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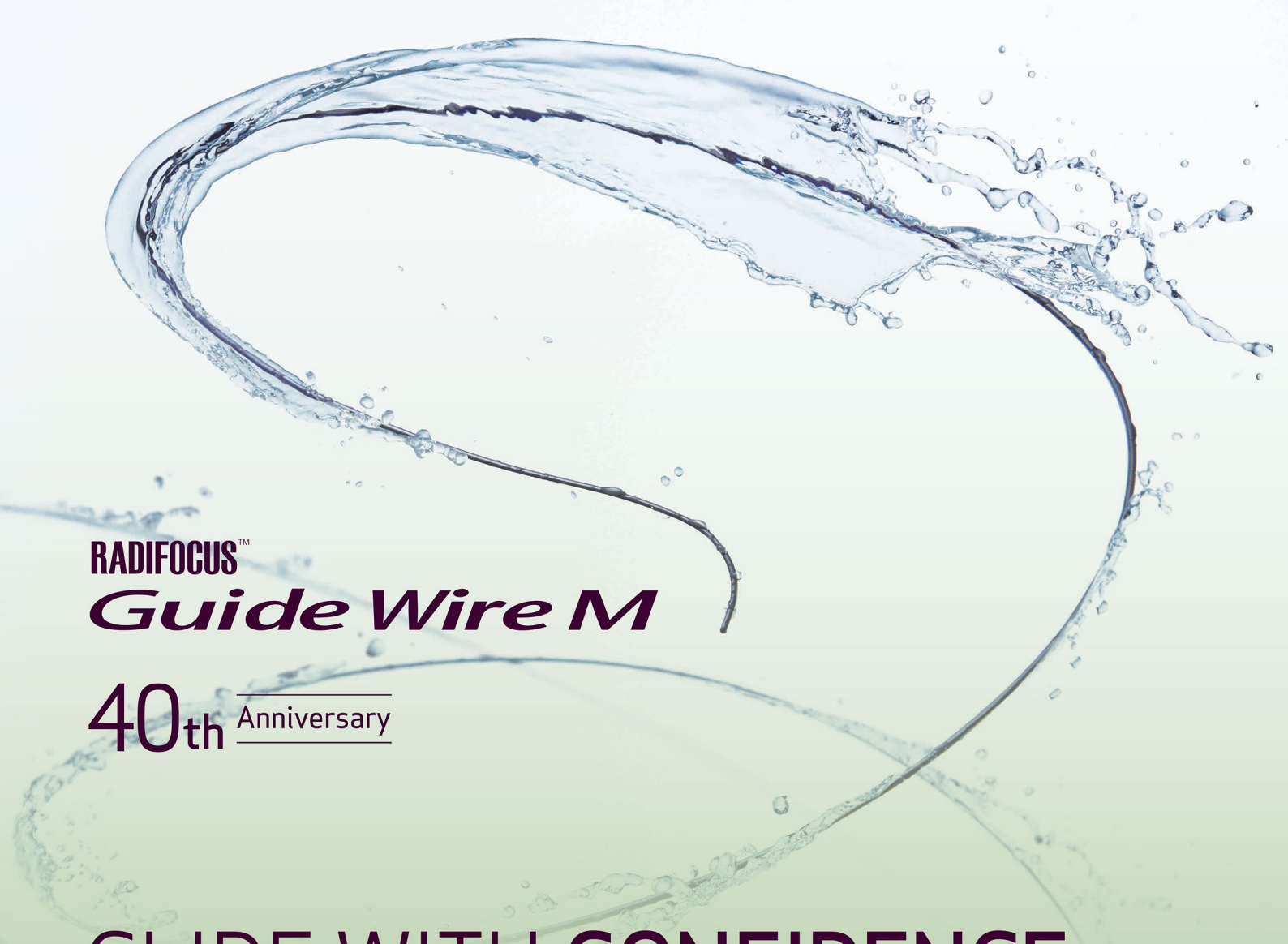

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Cardiogenic shock in women; PCSK9 inhibitors and non-culprit lesions; coronary microvascular dysfunction; residual shunt after PFO closure; the SESAME technique; TAVI in pure aortic regurgitation; design of the ALL-RISE trial; 3-year results from BIOMAG-I; scaffold therapy for infrapopliteal disease; carbon footprint of an angiogram; the Cathpax AIR cabin; and more

Davide Capodanno, *Editor-in-Chief*

It's now been five years since I took on the responsibility of leading this Journal; five occasions to experience the unique anticipation that accompanies the announcement of a new Impact Factor. This moment typically arrives towards the end of June, putting an end to weeks of projections and calculations that, as you might imagine, every journal performs using the data available to them. Over time, we've all become more adept at interpreting the trends and estimating our likely score; in fact, our recent forecasts were only off by a few decimal points. This year, however, we had strong reason to expect a milestone – and indeed, it came: an Impact Factor of 9.5, the highest ever recorded in EuroIntervention's 20-year history.

We always say that an Impact Factor is just a number, and this year is still no exception. But what many may not realise is that, in the days that follow the release, there is an intense effort to understand what, exactly, went right. In this case, the increase has been so pronounced that it feels like a genuine leap forward – qualitatively as well as quantitatively – into a new phase of the Journal's development.

And yet, identifying the specific drivers behind this result is not straightforward. The formula is simple, but deceptively so. Ultimately, the rise can be attributed to a marked increase in citations – seen, of course, in the numerator of the equation – combined with careful control of the denominator, the only element truly under editorial control. The citations, however, were the key factor. And when we look more closely at our most-cited content, a clear pattern emerges – that original research articles play the leading role – followed by other formats we value deeply and continue to cultivate.

And when we do an even deeper analysis of citation patterns, no single dominant theme emerges. While innovation is certainly highly cited, no single topic stands above another. This confirms what we have long aimed for: that EuroIntervention is considered a well-rounded journal, capable of engaging a diverse readership with varied interests.

One of the most rewarding effects of a rising Impact Factor is the ability to attract ever more impactful submissions. Remaining just shy of the symbolic threshold of 10 is, in some ways, beneficial – it keeps us grounded and focused on the work still ahead.

The fact that our rising impact is grounded in the original science entrusted to us by the community to be amplified and promoted through our publication is a particular source of pride, and I wanted to share that with all of you: authors, readers, editors, and reviewers alike.

And now, let me show you why this current issue follows closely in the tradition that has allowed EuroIntervention to be where we are today.

We start with a joint expert consensus statement on cardiogenic shock (CS) in women from the Society for Cardiovascular Angiography & Interventions (SCAI), the European Association of Percutaneous Cardiovascular Interventions (EAPCI) and the Association for Acute Cardiovascular Care (ACVC). Current practice guidelines provide no sex-specific guidance to optimise outcomes in women who experience CS, and the in-hospital mortality rates for women due to CS remain close to 50%. Intended as a resource to guide practitioners and to help orient the urgently needed future studies, **Suzanne J. Baron, Alexandra J. Lansky and colleagues** examine how women are currently treated for CS across the spectrum of cardiovascular disease, identify the major evidentiary gaps that remain and provide consensus tips for sex-specific treatment.

Our series of original research articles begins with one from the FITTER trial, conducted by **Frans B. Mensink, Robert-Jan M. van Geuns and colleagues**. The authors investigate the effects of intensive lipid-lowering therapy on the haemodynamics of non-culprit lesions in acute coronary syndrome patients at 12-week follow-up. Patients received either evolocumab or placebo added to a high-dose statin with primary endpoints of changes to fractional flow reserve and lipid core burden index. In an accompanying editorial, **Hector M. Garcia-Garcia** argues that despite the lack of statistically significant differences between the two groups, this study provides important insights on how PCSK9 inhibitors influence coronary plaques.

Next, in original research, **Thabo Mahendiran, Bernard De Bruyne and colleagues** probe the relationship between coronary flow, microvascular resistance and subtended myocardial mass. Using data from patients with angina with non-obstructive coronary arteries who underwent both continuous intracoronary thermodilution and coronary computed tomography angiography, they investigate whether the disturbed resistance and flow patterns seen in coronary microvascular dysfunction (CMD) persisted after indexing by subtended myocardial mass. Their findings support the notion of hyperaemic flow restriction at the tissue level in patients with structural CMD but do not find a clear pathophysiological mechanism for symptoms in functional CMD.

We then turn to an original study on evaluating residual shunt (RS) after patent foramen ovale closure and the safety and feasibility of percutaneous treatment of the shunt. As there is no consensus on an optimal device for this procedure, authors **Kristian Ujka, Giuseppe Santoro and colleagues** identify and classify the mechanisms of RS and perform detailed imaging of the atrial septal anatomy to select the most effective closure approach. Using five different devices, the authors conclude that, regardless of the device chosen, the procedure is safe and effective. In an accompanying editorial, **Eric Horlick and Lusine Abrahamyan** comment on intervening after this type of treatment.

Continuing in original research, **James M. McCabe, G. Burkhard Mackensen and colleagues** evaluate the safety and efficacy of septal scoring along the midline endocardium – the SESAME technique – a novel transcatheter intervention that mimics surgical myotomy. In this single-centre, real-world registry, the authors describe the evolution of their use of SESAME for septal

reduction therapy prior to transcatheter mitral valve replacement to include patients with obstructive hypertrophic cardiomyopathy and subvalvular aortic stenosis. Despite the technical challenges of the procedure, SESAME provides an alternative for high-risk surgical patients; it has demonstrated favourable gains in the left ventricular outflow tract area and improved safety.

The lack of calcified structures in patients with pure aortic regurgitation means there are limited possibilities for anchoring a valve in patients undergoing transcatheter aortic valve implantation. In our final original research article, **Fei-Cheng Yu, Guang-Yuan Song and colleagues** propose a novel anatomical classification system using multidetector computed tomography. Their AURORA classification system incorporates multiplanar assessments of the aortic root and strategic device positioning to yield high device success rates and low permanent pacemaker implantation rates.

Turning to trial design, **Björn Redfors, Martin B. Leon and colleagues** present the design and rationale of the ALL-RISE trial, in which fractional flow reserve angio-guided treatment is compared for non-inferiority to pressure wire-guided treatment in patients with coronary artery disease. The primary endpoint is major adverse cardiovascular events at 1 year, including all-cause death, myocardial infarction (MI), or unplanned clinically driven revascularisation. The secondary endpoints include assessments of procedure time, contrast and resource use, and the procedure's cost-effectiveness. Enrolment was completed in January 2025.

In the first of three research correspondences, **Michael Haude, Ron Waksman and colleagues** present the 3-year clinical outcomes of the BIOMAG-I study. A full two years after complete scaffold resorption of the study device, the DREAMS 3G, there was no cardiac death, no target vessel MI, and no definite, probable or possible scaffold thrombosis reported, along with a low rate of target lesion failure. These favourable results suggest that bioresorbable scaffolds may have a comeback in future therapeutic options.

Next, **Michael K.W. Lichtenberg, Thomas Zeller and colleagues** share the 1-year outcomes of the DEEPER OUS Study in which patients with infrapopliteal disease were treated with retrievable scaffold therapy (RST) prior to drug-coated balloon angioplasty. RST uses a temporary self-expanding stent with microspikes to create arterial wall microchannels for enhanced drug delivery. The 1-year outcomes show RST to be safe and effective, and that, in addition to leaving no permanent implant behind, it may mitigate the negative impact of arterial recoil seen in percutaneous transluminal angioplasty and improve drug delivery.

We then take a look at the healthcare sector's prominent role in global greenhouse gas emissions – the 5th largest emitting entity on the planet – by estimating the overall carbon footprint of a coronary angiography procedure. **Coralie Leiszt, Vassili Panagides and colleagues** document how they estimated this carbon footprint. In addition to calculating an overall footprint, the authors detail the constituent elements of the procedure – medications, disinfection, drapes, building energy, and disposal – and offer some initial ideas on how to make a coronary angiography less impactful on the environment.

In our final research correspondence, **Axelle Merieau, Patrice Guerin and colleagues** report on the radiation protection and ergonomics of the Cathpax AIR cabin, designed to improve operator safety during structural procedures and coronary angiography/angioplasty. The different procedures were randomised and performed with or without the cabin, and the endpoints examined total radiation as well as individual body part exposure with results showing reduced exposure, particularly concerning the skull, eyes and extremities.

This issue also includes a flashlight from authors **Teresa Bastante, David del Val and Fernando Alfonso** on an atypical finding on optical coherence tomography during coronary vasospasm; a letter and reply to the editor; and more, so let's begin.

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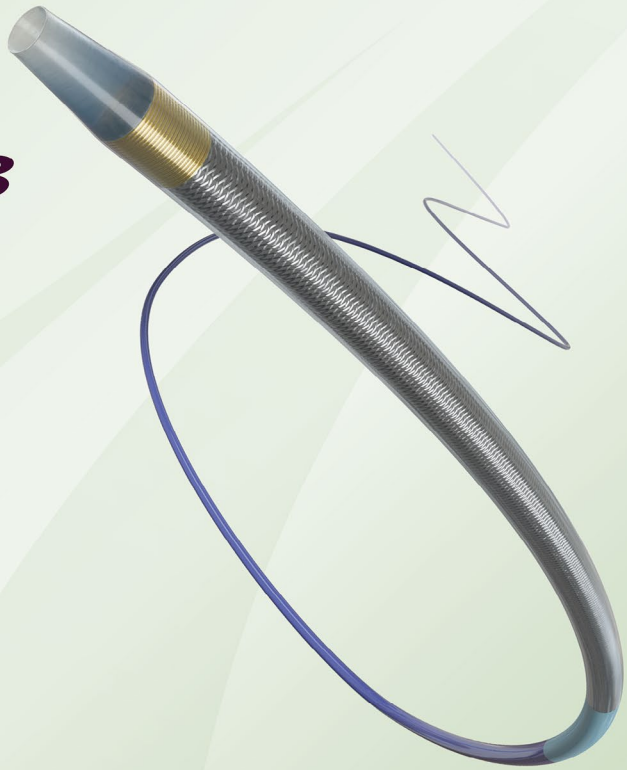

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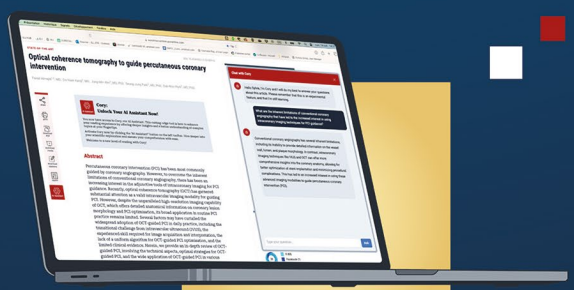

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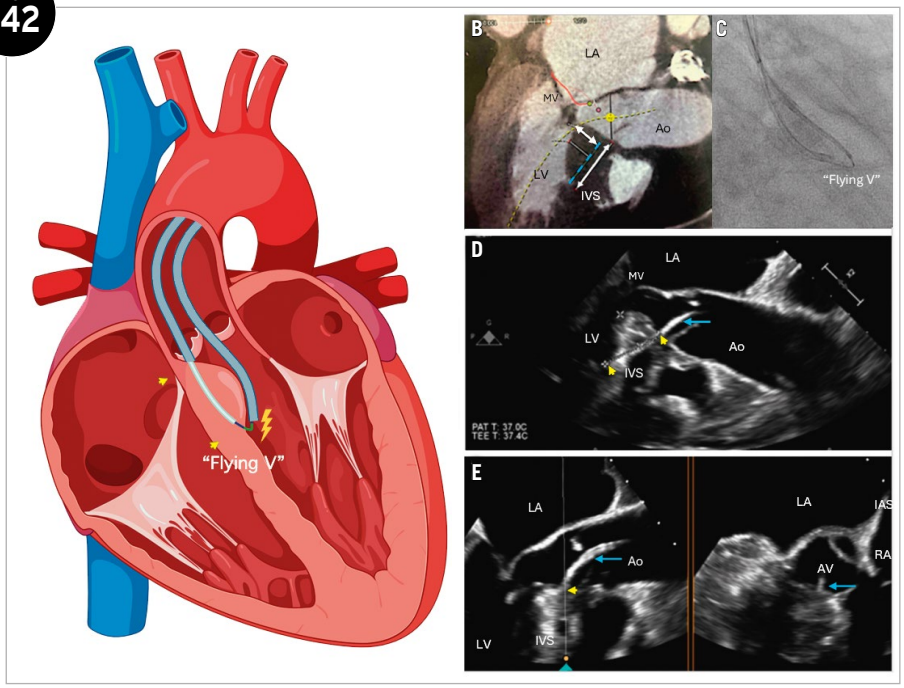

Image taken from the following paper printed in this issue:
SESAME technique: septal scoring along the midline endocardium
James M. McCabe, Shauna Newton, Barbara A. Danek, David Elison, Christine J. Chung, Richard Sheu, Srdjan Jelacic, Gregory J. Condos, Ester Canovas, Adam B. Greenbaum, Vasilis C. Babaliaros, Robert J. Lederman, G. Burkhard Mackensen
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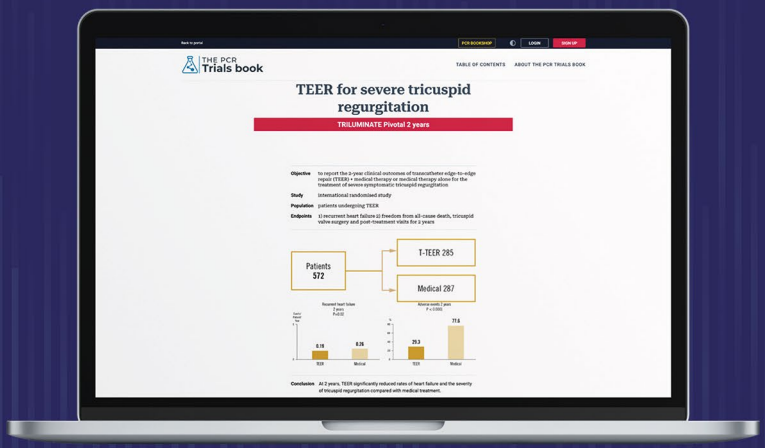

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"He who has eyes to see, let him see"

Hector M. Garcia-Garcia*, MD, PhD

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Over the past two decades, lipid-lowering interventions have been one of the most used and effective treatments for modifying a patient's cardiovascular risk and plaque composition. It has also been demonstrated that the intensity of their effect matters; the lower the low-density lipoprotein cholesterol (LDL-C), the higher the reduction in risk and the more "stabilising" the plaque modifications.

In this issue of EuroIntervention, Mensink et al present the results of the FITTER study[1], in which the main research question was whether evolocumab, plus statin, influences ischaemia-producing coronary plaques in a short period of time. Following a well-executed randomised clinical trial, the authors summarised the main results as follows: "… no between-group differences were found between evolocumab- and placebo-treated patients". I agree with the authors that there was no statistically significant difference, but this does not equate to the absence of clinical relevance, since their results help to understand the developing changes in coronary plaque as induced by proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i).

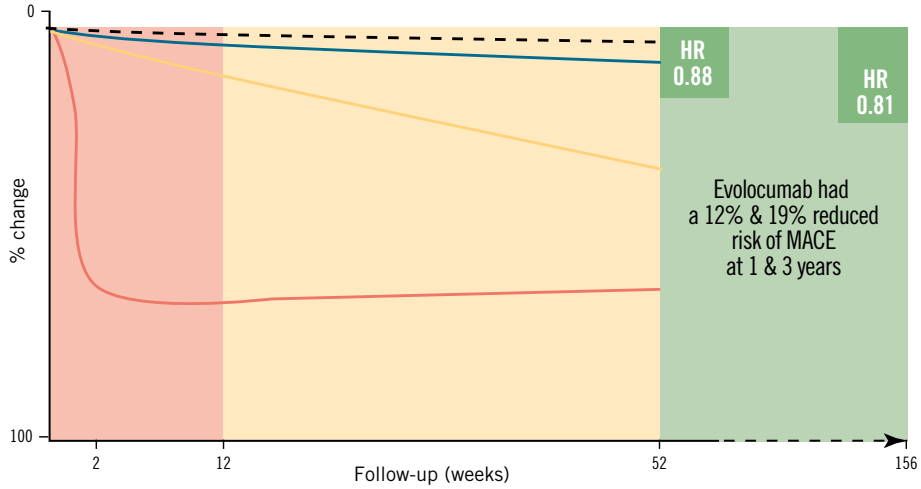
Article, see page 910

The study's main endpoints were lipid core burden index (LCBI) and fractional flow reserve (FFR). The merits of each of these variables are discussed here below.

The lipid core burden index: coronary lipid content, as measured by near-infrared spectroscopy (NIRS) intravascular ultrasound (IVUS), has been associated with an increased risk of cardiovascular events[2]. The main outcome variable is LCBI. LCBI is then a high-risk plaque future whose changes have been assessed by using high-intensity statin therapy (HIST) alone or in combination with PCSK9i. In the IBIS-3 study[3], HIST (i.e., rosuvastatin) alone did not show a sizeable effect on LCBI after 1 year of treatment. Conversely, the PACMAN-AMI trial[4,5] showed that the combination of HIST plus alirocumab (PCSK9i) changed the LCBI by –79.42 at 52 weeks (from 260.6; the % difference is 30.48) **(Figure 1)**; whereas in the FITTER study, LCBI changed by –27.8 at 12 weeks (from 354.7; the % difference is 7.78) **(Figure 1)**. Of note, the extent of these compositional changes was not followed by a change of similar magnitude in plaque size as measured by percent atheroma volume (PAV); in the former study the PAV changed by 5.2%, and in the latter, the PAV changed by 1%. Furthermore, these plaque changes should be put into context with the LDL-C reduction occurring in these patients; the LDL-C values reduced by ~60% within two weeks.

The beneficial PCSK9i effects are seen across three periods **(Figure 1)**: first, in the blood, followed by the plaque, and finally, clinically. The chemical changes in blood are seen within 2 weeks and maintained thereafter. The compositional (lipid) changes start to be relevant by the 12-week timepoint and are probably at their best at 52 weeks, when we observed the divergence of the Kaplan-Meier curves, showing a reduction in clinical outcomes in the FOURIER study[6]. Thus, it is assumable that blood and plaque composition needed to change first to matter in terms of the reduction of clinical outcomes.

The fractional flow reserve: it is uncommonly used as an endpoint in lipid-lowering trials. Looking at **Figure 1**, the reader may understand that it is because the changes in minimum lumen area (MLA), which are the strongest determinant of FFR, are small and slow to develop. Thus, the FFR is not expected to change rapidly. In the FITTER study,



	Relative change from baseline		
Follow-up, weeks	12 (FITTER study)	52 (PACMAN-AMI trial)	156 (FOURIER study)
Minimum lumen area, mm²	**=0.0%**	**↑2.5%**	
Percent atheroma value	**↓1.0%**	**↓5.2%**	
Lipid core burden index (LCBI)	**↓7.78%**	**↓30.48%**	
LDL-cholesterol	**~↓60%**	**~↓60%**	
***MACE is cardiovascular death, myocardial infarction, stroke, hospitalisation for unstable angina, or coronary revascularisation**		**Hazard ratio 0.88 (95% CI: 0.80-0.97)**	**Hazard ratio 0.81 (95% CI: 0.73-0.89)**

Figure 1. *Proprotein convertase subtilisin/kexin type 9 inhibitors' effects on coronary plaque and outcomes. Blood (shaded red) and plaque (shaded orange) changes are observed before clinical outcomes (shaded green). The graph shows the overall rate of change in minimum lumen area (black dashed line), percent atheroma value (blue line), lipid core burden index (yellow line) and LDL-cholesterol (red line) in the FITTER study up to 12 weeks and in the PACMAN-AMI study up to 52 weeks. The far-right green shaded area shows the clinical outcome results up to 156 weeks in the FOURIER study. CI: confidence interval; HR: hazard ratio; LDL: low-density lipoprotein; MACE: major adverse cardiac event*

the MLA did not change from baseline to 12 weeks, while in the PACMAN-AMI study, MLA increased by 0.15 mm², which represents a 2.5% increase **(Figure 1)**.

Taken all together, it means that the patients/lesions enrolled in the FITTER study started to get "fit" by experiencing changes in the composition of the plaque that was "converting" lipid into a different tissue type and thereby not impacting overall plaque size; this dynamic process of "substituting" tissue types has been documented in the optical coherence tomography trials, in which fibrotic tissue increased thickening of the cap while the lipid arc decreased[7]. Additionally, through the PACMAN-AMI trial results, it appears that the compositional changes continue to occur at a faster rate compared to the overall plaque size and a discreet change in lumen size at 52 weeks.

Unlike most clinical randomised trials evaluating coronary artery disease progression/regression, the FITTER study included more severe and advanced lesions which were ischaemia-producing (FFR range of 0.67-0.85). The investigators' rationale for including these lesions was based on the expectation of observing a more pronounced effect. While their expectation is based on previous research reports, it may also mean that the lesions were more calcified – lesions which have been reported to be more "resistant" to undergoing changes in size in response to systemic therapies[8].

Mechanistic studies using imaging advance the understanding of the evolution of atherosclerosis and its response to systemic therapies. More importantly, they provide information that may explain the clinical benefits of these therapies.

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Conflict of interest statement

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EDITORIAL

Does a positive bubble study after PFO closure matter: is it much ado about nothing or an indication for reintervention?

Eric Horlick[1]*, MDCM; Lusine Abrahamyan[2,3], MD, MPH, PhD

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The publication of major randomised controlled trials (RCTs) about patent foramen ovale (PFO) provided much needed evidence that made a longstanding intervention a mainstream cryptogenic stroke prevention strategy. In our real-world study of 479 patients with the Amplatzer PFO Occluder (Abbott), at the median follow-up of 9.3 years, we noted a 1.5% risk of stroke (0.16/100 person-years) and 4% risk of transient ischaemic attack (TIA; 0.44/100 person-years)[1].

Few things are as disheartening to patients and physicians alike than a positive bubble study after PFO closure. Wasn't this the reason we pursued device closure at the outset? It is a source of anxiety and consternation that prompts the question "what do we do now?"

We do not have an ideal methodology to evaluate the risk of stroke recurrence after PFO closure. We default to the use of saline contrast echocardiography, which typically has 16-38 µm microbubbles, larger than the 7-8 µm diameter of pulmonary capillaries. These bubbles may shrink in size when dissolved in a solution because of the effects of diffusion and surface tension. Smaller bubbles may traverse the lung circulation, leading to false positive results. Pseudocontrast, the appearance of weakly echodense material from the pulmonary veins following a Valsalva or cough, may also contribute[2].

In practice, bubble studies are rarely homogeneous as a group, with variable right atrial opacification. A large Eustachian valve often prevents bubbles from approximating the septum diagnostically. While different quantification schemas have been used in RCTs, it seems almost absurd to use a single two-dimensional image to quantitate a three-dimensional volume where bubbles move rapidly in and out of the echocardiographic imaging plane.

Whether or not a positive bubble study after PFO closure is materially significant as a risk for recurrent stroke is a very important and, as yet, unresolved issue. Cohort studies examining this issue are often methodologically flawed, lump stroke and TIA together to increase power, and are insufficiently adjudicated[3,4]. If a positive bubble study is going to be used to justify a second, much less studied intervention, it is quite important to establish this more definitively.

In a pooled analysis of individual patient data from all PFO RCTs, complete PFO closure, defined as no residual shunt (RS) at 6-18 months post-procedure, was observed among 89.9% of 1,475 patients[5]. At a median follow-up of 57 months, recurrent ischaemic stroke was reported in 2.3% of patients with complete closure compared with 2.7% with any RS (p=0.74). The rate of the composite outcome of recurrent ischaemic stroke, TIA, or vascular death was also not different between the groups (5.0% vs 6.0%; p=0.58). Is a positive bubble study important, or is the device which holds the PFO, previously wafting in the breeze, approximated?

In this issue of EuroIntervention, Ujka et al examine a retrospective cohort of 2,362 patients who underwent PFO closure from 2000-2022 at three Italian centres using five different devices[6]. The outcome reporting was focused on 207 patients with confirmed RS on contrast-enhanced transcranial Doppler at 12 months post-procedure, of whom 84 had a significant shunt (>10 bubbles), and 106 agreed to undergo a repeat procedure. They classified patients morphologically into 3 types: (1) a tunnel-like intradevice shunt, (2) extradevice shunt, (3) RS consisting of characteristics that were not present in the other 2 groups. The type 1 shunts were treated with a variety of plugs, type 2 with double-disc devices, and type 3 with double-disc devices in the case of incomplete closure with NobleStitch EL (Heartstitch), or coils and plugs as necessary.

Article, see page 933

Aside from the NobleStitch EL device which had a 20% RS rate, no other analysis is pertinent with respect to device type or size and the contribution to RS, given there was no systematic approach to *a priori* device selection, as acknowledged by the authors in their discussion.

Of the 41 patients with type 1 RS, vascular plugs were used to close 80.4% of leaks, while 7 had leaks that could not be crossed with a wire. In the type 2 group, 30/33 patients were found to have an accessory atrial septal defect (ASD). This is unexpected given the original procedures were done with transoesophageal echocardiography (TOE) guidance, balloon interrogation and a bubble study at the end of the procedure. Of the type 3 leaks, 10/14 patients had a suspected loosening of the NobleStitch knot, and two had a potential late onset tear in the septum. The RS closure procedure failed in 10/94 patients. While 89% (84/94) of all the RS closure procedures had a negative TOE bubble test at the end of the procedure, only 79 of 84 patients underwent a 1-year contrast-enhanced transcranial Doppler evaluation reporting any grade RS in 15.2% and significant RS in 8.9%. Given 30 ASDs were missed originally, it is unclear how to view these results.

The authors should be congratulated for sharing a series of complex interventions for dealing with RS after PFO closure. Their study suffers from typical sources of uncertainty present in retrospective studies, and we would scarcely criticise them for that; experience is a powerful teacher, and demanding prospective standards from this type of study are misplaced.

The context of this study is important. We lack an optimal diagnostic test to predict which of our patients post-PFO closure are at risk for recurrent events. The saline contrast study is ill-suited, but widely available and used, to evaluate this risk, especially when it is exceptionally low. A positive saline contrast study introduces pressure to reintervene, which may not be justified, and the results of reintervention remain unclear. Using the lack of an RS after repeat intervention as a surrogate for a successful stroke prevention intervention is a difficult jump to make.

Despite the lack of serious adverse events in this study, a cautious approach is mandated when considering "fixing" an intervention that by rigorous RCTs has exceptionally low event rates[5]. We know far less about fixing leaks related to the devices we choose than we do about the original intervention for PFO closure. As a community, we are desperately in need of not only studies that compare devices after their market approval, but also better algorithms to match the original closure device to the anatomy of the defect. Finding the sweet spot for the latter in a systematic way may reduce the likelihood of an RS. A wholehearted attempt to understand the natural history of patients with RS after PFO closure is an important piece of our management of these patients.

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Conflict of interest statement

E. Horlick reports grants or contracts from Occlutech; grants/contracts, honoraria, consulting fees from Abbott; and participation in an Abbott advisory board. L. Abrahamyan has no conflicts of interest to declare.

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SCAI/EAPCI/ACVC Expert Consensus Statement on Cardiogenic Shock in Women

This statement was endorsed by the Heart Failure Society of America (HFSA)

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ABSTRACT

Cardiovascular disease is the leading cause of death for women worldwide, with mortality rates due to cardiogenic shock (CS) remaining exceedingly high. Sex-based disparities in the timely delivery of optimal CS treatment contribute to poor outcomes; addressing these disparities is a major priority to improve women's cardiovascular health. This consensus statement provides a comprehensive summary of the current state of treatment of CS in women across the spectrum of cardiovascular disease states and identifies important gaps in evidence. As sex-based data are limited in contemporary literature, clinicians may use this document as a resource to guide practice. Further investigations are necessary to inform best practices for the diagnosis and treatment of women with CS.

Cardiovascular disease is the leading cause of death for women worldwide, claiming 8.94 million lives annually, representing a global age-standardized mortality rate of 204 deaths per 100,000 women in 2019[1]. While cardiovascular disease–related mortality rates have decreased over the past 2 decades, there has been no meaningful improvement in the dismal 30% to 50% in-hospital mortality rate of patients who experience cardiogenic shock (CS)[2]. The burden of CS is recognized as one of the most relevant, and improving CS outcomes has been identified as a priority to reduce women's mortality associated with cardiovascular disease by 2030[3]. Current evidence points to significant sex-based disparities in the timely delivery of optimal treatment for CS in women, which contributes to persistent poor outcomes[4]. Not only do women encounter delays in treatment, but they are less likely to receive guideline-recommended coronary interventions or device therapies compared with men, independent of disease severity[5,6]. Furthermore, there are limited data to guide management of CS in women despite biologic and pathophysiologic differences in disease presentation. Clinical research and randomized trials in CS pose significant ethical

KEYWORDS: cardiogenic shock; mechanical circulatory support; sex differences

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challenges, and women are consistently underrepresented, limiting our ability to evaluate the risks and benefits of cardiovascular drugs or devices in women. Accordingly, current society practice guidelines do not have sex-specific recommendations and do not highlight instances where evidence is insufficient for the diagnosis or management recommendations to optimize outcomes in women with CS. Therefore, this consensus statement aims to provide a comprehensive summary of available evidence on CS in women, identify knowledge gaps, and suggest directions for future clinical investigation.

Methodology

This statement has been developed according to Society for Cardiovascular Angiography & Interventions (SCAI) Publications Committee policies[7] for writing group composition, disclosure and management of relationships with industry, internal and external review, and organizational approval. The writing group has been organized to ensure diversity of perspectives (including representation from heart failure [HF], interventional cardiology, cardio-obstetrics, and critical care cardiology) and demographic characteristics, and appropriate balance of relationships with industry. Relevant author disclosures are included in **Supplementary Table 1**. The work of the writing group was supported exclusively by SCAI, a nonprofit medical specialty society, without commercial support. Writing group members contributed to this effort on a volunteer basis and did not receive payment from SCAI. This was done in collaboration with the European Association of Percutaneous Cardiovascular Interventions (EAPCI) and the Association for Acute Cardiovascular Care (ACVC), which appointed authors within their associations according to their expertise. Literature searches were performed by group members designated to lead each section and were balanced to reflect differences or similarities in findings and noting risk-adjusted outcomes when available to address potential confounding between sexes. Initial section drafts were authored by the section leads in collaboration with other members of the writing group. Consensus tips were discussed and voted on by the full writing group using a modified Delphi method. Electronic surveys were sent to members of the writing group and responses discussed in teleconference format. Consensus was defined as 75% agreement with at least an 80% response rate. All advisements are supported by a short summary of the evidence or specific rationale. The draft manuscript was independently peer reviewed both by SCAI and EuroIntervention in March and April 2024 and revised to address comments. The writing group unanimously approved the final version of the document. ACVC approved the document in May 2024. EAPCI approved the document in October 2024. SCAI Publications Committee and Executive Committee endorsed the document as official Society guidance in October 2024. SCAI statements are primarily intended to help clinicians make decisions about treatment alternatives. Clinicians also must consider the clinical presentation, setting, and preferences of individual patients to make judgments about the optimal approach.

Sex-based differences in CS: etiology and presentation

The incidence and etiology of CS differs in women and men **(Figure 1)**. Acute myocardial infarction (AMI) is a major cause of CS, accounting for 20% to 30% of CS in both women and men[2,8]. The majority of CS complicating AMI (AMI-CS) is due to atherosclerotic disease; however, spontaneous coronary artery dissection (SCAD) is an important contributor to CS (SCAD-CS) in women, occurring in up to 10% of SCAD cases[9]. Nonischemic HF–related CS (HF-CS) is more common than AMI-CS, accounting for 50% to 55% of CS in both women and men[2,8]. Within HF-CS, women are more likely to have *de novo* HF-CS (incidence, women 26% vs men 19%)[8], Takotsubo syndrome (TTS) (1% vs 0.2%)[10], and myocarditis (13% vs 3%) compared with men[11]. Peripartum and postpartum cardiomyopathy–related (PPCM)-CS uniquely affects women, and valvular heart disease (VHD)-related CS (VHD-CS), specifically aortic stenosis (AS), is more common in men but remains an important consideration for women[12]. Hormonal differences between the sexes may account for some of the observed differences in CS etiologies and outcomes. Estrogen has anti-inflammatory effects that protect against cardiac cell death, oxidative damage from ischemic/reperfusion injury, endothelial dysfunction, and adverse cardiac remodeling[13]; however, these hormonal differences may have paradoxical harmful effects by decreasing ischemic preconditioning in women compared with that in men[13]. Furthermore, varying estrogen levels throughout reproductive development and life transitions (ie, pregnancy and menopause) may contribute to disease states, such as PPCM and SCAD, which can progress to CS[13].

Beyond the different underlying CS etiologies, the clinical presentation of CS differs based on sex. Women with AMI-CS tend to present with higher left ventricular ejection fraction (LVEF) and similar or lower rates of renal/liver insufficiency compared with men[14]. Despite this, hemodynamic studies have shown that women have worse cardiac contractility (lower cardiac index or cardiac power output) and a higher risk of death with AMI-CS as predicted by Society of Thoracic Surgeons mortality scores[14]. As a consequence, women with AMI-CS can be mischaracterized as being clinically stable despite ongoing systemic hypoperfusion, leading to delays in the initiation of appropriate advanced care. Sex-based differences in HF-CS also exist, and women are more likely to present with cardiac arrest, higher vasopressor requirements, and advanced SCAI SHOCK stages D and E[8].

Abbreviations

AMI	acute myocardial infarction	**PAC**	pulmonary artery catheter	**VA-ECMO**	venoarterial extracorporeal membrane oxygenation
CS	cardiogenic shock	**PPCM**	peripartum/postpartum cardiomyopathy		
IABP	intra-aortic balloon pump	**SCAD**	spontaneous coronary artery dissection	**VHD**	valvular heart disease
LVEF	left ventricular ejection fraction	**tMCS**	temporary mechanical circulatory support		

Contemporary shock management

The cornerstones of CS treatment include (1) early identification of CS with timely initiation of hemodynamic support to maintain systemic perfusion and end-organ function and (2) early diagnosis and targeted treatment of the underlying cause of CS. SCAI SHOCK classification, initially released in 2019 and updated in 2021, provides a 3-axis model that integrates shock severity, clinical phenotype, and risk modifiers across both men and women[15]. Building on SCAI SHOCK classification, we provide a consensus on best evidence-based practice pathways of care to optimize early diagnosis, monitoring, and treatment recommendations for women with CS **(Figure 1)**.

Diagnosis of CS in women

Early assessment of end-organ damage and perfusion status is essential for establishing early the diagnosis and prognosis of CS as a continuum, as there is growing evidence that preshock and at-risk patients can be further risk stratified to inform management and outcomes[16]. Lactate is an objective biomarker that correlates with mortality in all types of shock and helps appropriately risk stratify patients; it is available as point-of-care testing with immediately available results. Despite universal society and expert guideline recommendations for frequent measurement of lactate levels for patients in or at risk of CS[17-20], only 1 in 4 women and 1 in 2 men in the global RECOVER III study of AMI-CS had lactate levels measured before percutaneous coronary intervention (PCI), likely resulting in diagnostic delays of AMI-CS for both sexes and particularly for women[21]. Invasive hemodynamic monitoring provides important diagnostic and clinical information in the setting of CS to guide phenotyping (univentricular or biventricular shock), characterize severity, and guide pharmacologic and temporary mechanical circulatory support (tMCS) escalation **(Table 1)**[20]. Characterizing CS phenotypes predicts prognosis and may improve short-term outcomes by initiating earlier management guided by real-time data and serial assessments, thus accelerating end-organ perfusion and reducing progression to CS[22]. While randomized trials of pulmonary artery catheters (PAC) in acute HF and critical illness have failed to show a reduction in mortality, these trials evaluated routine, unselected use of PAC and

Consensus tips for contemporary shock management

- Early and frequent assessments of end-organ function including lactate measurements (ie, serial testing every 2-6 hours) are useful to improve early CS diagnosis and risk stratification and to guide the need for early invasive monitoring and advanced therapies.
- Early PAC use in women to assist early CS diagnosis and management may improve survival.
- PAC should be strongly considered in all patients on tMCS.

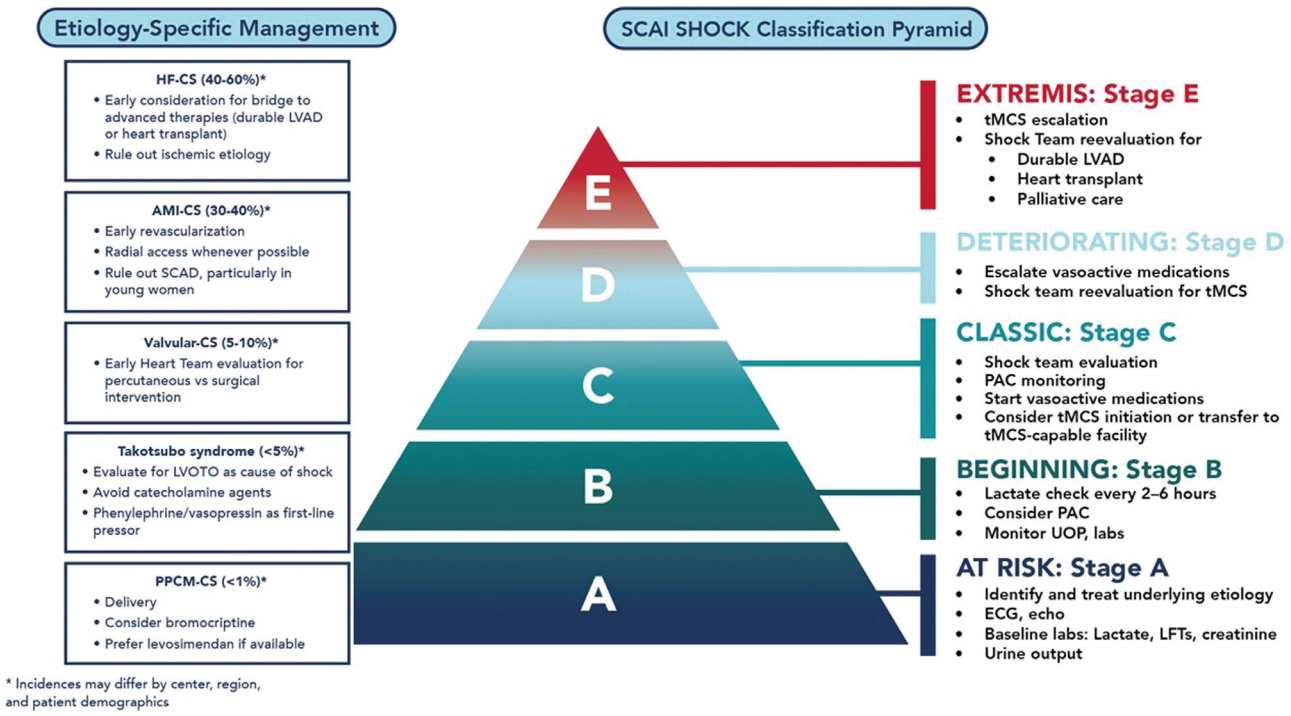

Figure 1. *Etiology-specific management of cardiogenic shock in women. AMI-CS: acute myocardial infarction–related cardiogenic shock; HF-CS: heart failure–related cardiogenic shock; LFT: liver function test; LVAD: left ventricular assist device; PAC: pulmonary artery catheter; PPCM-CS: peripartum cardiomyopathy–related cardiogenic shock; STEMI: ST-elevation myocardial infarction; tMCS: temporary mechanical circulatory support; valvular-CS: valvular-heart disease–related cardiogenic shock.*

Table 1. Invasive cardiac hemodynamics and indicators of cardiogenic shock.

Left ventricular metrics	Calculation	Indicator of cardiogenic shock
Cardiac index (CI)	CO/body surface area	≤2.2 L/min/m^2
Cardiac power output (CPO)	(MAP × CO)/451	<0.6 W
Cardiac power index	(MAP × CI)/451	<0.4 W/m^2
Pulse pressure	Systolic blood pressure – diastolic blood pressure	<25 mm Hg
Systemic vascular resistance	([MAP – CVP]/CO) × 80	Variable
Right ventricular metrics	**Calculation**	**Indicator of RV dysfunction**
RAPs		>10/15 mm Hg
RAP/PCWP ratio		>0.86 (in AMI) >0.63 (after LVAD)
Pulmonary artery pulsatility index	(PASP – PDP)/RAP	≤0.9 (in AMI) <1.85 (after LVAD)
Right ventricular stroke work index	0.0136 × SVI × (mPAP – RAP)	<6 g/m/beat/m^2

AMI: acute myocardial infarction; CO: cardiac output; CVP: central venous pressure; LVAD: left ventricular assist device; MAP: mean arterial pressure; mPAP: mean pulmonary artery pressure; PADP: pulmonary artery diastolic pressure; PASP: pulmonary artery systolic pressure; PCWP: pulmonary capillary wedge pressure; RAP: right atrial pressures; SVI: stroke volume index.
Adapted from Geller, et al[20].

excluded patients in whom clinicians thought a PAC was required for treatment[23]. Retrospective studies have shown that early targeted PAC use in CS prior to initiating tMCS is associated with lower mortality across all SCAI SHOCK stages[24]. Women with CS remain less likely to receive PAC monitoring[8] despite observational evidence of survival benefit with a standardized PAC-guided CS pharmacologic and tMCS treatment protocols[25]. Thus, PAC monitoring is advised early for women with persistent symptoms or worsening end-organ function despite initial treatment[17].

