnostic accuracy. However, there are concerns over the development of the ML models. Methods of dealing with missing data were problematic. Four studies did not discuss how missing data were handled. One study removed patients if any of the predictor variable data points were missing. Moreover, at the validation stage, only three studies externally validated the models presented. There could be concerns over the applicability of these models. None of the studies discussed the cost-effectiveness of implementing the models.

Conclusions: ML models show promise as a useful clinical adjunct to traditional risk stratification scores in predicting outcomes post-PCI. However, significant challenges need to be addressed before ML can be integrated into clinical practice.

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SUBMITTED ON 14/04/2023 - REVISION RECEIVED ON 1st 24/04/2024 / 2nd 13/06/2024 - ACCEPTED ON 14/06/2024

DOI: 10.4244/AIJ-D-23-00023

Abbreviations

AUC	area under the curve
LASSO	least absolute shrinkage and selection operator
ML	machine learning
NPV	negative predictive value
PCI	percutaneous coronary intervention
PPV	positive predictive value

Introduction

Ischaemic heart disease is the greatest cause of mortality and loss of disability-adjusted life years worldwide, accounting for approximately 7 million deaths and 129 million disability-adjusted life years annually[1]. Percutaneous coronary intervention (PCI) is indicated in patients with acute coronary syndrome and has been shown to improve quality of life in those on the maximal tolerated medical therapy[2]. Such intervention may be associated with complications, such as postprocedural acute kidney injury, bleeding, heart failure and others.

Traditional statistical modelling methods have been adopted to predict outcomes post-PCI, involving preselecting and transforming candidate variables based on prior knowledge, applying hierarchical logistic regression to model relationships between variables and outcomes, and reducing the number of variables to create the final model[3]. However, this approach is limited, as it assumes a linear relationship between the variables and logarithmic odds of outcomes, and is weak to collinearity between the variables[4]. Conversely, machine learning (ML) algorithms are free of these linear assumptions and have the additional benefit of being able to control collinearity by regularisation of hyperparameters[5].

ML is a branch of artificial intelligence which uses large datasets to produce algorithms with minimal human intervention, allowing for automated learning. ML learns from examples in training datasets by optimising algorithms according to a loss function. Different ML models exist, including adaptive boosting, k-nearest neighbours, least absolute shrinkage and selection operator (LASSO), random forest, artificial neural network, and support vector machine, amongst others.

In an age of precision medicine, ML has demonstrated its capabilities in sifting through vast amounts of clinical data and reliably predicting outcomes[6], guiding clinicians in efficiently stratifying patients and making individualised treatment decisions[7]. Several studies have also shown significant potential in introducing ML algorithms to predict post-PCI outcomes[8,9]. Nonetheless, other studies have shown no performance benefit of ML over traditional statistical methods for clinical prediction models[10]. Hence, we conducted a systematic review to evaluate the effectiveness and validity of current ML models as a clinical tool to predict outcomes following PCI.

Methods

This systematic review was registered on PROSPERO (International prospective register of systematic reviews; CRD258014) and was reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines[11]. Searches of four databases (PubMed, Embase, Cochrane, and Scopus) were conducted for articles published from the date of inception up to 29 May 2021. A literature search was performed using terms synonymous with "machine learning", "prediction" and "PCI". The full list of search terms can be found in **Supplementary Table 1**.

Table 1 summarises the population, intervention, comparison, outcomes, and inclusion and exclusion criteria used for study selection. Briefly, we included all cohort studies, case-control studies, and randomised controlled trials using ML to predict outcomes post-PCI. Outcomes post-PCI included those relating to mortality (all-cause mortality and in-hospital mortality), the heart (myocardial infarction, heart failure, cardiovascular death, arrhythmia, emergency coronary artery bypass graft, stent thrombosis, and coronary artery restenosis), haemodynamics (bleeding), the kidneys (acute kidney injury, contrast-induced nephropathy, and dialysis) and others (prolonged length of stay ≥7 days and stroke). The range in timeframes for outcome measurement spanned from 72 hours to 1 year.

Three reviewers independently performed the literature search, title and abstract review, full text sieve and data extraction, and all disagreements were resolved by mutual consensus. Baseline demographic information, comorbidities, follow-up duration, medication information and procedural information were collected.

For individual post-PCI outcomes, the number of patients with confirmed disease (N^D), sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), area under the curve (AUC), and accuracy were collected for each ML model, when reported. The checklist developed by Banerjee et al[12] was used in this study to critically appraise the included studies, mainly along the stages of the translational pathway: development, validation and impact. Quality of training data and methods of dealing with missing data were evaluated.

Data related to blinding and withdrawals were extracted to assess the risk of bias. Quality control was performed by two independent reviewers using the Newcastle-Ottawa Scale[13] **(Supplementary Table 2)** and the Prediction Risk of Bias ASsessment Tool (PROBAST)[14] **(Supplementary Table 3)**. The Newcastle-Ottawa Scale for cohort studies considers three different domains: selection, comparability, and outcome. PROBAST considers four different domains: participants, predictors, analysis, and outcomes. Studies are graded as having a low, high, or an unclear risk of bias/concern regarding applicability. The Preferred Reporting Items for Systematic reviews and Meta-Analyses checklist[11] is included in **Supplementary Figure 1**.

We included ML models that predicted in-hospital mortality, myocardial infarction, and bleeding. Diagnostic accuracy data for the included models were extracted. The ML models used comprised adaptive boosting, k-nearest neighbours, LASSO, random forest, artificial neural network, support vector machine, multilayer perceptron neural network, Naïve Bayes, extreme gradient boosting, blended model with gradient descent boosting,

Table 1. Population, intervention, comparison, outcomes and study (PICOS) inclusion criteria and exclusion criteria applied to database search.

PICOS	Inclusion criteria	Exclusion criteria
Population	Patients who have undergone PCI	
Intervention	ML model	
Comparison	Traditional risk stratification tools (i.e., CADILLAC risk score, PAMI risk score, Zwolle risk score, GRACE hospital discharge score, dynamic TIMI risk score, RISK-PCI score, APEX AMI risk score, residual SYNTAX score, DAPT Score, GUSTO score, EPICOR prognostic model, and other scores that may be relevant) and statistical modelling	
Outcome	Bleeding, acute kidney injury, contrast-induced nephropathy, dialysis, heart failure, myocardial infarction, cardiovascular deaths, arrhythmias, emergency CABG, stent thrombosis, coronary artery restenosis, all-cause mortality, in-hospital mortality, prolonged length of stay more than or equal to seven days, and stroke	
Study design	Articles in English	Case reports and series, systematic reviews, narrative reviews, qualitative reviews, letters to the editor, non-human studies, abstract only (conference papers), non-peer-reviewed articles
	Cohort studies, case-control studies, randomised controlled trials	
	Year of publication: date of inception-29 May 2021	
	Databases: PubMed, Embase, Cochrane, Scopus	

APEX AMI: Assessment of Pexelizumab in Acute Myocardial Infarction; CABG: coronary artery bypass graft; CADILLAC: Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications; DAPT: dual antiplatelet therapy; EPICOR: long-tErm follow uP of antithrombotic management patterns In acute CORonary syndrome patients; GRACE: Global Registry of Acute Coronary Events; GUSTO: Global Use of Strategies To Open Occluded Coronary Arteries; ML: machine learning; PAMI: Primary Angioplasty in Myocardial Infarction; PCI: percutaneous coronary intervention; PICOS: population, intervention, comparison, outcome, study; TIMI: Thrombolysis in Myocardial Infarction

boosted classification trees algorithm model, and existing simplified risk score with LASSO regression.

Results

The Preferred Reporting Items for Systematic reviews and Meta-Analyses flowchart is presented in **Figure 1**. A literature search of the four databases (PubMed, Embase, Cochrane, Scopus) retrieved 2,546 results. There were 727 duplicates, which were removed. Title and abstract screening excluded a further 1,635 articles as they either did not use ML to predict outcomes post-PCI, did not mention PCI, or had insufficient statistical reporting of post-PCI outcomes. Full text screening excluded 173 articles. Eleven studies were included for the systematic review.