Management of CS in women

Inotropes and vasopressors are first-line treatment in CS due to their rapid onset of action and ease of use. Sex-based data are sparse, and the optimal pharmacologic agent for hemodynamic support for CS in women is unknown. Society recommendations suggest using norepinephrine or dobutamine as first-line vasoactive support in hypotensive patients[18,19]. Inodilators (milrinone, dobutamine, and levosimendan) may be appropriate in patients with low cardiac output who are normotensive. A study comparing dobutamine with milrinone in CS showed no difference in outcomes overall or based on sex between the 2 medications[26], and the calcium sensitizer levosimendan has not been shown to reduce mortality in the context of preshock compared with dobutamine[27]. In women with CS, aggressive escalation of vasopressors and inotropes at the expense of delays in tMCS should be avoided, as retrospective evidence suggests higher mortality in women compared with that in men. Although speculative, it is possible that women may have greater susceptibility to the toxic effects of vasopressors, including increased myocardial oxygen consumption, arrhythmias, and reduced end-organ microcirculatory perfusion[20,21,28].

Beyond pharmacologic support for CS, several tMCS options are available, including the intra-aortic balloon pump (IABP), the Impella family of pumps (Abiomed), and venoarterial extracorporeal membrane oxygenation (VA-ECMO). The TandemHeart device (LivaNova) is no longer marketed. While these devices are advised early to avoid the toxic effects associated with inotropes/vasopressors escalation in women, device-specific complications including vascular complications, limb ischemia, hemolysis, and stroke should be weighed against potential benefits[29]. Support strategies and their differential hemodynamic and physiologic effects are summarized in **Table 2**. Protocols for device selection, utilization, and deescalation and the advantages/disadvantages of each device have been previously detailed[20].

Although the use of tMCS in CS has increased over the past 2 decades, prospective randomized controlled trial (RCT) evidence clearly establishing the clinical benefit of any tMCS device in CS is limited, and our ability to generalize results to women is further limited by underrepresentation of women in shock trials[17,18,31-33]. Most contemporary randomized and observational tMCS trials are focused on AMI-CS, and data specific to non-AMI causes of CS, including HF, VHD, peripartum cardiomyopathy, myocarditis, and TTS, are limited[34]. Available sex-specific evidence for tMCS strategies are detailed in the disease-specific sections further (specifically AMI-CS and HF-CS).

Consensus tips for the management of CS in women

- tMCS is advised early for women in CS on inotropes/vasopressors, with persistent low cardiac output, rising lactate levels, or other signs of end-organ hypoperfusion, based on disease-specific and device-specific risk-benefit assessment.

Evidence gaps in the management of CS in women

- Randomized evidence is needed to inform the benefit of tMCS, the optimal tMCS device selection, and timing for women with CS based on CS etiology to determine device-specific complications and outcomes.

Table 2. Summary of temporary mechanical circulatory support strategies.

	RV support		LV support			Biventricular support
	Impella RP (Abiomed)	TandemHeart RVAD (±Protek Duo) (LivaNova)	IABP	Impella (Abiomed)	TandemHeart LVAD[a] (LivaNova)	VA-ECMO[b]
Mechanism	Axial-flow continuous pump (RA to PA)	Centrifugal-flow continuous pump (RA to PA)	Balloon inflation-deflation (aortic counterpulsation)	Axial-flow continuous pump (LV to AO)	Centrifugal-flow continuous pump (LA to FA through transseptal cannula)	Centrifugal-flow continuous pump (RA to AO)
Support	RV	RV	LV	LV	LV Oxygenator may be added to the circuit	RV and LV Includes oxygenator
Insertion/ placement	Femoral vein	IJ vein	Femoral artery Axillary artery	Femoral artery or axillary artery (2.5, CP) Axillary artery (5.5)	Femoral vein to LA Femoral artery	Femoral vein Femoral artery
Cannula size	22F venous	29F/31F venous	7F-8F arterial	2.5-12F arterial CP-14F arterial 5.5-21F arterial	21F venous 12F-19F arterial	17F-28F venous 14F-22F arterial
Flow, L/min	2-4	Maximum 4.5	0-1	2.5-5.5	Maximum 5-8	2-7
Maximum pump speed, rpm	33,000	7500	NA	2.5[c]/CP 51,000/46,000 5.0[c]/5.5 33,000/33,000	7,500	5,000
LV unloading	—	—	↑	↑-↑↑↑	↑↑	↓↓
RV unloading	↑	↑	—	—	—	↑↑
Cardiac power	↑	↑	↑	↑↑	↑↑	↑↑
Coronary perfusion	—	—	↑	↑	—	—
CVP	↓	↓	↔ or ↓	↔ or ↓	↔ or ↓	↓
MAP	—	—	↑	↑↑	↑↑	↑↑
LVEDP	↑	↑	↓	↓↓	↓↓	↔
PCWP	↑	↑	↓	↓↓	↓↓	↔ or ↑
Myocardial oxygen demand	↓	↓	↓	↓↓	↔↓	↔ or ↑
Surgical tMCS considerations	Pump options include Centrimag (Abbott), Cardiohelp (Getinge), and Rotaflow (Getinge). These can be used with or without an oxygenator in multiple configurations, including the following: (1) a temporary RVAD can have a drainage cannula in the femoral vein or RA with a return cannula from the IJ into the PA; (2) a temporary central RVAD can have a drainage cannula in the RA or RV with a return cannula into the PA; (3) a temporary central LVAD can have a drainage cannula in the LA or LV with a return cannula into the aorta; or (4) multiple central and percutaneous BiVAD configurations are possible.					

[a]TandemHeart LVAD is no longer commercially available. [b]Other percutaneous cannulation sites and multiple cannulation sites can be used: arterial access (axillary, subclavian, or carotid) or venous access (IJ). Central configurations are also possible. [c]Impella 2.5 and 5.0 are no longer commercially available. Adapted from Tehrani, et al[30].
AO: aorta; BiVAD: biventricular assist device; CS: cardiogenic shock; CVP: central venous pressure; FA: femoral artery; IABP: intra-aortic balloon pump; IJ: internal jugular; LA: left atrium; LV: left ventricle; LVAD: left ventricular assist device; LVEDP: left ventricular end-diastolic pressure; MAP: mean arterial pressure; NA: not applicable; PA: pulmonary artery; PCWP: pulmonary capillary wedge pressure; RA: right atrium; RV: right ventricle; RVAD: right ventricular assist device; tMCS: temporary mechanical circulatory support; VA-ECMO: venoarterial extracorporeal membrane oxygenation.

Specific etiologies and management of CS in women

AMI-RELATED CS

ATHEROSCLEROTIC AMI-CS

AMI is a common cause of CS in women. Approximately 12% of patients with ST-elevation myocardial infarction (STEMI) and 4.5% of patients with non-ST-elevation myocardial infarction (NSTEMI) develop CS according to a National Cardiovascular Data Registry report; overall, women comprised 45% of patients presenting with AMI-CS[35]. Women with AMI-CS are older with a higher prevalence of hypertension, diabetes, previous HF, atrial fibrillation, cerebrovascular disease, and renal disease[36-42]. Women have greater hemodynamic compromise at the time of AMI-CS presentation, characterized by more profound hypotension, lower cardiac output, and more acute complications such as acute severe mitral regurgitation and ventricular septal defects compared with men[40,42]. Despite this, sex-specific substudies of the IABP-SHOCK II, SHOCK, and CULPRIT-SHOCK trials have shown consistent results based on sex, namely women with AMI-CS derive the same survival benefit as men with culprit-only revascularization without benefit from IABP support[40-42]. Thus, early culprit-only revascularization with PCI is the mainstay of therapy in AMI-CS and improves mortality in selected patients of both sexes[37-39,43]. Despite that fact, women are less likely to receive aggressive AMI-CS

treatment and undergo less primary PCI compared with men[44]. A study of 9,750 patients with AMI-CS (including 44% women) from the Ontario Myocardial Infarction Database showed that compared with men, women with AMI-CS were more likely to be admitted to hospitals without revascularization capabilities (16% vs 19.2%; $P < .001$) and less likely to be transferred to PCI-capable centers (11.3% vs 14.2%; $P < .001$)[36]. Even when admitted to PCI-capable centers, women experience delays in AMI-CS care. A National Inpatient Sample study of AMI-CS admissions showed that young women (age, 18-55 years) compared with age-matched men were less likely to receive early coronary angiography (49.2% vs 54.1%), PCI (59.2% vs 64.0%), and tMCS (50.3% vs 59.2%) and experienced higher in-hospital mortality (23.0% vs 21.7%; adjusted odds ratio [aOR], 1.11; 95% CI, 1.07-1.16; $P < .001$)[44]. Furthermore, women are more likely to present with NSTEMI-related CS[41] and thus are disproportionately affected by the longer delays to PCI or coronary artery bypass grafting (CABG) experienced by patients with NSTEMI, regardless of sex, as compared with patients with STEMI[35,44]. The newly developed SEX-SHOCK score to predict CS in AMI, using machine learning and incorporating ST-segment elevation, creatinine, C-reactive protein, and LVEF, outperformed other risk scores for both sexes in external validation (AUC females: 0.81 [0.78-0.83]; males: 0.83 [0.82-0.85]; $P < .001$) across the spectrum of ACS. The importance of a gender-specific risk prediction approach for CS, could mitigate sex inequities in early risk stratification of contemporary shock management[45].

Sex-specific evidence for tMCS use in AMI-CS is summarized in **Supplementary Table 2**. IABP use for AMI-CS has declined over the past decade (29.8% in 2005 to 17.7% in 2014)[46] after the randomized IABP-SHOCK II trial failed to show a benefit of IABP in reducing 30-day mortality overall[31] or for women[31,40,47]. At the same time, the use of Impella for AMI-CS has increased[46]. Nevertheless use of tMCS remains lower in women than in men with CS[44] and in-hospital mortality is higher in those women who do receive tMCS, which is likely related, in part, to a higher burden of comorbidities and older age at presentation and lower rates of pulmonary artery catheter use[48]. While small-scale trials comparing Impella 2.5 or CP with IABP failed to show a reduction in mortality[49,50]; subsequent registries have suggested a mortality benefit from earlier Impella use (either before or early in PCI)[21,51]. Women, in particular, appear to have a greater survival benefit with early Impella support pre-PCI in AMI-CS as suggested by the international cVAD registry (survival in women: early 68.8% vs late 24.4%; $P = .005$) compared with men (early 43.2% vs late 40.3; $P = .1$)[52]. A subsequent sex-specific analysis of the global RECOVER III registry showed that women with AMI-CS on ≥2 inotropes before tMCS had significantly higher adjusted mortality (odds ratio [OR], 3.03; 95% CI, 1.26-7.29) compared with men (OR, 1.18; 95% CI, 0.89-1.56)[21].

The recent landmark randomized DanGer Shock trial comparing the Impella CP with standard of care alone, enrolled 360 patients with STEMI-CS, excluding comatose patients or those with overt right ventricular HF. Impella reduced all-cause mortality at 180 days compared with standard of care (45.8% vs 58.5%; hazard ratio [HR], 0.74; 95% CI, 0.55-0.99; $P = .04$)[33]. Notably, 55.3% of patients underwent Impella implant before percutaneous revascularization, and median time from randomization to tMCS placement was 14 minutes. The subgroup of women in DanGer Shock did not show a benefit with Impella use (HR, 1.01; 95% CI, 0.58-1.79); however, randomization was not stratified by sex, the trial enrolled only 20% women and was underpowered to assess sex differences, and no formal interaction test was performed. The overall mortality benefit of Impella in DanGer Shock was offset by a 2-fold increase in bleeding and a 5-fold increase in vascular complications. The numbers needed to treat for survival was 8 and number needed to harm was 6 for a composite safety outcome (severe bleeding, limb ischemia, hemolysis, device failure, and worsening of aortic regurgitation). Complications were not reported by sex, and the overall risk benefit of Impella in women with AMI-CS remains difficult to assess. The need for additional randomized evidence on the use of Impella in women with AMI-CS is an imperative. Until then, based on the totality of evidence, Impella should be considered selectively but early in women with AMI-CS while weighing the risk of potential complications[53].

VA-ECMO is used infrequently in AMI-CS compared with Impella and IABP[46]. Recent RCTs have failed to show a mortality benefit with early VA-ECMO use in AMI-CS and is associated with significantly higher bleeding and vascular complications. The extracorporeal life support (ECLS)-SHOCK trial[54] randomized 420 patients (19% women) to early ECLS vs standard of care. There was no difference in 30-day all-cause mortality overall (ECLS 47.8% vs controls 49%) or among women (ECLS 59.5% vs control 56.4%). Moderate and severe bleeding (ECLS 23.4% vs control 9.6%; relative risk, 2.44; 95% CI, 1.50-3.95) and peripheral vascular complications requiring surgery (ECLS 11% vs control 3.8%; relative risk, 2.86; 95% CI, 1.31-6.25) were significantly higher with ECLS. A patient-level meta-analysis of 4 VA-ECMO RCTs including 567 patients (19% women) with AMI-CS failed to show a mortality benefit at 30 days with early VA-ECMO (46% vs control 48%), including in women (OR, 1.09; $P_{interaction} = .65$)[55]. Major bleeding (VA-ECMO 25% vs control 12%; OR, 2.44; 95% CI, 1.55-3.84) and vascular complications (OR, 3.53; 95% CI, 1.70-7.34) were 2-4 fold higher with VA-ECMO.

A meta-analysis of registries in mixed CS populations suggests possible improved mortality with left ventricular (LV) unloading primarily with IABP in VA-ECMO (54% all-cause mortality with LV unloading vs 65% without); women were less likely to receive LV unloading (women 25.5% unloading vs 31.9% no-unloading). Whether women benefit more from unloading remains speculative[56]. The ongoing randomized study evaluating VA-ECMO with Impella unloading vs VA-ECMO alone in a mixed CS population will provide further insight on the potential clinical impact of LV unloading (UNLOAD-ECMO; NCT05577195). Until then, the lack of a mortality benefit and an increased risk of vascular complications does not support use of VA-ECMO in women with AMI-CS.

A recent patient-level meta-analysis of 9 RCTs including 1,114 patients (20.1% female) of mixed tMCS vs controls in AMI-CS, including 4 VA-ECMO randomized trials

(611 patients), demonstrated that in aggregate, independent of sex, early routine use of tMCS did not reduce mortality at 6 months (HR, 0.87; 95% CI, 0.74-1.03; P = .10) and increased vascular complications compared with controls[53,57]. In contrast, early tMCS use significantly improved survival in patients with AMI-CS but without hypoxic brain injury (HR, 0.77; 95% CI, 0.61-0.97; P = .024) independent of sex, age, and tMCS type[53].

Based on the 2025 American College of Cardiology or American Heart Association guidelines, selective use of Impella for severe refractory CS is reasonable in patients with AMI-CS and without coma, and the routine use of IABP or VA-ECMO provides no benefit and is not recommended[58].

SPONTANEOUS CORONARY ARTERY DISSECTION-RELATED CS

SCAD is an important underlying cause of nonatherosclerotic myocardial infarction (MI) in women and accounts for 20% to 25% of AMI in women younger than 50 years. In contrast with atherosclerotic AMI, the majority of SCADs will heal within 30 days. A conservative management is the preferred approach[59] as revascularization for SCAD is associated with >50% acute procedure failure, high complication rates (iatrogenic dissection and abrupt vessel occlusion), and high reintervention rates (30% vs 19% with conservative management)[59]. Selective revascularization is reserved for patients with SCAD and ongoing ischemia, high-risk lesions (eg, left main involvement), or multivessel disease and, as a consequence, is more likely to be associated with shock[60]. In an analysis of 664,292 patients from the US National Readmission Database from 2015 to 2018, SCAD AMI was associated with higher rates of CS compared with non-SCAD AMI (9% vs 5%; P < .01), even after adjusting for younger age at presentation and lower baseline comorbidities (aOR, 1.5; 95% CI, 1.2-1.7). Patients with SCAD-CSCS were more likely to receive tMCS support with IABP (45% vs 28%, P < .001), percutaneous left ventricular assist device (LVAD) (17% vs 10%, P < .01), or ECMO (2.7% vs 1.2%, P = .03) compared with patients without SCAD and had lower in-hospital mortality (31% vs 39%, P < .01)[9]. This suggests that tMCS use is feasible in the setting of SCAD-CS and may allow for myocardial rest during coronary healing. There are no sex-specific data regarding outcomes or treatment strategies in patients with SCAD-CS.

Consensus tips for the treatment of AMI-CS in women

- Early revascularization with PCI and/or CABG is the mainstay of therapy in AMI-CS.
- In patients presenting with SCAD-CS, tMCS support to recovery and selective revascularization strategies in high-risk lesions may be appropriate.
- Selective early Impella use (either before or early in PCI) in women with AMI-CS without coma is reasonable; however, additional randomized evidence in women is needed.
- Current evidence does not support routine use of VA-ECMO or IABP in AMI-CS due to lack of mortality benefit and increased risk of vascular complications.

Evidence gaps in the treatment of AMI-CS in women

- Addressing local barriers and delays to care access in women with AMI-CS are institutional imperatives.
- RCT evidence in women to evaluate the risk benefit of Impella use in AMI-CS is an imperative.
- Evidence is needed to determine the optimal timing of tMCS in women with AMI-CS.
- Studies are needed to determine whether a complete revascularization approach and its timing improve outcomes in women with AMI-CS.

CS in the pregnant/postpartum patient

CS is rare in pregnancy and occurs in 3.8 of 100,000 antepartum and postpartum hospitalizations; however, CS in this context is associated with high maternal mortality (18.8% in peripartum CS vs 0.02% peripartum without CS) and higher rates of intrauterine fetal death (1.4% in peripartum CS vs 0.1% peripartum without CS)[61]. Peripartum cardiomyopathy is the most common cause of shock related to pregnancy, accounting for 56% of cases during pregnancy and 82% of cases postpartum. Other etiologies include acute coronary syndrome (either from plaque rupture or SCAD), pre-existing dilated cardiomyopathy, pulmonary arterial hypertension, severe VHD, and amniotic fluid embolism[62,63].

Similar to the nonpregnant patient with CS, invasive hemodynamics are critical to early identification of shock in the setting of pregnancy, and when identified, hemodynamic support is a priority **(Figure 2)**. Levosimendan, where available, is considered the preferred inotropic agent, as it does not increase myocardial oxygen demand. Otherwise, dobutamine and norepinephrine may be used as first-line inotropic/vasopressor support agents[64]. Consideration for tMCS is advised early after starting intravenous therapy because medical therapy may be insufficient. Registry data suggest that early use of tMCS in pregnancy-related CS (defined as ≤6 days from onset) is associated with greater survival (18% mortality with support ≤6 days vs 38% with >6 days)[61]. Successful tMCS support during pregnancy has been described using IABP, temporary percutaneous or surgical LVADs (Impella, Tandemheart, and Centrimag [Abbott]), and VA-ECMO, but there is little evidence regarding a preferred device[64]. Need for tMCS support during birth further complicates device selection, with anticoagulation considerations (discussed further) and obstetric recommendations for assisted vaginal delivery (necessitating flexion at the hips) or cesarian section, both contributing toward device and access site selection.

Targeted therapies for the specific condition underlying the CS are advised. SCAD is the most common cause of MI in pregnancy, and patients with pregnancy-related SCAD have more severe disease compared with those with nonpregnant SCAD as evidenced by more frequent presentation with STEMI (57% vs 36%; P = .009), multivessel or left main disease (24% vs 5%, P < .001), and severe LV dysfunction, with LVEF of ≤35% (26% vs 10%, P = .007)[65]. For severe symptomatic VHD, especially stenotic left-sided lesions, cardiac surgery is an option, although it is associated with high fetal mortality rates up to 30%[66]. Catheter-based approaches

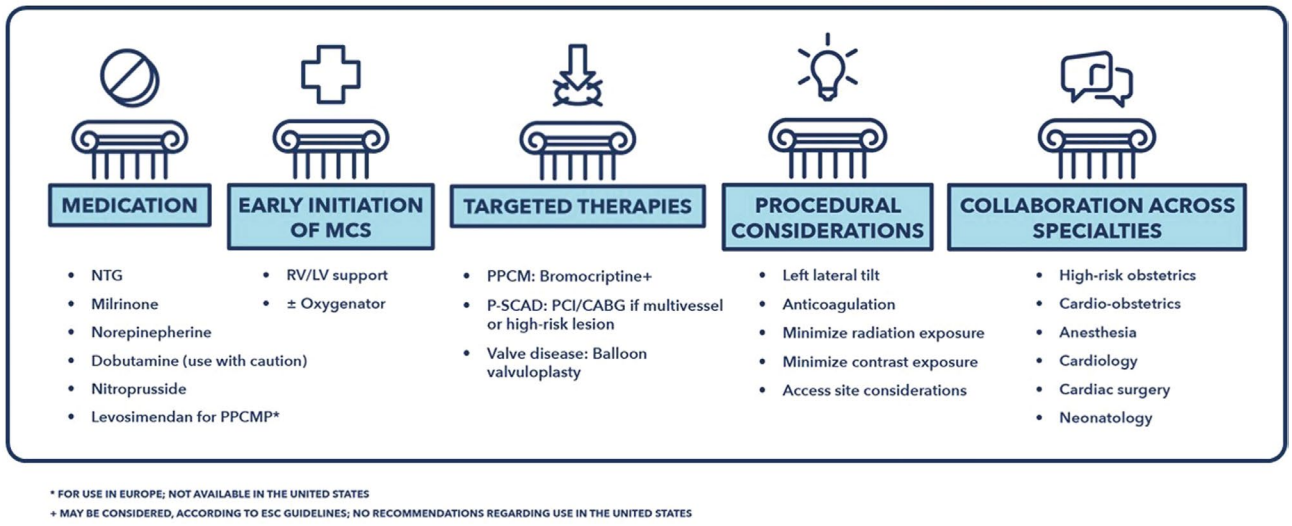

Figure 2. *Cardiogenic shock in pregnancy. CABG: coronary artery bypass grafting; LV; left ventricle; MCS; mechanical circulatory support; NTG: nitroglycerin; PCI: percutaneous coronary intervention; PPCMP: peripartum cardiomyopathy; RV; right ventricle; P-SCAD; pregnancy-related spontaneous coronary artery dissection.*

may be appropriate (eg, mitral balloon valvuloplasty, aortic balloon valvuloplasty, and transcatheter aortic valve replacement [TAVR]); however, data in this population are limited to case reports and case series[67].

Care of the pregnant patient with CS during cardiac procedures poses unique challenges[68]. In the supine position, the gravid uterus may cause aortocaval compression, which can further reduce preload and cardiac output. Placing the patient with a slight left lateral tilt can help relieve this and is especially important if tMCS is used. Meticulous attention to anticoagulation is imperative, as pregnancy is a hypercoagulable state with increased risk of thromboembolism compared with the nonpregnant state[69]. Both unfractionated heparin (UFH) and low-molecular weight heparin (LMWH) can be used during pregnancy; however, presence of anticoagulation at the time of delivery affects candidacy for epidural or spinal anesthesia, and close coordination with obstetrical anesthesia is required. Additionally, UFH use may be associated with higher rates of postpartum hemorrhage compared with LMWH[69]. Thus monitoring to maintain therapeutic anticoagulation is critical—UFH doses should be adjusted to within a therapeutic activated partial thromboplastin time range (1.5-2.5 times control), and LMWH doses should be adjusted to maintain anti-Xa levels of 0.6 to 1.0 units/mL[70]. Measures should be taken to reduce fetal radiation exposure include using external abdominal shielding, reducing fluoroscopy time, lower magnification and frame rates, and careful collimation[68]. Iodinated contrast is also associated with potential risk of fetal congenital hypothyroidism but does not preclude its use when lifesaving[68]. All measures to reduce fetal exposure are warranted, but these should not take precedence over procedures to preserve maternal life. Special considerations for the management of cardiac arrest in the pregnant or postpartum patient are in **Supplementary Table 3**.

Most importantly, a multidisciplinary team collaboration among cardiology, obstetrics, anesthesiology, and critical care are paramount to maternal and fetal/neonatal safety[71]. A pregnancy-heart team is advised for the evaluation and management of high-risk cardiac disease in pregnancy and is required for rapid decision making in pregnant patients with CS[72], especially in conditions with high maternal mortality where pregnancy termination may be appropriate[73]. Other considerations such as choice of medications and anesthesia should be made based on the individual clinical situation, maternal benefit, and fetal exposure. Managed anesthesia care improves maternal airway and hemodynamic control while limiting maternal and fetal anesthetic exposure. Continuous fetal monitoring is advised if the gestational age is at ex utero viability (typically ≥23 weeks of gestation) and emergent cesarean delivery is an option; thus, the decision to implement fetal monitoring should be made in collaboration with obstetrics[74]. Timing and mode of delivery depends on maternal stability and fetal status and requires multidisciplinary coordination between cardiac and obstetric teams.

PPCM complicated by CS

CS complicates ~4% of PPCM, which is defined as idiopathic LV dysfunction (LVEF ≤ 45%) that presents toward the end of pregnancy or in the months following delivery[75]. The etiology of PPCM is thought to be multifactorial, with contributions from genetic factors, autoimmune responses, fetal microchimerism, and excessive prolactin production[75]. As with patients afflicted by CS during pregnancy, a multidisciplinary pregnancy-heart team is paramount to rapid decision making for patients with peripartum or postpartum CS[72].

In addition to the general principles of CS treatment with typical pharmacologic therapies, bromocriptine may have a role as targeted treatment of PPCM-CS. Bromocriptine is a dopamine agonist that inhibits prolactin release and has been associated with higher rates of LV recovery in mostly pilot and observational studies[76]. While bromocriptine may be considered according to the 2018 European Society of Cardiology guidelines on the management of cardiovascular diseases during pregnancy[71], bromocriptine is considered experimental in the United States and Canada. Accordingly, its clinical benefit is being investigated in a randomized, double-blind, placebo-controlled clinical trial (Randomized Evaluation of Bromocriptine in Myocardial Recovery Therapy [REBIRTH]; NCT05180773), comparing bromocriptine therapy vs placebo in women with PPCM (LVEF ≤ 35%)[76]. If used, bromocriptine has been associated with thrombotic complications and should be accompanied by at least prophylactic anticoagulation[71,76].

As with other CS etiologies, tMCS is advised in patients with PPCM-CS who cannot be stabilized on medical therapy alone. A small study reported excellent short-term survival (100% at 30 days and 80% at 6 months) with early use of tMCS and bromocriptine therapy[77]. Increased prolactin levels during ECMO treatment have been reported, which may be detrimental in PPCM-CS, and higher bromocriptine doses may be appropriate if used[64]. Because many patients have at least partial LV recovery, a bridge-to-recovery strategy is the preferred approach[64]; however, the evaluation for long-term advanced HF therapies—durable mechanical circulatory support (MCS; surgical LVADs or biventricular assist devices) and/or cardiac transplantation—should be initiated soon after implantation of tMCS, with plans to transition to long-term strategies if temporary support cannot be weaned after 7 to 10 days. Surprisingly, LV recovery with durable MCS is uncommon. An Interagency Registry for Mechanically Assisted Circulatory Support registry analysis of 1,258 women, including 99 women with PPCM, showed similarly low rates of recovery/explant in both patients with PPCM and patients without PPCM (6% for both), which may be due to variability in patient selection or recovery protocols between centers[78]. Cardiac transplantation is considered for patients for whom durable MCS is not an option or who do not exhibit substantial LV recovery on durable MCS after 6 to 12 months. Nevertheless, it should be noted that patients with PPCM have worse postheart transplant outcomes compared with women with other cardiomyopathies[79].

Consensus tips for treatment of pregnant patients with CS, including PPCM

- An established multidisciplinary cardio-obstetrics team, including cardiology, obstetrics or maternal fetal medicine, anesthesiology, critical care, and nursing, is paramount to rapid decision making in pregnant patients with CS and may require transfer to a center with a dedicated cardio-obstetrics program.
- Early invasive hemodynamics assessment and consideration for early tMCS are critical to maternal survival.
- Measures to reduce fetal exposure to radiation and medications are warranted but should not take precedence over treatments to preserve maternal life.
- For patients with PPCM-CS, a bridge-to-recovery strategy is the preferred approach because of high rates of at least partial LV recovery.

Evidence gaps in the treatment of pregnant patients with CS, including PPCM

- Further data are needed to clarify the safety and efficacy of bromocriptine on LV recovery in PPCM and PPCM-CS.

Heart failure-related CS

HF-CS is the most common etiology of CS in the modern cardiac intensive care unit, with women representing one-third of these patients[34,80]. The most common etiology of HF-CS is acute decompensation of chronic HF, accounting for >70% of HF-CS cases in women. *De novo* HF causes such as myocarditis and TTS are also more likely to occur in women compared with men (26.3% vs 19.3%) (see **Supplementary Table 3** for Acute and Fulminant Myocarditis)[8].

A sex-based analysis by the Cardiogenic Shock Working Group (CSWG) showed that women with HF-CS have higher baseline SCAI SHOCK stage compared with men (stage E 26% vs 21%) and have worse survival at discharge (69.9% vs 74.4%)[8]. This is, in part, related to the fact that women with chronic HF are more likely to be older, have more cardiovascular comorbidities (hypertension and diabetes mellitus)[14], and have less evidence-based pharmacologic therapy and implanted device (internal cardiac defibrillator and cardiac resynchronization) therapies compared with men[81]. Despite presenting with higher clinical acuity, women with HF-CS were less likely to receive pulmonary artery catheterization (52.9% vs 54.6%), more likely to be treated without tMCS support (26.2% vs 18.8%), and less likely to receive heart replacement therapy with durable LVAD (7.8% vs 10%) or cardiac transplantation (6.5% vs 10.3%) when compared with men in a study[8]. Accordingly, there is a distinct need to develop care pathways to ensure that women have equal and timely access to durable LVAD and cardiac transplantation.

The use of tMCS for HF-CS has increased over the past 2 decades[46] and is most commonly used as a bridge to advanced HF therapies (durable LVAD or cardiac transplantation). A retrospective analysis from the CSWG registry showed that for HF-CS, IABP is the most commonly used initial device, being used in 45% of the overall CSWG cohort, followed by Impella in 12% and VA-ECMO in 7%[74]. The CSWG registry sex-specific analysis showed that IABP and ECMO use is similar based on sex within the first 24 hours of admission, but women were less likely to receive an Impella[8,34,46]. There are no randomized trials evaluating tMCS efficacy in HF-CS, and thus, there is no informed guidance for device selection or timing[24]. Early initiation of tMCS in HF-CS has a small but incremental benefit on mortality based on observational studies. A retrospective National Inpatient Sample database analysis of ~85,000 patients with HF-CS (30% women) supported with either IABP or Impella showed a modest

mortality benefit with earlier support (within 48 hours of admission) compared with later support (after 48 hours), with an improved adjusted all-cause in-hospital mortality of 23.67% vs 27.67%[82]. Similarly, a retrospective Extracorporeal Life Support Organization registry analysis evaluating timing of VA-ECMO in ~8600 patients with predominantly non-AMI CS showed a small but significant improvement of in-hospital mortality with early (within 24 hours) vs later (after 24 hours) support (mortality 51.6% vs 54.7%; aOR, 1.2 with late ECMO) and that each 12-hour delay increased mortality (aOR, 1.06); the results were consistent across the sexes[83]. Additional sex-specific studies are needed to guide device selection and timing.

TAKOTSUBO SYNDROME

TTS is a specific, acute, nonischemic cardiomyopathy that can present as CS in 5% to 10% of cases. TTS classically follows an intense emotional or physical stress and tends to present similar to MI but without plaque rupture[10]. Approximately 90% of TTS occur in women, and it is particularly prevalent in post-menopausal women. Younger patients (<50 years) account for 11.5% of TTS and are more likely to present with CS (15.3% vs 9.1%; P = .004) compared with older patients (age, 51-74 years)[84]. TTS with CS (TTS-CS) is associated with substantially higher mortality rates compared with TTS without CS (23.5% vs 2.3%)[85], with the majority of death occurring in the first 24 hours after presentation when patients are most severely hypotensive[86]. The development of CS in TTS is likely multifactorial—LV systolic dysfunction may be exacerbated by RV dysfunction, and LV outflow tract obstruction from hyperkinetic basal ventricular segments may contribute to poor cardiac output[86]. As a result, the administration of catecholamines should be avoided in TTS and their potential to exacerbate hemodynamic instability[86]. Consequently, tMCS is frequently used as a bridge-to-recovery strategy for TTS-CS (38% of TTS-CS cases in 1 series[10]), aiming to reduce acute stage mortality[85]. A propensity score–matched analysis of the International Takotsubo Registry showed lower in-hospital mortality for patients with CS who received tMCS when compared with patients who did not receive tMCS (OR, 0.34; 95% CI, 0.12–0.95; P = .04)[85].

Consensus tips for the treatment of HF-CS and use of advanced HF therapies in women

- There is a need to develop pathways of care to address the treatment disparities in women with HF-CS and ensure equal and timely access to durable LVAD and cardiac transplantation.
- Clinical evidence is needed to inform optimal tMCS selection (Impella, VA-ECMO) and timing in women with HF-CS.

VHD-related CS

AORTIC STENOSIS

CS associated with severe AS occurs in up to 12% of patients and has been associated with an extremely high mortality rate in the absence of a corrective valve procedure[87]. Often, patients are treated with MCS or percutaneous valvular intervention (either balloon aortic valvuloplasty or TAVR) to stabilize CS, as immediate surgical intervention portends a higher risk of mortality in this context.

Sex-specific data regarding the outcomes and treatment of AS-CS are very limited and are mostly derived from the TAVR population. An analysis of 15,071 patients with AS treated with TAVR (2,200 of whom presented with CS) in the Transcatheter Valve Therapy (TVT) registry demonstrated that men presented with CS at a higher rate compared with women (17.5% vs 12.3%; P < .001)[12]. Despite potential differences in incidence of AS-related CS, a TVT registry study of 5,006 patients (~35% women) with AS-related CS showed that sex was not an independent predictor of 1-year mortality in patients with AS-CS treated with TAVR[88]. Although studies using first-generation and second-generation TAVR prostheses have demonstrated higher rates of bleeding or vascular complications in women treated with TAVR[89,90], recent studies have demonstrated no sex-specific differences in survival or stroke[91,92], which may reflect the changing demographic characteristics of the patient population being treated with TAVR (eg, lower risk) as well as advances in device technology and procedural techniques. Hence, although sex-specific data for the treatment of AS-related CS are lacking, TAVR may be appropriate as a viable treatment option for women with this condition[93].

AORTIC REGURGITATION

As for AS, there are no sex-specific data on outcomes or management of acute aortic regurgitation in the setting of CS. For additional information, see **Supplementary Table 3**.

MITRAL REGURGITATION

Both acute and chronic mitral regurgitation (MR) can lead to CS either due the acute rupture of chordae or papillary muscle caused by AMI (which accounts for 22.5% of MR with CS) or worsening of chronic MR from leaflet restriction in the setting of decompensated HF[94]. While treatment of the underlying CS pathology (whether AMI-CS or HF-CS) remains paramount, shock may persist without management of the MR, and so, early intervention is advised if clinically feasible[95]. Studies have demonstrated that tMCS, particularly IABP, is useful in stabilizing patients with MR-CS and can act as a bridge to definitive mitral valve intervention, be it surgical or percutaneous[96,97].

Similar to AS-CS, there are minimal sex-specific data regarding the outcomes and treatment of MR-CS, and the data available are largely derived from patients treated with transcatheter mitral edge-to-edge repair (mTEER). A TVT registry analysis of 3,797 patients with MR-CS (40.5% women) showed that successful mTEER was associated with lower in-hospital mortality (9.1% vs 16.1%; P < .001) and 1-year mortality (34.6% vs 55.5%; P > .001) compared with patients with unsuccessful procedures. Similarly, a propensity score–matched analysis of 596 US Medicare beneficiaries (43.1% women) with CS who received mTEER had lower in-hospital mortality (OR, 0.6; 95% CI, 0.47-0.77; P < .001) and 1-year mortality (HR, 0.76; 95% CI, 0.65-0.88; P < .001) compared with patients who did not receive a mTEER[98].

Neither of these studies identified sex as an effect modifier of outcomes in patients with MR-CS treated with mTEER[98,99], thereby suggesting that appropriately selected men and women alike may benefit from mTEER in the setting of MR-CS.

Evidence gaps in the treatment of VHD-CS in women

- Sex-specific analyses of outcomes and treatment strategies are needed in patients with VHD-CS.
- Inclusion of an adequate subset of women in percutaneous valve intervention trials is paramount to understanding the sex-specific benefits and complications of these devices in the setting of CS.

Advanced HF therapies: limitations in care for female survivors of CS

Patients with CS who fail to recover with medical therapy or tMCS may be appropriate for advanced HF therapies (LVAD and cardiac transplant). While pivotal durable LVAD trials have shown mortality benefit for patients with chronic end-stage HF[100-102], women have been underrepresented in these trials, so evidence regarding sex-specific differences in outcomes is indeterminate. For example, in the recent MOMENTUM 3 trial, which compared the Heartmate III and Heartmate II devices, only ~20% of enrollees were women[103]. While early generation pulsatile-flow durable LVADs were associated with higher mortality for women (OR, 2.13; 95% CI, 1.45-3.10; $P < .0001$), current generation continuous-flow LVADs show similar survival between the sexes[104]. There have also been specific concerns about an excess risk of neurologic events in women receiving durable MCS. In a Heartmate II cohort, the risk of hemorrhagic stroke was greatest in women younger than 65 years, whereas the risk of thromboembolic events was greatest in women older than 65 years[105]. With the contemporary Heartmate III LVAD, risk of stroke overall is much lower, but women continue to be at higher risk. A sex-specific analysis of the MOMENTUM 3 trial showed that women had an increased risk of stroke (adjusted incidence rate ratio [aIRR], 1.52; $P = .12$) in addition to higher risk of major bleeding (aIRR, 1.28; $P < .0001$) and infection (aIRR, 1.14; $P = .01$)[106]; however, this analysis also showed that there were no sex-based differences in overall survival or in the primary outcome (survival free of disabling stroke or need for pump replacement or removal at 2 years postimplant). In the context of the limited number of women enrolled and the lack of power, these findings highlight the need for additional studies in women specifically to establish the outcomes associated with durable LVADs.

Cardiac transplantation remains the gold standard treatment option for patients who develop end-stage HF and prolonged CS[107]. Women remain less likely to undergo transplant compared with men, accounting for only 23% of heart transplant patients[108]. In a United Network for Organ Sharing analysis, women receiving a durable LVAD as a bridge to transplantation had lower rates of heart transplantation (55.1% vs 67.5%), greater waitlist mortality (7.0% vs 4.2%), and more delisting for clinical deterioration (8.5% vs 4.7%) at 2 years of LVAD support, compared with men (all $P < .001$)[109]. Another sex-based analysis evaluating patients at the highest heart transplant urgency strata (status 1) found similar trends for women with lower rates of transplant and higher rates of delisting for death or clinical deterioration[110]. Contributing factors identified in these studies include higher allosensitization in women (which makes finding suitable donors more difficult) and/or MCS-related complications, but precise reasons underlying lower transplant rates in women remain unclear[109,110]. Women who do proceed to cardiac transplantation have a similar posttransplant survival rate compared with men[111]. These findings underscore the importance of developing best practices in post-CS care to ensure women with HF have equal and timely access to transplant.

Barriers to care for women with CS upon presentation to medical attention

Vascular and bleeding complications remain major obstacles to the adoption of cardiac interventional treatments, including tMCS, in women. In the US multicenter CSWG research consortium of 5083 patients (30% women) with CS of any etiology, women had higher rates of adjusted vascular complications requiring intervention (10.4% in women vs 7.4% in men; $P = .06$) and vascular complications predicted mortality in women but not in men[8]. Further analysis of the CSWG registry identified that acute limb ischemia occurs in 3% to 19% of patients with CS and is associated with a near-doubling of in-hospital mortality. This analysis further identified female sex as a significant risk factor for development of acute limb ischemia in CS[29]. Nevertheless, major bleeding and vascular complications with tMCS devices have significantly improved over the past decade, particularly for women[21,33,52]. Guidance for best practices for large-bore access for tMCS should be followed to minimize complications and include ensuring ideal femoral arteriotomy access (ie, using palpation, fluoroscopy, ultrasound, and micropuncture techniques), consideration of alternative tMCS implantation sites with experienced proceduralists and institutions, appropriate tMCS device care (ie, routine monitoring for acute bleeding or limb ischemia), and ensuring safe device removal with successful hemostasis (ie, use of vascular closure devices with or without balloon tamponade for large-bore closure)[112]. Potentially lifesaving procedures should not be avoided in women for fear of complications, rather improved vascular access techniques and device innovation should be implemented to mitigate risks of bleeding and vascular injury.

Low enrollment of women in clinical trials of CS spanning revascularization[37,41], tMCS[47], and advanced HF therapies[100] remains a major impediment to establishing best practices in this high-risk population **(Figure 3)**. Approaches to improve enrollment of women in clinical trials should address age limits and exclusions that impact women specifically. Facilitated consent should be adopted in shock trials to better determine risks and benefits of novel treatments in women.

Lastly, standardization of shock treatment protocols can also help improve early diagnosis and recognition of shock

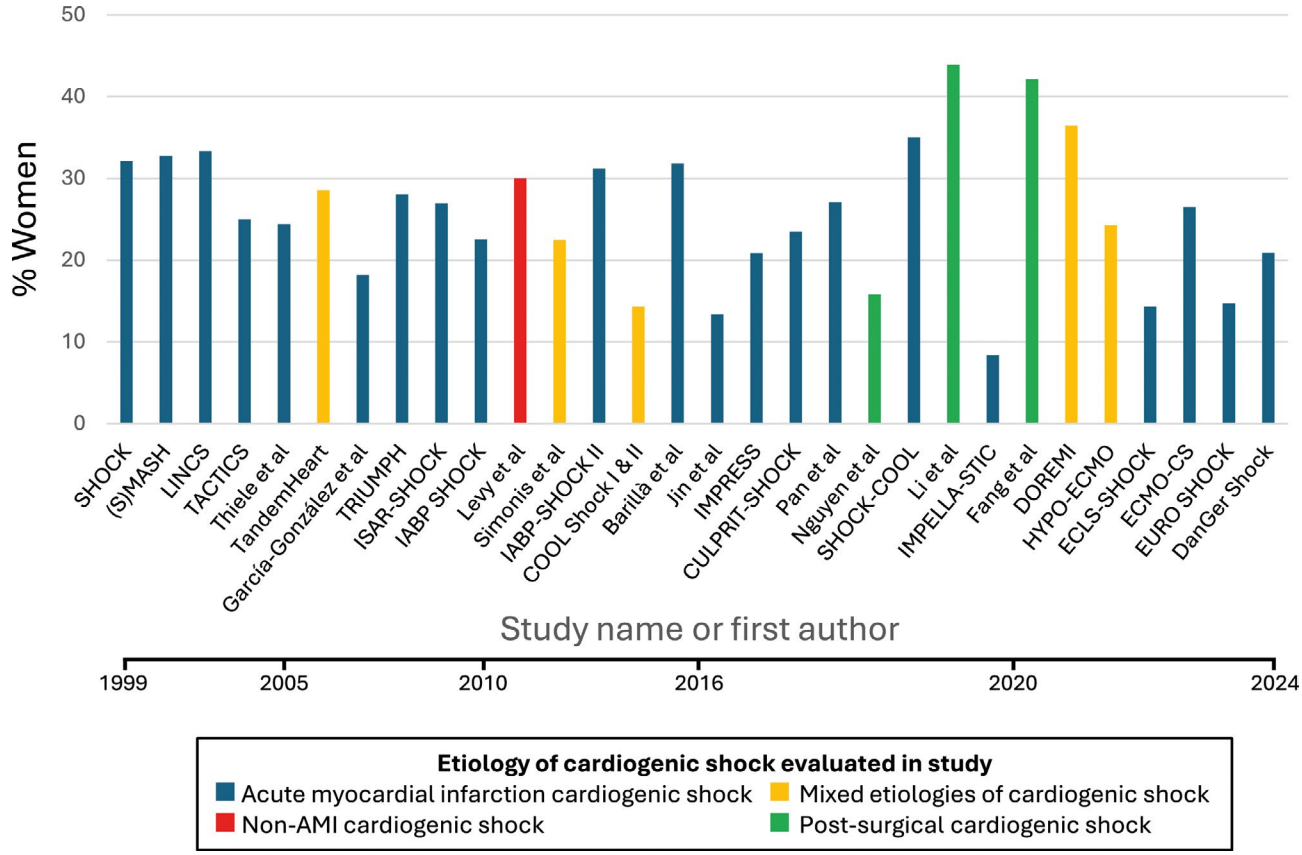

Figure 3. *Rates of women enrollment in randomized clinical trials of cardiogenic shock. AMI: acute myocardial infarction.*

in women and reduce sex-based disparities. Multidisciplinary shock teams (inclusive of advanced HF, cardiothoracic surgery, interventional cardiology, and cardiovascular critical care)[113] can quickly identify and define the severity of CS, establish the etiology, rapidly implement measures for hemodynamic support, and initiate etiology-specific treatments. A standardized team-based CS treatment protocol including mandatory hemodynamic assessment, timely diagnosis, and early, appropriate tMCS use may reduce sex disparities and improve outcomes in CS outcomes[14]. Established shock teams and treatment algorithms have demonstrated faster and more appropriate treatments for patients with CS and improvements in survival in multiple centers[25,113,114].

Consensus tips to address barriers to care for women with CS

- Anticipated vascular complications should not deter use of potentially lifesaving tMCS; rather, risks should be mitigated with improved techniques for vascular access and follow best practices for indwelling devices.
- A standardized, team-based CS treatment protocol including mandatory hemodynamic assessment, timely diagnosis, and early, appropriate tMCS use may reduce sex disparities in CS outcomes.

Evidence gaps in addressing barriers to care for women with CS

- Improve enrollment in CS trials by setting a prespecified quota of women in ongoing and future CS clinical trials to determine risks and benefits of novel treatments in women.
- Device innovation for smaller profile devices and new approaches to mitigate vascular complications should be a priority.
- Validation of SCAI SHOCK classification in women is necessity.

Future directions and conclusions

Early identification of CS and its etiology and early referral for mechanical support are paramount to improving mortality outcomes in women. A standardized approach to CS diagnosis and early treatment as proposed **(Figure 1)** will help address disparities in current clinical care. The importance of a gender-specific approach is also underscored by the recent SEX-SHOCK score[45], which could mitigate sex inequities in early risk stratification of contemporary shock management. Future trials in CS must enroll an appropriate number of women to inform the balance of risk and benefit in this population. Beyond this, dedicated randomized trials of women are necessary to determine the best treatment strategy to improve outcomes.

This consensus provides a comprehensive summary of the current state of treatment of CS in women in relevant disease states and identifies important evidence gaps. As there are limited sex-based data in contemporary literature, clinicians may use this document as a resource to guide practice. Further investigations are necessary to inform best practices for women with CS.

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Peer review statement

Suzanne J. Baron, Cindy L. Grines, and Alexandra J. Lansky hold editorial roles in *JSCAI*. As lead authors of this consensus document, they participated in drafting and review of the consensus and in all pre-submission responses to reviewers; however, after submission, they had no involvement in the peer-review process or decision for publication.

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Suzanne J. Baron leads the economic substudy of the STEMI-DTU trial for Abiomed. Josephine Chou is a consultant for Abiomed. Tayyab Shah is a consultant for Abiomed. Cristina Aurigemma is a speaker for Abiomed. Anna Bortnick reports honoraria from ClearView Healthcare and is a site PI for AEGIS-II trial (funded by CSL Behring). Alaide Chieffo is a speaker for Abiomed and is the PI for prospective, multicenter registry on INOCA-Italian MOH. Cindy L. Grines is in the advisory board of Abiomed. Navin K. Kapur is a consultant/speaker and the principal investigator for Abiomed clinical trials and registries and Getinge clinical trials and registries. Jacqueline Saw is the principal investigator for Hispanic Scholarship Fund—Spontaneous Coronary Artery Dissection (SCAD) genetics, and for Canadian Institutes of Health Research-SCAD genetics. Alexandra J. Lansky is in the advisory board and a consultant for Abiomed and in the echocardiography core laboratory of Abiomed clinical trials. Amanda R. Vest, J. Dawn Abbott, Mirvat Alasnag, Emanuele Barbato, Lavanya Bellumkonda, Robert-Jan van Geuns, Sigrun Halvorsen, Christian Hassager, Srihari Naidu, and Vivian Ng: none.

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Supplementary data

Supplementary Table 1. Relevant author disclosures.

Supplementary Table 2. Sex-based substudies of randomized clinical trials and registries in AMI complicated by cardiogenic shock.

Supplementary Table 3. Special considerations for the management of cardiac arrest in the pregnant or post-partum patient.

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ORIGINAL RESEARCH

Changes in non-culprit coronary lesions with PCSK9 inhibitors: the randomised, placebo-controlled FITTER trial

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ABSTRACT

BACKGROUND: Prolonged lipid-lowering therapy has demonstrated its ability to induce plaque regression and improve the plaque morphology of mild atherosclerotic lesions.

AIMS: This trial aimed to assess the short-term effect of evolocumab in addition to high-intensity statin therapy (HIST) on relevant non-culprit coronary artery lesions using fractional flow reserve (FFR) measurements and multimodality intracoronary imaging.

METHODS: Patients with an acute coronary syndrome (ACS) and relevant multivessel disease were randomised to receive either evolocumab or placebo for 12 weeks in addition to HIST. Patients underwent serial FFR and intravascular ultrasound (IVUS)-near-infrared spectroscopy imaging of a non-culprit vessel. The primary endpoints were the differences in the change in FFR and in the maximum lipid core burden index within any 4 mm segment ($maxLCBI_{4mm}$). The secondary endpoints were the differences in the change in IVUS-derived atheroma volume parameters.

RESULTS: Among 150 patients (mean age 64.2±8.5 years; 27 [18.0%] female) randomised to evolocumab (n=74) or placebo (n=76), 143 underwent follow-up coronary angiography. After 12 weeks of treatment, the adjusted mean change in FFR was 0.00 (95% confidence interval [CI]: −0.02 to 0.02) with evolocumab versus 0.01 (95% CI: −0.01 to 0.03) with placebo (adjusted mean difference: −0.01, 95% CI: −0.03 to 0.01; p=0.6). The adjusted mean change in the $maxLCBI_{4mm}$ was −27.8 (95% CI: −72.2 to 16.6) for evolocumab-treated patients versus −35.6 (95% CI: −82.5 to 11.4) for placebo-treated patients (adjusted mean difference: 7.8, 95% CI: −40.9 to 56.4; p=0.8). No between-group differences in any IVUS-derived parameter were found.

CONCLUSIONS: In patients with ACS and relevant non-culprit coronary artery lesions, the addition of evolocumab to HIST for 12 weeks, compared to placebo, did not result in improvement of FFR or $maxLCBI_{4mm}$. (ClinicalTrials.gov: NCT04141579)

KEYWORDS: acute coronary syndrome; fractional flow reserve; intravascular ultrasound; lipid-lowering therapy; multivessel disease; near-infrared spectroscopy

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The risk of recurrent major adverse cardiac events (MACE) after acute coronary syndrome (ACS) remains high[1]. After initial treatment of the culprit lesion with percutaneous coronary intervention (PCI), the majority of recurrent myocardial infarctions (MIs) originate from other pre-existing, non-culprit atherosclerotic lesions[2]. The presence of severe non-culprit lesions (e.g., >70% diameter stenosis) is the strongest predictor of recurrent ischaemic events after MI[3]. A high plaque volume, assessed via intravascular ultrasound (IVUS), and a lipid-rich composition, assessed via near-infrared spectroscopy (NIRS), in less severe non-culprit lesions have also been shown to identify lesions at risk of new events[3,4].

Immediate adjunctive pharmacotherapy with hydroxymethylglutaryl-CoA reductase inhibitors (statins) reduces recurrent events and has been shown to induce plaque regression and to improve plaque composition over time[5-10]. The introduction of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors leads to a further reduction in low-density lipoprotein cholesterol (LDL-C) levels within weeks after ACS[11,12]. Multiple trials have demonstrated that the addition of PCSK9 inhibitors to high-intensity statin therapy (HIST) has favourable effects on atherosclerotic plaque by improving plaque dimensions and reducing lipid content[13-15]. While these trials included non-target lesions with only mild visual obstruction, the effect on more severe lesions might be more pronounced. Consequently, short-term effects might influence the decision on additional PCI of these lesions. Fractional flow reserve (FFR) as a haemodynamic assessment of coronary lesions has served as an objective measurement to guide treatment decisions on PCI of visually indeterminate lesions[16]. Therefore, the "Functional Improvement of Non-infarcT relaTed Coronary Artery Stenosis by Extensive LDL-C Reduction With a PCSK9 Antibody" (FITTER) trial sought to evaluate the effect of 12 weeks of maximal LDL-C reduction by evolocumab in addition to HIST compared to placebo on non-culprit vessel FFR and on the plaque composition of haemodynamically relevant lesions in patients with ACS and multivessel disease.

Editorial, see page 889

Impact on daily practice

In this multicentre, double-blind, placebo-controlled, randomised clinical trial of patients presenting with acute coronary syndrome and relevant non-culprit lesions, immediate introduction of intensive lipid-lowering therapy resulted in significant non-culprit plaque lipid regression in only 12 weeks. No short-term additional reduction of plaque lipid content by proprotein convertase subtilisin/kexin type 9 inhibition was found. Non-culprit plaque volume and coronary physiology showed no significant improvement after 12 weeks. Further studies with longer follow-up are needed to assess the effect and clinical outcomes of very high-intensity lipid-lowering therapy on significant non-critical, non-culprit coronary artery lesions.

Methods

TRIAL DESIGN

The FITTER trial (ClinicalTrials.gov: NCT04141579) was an investigator-initiated, multicentre, double-blind, placebo-controlled, randomised clinical trial conducted at seven centres in the Netherlands. The medical ethical committee (METC Oost-Nederland) approved the study protocol, and all patients provided written informed consent. The study protocol and statistical analysis plan are available in **Supplementary Appendix 1** and **Supplementary Appendix 2**, respectively, and the study design has been previously described[17]. Patients 18 years or older hospitalised with ST-segment elevation myocardial infarction (STEMI), non-STEMI (NSTEMI), or unstable angina pectoris (UAP) were screened. In short, patients were deemed eligible if successful PCI of the infarct-related artery (IRA) was performed and if at least one epicardial coronary artery stenosis with an FFR of 0.67-0.85 amenable for PCI was present. Lesions in the non-IRA with a visually estimated angiographic stenosis exceeding 30% were considered suitable for FFR measurement. Major exclusion criteria were prior coronary artery bypass grafting, untreated functional left main stem stenosis (FFR ≤0.80), or severe kidney dysfunction. For detailed inclusion/exclusion criteria, see **Supplementary Table 1**. Written informed consent was preferably obtained before the index procedure. However, in some emergency cases (i.e., STEMI), oral informed consent was given for invasive study procedures during the index procedure, with full written informed consent for the entire study acquired afterwards. In preselected centres with the ability to perform additional IVUS-NIRS, baseline imaging acquisition was achieved after FFR measurement in a subset of the overall study population. After the index study procedure, patients were randomised in a 1:1 fashion into two groups (evolocumab or placebo) using a 2:4:6 random block randomisation algorithm. Randomisation was stratified

Abbreviations

ACS	acute coronary syndrome	**$LCBI_{total}$**	total segment lipid core burden index	**PAV**	percent atheroma volume
ANCOVA	analysis of covariance			**PB**	plaque burden
EEM	external elastic membrane	**LDL-C**	low-density lipoprotein cholesterol	**PCI**	percutaneous coronary intervention
FFR	fractional flow reserve	**$MaxLCBI_{4mm}$**	maximum lipid core burden index within any 4 mm segment	**PCSK9**	proprotein convertase subtilisin/kexin type 9
HIST	high-intensity statin therapy				
IRA	infarct-related artery	**MLA**	minimum lumen area	**STEMI**	ST-segment elevation myocardial infarction
IVUS	intravascular ultrasound	**NIRS**	near-infrared spectroscopy		
LCBI	lipid core burden index	**NSTEMI**	non-ST-segment elevation myocardial infarction	**TAV**	total atheroma volume
				UAP	unstable angina pectoris

per study site. The first study drug (biweekly 140 mg evolocumab or matching placebo) dose was given as soon as possible after randomisation, preferably within 24 hours after the index procedure. Patients received HIST as background therapy, e.g., atorvastatin 40 mg daily or rosuvastatin 20 mg daily. During the follow-up phase of the study, patients were contacted regularly (at weeks 1, 4, 6, and 8) to monitor clinical status, evaluate treatment adherence, and to screen for potential adverse events. At week 12, repeat coronary angiography with FFR measurement and IVUS-NIRS imaging of the non-IRA lesions was performed. Patients, treating physicians, and the research team were blinded to LDL-C measurements throughout the study.

FFR MEASUREMENT AND IVUS-NIRS IMAGING ACQUISITION

Details about FFR measurements, as well as the acquisition and analysis of IVUS-NIRS imaging, have been described in the protocol and statistical analysis plan. At week 12, FFR measurements were repeated with the pressure wire at the exact same position as baseline. Hyperaemia was achieved similarly for baseline and follow-up measurements. When IVUS-NIRS imaging was performed at baseline, follow-up imaging of the same artery was also performed at week 12. IVUS and NIRS images were analysed offline by an independent core laboratory (Cardiovascular Research Institute, Dublin, Ireland). Core laboratory personnel were blinded to all other patient data, outcome data, and the sequence of imaging (baseline vs follow-up). For IVUS, frames were analysed every 1 mm in matched coronary artery segments. The arterial lumen and external elastic membrane (EEM) borders were delineated from IVUS images. For NIRS, the 4 mm segment with the maximum lipid core burden index ($maxLCBI_{4mm}$) was identified within the same segments used for IVUS analyses. IVUS outcome parameters were derived as follows:

- Percent atheroma volume (PAV) was calculated according to the following equation:
  $[\Sigma(EEM_{area} - lumen_{area}) / \Sigma EEM_{area}] \times 100$
- Normalised total atheroma volume (TAV) was calculated according to the following equation:
  $[\Sigma(EEM_{area} - lumen_{area})$ / number of images in pullback] × median number of images in cohort
- The maximum plaque burden (PB) was defined as the highest single-slice PB within the coronary artery segment:
  $[(EEM_{area} - lumen_{area}) / EEM_{area}] \times 100$
- The minimum lumen area (MLA) refers to the smallest lumen area within the coronary artery segment.

OUTCOMES

The two primary endpoints of this trial were the differences in the change in FFR (primary physiological endpoint) and in $maxLCBI_{4mm}$ (primary imaging endpoint) from baseline to follow-up in the non-IRA between evolocumab- and placebo-treated patients.

The secondary endpoints of this trial were the differences in change in IVUS-derived plaque characteristics of the non-IRA:

- percent atheroma volume
- normalised total atheroma volume
- maximum plaque burden
- minimum lumen area

A detailed list of all study endpoints is presented in **Supplementary Table 2**.

STATISTICAL METHODS

The study was originally designed with a single primary endpoint (the change in FFR) and a powered secondary endpoint (the change in $maxLCBI_{4mm}$). During the execution of the study, the importance of plaque composition as a predictor of non-culprit MACE and as a target for PCSK9 inhibitors was further recognised in contemporary publications[3,13]. Therefore, before completion of the trial and prior to unblinding, the powered secondary endpoint was upgraded to a second primary endpoint in an official amendment to the study protocol (version 8.0), which included a correspondingly updated statistical analysis plan.

Statistical comparisons of baseline to follow-up between the two groups were performed using an analysis of covariance (ANCOVA) model including the treatment and randomisation stratification centre as fixed factors, corrected for the baseline value of that specific outcome. The analysis of the first primary endpoint (the change in FFR) was performed on the full analysis set, which included all patients with available serial FFR data. The analyses of the second primary endpoint (the change in $maxLCBI_{4mm}$) and IVUS-derived secondary endpoints included all patients in the full analysis set with available serial NIRS or IVUS data, respectively. Participants were grouped according to their randomised treatment group assignment. Analyses of adverse events included patients who had received at least one administration of the study drug.

The study was considered positive in the presence of a statistically significant difference in at least one primary endpoint. Both primary endpoints were tested independently. A Hochberg correction was performed to maintain the overall familywise error rate at 0.05. In short, if the largest p-value was <0.05, both null hypotheses were rejected; if the largest p-value was ≥0.05, the smaller p-value was compared with alpha=0.025. If the smallest p-value was <0.025, then the null hypothesis corresponding to that primary outcome variable was rejected. The p-values for the secondary endpoints were only interpreted (i.e., the subsequent null hypotheses can only be rejected) if at least one of the null hypotheses of both primary endpoints was rejected. The secondary endpoints were tested using a hierarchical procedure, and a p-value of <0.05 was considered statistically significant.

The overall changes from baseline to follow-up were also examined using paired t-tests. Analysis of the LDL-C measurements over time was carried out using a repeated measures model with an unstructured variance-covariance matrix. All reported p-values are two-sided. Statistical analyses were performed using SPSS Statistics, version 29.0 (IBM).

SAMPLE SIZE: POWER ANALYSIS OF THE PRIMARY ENDPOINTS

Details about the sample size calculation are provided in the statistical analysis plan **(Supplementary Appendix 2)**. For our first primary endpoint (FFR), based on ANCOVA, a total sample size of 127 would provide 80% power to detect an expected between-group difference at follow-up of 0.03, using a 2-sided alpha level of 0.05. To compensate for a dropout rate of about

15%, a total of 150 patients were to be included at baseline. After upgrading the powered secondary endpoint to a second primary endpoint, no change was made to the initial sample size. In case the FFR had to be tested with an alpha of 0.025, this would result in less power (approximately 76%, under similar conditions and considering our eventual lower dropout ratio of 5.3%). For our second primary endpoint ($maxLCBI_{4mm}$), based on ANCOVA, an expected 14.2% larger decrease in the evolocumab group, at a 2-sided alpha level of 0.025, and to compensate for a dropout rate of about 20%, a total of 84 patients were to be included at baseline to reach 90% power.

Results

PATIENT CHARACTERISTICS

Between 10 November 2020 and 17 August 2023, a total of 150 patients (35.3% STEMI, 60% NSTEMI, 4.7% UAP) were included and randomised to receive treatment with evolocumab (n=74) or placebo (n=76). The patient flowchart is presented in **Figure 1**. Overall, 143 patients underwent coronary angiography for follow-up endpoint measurements. At baseline, successful IVUS and NIRS pullbacks were performed in 95 and 94 patients, respectively (1 IVUS-NIRS catheter failed to record the NIRS signal). At follow-up, IVUS-NIRS was successfully repeated in 86 patients. All patients received at least one study drug administration, and a total of 138 patients received all study drug injections per protocol. The clinical characteristics of all randomised patients are presented in **Table 1**. At admission, 41 patients (27.3%) were receiving any statin therapy, of whom 15 patients (10.0%) were on HIST. At discharge and follow-up, 141 (94.6%) and 136 (93.8%) patients were on HIST, respectively **(Supplementary Table 3, Supplementary Table 4)**. Overall, 142, 85, and 86 patients were included in the paired analyses of FFR, $maxLCBI_{4mm}$, and IVUS-derived parameters, respectively. Patients with additional IVUS imaging at baseline were similar to the overall group of patients **(Supplementary Table 5)**. Of the 143 patients who

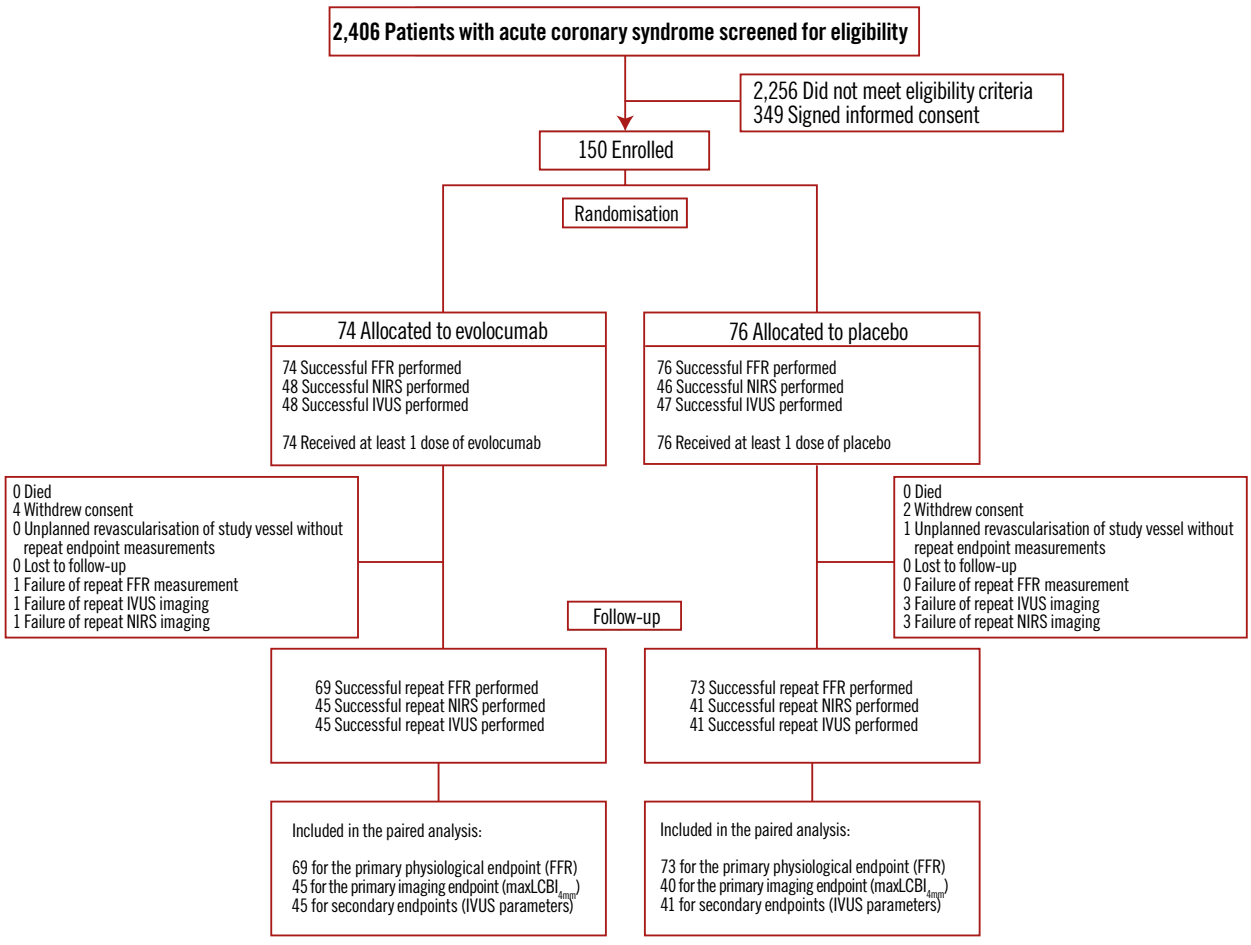


Figure 1. *Flow of patients in the FITTER trial. Overall, 143 patients underwent coronary angiography for follow-up endpoint measurements. At baseline, successful IVUS and NIRS pullbacks were performed in 95 and 94 patients, respectively (one IVUS-NIRS catheter failed to record the NIRS signal). At follow-up, IVUS-NIRS was repeated in 86 patients. In 9 patients, repeat IVUS-NIRS was not available: 4 patients withdrew consent, the IVUS-NIRS catheter was unable to cross the lesion in 2 patients, repeat IVUS-NIRS was not possible in 2 patients due to a defective device, and 1 patient was revascularised at the request of the treating physician because of poor left ventricular function 2 weeks after inclusion (unplanned revascularisation of the study vessel without repeat endpoint measurements). FFR: fractional flow reserve; IVUS: intravascular ultrasound; $maxLCBI_{4mm}$: maximum lipid core burden index within a 4 mm segment; NIRS: near-infrared spectroscopy*

Table 1. Baseline characteristics of all patients randomised in the FITTER trial.

	Evolocumab (n=74)	Placebo (n=76)
Demographics		
Age, years	63.5±8.3	65.0±8.8
Male sex	58 (78.4)	65 (85.5)
Female sex	16 (21.6)	11 (14.5)
BMI, kg/m^2	27.3±4.1	27.4±3.9
Cardiovascular risk factors		
Hypertension	29 (39.2)	30 (39.5)
Dyslipidaemia	29 (39.2)	34 (44.7)
Family history of premature CAD	25 (34.7)	32 (42.1)
Smoking history	54 (73.0)	56 (73.7)
Current smoker	24 (32.4)	21 (27.6)
Diabetes mellitus	6 (8.1)	9 (11.8)
Insulin-treated diabetes mellitus	1 (1.4)	3 (3.9)
Medical history		
Stroke or TIA	4 (5.4)	3 (3.9)
Peripheral artery disease	3 (4.1)	0 (0)
Prior myocardial infarction	7 (9.5)	13 (17.1)
Prior PCI	11 (14.9)	13 (17.1)
Premature CVD (CAD/stroke/TIA/PAD)	5 (6.8)	3 (3.9)
Baseline lipid-lowering therapy		
Any statins	18 (24.3)	23 (30.3)
High-intensity statin therapy[a]	8 (10.8)	7 (9.2)
Ezetimibe	2 (2.7)	3 (3.9)
Fibrates	1 (1.4)	0 (0)
Niacin	0 (0)	0 (0)
Resins	0 (0)	0 (0)
Other cardiac medications		
Aspirin	14 (18.9)	19 (25.0)
ADPRI (ticagrelor/clopidogrel/prasugrel)	3 (4.1)	5 (6.6)
DAPT	1 (1.4)	3 (3.9)
ACE inhibitor	10 (13.5)	8 (10.5)
ARB	6 (8.1)	7 (9.2)
Beta blocker	11 (14.9)	16 (21.1)
Type of ACS		
STEMI	26 (35.1)	27 (35.5)
NSTEMI	45 (60.8)	45 (59.2)
UAP	3 (4.1)	4 (5.3)
Study vessel		
LAD	60 (81.1)	49 (64.5)
RCA	5 (6.8)	9 (11.8)
Cx	9 (12.2)	18 (23.7)

Data are given as mean±SD or n (%). [a]Atorvastatin ≥40 mg, rosuvastatin ≥20 mg or simvastatin ≥80 mg. Note: BMI calculated as weight in kilograms divided by height in metres squared. ACE: angiotensin-converting enzyme; ACS: acute coronary syndrome; ADPRI: adenosine diphosphate receptor inhibitor; ARB: angiotensin receptor blocker; BMI: body mass index; CAD: coronary artery disease; CVD: cardiovascular disease; Cx: circumflex artery; DAPT: dual antiplatelet therapy; LAD: left anterior descending artery; NSTEMI: non-STEMI; PAD: peripheral artery disease; PCI: percutaneous coronary intervention; RCA: right coronary artery; SD: standard deviation; STEMI: ST-segment elevation myocardial infarction; TIA: transient ischaemic attack; UAP: unstable angina pectoris

underwent repeat coronary angiography, additional PCI was performed in 60 (42.0%) patients.

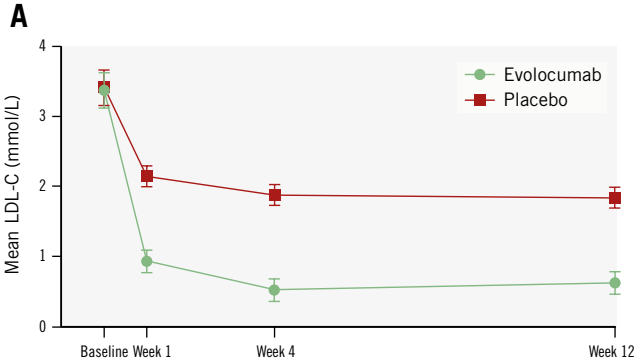
BIOCHEMICAL MEASUREMENTS

The change in lipid levels for all patients who completed clinical follow-up of the study are summarised in **Supplementary Table 6**. As the majority of patients were not on any statin therapy at baseline, both the placebo and evolocumab group showed significant improvement in their lipid levels. After 12 weeks of treatment, evolocumab-treated patients demonstrated greater reductions in levels of triglycerides (adjusted mean difference: –0.2 mmol/L, 95% confidence interval [CI]: –0.4 to –0.0; p=0.03), total cholesterol (adjusted mean difference: –1.3 mmol/L, 95% CI: –1.5 to –1.0; p<0.001), non-high-density lipoprotein cholesterol (adjusted mean difference: –1.3 mmol/L, 95% CI: –1.5 to –1.0; p<0.001) and LDL-C (adjusted mean difference: –1.2 mmol/L, 95% CI: –1.4 to –1.0; p<0.001). **Figure 2** emphasises the faster and larger reduction of LDL-C in the evolocumab group. After just 1 week, LDL-C was already significantly lower compared to the placebo group (between-group difference: –1.2 mmol/L, 95% CI: –1.4 to –1.0). This difference was maintained throughout the 12-week period.

PRIMARY AND SECONDARY ENDPOINTS

PRIMARY HAEMODYNAMIC ENDPOINT: FFR

At baseline, the mean FFR was 0.78±0.04 in the evolocumab group and 0.78±0.05 in the placebo group. After 12 weeks of treatment, the adjusted mean change in FFR was 0.00 (95% CI: –0.02 to 0.02) with evolocumab versus 0.01 (95% CI: –0.01 to 0.03) with placebo (adjusted mean



B

	Baseline	Week 1	Week 4	Week 12
Mean difference compared to placebo, mmol/L (95% CI)	0.0 (–0.4 to 0.3)	–1.2 (–1.4 to –1.0)	–1.3 (–1.5 to –1.1)	–1.2 (–1.4 to –1.0)

Figure 2. *A) Mean LDL-C values in the two study groups over time; error bars indicate 95% CIs. B) Mean difference between the evolocumab and placebo groups. To convert LDL-C values to mg/dL, divide by 0.0259. CI: confidence interval; LDL-C: low-density lipoprotein cholesterol*

difference: –0.01, 95% CI: –0.03 to 0.01; p=0.6) **(Table 2, Figure 3, Central illustration)**. The overall difference in FFR from baseline to follow-up is listed in **Supplementary Table 7**. Thirty patients (12 in the evolocumab group and 18 in the placebo group) with an impaired FFR at baseline (≤0.80) improved to a level >0.80 at follow-up, which often resulted in cancelled PCI **(Figure 3)**. Ten patients with a negative FFR at baseline had a positive FFR at follow-up.

PRIMARY IMAGING ENDPOINT: MAXLCBI$_{4MM}$

The adjusted mean change in maxLCBI$_{4mm}$ was –27.8 (95% CI: –72.2 to 16.6) for patients treated with evolocumab versus –35.6 (95% CI: –82.5 to 11.4) for patients treated with placebo (adjusted mean difference: 7.8, 95% CI: –40.9 to 56.4; p=0.8) **(Table 2, Figure 4, Central illustration)**. In line with this, no difference in the change in LCBI$_{total}$ was found (adjusted mean difference: 4.2, 95% CI: –11.7 to 20.2) **(Table 2)**. **Supplementary Table 7** provides a summary of the

Table 2. Primary and secondary outcome parameters of the FITTER trial.

Intracoronary physiology	Evolocumab (n=69)	Placebo (n=73)	*p*-value
Fractional flow reserve			
Baseline	0.78±0.04	0.78±0.05	
Follow-up	0.77±0.06	0.79±0.08	
Adjusted mean change	0.00 (–0.02 to 0.02)	0.01 (–0.01 to 0.03)	
Adjusted mean difference in change compared to placebo	–0.01 (–0.03 to 0.01)		0.6
Near-infrared spectroscopy parameters	**Evolocumab (n=45)**	**Placebo (n=40)**	***p*-value**
MaxLCBI$_{4mm}$			
Baseline	357.4±177.2	359.9±175.7	
Follow-up	324.2±184.8	318.0±155.1	
Adjusted mean change	–27.8 (–72.2 to 16.6)	–35.6 (–82.5 to 11.4)	
Adjusted mean difference in change compared to placebo	7.8 (–40.9 to 56.4)		0.8
LCBI$_{total}$[a]			
Baseline	86.5±52.8	88.8±69.4	
Follow-up	73.6±47.8	70.8±56.0	
Adjusted mean change	–14.9 (–29.2 to –0.5)	–19.1 (–34.4 to –3.8)	
Adjusted mean difference in change compared to placebo	4.2 (–11.7 to 20.2)		
Intravascular ultrasound parameters	**Evolocumab (n=45)**	**Placebo (n=41)**	***p*-value**
Percent atheroma volume, %			
Baseline	48.3±6.8	47.0±7.7	
Follow-up	47.6±5.9	46.7±7.7	
Adjusted mean change	–0.5 (–1.7 to 0.6)	–0.4 (–1.5 to 0.8)	
Adjusted mean difference in change compared to placebo	–0.2 (–1.4 to 1.0)		
Normalised total atheroma volume, mm^3			
Baseline	381.7±135.1	370.7±123.6	
Follow-up	370.5±127.1	364.1±116.9	
Adjusted mean change	–7.5 (–23.5 to 8.6)	–3.9 (–20.8 to 13.1)	
Adjusted mean difference in change compared to placebo	–3.6 (–21.1 to 13.9)		
Maximum plaque burden, %			
Baseline	71.2±6.8	70.4±7.3	
Follow-up	70.2±6.7	69.8±7.2	
Adjusted mean change	–0.6 (–2.1 to 0.9)	–0.3 (–1.8 to 1.3)	
Adjusted mean difference in change compared to placebo	–0.3 (–1.9 to 1.3)		
Minimum lumen area, mm^2			
Baseline	3.7±1.1	3.7±0.7	
Follow-up	3.6±1.2	3.6±0.7	
Adjusted mean change	0.0 (–0.2 to 0.3)	–0.0 (–0.3 to 0.2)	
Adjusted mean difference in change compared to placebo	0.1 (–0.2 to 0.3)		

Data are presented as mean±SD or as mean (95% CI). [a]Serial LCBI$_{total}$ values were missing for two evolocumab- (n=43) and two placebo-treated (n=38) patients. CI: confidence interval; LCBI$_{total}$: total segment lipid core burden index; maxLCBI$_{4mm}$: maximum lipid core burden index within any 4 mm segment; SD: standard deviation

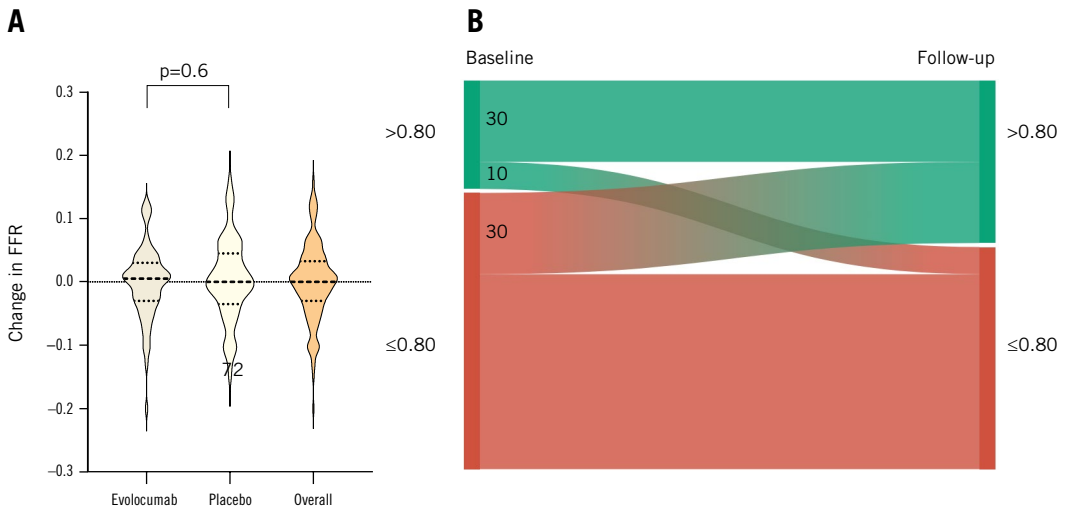


Figure 3. *Changes in FFR (primary haemodynamic endpoint) and FFR reclassification of the patients in the FITTER trial. A) The violin plot displays the observed changes in FFR values from baseline to follow-up. Dotted lines within the violin plots present the median, 25th, and 75th percentiles. No difference in change between evolocumab- and placebo-treated patients was found (adjusted mean difference: –0.01, 95% CI: –0.03 to 0.01; p=0.6). Also, no overall change in FFR was observed (overall change: 0.00, 95% CI: 0.01 to –0.01). B) The Sankey diagram shows the overall change in the FFR group (>0.80 or ≤0.80) from baseline to follow-up. CI: confidence interval; FFR: fractional flow reserve*

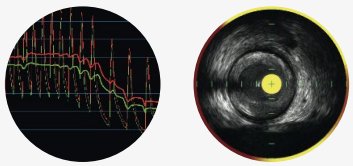
EuroIntervention — Central Illustration

Efficacy of 12 weeks of evolocumab treatment in addition to high-intensity statin therapy to improve the functional and morphological characteristics of relevant non-culprit coronary artery stenosis.

A Population

ACS patients undergoing PCI of the culprit lesion with an important non-culprit lesion (FFR 0.67-0.85)

B Non-culprit lesion measurements



FFR IVUS-NIRS

C Intervention

150 patients included and randomised

74 Evolocumab + High-dose statin

76 Placebo + High-dose statin

Repeat FFR and IVUS-NIRS after 12 weeks

D Results

FFR

	Evolocumab	Placebo
Baseline	0.78	0.78
Follow-up	0.77	0.79
Adjusted mean change (95% CI)	0.00 (–0.02 to 0.02)	0.01 (–0.01 to 0.03)

Difference compared to placebo: –0.01 (95% CI: –0.03 to 0.01; p=0.6)
Overall change: 0.00 (95% CI: –0.01 to 0.01)

maxLCBI$_{4mm}$

	Evolocumab	Placebo
Baseline	357.4	359.9
Follow-up	324.2	318.0
Adjusted mean change (95% CI)	–27.8 (–72.2 to 16.6)	–35.6 (–82.5 to 11.4)

Difference compared to placebo: 7.8 (95% CI: –40.9 to 56.4; p=0.8)
Overall change: –37.3 (95% CI: –63.2 to –11.3)

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A) Trial population; (B) non-culprit lesion assessment: FFR and IVUS-NIRS; (C) trial design; (D) results. In this double-blind, placebo-controlled, randomised clinical trial among patients presenting with ACS and relevant multivessel disease, the addition of evolocumab to high-intensity statin therapy for 12 weeks, compared to placebo, did not result in the improvement of FFR or plaque lipid content. ACS: acute coronary syndrome; CI: confidence interval; FFR: fractional flow reserve; IVUS-NIRS: intravascular ultrasound-near-infrared spectroscopy; maxLCBI$_{4mm}$; maximum lipid core burden index within a 4 mm segment; PCI: percutaneous coronary intervention

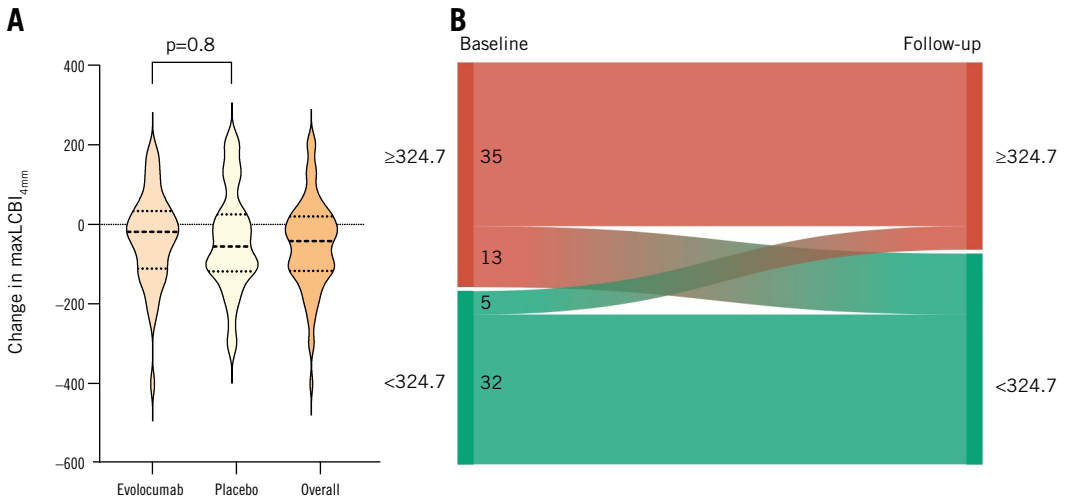

Figure 4. *Changes in maxLCBI$_{4mm}$ (primary imaging endpoint) and maxLCBI$_{4mm}$ reclassification of the patients in the FITTER trial. A) The violin plot displays the observed changes in maxLCBI$_{4mm}$ values from baseline to follow-up. Dotted lines within the violin plots present the median, 25th, and 75th percentiles. There was no significant difference between the change in evolocumab- and placebo-treated patients (adjusted mean difference: 7.8, 95% CI: −40.9 to 56.4; p=0.8). An overall reduction in maxLCBI$_{4mm}$ was observed (overall change: −37.3, 95% CI: −63.2 to −11.3). B) The Sankey diagram shows the overall transition of lipid-rich plaque (maxLCBI$_{4mm}$ ≥324.7) to non-lipid rich (maxLCBI$_{4mm}$ <324.7) from baseline to follow-up. CI: confidence interval; maxLCBI$_{4mm}$: maximum lipid core burden index within any 4 mm segment*

overall differences observed in LCBI values. After 12 weeks of treatment, 13 out of 48 vessels (27.1%) displaying lipid-rich regions (in 7 and 6 patients randomised to evolocumab and placebo, respectively) were reclassified as non-lipid rich according to the previous reported cutoff of 324.7 **(Figure 4)**[3].

SECONDARY ENDPOINTS: IVUS PARAMETERS

At baseline, the mean PAV was 48.3±6.8% in the evolocumab group and 47.0±7.7% in the placebo group. At follow-up, the adjusted mean change in PAV was −0.5% (95% CI: −1.7 to 0.6) for evolocumab-treated patients versus −0.4% (95% CI: −1.5 to 0.8) for placebo-treated patients (adjusted mean difference: −0.2%, 95% CI: −1.4 to 1.0). Similarly, no significant differences between patients treated with evolocumab or placebo were found in normalised TAV (adjusted mean difference: −3.6 mm^3, 95% CI: −21.1 to 13.9), maximum PB (adjusted mean difference: -0.3%, 95% CI: −1.9 to 1.3), or MLA (adjusted mean difference: 0.1 mm^2, 95% CI: −0.2 to 0.3) **(Table 2)**. The overall changes from baseline to follow-up are presented in **Supplementary Table 7**.

SAFETY AND CLINICAL EVENTS

During the execution of the study, clinical events were scarce. No myocardial infarction due to a culprit lesion in the study vessel occurred. One patient experienced a stroke after the index procedure. Two patients had an expedited follow-up procedure due to progressive chest pain. However, in one of the patients, the chest pain was likely of non-cardiac origin, as the FFR results were not significant. One patient died due to an unknown cause nine days after the follow-up procedure and PCI of the study vessel.

Discussion

The FITTER trial aimed to investigate the full potential of intensive lipid-lowering therapy on relevant non-culprit lesions in ACS patients at very short follow-up. A more profound reduction in LDL-C was already achieved after 1 week of evolocumab therapy compared to the placebo group. Regarding the trial's primary and secondary outcomes, no between-group differences were found between evolocumab- and placebo-treated patients. Deferral of PCI of non-culprit lesions with an FFR of 0.67-0.85 did not result in safety issues in this trial.

Few studies have examined the impact of lipid-lowering therapy on change in intracoronary physiology. In the YELLOW trial, patients with chronic stable angina and a non-target lesion with an FFR ≤0.80 were imaged with IVUS-NIRS and randomised to HIST or a moderate statin-therapy dose[7]. After 6-8 weeks, FFR and IVUS-NIRS were repeated. A non-significant increase in FFR was observed in patients on HIST, while no improvement was noted in those treated with moderate statin therapy. The non-randomised FORTE trial assessed the effect of 12-month atorvastatin therapy on non-significant lesions in 95 patients[18]. Overall, no significant change in FFR was found. However, patients who achieved optimal LDL-C targets did demonstrate a significant increase in FFR. Furthermore, an inverse correlation between achieved LDL-C and change in FFR was found. In a substudy of the PACMAN-AMI trial, in which ACS patients were also randomised to PCSK9 inhibitors or placebo in addition to HIST, no significant improvement of quantitative flow ratio (QFR) in any group was found after 52 weeks of therapy[19]. Theoretically, LDL-C lowering reduces non-culprit plaque size, which in turn could increase FFR. In our study, a substantial fraction of non-culprit lesions improved from an impaired FFR to a non-significant FFR at follow-up. However, since the baseline FFR was close

to the normal cutoff value, slight improvements and minimal variability might have contributed to this transition. Plaque size did not significantly differ after 12 weeks of therapy in either group, which may partially explain the absence of any observed differences on a continuous scale. Yet, patients in the FORTE trial and in the QFR substudy of PACMAN-AMI demonstrated no physiological improvement despite significant plaque size reduction. Therefore, greater plaque size reductions appear to be necessary to achieve improvements in intracoronary physiology. In addition, variability in non-culprit physiology between acute and late stages have been reported before[20]. It is hypothesised that the adenosine response is blunted to some degree in STEMI patients at presentation[20]. In addition, myocardial oedema and elevated left ventricular filling pressures might decrease initial hyperaemic non-culprit flow in the acute setting[21,22]. However, data are conflicting. Multiple trials have reported stable non-culprit FFR measurements in STEMI and NSTEMI patients between the acute and stabilised phases[23-25]. Therefore, the impact of ACS on non-culprit FFR seems to be reserved for patients presenting with large STEMI at very early stages. This appears to apply only minimally to the FITTER trial population, as only 35.3% of the patients presented with STEMI, and study vessel assessment was often performed during a second coronary angiography at the index hospitalisation. Nevertheless, the physiological differences between the acute and chronic phases after ACS might have masked slight changes.