The 11 studies comprised a combined cohort of 4,943,425 patients[3,9,15-23]. Gao 2020 included 2 separate cohorts, comprising 1 retrospective and 1 prospective cohort[17]. Thus, while the flowchart in **Figure 1** shows 11 included studies, 12 cohorts were analysed in total. Across the studies, the reported post-PCI outcomes included in-hospital mortality, myocardial infarction, bleeding, and acute kidney injury. The characteristics of the included studies are shown in **Table 2**. Additional data relating to participant baseline characteristics, including demographics, medications used, and information relating to procedure(s), are presented in **Supplementary Table 4**, **Supplementary Table 5**, and **Supplementary Table 6**, respectively.

The sensitivity, specificity, PPV, NPV, and accuracy for the ML models used to predict in-hospital mortality, myocardial infarction, bleeding, in-hospital mortality and acute kidney injury for each included study are presented in **Table 3**. As seen, the sensitivity, specificity, PPV, NPV and accuracy are consistently high across all models.

Among the 11 studies, different ML models were used, and their methods of derivation varied. Clinical predictors and outcomes for training the ML models utilised in the 11 studies are summarised in **Table 4**. A summary of ML modalities, including the ML model used, software algorithm, training procedure, and optimisation of metrics, is presented in **Table 4**. The quality of training data, including type of study, cohort size, normalisation/standardisation, and validation, is presented in **Table 4** and **Supplementary Table 7**. **Table 5** summarises the studies included for each post-PCI outcome. In all, four studies investigated bleeding outcomes, three studies investigated acute kidney injury outcomes, five studies investigated in-hospital mortality and one study investigated myocardial infarction **(Table 3, Table 5)**. Two studies used artificial neural networks, two used support vector machines, two used random forest algorithms, three used logistic regression models, one used a blended model with gradient descent boosting, two used LASSO techniques, two used adaptive boosting, two used extreme gradient boosting, one used a boosted classification tree algorithm (AI-BR) model, and one used a k-nearest neighbour algorithm. There were concerns about the development of the models. Of the 11 included studies, 10 were studies conducted using data from a single country (seven in the USA, two in China, one in Japan); only one study was a multinational study. The methods of dealing with missing data

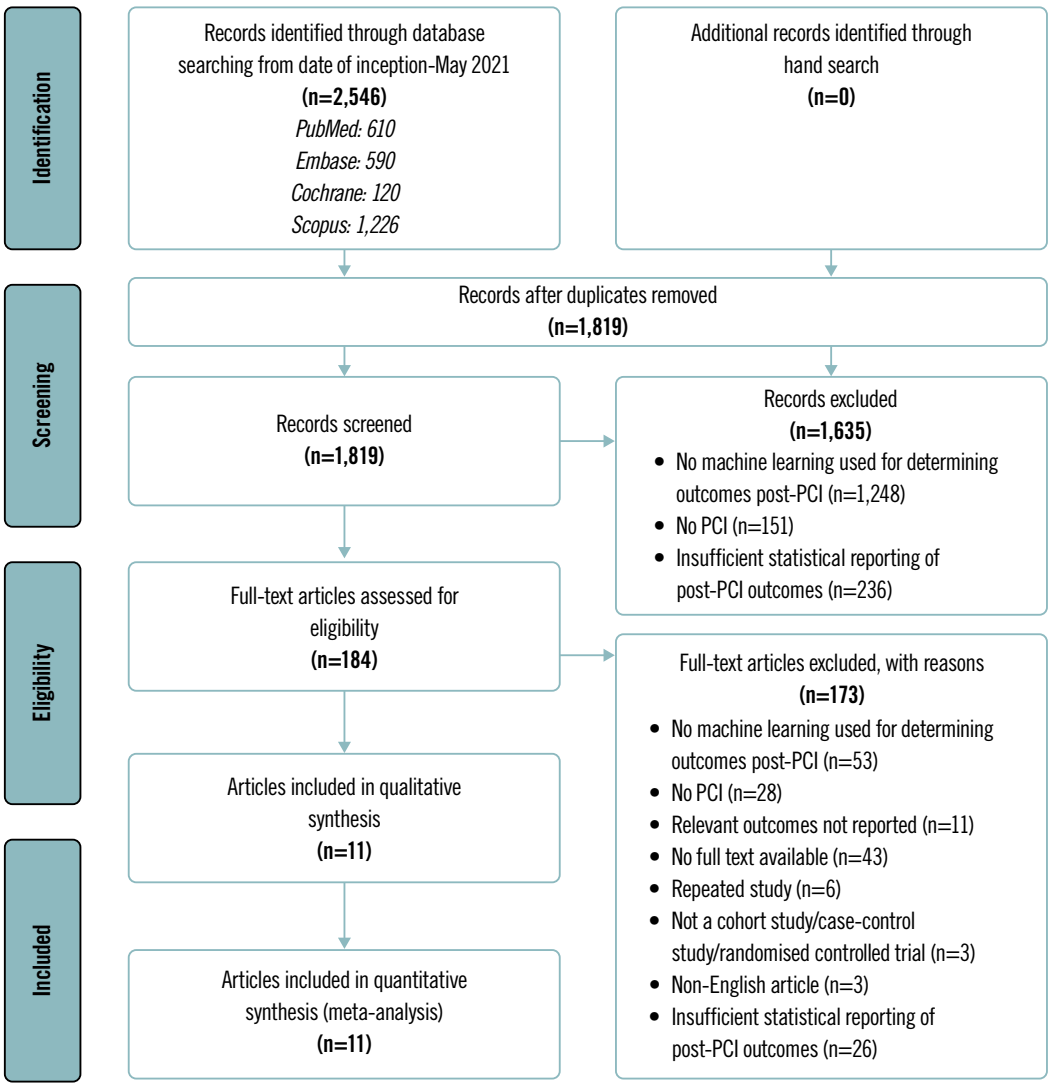

Figure 1. *Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow diagram of study selection. PCI: percutaneous coronary intervention*

were another issue that surfaced. The most common way of dealing with missing data was imputation. However, four studies did not discuss how missing data were handled. One study removed patients if any of the predictor variable data points were missing. In the validation stage, most studies utilised internal validation methods, with four studies using holdout analysis by splitting the dataset into training and test sets, and five studies using N-fold cross-validation. Only three studies externally validated the models presented. There could be concerns over the applicability of the models. While most of the studies presented evidence that the model can be used and interpreted in the clinical context, none of the studies discussed the cost-effectiveness of implementing the model.

Discussion

In this systematic review, we demonstrated that ML models may be useful as an adjunct to existing traditional risk stratification scores in predicting outcomes post-PCI, with moderate to high NPV and AUC.

Traditional risk stratification scores used to predict outcomes post-PCI include the Primary Angioplasty in Myocardial Infarction risk score[24], the RISK-PCI score[25], and the New Mayo Clinic Risk Score[26]. However, such scores are limited by their primary reliance on linear models and diminished ability to explore higher order interactions[27], as they are built on parametric and semiparametric regression scoring systems. Traditional statistical modelling, which is also used to predict outcomes post-PCI, assumes a linear relationship between the variables and logarithmic odds of outcomes[4]. These limitations render traditional risk stratification scores and statistical modelling effective at making predictions at a population level, but less effective at accurately predicting an individual's risk[28].

Compared to the ML models[21], the AUCs for bleeding using traditional scores, such as the Primary Angioplasty in Myocardial Infarction risk score, Thrombolysis in Myocardial Infarction (TIMI) risk score, Global Registry of Acute Coronary Events risk score, and Controlled Abciximab and Device Investigation

Table 2. Characteristics of included studies.