The overall decreases of $maxLCBI_{4mm}$ and $LCBI_{total}$ align with previous trials investigating the effect of lipid-lowering therapy on plaque composition[7,13,26]. The reduction of intraplaque lipid occurs rapidly after intensification of lipid-lowering therapy[7,26]. In the YELLOW trial, the median change in $maxLCBI_{4mm}$ was 149.1 points in patients treated with HIST, while the moderate statin-therapy group demonstrated no improvement[7]. Moreover, a recent, small, single-arm trial by Kataoka et al observed a significant $maxLCBI_{4mm}$ reduction, from 387 to 315, in only 2 to 6 weeks after a single dose of a PCSK9 inhibitor[26]. In the FITTER trial, $maxLCBI_{4mm}$ decreased by 37.3 overall, which represents a markedly smaller reduction compared to the other trials assessing the short-term impact of LDL-C reduction[7,26]. The FITTER trial differs from other trials by including ACS patients in whom atherosclerotic disease has become destabilised, potentially featuring more vulnerable plaques that are less likely to show improvement[27]. Surprisingly, no between-group differences were found in $maxLCBI_{4mm}$ or $LCBI_{total}$ in the FITTER trial. The short timeframe conceivably plays a major role. Also, only 41 patients (27.3%) were on any statin therapy at baseline. This is notably lower compared to the YELLOW trial and the study by Kataoka et al, in which approximately 82% and 85% of the patients, respectively, were on statin therapy at baseline[7,26]. Our findings may suggest a maximum speed of "lipid washout" when HIST is initiated. Over time, prolonged LDL-C reduction through PCSK9 inhibition has been shown to lead to a more profound decrease in $maxLCBI_{4mm}$, as observed in the PACMAN-AMI trial[13].

The GLAGOV, PACMAN-AMI, and HUYGENS trials reported incremental plaque regression when patients were treated with PCSK9 inhibitors in addition to HIST compared to HIST alone[13-15]. Moreover, the HUYGENS and PACMAN-AMI trials observed a greater decline in PAV than the GLAGOV study, possibly due to a higher PAV at baseline[13-15]. Since these trials only included patients with ≤50% visual lumen obstruction, we hypothesised that an even greater effect could be expected when significant lesions were included. Despite focusing on relevant lesions, baseline PAV was only modestly higher (47.6%) compared to PACMAN-AMI and HUYGENS (approximately 42% and 45%, respectively). On the other hand, baseline normalised TAV was notably greater (376.5 mm^3 vs approximately 256 mm^3 and 245 mm^3 in PACMAN-AMI and HUYGENS, respectively), suggesting longer diseased arterial segments assessed by the FITTER trial. Moreover, vessels undergo positive remodelling in response to plaque growth, which preserves lumen area and limits initial PAV increase[28]. We observed an overall trend toward a reduction in normalised TAV and maximum PB; however, this was not statistically significant. Also, no between-group differences were found. In line with our results, no significant improvement of plaque volume parameters were reported in the YELLOW trial or the study by Kataoka et al, which also investigated the immediate impact on plaque volume[7,26].

In view of current results and contemporary related trials, plaque stabilisation seems to precede plaque volume reduction when lipid-lowering therapy is intensified[7,13,26]. The short-term overall reduction of plaque lipid content observed in the FITTER trial reinforces the fundamental importance of implementing lipid-lowering therapy immediately after ACS to mitigate future risk associated with vulnerable lipid-rich lesions. Our findings suggest that continuous treatment is required to induce significant plaque regression and further lipid content reduction. The potential of improving FFR within a very short timeframe seems limited. Further research with extended follow-up is needed to explore the long-term effects of an aggressive lipid-lowering therapy regimen on non-critical but relevant coronary artery lesions.

Limitations

This study has some limitations. First, baseline LDL-C values were lower compared to the PACMAN-AMI and HUYGENS trials (3.4 mmol/L vs approximately 4.0 mmol/L and 3.7 mmol/L, respectively), reducing treatment potential[13,14]. On the other hand, the lack of LDL-C thresholds in the FITTER trial indicates that the current population represents a typical ACS population. Second, non-culprit FFR measurements might be overestimated in the ACS setting, particularly in patients presenting with large STEMI, potentially obscuring small effects on the changes in FFR. Third, despite focusing on relevant coronary artery lesions, baseline PAV was only moderately higher compared to other trials, curtailing therapeutic efficacy. Fourth, quantitative coronary analysis was not performed, which could have been useful in comparing current lesions with those from other trials. Finally, although the target sample size for the primary imaging endpoint was achieved, the cohort with serial IVUS imaging was still relatively small, limiting power to demonstrate significant overall and between-group differences.

Conclusions

Among patients presenting with ACS and relevant multivessel disease, the addition of evolocumab to HIST for 12 weeks,

compared to placebo, did not result in the improvement of FFR or plaque lipid content. Further studies with extended follow-up are necessary to evaluate the impact of prolonged very high-intensity lipid-lowering therapy.

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Conflict of interest statement

M.M. Reda Morsy reports funding from the European Association of Percutaneous Cardiovascular Interventions (EAPCI) Education and Training Grants Programme. R.M. Oemrawsingh reports speaker fees from Abbott and Terumo. C. von Birgelen reports institutional research grants from Abbott, Boston Scientific, Biotronik, and Medtronic, outside the current study. A.J.J. IJsselmuiden reports institutional fees from Medtronic, Meril Life Sciences, and Abbott; and consulting fees from Meril Life Sciences, Angiocare, Abbott, Philips, and Translumina. P.C. Smits reports institutional research grants from Abbott and SMT; and consulting or speaker fees from Abbott, MicroPort, SMT, and Terumo; he participates on a data safety monitoring board or advisory board of the LEGACY trial, PROCTOR trial, and on the global coronary advisory board of Abbott; he is a minor shareholder of the European Cardiovascular Research Center. V. Paradies reports institutional grants from Abbott; and personal consulting or speaker fees from Abbott, Boston Scientific, Elixir, and Novo Nordisk; she participates on advisory boards or committees of Boston Scientific, EAPCI Chair Congress Committee, and is an ESC CPC member. C. Camaro reports institutional speaker fees from AstraZeneca and from regional interventional cardiology meetings. P. Damman reports research grants from Abbott, Philips, Pie Medical Imaging, and AstraZeneca; and consulting fees from Philips and Abbott. M.H. van Wely reports consulting fees from Boston Scientific and Abbott. R.A. Byrne reports grants received by the institutions of employment for research or education from Abbott, Biosensors, Boston Scientific, and Translumina, without impact on personal remuneration, and he does not accept personal payments from the medical device or pharmaceutical industry. N. van Royen reports research grants from Biotronik, Abbott, Medtronic, and Philips; and speaker fees from Abbott, RainMed, MicroPort, and Bayer. R.-J.M. van Geuns reports consulting and speaker fees from Abbott and AstraZeneca; and has received institutional research grants from Amgen, InfraRedx, AstraZeneca, and Sanofi. The other authors have no conflicts of interest to declare.

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Supplementary data

Supplementary Table 1. Inclusion and exclusion criteria.
Supplementary Table 2. Study endpoints.
Supplementary Table 3. Medication at discharge.
Supplementary Table 4. Medication at follow-up.
Supplementary Table 5. Baseline characteristics of all patients and of patients who underwent baseline intravascular ultrasound imaging.
Supplementary Table 6. Change in lipid levels of all patients from baseline to 12-week follow-up.
Supplementary Table 7. Overall changes in FFR, maxLCBI$_{4mm}$, and atheroma volume parameters.
Trial sponsor
Data availability statement
Author statement
Supplementary Appendix 1. FITTER study protocol.
Supplementary Appendix 2. FITTER statistical analysis plan.

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ORIGINAL RESEARCH

Coronary flow and resistance patterns indexed by subtended myocardial mass in coronary microvascular dysfunction

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ABSTRACT

BACKGROUND: Patients with coronary microvascular dysfunction (CMD) exhibit impaired vasodilatation of the microcirculation. This manifests as reduced microvascular resistance reserve (MRR) due to either increased resting flow (Q_{rest}; functional CMD) or decreased hyperaemic flow (Q_{hyper}; structural CMD). However, coronary flow is intimately linked to myocardial mass, potentially confounding the interpretation of flow and resistance measurements.

AIMS: We investigated the relationship between subtended myocardial mass, microvascular resistance, and coronary flow to determine whether the disturbed resistance and flow patterns seen in CMD persisted after indexing by subtended myocardial mass.

METHODS: We recruited 100 patients with angina with non-obstructive coronary arteries who underwent coronary computed tomography angiography to quantify vessel-specific subtended myocardial mass. Continuous intracoronary thermodilution was used to quantify absolute coronary flow and microvascular resistance, both at rest and during hyperaemia. Among patients with an MRR <3.0, hyperaemic microvascular resistance ($R_{\mu,hyper}$) ≥475 Wood units (WU) defined structural CMD (versus functional CMD). Flow and resistance measurements were analysed both in absolute terms and after indexing by subtended mass.

RESULTS: Mass and flow were analysed in 100 patients in the left anterior descending artery. The mean subtended myocardial mass in the structural CMD group (47.00±13.83 grams) was significantly lower than in the control group (59.64±21.69 grams; p=0.027), with no significant difference between the control group and the functional CMD group (53.75±13.99 grams; p=0.339). After indexing by the subtended mass, patients with structural CMD still had higher $R_{\mu,hyper}$ (control: 20.68±7.99 WU·kg vs structural CMD: 30.58±11.63 WU·kg; p<0.001) and lower Q_{hyper} (control: 4.56±2.20 ml/min/g vs structural CMD: 3.20±0.90 ml/min/g; p=0.013). Conversely, patients with functional CMD exhibited similar indexed values of $R_{\mu,hyper}$ and Q_{hyper} to controls.

CONCLUSIONS: Despite significantly lower subtended mass, patients with structural CMD exhibit abnormal indexed $R_{\mu,hyper}$ and Q_{hyper}, supporting the notion of hyperaemic flow restriction at the tissue level that is independent of subtended mass. However, patients with functional CMD have similar subtended myocardial mass to controls and exhibit no flow restriction during hyperaemia.

KEYWORDS: angina with non-obstructive coronary arteries; coronary flow; coronary microvascular dysfunction; microvascular resistance

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Coronary microvascular dysfunction (CMD) is defined as a decrease in the vasodilatory reserve of the coronary microcirculation. It can be diagnosed invasively using either coronary flow reserve (CFR)[1] or microvascular resistance reserve (MRR)[2], with the latter having recently been shown to be specific for the microvascular compartment[3]. A reduction in CFR or MRR can arise via one of two mechanisms. Reduced resting microvascular resistance, postulated to be related to increased nitric oxide synthase activity[4], can lead to increased resting coronary flow – a pattern referred to as functional CMD. Alternatively, an increase in minimal microvascular resistance, secondary to architectural changes to the microvasculature such as remodelling and plugging[5], can lead to a limitation of maximal hyperaemic coronary flow – a pattern defined as structural CMD.

Importantly, the classification of patients with low vasodilatory reserve into one of these CMD subtypes requires the measurement of minimal microvascular resistance, for which the exact cutoff depends on the modality being used. When using continuous thermodilution, an absolute microvascular resistance of ≥475 Wood units (WU) has been proposed[6], whilst when using bolus thermodilution, an index of microcirculatory resistance (IMR) of >25 is widely accepted[7].

However, whilst microvascular resistance and coronary flow are heavily influenced by the health of the microcirculation, they are also intimately linked to the quantity of subtended myocardial mass, which has the potential to confound the interpretation of these measurements[8]. More specifically, minimal microvascular resistance is theoretically inversely proportional to subtended myocardial mass: the larger the subtended mass, the lower the resistance, and thus, the higher the coronary flow. As a consequence, patients with smaller than average perfusion territories will naturally exhibit higher values of minimal microvascular resistance and thus risk being misdiagnosed as having structural CMD.

To address this issue, we recruited patients with angina with non-obstructive coronary arteries (ANOCA) who underwent both continuous intracoronary thermodilution – for the measurement of absolute coronary flow and microvascular resistance – and coronary computed tomography angiography (CCTA) for the quantification of vessel-specific subtended myocardial mass. We explored the relationship between subtended myocardial mass and absolute coronary flow and resistance, and we investigated whether the disturbed resistance and flow patterns seen in CMD persisted after indexing by subtended myocardial mass.

Impact on daily practice

Coronary flow is intimately linked to myocardial mass, potentially confounding the interpretation of flow and resistance measurements. In the present study, despite having significantly lower subtended mass, patients with structural coronary microvascular dysfunction (CMD) had significantly higher microvascular resistance and lower coronary flow during hyperaemia after indexing by subtended myocardial mass, supporting the notion of flow restriction at the tissue level. However, patients with functional CMD had similar subtended myocardial mass to controls and exhibited no flow restriction during hyperaemia. This study provides valuable pathophysiological insights as it confirms the flow/resistance abnormality driving symptoms in structural CMD whilst highlighting the lack of a clear pathophysiological mechanism for symptoms in functional CMD.

Methods

PATIENT POPULATION

A total of 149 patients with ANOCA were screened for study inclusion. ANOCA was defined as the absence of an angiographically significant epicardial disease, specifically no diameter stenosis >50% and no fractional flow reserve (FFR) ≤0.80. Only patients who underwent continuous intracoronary thermodilution in the left anterior descending artery (LAD) were included. Patients with a history of myocardial infarction were excluded due to the potentially confounding effect of significant myocardial scarring on the analysis.

Patients were recruited from Cardiovascular Center OLV, Aalst, Belgium, between January 2019 and May 2023. Patients were included if they (i) had previously undergone a CCTA scan permitting the calculation of subtended myocardial mass and (ii) subsequently underwent invasive coronary angiography, including an assessment for CMD using continuous intracoronary thermodilution. The median time between CCTA and the invasive assessment was 28 days (interquartile range [IQR] 9-93). All patients provided informed consent. The study protocol was approved by the institutional review board of the Onze-Lieve-Vrouw Clinic in Aalst, Belgium (registration number: 2020/033).

CCTA FOR MYOCARDIAL MASS CALCULATION

CCTA was acquired using a dual source computed tomography (CT) scanner (SOMATOM Force [Siemens Healthineers]) with 256 detectors, a pitch of 3.2, and 240 microns of spatial resolution. Before CCTA, all patients received 0.8 mg

Abbreviations

ANOCA	angina with non-obstructive coronary arteries	**CMD**	coronary microvascular dysfunction	**R_μ**	microvascular resistance
CCTA	coronary computed tomography angiography	**FFR**	fractional flow reserve	**T**	temperature of mixed blood and saline in the distal vessel
CFR	coronary flow reserve	**MRR**	microvascular resistance reserve	**T_i**	entry temperature of saline
		Q	absolute coronary flow	**WU**	Wood units
		Q_i	saline infusion rate		

sublingual nitroglycerine and, in addition, intravenous metoprolol if the heart rate was ≥65 beats/min. Vessel-specific myocardial mass was quantified automatically using the Voronoi algorithm with dedicated software (Synapse 3D [Fujifilm Healthcare Solutions])[9]. The Voronoi algorithm is utilised to precisely partition the left ventricular (LV) volume by associating each voxel of the LV with the nearest voxel of an adjacent coronary artery. This process effectively maps the myocardial volume subtended by each coronary artery. The algorithm works by creating a Voronoi diagram, where each region contains all points closer to a specific coronary artery voxel than to any other. This detailed partitioning enables accurate quantification of the myocardial volume supplied by each artery. The Voronoi-based segmentation algorithm has been validated in an *ex vivo* swine heart study, demonstrating excellent accuracy[9]. In addition, the approach exhibits excellent intraobserver and interobserver repeatability[10]. Subtended mass values derived from this method have also been shown to correlate closely with invasively measured myocardial perfusion[8]. In addition, the approach has since been used as a gold-standard comparator to validate new approaches to the quantification of subtended mass[11].

To convert the algorithm-derived volume into mass, the myocardial volume was multiplied by a constant representing myocardial tissue density (1.05 g/cm^3). This is a widely accepted constant in cardiovascular imaging, having been used to convert myocardial volume to mass in numerous previous studies[12-14].

STUDY PROTOCOL

CORONARY ANGIOGRAPHY

Coronary angiography was performed via radial or femoral artery access. A 6 Fr guiding catheter was used, and 0.2 mg of intracoronary isosorbide dinitrate was administered.

CONTINUOUS THERMODILUTION

A guidewire equipped with a pressure/temperature sensor (PressureWire X [Abbott]) was connected to dedicated software for trace visualisation and analysis (CoroFlow Cardiovascular System [Coroventis]) and, after zeroing, was advanced through the guiding catheter. The pressures recorded by the pressure/temperature wire and by the fluid-filled guide catheter were equalised close to the tip of the guiding catheter. The wire was advanced into the distal part of the artery, and the temperature zeroed.

For the measurement of absolute coronary flow, a dedicated monorail infusion 2.52 Fr microcatheter with four distal side holes (RayFlow [HEXACATH]) was advanced over the pressure/temperature wire and connected to the 200 ml motorised syringe of an automated injection system (Medrad Stellant [Medrad Inc., now Bayer]) filled with room temperature saline (typically between 20°C and 23°C). The infusion catheter was advanced into the artery being investigated, and its tip was positioned into the first millimetres of the vessel. Absolute resting (Q_{rest}) and hyperaemic (Q_{hyper}) flow measurements were obtained using saline infusion rates of 10 ml/min and 20 ml/min, respectively. The resting and hyperaemic infusion protocols were either performed with separate runs for resting and hyperaemic states with a manually programmed infusion pump or a single run with an automatically programmed infusion pump[15]. Further details on performing flow measurements using coronary continuous thermodilution have been described elsewhere[16].

CORONARY FLOW AND RESISTANCE INDICES

Absolute coronary flow (Q) in ml/min was calculated as per **Equation 1**, where T_i is the temperature of the infusate at the tip of the catheter, T is the temperature of mixed saline and blood in the distal vessel, and Q_i is the saline infusion rate. Importantly, the values of T and T_i are relative to blood temperature.

$$Q = 1.08 \cdot \frac{T_i}{T} \cdot Q_i$$

Absolute resting microvascular resistance ($R_{\mu,rest}$) in WU was calculated using **Equation 2**, where $P_{a,rest}$ is central aortic pressure under resting conditions. Importantly, coronary autoregulation reduces $R_{\mu,rest}$ in the face of any epicardial resistance to ensure sufficient Q_{rest}[17]. Accordingly, the use of $P_{a,rest}$ adjusts for the presence of epicardial resistance, permitting the calculation of "true" $R_{\mu,rest}$, i.e., $R_{\mu,rest}$ as would be expected in the absence of any epicardial resistance.

$$R_{\mu,rest} = \frac{P_{a,rest}}{Q_{rest}}$$

Absolute hyperaemic microvascular resistance ($R_{\mu,hyper}$) in WU was calculated using **Equation 3**, where $P_{d,hyper}$ is the distal coronary pressure during hyperaemia:

$$R_{\mu,hyper} = \frac{P_{d,hyper}}{Q_{hyper}}$$

CFR was calculated using the following equation **(Equation 4)**:

$$CFR = \frac{Q_{hyper}}{Q_{rest}}$$

MRR was calculated with the following equation **(Equation 5)**, where $P_{a,rest}$ and $P_{a,hyper}$ correspond to aortic pressure measured during resting and hyperaemic conditions, respectively. Unlike CFR, MRR is not influenced by the presence of epicardial resistance, making it a more specific index of microvascular function[3].

$$MRR = \frac{CFR}{FFR} \cdot \frac{P_{a,rest}}{P_{a,hyper}}$$

STRATIFICATION BY CMD SUBTYPE

Given the greater specificity of MRR than CFR for the microvascular compartment[3], MRR was used to diagnose CMD, using a cutoff of <3.0, as proposed in a recent, large-scale study[18]. Patients with an MRR ≥3.0 were defined as controls. Among patients with an MRR <3.0, an $R_{\mu,hyper}$ of ≥475 WU defined structural CMD, whereas a value <475 WU defined functional CMD[6]. The cutoff of 475 WU was chosen as this represents the upper limit of the 95% confidence interval for $R_{\mu,hyper}$ in the LAD territory in normal controls[19]. This cutoff was subsequently proposed in a recent study by de Vos et al[6]. To assess the robustness of any findings, the analysis was also performed with CMD defined as a CFR <2.5[1]. For the analysis stratified by CMD subtype (control vs

functional CMD vs structural CMD), only measurements in the LAD were used, in keeping with current clinical practice[16].

INDEXING Q AND R_μ BY SUBTENDED MYOCARDIAL MASS AND BODY SURFACE AREA

The indexing of Q and R_μ values by subtended myocardial mass is based upon the following theory: the larger the subtended mass, the higher the Q and thus the lower the R_μ. Likewise, the smaller the subtended mass, the higher the R_μ and thus the lower the Q. Given that Q is proportional to mass, indexing requires Q to be divided by mass, and thus indexed Q (in ml/min/g)=Q/mass. On the other hand, as R_μ is proportional to 1/mass, indexing R_μ by mass requires R_μ to be divided by 1/mass, and thus indexed R_μ (in WU·kg)=R_μ x mass[19]. A numerical example is provided in **Supplementary Figure 1**. Indexed values were further indexed by body surface area (BSA) to adjust for the potential impact of body size on cardiac volume. BSA was calculated using the Mosteller formula[20].

STATISTICS

Continuous variables with a normal distribution are expressed as mean±standard deviation and non-normally distributed variables as median and IQR. Categorical variables are expressed as counts and percentages.

Logistic regression was used for the prediction of binary variables. Multivariate regression was used to control for potential confounding variables. The following variables were included as covariates: age, sex, body mass index, smoking, hypertension, diabetes, dyslipidaemia, previous percutaneous coronary intervention, estimated glomerular filtration rate (eGFR), LV ejection fraction, baseline medications (statin, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, aspirin, other antiplatelet, antidiabetic medication), as well as heart rate and blood pressure (both extracted at the exact time of flow measurement). The final variables included in multivariate models were selected using both forward and backward selection, with only variables with a p-value<0.05 included in the final models.

Analysis of variance (ANOVA) was used to compare the mean of a given parameter across different subgroups. If ANOVA identified a significant difference between mean values, pairwise comparisons were performed using the Bonferroni *post hoc* test to identify which specific mean values differed. To counteract the impact of multiple testing, the Bonferroni correction was applied to p-values by multiplying them by the number of comparisons performed.

As an alternative approach to control for the impact of subtended mass on $R_{\mu,hyper}$, patients with structural CMD were matched by subtended mass with control patients using propensity score matching. Balance after matching was assessed using the standardised mean difference (SMD), with an SMD <0.1 indicating an acceptable balance between groups.

All analyses were performed using Python 3.11.4 (Python Software Foundation). A p-value<0.05 was considered statistically significant.

Results

STUDY POPULATION

In total, 149 patients with ANOCA who underwent CCTA and subsequent invasive measurements of coronary flow and resistance in the LAD were screened for inclusion. Among them, 43 patients were excluded because of an FFR ≤0.80, and a further 6 patients were excluded because of a history of myocardial infarction. Thus, in total, 100 patients were included in the final analysis. The baseline clinical characteristics of the overall population are shown in **Table 1**.

ANALYSIS STRATIFIED BY CMD SUBTYPE

The population was classified into functional CMD (n=31), structural CMD (n=20), and controls (n=49). Of note, patients with structural CMD were older (control: 61.2±10.6 years, functional CMD: 61.7±10.4 years, structural CMD: 69.3±7.3 years; p=0.01), and more likely to be female (control: 36.7%, functional CMD: 58.1%, structural CMD: 75.0%; p=0.01) **(Table 1)**. The structural CMD group also had the highest prevalence of hypertension (control: 55.1%, functional CMD: 38.7%, structural CMD: 80.0%; p=0.02) and the lowest eGFR (control: 80.4±14.6 ml/min, functional CMD: 84.3±11.3 ml/min, structural CMD: 71.2±17.3 ml/min; p=0.01). However, in a multivariate logistic regression analysis, age was the only baseline characteristic independently associated with structural CMD **(Supplementary Table 1)**.

SUBTENDED MYOCARDIAL MASS

The mean subtended myocardial mass in the structural CMD group (47.00±13.83 grams) was significantly lower compared to the control group (59.64±21.69 grams; p=0.027). However, there was no significant difference in subtended mass between the control and functional CMD groups (53.75±13.99 grams; p=0.339) **(Table 2)**. In a multivariate logistic regression analysis, subtended mass was independently associated with structural CMD **(Supplementary Table 1)**.

These differences in subtended mass corresponded to differences in total LV mass, with structural CMD having lower LV mass than the control and functional CMD groups (control: 147.46±36.57 grams, functional CMD: 133.71±34.06 grams, structural CMD: 122.74±40.77 grams; p=0.032). However, the percentage of left ventricular mass subtended by the LAD was similar between groups (control: 40.22±9.57%, functional CMD: 40.70±7.36%, structural CMD: 39.56±8.71%; p=0.903).

CFR AND MRR

Compared with patients without CMD, those with functional and structural CMD had significantly lower mean CFR (control: 3.44±0.81, functional CMD: 2.00±0.45, structural CMD: 1.97±0.56; p<0.001) **(Figure 1A)** and MRR (control: 3.96±0.76, functional CMD: 2.31±0.49, structural CMD: 2.16±0.63; p<0.001) **(Figure 1B, Table 2)**. Of note, there were no significant differences in CFR and MRR between the functional and structural CMD groups **(Figure 1A, Figure 1B).**

FLOW AND RESISTANCE IN FUNCTIONAL CMD

As per its definition, the functional CMD group had a significantly higher mean Q_{rest} (117.18±38.68 ml/min) compared to the control group (71.04±18.33 ml/min; p<0.001), but there was no significant difference in mean Q_{hyper} between these two groups (control: 241.09±72.87 ml/min, functional CMD: 222.40±46.35 ml/min; p=0.364) **(Figure 2A, Table 2)**.

Table 1. Baseline characteristics of the study population, stratified by CMD subtype.

Characteristic	Overall (n=100)	No CMD (n=49)	Functional CMD (n=31)	Structural CMD (n=20)	*p*-value
Age, years	63.0±10.4	61.2±10.6	61.7±10.4	69.3±7.3	0.01*
Female	51 (51.0)	18 (36.7)	18 (58.1)	15 (75.0)	0.01*
BMI, kg/m^2	27.3±4.7	27.3±5.1	26.7±4.5	28.4±3.9	0.49
BSA, m^2	1.9±0.2	2.0±0.2	1.9±0.2	1.8±0.2	0.13
Current smoker	16 (16.0)	8 (16.3)	7 (22.6)	1 (5.0)	0.25
Smoking history	28 (28.0)	13 (26.5)	9 (29.0)	6 (30.0)	0.95
Hypertension	55 (55.0)	27 (55.1)	12 (38.7)	16 (80.0)	0.02*
Diabetes	18 (18.0)	6 (12.2)	5 (16.1)	7 (35.0)	0.08
Dyslipidaemia	74 (74.0)	36 (73.5)	21 (67.7)	17 (85.0)	0.39
FH of CAD	10 (10.0)	6 (12.2)	4 (12.9)	0 (0.0)	0.25
Previous PCI	5 (5.0)	2 (4.1)	2 (6.5)	1 (5.0)	0.89
eGFR, ml/min/1.73 m^2	79.8±14.9	80.4±14.6	84.3±11.3	71.2±17.3	0.01*
LVEF, %	58.0±8.3	57.5±8.9	58.1±7.5	59.0±8.3	0.77
Statin	61 (61.0)	28 (57.1)	17 (54.8)	16 (80.0)	0.15
ACEi/ARBs	29 (29.0)	14 (28.6)	7 (22.6)	8 (40.0)	0.41
Aspirin	30 (30.0)	16 (32.7)	5 (16.1)	9 (45.0)	0.08
Anticoagulation	8 (8.0)	5 (10.2)	0 (0.0)	3 (15.0)	0.11
Oral antidiabetic	13 (13.0)	4 (8.2)	4 (12.9)	5 (25.0)	0.17
Insulin	1 (1.0)	1 (2.0)	0 (0.0)	0 (0.0)	0.59

Data are n (%) or mean±standard deviation. *Indicates statistical significance. ACEi: angiotensin-converting enzyme inhibitors; ARB: angiotensin II receptor blockers; BMI: body mass index; BSA: body surface area; CAD: coronary artery disease; CMD: coronary microvascular dysfunction; eGFR: estimated glomerular filtration rate; FH: family history; LVEF: left ventricular ejection fraction; PCI: percutaneous coronary intervention

These findings were also reflected in the measured resistances, with a lower mean $R_{\mu,rest}$ in the functional CMD group (842.03±240.70 WU) compared to the control group (1,385.11±380.67 WU; p<0.001), and similar mean $R_{\mu,hyper}$ between these two groups (control: 355.78±93.43 WU, functional CMD: 362.84±63.51 WU; p=0.951) **(Figure 2B, Table 2)**.

Importantly, these patterns persisted after indexing by subtended mass, with high indexed Q_{rest} (control: 1.36±0.70 ml/min/g, functional CMD: 2.31±0.86 ml/min/g; p<0.001), low indexed $R_{\mu,rest}$ (control: 80.82±31.30 WU·kg, functional CMD: 45.07±17.98 WU·kg; p<0.001), but normal indexed values of Q_{hyper} (control: 4.56±2.20 ml/min/g, functional CMD: 4.39±1.32 ml/min/g; p=1.000) and $R_{\mu,hyper}$ (control: 20.68±7.99 WU·kg, functional CMD: 19.33±5.68 WU·kg; p=0.757) **(Figure 2C, Figure 2D, Table 2)**. These findings also persisted after further indexation by BSA **(Supplementary Figure 2A, Supplementary Figure 2B)**.

Of note, the functional CMD group also exhibited a significantly higher resting heart rate than controls (control: 66.06±11.85 bpm, functional CMD: 76.58±13.93 bpm; p=0.001), with resting heart rate also shown to be an independent predictor of absolute Q_{rest} and $R_{\mu,rest}$ **(Supplementary Table 2)**. Furthermore, in multivariate logistic regression, resting heart rate was an independent predictor of functional CMD (p=0.006).

FLOW AND RESISTANCE IN STRUCTURAL CMD

Structural CMD had a significantly lower mean Q_{hyper} (142.76±37.42 ml/min) compared to the control group (241.09±72.87 ml/min; p<0.001), but with no significant difference in mean Q_{rest} between these groups (control: 71.04±18.33 ml/min vs structural CMD: 80.34±41.76 ml/min; p=0.502). This corresponded to a higher mean $R_{\mu,hyper}$ (control: 355.78±93.43 WU vs structural CMD: 652.49±158.17 WU; p<0.001), but a similar mean $R_{\mu,rest}$ (control: 1,385.11±380.67 WU vs structural CMD: 1,432.36±587.84 WU; p=0.895) **(Figure 2A, Table 2)**.

These findings persisted after indexing by subtended mass for both Q_{hyper} (control: 4.56±2.20 ml/min/g vs structural CMD: 3.20±0.90 ml/min/g; p=0.013), and $R_{\mu,hyper}$ (control: 20.68±7.99 WU·kg vs structural CMD: 30.58±11.63 WU·kg; p<0.001) **(Figure 2B, Table 2)**.

Indexed Q_{rest} was also higher in the structural CMD group (control: 1.36±0.7 ml/min/g vs structural CMD: 1.85±1.16 ml/min/g; p=0.082), with a corresponding lower indexed $R_{\mu,rest}$ (control: 80.82±31.3 WU·kg vs structural CMD: 67.31±30.83 WU·kg; p=0.132), although these differences did not reach statistical significance **(Figure 2C, Figure 2D, Table 2)**.

As seen with functional CMD, patients with structural CMD had a significantly higher resting heart rate compared with controls (control: 66.06±11.85 bpm vs structural CMD: 74.64±12.39; p=0.032). However, unlike with functional CMD, heart rate was not an independent predictor of structural CMD in multivariate analysis.

The robustness of these findings was also confirmed using a propensity score-matched analysis, matching patients with structural CMD with normal controls by subtended myocardial mass **(Supplementary Table 3)**. These findings

Table 2. Mean values and standard deviations of measured parameters and calculated metrics of flow and resistance, stratified by the presence of CMD subtypes.

Parameter	Overall (n=100)	No CMD n=49)	Functional CMD (n=31)	Structural CMD (n=20)	*p*-value
Subtended mass, g	55.29±18.66	59.64±21.69	53.75±13.99	47.00±13.83	0.03*
Total LV mass, g	138.25±37.63	147.46±36.57	133.71±34.06	122.74±40.77	0.03*
Percentage of total LV mass	40.24±8.69	40.22±9.57	40.70±7.36	39.56±8.71	0.90
CFR	2.70±0.99	3.44±0.81	2.00±0.45	1.97±0.56	<0.001*
MRR	3.09±1.08	3.96±0.76	2.31±0.49	2.16±0.63	<0.001*
FFR	0.86±0.03	0.86±0.03	0.87±0.03	0.86±0.03	0.50
Q_{rest}, ml/min	87.20±37.03	71.04±18.33	117.18±38.68	80.34±41.76	<0.001*
Mass-indexed Q_{rest}, ml/min/g	1.75±0.94	1.36±0.70	2.31±0.86	1.85±1.16	<0.001*
Q_{hyper}, ml/min	215.63±70.02	241.09±72.87	222.40±46.35	142.76±37.42	<0.001*
Mass-indexed Q_{hyper}, ml/min/g	4.23±1.82	4.56±2.20	4.39±1.32	3.20±0.90	0.02*
$R_{\mu,rest}$, WU	1,226.20±470.57	1,385.11±380.67	842.03±240.70	1,432.36±587.84	<0.001*
Mass-indexed $R_{\mu,rest}$, WU·kg	67.04±31.63	80.82±31.30	45.07±17.98	67.31±30.83	<0.001*
$R_{\mu,hyper}$, WU	417.31±155.67	355.78±93.43	362.84±63.51	652.49±158.17	<0.001*
Mass-indexed $R_{\mu,hyper}$, WU·kg	22.24±9.20	20.68±7.99	19.33±5.68	30.58±11.63	<0.001*
HR_{rest}	71.04±13.45	66.06±11.85	76.58±13.93	74.64±12.39	0.001*
HR_{hyper}	73.42±48.84	64.07±12.75	88.62±84.52	72.78±11.67	0.09
$P_{a,rest}$	93.10±13.14	93.07±12.18	90.44±12.75	97.31±15.45	0.19
$P_{a,hyper}$	93.67±14.69	92.53±13.62	90.26±14.05	101.73±15.94	0.02*

Data are mean±standard deviation. *Indicates statistical significance. Only measurements from the LAD were included. The p-value for ANOVA is shown, with pairwise comparison p-values shown in the corresponding figure. ANOVA: analysis of variance test; BSA: body surface area; CFR: coronary flow reserve; CMD: coronary microvascular dysfunction; FFR; fractional flow reserve; HR: heart rate; hyper: hyperaemic; LAD: left anterior descending artery; LV: left ventricular; MRR: microvascular resistance reserve; rest: resting; P_a: central aortic pressure; Q: absolute coronary flow; R_μ: microvascular resistance; WU: Wood units

also persisted after further indexation by BSA **(Supplementary Figure 2A, Supplementary Figure 2B)**. In addition, stratifying measurements by CFR (using a cutoff of 2.5) instead of MRR resulted in similar findings **(Supplementary Figure 3)**.

Plots of subtended mass against flow and microvascular resistance are shown in **Supplementary Figure 4**. There was no significant correlation between subtended myocardial mass and resting indices. However, subtended mass exhibited a significant correlation with hyperaemic indices (Q_{hyper} r=0.30; p=0.003; $R_{\mu,hyper}$ r=–0.29; p=0.004).

A summary of the study design and its main findings is shown in the **Central illustration**.

Discussion

The present study provides the first analysis of coronary flow and resistance patterns in CMD, both in absolute terms and after indexing by subtended myocardial mass. The principal findings of this study can be summarised as follows:

i. Patients with functional CMD had similar subtended mass and exhibited similar indexed values of $R_{\mu,hyper}$ and Q_{hyper} to controls, suggesting the absence of any restriction of hyperaemic coronary flow.

ii. Patients with structural CMD, despite having significantly lower subtended myocardial mass, exhibited higher indexed $R_{\mu,hyper}$ and lower indexed Q_{hyper} than both controls and patients with functional CMD.

Taken together, these findings support the notion of restricted hyperaemic coronary flow at the tissue level in structural CMD. However, the present data also highlight the lack of a clear pathophysiological mechanism for the symptoms experienced by patients with functional CMD.

THE RELATIONSHIP BETWEEN SUBTENDED MYOCARDIAL MASS, Q AND R_μ

Whilst the relationship between subtended myocardial mass and vessel geometry (e.g., luminal diameter/area, vessel length) has long been established[21,22], data on the relationship between subtended mass and coronary flow have been limited to porcine studies and *in vitro* simulations[23]. The recent development of continuous intracoronary thermodilution has permitted the accurate and precise measurement of absolute coronary flow which, when combined with the concomitant measurement of P_a and P_d, also permits the calculation of absolute microvascular resistance[16]. Furthermore, the accuracy of the Voronoi-based segmentation algorithm for the calculation of subtended myocardial mass has already been demonstrated[9]. Keulards et al previously demonstrated the feasibility of combining continuous intracoronary thermodilution with CT-derived vessel-specific subtended myocardial mass for the calculation of myocardial perfusion[8].

It is worth noting that positron emission tomography (PET) also permits the quantification of blood flow per gram

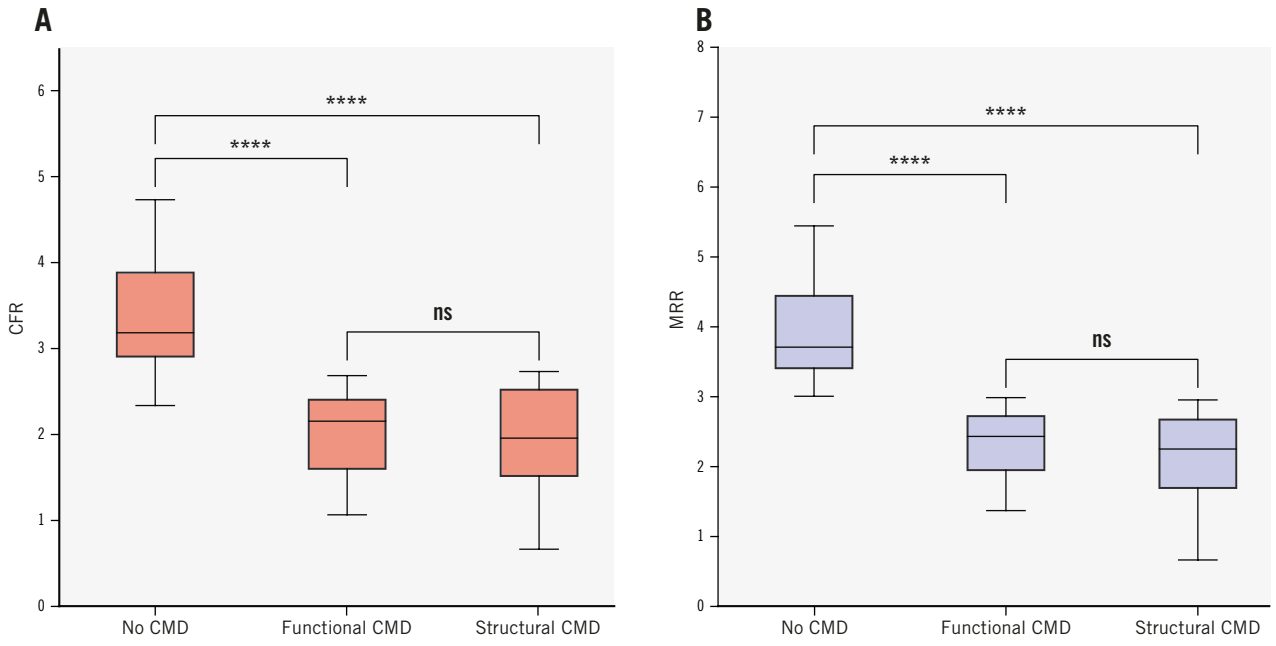


Figure 1. *CFR and MRR stratified by CMD subtype. A) CFR; (B) MRR. Patients were classified into the control (MRR ≥3.0), functional CMD (MRR <3.0 and $R_{\mu,hyper}$ <475 WU), or structural CMD (MRR <3.0 and $R_{\mu,hyper}$ ≥475 WU) group. The displayed symbols correspond to the following p-values for pairwise comparisons: ns: p≥0.05; ****: p<0.0001. The Bonferroni correction was applied to p-values by multiplying them by the number of comparisons performed. CFR: coronary flow reserve; CMD: coronary microvascular dysfunction; MRR: microvascular resistance reserve; ns: non-significant; WU: Wood units*

of tissue (myocardial blood flow; MBF)[24]. The mean indexed Q_{rest} in the control group (1.36 ml/min/g) corresponded with the upper limit of previously reported PET MBF measured in healthy volunteers (0.7-1.2 ml/min/g)[24]. In addition, the mean indexed Q_{hyper} in the control group of 4.56 ml/min/g also corresponded with the 3- to 5-fold increase in MBF typically seen during stress with PET[25]. However, combining continuous intracoronary thermodilution and CCTA provides two distinct advantages. First, it permits the absolute quantification of total coronary blood (i.e., in ml/min) for a given artery. Second, combining invasive flow measurements with concomitant invasive pressure measurements permits the calculation of the quintessential metric of microvascular function, microvascular resistance (both total and indexed).

FUNCTIONAL CMD IS ASSOCIATED WITH NORMAL ABSOLUTE AND INDEXED $R_{\mu,HYPER}$ AND Q_{HYPER}

This study also demonstrates that the absolute flow and resistance pattern seen in functional CMD is also present after indexing by subtended myocardial mass. This finding is unsurprising given that these patients exhibited similar overall LV mass and similar quantities of myocardial mass subtended by the LAD as compared to controls. However, $R_{\mu,hyper}$ and Q_{hyper}, both in absolute terms and after indexing by subtended mass, were shown to be strictly normal in these patients, suggesting a complete absence of a disease process that limits the physiological decrease of R_{μ} during hyperaemia. These findings raise questions about the plausibility of the functional CMD phenotype as an explanation for exertional symptoms in these patients. Whilst increased resting nitric oxide synthase activity is the likely explanation for the increased Q_{rest}[4], from a pathophysiological standpoint, it remains difficult to attribute patient symptoms to this finding. It is postulated that the reduced resting microvascular resistance and elevated resting coronary flow are related to increased nitric oxide synthase activity in functional CMD[4]. Yet, coronary flow is controlled by more than just nitric oxide. At any given moment, flow is carefully regulated to match current myocardial oxygen demand. A multitude of factors ultimately define myocardial oxygen demand, with heart rate, contractility, and left ventricular wall stress – i.e., mechanical factors – logically being the predominant drivers[26]. In the present study, a higher resting heart rate was seen in patients with functional CMD as compared to controls, with resting heart rate also shown to be an independent predictor of Q_{rest} and functional CMD (but not structural CMD). This finding provides a potentially interesting mechanistic insight into its pathology.