Study name	Study type	Country	Data source	Dates	Inclusion	Exclusion	Sample size	Machine learning model
Al'Aref 2019[19]	Cohort – retrospective	USA	New York PCIRS	1 January 2004 to 31 December 2012	All patients who underwent PCI in the state of New York from 1 January 2004 until 31 December 2012 as documented in the PCIRS database, comprising all elective and emergent cases covering the spectrum of coronary artery disease presentations	Nil	479,804	Adaptive boosting, random forest, XGBoost
D'Ascenzo 2021[16]	Cohort – retrospective	BleeMACS: North and South America, Europe, and Asia; RENAMI: Spain, Italy, Switzerland, Greece, Serbia, United Kingdom	BleeMACS and RENAMI registries	BleeMACS: 1 January 2003 to 31 December 2014 RENAMI: 1 January 2012 to 31 December 2016	BleeMACS: consecutive patients discharged with a diagnosis of ACS undergoing PCI at 1-year follow-up (except death) RENAMI: patients with ACS who underwent PCI and were discharged with DAPT with acetylsalicylic acid plus prasugrel 10 mg once daily or acetylsalicylic acid plus ticagrelor 90 mg twice daily between January 2012 and January 2016	BleeMACS: patients who died during hospitalisation, patients without coronary artery disease, patients who did not undergo PCI (simple balloon angioplasty, stent implantation and/or thromboaspiration). RENAMI: nil	19,826	Adaptive boosting, k-nearest neighbours, Naïve Bayes, random forest
Gao 2020[17]	Cohort – retrospective (training set) – prospective (validation set)	China	Hebei General Hospital, Baoding First Central Hospital, and Cangzhou Central Hospital	Training set: January 2016 to December 2018 Validation set: July 2018 to December 2018	Patients who met the diagnostic criteria of acute STEMI and underwent primary PCI according to current guidelines between the respective time periods for training and validation sets	NR	1,169 (training set); 316 (validation set)	LASSO
Gurm 2014[21]	Cohort – retrospective	USA	BMC2	July 2009 to December 2012	All consecutive patients who underwent PCI between July 2009 and December 2012	Patients who underwent coronary artery bypass grafting during the same hospitalisation	72,328 (training cohort); 30,966 (validation cohort) (PCI procedures)	Random forest
Huang 2018[3]	Cohort – retrospective	USA	NCDR CathPCI Registry	1 June 2009 to 30 June 2011	Patients who underwent PCI procedures	PCIs that were not the first procedure during a single hospitalisation (n=32,999), procedures with same-day discharge (n=41,570), missing serum creatinine before or after the procedure (n=208,158), procedures on patients already on dialysis at the time of their PCI (n=24,271)	947,091	Logistic regression, XGBoost, LASSO regularisation, LASSO regression
Kulkarni 2021[23]	Cohort – retrospective	USA	NCDR CathPCI Registry for 5 BJC HealthCare hospitals	1 July 2009 to 30 April 2018	Patients undergoing PCI at 5 hospitals in the Barnes-Jewish hospital system	NR	28,005 PCIs on 26,784 patients	ANN MLP model

Table 2. Characteristics of included studies (cont'd).

Study name	Study type	Country	Data source	Dates	Inclusion	Exclusion	Sample size	Machine learning model
Kuno 2021[22]	Cohort – prospective	Japan	JCD-KiCS registry	September 2008 to March 2019	Patients undergoing PCI under JCD-KiCS	Patients undergoing chronic dialysis (n=912), patients with missing data on creatinine (n=3,144), haemoglobin (n=3,617) or baseline information e.g., age, sex (n=2,216)	14,273	MLP neural network, logistic model
Matheny 2007[20]	Cohort – retrospective	USA	BWH	1 January 2002 to 31 December 2005	All cases of percutaneous coronary intervention performed at BWH	NR	7,914 PCIs	Support vector machine
Mortazavi 2019[15]	Cohort – retrospective	USA	NCDR CathPCI Registry data, version 4.4	1 July 2009 to 1 April 2015	Patients undergoing the first PCI procedure within same hospitalisation	Not the index PCI of admission, hospital site missing outcome measures, patients who underwent subsequent coronary artery bypass grafting, patients who died in the hospital the same day as the procedure	3,316,465	Blended model with gradient descent boosting, existing simplified risk score with LASSO regularisation
Rayfield 2020[9]	Cohort – retrospective	USA	Mayo Clinic PCI database across 4 sites (La Crosse, Wisconsin; Mankato, Minnesota; Rochester, Minnesota; and Phoenix, Arizona)	January 2006 to December 2017	Patients who had PCI done between January 2006 and December 2017	If any of the 86 variable data points, including bleeding data, were missing	15,603	AI-BR model
Wang 2020[18]	Cohort – retrospective	China	EHR of inpatients who were admitted to the Department of Cardiology at Sir Run Run Shaw Hospital (Hangzhou, Zhejiang, China)	December 2007 to April 2019	1. Inpatients with single coronary artery stenosis (left main artery, left anterior descending artery, left circumflex artery, or right coronary artery); 2. Inpatients with stent implantation during this in-hospital period; 3. From December 2007 to April 2019	1. Myocardial infarction patients or elevated preprocedural cTnI or CK-MB; 2. PCI for more than one artery; 3. Coronary artery with thrombosis; 4. Transluminal extraction-atherectomy therapy for culprit artery; 5. Severe heart failure (EF <45% or NT-proBNP >2,000); 6. Severe valve disease	10,886	Artificial neural networks, support vector machine

ACS: acute coronary syndrome; AI-BR: boosted classification tree algorithm; ANN: artificial neural network; BJC: Barnes-Jewish Corporation; BleeMACS: Bleeding complications in a Multicenter registry of patients discharged with diagnosis of Acute Coronary Syndrome; BMC2: Blue Cross Blue Shield of Michigan Cardiovascular Consortium 2; BWH: Brigham and Women's Hospital; CK-MB: creatinine kinase myocardial band; cTnI: cardiac troponin I; DAPT: dual antiplatelet therapy; EF: ejection fraction; EHR: electronic health record; JCD-KiCS: Japanese Cardiovascular Database-Keio interhospital Cardiovascular Studies; LASSO: least absolute shrinkage and selection operator; MLP: multilayer perceptron; NCDR: National Cardiovascular Data Registry; NR: not reported; NT-proBNP: N-terminal pro B-type natriuretic peptide; PCI: percutaneous coronary intervention; PCIRS: Percutaneous Coronary Interventions Reporting System; RENAMI: REgistry of New Antiplatelets in patients with Myocardial Infarction; STEMI: ST-segment elevation myocardial infarction; XGBoost: eXtreme Gradient Boosting

Table 3. Sensitivity, specificity, PPV, NPV, and accuracy reported by studies that applied an ML method to predict different clinical outcomes post-percutaneous coronary intervention.