In our cohort of ANOCA patients, subtended mass exhibited a significant, weak linear relationship with flow and microvascular resistance in the hyperaemic state, with no significant relationship seen in the resting state. This suggests that other factors contribute significantly to determining coronary flow, although there are some important caveats to this finding. First, the present cohort contained many patients with CMD – both functional and structural – with the resultant impairment of resting and hyperaemic indices, respectively, likely affecting correlations. Second, during hyperaemia, the presence of concomitant epicardial disease (even non-significant) has a clear impact on Q_{hyper} which exhibits a linear

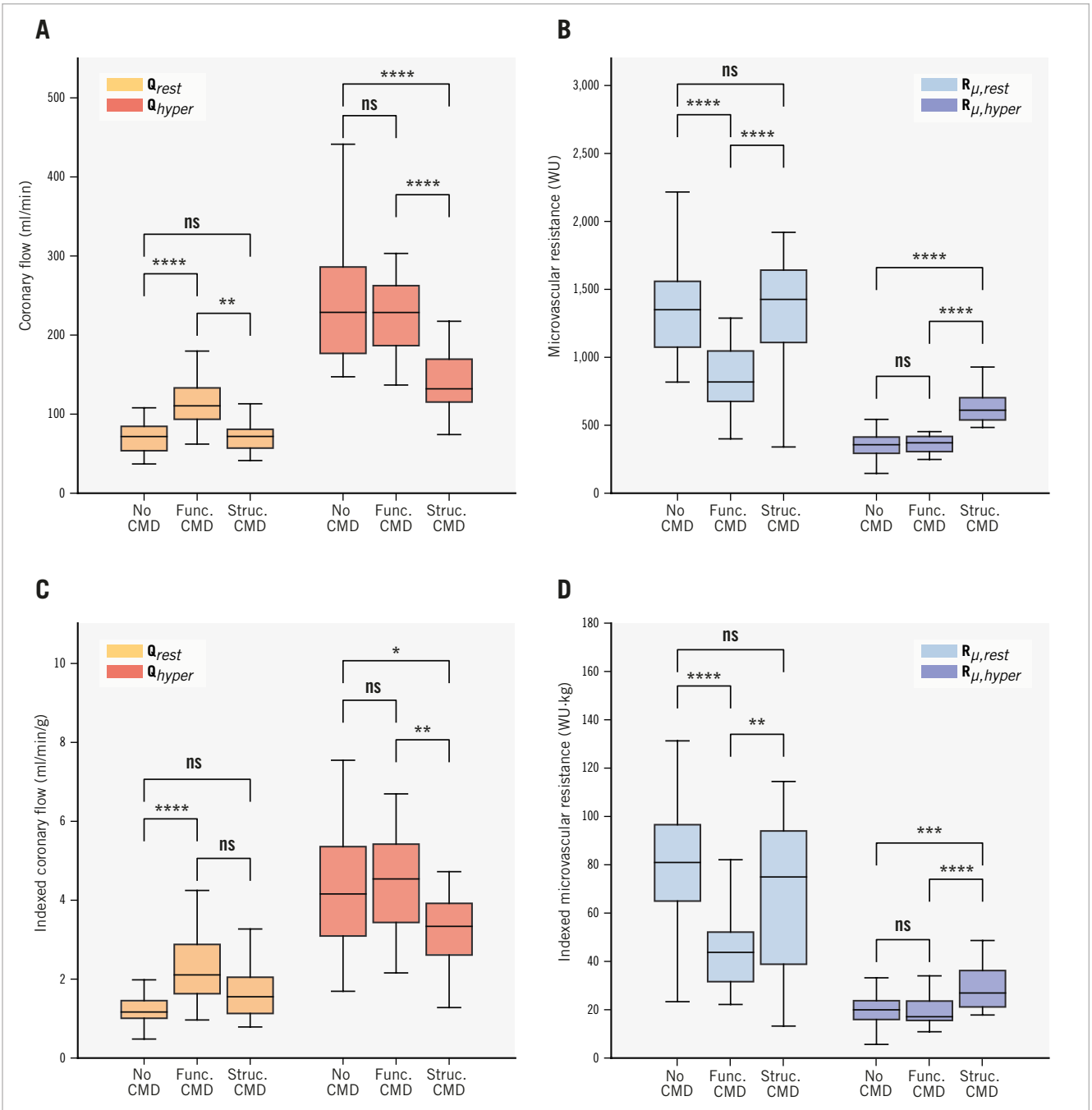
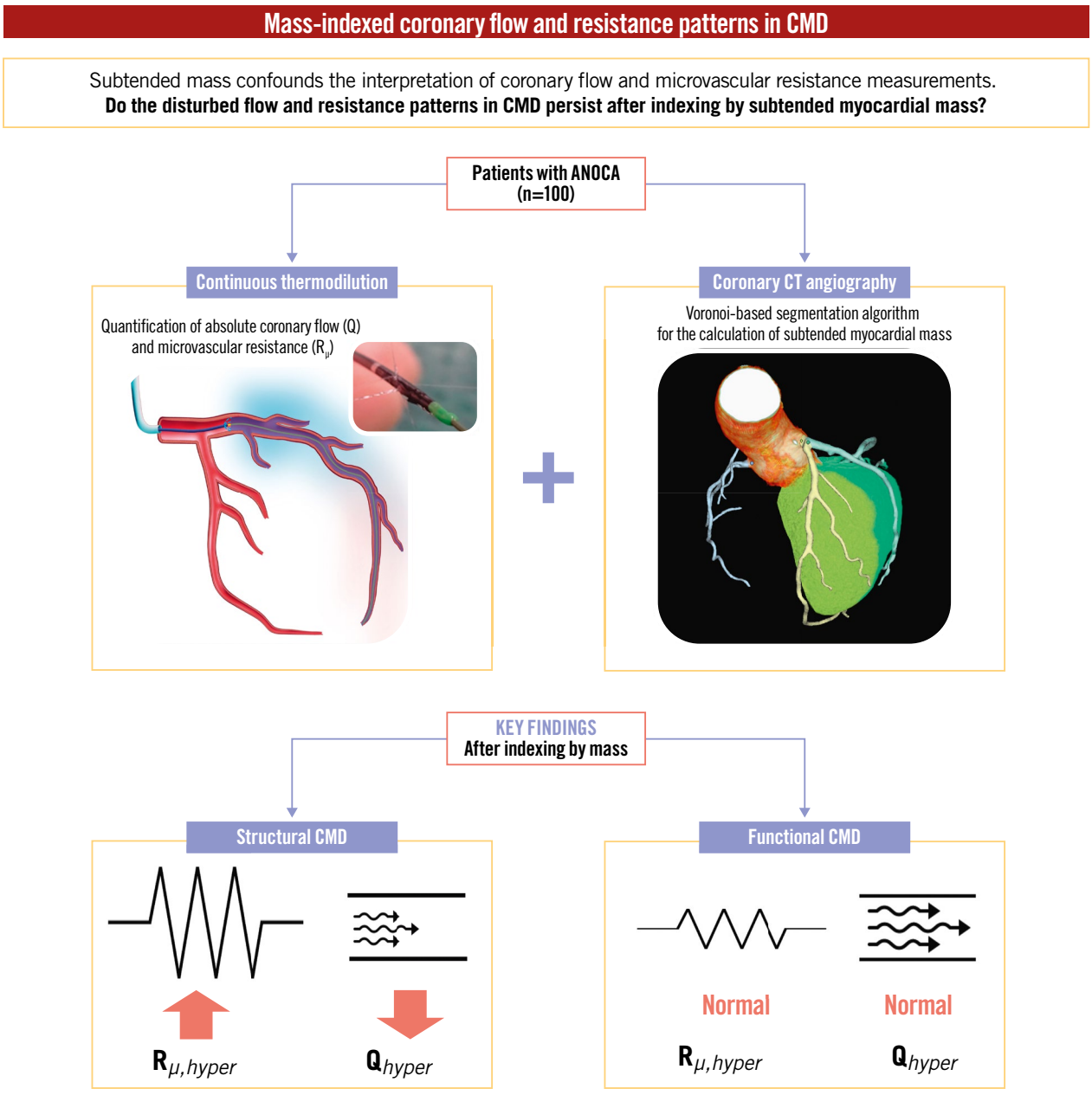


Figure 2. *Comparison of flow and microvascular resistance parameters in vessels with no CMD (MRR ≥3.0), those with functional CMD (MRR <3.0 and $R_{\mu,hyper}$ <475 WU), and those with structural CMD (MRR <3.0 and $R_{\mu,hyper}$ ≥475 WU). A) Absolute coronary flow (ml/min); (B) absolute microvascular resistance (WU); (C) indexed absolute coronary flow (ml/min/g); (D) indexed absolute microvascular resistance (WU·kg). The displayed symbols correspond to the following p-values for pairwise comparisons: ns: p≥0.05; *: p<0.05; **: p<0.01; ***: p<0.001; ****: p<0.0001. The Bonferroni correction was applied to p-values by multiplying them by the number of comparisons performed. CMD: coronary microvascular dysfunction; func.: functional; MRR: microvascular resistance reserve; ns: non-significant; Q_{hyper}: hyperaemic coronary flow; Q_{rest}: resting coronary flow; $R_{\mu,hyper}$: hyperaemic microvascular resistance; $R_{\mu,rest}$: resting microvascular resistance; struc.: structural; WU: Wood units*

relationship with FFR[17]. Given the definition of ANOCA includes patients with an FFR as low as 0.81, Q_{hyper} can be reduced to as low as 81% of what would be expected in the complete absence of epicardial disease. Importantly, in the resting state, epicardial disease has no impact on Q_{rest} unless it is extremely severe due to coronary autoregulation[17]. Third, this study likely highlights an underestimated phenomenon – the elusiveness of the "resting" state. Whilst the induction

EuroIntervention — Central **Illustration**

Summary of study design and main findings.



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ANOCA: angina with non-obstructive coronary arteries; CMD: coronary microvascular dysfunction; CT: computed tomography; Q_{hyper}: hyperaemic coronary flow; $R_{\mu,hyper}$: hyperaemic microvascular resistance

of maximal hyperaemia results in a consistent and repeatable decrease in $R_{\mu,hyper}$, it is not possible to assess a fixed "resting" state as microvascular resistance and coronary flow are constantly adapting to match myocardial needs, making the true "resting" state fragile and transient in nature[27]. This is further illustrated by the increased variability of flow and resistance measurements at rest as compared with hyperaemia[28]. The importance of mechanical factors that are influenced by sympathetic tone in determining resting flow raises the possibility that some patients with increased Q_{rest} may simply be manifesting increased sympathetic drive (e.g., anxiety, stress, autonomic dysfunction)[29]. We speculate that the functional CMD phenotype may, at least in part, be explained by this phenomenon.

STRUCTURAL CMD: PATTERN OF Q AND R_{μ} IS INDEPENDENT OF SUBTENDED MASS

Our results demonstrate that patients with structural CMD have a lower overall LV mass and a lower myocardial mass subtended by the LAD. As a consequence, the higher $R_{\mu,hyper}$ (and thus lower Q_{hyper}) seen in structural CMD could theoretically simply be attributed to the lower subtended mass seen in this group. However, our data demonstrate that these findings are independent of subtended mass, suggesting that this flow/resistance pattern persists at the gram of tissue level. This finding provides support for the notion that a pathological process at the myocardial level is responsible for the increased resistance seen in these patients[30]. Numerous architectural changes to the microvasculature have been proposed to induce structural CMD, including microcirculatory remodelling, capillary rarefaction and microcirculatory plugging[5]. It is these changes that are likely responsible for the increase in $R_{\mu,hyper}$ that manifests as a reduced vasodilatory response[4], and ultimately, the angina seen in these patients.

Limitations

First, this analysis focused on measurements in the LAD. This approach reflected current clinical practice, where it is recommended to assess CMD in this vessel[16]. However, whilst the inclusion of right coronary and left circumflex arteries would have enriched the dataset, we do not believe it would have changed the findings of this study.

Second, only continuous thermodilution was used to measure flow and resistance, as the use of other modalities such as bolus thermodilution and Doppler was not within the remit of this work. Whilst we recognise that continuous thermodilution is less widely available than bolus thermodilution, its superior precision and accuracy, along with its capacity to quantify both flow and resistance in absolute terms, justified its choice in this proof-of-concept study[31-34].

Third, only a modest number of patients were included in this study, reflecting the novel use of both CCTA and continuous intracoronary thermodilution. However, the cohort was of sufficient size to address the scientific questions addressed by this study.

Fourth, the study population includes only patients who underwent both CCTA and the invasive microvascular assessment. Whilst we frequently employ CCTA and subsequently refer patients with highly suggestive symptoms and no evidence of significant epicardial disease for an invasive evaluation, there is an inevitable risk of selection bias in this study.

Fifth, the present study stratified patients with CMD into functional/structural CMD as proposed by Rahman et al[4]. Whilst this system identifies two distinct physiological CMD subtypes, other CMD endotypes likely exist beyond this system that remain to be elucidated. Overall, it is important to recognise that the diagnosis of CMD should be made by using $R_{\mu,hyper}$ and MRR (or CFR) in conjunction, as these parameters provide complementary information on microvascular function[35].

Finally, the presence of disease processes such as diabetes, kidney disease, or hypertension could theoretically impact myocardial structure and, thus, density. However, there is currently no validated approach for adjusting the myocardial tissue density constant for the presence of such diseases. Consequently, we applied the widely accepted value of 1.05 g/cm^3 for the present study[12-14].

Conclusions

Despite a significantly lower subtended mass, patients with structural CMD still exhibit abnormal indexed $R_{\mu,hyper}$ and Q_{hyper}, supporting the notion of hyperaemic flow restriction at the tissue level. However, patients with functional CMD exhibit similar indexed $R_{\mu,hyper}$ and Q_{hyper} to controls, indicating the absence of any flow restriction during hyperaemia in these patients.

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Conflict of interest statement

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Supplementary data

Supplementary Table 1. Multivariate logistic regression analysis of factors associated with structural CMD.

Supplementary Table 2. Univariate and multivariate linear regression analysis of the relationship between subtended myocardial mass and absolute coronary flow and resistance.

Supplementary Table 3. Propensity score-matched analysis.

Supplementary Figure 1. Indexing microvascular resistance and coronary flow by subtended myocardial mass.

Supplementary Figure 2. Comparison of flow and microvascular resistance parameters after indexation by both subtended mass and body surface area.

Supplementary Figure 3. Comparison of flow and microvascular resistance parameters in vessels with no, functional and structural CMD as defined by CFR.

Supplementary Figure 4. Correlation between myocardial mass, absolute coronary flow and microvascular resistance.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-25-00229

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ORIGINAL RESEARCH

Prevalence, classification, and treatment of residual shunt after patent foramen ovale closure

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ABSTRACT

BACKGROUND: Residual shunt (RS) after transcatheter patent foramen ovale (PFO) closure has been associated with an increased risk of recurrent stroke over long-term follow-up. However, RS prevalence, anatomical characteristics, and treatment strategies are poorly understood.

AIMS: This study aimed to assess the prevalence and causes of RS, as well as to evaluate the safety and feasibility of its percutaneous treatment.

METHODS: Patients with RS at transcranial Doppler after transcatheter PFO closure in three Italian high-volume centres between 2000 and 2022 were included. The prevalence and anatomical characteristics of RS, its relationship with the original occluding device, and the procedural details of percutaneous treatment were assessed.

RESULTS: Among the 2,362 patients who underwent PFO closure, any grade and significant RS were diagnosed in 8.8% and 3.6% of patients, respectively. It was more frequently found after use of the NobleStitch system than after double-disc device implantation (20.0% vs 8.5%; p<0.00001). Among double-disc device implantations, a higher rate of shunt was found with stiffer devices (9.8% vs 7.1%; p<0.05) and with devices larger than 25 mm (13.9% vs 6.6%; p<0.00001). Intradiscal RS (type 1) was most common (43.6%), followed by extradiscal RS (type 2; 35.1%) and RS due to unusual causes (type 3; 14.9%). Percutaneous treatment was successful in 89.4% of patients using different, anatomically tailored devices.

CONCLUSIONS: RS is commonly found after transcatheter PFO closure and is significantly associated with the type and size of the occluding device implanted. It results from different mechanisms and can be safely and effectively treated by a percutaneous, patient-tailored approach in a high percentage of cases.

KEYWORDS: device; patent foramen ovale; shunt

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Transcatheter closure of patent foramen ovale (PFO) is now widely considered as the first-choice treatment for patients with cryptogenic stroke that is likely due to paradoxical embolism[1-4]. However, residual shunt (RS) after successful percutaneous PFO closure has been reported in up to 26% of patients[5-12] and has been associated with an increased risk of recurrent cerebrovascular events and persistent PFO-related migraine[10,13-17]. Thus, percutaneous closure of RS has recently emerged as a new therapeutic target to reduce the risk of persistent symptoms and recurrent ischaemic events[5-7]. However, large studies addressing the prevalence, causes, and treatment strategies for RS are still lacking.

The aim of this study was to assess the prevalence and causes of RS after transcatheter PFO closure in a large, multicentre registry of paediatric and adult congenital cardiology units in Italy, reporting the anatomical characteristics of RS as well as the safety and feasibility of its percutaneous treatment.

Editorial, see page 892

Impact on daily practice

Residual paradoxical shunt is frequently found after patent foramen ovale closure and is associated with the type and size of the occluding device. The mechanisms of residual shunt (RS) are multiple and can be classified into 3 categories: type 1: intradevice; type 2: extradevice; type 3: any other unusual cause of RS. Transcatheter closure of RS can be safely and effectively performed in a high percentage of patients, regardless of its mechanism, by using different dedicated or off-label devices.

Methods

STUDY POPULATION

Between January 2000 and December 2022, 2,362 patients underwent percutaneous PFO closure at three Italian high-volume tertiary referral centres of paediatric cardiology and adult congenital heart disease units: Heart Hospital "G. Pasquinucci", Tuscany Foundation "G. Monasterio", Massa; "Ospedali dei Colli" Hospital, "L. Vanvitelli" University of Naples, Naples; and "Careggi" University Hospital, Florence. Previous stroke and transient ischaemic attack (TIA) presumably due to paradoxical embolism were the most frequent indications for PFO closure (78.3%), followed by drug-resistant migraine (14.5%), decompression disease (3.9%) and platypnoea-orthodeoxia syndrome (1.9%). Based on metallic content and mechanical properties, the originally used occluding devices were arbitrarily classified as stiff (Amplatzer device [Abbott], Occlutech device [Occlutech GmbH] and other Amplatzer-like devices) or soft devices (GORE CARDIOFORM Septal Occluder device [W. L. Gore & Associates] and Cardia Ultrasept device [Cardialogic]). The index procedure was always performed under deep sedation or general anaesthesia guided by transoesophageal (TOE) or intravascular echocardiography. PFO sizing using a static or dynamic balloon technique was performed based on the centre's and operator's choice. An intraoperative bubble test was always performed after device deployment, and additional sources of paradoxical shunt were consequently addressed in the same procedure.

After PFO closure, routine clinical assessment, electrocardiography and transthoracic echocardiography were performed at 1 and 12 months. Control contrast-enhanced transcranial Doppler (c-TCD) with agitated saline injection at rest and during the Valsalva manoeuvre was performed at least 12 months after device implantation. At c-TCD, a semiquantitative estimation of RS was defined according to the number of microbubbles: grade 0=none, grade 1=mild (1-10 bubbles), grade 2=moderate (>10 bubbles without a curtain pattern), and grade 3=severe (curtain or shower-like pattern)[8-9]. RS was defined as any grade of microbubble passage at rest or during the Valsalva manoeuvre, while significant RS was defined as any shunt higher than grade 1. Medical therapy after PFO closure included dual antiplatelet therapy (aspirin+clopidogrel) for 1 month, followed by aspirin monotherapy until the 1-year follow-up when patients were assessed for RS with c-TCD. If c-TCD confirmed complete closure of the PFO (no RS at c-TCD), aspirin therapy was stopped. On the other hand, in patients with confirmed RS, aspirin therapy was continued.

The study population included 207 patients with confirmed RS at c-TCD. The exclusion criterion was the presence of an extracardiac cause of paradoxical shunt. The patients' clinical and demographic characteristics, the presence of an atrial septum aneurysm at baseline transthoracic echocardiography, and the type and size of the PFO closure device were assessed. Follow-up data regarding recurrent paradoxical embolic events, such as stroke, TIA or resistant migraine after PFO closure, were also recorded for patients. Recurrent stroke and TIA were defined by the treating neurologist. Recurrent stroke was defined as a new clinically evident and permanent neurological deficit associated with new evidence of cerebrovascular embolism at imaging (computed tomography [CT] or magnetic resonance imaging [MRI]), while TIA was defined as any associated transient ischaemic event, with or without evidence of cerebrovascular embolism on imaging. This study was approved by the ethics committee of each involved institution, which waived informed consent for this retrospective, non-invasive study.

PERCUTANEOUS RS CLOSURE

Percutaneous RS closure was considered in all patients with RS based on the following criteria: presence of recurrent symptoms after PFO closure (stroke, TIA, persistent treatment-resistant migraine); the degree of RS (moderate-to-severe vs mild RS); and patient preference about a second percutaneous procedure versus long-term aspirin therapy. The interventional procedure was performed under general anaesthesia with

Abbreviations

c-TCD	contrast-enhanced transcranial Doppler	**RS**	residual shunt	**TOE**	transoesophageal echocardiography
PFO	patent foramen ovale	**TIA**	transient ischaemic attack		

fluoroscopic and TOE guidance. A comprehensive TOE assessment was performed to assess the mechanism of RS and any other complication caused by the previously implanted device. All patients gave informed consent for the interventional procedure. The site of paradoxical shunt was angiographically imaged in the left anterior oblique view and confirmed by local angiography and a bubble test. Based on the anatomical characteristics, RS was classified into 3 types:

Type 1 shunt was defined as a tunnel-like intradevice shunt, located between the discs of the previously implanted device **(Figure 1A, Moving image 1)**.

Type 2 shunt was defined as any extradevice shunt due to an accessory atrial septal defect far from the device, incomplete coverage of the PFO by an undersized device, or device malposition **(Figure 2A, Moving image 2)**.

Type 3 shunt was defined as any other RS with characteristics not included in the two previous types. This category included unusual causes of shunt such as atrial septal fistulas **(Figure 3A, Moving image 3)**, atrial septum tears, or incomplete PFO sealing late after a NobleStitch approach (NobleStitch EL [Heartstitch]) **(Figure 4A, Moving image 4).**

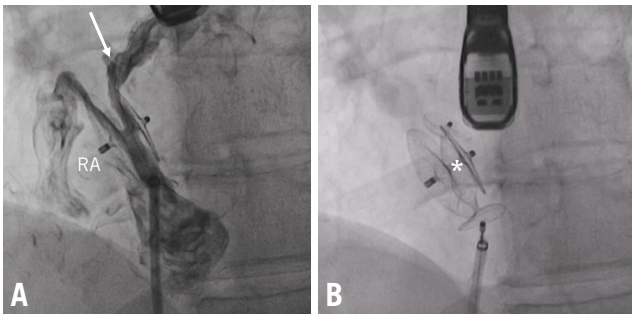


Figure 1. *Transcatheter closure of a large interdiscal shunt. A) RS through a 35 mm Amplatzer PFO Occluder (Abbott; arrow) was closed by implantation of a 10 mm Amplatzer Vascular Plug II (Abbott; asterisk; B) PFO: patent foramen ovale; RA: right atrium; RS: residual shunt*

The site of RS was probed from femoral vein access in all but two patients, in whom the right internal jugular vein was instead used because of an unusual shunt location. Catheters and guidewires of different shapes, sizes, and characteristics were used to cross the shunt site. The closure device was selected based on the type, size, and anatomical characteristics of the shunt. In the case of a type 1 shunt, the Amplatzer Vascular Plug II or 4 devices, or the Amplatzer Duct Occluder II or Piccolo Occluder devices (all Abbott) were chosen. In the case of a type 2 shunt, a double-disc occluding device was selected after balloon sizing to better detail the defect morphology and distance from the previously implanted device. In the case of a type 3 shunt, controlled-release vascular coils or vascular plug devices were chosen in the case of atrial fistulas, or double-disc devices in the case of incomplete closure after the NobleStitch approach.

After the procedure, the device position, any RS and any potential device-related complications were assessed by right atrial contrast angiography and contrast-enhanced TOE. Procedural success was defined as device implantation without any residual shunt as assessed with contrast-enhanced TOE and without any procedural complications. All patients were discharged 24 h after the procedure and followed up by electrocardiography and transthoracic echocardiography at 1 and 12 months, as well as by c-TCD 12 months after the procedure. After RS closure, medical therapy included dual antiplatelet therapy for 1 month and, thereafter, aspirin therapy for up to 12 months. If the c-TCD at 12 months showed no RS, aspirin therapy was stopped; otherwise, aspirin therapy was continued indefinitely.

STATISTICAL ANALYSIS

Statistical analysis was performed using SPSS Statistics, version 29.0 (IBM). Continuous variables are expressed as mean±standard deviation for normally distributed variables and as median and percentiles for non-normally distributed variables. Categorical data are expressed in percentages. The independent samples t-test for was used to assess differences between means for normally distributed variables, while the Mann-Whitney U test was used for non-normally

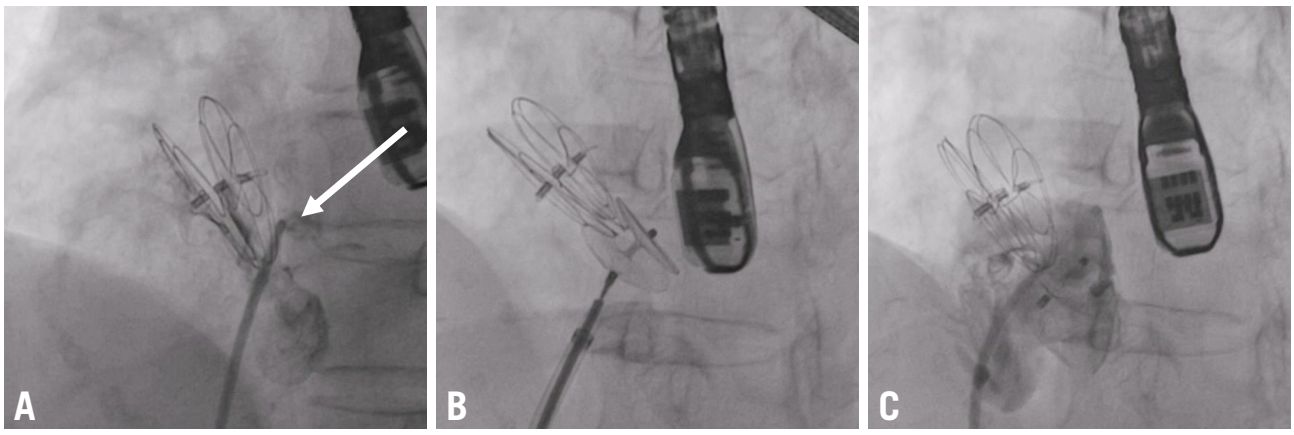


Figure 2. *Transcatheter closure of an extradiscal shunt. A) The shunt was located in the lower part of a 30 mm GORE CARDIOFORM Septal Occluder device (arrow) and was occluded by implantation of a 25 mm Amplatzer PFO Occluder (B,C). PFO: patent foramen ovale*

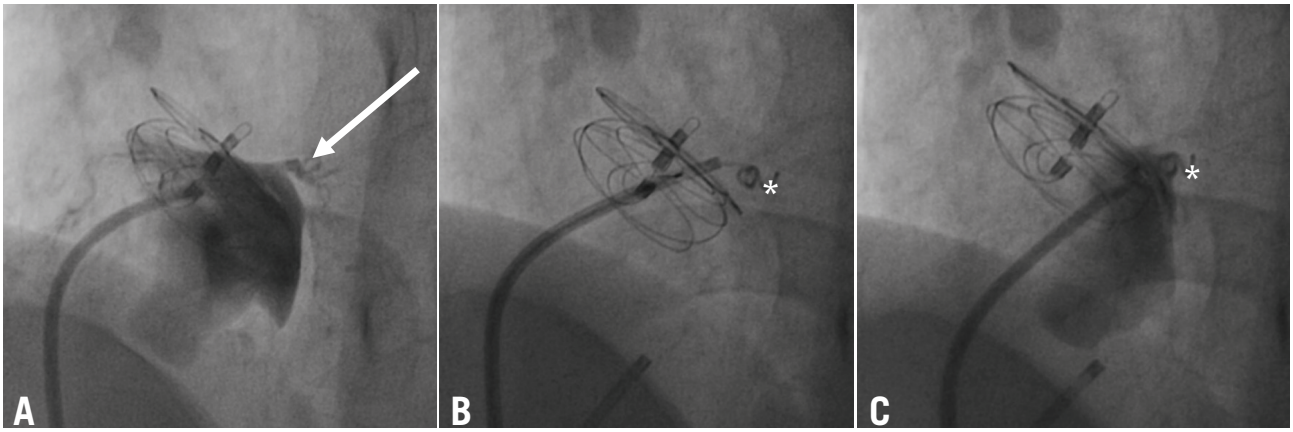


Figure 3. *Coil embolisation of a serpiginous, fistulous atrial communication distant from a previously implanted 25 mm GORE CARDIOFORM Septal Occluder. The right-to-left shunt was imaged using a multipurpose catheter (A) and occluded by deployment of a 5PDA-5 controlled-release Cook coil (Cook Medical; asterisk) (B,C). The serpiginous, fistulous atrial communication is indicated with an arrow. PDA: patent ductus arteriosus*

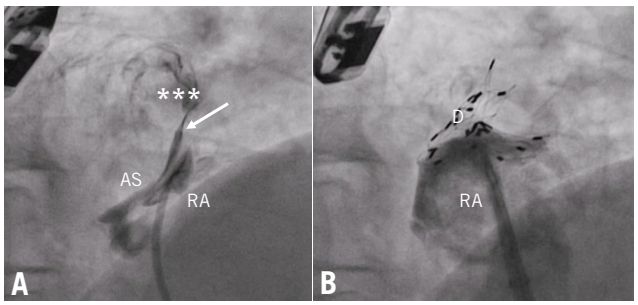


Figure 4. *Transcatheter closure of a complex PFO in a patient with situs visceroatrial inversus. After the NobleStitch approach (arrow marks the occluding knot), whose aim was to straighten a severely aneurysmal septum, a tiny RS was imaged (asterisks; A) and occluded by deployment of a 30 mm Cardia Ultrasept device (B). AS: aneurysmal septum; D: Cardia Ultrasept device; PFO: patent foramen ovale; RA: right atrium; RS: residual shunt*

distributed variables. Normal distribution was tested using the Kolmogorov-Smirnov test. Categorical variables were analysed using the χ^2 test, and Fisher's exact test was used when appropriate.

Results

PATIENT CHARACTERISTICS

Among the 2,362 patients submitted to percutaneous PFO closure, any grade and significant RS were found in 207 (8.8%) and 84 (3.6%) patients, respectively. One hundred and twenty of these patients (58%) had an interatrial septal aneurysm at the time of the first procedure. RS severity was mild (grade 1) in 59.4%, moderate (grade 2) in 24.2%, and severe (grade 3) in 16.4% of patients. During a median follow-up of 3.6 (25^{th}-75^{th} percentile: 2.1-11.8) years after PFO closure, 2 (1%) of the 207 patients with RS had recurrent stroke, 15 (7.2%) experienced recurrent TIA and 14 (6.8%) reported residual disabling migraine **(Table 1)**. The severity of the RS was significantly associated with recurrent symptoms (odds ratio 2.467; p<0.001; moderate-severe RS: 72.4% in symptomatic vs 35.4% in asymptomatic patients; p<0.001).

RS was observed with all types of devices but was significantly higher after the NobleStitch approach as compared to use of double-disc devices (20.0% vs 8.5%; p<0.0001). Among the patients who underwent double-disc device implantation, a higher rate of RS was found in the case of stiff prostheses compared to soft prostheses (9.8% vs 7.1%; p<0.05) and with larger protheses (>25 mm) compared to smaller ones (13.9% vs 6.6%; p<0.0001). This latter comparison was significant only in the case of stiff devices (18.3% vs 6.7%; p<0.00001), while no significant difference was found between large- and small-size soft devices **(Table 2)**. Finally, after implantation of large devices, RS was significantly more frequent with stiff prostheses as compared to soft ones (18.3% vs 7.5%; p<0.0001).

In all, 101 patients with RS agreed to a second interventional procedure and were included in the analysis, while 106 patients (51.2%) were maintained on medical therapy. No significant differences in age, sex, baseline clinical and anatomical characteristics, or the size of the occluding device was found between the 2 groups. However, patients submitted to percutaneous closure of RS showed a higher symptom burden (any symptom: 21.8% vs 8.4%; p<0.01; recurrent stroke: 2% vs 0%; p>0.05; recurrent TIA 9.9% vs 4.7%; p>0.05; treatment-resistant migraine 9.9% vs 3.8%; p>0.05) and a higher degree of paradoxical shunt (moderate RS: 41.6% vs 7.5%; p<0.001; severe RS: 29.7% vs 3.8%; p<0.001) as compared to those remaining under pharmacological therapy.

RS CHARACTERISTICS AND PERCUTANEOUS TREATMENT

At cardiac catheterisation, paradoxical intracardiac shunt was confirmed in 94 patients (93.1%) **(Central illustration)**. One patient (1%) exhibited an extracardiac shunt due to a small pulmonary arteriovenous fistula, while in the remaining 6 patients (5.9%), no shunt site was found

Table 1. Clinical characteristics of the study population.

	Residual shunt (N=207)	No residual shunt closure N=106 (51.2%)	Residual shunt closure N=101 (48.8%)	*p*-value
Age, years	49.3±12.6	50±12.9	48.6±12.4	0.42
Male	86 (41.5)	43 (40.6)	43 (42.6)	0.77
Hypertension	70 (33.8)	37 (34.9)	33 (32.7)	0.73
Diabetes	14 (6.8)	7 (6.7)	7 (6.9)	0.92
Obesity	15 (7.2)	5 (4.7)	10 (9.9)	0.06
Smoker	85 (41.1)	45 (42.5)	40 (39.6)	0.81
IAS aneurysm	120 (58.0)	68 (64.2)	52 (51.5)	0.065
Prosthesis diameter, mm	30 (25-35)	28 (25-35)	30 (25-30)	0.68
Indication for PFO closure: stroke/TIA	162 (78.3)	81 (78.6)	81 (80.2)	0.51
Indication for PFO closure: treatment-resistant migraine	30 (14.5)	13 (12.3)	17 (16.8)	0.35
Recurrent stroke after PFO closure	2 (1)	0 (0)	2 (2)	N/A
Recurrent TIA after PFO closure (imaging-negative)	15 (7.2)	5 (4.7)	10 (9.9)	0.15
Recurrent stroke or TIA after PFO closure	17 (8.2)	5 (4.7)	12 (11.9)	0.06
Resistant migraine after PFO closure	14 (6.8)	4 (3.8)	10 (9.9)	0.12
Any symptom after PFO closure	31 (14.9)	9 (8.4)	22 (21.8)	0.01*
Shunt severity: mild	123 (59.4)	94 (88.7)	29 (28.7)	<0.001*
Shunt severity: moderate	50 (24.2)	8 (7.5)	42 (41.6)	<0.001*
Shunt severity: severe	34 (16.4)	4 (3.8)	30 (29.7)	<0.001*
Significant shunt: moderate/severe RS	84 (40.6)	12 (11.3)	72 (71.3)	<0.001*

Data are n (%), mean±standard deviation, or median (interquartile range). *p<0.05. TIA is included with or without evidence on imaging. IAS: interatrial septal; N/A: not applicable; PFO: patent foramen ovale; RS: residual shunt; TIA transient ischaemic attack

Table 2. Residual shunts according to PFO closure device.

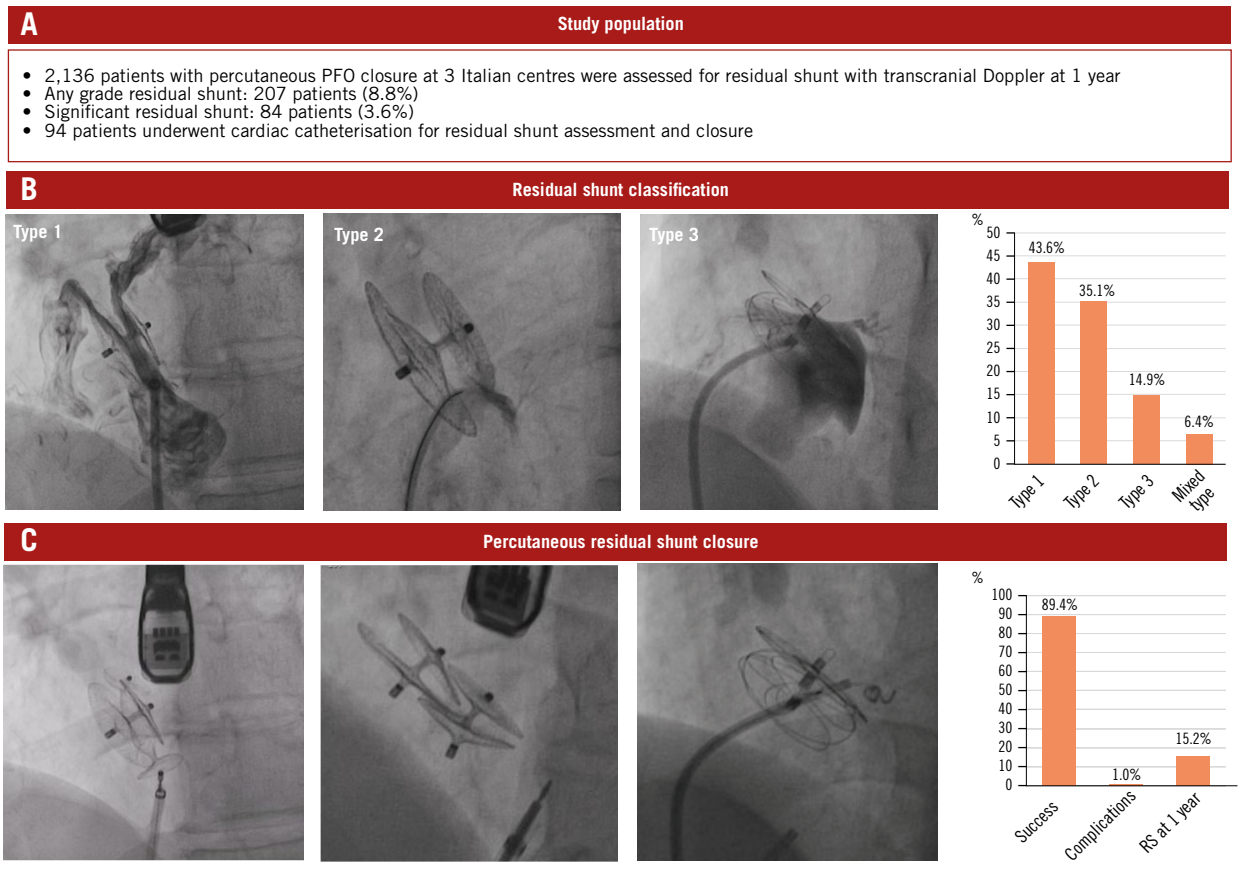
PFO device	Patients who underwent PFO closure 2000-2022	Residual shunt[§]	Residual shunt ø ≤25 mm, %	Residual shunt ø >25 mm, %	*p*-value
All devices	2,362	207 (8.8)	6.6	13.9	p<0.0001*
Amplatzer PFO Occluder[a]	1,437	136 (9.5)	6.3	16.7	p<0.0001*
Occlutech PFO Occluder[a]	66	11 (16.7)	5.9	60.0	p<0.0001*
GORE CARDIOFORM Septal Occluder[c]	389	33 (8.5)	6.1	11.3	p=NS
Cardia Ultrasept[d]	204	10 (4.9)	8.5	2.5	p=NS
Stiff devices (Amplatzer+Occlutech)	1,503	148 (9.8)[&]	6.7	18.3[@]	p<0.00001*
Soft devices (GORE+Cardia)	593	42 (7.1)[&]	6.7	7.5[@]	p=NS
Other double-disc devices	206	5 (2.4)	[$]	[$]	
NobleStitch EL[e]	60	12 (20.0)[#]	N/A	N/A	N/A
All double-disc devices	2,302	195 (8.5)[#]	[$]	[$]	

Data are n or n (%), unless otherwise indicated. Other devices: CeraFlex[f], STARflex[g], Helex[c], CardioSEAL[g], FlatStent[h], Solysafe[i]. *Shows statistical significance. [#], [@] and [&] indicate the p-values for the chi-square test between two variables as follows: [#]NobleStitch RS 20% vs all double-disc devices RS 8.5%; [&]stiff devices RS 9.8% vs soft devices RS 7.1% (all sizes); [@]stiff devices 18.3% vs soft devices 7.5% (ø >25 mm). [§]p-value for comparison of RS rates between all devices in the column.[#]p<0.0001; [§]p<0.001; [@]p<0.0001; [&]p<0.05; [$]analysis not performed. [a]By Abbott; [b]by Occlutech GmbH; [c]by W. L. Gore & Associates; [d]by Cardialogic; [e]by Heartstitch; [f]by LifeTech Scientific Corporation; [g]by NMT Medical; [h]by Coherex Medical; [i]by Swissimplant AG. N/A: not applicable; NS: non-significant; PFO: patent foramen ovale; RS: residual shunt

despite multiple angiographies and intraprocedural bubble test injections. Type 1 (intradevice) shunt was found in 41 patients (43.6%). Type 2 (extradevice) shunt was observed in 33 (35.1%) patients. It was caused by device dislocation in 1 patient, incomplete sealing of the PFO by an undersized device in 2 patients, and an accessory interatrial septal defect in the remaining 30 patients. Fourteen patients (14.9%) showed type 3 residual shunt, caused by an interatrial septum fistula in 2 cases and an incomplete PFO closure after the NobleStitch approach in 12 patients. In 2 patients, a potential late-onset atrial septum tear caused by the NobleStitch EL device was suspected at intraprocedural transoesophageal evaluation, while in the remaining 10 patients, loosening of the occluding knot was considered as a potential cause of the RS since it had not been evident at the end of the first procedure. Finally, 6 (6.4%) patients had multiple mechanisms of shunt due to combinations of the 3 types of shunts.

Transcatheter closure of RS was successful in 84 patients (89.4% success rate). The most used devices were vascular plugs, which were implanted in 51.1% of cases. Double-disc devices were used in 31.9% of patients and controlled-release coils in 4.3% of patients. A combination of different devices was used in 5.3% of patients **(Table 3)**.

Residual shunt after PFO closure.



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A) Study population details. B) Classification system and prevalence of RS. Type 1 shunt: a tunnel-like intradevice shunt located between the discs of the previously implanted device. Type 2 shunt: any extradevice shunt due to incomplete coverage of the PFO, device dislocation, or an accessory atrial septal defect. Type 3 shunt: any other residual shunt with characteristics not included in the two previous types. C) RS closure techniques and results. PFO: patent foramen ovale; RS: residual shunt

The choice of the closure device was influenced by the type and mechanism of RS. Type 1 shunts were treated with a vascular plug device in 80.4% of cases, while coils or double-disc devices were used in 4.8% and 2.4% of cases, respectively. Type 2 shunts were treated with a second non-self-centring device in 51.5% of cases and with a vascular plug in 36.4% of cases. Type 3 shunts were treated with a second non-self-centring device in 78.6% of patients and with a vascular plug or controlled-release coils in the remaining patients **(Central illustration)**. Mixed-type shunts were treated with a combination of devices tailored to the specific type of shunt **(Figure 5)**, as shown in **Table 4**. The success rate was slightly, though not significantly, lower in type 1 (82.9%) as compared to type 2 (90.9%) and type 3 shunts (100%).

Among the 10 patients (10.6%) in whom the closure procedure failed, 7 had type 1 shunts and 3 had type 2 shunts. In 7 patients, the RS could not be closed because of a failure to pass the guidewire through the previously implanted device, while in 3 patients, the new implanted device did not completely seal the shunt site. No major or device-related complications were reported, and only 1 minor complication (a femoral haematoma requiring local prolonged compression and immobilisation) occurred. Of the 94 patients submitted to RS closure, 79 (84%) completed the recommended 1-year follow-up and underwent c-TCD assessment. In these patients, any grade RS was found in 12 (15.2%) patients (9 with type 1 and 3 with type 2 RS), while significant RS was still present in 7 (8.9%) patients (5 with type 1 and 2 with type 2 RS). No recurrent ischaemic events were observed during the 1-year follow-up, and only 3 patients showed persistent treatment-resistant migraine. Finally, no erosions, pericardial effusions, or other mechanical complications, nor any episodes of atrial fibrillation were reported during this follow-up period.

Discussion

Percutaneous PFO closure is currently recommended as the first-line treatment of ischaemic stroke caused by PFO-related paradoxical embolism[2-4]. However, persistence of significant

Table 3. Residual shunt classification and devices used for closure.