Model	ML model	Sensitivity	Specificity	PPV	NPV	Accuracy	AUC
In-hospital mortality (best)							
D'Ascenzo 2021[16]	K-nearest neighbour	0.57 (0.53, 0.61)					
D'Ascenzo 2021[16]	Adaptive boosting		0.91 (0.91, 0.91)	0.21 (0.19, 0.23)	0.98 (0.98, 0.98)	0.89 (0.89, 0.90)	0.82 (0.79, 0.85)
Gao 2020[17] (training set)	LASSO	0.98 (0.93, 0.99)					
Gao 2020[17] (validation set)	LASSO		0.95 (0.92, 0.97)	0.63 (0.47, 0.77)	1.00 (0.98, 1.00)	0.95 (0.92, 0.97)	0.99 (0.98, 1.00)
Al'Aref 2019[19]	Adaptive boosting						0.93 (0.92, 0.93)
Matheny 2007[20]	SVM						0.92 (0.91, 0.92)
Kulkarni 2021[23]	ANN						0.92 (0.90, 0.94)
In-hospital mortality (worst)							
D'Ascenzo 2021[16]	K-nearest neighbour		0.88 (0.87, 0.89)	0.17 (0.16, 0.19)	0.98 (0.98, 0.98)	0.87 (0.86, 0.87)	
D'Ascenzo 2021[16]	Adaptive boosting	0.55 (0.51, 0.59)					0.82 (0.79, 0.85)
Gao 2020[17] (training set)	LASSO		0.92 (0.90, 0.93)	0.51 (0.44, 0.58)	1.00 (0.99, 1.00)	0.92 (0.90, 0.94)	0.99 (0.98, 0.99)
Gao 2020[17] (validation set)	LASSO	0.96 (0.80, 0.99)					
Al'Aref 2019[19]	Random forest						0.89 (0.89, 0.90)
Matheny 2007[20]	SVM						0.88 (0.87, 0.88)
Kulkarni 2021[23]	ANN						0.81 (0.76, 0.86)
Myocardial infarction (best)							
D'Ascenzo 2021[16]	Random forest	0.67 (0.63, 0.71)					
D'Ascenzo 2021[16]	Adaptive boosting		0.79 (0.78, 0.80)	0.10 (0.09, 0.11)	0.98 (0.98, 0.98)	0.78 (0.78, 0.79)	
Wang 2020[18]	SVM	0.73 (0.71, 0.75)					
Wang 2020[18]	ANN		0.72 (0.70, 0.74)	0.71 (0.69, 0.73)	0.73 (0.71, 0.75)	0.72 (0.71, 0.73)	
Myocardial infarction (worst)							
D'Ascenzo 2021[16]	Random forest		0.63 (0.62, 0.64)	0.07 (0.06, 0.07)	0.98 (0.98, 0.98)	0.63 (0.62, 0.64)	
D'Ascenzo 2021[16]	Adaptive boosting	0.58 (0.54, 0.62)					
Wang 2020[18]	SVM		0.65 (0.63, 0.67)	0.67 (0.65, 0.69)	0.71 (0.69, 0.73)	0.69 (0.68, 0.70)	
Wang 2020[18]	ANN	0.72 (0.70, 0.74)					
Bleeding (best)							
Mortazavi 2019[15]	Blended model with gradient descent boosting	0.37 (0.37, 0.37)	0.95 (0.95, 0.95)	0.27 (0.26, 0.27)	0.97 (0.97, 0.97)	0.93 (0.93, 0.93)	
Rayfield 2020[9]	Boosted classification tree algorithm	0.77 (0.72, 0.82)	0.81 (0.80, 0.82)	0.07 (0.06, 0.08)	0.99 (0.99, 1.00)	0.81 (0.80, 0.81)	
Gurm 2014[21]	Random forest						0.89 (0.88, 0.90)
Kulkarni 2021[23]	ANN						0.80 (0.86, 0.89)
Bleeding (worst)							
Mortazavi 2019[15]	Existing simplified risk score with LASSO regularisation	0.35 (0.35, 0.35)	0.93 (0.93, 0.93)	0.20 (0.20, 0.20)	0.97 (0.97, 0.97)	0.91 (0.91, 0.91)	
Rayfield 2020[9]	Boosted classification tree algorithm	0.77 (0.72, 0.82)	0.81 (0.80, 0.82)	0.07 (0.06, 0.08)	0.99 (0.99, 1.00)	0.81 (0.80, 0.81)	
Gurm 2014[21]	Random forest						0.88 (0.87, 0.89)
Kulkarni 2021[23]	ANN						0.73 (0.71, 0.76)
Acute kidney injury (best)							
Huang 2018[3]	XGBoost						0.76 (0.76, 0.76)
Kulkarni 2021[23]	ANN						0.82 (0.81, 0.83)
Kuno 2021[22]	Logistic regression						0.83 (0.81, 0.84)
Acute kidney injury (worst)							
Huang 2018[3]	Logistic regression						0.71 (0.71, 0.71)
Kulkarni 2021[23]	ANN						0.63 (0.59, 0.66)
Kuno 2021[22]	Logistic regression						0.81 (0.80, 0.83)

Values in parentheses are 95% confidence intervals. ANN: artificial neural network; AUC: area under the curve; LASSO: least absolute shrinkage and selection operator; ML: machine learning; NPV: negative predictive value; PPV: positive predictive value; SVM: support vector machine; XGBoost: eXtreme Gradient Boosting

to Lower Late Angioplasty Complications risk score (AUC=0.60, 0.62, 0.58, and 0.79, respectively)[29], demonstrated lower values. This suggests a better performance of ML models, compared to traditional predictive models, in prognosticating patients for bleeding risk post-PCI. Compared to that of the best ML models[22,23], the AUC for predicting acute kidney injury using the Primary Angioplasty in Myocardial Infarction risk score (AUC=0.71)[29] demonstrated a lower value, whilst ML models were outperformed by other traditional risk models such as the TIMI risk score, Global Registry of Acute Coronary Events risk score, and Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications risk score (AUC=0.83, 0.78, and 0.98, respectively)[29]. Several studies have also shown traditional statistical methods to have a similar performance to ML in clinical prediction situations[10,30]. Hence, traditional risk stratification scores and statistical modelling are still crucial in clinical practice, but ML models, which are free of linear assumptions and have the additional benefit of being able to control collinearity by optimising hyperparameters[5], may be used as an adjunctive tool to augment clinicians' decision-making regarding personalised risk-benefit analysis[31,32] on whether or not a patient should undergo elective PCI.

In contrast to traditional statistical methods, ML models tend to incorporate a diverse range and greater number of clinically relevant key variables in the training process, comprising demographic characteristics, medical history, preprocedural imaging characteristics, and procedural characteristics, as well as postprocedural complications and outcomes **(Supplementary**

Table 4. Systematic review and quality assessment of included studies.

Author	Al'Aref[19]	D'Ascenzo[16]	Gao[17]	Gurm[21]	Huang[3]
Type of study	Cohort – retrospective	Cohort – retrospective	Cohort – retrospective (training set) Cohort – prospective (validation set)	Cohort – retrospective	Cohort – retrospective
Cohort size	479,804	19,826	316	30,985	947,091
Cohort country	USA	15 tertiary hospitals in North and South America, Europe, and Asia+12 European hospitals	China	USA	USA
Development					
Cohort population	PCIRS database	BleeMACS registry (ClinicalTrials.gov: NCT02466854) and the RENAMI registry+RENAMI	Hebei General Hospital, Baoding First Central Hospital, and Cangzhou Central Hospital	BMC2: all non-federal hospitals in the state of Michigan	NCDR CathPCI
Normalisation/ standardisation	Yes – done before use in model training and validation	Not reported	Yes – all data were normalised by transforming the data into new scores (z-score transformation) with a mean of 0 and a standard deviation of 1	Not reported	Yes – may be performed during feature engineering step
Validation	Yes (5-fold cross-validation)	Yes (internal validation, external validation)	Yes (internal validation, external validation)	Yes (independent validation)	Yes (temporal validation performed on a more contemporary cohort of PCI patients from the NCDR CathPCI registry)
Machine learning model	Adaptive boosting, random forest, XGBoost, logistic regression	Adaptive boosting, k-nearest neighbour	LASSO	Random forest	Logistic regression, XGBoost
Software algorithm	Not reported	SPSS Statistics, version 24.0 (IBM)	R software, version 3.3.0 (R Foundation for Statistical Computing) and Glmnet R package was used for the LASSO regression model	R software, version 2.14.1, using freely distributed contributed packages	All analyses were developed in R. LASSO regularisation with logistic regression was performed using the Glmnet R package. XGBoost was performed using the XGBoost R package. Brier score, reliability, and resolution were calculated with the SpecsVerification R package

Table 8). This facilitates the development of a more robust algorithm, guiding the prediction of post-PCI outcomes in clinical practice in a more precise manner.

Moreover, ML models, especially deep learning models, are adept in handling high-dimensional and complex data. This is particularly beneficial in healthcare systems, where a vast amount of data is constantly generated from diverse sources. While traditional methods can capture non-linear relationships, ML models can do so in a more flexible manner and without need for explicit specification of polynomial terms and interaction variables. In addition, techniques like cross-validation and regularisation in ML can facilitate the development of models that generalise better on unseen data, a key consideration in clinical applications.

It is worthwhile to note that Greenhalgh et al previously published a multilevel non-adoption, abandonment, scale-up, spread, and sustainability (NASSS) framework for studying the diffusion of innovations and promoting technology adoption in healthcare systems[33]. This framework takes into account key factors including the condition, technology, value proposition, adopters, organisation, the wider system, and adaptation over time. Application of this framework to ML models in PCI could potentially aid in the translation of algorithmic success to patient benefit.

The high NPVs using the ML models for in-hospital mortality, myocardial infarction, and bleeding, of 100%, 99%, and 98%, respectively, demonstrate that patients who were predicted not to have poor outcomes post-PCI indeed did not suffer from such complications, thus guiding risk-benefit analysis for PCI. Poor

Table 4. Systematic review and quality assessment of included studies (cont'd).

Kulkarni[23]	Kuno[22]	Matheny[20]	Mortazavi[15]	Rayfield[9]	Wang[18]
Cohort – retrospective	Cohort – retrospective	Cohort – retrospective	Cohort – retrospective	Cohort – retrospective	Cohort – retrospective
26,784	14,273	7,914 PCIs	3,316,465	15,604	10,886
USA	Japan	USA	USA	USA	China
Seven hospitals – Alton Memorial Hospital, Alton, IL; Barnes-Jewish Hospital, St. Louis, MO; Barnes-Jewish St. Peters Hospital, St. Peters, MO; Boone Hospital Center, Columbia, MO; Christian Hospital, St Louis, MO; Missouri Baptist Medical Center, St. Louis, MO; and Progress West HealthCare, O'Fallon, MO	JCD-KiCS registry	BWH (Boston, MA) containing all cases (7,914) of PCI performed at the institution from 1 January 2002 to 31 December 2005	NCDR CathPCI	Mayo Clinic CathPCI registry data	Sir Run Run Shaw hospital (Hangzhou, Zhejiang, China)
Yes – normalisation done for continuous variables before use in model training and validation	Not reported	Not reported	Not reported	Not reported	Not reported
Yes (validation with a separate retrospective dataset)	Yes (automatic system validation)	Yes (3-fold cross-validation inner and outer loop method)	Yes (5-fold cross-validation)	Yes (10-fold cross-validation)	Yes (4-fold cross-validation)
ANN MLP model	Logistic model	Support vector machine-P (CEE)-optimised, support vector machine-R (MSE)-optimised	Blended model with gradient descent boosting, existing simplified risk score with LASSO regression	AI-BR model	Artificial neural networks, support vector machine
All analyses were carried out on R statistical software or Stata (StataCorp)	Statistical calculations and analyses performed using SPSS Statistics, version 24, R 3.5.3 and Python 3.7 (Python Software Foundation)	SVM models were developed using GIST (Columbia University, New York, NY, USA) 2.2.1. LR models were developed using SAS, version 9.1 (SAS Institute)	All analyses were conducted in R (version 3.3.2), with Glmnet used for LASSO regularisation, XGBoost for gradient descent boosting and pROC for C statistics; mgcv and sandwich were used for the continuous calibration curves and SpecsVerification was used for the Brier score	R software, version 3.5.1	Python 3.x software+SPSS Statistics for macOS, version 23

Table 4. Systematic review and quality assessment of included studies (cont'd).

Author	Al'Aref[19]	D'Ascenzo[16]	Gao[17]	Gurm[21]	Huang[3]
Development					
Training procedure	5-fold cross-validation on the dataset for each model. Attribute selection was done after fine-tuning of the hyperparameter – defined as the model parameters that are given an arbitrary value before the initiation of the learning process. Attribute selection was performed using the information gain ranking method that aims at ranking features based on high information gain entropy. The attributes with information gain >0 were only used for the ML approach.	The derivation cohort was randomly split into 2 datasets: a training (80%) cohort, which was used to train the 4 ML models and tune their parameters, and an internal validation (20%) cohort, which was used to test the developed models on unseen data and to fine-tune the hyperparameters. To determine the major predictors of each study outcome in our patient population, the importance of each permutation feature was measured from the final model. Permutation feature importance computes the value of each feature included in the model by calculating the increase in the model's prediction error after permuting its values. A feature is considered important if permuting its values decreases the model's discriminative capability, as the model relies heavily on that feature for the prediction.	The LASSO method was used to select the features that were the most significantly associated with the outcome (in-hospital mortality). Then, a regression model was built using the selected variables. The λ value was selected for which the cross-validation error was the smallest. Finally, the model was refitted using all available observations and the selected λ. Thus, most of the coefficients of the covariates were reduced to 0, and the remaining non-zero coefficients were selected by LASSO.	The study cohort was divided randomly into training and validation datasets, with 70% of procedures assigned to training, and the remaining 30% utilised for validation. A random forest regression model was trained for predicting transfusion using 45 baseline clinical variables including preprocedural medications, with missing predictors imputed to be the overall median for continuous values and mode for categorical variables. The transfusion outcome was entered as a continuous variable coded as 1 in patients who were transfused, and 0 for those not meeting the criteria to facilitate regression rather than classification modelling, so that estimated means (leaf node probabilities of transfusion) assigned to a given observation were then aggregated in the ensemble. To facilitate the development of an easy-to-use bedside tool, a reduced model was also trained using only the 14 most important predictors as assessed in the full model by the incremental decrease in node impurity (residual sum of squares) associated with splitting on the predictor averaged over all trees in the ensemble.	9 prediction models were developed, with combinations of the following 3 categories: (1) preprocessing models (strategy A vs strategy B), (2) variable selection (stepwise backward selection with logistic regression vs LASSO regularisation with logistic regression vs permutation-based selection with XGBoost) and (3) relationship modelling: (logistic regression model vs ML method XGBoost). Analytic cohort was randomly split into a training set (70% of the cohort) and a test set (30% of the cohort). The 9 models were built using data from the training set only, and the corresponding selected variables were recorded. Finally, the performance of the models was assessed on the internal test set.
Optimising metrics	AUC	AUC	AUC	AUC	AUC, Brier score, resolution, reliability

AI-BR: boosted classification tree algorithm; AKI: acute kidney injury; ANN: artificial neural network; AUC: area under the curve; BleeMACS: Bleeding complications in a Multicenter registry of patients discharged with diagnosis of Acute Coronary Syndrome; BMC2: Blue Cross Blue Shield of Michigan Cardiovascular Consortium 2; BWH: Brigham and Women's Hospital; CEE: cross-entropy error; HL: Hosmer-Lemeshow; JCD-KiCS: Japanese Cardiovascular Database-Keio interhospital Cardiovascular Studies; LASSO: least absolute shrinkage and selection operator;

outcomes such as in-hospital mortality, myocardial infarction, and bleeding, might diminish the overall utility of PCI. The high discriminatory value serves as a good adjunctive clinical tool to allow clinicians to weigh the risks and benefits of PCI for their patients.

We have also critically appraised the studies along the key elements of the translational pathway. Development is hampered by the population in each cohort. Of the 12 cohorts included, seven cohorts analysed populations in the USA[3,9,15,19-21,23], three

Table 4. Systematic review and quality assessment of included studies (cont'd).