	Intracardiac confirmed shunt (n=94)
Type 1 shunt (intradiscal)	41 (43.6)
Type 2 shunt (extradiscal/accessory defect)	33 (35.1)
Type 3 shunt (other)	14 (14.9)
Mixed shunt	6 (6.4)
New double-disc device implantation	30 (31.9)
Vascular device implantation	48 (51.1)
Coil implantation	4 (4.3)
Multiple device implantation	5 (5.3)
No device implantation	7 (7.4)
Treatment success – no RS at end-procedure TOE bubble test	84 (89.4)
Procedural major complications	0 (0)
Procedural minor complications	1 (1)
Device-related complications	0 (0)
Atrial fibrillation at follow-up*	0 (0)
Stroke or TIA at follow-up*	0 (0)
Persistent RS at 1-year follow-up: any grade shunt*	12 (15.2)
Persistent RS at 1 year follow-up: significant shunt only*	7 (8.9)
Device erosion at follow-up*	0 (0)
Pericardial effusion at follow-up*	0 (0)
Any mechanical complication at follow-up*	0 (0)

Data are n (%). *1-year follow-up was available for only 79 (81.4%) patients. RS: residual shunt; TIA: transient ischaemic attack; TOE: transoesophageal echocardiography

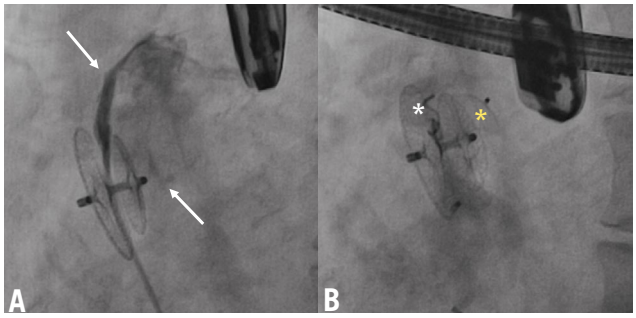

Figure 5. *Mixed-type RS caused by multiple mechanisms successfully treated with multiple devices. Multiple RS sites (arrows) after closure of a large PFO by implantation of a 35 mm Amplatzer PFO device (A). The tunnel-like intradevice shunt was treated by implantation of a controlled-release Cook coil (white asterisk) and the extradevice shunt by implantation of an ADO II (yellow asterisk) device (B). ADO: Amplatzer Duct Occluder; PFO: patent foramen ovale; RS: residual shunt*

shunt after a seemingly successful transcatheter closure has been reported with different prevalence rates in previous studies, mainly due to differences in definitions, diagnostic techniques and grading methods[10-14]. Overall, the rate of any grade RS ranged from 23% to 26%[13,14], while the rate of significant RS has been reported between 5%[11] and 16%[10,12,14]. In our study, the rates of any grade and significant RS detected by c-TCD were 8.8% and 3.6%, respectively. These figures are lower than previously reported in literature, possibly due to the larger population size and the more detailed approach to PFO sizing and prosthesis selection in our series.

Although the clinical and prognostic impact of RS is still debated, mild RS does not appear to predict significant adverse outcomes[15], whereas higher grades of shunt may be associated with an increased risk of recurrent stroke, peripheral embolism, and residual migraine burden[16-19]. In accordance with the current literature, in our experience, patients with significant RS showed a higher prevalence of symptoms and more frequently agreed to a second interventional approach. Over time, transcatheter treatment of high-grade RS has emerged as a novel, cost-effective therapeutic option compared to chronic pharmacological therapy[5-7]. However, although previous studies have shown transcatheter closure of residual shunt to be safe and feasible, little is known as to whether further intervention is necessary compared to medical therapy alone. Furthermore, there is no consensus on the optimal device for the treatment of this condition. Susuri et al and Diaz et al used a second double-disc device, while Butera et al selected the type of device based on the anatomical characteristics of the shunt[5,6,11]. In accordance with the latter study, we identified multiple mechanisms of RS, prompting a detailed anatomical assessment in each patient to choose the most appropriate closure approach.

Paradoxical RS was significantly more common following the NobleStitch technique than with standard double-disc devices. In this latter group, the rate of RS was significantly dependent on the mechanical properties and the size of the occluding device. Indeed, it was more frequently found after implantation of stiff and large prostheses. This finding might presumably be due to their lower capacity to adhere to the entire surface of the fossa ovalis compared to softer and smaller devices. A potential role may be played by the original anatomical characteristics of the septum at the time of the first procedure, since a floppy, highly mobile, aneurysmal atrial septum with severe paradoxical shunt often prompted the use of larger stabilising devices, which less frequently sealed the entire fossa ovalis, as confirmed by the current literature[10]. In our opinion, a key role in causing this sequela might be played by the different thickness between the septum secundum and the thinner and hollower septum primum, which precludes 360-degree adherence of the device to the bottom of the fossa ovalis. In fact, this anatomical arrangement causes the posterior-inferior part of the device not to adhere to the septum, and this phenomenon is mainly evident in the case of stiffer devices and results in a higher risk of intradevice RS. Indeed, in our experience, RS was less common after implantation of softer devices, likely due to their higher anatomical compliance and adherence to the atrial septum in the case of aneurysmal and mobile septa[10,14]. However, there was no significant difference in RS rates between stiffer and softer devices in the case of small-size prostheses, while the difference was statistically significant with larger ones. Thus, it could be cost-effective to prefer softer devices in the case of aneurysmal, floppy, mobile atrial septa with large PFOs, while no significant difference

Table 4. Treatment of RS according to the shunt type.

	Type 1 (n=41)	Type 2 (n=33)	Type 3 (n=14)	Mixed shunt (n=6)
Device diameter, mm*	30 (25-30)	25 (25-35)	30 (25-35)	30 (25-30)
PFO device	1 (2.4)	17 (51.5)	11 (78.6)	1 (16.6)
Vascular plug	33 (80.4)	12 (36.4)	1 (7.1)	2 (33.3)
Coil	2 (4.8)	0 (0)	2 (14.2)	0 (0)
Multiple device types	1 (2.4)	1 (3.0)	0 (0)	3 (50.0)
Procedural success*	34 (82.9)	30 (90.9)	14 (100)	6 (100)
Persistent RS at 1-year follow-up§	9 (21.9)	3 (9.1)	0 (0)	0 (0)

Data are n (%) or median (interquartile range). *Procedural success was not statistically significant between the 3 types of RS (p=ns). §Assessment of RS with transcranial Doppler 1 year after the procedure was available only for 79 (81.4%) patients. NS: non-significant; PFO: patent foramen ovale; RS: residual shunt

exists among the different commercially available brands in the case of small PFOs that require small-sized occluding devices.

Several mechanisms may underlie paradoxical RS after PFO closure, and an understanding of these mechanisms is crucial to selecting the best therapeutic approach. In our study, nearly half of cases were due to incomplete sealing of the device discs, resulting in interdiscal, tunnel-like communication. The prevalence of this mechanism was significantly higher with large occluding devices, and it was treated by implanting single or multiple vascular plugs inside the previously deployed device **(Figure 1B, Moving image 1)**. The second most frequent cause of RS was extradevice interatrial communication due to incomplete coverage of the PFO by an undersized or dislocated device or an accessory atrial septal defect outside the fossa ovalis and far from the previously implanted device. This type of RS was mainly found in patients with an aneurysmal septum, in whom detecting accessory sites of shunt at the time of the first procedure may have been challenging because of the high mobility of the septum. Additionally, significant device traction on the atrial septum, particularly in cases with a stiff PFO tunnel, may lead to type 2 RS caused by a septum primum tear near the posterior edge of the device. In all these cases, the use of a second non-self-centring or self-centring device should be suggested as the best choice **(Figure 2B, Figure 2C, Moving image 2)**. Less common causes of RS included unusual right-to-left communications, such as a serpiginous fistula into the atrial septum or right atrium-to-pulmonary vein fistulas. In these cases, an individualised treatment using detachable coils **(Figure 3B, Figure 3C, Moving image 3)** or vascular plugs could be the best approach. A novel type of RS identified in our study was the recurrence of paradoxical shunt following the NobleStitch approach[20,21]. It was presumably due to loosening of the occlusion knot or atrial septal tears and appeared over a short-term follow-up after a seemingly successful procedure. The higher rate of RS associated with the NobleStitch approach raises questions about whether this technique should continue to be used in clinical practice. In such cases, implanting a small double-disc non-self-centring device might be the preferred option for RS treatment **(Figure 4B, Moving image 4)**. Finally, RS was caused by a combination of different mechanisms of paradoxical shunt in a small percentage of patients. These cases were successfully treated with a combination of devices targeted to the specific anatomical type of shunt **(Figure 5B, Moving image 5)**.

In our approach, the closure strategy and device selection were strongly dependent on the anatomical characteristics of each patient. Thus, a detailed assessment of the atrial septum, along with the availability of different devices, was crucial for effectively performing this complex procedure. Based on these considerations, the treatment of RS was successful in a high percentage of cases with a low risk of complications, in line with the current literature[5,6,11,22], and without any significant difference between the 3 types of RS. Failure to cross small intradisc shunt sites or incomplete shunt sealing due to tortuous anatomy were the most frequent causes of procedure failure. Persistence of significant RS after the second procedure was still found in nearly 9% of cases. However, it was deemed not prognostically relevant, since it was presumably due to intraplug foaming and therefore not worthy of further interventional treatment since the occluding device acted as a mechanical barrier to large clots. Thus, these patients remained on chronic antiplatelet therapy.

Limitations

This retrospective study has several limitations, primarily due to its multicentre nature, which precluded a standardised approach to both the original anatomical characteristics and the technique in the previous PFO closure procedure and the RS closure procedure. Specifically, the anatomical description of the septum and the choice of the type and size of the occluding device were not based on the same criteria across the three centres. Consequently, it was not possible to identify any predictive risk factors for RS. However, the aim of this study was to report the prevalence and the anatomical classification of RS in a real-world experience and to describe an anatomically tailored approach for transcatheter treatment of this condition. Another limitation is that RS was identified by a positive c-TCD rather than TOE, which may have overestimated the true prevalence of RS. Nonetheless, c-TCD is routinely used as an alternative to TOE for RS screening, with a high sensitivity and specificity[6,10,13]. Additionally, the 1-year c-TCD follow-up was not available for all patients who underwent percutaneous treatment of RS, so the efficacy of the procedure could only be assessed based on the end-procedure TOE bubble test. Finally, we were unable to perform a comparative analysis between medically and interventional-treated patients with RS, resulting in a significant gap in the evidence regarding whether RS closure is indicated. Further prospective studies are necessary to assess the true benefit of this approach.

Conclusions

Residual paradoxical shunt is frequently found after transcatheter PFO closure and is significantly associated with the type and size of the occluding device. The causes of RS are multiple, and a comprehensive assessment of their mechanisms,

as well as detailed imaging of atrial septal anatomy, is crucial in defining a patient-tailored approach to shunt closure. Percutaneous treatment of RS with different dedicated or off-label devices is safe and effective in a high percentage of cases.

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Conflict of interest statement

G. Gaio is a proctor for W. L. Gore & Associates and Heartstitch. F. Meucci is a proctor for Boston Scientific and Innova HTS. G. Santoro is a proctor for Abbott, W. L. Gore & Associates, and Occlutech. The other authors have no conflicts of interest to declare.

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Supplementary data

Moving image 1. Transcatheter closure of an intradiscal RS by implantation of an Amplatzer Vascular Plug type II.

Moving image 2. Transcatheter closure of an extradevice RS by implantation of an Amplatzer PFO Occluder.

Moving image 3. Transcatheter closure of multiple atrial septum fistulas by deployment of controlled-release coils.

Moving image 4. Closure of RS after the NobleStitch technique in a complex PFO in situs visceroatrial inversus by implantation of a 30 mm Cardia Ultrasept.

Moving image 5. Transcatheter closure of multiple shunts of different types by implantation of an Amplatzer Duct Occluder II and a controlled-release Cook coil.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-24-00856

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ORIGINAL RESEARCH

SESAME technique: septal scoring along the midline endocardium

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ABSTRACT

BACKGROUND: The management of interventricular septal hypertrophy is an area of rapidly increasing interest, spurred by continued challenges with transcatheter mitral valve replacement (TMVR) and the management of obstructive hypertrophic cardiomyopathy (oHCM).

AIMS: We sought to evaluate the reproducibility of septal scoring along the midline endocardium (SESAME), a novel transcatheter intervention designed to replicate surgical myotomy.

METHODS: This single-centre, retrospective review included all patients who underwent the SESAME procedure at the University of Washington from January 2022 to September 2024.

RESULTS: A total of 54 consecutive patients underwent SESAME at our institution: 47 prior to TMVR, 6 for oHCM, and 1 for a subaortic membrane. Technical success was achieved in 100% of patients. In pre-TMVR patients, the median neo-left ventricular outflow tract (LVOT) and the median skirt neo-LVOT areas gained were 146 (first quartile [Q1]: 76.5, third quartile [Q3]: 286.3) mm^2 and 54 (Q1: 32.8, Q3: 100.2) mm^2, respectively. In the oHCM population, invasive resting and provocable LVOT gradients immediately decreased from 59 (Q1: 32, Q3: 99) mmHg to 10 (Q1: 5, Q3: 19) mmHg and from 121 (Q1: 53, Q3: 205) mmHg to 34 (Q1: 16, Q3: 56) mmHg, respectively. The median echo gradients decreased from 62 (Q1: 53, Q3: 64) mmHg at baseline to 6 (Q1: 6, Q3: 8) mmHg at 30 days. Among the pre-TMVR population, there were 2 procedural deaths from free-wall rupture early in the experience and 3 restrictive ventricular septal defects that did not require intervention. Three patients (5.5%) required a pacemaker. Procedural complications significantly decreased after the first 10 cases in 2022 (p<0.01).

CONCLUSIONS: Our study corroborates the feasibility and efficacy of SESAME for prohibitive surgical risk patients needing septal reduction therapy prior to TMVR or for treatment of oHCM or a subaortic membrane.

KEYWORDS: left ventricular outflow tract; mitral valve; obstructive hypertrophic cardiomyopathy; SESAME; transcatheter mitral valve replacement

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Ventricular septal reduction therapy is an area of rapidly increasing interest, spurred by continued challenges with transcatheter mitral valve replacement (TMVR) and therapeutic approaches to obstructive hypertrophic cardiomyopathy (oHCM). Early TMVR experience revealed acute left ventricular outflow tract obstruction (LVOTO) as a potentially fatal complication of the procedure, occurring in at least 9.3% of patients[1]. This complication is based on the relationship between the displaced subvalvular mitral apparatus or the ventricular aspect of the mitral prosthesis and the basal interventricular septum. Given the morbidity and mortality associated with LVOTO after TMVR, several techniques have evolved to reduce this risk, but each has its limitations. Intentional laceration of the anterior mitral leaflet to prevent outflow obstruction (LAMPOON) allows blood flow across the subvalvular transcatheter mitral valve (MV) stent struts because they are not covered by the anterior mitral leaflet[2], but contemporary mitral prostheses have a closed-cell structure which undermines the value of this technique. Alcohol septal ablation (ASA) can reduce basal septal hypertrophy and mitigate LVOTO[3]. However, the myocardial response to ethanol is unpredictable, a favourable septal perforator anatomy is required, and permanent pacemaker (PPM) rates can exceed 20%, particularly when the septum is not significantly thickened[3,4].

More recently, septal scoring along the midline endocardium (SESAME) has emerged as a novel transcatheter electrosurgical procedure mimicking surgical myotomy[5]. Greenbaum et al[6] reported the first single-centre case series utilising this technique to successfully facilitate transcatheter valve implantation or treat oHCM. The reported outcomes of this case series were very favourable, with a 2.6% procedural mortality rate, 5.3% PPM rate, and a mean left ventricular outflow tract (LVOT) area gain of 141 mm^2 despite the ongoing refinement of the technique[6]. Questions remain, however, about the reproducibility of this technique at different medical centres given the perceived technical challenges of the procedure.

As early adopters of SESAME for our TMVR population and, more recently, our oHCM population, we hereby report the safety and efficacy of this technique in another single-centre, real-world registry to validate its feasibility and reproducibility.

Impact on daily practice

Septal scoring along the midline endocardium (SESAME) is a novel transcatheter intervention designed to replicate surgical myotomy and holds great promise, but clinical results have only been published from a single medical centre. This second report on the clinical outcomes of SESAME, however, validates the role of this technique as a septal reduction strategy in preparation for transcatheter mitral valve replacement or obstructive hypertrophic cardiomyopathy. We identify a learning curve of 10 cases.

Methods

COHORT

All patients who underwent a SESAME procedure at the University of Washington are included in this report. The majority of these patients had MV disease and were being evaluated for TMVR. Initially, patients deemed poor candidates for ASA were treated with SESAME, although, gradually, SESAME became the default technique for septal reduction therapy prior to TMVR. As comfort with the technique grew, this procedure was introduced for patients with oHCM phenotypes and for 1 patient with subaortic stenosis. The procedure was performed on a compassionate basis with informed consent. The University of Washington Institutional Review Board approved this single-centre retrospective review.

PROCEDURAL TECHNIQUE

A detailed description of the technique has been reported elsewhere[6]. Briefly, percutaneous septal myotomy was performed via femoral vascular access with biplane fluoroscopy and transoesophageal echocardiography (TOE) guidance. Fluoroscopic projections were derived from contrast-enhanced computed tomography (CT) illustrating a long-axis view of the left ventricle (generally right anterior oblique and caudal) and an *en face* LVOT view (generally left anterior oblique and cranial). A steerable guide (DIREX [Boston Scientific]) was positioned in the ascending aorta, through which a guide catheter was advanced retrogradely across the aortic valve to the basal interventricular septum. The guide catheter – typically a hockey stick catheter – was positioned against the septum at the planned myocardial entry point. Through this, a distally amputated 0.014" CONFIANZA Pro 12 guidewire (Asahi Intecc) within a Turnpike Spiral microcatheter (Teleflex) was used to puncture the septal myocardium encroaching into the LVOT (the "septal knuckle"). In some cases, an Astato XS 40 wire (Asahi Intecc), with a brief pulse of 50 watts of electric current, was used to facilitate myocardial entry. Following septal entry and engagement of the Turnpike Spiral into the muscle, the wire was exchanged for a 300 cm Astato XS 20 wire (Asahi Intecc) with a small (1-2 mm, 20-30 degree)

Abbreviations

ASA	alcohol septal ablation	**LVOTO**	left ventricular outflow tract obstruction	**SESAME**	septal scoring along the midline endocardium
CT	computed tomography	**MAC**	mitral annular calcification	**TMVR**	transcatheter mitral valve replacement
ICE	intracardiac echocardiography	**MV**	mitral valve	**TOE**	transoesophageal echocardiography
LAMPOON	laceration of the anterior mitral leaflet to prevent outflow obstruction	**oHCM**	obstructive hypertrophic cardiomyopathy	**TTE**	transthoracic echocardiography
LVOT	left ventricular outflow tract	**PPM**	permanent pacemaker	**VSD**	ventricular septal defect

"chronic total occlusion (CTO)-like" tip bend. This wire was then steered and advanced through the myocardium under fluoroscopic and TOE guidance, followed by a microcatheter, to the predetermined cavitary re-entry point.

During the early experience, multiple imaging modalities were utilised to best understand the exact course of the wire trajectory through the septum and ensure appropriate wire position and depth. These included biplane fluoroscopy, TOE, transthoracic echocardiography (TTE), intravascular ultrasound in the myocardium, intracardiac echocardiography (ICE), and ventriculography. Most of these modalities were abandoned due to minimal perceived benefit, with biplane fluoroscopy (rather than the simulated trajectory on CT) and TOE being favoured.

Following confirmation of optimal wire position, the distal end of the lacerating wire was snared. The contemporary technique now includes dilating the intramyocardial tract using a 1.5 mm coronary balloon to facilitate delivery of a larger microcatheter, which double-insulates the wire in the myocardium to minimise the build-up of heat and the potential for steam pops. Following balloon dilation, a "flying V" cutting element was formed in the middle of the exchange-length lacerating wire, and the afferent limb of the wire was sheathed within a mother-daughter microcatheter system (0.014" Finecross and 0.035" NaviCross [both Terumo]) to concentrate the electric current at the cutting element. The efferent limb was typically not insulated with a microcatheter, but continuous flush saline was provided via the snaring catheter during cutting. The "flying V" was positioned across the intramyocardial segment. Gentle retraction of both limbs of the externalised wire was then performed, and the MV was assessed with TOE to ensure the subvalvular mitral apparatus was not entangled. The wire was then electrified using a continuous current delivery of 50 watts. At the same time, gentle traction was applied to both limbs of the wire until fluoroscopy suggested complete muscle laceration.

ANALYSIS

Pre- and post-procedure CT analyses were performed using 3mensio, version 10.3 (Pie Medical Imaging). Predicted neo-LVOT and skirt neo-LVOT area measurements were standardised by obtaining them in end-systole (30-40% cardiac cycle) using a modelled 29 mm wide, 22 mm tall prosthesis positioned 25% atrial (e.g., in a "SAPIEN [Edwards Lifesciences] in mitral annular calcification [MAC]" setting). Although a "SAPIEN in MAC" configuration was used for standardisation in this report, for many patients, the clinical goal was to qualify for a dedicated mitral prosthesis. Consequently, the "SAPIEN in MAC" neo-LVOT and skirt neo-LVOT values were not always germane to the clinical decision-making for proceeding with SESAME. The smallest cross-sectional area measured was recorded from CT scans both pre- and post-procedure, with the post-procedure CT scan typically occurring 1 month after the SESAME procedure. The neo-LVOT was recorded as a negative number when there was no visible neo-LVOT path around the prosthesis and the septal muscle appeared to encroach inside the simulated valve. The cross-sectional muscle area inside the prosthesis at maximal encroachment was then traced to record a negative neo-LVOT. The maximal septal thickness was measured by CT during end-systole, consistent with the neo-LVOT measurements. Right ventricular trabeculations were not included in the septal thickness measurements.

Technical success was defined as a septal laceration visually confirmed by intraprocedural TOE. Consistent with prior reports, we also analysed neo-LVOT failure and skirt neo-LVOT failure, which were defined as minimal post-SESAME LVOT areas below the thresholds of 200 mm^2 and 150 mm^2, respectively.

All patients who underwent attempted SESAME at our institution were included, irrespective of the intended TMVR plan or prior septal modification with ASA. Data were abstracted retrospectively from the medical records. Serial measurements were analysed as pairs. Data are reported as mean±standard deviation if normally distributed or median (first quartile [Q1], third quartile [Q3] if not. Statistical analysis was performed using Stata, version 15 (StataCorp), and JMP Pro 17 (SAS Institute). Figures were created with Biorender.com. A two-sided p-value<0.05 was considered statistically significant.

Results

In all, 54 consecutive patients who underwent SESAME at our institution from January 2022 to September 2024 were included in the analysis. The majority (87%) were female. The mean patient age was 75.2±9.5 years. A total of 28% of patients had prior stroke or TIA, and 57% had chronic kidney disease (CKD) stage 3 or greater. In all, 53% of patients had prior aortic valve replacement. In patients with MV disease, 91% had moderate or greater MAC, and the mean Society of Thoracic Surgeons (STS)-predicted 30-day mortality for isolated MV replacement was 15±9.5%. Baseline patient characteristics are summarised in **Table 1**.

Indications for SESAME were septal modification prior to TMVR (n=47), symptomatic LVOT obstruction due to oHCM phenotypes (n=6), or subaortic membrane (n=1). SESAME was performed on an elective basis in 85% of cases, urgently in 13% (for patients admitted with decompensated heart failure symptoms at the time of SESAME), and emergently in 2% (as a post-TMVR rescue). Technical success was 100%. The mean procedural duration was 137±57 minutes. Procedural survival was 96% (52 of 54), and 1-month survival was 90%.

MITRAL VALVE DISEASE POPULATION

Among the pre-TMVR patients, the median baseline predicted neo-LVOT area was 44.5 (Q1: –22.6, Q3: 94.5) mm^2, and the median baseline predicted skirt neo-LVOT area was 195.6 (Q1: 157.4, Q3: 272.0) mm^2. The mean baseline maximal septal thickness in end-systole by CT was 20.7±4.1 mm. The mean time to postprocedural CT was 34±18 days. Following SESAME, the median neo-LVOT and skirt neo-LVOT areas gained were 146.5 (Q1: 76.5, Q3: 286.3) mm^2 and 54.1 (Q1: 32.8, Q3: 100.2) mm^2, respectively. Representative analyses of large, medium, and small SESAME slices throughout the full cardiac cycle are included in **Supplementary Figure 1**. Fifteen (32%) patients had neo-LVOT failure (7 of 12 patients with baseline neo-LVOTs <0 mm^2 and 8 of 35 patients with baseline neo-LVOTs >0 mm^2). One patient (3%) had skirt neo-LVOT failure. **Table 2** summarises the procedural results.

Table 1. Baseline characteristics.

Clinical and demographic variables	N=54
Age, years	75.2±9.5
Female	46 (87)
Race	
White	52 (98)
Black	1 (2)
Ethnicity	
Hispanic or Latino/a or Latinx	1 (2)
Non-Hispanic or Latino/a or Latinx	52 (98)
Body mass index, kg/m^2	29.2±6.5
NYHA Class	
II	4 (7)
III	39 (74)
IV	10 (19)
LVEF, %	67±9
Known coronary artery disease	33 (62)
Prior stroke or transient ischaemic attack	15 (28)
Prior myocardial infarction	12 (23)
Peripheral artery disease	19 (36)
Hypertension	54 (100)
Diabetes	27 (51)
Chronic kidney disease stage ≥3	30 (57)
Obstructive lung disease (asthma or COPD)	24 (45)
Obstructive sleep apnoea	21 (40)
Atrial fibrillation	26 (49)
Former or current tobacco use	27 (51)
Cardiac pacemaker, CRT, or defibrillator	12 (23)
Prior alcohol septal ablation	2 (3)
Mitral valve disease	
None	4 (8)
Predominant mitral regurgitation	8 (15)
Predominant mitral stenosis	34 (64)
Mixed	7 (13)
Aortic valve disease	
None	25 (47)
Prior TAVI	21 (40)
Prior SAVR	7 (13)
STS-predicted 30-day mortality for mitral valve replacement, %	15±9.5%

Data are given as n (%) or mean±standard deviation. COPD: chronic obstructive pulmonary disorder; CRT: cardiac resynchronisation therapy; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; SAVR: surgical aortic valve replacement; STS: Society of Thoracic Surgeons; TAVI: transcatheter aortic valve implantation

Table 2. SESAME area and gradient outcomes.

Pre-TMVR population	N=47
Baseline CT neo-LVOT, mm^2	44.5 (–22.6, 94.5)
Baseline CT skirt neo-LVOT, mm^2	195.6 (157.4, 272.0)
Baseline CT maximal septal thickness, mm	20.7±4.1
Neo-LVOT area change, mm^2	146 (76.5, 286.3)
Skirt neo-LVOT area change, mm^2	54 (32.8, 100.2)
Neo-LVOT failure	15 (32)
Skirt neo-LVOT failure	1 (3)
Patients who have undergone TMVR to date	34 (81)
Pre-TMVR inv. LVOT gradient, mmHg	10.5±5.8
Post-TMVR inv. LVOT gradient, mmHg	13.0±8.7
Time from SESAME to TMVR, days	80.5 (58, 125)
oHCM population	**N=6**
Baseline peak LVOT gradient by TTE, mmHg	62 (53, 64)
Baseline inv. resting LVOT gradient, mmHg	59 (32, 99)
Baseline inv. provocable LVOT gradient, mmHg	121 (53, 205)
Post-SESAME inv. resting LVOT gradient, mmHg	10 (5, 19)
Post-SESAME inv. provocable LVOT gradient, mmHg	34 (16, 56)
Post-SESAME peak LVOT gradient at 30 days, mmHg	6 (6, 8)

Data are given as n (%), mean±standard deviation, or median (Q1, Q3). CT: computed tomography; inv.: invasive; LVOT: left ventricular outflow tract; oHCM: obstructive hypertrophic cardiomyopathy; Q1: first quartile; Q3: third quartile; SESAME: septal scoring along the midline endocardium; TMVR: transcatheter mitral valve replacement; TTE: transthoracic echocardiography

Eleven patients had complications during their index hospitalisations **(Table 3)**. There were two procedural deaths: one from a free-wall perforation caused by an ICE probe in the left ventricle that punctured the lateral wall and one from a free-wall laceration caused by a SESAME slice that was too deep and too apical; both occurred early in our experience **(Figure 1)**. There were 3 additional deaths during the index hospitalisation: a patient with an iatrogenic restrictive ventricular septal defect (VSD) and bradycardia requiring a temporary pacemaker died 4 days post-procedure, and 2 patients died of pre-existing but continued shock without procedural complications.

Two additional patients developed restrictive VSDs that were treated conservatively. Both ultimately required pacemakers. One also underwent a 26 mm Evolut FX (Medtronic) transcatheter aortic valve implantation at the time of SESAME. Both patients ultimately proceeded on to TMVR without complication.

There was one ischaemic stroke without persistent neurological deficits. One patient had MV injury related to SESAME, resulting in a mild increase in already severe mitral regurgitation, and underwent TMVR 67 days later as planned. Three patients developed stage 5 acute kidney injury (AKI) requiring temporary renal replacement therapy. The mean contrast provided to these patients was 6.7±11.5 mL. Two-sample t-testing demonstrated no statistically significant difference between the average contrast use and development of AKI (p=0.21). One patient experienced frequent non-sustained ventricular tachycardia intraprocedurally that did not require additional treatment.

Of 47 patients who underwent SESAME prior to anticipated TMVR, 42 survived to hospital discharge and 34 (81%) have subsequently proceeded to TMVR thus far (5 with trial-based valves and 29 valve-in-MAC procedures).

Table 3. Procedural characteristics and complications.

Characteristic/complication	Value n=54
Indication	
Pre-TMVR	47 (87)
Hypertrophic cardiomyopathy	6 (11)
Subaortic stenosis	1 (2)
Setting	
Elective	45 (85)
Urgent	7 (13)
Emergent	1 (2)
Technical success	54 (100)
Case duration, min	137±57
Contrast, mL	24 (0, 45)
Fluoroscopy time, min	37.1 (23.5, 57.9)
Air kerma, mGy	1,089 (449, 1,590)
Any major complication	11 (20.8)
Death during procedure	2 (3.8)
Acute kidney injury stage 4	3 (5.7)
Permanent pacemaker placement	3 (5.7)
Ventricular septal defect	3 (5.7)
Mitral leaflet laceration	2 (3.8)
Major vascular complication	0 (0)
Stroke	1 (1.9)
Ventricular arrhythmia	1 (1.9)
Ventricular free-wall perforation	2 (3.8)
Bleeding, major or life-threatening	0 (0)
In-hospital mortality	5 (9.4)
30-day mortality	6 (11.3)

Data are given as n (%), mean±standard deviation, or median (Q1, Q3). Q1: first quartile; Q3: third quartile; TMVR: transcatheter mitral valve replacement

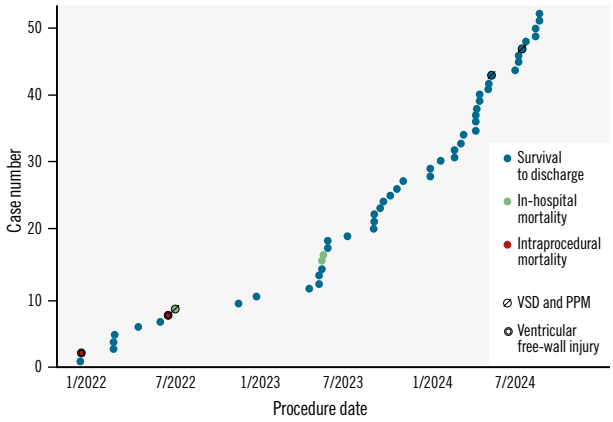


Figure 1. *Enrolment cadence and procedural complications. The date of the SESAME procedure is indicated on the x-axis and the case number on the y-axis. Blue dots represent patients with survival to hospital discharge; green dots represent in-hospital mortality; red dots represent intraprocedural mortality. A ventricular septal defect and complete heart block requiring a pacemaker is indicated by a slashed circle. Ventricular free-wall injury is indicated by concentric circles. PPM: permanent pacemaker; SESAME: septal scoring along the midline endocardium; VSD: ventricular septal defect*

The median time from SESAME to TMVR was 80.5 (Q1: 58, Q3: 125) days. One patient died from her mitral valve disease following SESAME during screening for TMVR options. Of patients receiving a valve-in-MAC TMVR, 23 of 29 (79%) also underwent concomitant LAMPOON. The mean post-SESAME neo-LVOT among those receiving LAMPOON was significantly smaller than that among those who did not (196±40 mm^2 vs 386±39 mm^2; p<0.01). **Figure 2** demonstrates the mean projected baseline neo-LVOT and skirt neo-LVOT, and post-SESAME neo-LVOT and skirt neo-LVOT among the TMVR population. The mean LVOT gradient by invasive measurement following any TMVR was unchanged from baseline (10.6±5.7 mmHg baseline vs 13.4±8.9 mmHg post-TMVR; p=0.11). Thirty-day survival following TMVR was 91%.

LVOT OBSTRUCTION POPULATION

Seven patients underwent SESAME for indications other than MV disease (6 for oHCM and 1 for a subaortic membrane). In the oHCM population, the septal thickness at end-systole as measured by CT scan was 25.2±4.5 mm. Baseline and postprocedural TTE and invasive gradients are summarised in **Table 3**. Invasive measurements demonstrated immediate resolution of resting peak gradients, which was corroborated by echocardiography at 30 days, showing a median peak residual gradient of 6 (Q1: 6, Q3: 8) mmHg.

For the single patient with a subaortic membrane, the invasive gradient was reduced from 51 mmHg to 4 mmHg immediately after SESAME. However, the 30-day TTE results were less dramatic, with a residual peak gradient of 31 mmHg compared to her baseline preprocedural TTE gradient of 70 mmHg. Her procedure was also unusual in that the septal traversal distance was significantly shorter (~10 mm) and less deep (3-4 mm) than is typical. This was specifically intended to split only the limbus of the fibromuscular ridge, rather than to create a splay within the septum itself.

In the oHCM population, there were no deaths, pacemaker requirements, VSDs, or free-wall ruptures. One early patient suffered lacerated mitral chordae requiring transcatheter edge-to-edge repair, which occurred before we routinely checked for chordal entanglement prior to laceration.

LEARNING CURVE

Ten patients were treated with SESAME in 2022, 18 in 2023 and 26 in 2024 (up to August). There was a statistically significant decrease in complications following the first 10 cases performed in 2022 as compared to the 44 cases subsequently performed (p<0.01), including reductions in procedural deaths (20% vs 0%), index hospitalisation deaths (30% vs 4%), VSDs (10% vs 4%), need for PPM (10% vs 4%), and damage to the mitral apparatus (10% vs 2%). Simultaneously, the mean resultant SESAME size, measured as a cross-sectional area by follow-up CT, was not statistically different per year and numerically increased each year (92.6 mm^2 in 2022, 104.7 mm^2 in 2023, and 164.3 mm^2 in 2024; p=0.20).

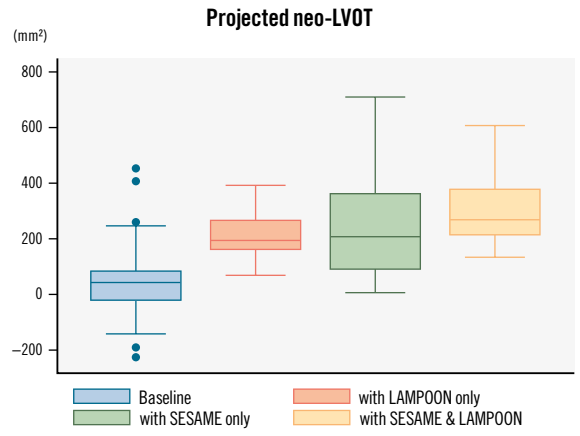


Figure 2. *Projected neo-LVOT after TMVR. Box plot demonstrating the anticipated neo-LVOT following TMVR at baseline (blue), with LAMPOON at the time of TMVR (orange), following SESAME without LAMPOON (green) and following SESAME and LAMPOON (yellow). Each box represents the range of results from the 1st to the 3rd quartile with the median value as the horizontal line inside the box. Whiskers are the minimum and maximum values excluding outliers, which are represented as single dots. LAMPOON: laceration of the anterior mitral leaflet to prevent outflow obstruction; LVOT: left ventricular outflow tract; SESAME: septal scoring along the midline endocardium; TMVR: transcatheter mitral valve replacement*

Discussion

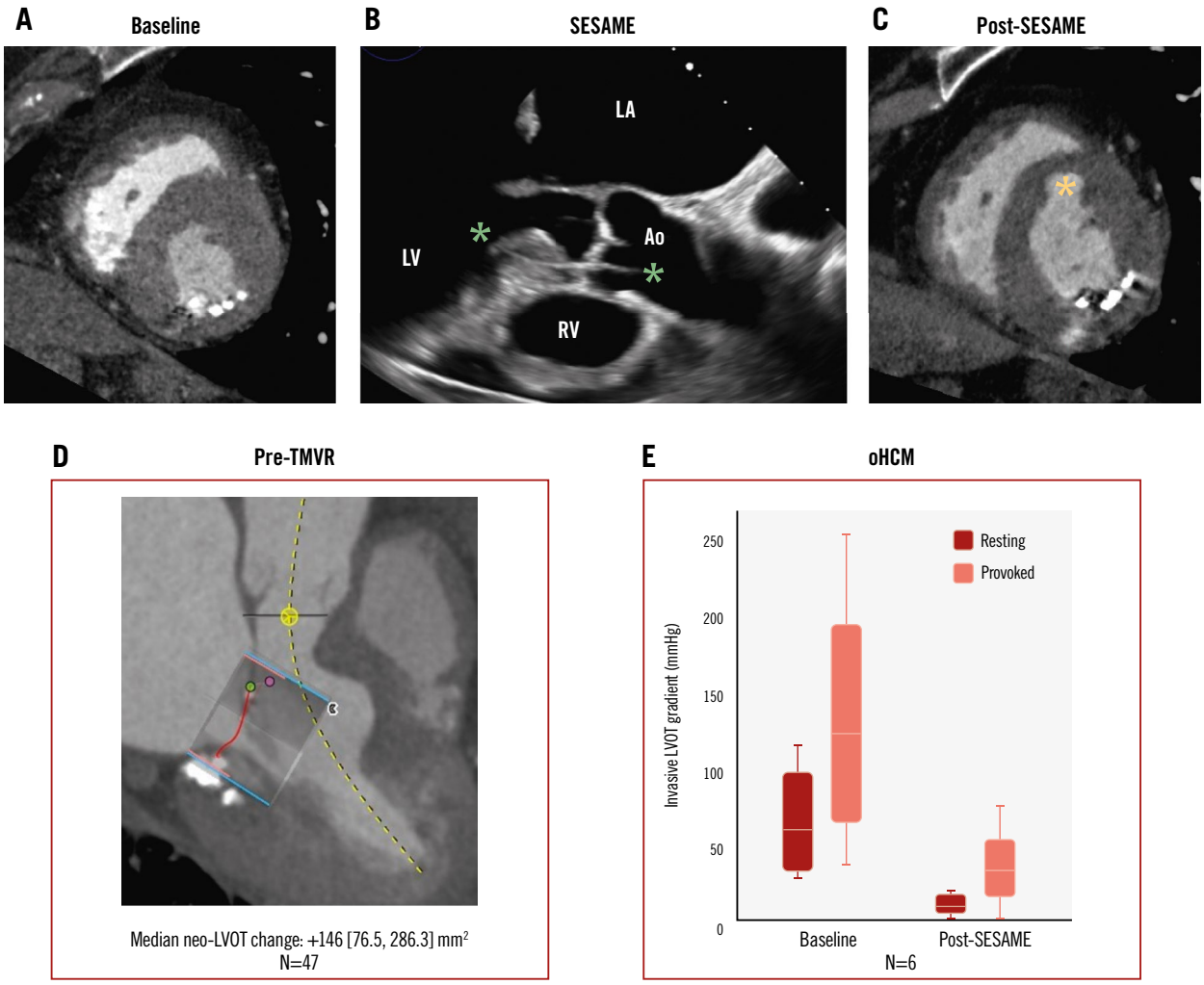
We present the second human cohort of patients undergoing SESAME, a novel transcatheter electrosurgical procedure that mimics surgical myotomy. We initially used SESAME to facilitate septal reduction therapy prior to TMVR in a highly morbid and complex population with significant MAC but evolved our use of the technique to treat high-risk patients with LVOT obstruction from hypertrophic cardiomyopathy or subvalvular aortic stenosis. All patients were considered too high risk to undergo open mitral valve replacement or myectomy, and 15% were already in the hospital for acute decompensated heart failure at the time of their SESAME. We observed the following: (1) SESAME is a highly effective septal reduction technique that enlarges the LVOT and reduces LVOT gradients without tissue excision; (2) SESAME was an acceptably safe procedure in this inoperable and complex patient cohort, with patient risks diminishing over time; (3) as might be expected for a novel procedure under continued refinement during the study period, SESAME was associated with a learning curve where significantly better outcomes were seen following the first 10 cases at our institution **(Central illustration)**.

In the pre-TMVR population, the median augmentation in LVOT area was 146 mm², which is almost exactly the same as the previously reported neo-LVOT gains following SESAME, and compares very favourably to changes in neo-LVOT reported following ASA[3,7]. Despite significant gains in the LVOT area in general, the results following SESAME were heterogeneous, with 32% of pre-TMVR patients not achieving a desired post-SESAME predicted neo-LVOT of 200 mm². Most of these patients started with predicted neo-LVOTs less than 0 mm², and as such, it stands to reason that a median result of 150 mm² gained would not be sufficient. However, 6 patients gained less than 50 mm² of neo-LVOT following SESAME. This may be due to differences in the myocardial response to SESAME laceration, a procedural wire traversal that was too shallow to result in sufficient splay, or geographical deviation from the intended SESAME laceration, particularly not initiating the laceration sufficiently basally and thereby leaving a ridge of muscle just underneath the aortic valve. Nevertheless, only 1 patient had a resultant skirt neo-LVOT less than 150 mm². In fact, 81% of our SESAME population has already moved on to TMVR. The remaining patients in the cohort are under evaluation for treatment with a dedicated prosthesis via clinical trial pathways.

Though our oHCM population was small, the immediate and 30-day SESAME results have been quite striking, with statistically significant reductions in immediate resting (59 mmHg vs 10 mmHg) and provocable (121 mmHg vs 34 mmHg) invasive gradients. This finding also carried over to 30-day TTE results (62 mmHg vs 6 mmHg). The immediacy of these results in the oHCM population is particularly notable. Since the splay does not mature immediately and no myocardial mass is removed, the immediate reduction in LVOT gradients may be due to alterations in flow dynamics and abrogation of the Venturi forces that draw the anterior mitral leaflet towards the septum. Further study in a larger population of patients will be required to understand this phenomenon better.

We observed a marked improvement in the safety of this procedure following the initial experience in 2022. This improvement can be attributed to several developments, the most important of which was developing our procedural plans internally using dedicated CT software (3mensio). This software allows curved multiplanar reconstructions along the LVOT centreline to better understand the three-dimensionality of the septum as represented in procedural biplane fluoroscopy. The importance of this evolution in our preprocedural planning cannot be overstated for centres that wish to start a SESAME programme, particularly in the absence of dedicated lacerating equipment. Other evolutionary and local changes to the SESAME technique also played a role in improving the safety of this procedure. These included abandoning ICE assessment from the left ventricle, which was the cause of an early fatal left ventricular free-wall perforation, and double insulating the traversing wire in the myocardium to limit the chance of steam pop. Despite early and frequent collaboration, we also paused our programme at the end of 2022 until our team could attend a "reverse proctoring" opportunity to more directly observe cases and interface with colleagues at another centre. The most notable lesson from that experience was increasing dedication to the aforementioned CT plan as a "source of truth" to be subsequently corroborated by TOE. Specifically, as seen on fluoroscopy, the wire's trajectory in the myocardium must adhere with high fidelity to the preplanned trajectory described on the CT **(Figure 3)**. TOE is then used to confirm or raise concerns about wire

The SESAME technique.



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Representative CT scan short-axis view of the left ventricle before (A) and after (C) SESAME. B) Trajectory and depth of the SESAME wire traversal in the intraventricular septum as seen on TOE. Green asterisks highlight the wire course. D) SESAME effects in the pre-TMVR population. E) SESAME effects in the obstructive hypertrophic cardiomyopathy (oHCM) population. Ao: aorta; LA: left atrium; LV: left ventricle; LVOT: left ventricular outflow tract; RV: right ventricle; SESAME: septal scoring along the midline endocardium; TMVR: transcatheter mitral valve replacement; TOE: transoesophageal echocardiography

depth and traversal length within the myocardium before considering wire externalisation and laceration **(Figure 4)**. With these changes in place, we saw marked reductions in procedural complications. Nevertheless, the inoperable, pre-TMVR population that makes up the majority of our study participants remains a highly morbid cohort, as reflected in our data and all TMVR datasets[8-10].