Kulkarni[23]	Kuno[22]	Matheny[20]	Mortazavi[15]	Rayfield[9]	Wang[18]
Randomly shuffled dataset was split into a derivation set (n=21,004) and a validation dataset (n=7,001). All training for ML algorithms used data from the derivation set, while all models were validated on data from the validation set. Data preprocessing was undertaken using variable encoding. The 2 generated datasets were used to develop 2 separate learning models for each outcome – one incorporating baseline and pre-PCI variables, and the other incorporating variables related to the PCI procedure. Predictions from these two models were then finally combined into a single prediction model using logistic regression. For each training epoch, the estimated best fitting model was independently applied to the test set (the encoded dataset obtained from the validation set) to trace the classification accuracy. Model training continued as long as there was improvement in the classification accuracy for both the training and the independently assessed test set. If the model only showed accuracy improvement in the training set but showed a decreased accuracy for the test set, then a potential overfitting was interpreted, and model training was stopped.	Restricted cubic spline with multivariate logistic regression models were used to assess the association between absolute/ relative decrease in haemoglobin and AKI. ML was constructed with a neural network to evaluate the association between periprocedural haemoglobin reduction and AKI and for risk stratification of AKI, by comparing the effect of NCDR variables versus NCDR variables plus haemoglobin absolute change (continuous value) versus NCDR variables plus haemoglobin relative change (continuous value) and with logistic models.	The cases were used to generate 100 random datasets. All cases were used in each set, and 5,540 were allocated for training and 2,374 were allocated for testing. For SVM evaluation, each training set was randomly divided into 3,957 kernel training and 1,583 sigmoid training portions. The parameter of each kernel type (d and w for the polynomial and Gaussian kernels, respectively) and the magnitude of the constant applied to the soft margin were optimised on the kernel training set separately for AUC, HL χ^2, MSE, and CEE indices by a grid search method, using 3-fold cross-validation. The sigmoid training set was used to convert SVM results into probabilities. Using the training set cross-validation results for each of the performance measures, the best set of parameters for the radial and polynomial kernels were used to generate a model on the entire kernel training set, and a sigmoid for discriminant conversion was generated using the sigmoid training set. Each of the models was then evaluated using the respective test dataset. Logistic regression was chosen to provide the benchmark for SVM comparisons, with similar 3-fold cross-validation performed on each training dataset to optimise feature selection threshold for AUC, HL χ^2, MSE, and CEE performance measures.	Derivation and validation cohorts were created using stratified 5-fold cross-validation. Each variable set was divided randomly into 5 equal subsets, preserving the same event rate in each subset, by first randomly dividing bleeding cases and then non-bleeding cases. Each bleeding subset was then paired with 1 non-bleeding subset. The derivation cohort combined 4 (80%) of the subsets; the remaining subset (20%) was reserved as a validation set. This process was repeated 5 times, such that each of the subsets served as the validation set. Two methods were used to train models in the analysis: logistic regression with LASSO regularisation and gradient descent boosting – XGBoost. The final model used 1,000 trees, a learning rate of 0.1, and a maximum depth of each tree of 6, and it was trained with an objective function aimed at minimising errors similar to logistic regression for binary classification (bleed vs non-bleed).	All recorded variables were considered candidate variables. The variables, once scaled, were fed into an AI-BR. This model trained the base estimator on the training set and observed the training data samples that the base estimator misclassified and created a weighted coefficient for these samples. A second base estimator was then trained, applying the above weight coefficient, to samples when calculating the entropy measure of homogeneity. Boosting was performed to create successive base classifiers that were programmed to place greater emphasis on the misclassified samples from the training data. Finally, a probability of class membership was calculated based on the sum of the individual tree results for each patient. If the sum was >50% probability of bleeding, the patient was predicted to have bled.	Feature selection by information gain measured how much information an attribute gave researchers about the outcome to be predicted. Class-balanced oversampling method was another approach to balance the imbalanced dataset. Drop imputation and mean imputation were individually applied in the dataset to build ML models.
AUC	AUC	AUC, mean squared error, mean CEE, HL goodness-of-fit test	AUC	ROC curve	AUC of ROC curve

LR: logistic regression; ML: machine learning; MLP: multilayer perceptron; MSE: mean squared error; NCDR: National Cardiovascular Data Registry; PCI: percutaneous coronary intervention; PCIRS: Percutaneous Coronary Interventions Reporting System; RENAMI: REgistry of New Antiplatelets in patients with Myocardial Infarction; ROC: receiver operating characteristic; SVM: support vector machine; XGBoost: eXtreme Gradient Boosting

cohorts analysed populations in China[17,18], one cohort analysed populations in Japan[22], and one cohort analysed populations across North America, South America, Europe, and Asia[16]. The small number of countries where these ML models have been developed could limit the generalisability of the results to other potentially underinvestigated, underserved populations. The applicability of the results could also be reduced by the lack of external validation. To date, only one study[16] externally validated

Table 5. Summary table of studies included for each outcome.

Outcome	Number of studies	Studies included
Bleeding AUC	2	Gurm 2014[21] Kulkarni 2021[23]
Acute kidney injury AUC	3	Huang 2018[3] Kulkarni 2021[23] Kuno 2021[22]
In-hospital mortality AUC	5	D'Ascenzo 2021[16] Gao 2020[17] Al'Aref 2019[19] Matheny 2007[20] Kulkarni 2021[23]
Bleeding sensitivity, specificity, PPV, NPV, and accuracy	2	Mortazavi 2019[15] Rayfield 2020[9]
Myocardial infarction sensitivity, specificity, PPV, NPV, and accuracy	1	D'Ascenzo 2021[16]
In-hospital mortality sensitivity, specificity, PPV, NPV, and accuracy	2	D'Ascenzo 2021[16] Gao 2020[17]

AUC: area under the curve; NPV: negative predictive value; PPV: positive predictive value

the model in a multinational cohort. More resources should be allocated to validate the model and apply the results in more diverse patient populations. Another issue of missing data surfaced in our analysis. Four studies did not discuss how missing data were handled. One study conducted complete case analysis by removing patients with missing predictor variable data points. Unclear methods of handling missing data, or complete case analysis, may lead to underpowered studies or bias, especially if the data are not missing at random[34].

Limitations

To the best of our knowledge, this is the first review to critically appraise and review the accuracy of ML models used in predicting outcomes post-PCI. Comprehensive data comprising baseline clinical characteristics, training procedures for ML models, quality of training data and ML outcomes were retrieved, analysed, and synthesised from individual studies to evaluate the accuracy of ML models in predicting pertinent post-PCI outcomes.

Nonetheless, this study should be interpreted in the context of known and potential limitations. Firstly, there existed significant heterogeneity among the studies included in this systematic review. For the clinical predictors reported, while the categories of predictors used were largely similar, the individual predictors included in each category differed across the studies. The baseline demographics of study populations also differed, and the duration of follow-up for post-PCI outcomes was not reported in the majority of the included studies. Most studies examined supervised machine learning techniques such as LASSO and random forest models **(Table 4)**. Also, the performance between different models, particularly that of deep learning networks and traditional supervised ML models, was not reported. Further studies should be conducted to explore the different ML models and to determine which ML models have the best predictive performance.

Secondly, while the quality of training data was overall high, the majority of the studies (n=10) were retrospective in nature, which may further introduce bias into the training of ML models. Moreover, software algorithms and training procedures employed for ML models across studies were not standardised. Also, ML models can be very sensitive to the optimisation model chosen[20]. Thus, caution should be exercised before declaring any model to be superior to other risk prediction tools.

Thirdly, the "black box" technology of ML models leads to these models being complex and unpredictable because of a lack of transparency about the underlying decision-making processes. Input data may undergo complex transformations in multiple layers of the algorithm, with the relationship between individual clinical predictors and contribution of each predictor to the outcome unknown to the user[35]. The complex datasets utilised in ML models may also be prone to missing data, unmeasured confounding, and systemic errors, all of which may further compromise the validity of the models' predictions[35]. Also, ML models with low sensitivity may miss patients at risk of adverse outcomes post-PCI. This may impact clinicians' ability to accurately weigh the risks and benefits of elective PCI, affect preprocedural counselling, and may potentially lead to medico-legal issues. To mitigate this issue, the developers of ML algorithms should define the purpose (screening vs diagnosis) of the ML models and choose a binary threshold in the validation set to derive appropriate sensitivities. In the usage of low-sensitivity ML models, outcome predictions made using ML models must ultimately still be interpreted cautiously in appropriate clinical contexts, which should be done by experienced clinicians.

Lastly, while the findings of our research are informative and useful for understanding PCI outcomes, it is important to acknowledge that they may not be universally applicable to all scenarios. This is due to the fact that all of the included studies are single-centre studies, four of them have unclear data handling strategies, and only three externally validated the models presented. This significantly increases the risk of overfitting to training data, limiting the interpretation of good model performance. Thus, it is challenging to comment on the definitive benefit of real-world effectiveness. The majority of the studies also focused on the USA (seven studies), with two studies focused on China, but not other countries, limiting generalisability. In light of the fact that the robustness and generalisability may be overstated, PROBAST was performed. Ultimately, outcome predictions by ML models must still be interpreted judiciously and contextualised to each case.

Conclusions

In this systematic review, we demonstrated that ML models may be a valuable clinical adjunct to existing traditional risk stratification scores in predicting outcomes post-PCI, with moderate to high NPV and AUC. Such a clinical tool may one day guide clinicians in prognostication of complications and the selection of patients with

the most optimal risk-benefit profile to undergo the procedure. The limitations of the findings are difficult to address in the near future, as the data and technological needs to incorporate ML models into daily clinical practice would require some time to develop. Given the heterogeneity and retrospective design of the studies analysed, future prospective studies are required to investigate the accuracy of ML models more consistently. Employment of larger datasets to train ML models, and refinement of existing ML algorithms via improvements in development and validation may also help to improve the sensitivity, specificity, predictive values, and accuracy of ML models to facilitate their meaningful use in clinical practice.

Impact on daily practice

We suggest that machine learning (ML) can be used as an adjunct to help clinicians weigh the risks and benefits of percutaneous coronary intervention (PCI) versus continued medical therapy in elderly patients with multiple comorbidities who are at higher risk of complications. When a patient presents for elective PCI, clinicians can extract demographic data and past medical history from the electronic health records and enter them into the ML algorithm. Following a targeted history, physical examination, and investigations, clinicians can input further relevant data, including preprocedural imaging data, into the ML algorithm, to determine the potential benefit and personalised risk, so that patients can make a better-informed decision. By selecting the most suitable patients with precision medicine, morbidity, mortality, and healthcare burden can be decreased.

Availability of data and materials

Data used for this study can be accessed upon request from the principal investigator (Dr Ching-Hui Sia) at: ching_hui_sia@nuhs.edu.sg

Funding

C.-H. Sia was supported by the National University of Singapore Yong Loo Lin School of Medicine's Junior Academic Fellowship Scheme.

Conflict of interest statement

H.C. Tan is a deputy editor at AsiaIntervention. The other authors have no conflicts of interest to declare.

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Supplementary data

Supplementary Table 1. Search terms.

Supplementary Table 2. Evaluation of risk of bias using the Newcastle-Ottawa Scale (NOS).

Supplementary Table 3. Evaluation of risk of bias using the Prediction Risk of Bias ASsessment Tool (PROBAST).

Supplementary Table 4. Additional data on participant baseline characteristics (demographics).

Supplementary Table 5. Additional data on participant baseline characteristics (medications).

Supplementary Table 6. Additional data on participant baseline characteristics (procedure).

Supplementary Table 7. Quality assessment of included studies.

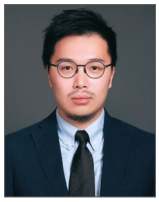
Supplementary Table 8. Clinical predictors and outcomes involved in the training of different ML models.

Supplementary Figure 1. PRISMA 2020 checklist.

The supplementary data are published online at: https://www.asiaintervention.org/
doi/10.4244/AIJ-D-23-00023

AsiaIntervention 2024;10:233-235

First-in-human novel pacing-over-the-wire technique during TAVR with the SENTINEL cerebral protection device: the SENTIPACE pilot study



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When performing transcatheter aortic valve replacement (TAVR), intraprocedural rapid ventricular pacing is mandatory to ensure transient ventricular standstill during certain moments of transcatheter aortic valve (TAV) positioning and deployment, as well as during pre- and post-balloon dilatation, if necessary. Compared with right ventricular (RV) stimulation using a temporary pacing lead, left ventricular (LV) stimulation during TAVR has been shown to be associated with significantly reduced procedure duration, fluoroscopy time, and cost, with similar efficacy and safety[1]. The conventional LV pacing-over-the-wire technique utilises an external pacemaker (pulse generator) with two alligator clamps. One alligator clip, which acts as a cathode, is attached to the external part of the LV guidewire, with either the balloon catheter or TAV delivery catheter as an insulator. Another alligator clip, which acts as a grounding anode, is attached to the patient's subcutaneous tissue by either a fine-gauge needle or directly biting the skin at the edge of the skin incision[1]. The major disadvantages of this conventional LV pacing technique include (1) the patient's discomfort, incurred when attaching the alligator clip to the subcutaneous tissue, (2) inadvertent muscle stimulation at the groin region where the alligator clip is attached to the subcutaneous tissue, and (3) risk of operator injury if a fine-gauge needle is used to attach the alligator clip. Therefore, a novel LV pacing-over-the-wire technique, the SENTIPACE technique for TAVR using the SENTINEL (Boston Scientific) cerebral protection device (SENTIPACE: SENTInel coronary guidewire – LV guidewire PACing stratEgy), was invented to mitigate the above-mentioned disadvantages and further streamline TAVR procedural steps[2].

The current study was a physician-initiated, prospective, single-arm, first-in-human, pilot study using the SENTIPACE technique for intraprocedural rapid ventricular pacing during TAVR. The study included 25 consecutive patients who underwent transfemoral TAVR with the SENTINEL cerebral protection device at Queen Elizabeth Hospital, Hong Kong SAR, during 2023. It was approved by an internal ethical committee. All patients provided written informed consent. In the SENTIPACE technique, the alligator clip that acts as the grounding anode is attached to the external part of the coronary guidewire that is loaded in the SENTINEL device, instead of the patient's subcutaneous tissue. The other alligator clip, which acts as a cathode, is attached to the external part of the LV guidewire **(Figure 1)**. The ventricular output of the pacemaker delivering a constant voltage (V) was standardised and set at an output of 10 V. The primary endpoint was the efficacy and safety of pacemaker stimulation. Efficacy was defined as achievement and maintenance of a systolic blood pressure of less than 60 mmHg for more than 10 seconds without loss of capture. The safety of pacemaker stimulation was characterised by a combination of procedural success and major adverse clinical and cerebrovascular events.

A total of 25 patients were enrolled. Baseline patient, procedural and postprocedural characteristics are reported in **Table 1**. Effective

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SUBMITTED ON 14/01/24 - REVISION RECEIVED ON 02/06/24 - ACCEPTED ON 26/06/24

DOI: 10.4244/AIJ-D-24-00002

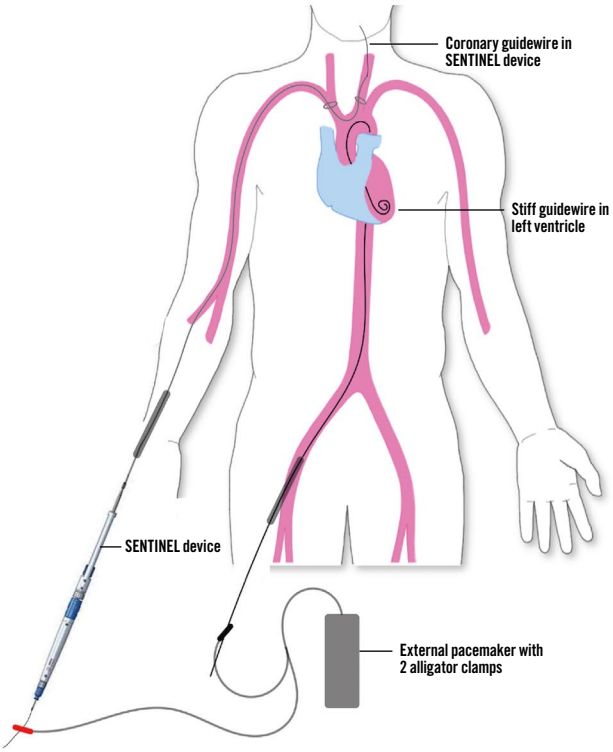

Figure 1. *Schematic diagram of the SENTIPACE setup during TAVR. Either a balloon catheter or TAV delivery catheter is required as an insulator over the LV stiff wire. LV: left ventricle; TAV: transcatheter aortic valve; TAVR: transcatheter aortic valve replacement*

ventricular stimulation was achieved in all patients using a voltage output at 10 V. There was no conversion to conventional LV pacing-over-the-wire or RV stimulation strategy. Both balloon-expandable valves (SAPIEN 3 [Edwards Lifesciences]; 20%) and self-expanding valves (Evolut PRO+ [Medtronic], Navitor [Abbott], ACURATE *neo*2 [Boston Scientific], ALLEGRA [Biosensors]; 80%) were used. The TAVR procedural success rate was 100% with a single TAV deployed. There was no more than or equal to moderate paravalvular leakage on the transthoracic echocardiogram post-TAVR. There were no cerebrovascular events at clinical follow-up at 30 days. One patient, who had severe aortic valve stenosis with septic shock and emergency TAVR, succumbed at day 14 post-TAVR because of severe pneumonia. In one patient, TAVR was complicated with a ruptured sinus of Valsalva and cardiac tamponade, though the procedure was successfully rescued by pericardiocentesis and coil embolisation.