The SESAME procedure is an innovative and distinctive technique that offers new opportunities for patients needing septal reduction therapy. Alternative minimally invasive procedures, such as ASA, are commonly used but come with notable drawbacks. ASA is associated with high rates of PPM placement[3,4], is dependent on specific coronary anatomy, and frequently does not result in an adequate increase in the neo-LVOT area[3]. Another alternative, radiofrequency ablation, varies in risk depending on the technique used and can also result in near-universal rates of PPM placement[11,12] and elevated rates of pericardial effusion[13]. Novel pharmaceutical agents may play a significant role in the management of oHCM specifically, but these medicines are quite expensive, require substantial monitoring that may not be feasible for everyone, and have a non-durable effect if the medication is discontinued. These limitations underscore the need for additional effective solutions. In this context,

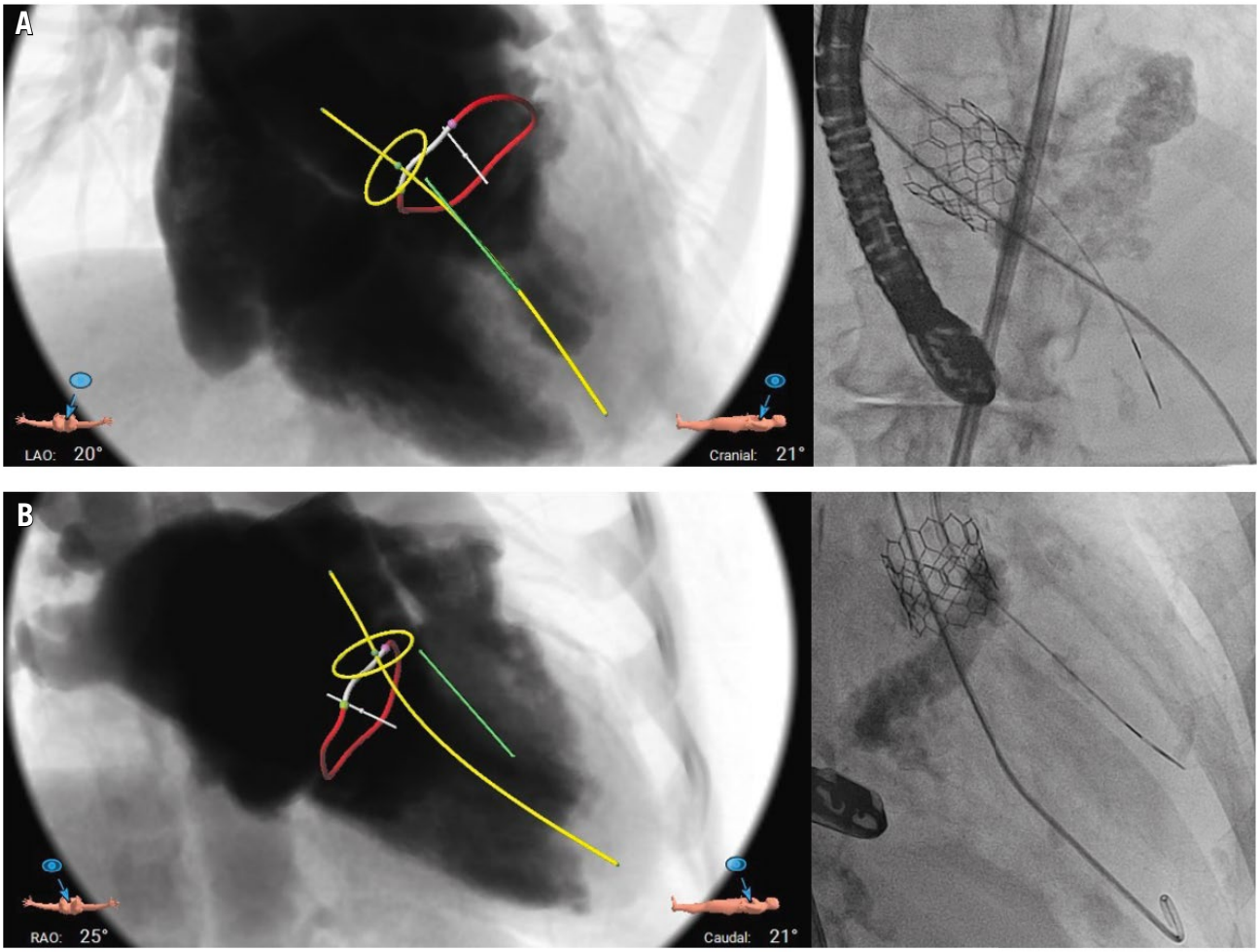

Figure 3. *Preprocedural planning using simulated fluoroscopic views by CT scan, shown with corresponding actual procedural fluoroscopy images. Left anterior oblique (LAO) cranial projection (A) and right anterior oblique (RAO) caudal projection (B) demonstrating the relationship between the CT-derived aortic annulus (yellow ring), mitral annulus (red ring), left ventricular outflow tract midline (yellow line), as well as the desired SESAME wire trajectory (green line). Actual wire position is consistent with the intended course. CT: computed tomography; SESAME: septal scoring along the midline endocardium*

SESAME emerges as a crucial alternative. It provides a more effective way to manage interventricular septal hypertrophy in a broad range of patients and addresses the limitations of other procedures. Specific to the issues of heart block, our experience with SESAME suggests a PPM rate <6% and no episodes of delayed heart block. This is because we explicitly lacerate anterior to the membranous septum away from the His system. Nevertheless, continued refinement of this nascent technique will be necessary.

Limitations

This study has significant limitations. The data originate from a single-centre, non-randomised, retrospective study conducted by experienced operators. The SESAME procedure requires biplane fluoroscopy and dedicated procedural echocardiography. The results may not be reproducible in all centres, particularly where operators might have less experience with electrosurgical techniques and the required interventional echocardiographic skills. Dedicated devices for SESAME that require only a single plane of fluoroscopy and less sophisticated TOE imaging are currently in development and should help relieve this limitation. Secondly, the small sample size may limit the generalisability of the findings to a broader population, though it is notable that most of our patients are female. Also, the SESAME procedure was offered as compassionate use to patients with significant comorbidities who were not candidates for surgery, leading to a selection bias towards the most critically ill patients. Additionally, our population is too small to develop technical or patient-related predictors of success at this time. Furthermore, we have not yet tried to treat patients with mid-cavitary or distal cavity obstruction, and it is unclear whether this is a solution for those phenotypes of oHCM. Finally, a retrospective study design lends itself to gaps in data collection, which may affect the reliability of the results.

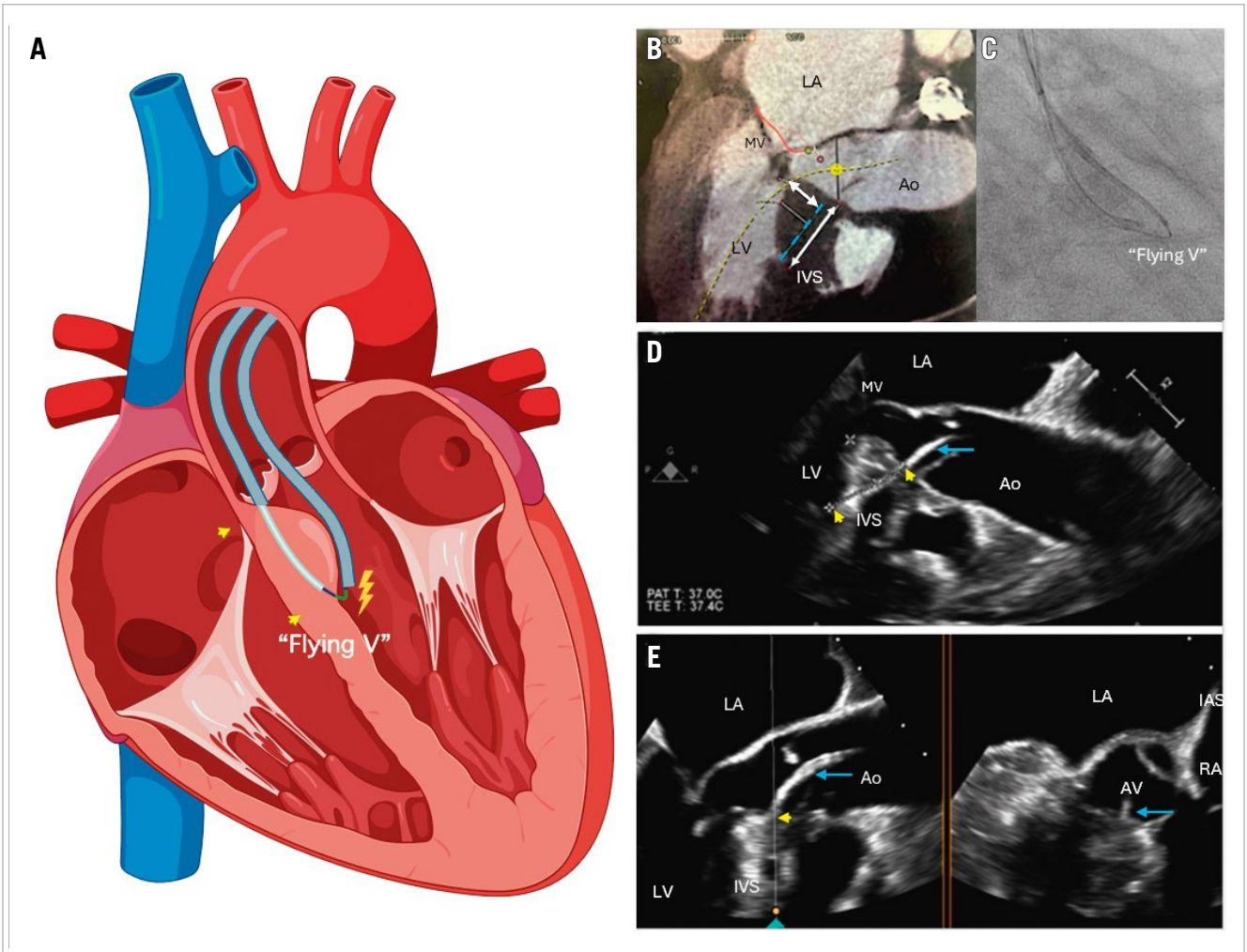

Figure 4. *Procedural schematic. A) Schematic illustration of the SESAME technique. The darker blue lines represent the guide catheter, while the light blue line shows the microcatheter navigating through the septum. The "flying V" marks the location where electricity is applied. The yellow arrows indicate the wire's entrance and exit points. B) Cardiac CT image, with the dashed blue line indicating the desired trajectory of the wire navigating through the septum. The double-headed arrows represent the ideal width and length of the path. C) Fluoroscopic image of the "flying V". D) TOE showing the guide catheter (blue arrow) and the wire's entrance and exit points (yellow arrows). E) TOE biplane view, showing the guide catheter (blue arrow) and the wire's entry point (yellow arrow). Ao: aorta; AV: aortic valve; IAS: interatrial septum; IVS: interventricular septum; LA: left atrium; LV: left ventricle; MV: mitral valve; RA: right atrium; SESAME: septal scoring along the midline endocardium; TOE: transoesophageal echocardiogram*

Conclusions

Our study showcases contemporary experience with SESAME for high or prohibitive surgical risk patients needing septal reduction therapy prior to TMVR, for the treatment of oHCM with LVOT obstruction, or for the treatment of subvalvular aortic stenosis. Our data corroborate previously published data regarding the efficacy and feasibility of this procedure. SESAME is relatively safe and feasible, though technically challenging, and there does appear to be a relevant learning curve. Further research is needed to refine patient selection and procedural techniques.

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Conflict of interest statement

J.M. McCabe: equity: Excision Medical, Transmural Systems, and ConKay Medical; consulting: Edwards

Lifesciences, Medtronic, and Abbott. C.J. Chung: consulting: Edwards Lifesciences, Boston Scientific, and Medtronic. A.B. Greenbaum: equity: Excision Medical and Transmural Systems; consulting: Edwards Lifesciences, Medtronic, Abbott, and Polares. D. Elison: equity: Excision Medical. V.C. Babaliaros: equity: Transmural Systems; consulting: Edwards Lifesciences. R.J. Lederman: co-inventor on applicable patents assigned to his employer (NIH). G.B. Mackensen: research grants: Philips. The other authors have no conflicts of interest to declare.

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Supplementary data

Supplementary Figure 1. Comparison of SESAME effect size on projected neo-LVOT and skirt neo-LVOT throughout the cardiac cycle.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-25-00131

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ORIGINAL RESEARCH

Transcatheter aortic valve implantation in pure aortic regurgitation: one-year outcomes of the AURORA trial

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ABSTRACT

BACKGROUND: Transcatheter aortic valve implantation (TAVI) in pure aortic regurgitation (AR) remains challenging because of inadequate anchoring forces. Traditional approaches, which rely solely on virtual annulus oversizing, have demonstrated limited success. We propose a novel anatomical classification system and dual-anchoring theory to optimise the TAVI strategy in patients with pure AR.

AIMS: We aimed to evaluate the efficacy and safety of TAVI in pure AR using a novel anatomical classification system and dual-anchoring theory.

METHODS: The AURORA trial is a prospective, multicentre, single-arm study conducted across 16 centres in China. Patients with severe pure AR underwent comprehensive anatomical assessment using multidetector computed tomography (CT). Based on the ability to provide adequate anchoring forces (≥10% of oversizing) in three zones (left ventricular outflow tract, anatomical annulus, and ascending aorta), patients were classified into 4 types. Those with anatomical types 1-3 were enrolled and underwent TAVI using the VitaFlow valve system. The primary efficacy endpoint was device success, and the primary safety endpoints included 30-day mortality and major complications.

RESULTS: Among 187 screened patients, 100 patients with suitable anatomy (types 1-3) were enrolled. The mean age was 72.7±7.2 years, and the mean Society of Thoracic Surgeons Predicted Risk of Mortality score was 9.10±5.81%. Device success was achieved in 91% of cases, with no procedural mortality. The new permanent pacemaker implantation rate was 9%. Postprocedural CT analysis in 43 patients revealed that the maximum contact forces were primarily localised between the virtual annulus and the sinotubular junction (83.7% of cases). No device failure occurred in later cases.

CONCLUSIONS: The AURORA classification system shows that comprehensive anatomical assessment can lead to favourable outcomes in pure AR using conventional TAVI devices. The low pacemaker implantation rate and the absence of device failure in later cases suggest that optimal anatomical matching may be superior to aggressive oversizing strategies.

KEYWORDS: anatomical classification; anchoring force; aortic regurgitation; computed tomography; transcatheter aortic valve implantation

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Severe aortic regurgitation (AR) represents a substantial therapeutic challenge, particularly in patients at high surgical risk. Traditional surgical aortic valve replacement (SAVR) is often contraindicated for these patients due to the presence of prohibitive comorbidities and surgical risks. Transcatheter aortic valve implantation (TAVI) has emerged as a promising, less invasive alternative, with proven efficacy in treating aortic stenosis, largely due to the presence of calcified annular structures that facilitate secure valve anchoring[1-3]. However, the application of TAVI in AR remains limited by the absence of such anchoring structures, resulting in a higher incidence of device malposition and paravalvular leak, which can adversely impact procedural success and long-term outcomes[4-6].

Despite these challenges, recent advances in valve technology and procedural techniques have shown potential to improve TAVI outcomes in AR, warranting further investigation into optimised strategies for patient selection and device implantation.

This study aimed to evaluate the safety and efficacy of transfemoral TAVI in high-risk patients with severe AR utilising a novel anatomical classification system and dual-anchoring theory. The hypothesis underlying this approach is that optimal device stability can be achieved by identifying multiple anchoring sites along the aortic root, as delineated through multidetector computed tomography (MDCT).

This method seeks to overcome the challenges associated with the absence of calcified structures, which are typically critical for secure valve anchoring in conventional TAVI procedures.

Impact on daily practice

The AURORA classification system enhances anatomical assessment for transcatheter aortic valve implantation (TAVI) in pure aortic regurgitation (AR) patients by moving beyond the traditional virtual annulus-based evaluation. By incorporating multiplanar measurements of the entire aortic root, it enables better patient selection and improved procedural outcomes. The low permanent pacemaker rate suggests that precise anatomical matching may be more effective than aggressive oversizing. This approach is especially useful where AR-dedicated valves are unavailable, allowing effective use of conventional TAVI devices. The dual-anchoring theory and anatomical classification offer a structured framework for interventionalists, potentially reducing device failure and improving long-term outcomes.

Methods

STUDY DESIGN

The AURORA trial is a prospective, multicentre, single-arm cohort study conducted across 16 high-volume centres in China with expertise in TAVI. All patients with severe pure AR were initially screened by local Heart Teams, evaluating surgical risk based on available clinical data and obtaining written informed consent for further investigation. Transthoracic or transoesophageal echocardiographic data were subsequently uploaded to the echocardiographic core laboratory for confirmation of echocardiographic eligibility criteria in accordance with guidelines from the American Society of Echocardiography[7]. Patients deemed to meet the criteria for aortic valve replacement per established guidelines[1,3] and who were at high surgical risk underwent further assessment via MDCT evaluation. All computed tomography (CT) imaging analyses were performed at the Beijing Anzhen Hospital Core Laboratory. Only those patients with anatomical suitability for TAVI, as defined by types 1, 2, and 3 of the novel AURORA classification, were enrolled in the trial, as previously described[8]. All complications and TAVI-specific endpoints were defined as per the Valve Academic Research Consortium-3 definitions[9]. All adverse events were assessed and adjudicated by an independent clinical events committee. The study was registered with the Chinese Clinical Trial Registry (ChiCTR2200055415)[8].

MULTIDETECTOR COMPUTED TOMOGRAPHY AND AURORA CLASSIFICATION

All patients underwent preprocedural MDCT following a standardised TAVI protocol. The acquired images were analysed using 3mensio software (Pie Medical Imaging). Standardised techniques were employed to measure the annulus, left ventricular outflow tract (LVOT), and ascending aorta (40 mm above the annulus), as previously described[8,10,11]. Following identification of the virtual annular plane, contours were traced at 2 mm intervals (2, 4, 6, 8, and 10 mm) above the annular plane using a perfect circle defined by 3 points at the valve commissures, allowing for an estimation of the anatomical aortic annulus **(Figure 1)**.

The LVOT zone was defined as the region extending from 6 mm below the annulus to the annular plane, while the anatomical aortic annulus zone extended from the virtual annular plane to 10 mm above it. To assess the adequacy of anchoring forces, we established the following criteria using a 10% oversizing rate as the cutoff:

- For the LVOT zone, the bottom diameter of the transcatheter heart valve (THV) was used as a reference. The LVOT was considered to provide adequate anchoring force if at least 4 mm of the 6 mm LVOT zone allowed for a THV oversizing rate ≥10%.
- Similarly, the anatomical aortic annulus zone was considered capable of providing adequate anchoring force if at least 4 mm met the 10% oversizing criterion.

Abbreviations

AR	aortic regurgitation
CT	computed tomography
LVEDD	left ventricular end-diastolic diameter
LVESD	left ventricular end-systolic diameter
LVOT	left ventricular outflow tract
MDCT	multidetector computed tomography
NYHA	New York Heart Association
STJ	sinotubular junction
TAVI	transcatheter aortic valve implantation
THV	transcatheter heart valve

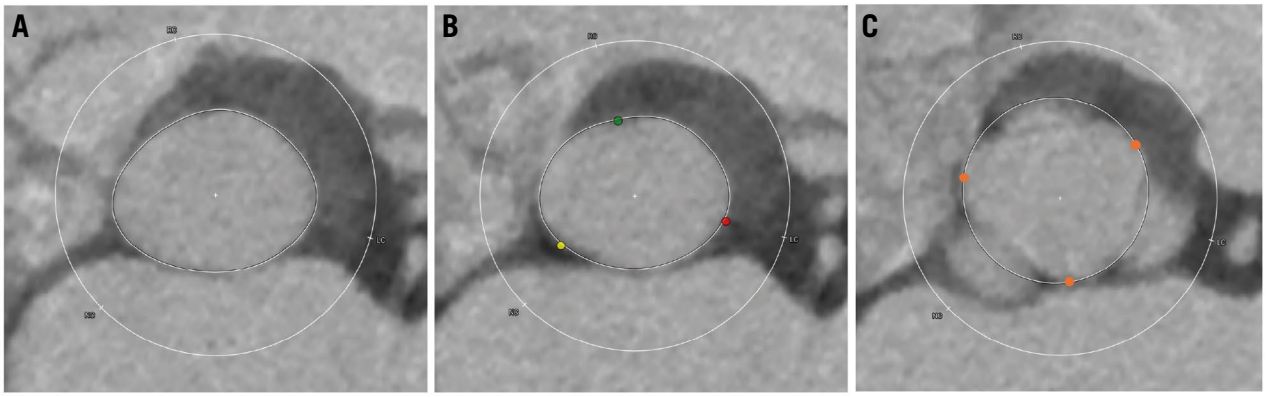


Figure 1. *Multiplanar measurement in preprocedural CT. A) Left ventricular outflow tract and subannular plane measurements using standard techniques. B) Virtual annular plane measurement using the standard technique, defined by the plane connecting the three nadirs of the aortic sinuses (red dot: the nadir of the left coronary sinus; green dot: the nadir of the right coronary sinus; yellow dot: the nadir of the non-coronary sinus). C) Supra-annular plane measurement using a perfect circle defined by the three commissural points (orange dots). CT: computed tomography*

- For the ascending aorta, the circumference was measured 40 mm above the annulus and compared to the diameter at the top of the THV. The ascending aorta was deemed adequate to provide anchoring force if the THV's top portion exceeded a 10% oversizing rate at this location.

Based on these criteria, anatomical classification was performed as follows **(Figure 1)**:

- AURORA type 1: all three zones (LVOT, annulus, and ascending aorta) are capable of providing adequate anchoring force;
- AURORA type 2: only the annulus and the ascending aorta are capable of providing adequate anchoring force;
- AURORA type 3: only the LVOT and the annulus are capable of providing adequate anchoring force;
- AURORA type 4: only one zone, or no zones, can provide adequate anchoring force.

TAVI STRATEGY AND PROCEDURE

In this study, all procedures were performed using the VitaFlow Valve (MicroPort), a domestic self-expanding TAVI device[12]. A multidisciplinary Heart Team conducted the interventions in a hybrid catheterisation laboratory under fluoroscopic guidance. Patients were administered either local anaesthesia or general anaesthesia with intubation, depending on the clinical indication. Transfemoral procedures followed standard protocols[13,14], with valve sizing and deployment strategies recommended by the Anzhen Hospital Core Laboratory.

The technical protocol[8] employed during the procedure included rapid pacing at 180 beats per minute to reduce regurgitation volume and systolic blood pressure. Deployment strategies were adapted based on the anatomical classification: for type 2 anatomy, rapid pacing was maintained throughout both stages of deployment to improve THV stability. For type 1 and type 3 anatomies, rapid pacing continued until two-thirds of the THV frame was deployed. Deployment was completed only after confirmation of the correct positioning at the angiography **(Figure 2)**. In cases of significant paravalvular regurgitation following initial THV deployment, a second THV could be implanted to address paravalvular leak, valve malposition, or to prevent embolisation of the first valve into the left ventricle.

BIOMECHANICAL ANALYSIS

Patient-specific computer simulations were conducted using finite element analysis (FEA) to predict device-host interactions during deployment. This platform integrates both the geometric and mechanical properties of the device and the patient's anatomy. The device model was reconstructed based on manufacturer-provided data (MicroPort). Patient-specific anatomy was segmented from preoperative MDCT images, with assigned mechanical elastic properties for each anatomical structure: native aortic wall (E=0.6 MPa, v=0.3), native leaflet tissue (E=2 MPa, v=0.45) and calcium nodules (E=4 MPa, v=0.3, yield stress=0.6 MPa). These details have been previously described[15,16].

The outward force exerted on the frame was calculated for each patient, and the total outward force was evaluated across 3 regions: the LVOT region, the anatomical annulus region, and the ascending aorta region **(Figure 3)**.

STATISTICAL ANALYSIS

Statistical analysis was performed using SPSS, version 21.0 (IBM). Continuous variables are expressed as mean±standard deviation and were compared using either the unpaired Student's t-test or the Mann-Whitney U test, depending on the data distribution. Categorical variables are presented as frequencies with corresponding percentages and were compared using the χ^2 test or Fisher's exact test, as appropriate.

Results

BASELINE CLINICAL CHARACTERISTICS

From February 2020 to March 2022, a total of 187 patients were screened for eligibility. Following anatomical assessment of the 187 screened patients using the AURORA classification system, 87 (46.5%) were classified as AURORA type 4 and were excluded from the study, resulting in 100 patients with anatomical types 1-3 being enrolled from 16 centres across China. The

excluded patients were characterised by insufficient anchoring zones according to our prespecified criteria. The majority of these patients had either inadequate anchoring in multiple zones or anatomical dimensions that exceeded the available THV sizing ranges. Common anatomical features leading to exclusion included excessive LVOT dimensions, significant dilation of the ascending aorta, or a combination of unfavourable measurements across multiple zones that would prevent stable valve anchoring. The study included both tricuspid and bicuspid aortic valve anatomies. Among the 100 enrolled patients, 98 had tricuspid anatomy, while only 2 had bicuspid anatomy. Given the small number of bicuspid cases, a subgroup analysis based on valve morphology was not performed. Regardless of valve morphology, all patients were assessed using the same AURORA classification criteria for anatomical suitability.

The study cohort (n=100) had a mean age of 72.7±7.2 years, with a male predominance (63%). The mean Society of Thoracic Surgeons Predicted Risk of Mortality score was 9.10±5.81%, indicating a high surgical risk. Hypertension was present in 64% of patients, and 28% had atrial fibrillation. Preprocedural echocardiography revealed a mean left ventricular ejection fraction of 53.02±10.65% and a mean left ventricular end-systolic diameter (LVESD) of 43.52±10.45 mm. Most patients (64%) were in New York Heart Association (NYHA) Functional Class III or IV at baseline. The distribution of AURORA classifications was as follows: 40 patients (40%) were type 1, 8 patients (8%) were type 2, and 52 patients (52%) were type 3. Anatomical characteristics differed significantly between types, with type 3 patients showing larger ascending aortic diameters

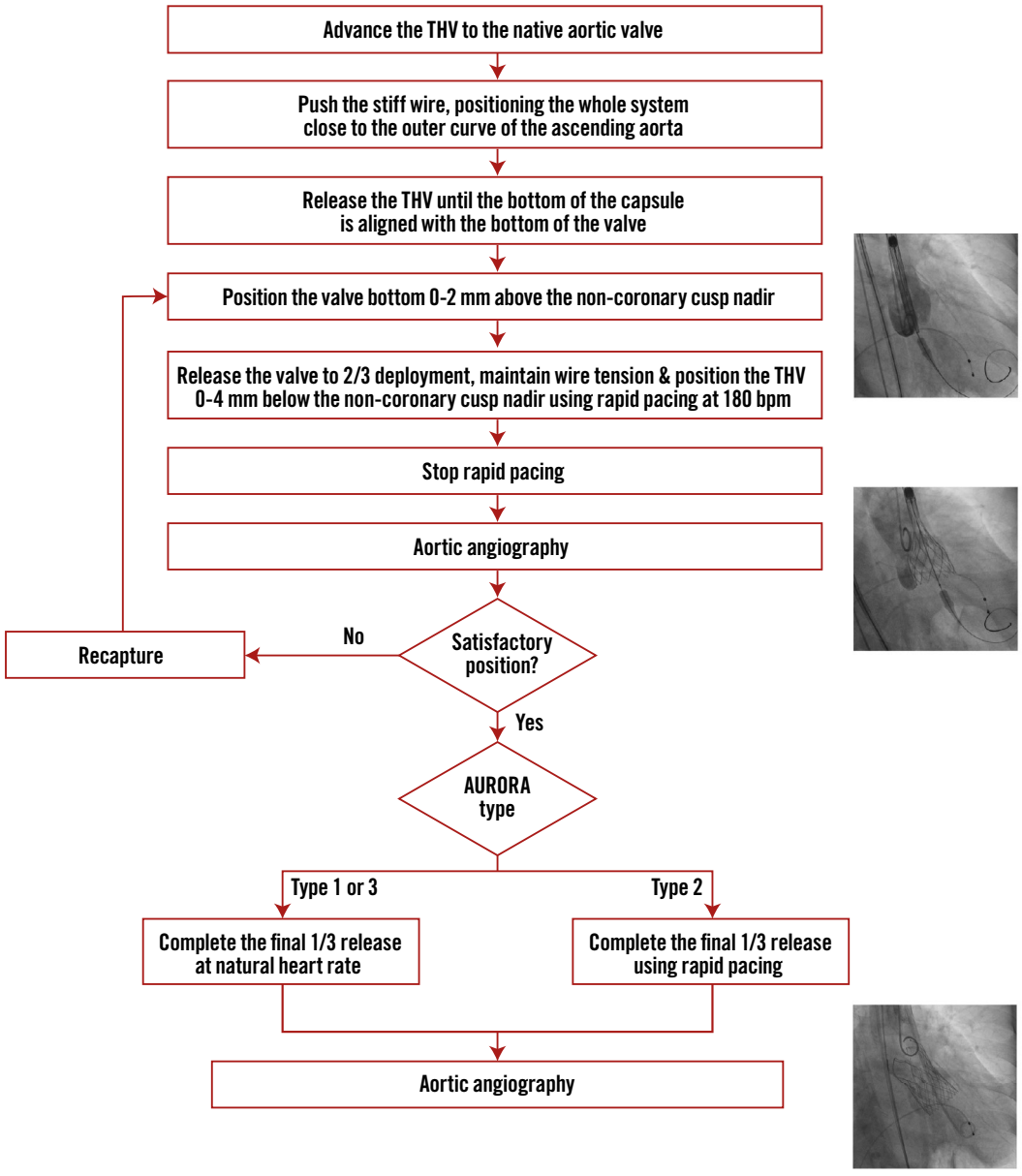


Figure 2. *Step-by-step TAVI procedure using the AURORA protocol. bpm: beats per minute; TAVI: transcatheter aortic valve implantation; THV: transcatheter heart valve*

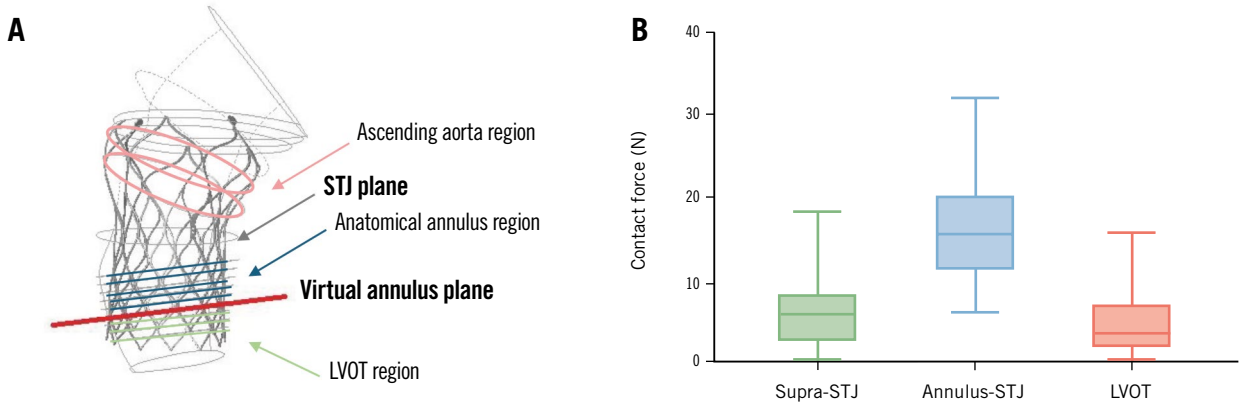


Figure 3. *Biomechanical analysis. A) Patient-specific computer simulation showing the 3 anatomical regions. B) Contact force distribution calculated using the finite element analysis, demonstrating significantly higher forces in the anatomical annulus region compared to other regions. LVOT: left ventricular outflow tract; STJ: sinotubular junction*

(41.29±3.47 mm) compared to type 1 (34.84±2.40 mm) and type 2 (35.40±1.85 mm; p<0.001) patients. Device success rates were comparable across all types, with 93% in type 1, 100% in type 2, and 88% in type 3 (p=0.663) **(Central illustration)**.

Baseline clinical characteristics are summarised in **Table 1**.

CLINICAL OUTCOMES

The primary efficacy endpoint, defined as device success, was achieved in 91 cases (91%). Nine patients required a second valve implantation (valve-in-valve) due to suboptimal initial results. One case involved displacement of the first valve into the ascending aorta, while 8 cases were attributed to excessive implantation depth. Additionally, 1 patient required surgical intervention due to heart failure resulting from paravalvular leak. Notably, all 9 device failures occurred within the first two-thirds of the trial cohort, with no device failures observed in the final third, suggesting a significant learning curve effect.

The 30-day safety outcomes were favourable, with no procedure-related mortality, major bleeding events, or renal failure. The stroke rate was 3%, affecting three patients, while 9 patients (9%) required a new permanent pacemaker implantation **(Central illustration)**. New left bundle branch block developed in 8 patients (8%), and 2 patients (2%) were hospitalised due to heart failure. Thirty-day clinical outcomes are summarised in **Table 2**.

Clinical follow-up demonstrated significant improvements in patient symptoms and cardiac function. Left ventricular remodelling was observed at 1-year follow-up, with a significant reduction in LVESD from 43.52±8.48 mm to 31.13±4.15 mm (p<0.001), accompanied by a corresponding improvement in left ventricular end-diastolic diameter (LVEDD) **(Figure 4)**. At 30 days post-procedure, NYHA Functional Class distribution was as follows: 28 patients in Class I, 65 in Class II, and 7 in Class III, with no patients remaining in Class IV. At 1-year follow-up, 94 of the initial 100 patients completed echocardiographic and functional evaluations, with 35 patients in Class I, 55 in Class II, and 4 in Class III. The remaining 6 patients were lost to follow-up or deceased. Among those followed, 85% demonstrated an improvement of at least 1 NYHA Class from baseline **(Figure 4)**.

POSTPROCEDURAL CT RESULTS

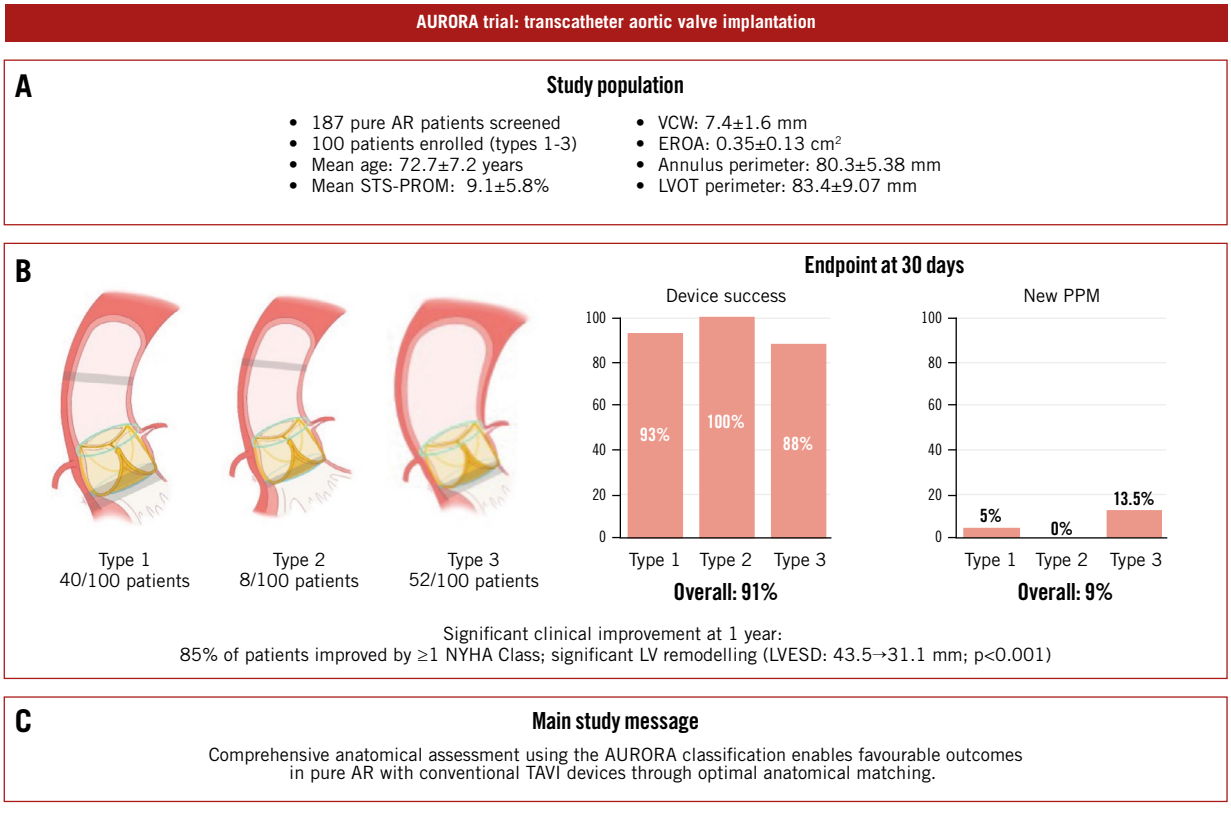
Postprocedural CT analysis was performed in 52 patients, with FEA completed in 43 cases. Nine patients were excluded due to valve-in-valve implantation or inadequate image quality. The mean THV implantation depth was 8.30±3.63 mm below the virtual annular plane. The maximum contact force was primarily localised between the annulus and the sinotubular junction (STJ; anatomical annulus) in 36 of 43 patients (83.7%). Contact forces in the anatomical annulus region were significantly higher compared to those observed in the LVOT and ascending aorta regions. These biomechanical findings provide strong support for the AURORA classification system, underscoring the importance of comprehensive anatomical assessment for optimal THV anchoring **(Figure 3)**.

Discussion

TAVI in patients with pure AR has historically posed significant technical challenges, primarily due to inadequate anchoring forces between the THV and native structures. This limitation has resulted in relatively low device success rates and a high incidence of moderate or greater paravalvular leak. The AURORA trial introduces an innovative approach to TAVI in pure AR by moving beyond the traditional single-plane virtual annulus assessment. Rather than relying solely on annular measurements and aggressive oversizing, this study incorporated a multiplanar evaluation of anatomical structures to optimise THV anchoring. This comprehensive anatomical assessment yielded two key outcomes: a high device success rate (91%) and a notably low permanent pacemaker implantation rate (9%). These findings suggest that detailed multiplanar anatomical evaluation may be more effective than conventional oversizing strategies in achieving stable THV anchoring while minimising complications. Additionally, biomechanical analysis confirmed this approach by demonstrating that contact forces were predominantly concentrated within the anatomical zones defined by our classification system.

EuroIntervention — Central **Illustration**

AURORA trial: transcatheter aortic valve implantation in pure aortic regurgitation.



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A) Study population. B) Key results stratified by the AURORA anatomical classification. C) Take-home message. AR: aortic regurgitation; AURORA: Anatomical classification and dUal anchoRing theory to Optimize the tavR strategy for pure severe Aortic regurgitation; EROA: effective regurgitant orifice area; LV: left ventricular; LVESD: left ventricular end-systolic diameter; LVOT: left ventricular outflow tract; NYHA: New York Heart Association; PPM: permanent pacemaker; STS-PROM: Society of Thoracic Surgeons Predicted Risk of Mortality; TAVI: transcatheter aortic valve implantation; TAVR: transcatheter aortic valve replacement; VCW: vena contracta width

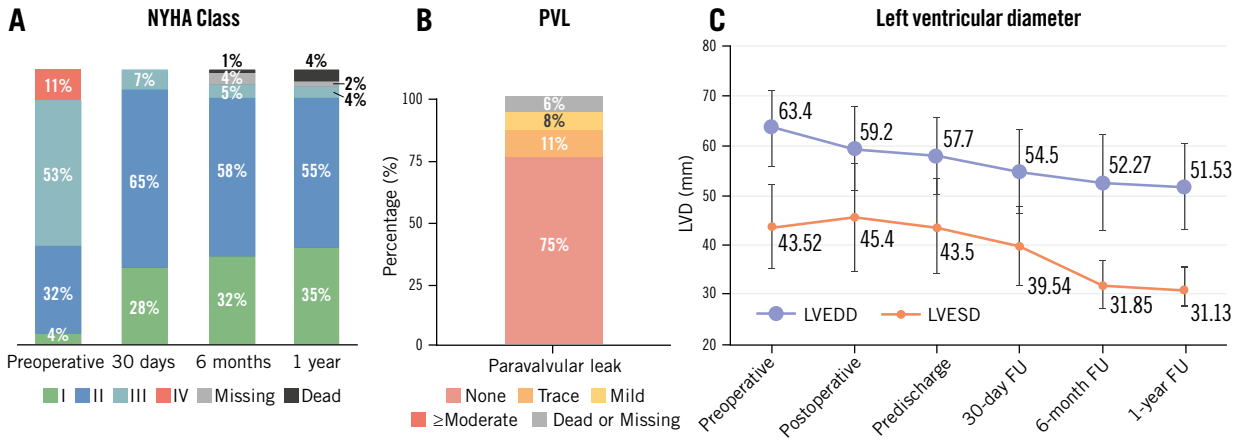

Figure 4. *Clinical outcomes. A) Improvement in NYHA Functional Class at 1-year follow-up. B) Absence of moderate or severe PVL at 1-year follow-up. C) Reduction in left ventricular diameters at follow-up. FU: follow-up; LVEDD: left ventricular end-diastolic diameter; LVESD: left ventricular end-systolic diameter; NYHA: New York Heart Association; PVL: paravalvular leak*

Table 1. Baseline clinical characteristics.

Characteristics	Patients (n=100)	Type 1 n=40	Type 2 n=8	Type 3 n=52	*p*-value
Age, years	72.74±7.16	72.30±7.56	69.25±7.30	73.69±6.87	0.230
Female sex	37 (37)	12 (30)	5 (63)	20 (39)	0.222
BMI, kg/m^2	22.94±3.45	22.41±3.21	23.04±2.51	23.33±3.75	0.460
BSA, m^2	1.64±0.17	1.65±0.17	1.61±0.14	1.64±0.17	0.835
AF	28 (28)	7 (17.5)	2 (25.0)	19 (36.54)	0.170
COPD	9 (9)	2 (5.0)	1 (12.5)	6 (11.5)	0.464
Prior permanent pacemaker	3 (3)	1 (2.5)	1 (12.5)	1 (1.9)	0.284
Prior myocardial infarction	5 (5)	1 (2.5)	0 (0)	4 (7.7)	0.393
Prior PCI	18 (18)	7 (17.5)	1 (12.5)	10 (19.2)	1.000
Prior CABG	0 (0)	0 (0)	0 (0)	0 (0)	1.000
Diabetes	9 (9)	5 (12.5)	1 (12.5)	3 (5.8)	0.491
Prior stroke	13 (13)	6 (15.0)	1 (12.5)	6 (11.5)	0.901
Hyperlipidaemia	21 (21)	9 (22.5)	2 (25.0)	10 (19.2)	0.809
Hypertension	64 (64)	23 (57.5)	6 (75.0)	35 (67.3)	0.534
Peripheral vascular disease	26 (26)	9 (22.5)	2 (25.0)	15 (28.8)	0.881
Smoker	24 (24)	7 (17.5)	1 (12.5)	16 (30.8)	0.343
Prior LBBB	3 (3)	2 (5.0)	0 (0)	1 (1.9)	0.672
Prior RBBB	3 (3)	1 (2.5)	0 (0)	2 (3.8)	0.897
STS-PROM score, %	9.10±5.81	9.93±6.07	7.37±2.55	8.76±6.00	0.460
KCCQ score	58.26±18.64	63.37±17.60	58.35±12.21	53.96±19.67	0.166
6-minute walk distance, m	309.93±148.23	292.14±87.68	270.50±66.31	325.61±178.73	0.760
eGFR, ml/min/1.73 m^2	94.91±37.30	95.44±43.56	99.35±31.35	93.78±33.14	0.921
NT-proBNP, pmol/L	2,464.13±5,268.72	1,372.01±2,636.40	4,388.25±7,198.60	3,055.43±6,385.37	0.191
NYHA Class					
I	4 (4)	0 (0)	0 (0)	4 (7.7)	0.144
II	32 (32)	17 (42.5)	0 (0)	15 (28.8)	0.046
III	53 (53)	22 (55)	7 (87.5)	24 (46.2)	0.094
IV	11 (11)	1 (2.5)	1 (12.5)	9 (17.3)	0.089
Echocardiographic and CT characteristics					
LVEF, %	53.02±10.65	53.66±10.64	43.67±11.92	53.96±9.97	0.033
LVEDD, mm	60.95±8.00	59.88±9.27	65.01±12.05	61.17±5.75	0.245
LVESD, mm	43.52±10.45	41.70±10.49	52.96±13.37	43.25±9.11	0.033
VCW, cm	0.74±0.16	0.72±0.17	0.70±0.08	0.77±0.17	0.315
EROA, cm^2	0.35±0.13	0.36±0.14	0.31±0.05	0.35±0.13	0.371
MR moderate to severe	33 (33)	10 (25)	3 (37.5)	20 (38.5)	0.236
TR moderate to severe	18 (18)	9 (22.5)	1 (12.5)	8 (15.4)	0.708
Annulus perimeter, mm	80.34±5.38	80.34±4.95	85.21±5.91	79.60±5.33	0.021
Angle, °	54.87±10.78	52.23±10.42	48.25±12.28	57.98±9.96	0.007
LVOT perimeter, mm	83.40±9.07	82.41±6.28	102.26±10.91	81.25±7.21	0.000
Ascending aortic diameter, mm	38.24±4.35	34.84±2.40	35.40±1.85	41.29±3.47	0.000
STJ diameter, mm	34.51±4.63	31.42±2.74	31.76±1.99	37.31±4.32	0.000
Left coronary sinus or major axis, mm	35.62±4.06	34.49±3.83	32.21±3.20	37.01±3.82	0.000
Right coronary sinus or minor axis, mm	34.58±4.24	32.85±3.80	34.23±4.66	35.96±4.07	0.002
Non-coronary sinus, mm	35.63±4.00	34.34±4.06	33.76±4.13	36.90±3.56	0.003

Variables are given as numbers (percentage) or mean value±SD. AF: atrial fibrillation; BMI: body mass index; BSA: body surface area; CABG: coronary artery bypass grafting; COPD: chronic obstructive pulmonary disease; CT: computed tomography; eGFR: estimated glomerular filtration rate; EROA: effective regurgitant orifice area; KCCQ: Kansas City Cardiomyopathy Questionnaire; LBBB: left bundle branch block; LVEDD: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; LVESD: left ventricular end-systolic diameter; LVOT: left ventricular outflow tract; MR: mitral regurgitation; NT-proBNP: N-terminal pro-brain natriuretic peptide; NYHA: New York Heart Association; PCI: percutaneous coronary intervention; RBBB: right bundle branch block; SD: standard deviation; STJ: sinotubular junction; STS-PROM: Society of Thoracic Surgeons Predicted Risk of Mortality; TR: tricuspid regurgitation; VCW: vena contracta width

Postprocedural CT analysis, combined with FEA, provided critical validation of our anatomical classification system. The findings indicated that the maximum contact forces were primarily localised between the virtual annulus and the STJ, specifically within the region encompassing the anatomical annulus and native leaflets. This biomechanical evidence supports the hypothesis that a comprehensive anatomical assessment is essential for optimising THV anchoring.