The main finding of this pilot study was that use of the LV stiff wire and coronary guidewire in the SENTINEL device for rapid ventricular pacing during TAVR was effective and safe across different TAV platforms. LV stimulation was shown to be as effective as RV stimulation and to have advantages over a standard temporary pacing wire[1]. By further modifying the LV stimulation technique, the SENTIPACE pacing strategy allows further simplification and streamlining of the TAVR procedure.

Table 1. Baseline patient, procedural and postprocedural characteristics.

Characteristic	Whole study population, N=25
Age, yrs	79.76±8.85
Sex	
Male	10 (40)
Female	15 (60)
BSA, m^2	1.62±0.18
Medical history	
Hypertension	14 (56)
Diabetes	9 (36)
Hyperlipidaemia	16 (64)
Smoker	2 (8)
Previous MI	0 (0)
Previous TIA/stroke	2 (8)
Previous PCI	6 (24)
Previous CABG	0 (0)
Previous cardiac surgery	1 (4)
Pacemaker	3 (12)
STS score, %	5.00±3.57
LVEF, %	51.10±14.49
AVA, cm^2	0.62±0.14
Transaortic mean gradient, mmHg	52.24±16.72
TAV type	
SAPIEN 3[a]	5 (20)
Evolut PRO+[b]	11 (44)
Navitor[c]	5 (20)
ACURATE *neo2*[d]	2 (8)
ALLEGRA[e]	2 (8)
Number of TAV devices implanted 1	25 (100)
Type of coronary guidewire used inside SENTINEL[d] device	
BMW UNIVERSAL II[c]	22 (88)
Runthrough NS Floppy[f]	3 (12)
Type of stiff guidewire used in left ventricle SAFARI[2d]	25 (100)
Efficacy of pacing stimulation	25 (100)
Predilatation	
Yes	24 (96)
No	1 (4)
Post-dilatation	
Yes	10 (40)
No	15 (60)
Procedural success	25 (100)
Procedural duration, min	81.96±48.36
Fluoroscopy time, min	26.40±17.76
Postprocedural LVEF, %	54.0±10.5
Postprocedural AVA, cm^2	1.85±0.46
Postprocedural mean gradient, mmHg	9.38±4.52
Postprocedural paravalvular leak	
None	15 (60)
Trivial	5 (20)
Mild	5 (20)
Clinical outcomes at 30 days	
All-cause mortality	1 (4)
Permanent pacemaker	1 (4)
Haematoma	1 (4)
Cardiac tamponade	1 (4)
Stroke	0 (0)
MI	0 (0)

Values are mean±standard deviation, or number (%). [a]By Edwards Lifesciences; [b]by Medtronic; [c]by Abbott; [d]by Boston Scientific; [e]by Biosensors; [f]by Terumo. AVA: aortic valve area; BMW: BALANCE MIDDLEWEIGHT; BSA: body surface area; CABG: coronary artery bypass graft; LVEF: left ventricular ejection fraction; MI: myocardial infarction; PCI: percutaneous coronary intervention; STS: Society of Thoracic Surgeons; TAV: transcatheter aortic valve; TAVR: transcatheter aortic valve replacement; TIA: transient ischaemic attack

The current first-in-human study lacks the power needed to determine the statistical significance of the main safety analysis or of the effectiveness endpoint. A larger randomised study would be needed to confirm our findings. The minimal pacing threshold was not tested. Although effective ventricular stimulation was achieved in all patients using a voltage output at 10 V in this study, a higher voltage output can be adopted in cases where effective ventricular stimulation cannot be achieved, as the pacing threshold depends on different combinations of guidewires and patient body resistance.

In this pilot study, the SENTIPACE technique was shown to provide a safe and effective method for rapid ventricular pacing during TAVR with the SENTINEL cerebral protection device. This pacing strategy can effectively and reliably streamline TAVR by further reducing procedural steps.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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AsiaIntervention 2024;10:236-238

Letter: Deciphering a "curious" coronary artery anatomy

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I enjoyed the contribution of Kharel et al[1] about a 74-year-old male patient with anterior wall ST-segment elevation myocardial infarction, in whom coronary angiography showed a bilaterally arising (type IV) dual left anterior descending coronary artery (LAD). A culprit diagonal artery was considered small in size; therefore, the patient was managed medically for the infarction. According to the authors, additional investigation with computed tomography coronary angiography (CTCA) showed a long LAD with a malignant interarterial course arising from the right coronary artery (RCA).

In this letter, I comment on the course of the long LAD connected to the RCA, which I believe is one that passes through the superior aspect of the crista supraventricularis in a subendocardial position and then intramyocardially inside the upper interventricular septum to reach the anterior interventricular sulcus, i.e., an intraseptal course. Previous studies demonstrated that when the initial trajectory of a left main coronary artery (LMCA) or LAD arising from the right aortic sinus, forms a caudal anterior loop to the left in the right anterior oblique (RAO) projection, it follows a subpulmonary or intraseptal course[2]. This course can also be identified by the presence of a septal perforator branch (SPB) that arises from the proximal segment of the anomalous artery as its first branch[2,3]. Furthermore, the site of origin of such an SPB typically indicates the passage of the anomalous artery through the upper interventricular septum; therefore, this segment of the anomalous vessel often shows αngiographic "milking" like a myocardial bridge. In contrast, the interarterial course, i.e., between the aortic root and pulmonary trunk, forms a cranial posterior loop in the RAO projection without proximal branching into an SPB and without phasic external muscular compression. Indeed, in the article in question, the proximal long LAD supplied an SPB as its first branch, which suggests an intraseptal course. Furthermore, the angiographic picture of the long LAD presented in an RAO cranial projection correlates with an intraseptal course, which appears stretched and is longer, more oblique and anterolateral in direction compared with an interarterial course, which is short and curved and is directed posteriorly between the aorta and the main pulmonary artery[4]. In making the distinction between interarterial and intraseptal courses, CTCA is of great value, as the interarterial proximal course of the long LAD would have been depicted above the pulmonary valve and, on coronal images, *en face* as a radiopaque oval structure between the ascending aorta and pulmonary trunk (Angelini/Cheong sign)[4]. However, it is unlikely that the Angelini/Cheong sign was displayed in the article in question, because the intraseptal proximal course of the long LAD was caudal to the pulmonary valve.

An anomalous right-sided LMCA or LAD with an intraseptal course generally has a benign clinical prognosis[3]. However, in

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SUBMITTED ON 08/03/2024 - ACCEPTED ON 31/05/2024

DOI: 10.4244/AIJ-D-24-00015

view of previous reports describing cardiac events, such as stable or unstable angina, malignant arrhythmias and sudden cardiac death, in association with an intraseptal LMCA, this course should be considered important in symptomatic patients[5]. Phasic muscular compression and/or spasm of the intramyocardial ectopic segment are likely mechanisms of ischaemia that can be tackled with pharmacological treatment, although surgery may be required in intractable cases.

Conflict of interest statement

A.Y. Andreou has no conflicts of interest to declare.

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