The AURORA classification system offers several key advantages. First, it enhances patient selection in regions where AR-dedicated valves are unavailable – such as mainland China – by delivering outcomes comparable to those with

Table 2. Thirty-day clinical outcomes.

Endpoints at 30 days	Patients (n=100)	Type 1	Type 2	Type 3	*p*-value
Primary efficacy endpoint					
Device success	91 (91)	37 (93)	8 (100)	46 (88)	0.663
Primary safety endpoints					
Death	0 (0)	0 (0)	0 (0)	0 (0)	1.000
Cardiac death	0 (0)	0 (0)	0 (0)	0 (0)	1.000
Stroke	3 (3)	2 (5.0)	0 (0)	1 (1.9)	0.672
Surgery related to device	1 (1)	0 (0)	0 (0)	1 (1.9)	1.000
MI	0 (0)	0 (0)	0 (0)	0 (0)	1.000
Renal failure	0 (0)	0 (0)	0 (0)	0 (0)	1.000
Rehospitalisation due to heart failure	2 (2)	1 (2.5)	0 (0)	1 (1.9)	1.000
New LBBB	8 (8)	3 (7.5)	1 (12.5)	4 (7.7)	0.729
New permanent pacemaker	9 (9)	2 (5)	0 (0.0)	7 (13.5)	0.336
Major or life-threatening bleeding	0 (0)	0 (0)	0 (0)	0 (0)	1.000
Major vascular complication	0 (0)	0 (0)	0 (0)	0 (0)	1.000

Variables are given as numbers (percentage). LBBB: left bundle branch block; MI: myocardial infarction

dedicated devices. Second, it establishes a framework for future valve design, emphasising the importance of multiple anchoring zones along the aortic root.

A particularly noteworthy outcome was the low permanent pacemaker implantation rate of 9%, which is significantly lower than previously reported aortic regurgitation TAVI rates[17,18] and those reported by studies evaluating dedicated AR valves[19]. This favourable outcome can be attributed to our strategic focus on anatomical compatibility rather than aggressive oversizing. By prioritising native structural length with a 10% oversizing threshold over maximal oversizing rates, we achieved stable anchoring while minimising the pressure on the conduction system. Furthermore, emphasising anatomical annulus anchoring facilitated controlled THV deployment depths, further reducing conduction system injury risk.

The observed 3% stroke rate in our study is comparable to the 2% rate reported in the recent ALIGN-AR Trial[19]. Although our protocol, which includes rapid pacing and potential valve recapturing, could theoretically increase stroke risk, differences in patient populations, device characteristics, and the study's limited sample size preclude a direct statistical comparison.

The cylindrical frame design of the VitaFlow Valve, distinct from more tapered self-expanding valves, may have contributed to our favourable outcomes by optimising contact with the anatomical annulus tissue, thereby enhancing anchoring forces. While dedicated AR devices primarily achieve stabilisation through specialised anchoring mechanisms in the aortic sinuses, the AURORA classification may still provide valuable anatomical insights. Although originally developed for conventional THVs, its systematic evaluation of multiple anatomical zones could aid in optimising sizing strategies even for dedicated AR devices, particularly in complex anatomies where relying solely on virtual annulus measurements may be inadequate.

Limitations

Despite these promising results, several limitations must be acknowledged. The study's single-arm, non-blinded, and non-randomised design introduces potential bias. Furthermore, the AURORA classification system has only been tested with the VitaFlow Valve system (MicroPort), and its applicability to other TAVI devices requires further validation. Future randomised controlled trials comparing this approach with AR-dedicated valves will be necessary to establish more robust evidence. Additionally, longer-term follow-up is required to assess the durability of these promising early outcomes.

Conclusions

In conclusion, the AURORA trial demonstrates that comprehensive anatomical assessment and strategic device positioning enable favourable outcomes in pure AR cases using conventional THVs. This approach not only provides an immediate solution for regions lacking AR-dedicated valves but also offers valuable insights for future device development. The low pacemaker implantation rate suggests that optimal anatomical matching may be superior to aggressive oversizing strategies, reinforcing the importance of detailed anatomical evaluation in TAVI procedures.

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Conflict of interest statement

The authors have no conflicts of interest to declare.

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FFRangio-guided versus pressure wire-guided PCI: design and rationale of the multicentre, randomised ALL-RISE trial

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ABSTRACT

Wire-based indices of coronary physiology are the gold standard for guiding revascularisation decisions in patients with coronary artery disease and angiographically intermediate coronary stenoses. FFRangio is a novel angiography-based technology for assessing the functional significance of epicardial coronary stenoses without pressure wires or hyperaemic stimulus. The primary objective of the Advancing Cath Lab Results with FFRangio Coronary Physiology Assessment trial (ALL-RISE; ClinicalTrials.gov: NCT05893498) is to compare clinical outcomes in patients with chronic coronary syndromes or non-ST-segment elevation acute coronary syndromes undergoing coronary angiography with ≥1 coronary lesion suitable for physiological assessment. Patients will be randomised to FFRangio-guided or to pressure wire-guided treatment. The primary endpoint is the occurrence of major adverse cardiovascular events (MACE) at 1 year (a composite of all-cause death, myocardial infarction, or unplanned clinically driven revascularisation), assessed for non-inferiority of FFRangio-based versus pressure wire-based guidance. If non-inferiority is met, reflex superiority guidance will be tested. Secondary endpoints include periprocedural and early complications up to 30 days, individual components of MACE at 1 year, patient-reported health status, procedural resource utilisation and healthcare-related costs, and operator-assessed usability of the FFRangio and pressure wire systems. With a sample size of 1,924 patients, the study has 82.7% power to assess non-inferiority with a non-inferiority margin of 3.5%. The ALL-RISE trial will provide prospective clinical outcomes data on the relative safety, efficacy, and cost-effectiveness of a workflow using FFRangio as compared with pressure wire-based approaches for coronary lesion assessment among patients being considered for percutaneous coronary intervention.

KEYWORDS: FFRangio; major adverse cardiovascular events; pressure wire; randomised clinical trial; trial design

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Pressure wire-based indices of coronary physiology are the gold standard for invasively guiding revascularisation decisions in patients with coronary artery disease and angiographically intermediate coronary stenoses[1,2]. Multiple studies have shown that fractional flow reserve (FFR; the ratio of the distal coronary pressure to the aortic pressure during maximal hyperaemia) is superior to coronary angiography alone for guiding revascularisation of angiographically intermediate lesions[3-8]. Non-hyperaemic pressure ratios (NHPRs; e.g., instantaneous wave-free ratio [iFR], resting full-cycle ratio, and diastolic pressure ratio) have also been developed and validated in recent years[9-12]. Accordingly, both the American and European revascularisation guidelines recommend using pressure wire-based physiology to guide the treatment strategy in stable coronary lesions[13,14]. However, despite multiple randomised clinical trials and guideline recommendations supporting its use, pressure wire-based physiological assessment continues to be underutilised in contemporary practice due to several factors, including additional procedural time, instrumentation of coronary vessels, and paucity of reimbursement[15,16].

Several angiography-based approaches for assessing the functional significance of coronary stenoses have recently been introduced and validated against pressure wire-based FFR[11,17-22]. However, some of these modalities require considerable manual interaction and a relatively long processing time for practical application in the cardiac catheterisation laboratory[11,17-20]. The FFRangio System (CathWorks) is a novel technology that provides three-dimensional functional mapping of the coronary arteries using routine diagnostic angiograms. It employs a resistance-based model to calculate coronary flow, requires three angiograms to maximise diagnostic accuracy, and utilises artificial intelligence to minimise the manual steps required to perform an analysis.

In the prospective FAST-FFR validation study, FFRangio, a novel angiography-based functional assessment, was compared with pressure wire-derived FFR and demonstrated excellent concordance with both wire-based FFR results and their threshold-based interpretation[23]. Additional studies have confirmed the concordance between FFRangio and wire-based FFR, including the assessment of non-culprit lesions in non-ST-segment elevation acute coronary syndrome (NSTE-ACS)[24]. In data from 492 patients, the use of FFRangio to guide clinical decisions had comparable 1-year outcomes to those reported previously for wire-based FFR[25].

However, there is a paucity of data evaluating clinical outcomes with FFRangio-guided treatment, particularly in direct comparison with the gold standard of pressure wire-based physiology. The primary objective of the ALL-RISE trial is to test whether FFRangio-guided treatment is non-inferior to pressure wire-guided treatment with respect to major adverse cardiovascular events (MACE) at 1 year in patients with coronary artery disease who are being evaluated for possible percutaneous coronary intervention (PCI). Secondary objectives include assessments of procedure time, contrast and resource utilisation, and the cost-effectiveness of FFRangio-guided treatment versus pressure wire-guided treatment.

Methods

DESIGN OF THE ALL-RISE TRIAL

The Advancing Cath Lab Results with FFRangio Coronary Physiology Assessment trial (ALL-RISE; ClinicalTrials.gov: NCT05893498) is a prospective, multicentre, 1:1 randomised, open-label trial with blinded event adjudication to test whether FFRangio-guided treatment is non-inferior to conventional pressure wire-guided treatment for preventing MACE in patients with coronary artery disease being evaluated for possible PCI **(Figure 1)**.

The study is funded by CathWorks, Inc., and is being conducted at up to 60 sites globally (USA, Israel, Japan, Switzerland, and the United Kingdom), with a maximum of 200 patients randomised per site. At least 60% of patients will be enrolled in the USA. Independent analytic groups at the Cardiovascular Research Foundation (New York, NY, USA) will oversee a clinical events adjudication committee, a data safety monitoring board, an angiographic core laboratory, and a coronary physiology core laboratory.

STUDY POPULATION

The study will enrol 1,924 patients with chronic coronary syndromes (CCS) or NSTE-ACS undergoing coronary angiography with at least 1 coronary lesion deemed appropriate for physiology-based assessment. Patients must meet all inclusion criteria and none of the exclusion criteria listed in **Table 1** to be enrolled. Briefly, patients must be ≥18 years old and present with an accepted indication for PCI with 1 or more study lesions (angiographic visual diameter stenosis 50-90%) deemed appropriate for PCI and for both pressure wire and FFRangio physiological assessment. A study lesion is defined as the assessed coronary segment that includes a portion with a luminal diameter stenosis between 50% and 90% based on visual angiographic assessment. A study vessel is defined as the entire major assessed coronary vessel, including side branches.

Patients with prior coronary artery bypass grafting (CABG) with patent grafts to the study vessels and patients undergoing coronary physiology assessment as part of assessment for possible CABG (i.e., in whom CABG may be recommended based on the outcome of the physiology assessment) will not be eligible. Patients with severe left-sided valvular heart disease will also not be eligible for enrolment. Other exclusion

Abbreviations

ARC	Academic Research Consortium	**FFRangio**	angiography-derived fractional flow reserve	**NHPR**	non-hyperaemic pressure ratio
CABG	coronary artery bypass grafting	**iFR**	instantaneous wave-free ratio	**NSTE-ACS**	non-ST-segment elevation acute coronary syndrome
CCS	chronic coronary syndrome	**MACE**	major adverse cardiovascular events	**PCI**	percutaneous coronary intervention
FFR	fractional flow reserve	**MI**	myocardial infarction		

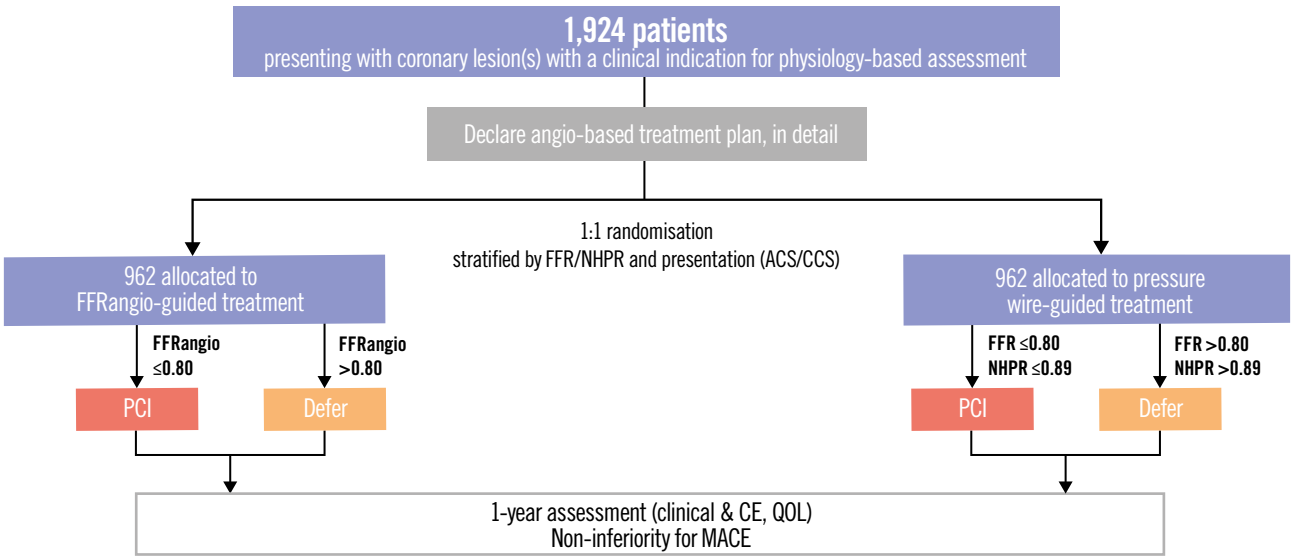

Figure 1. *Study CONSORT diagram. ACS: acute coronary syndrome; CCS: chronic coronary syndrome; CE: clinical events; FFR: fractional flow reserve; FFRangio: angiography-derived FFR; MACE: major adverse cardiovascular events; NHPR: non-hyperaemic pressure ratio; QOL: quality of life*

Table 1. Eligibility criteria.

Inclusion criterion
Adult patients (≥18 years of age) with 1 or more study lesion(s) (diameter stenosis 50-90%) deemed appropriate for both pressure wire and FFRangio physiological assessment
Exclusion criteria
General exclusion criteria
Subject with STEMI within the previous 72 hours of study enrolment
Prior CABG with patent grafts to study vessel(s)
Patients undergoing coronary physiological assessment where one possible outcome is referral for CABG
Study vessel supplying a significant non-viable territory (e.g., prior transmural MI)
Severe left-sided valvular heart disease
Most recent documented LVEF ≤30%
Women who are pregnant or breastfeeding (women of childbearing potential are required to have a negative pregnancy test within 1 week of index procedure)
Patients with life expectancy <1 year as estimated by the treating physician
Subjects enrolled in other ongoing non-registry clinical studies that would impact the conduct or outcomes of this study (registries and long-term follow-up of other studies are allowed)
Subjects who have undergone angiography- or wire-based coronary physiological assessment for 1 or more potential study lesions within 30 days of enrolment
Angiographic exclusion criteria
Coronary angiograms not acquired per instructions as defined in the study protocol
Study lesion is the clear culprit for an NSTE-ACS
Angiographic evidence of procedural complication (e.g., acute stent thrombosis, flow-limiting dissection, perforation, slow/no reflow) prior to randomisation
TIMI 2 flow or lower in study vessel at time of enrolment
Study vessel is in a left coronary vessel with a separate left anterior descending and left circumflex ostia arising from the aorta (i.e., no left main coronary artery)
Study lesion involves left main coronary artery (stenosis ≥50%)
Study lesion is in an ectatic or aneurysmal coronary segment (defined as a lumen diameter 1.5 times the diameter of the reference vessel)

CABG: coronary artery bypass grafting; CCS: chronic coronary syndrome; FFRangio: angiography-derived fractional flow reserve; LVEF: left ventricular ejection fraction; MI: myocardial infarction; NSTE-ACS: non-ST-segment elevation acute coronary syndrome; PCI: percutaneous coronary intervention; STEMI: ST-segment elevation myocardial infarction; TIMI: Thrombolysis In Myocardial Infarction

criteria include study lesions in the left main coronary artery and Thrombolysis in Myocardial Infarction flow grade 2 or lower in a study vessel. For patients presenting with NSTE-ACS, clear culprit lesions are not eligible for inclusion, but non-culprit lesions may be considered as study lesions. Non-study lesions must be treated without complication prior to randomisation.

PRIMARY AND SECONDARY ENDPOINTS

The primary endpoint is the incidence of MACE at 1 year, defined as the composite of all-cause death, myocardial infarction (MI), or unplanned clinically driven revascularisation. For the principal analysis of the primary endpoint, spontaneous MI will be adjudicated according to the 4th Universal Definition of MI, and Type 4 MI will be adjudicated according to the Academic Research Consortium (ARC)-2 definition of periprocedural MI **(Table 2)**.

Secondary endpoints include periprocedural complications and 30-day adverse events, individual components of MACE at 1 year, procedure duration and resource utilisation, patient-reported health status, healthcare-related costs, and usability of the FFRangio and pressure wire systems. Exploratory analyses will assess the relationship between post-PCI FFRangio results and the risk of adverse clinical outcomes.

ENROLMENT AND RANDOMISATION

Patients who have signed an institutional review board/ethics committee-approved informed consent form and who have met all inclusion criteria and none of the exclusion criteria will be eligible for enrolment and randomisation. After obtaining the necessary angiograms, and prior to randomisation, the investigator will identify the vessels in which physiology is indicated (i.e., identify the study lesions which they plan to interrogate by wire-based physiology assessment if the patient is randomised to wire-based physiology), as well as which pressure wire-based physiological test will be performed (i.e., FFR or NHPR) if the patient is randomised to wire-based physiology. Prior to randomisation, the investigator will also declare, in detail, an angiography-based treatment plan for each such study lesion based on the angiographic information alone (i.e., whether they would perform or defer PCI) using a standardised case report form.

Block randomisation using permuted block sizes of 2 and 4 will be performed, with stratification by site, mode of pressure wire-based physiology test (FFR vs NHPR) and clinical presentation (NSTE-ACS vs CCS). Each patient will be randomised in a 1:1 fashion to either FFRangio or pressure wire-based coronary physiology assessment using an online tool (study database/electronic data capture). The subsequent treatment will be determined by the results of the assigned physiological test **(Figure 1)**. Crossover to the alternative physiological guidance system will be considered a protocol deviation.

STUDY PROCEDURES

Diagnostic coronary angiography will be performed per the standard of care at each site but should adhere to the requirements for FFRangio assessment outlined in **Supplementary Table 1** (technical requirements) and **Supplementary Figure 1** (recommended angiographic projections). Intracoronary nitroglycerine is recommended but not required.

PRESSURE WIRE-BASED MEASUREMENTS

For subjects randomised to a pressure wire-based assessment, the acquisition of diagnostic images, the intended treatment plan, and the diagnostic FFR/NHPR measurements will be performed according to the standard of care at each site, in accordance with the guidelines below. An anticoagulant such as intravenous heparin will be administered, as will intracoronary nitroglycerine. If FFR is performed, use of adenosine will be preferred. In sites where adenosine is not available, administration of adenosine triphosphate (ATP) or papaverine will be permitted. FFR/NHPR measurements will follow the steps outlined in **Supplementary Table 1**.

FFRANGIO MEASUREMENT

For subjects randomised to FFRangio-based assessment, the initial FFRangio measurement will be performed after acquisition of the routine diagnostic images and only after the intended treatment plan has been fully documented. If additional angiographic images are required to allow for FFRangio assessment, the number of additional angiograms used will be recorded. The process of assessing FFRangio is shown in **Supplementary Table 2**.

PCI PROCEDURE

Based on the results of either the wire-based physiological assessment or FFRangio, PCI will be performed on all haemodynamically significant lesions using established cutoff points **(Figure 1)**[23,26]. PCI procedures will be performed according to standard techniques as determined by the primary operator. Staged procedures are permitted within 60 days in vessels not treated during the index procedure as per ARC-2 recommendations[27]. If no PCI procedure is indicated, the patient will be treated with optimal medical therapy alone at the discretion of the treating physician.

POST-PCI CORONARY ANGIOGRAPHY AND FFRANGIO ASSESSMENT

Two post-PCI angiograms performed at two of the original pre-PCI views will be acquired in all patients, irrespective of randomised treatment arm. Offline post-PCI FFRangio analysis will be performed using the 2 post-PCI angiograms and a third pre-PCI angiogram in which the treated lesion will be "ignored" to derive a post-PCI FFRangio measurement.

FOLLOW-UP

Postprocedural electrocardiograms and cardiac biomarkers (troponin T, if available, or biomarkers per local site standard of care) will be acquired only if there is a clinical suspicion of procedural complication or periprocedural MI. Follow-up visits will be performed at 30 days, 6 months, and 1 year after randomisation. Medication use and adverse events will be assessed at each visit. Both generic and disease-specific quality of life will be assessed at baseline, 30 days, and 1 year using the EuroQol 5-dimension 5-level (EQ-5D-5L) questionnaire, and the Seattle Angina Questionnaire-7 (SAQ-7) **(Table 3)**.

STATISTICAL METHODS

The primary analysis will be performed based on the intention-to-treat (ITT) population.

Table 2. Definition of the primary endpoint.

Death	**Death events will be adjudicated by the CEC using Academic Research Consortium-2 definitions.**
Cardiovascular death	Cardiovascular death is defined as death resulting from cardiovascular causes. The following categories may be collected: Death caused by acute MI Death caused by sudden cardiac, including unwitnessed, death Death resulting from heart failure Death caused by stroke Death caused by cardiovascular procedures Death resulting from cardiovascular haemorrhage Death resulting from other cardiovascular causes
Non-cardiovascular death	Non-cardiovascular death is defined as any death that is not thought to be the result of a cardiovascular cause. The following categories may be collected: Death resulting from malignancy Death resulting from pulmonary causes Death caused by infection (including sepsis) Death resulting from gastrointestinal causes Death resulting from accident/trauma Death caused by other non-cardiovascular organ failure Death resulting from another non-cardiovascular cause
Undetermined cause of death	Undetermined cause of death is defined as a death not attributable to any other category because of the absence of any relevant source documents. Such deaths will be classified as cardiovascular for endpoint determination.
Myocardial infarction	
Post-PCI (Type 4a) periprocedural MI	Periprocedural MI will be adjudicated as per Academic Research Consortium-2 definitions as follows: Absolute rise in cardiac troponin (from baseline) ≥35 times upper reference limit (if creatine kinase MB is used, an absolute rise of ≥5 times the upper reference limit is required) Plus 1 (or more) of the following criteria: New significant Q waves or equivalent (≥40 ms in duration and ≥1 mm deep in voltage in 2 contiguous leads) Flow-limiting angiographic complications New "substantial" loss of myocardium on imaging
Spontaneous MI (MI Type 1)	Spontaneous MI (MI Type 1) will be defined based on the 4th Universal Definition of Myocardial Infarction. Spontaneous MI (Type 1) will be defined as the detection of a rise and/or fall of cardiac troponin values with at least 1 value above 99th upper reference limit and with at least 1 of the following: Symptoms of acute myocardial ischaemia New ischaemic electrocardiogram changes Development of pathological Q waves Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with ischaemic aetiology Identification of a coronary thrombus by angiography including intracoronary imaging or by autopsy
Spontaneous MI (MI Type 2)	Spontaneous MI (MI Type 2) will be defined based on the 4th Universal Definition of Myocardial Infarction. Spontaneous MI (Type 2) will be defined as the detection of a rise and/or fall of cardiac troponin values with at least 1 value above 99th upper reference limit, and evidence of an imbalance between myocardial oxygen supply and demand unrelated to acute coronary atherothrombosis, requiring at least 1 of the following: Symptoms of acute myocardial ischaemia New ischaemic ECG changes Development of pathological Q waves Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with ischaemic aetiology
Clinically indicated revascularisation	A revascularisation is clinically indicated if angiography at follow-up shows a percentage diameter stenosis ≥50% (by core lab QCA*) and if 1 of the following is present: History of recurrent angina pectoris (or anginal equivalent symptoms), presumably related to the study vessel Objective signs of ischaemia at rest (ECG changes or biomarker changes) or during stress/exercise test (or equivalent) presumably related to the study vessel Abnormal results of any invasive physiological test Asymptomatic with ≥70% DS by core lab QCA or, if core lab QCA is not available, ≥90% DS by visual estimate (site reported)

*The QCA core laboratory will be preferred for assessment of the clinically indicated revascularisation by the CEC. If QCA or angiograms are not available (e.g., due to imaging not being readable or angiogram permanently missing), then catheterisation core laboratory reports could be used for event adjudication of revascularisation. The CEC will determine whether revascularisation is clinically indicated or not for all types of revascularisation (study lesion, study vessel, and non-study vessel). CEC: clinical events committee; DS: diameter stenosis; ECG: electrocardiogram; MI: myocardial infarction; PCI: percutaneous coronary intervention; QCA: quantitative coronary analysis

Table 3. Schedule of activities.

Study requirement	Baseline	Index procedure	30±7 days	6 months±14 days*	1 year±30 days
Informed consent	X				
Demographics	X				
Eligibility criteria	X				
Medical history	X				
Clinical assessment	X[†]		X		X
Pregnancy test[‡]	X				
Electrocardiogram[§]	X				
SAQ-7	X		X		X
EQ-5D-5L QOL assessment	X		X		X
Medications	X	X	X	X	X
Coronary angiography		X			
Procedural information		X			
Randomisation (FFRangio or wire-based FFR/NHPR)		X			
PCI procedure (if appropriate)		X[‖]			
Record of adverse events		X	X	X	X

*Six-month assessment to be performed via phone consultation. [†]Clinical assessment includes cardiac biomarkers in acute coronary syndrome presentation. [‡]Pregnancy test for women of childbearing potential. [§]For subjects presenting with NSTE-ACS. [‖]PCI can be staged. EQ-5D-5L: EuroQol 5-dimension 5-level; FFR: fractional flow reserve; FFRangio: angiography-derived FFR; NHPR: non-hyperaemic pressure ratio; NSTE-ACS: non-ST-segment elevation acute coronary syndrome; PCI: percutaneous coronary intervention; QOL: quality of life; SAQ: Seattle Angina Questionnaire

PRIMARY ENDPOINT ANALYSIS

A Kaplan-Meier survival analysis will compare the 12-month cumulative incidence of MACE between FFRangio and pressure wire-based physiology. The Com-Nougue method will test the 1-sided non-inferiority hypothesis by evaluating whether the difference in event probabilities remains within the predefined non-inferiority margin. Based upon an estimated 12-month MACE rate of 7.5% in both study arms, using a 3.5% absolute non-inferiority margin and a 1-sided p-value<0.025, and assuming that 5% of patients will be lost to follow-up, a sample size of 1,924 evaluable patients is required to provide 82.7% power. Missing data will not be imputed in the primary analysis. If the primary endpoint analysis demonstrates non-inferiority of FFRangio, reflex superiority testing will also be performed (testing superiority of FFRangio over pressure wire-based assessment)[28].

Sensitivity analyses of the primary endpoint will be performed on the ITT and per-protocol populations using multiple imputation.

JUSTIFICATION OF THE NON-INFERIORITY MARGIN

Based on the available literature including clinical trials that have evaluated the use of coronary physiology to guide revascularisation, coronary stent trials, and other cardiovascular studies, the 1-year rate of the primary endpoint has been estimated to be 7.5% **(Table 4)**. The prespecified non-inferiority margin is 3.5%, which represents <50% of the expected 1-year event rate of 7.5%, and was based on what the Steering Committee agreed was an acceptable upper bound for non-inferiority. This non-inferiority margin is similar to the non-inferiority margins used in the iFR-SWEDEHEART (3.2%)[10] and DEFINE-FLAIR (3.4%)[9] trials, which compared two invasive, wire-based physiology measures; and the FAVOR III Europe trial (3.4%), which compared non-invasive quantitative flow ratio (QFR) versus invasive FFR for guiding coronary revascularisation[21].

SECONDARY ENDPOINT AND SUBGROUP ANALYSES

These analyses will be considered exploratory without adjustment for multiplicity. The primary and secondary endpoints will be compared across the subgroups listed in **Supplementary Table 3**.

ECONOMIC ANALYSES

In addition to the main clinical study, data from the ALL-RISE trial will be used to perform an analysis of the economic benefit of FFRangio compared with wire-based assessments. Hospital costs will be assessed for all patients based on procedural and hospitalisation resource utilisation and standard US costs for each resource (including procedural time). Follow-up costs will be assessed for inpatient and outpatient cardiovascular care, including diagnostic testing, emergency room visits, hospitalisations, and additional coronary revascularisation procedures.

Given the non-inferiority design of the ALL-RISE trial, major differences in follow-up events or "downstream costs" between the two treatment groups are not expected. As such, the primary economic analysis will focus on index procedural costs and index hospitalisation costs and their differences. A secondary analysis will examine follow-up healthcare-related costs and total 1-year costs (including the index hospitalisation).

STUDY STATUS AND ONGOING TRIALS OF OTHER ANGIO-BASED FFR SYSTEMS

ALL-RISE completed recruitment in January 2025. The primary endpoint is at 1 year.

Several other angiography-derived coronary physiology indices are currently being evaluated in prospective, randomised

Table 4. Clinical trials evaluating coronary physiology prior to revascularisation.

Study	Citation	Comparators	N1	N2	1-year MACE		Notes
					Group 1	Group 2	
DEFINE-FLAIR	Davies et al[9]	iFR vs FFR	1,148	1,182	6.8	7	All-cause death, non-fatal MI, unplanned revascularisation
FAME 3	Fearon et al[29]	FFR PCI vs CABG	757	743	10.6	6.9*	Death, MI, stroke, repeat revascularisation, excluding CABG
FLOWER- MI	Puymirat et al[30]	FFR vs angiography	586	577	5.5	4.2*	All-cause death, non-fatal MI, unplanned hospitalisation for revascularisation, excluding angio-guided arm
FLAVOUR	Koo et al[31]	FFR vs IVUS	838	844	4.6	3.4*	Death, MI, revascularisation, excluding IVUS-guided arm
FAME 25	De Bruyne et al[5]	FFR PCI vs GDMT	447	441	4.3	12.7*	Death, MI, urgent revascularisation, excluding medical therapy arm
FAME	Tonino et al[4]	Angio-PCI vs FFR PCI	496	509	18.3*	13.2	Death, MI, revascularisation, excluding angio-guided group
iFR SWEDEHEART	Götberg et al[10]	iFR vs FFR	1,019	1,018	6.7	6.1	Death from any cause, non-fatal MI, unplanned revascularisation
COMPARE Acute	Smits et al[32]	FFR vs angiography	295	590	7.8	20.5*	STEMI post-infarct artery; MACCE; all-cause mortality, non-fatal MI, any revascularisation, cerebrovascular events (no cerebrovascular events in the complete arm, excluding infarct-only arm)
DEFER	Bech et al[33]	Deferral of PTCA/PCI based on FFR vs performance	91	144	-*	-*	Excluded given no clear MACE endpoint
DANAMI-3-PRIMULTI	Engstrøm et al[34]	FFR-guided complete revasc vs none after STEMI	313	314	22*	13	All-cause mortality, non-fatal MI, IDR; excluding the no further revascularisation group
FAVOR III China	Xu et al[35]	QFR vs angio-guided PCI	1,912	1,913	8.8*	5.8	All-cause death, MI, IDR; excluding angio-guided patients

*These cells were not included in the weighted calculation due to alternative revascularisation or treatment modalities or a lack of physiological assessment prior to revascularisation or MACE endpoint adjudication. CABG: coronary artery bypass grafting; FFR: fractional flow reserve; GDMT: guideline-directed medical therapy; IDR: ischaemia-driven revascularisation; iFR: instantaneous wave-free ratio; IVUS; intravascular ultrasound; MACCE: major adverse cardiovascular and cerebrovascular events; MACE: major adverse cardiovascular events; MI: myocardial infarction; PCI: percutaneous coronary intervention; PTCA: percutaneous transluminal coronary angioplasty; QFR: quantitative flow ratio; revasc: revascularisation; STEMI: ST-segment elevation myocardial infarction

clinical trials **(Supplementary Table 4)**. Notably, the Functional Assessment by Virtual Online Reconstruction III–Europe (FAVOR III Europe) trial reported that QFR-guided PCI was inferior to FFR-guided PCI for the primary composite endpoint of all-cause death, MI, and unplanned revascularisation at 12 months.

Discussion

FFRangio uses a lumped resistance model instead of computational fluid dynamics, 3 angiograms instead of 1-2, and assesses the whole coronary tree with all its main branches, not just a single vessel or vessel segment. A comparison of current angio-based coronary technologies is presented in **Supplementary Table 5**. All of these technologies are different, with varying levels of diagnostic accuracy and reliability, and each one needs to be assessed on its own merits instead of grouping them all into a class effect. These findings have raised important questions regarding the clinical performance and reliability of angiography-based physiological assessment tools. In this context, the design of ALL-RISE, with prerandomisation designation of study lesions and detailed adjudication of angiographic lesions and clinical events, will offer important insights into the diagnostic and prognostic performance of FFRangio.

Limitations

Study investigators and teams will not be blinded to treatment assignment. However, after obtaining coronary angiograms, investigators must document a detailed treatment plan prior to randomisation (i.e., for each lesion, state whether they would treat or defer based on angiography alone). To mitigate the risk of bias in endpoint assessment, the clinical events committee will be blinded to treatment allocation, unless unblinding is necessary to determine device/procedure relatedness.

Both FFR and NHPR indices may be used in the control arm of ALL-RISE. While most studies suggest comparable performance, some indicate that NHPR may be less reliable than FFR. If a patient is randomised to pressure wire-based physiology and the operator doubts the result, they may remeasure using the alternative method. In cases of discordance, clinical judgment will guide which result to follow. Randomisation is stratified by the intended use of FFR or NHPR in the control arm, enabling FFRangio to be compared separately with each in exploratory analyses.

The components of the primary endpoint differ in clinical relevance and, likely, in their causal link to the intervention. Events unrelated to the diagnostic strategy may dilute

any true differences between groups and increase the likelihood of meeting the non-inferiority margin. Therefore, considerable emphasis will be placed on interpreting the totality of the trial data, beyond the formal statistical test of non-inferiority.

Lastly, the high concordance between FFRangio and pressure wire-based FFR seen in FAST-FFR may limit the number of treatment decisions affected by randomisation, diluting observed effects and reducing power. However, if clinical outcomes after PCI are similar with both strategies, FFRangio may reasonably be considered non-inferior for guiding revascularisation.

Conclusions

ALL-RISE is a large-scale, prospective, randomised trial powered to test whether FFRangio-guided treatment leads to non-inferior rates of 1-year MACE when compared with conventional pressure wire-guided treatment in patients with coronary artery disease being evaluated for PCI. ALL-RISE will also assess the extent to which FFRangio-guided treatment affects short- and long-term resource utilisation and cost-effectiveness. With a goal of 1,924 patients randomised and followed up for 12 months, we expect that ALL-RISE will provide prospective clinical outcomes data on the relative safety, efficacy and cost-effectiveness of a workflow using FFRangio as compared with conventional wire-based approaches to coronary lesion assessment.

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Conflict of interest statement

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Supplementary data

Supplementary Table 1. Recommended steps in wire-based FFR/NHPR measurements.

Supplementary Table 2. Detailed process of assessing angiography-derived fractional flow reserve.

Supplementary Table 3. Secondary endpoint superiority comparisons.

Supplementary Table 4. Study status and comparison to ongoing trials of angio-based coronary physiology indices.

Supplementary Table 5. Comparison of current angio-based coronary technologies.

Supplementary Figure 1. Recommended projections.

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Clinical outcomes of the third-generation resorbable magnesium scaffold for coronary artery lesions: three-year results of the BIOMAG-I study

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Resorbable scaffolds were developed to provide temporary vessel support, maintaining patency during the healing phase and subsequently dissolving to eliminate long-term complications associated with permanent metallic drug-eluting stents (DES). However, early-generation polymeric scaffolds failed to meet clinical expectations, exhibiting higher event rates than DES. In contrast, magnesium-based scaffolds have emerged as a promising alternative, given that magnesium offers mechanical properties more akin to metallic DES. While earlier iterations demonstrated an excellent safety profile, they fell short in achieving competitive angiographic performance metrics such as low late lumen loss (LLL). The third-generation sirolimus-eluting resorbable magnesium scaffold (DREAMS 3G, commercial name Freesolve [Biotronik]) was developed to address these limitations. Leveraging an enhanced magnesium alloy, DREAMS 3G features thinner struts, increased radial strength, more uniform degradation, and a prolonged scaffolding duration compared to its predecessor. One-year results from the BIOMAG-I study confirmed that the design objectives were met, with a median LLL of 0.19 mm (interquartile range [IQR]: 0.06-0.36)[1-3]. Herein, we present the 3-year clinical outcomes, two years after complete scaffold resorption.

BIOMAG-I is a prospective, multicentre, single-arm, first-in-human trial conducted in Europe (ClinicalTrials.gov: NCT04157153). Study design and primary results have been published previously[3]. Eligible patients presented with symptomatic coronary artery disease involving up to two *de novo* lesions and clinical presentations ranging from stable angina to non-ST-segment elevation myocardial infarction. The study device, DREAMS 3G, is a balloon-expandable bioresorbable scaffold made of a proprietary magnesium alloy, with radiopaque markers at both ends. It is coated with poly-L-lactic acid, incorporating sirolimus as the antiproliferative agent. Strut thicknesses range from 99 µm to 147 µm, depending on device diameter. Scheduled follow-up extends to five years, and all clinical events are adjudicated by an independent clinical events committee.

A total of 116 patients were enrolled. Three-year data are available for 112 patients. There was no cardiac death, no target vessel myocardial infarction, and no definite, probable or possible scaffold thrombosis reported. The 3-year Kaplan-Meier estimate for target lesion failure (TLF) was 3.5% (95% confidence interval: 1.3-9.0) **(Figure 1)**, consisting of four clinically driven target lesion revascularisations (CD-TLR; on days 166, 204, 270, and 522 post-procedure). A review of the CD-TLR beyond one year identified a previously untreated plaque proximal to the scaffolded segment. By day 522 post-procedure, the previously moderate stenosis in this area progressed to 70% and therefore was treated with a permanent DES.

The low TLF rate at three years – particularly with only one event occurring beyond the scaffold resorption period – is highly encouraging and compares favourably to TLF rates of 6.7% to 13.6% reported in exemplary trials such as BIO-RESORT and BIOFLOW-V[4,5]. However, it should be noted that these trials employed broader inclusion criteria, encompassing high-risk lesion and patient characteristics.

Freedom from cardiac death, target vessel myocardial infarction, and any device thrombosis up to three years attests to excellent device performance. While the precursor devices of DREAMS 3G had already shown an excellent safety profile and lower thrombogenicity compared to other bioresorbable

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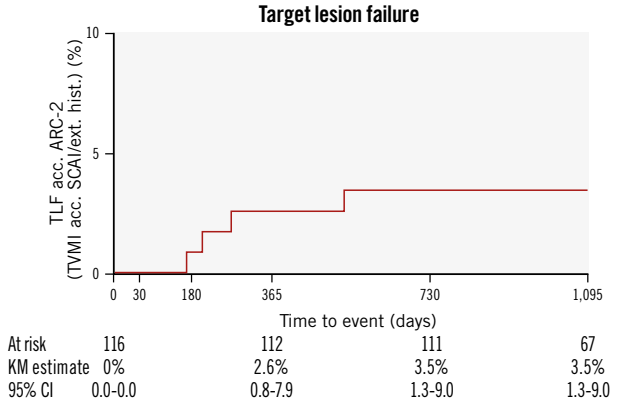

Figure 1. *Kaplan-Meier estimate of target lesion failure up to three years. All events were adjudicated by an independent clinical events committee. All target lesion failures were clinically driven target lesion revascularisations. There were no cardiac deaths, nor target vessel myocardial infarctions, and no definite, probable, or possible device thrombosis was observed. acc.: according to; ARC-2: Academic Research Consortium 2; CI: confidence interval; ext. hist.: extended historical definition; KM: Kaplan-Meier; SCAI: Society for Cardiovascular Angiography & Interventions; TLF: target lesion failure; TVMI: target vessel myocardial infarction*

scaffolds[1,3], preclinical studies suggest that DREAMS 3G further reduces thrombogenic potential[2]. Future randomised controlled trials are planned to validate these promising results in comparison to contemporary DES.

Study limitations include (i) the single-arm design, which precludes direct comparison with other stent technologies, particularly given the differences in patient characteristics and potential use of differing definitions; (ii) the first-in-human population, defined by its narrow inclusion and exclusion criteria, may not reflect broader real-world practice; (iii) the relatively small sample size (n=116), calculated for the primary endpoint, LLL at 6 months, results in wider confidence intervals for clinical event rates; and (iv) no imaging assessments were scheduled beyond 12 months.

In conclusion, the favourable 3-year outcomes of DREAMS 3G support renewed interest in bioresorbable scaffolds as a viable therapeutic option that combines temporary mechanical support with excellent long-term safety and efficacy. The randomised BIOMAG-II trial will determine whether DREAMS 3G can emerge as a competitive alternative to contemporary DES.

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Conflict of interest statement

R. Waksman was a core laboratory member; the remaining authors were investigators of the trial. M. Haude reports grants/contracts from Biotronik, Cardiac Dimensions, and Philips; consulting fees from Biotronik, Cardiac Dimensions, and Shockwave Medical; honoraria/speaker fees from Biotronik, Cardiac Dimensions, Shockwave Medical, and Philips; support to attend meetings/travel support from Biotronik; is a steering committee member of the BIOSOLVE and BIOMAG trials; and is a past President of EAPCI. J. Torzewski reports grants and contracts from Abbott paid to his institution; speaker honoraria and support for attending meetings from Biotronik; and is an Associated Editor of Cardiovascular Biologics and Regenerative Medicine and Frontiers in Cardiovascular Medicine. J. Escaned reports personal fees/speaker honoraria from Abbott, Boston Scientific, Philips, and Shockwave Medical; patents from Shared; and participation in advisory boards of Abbott and Philips. J.F. Iglesias reports unrestricted research grants to his institution or contracts from Terumo, Biosensors, Concept Medical, Biotronik, and SMT; consulting fees from Biotronik, Medtronic, Cordis, and Recor Medical; speaker fees/honoraria from Biotronik, Biosensors, Bristol-Myers Squibb/Pfizer, Cordis, Concept Medical, Medtronic, Penumbra, and Recor Medical; support to attend meetings from Biotronik and Medtronic; and is a Data Safety Monitoring Board member of the Co-STAR trial. The institution of J. Bennett receives grants or contracts from Shockwave IVLS; he receives consulting fees from Biotronik and Boston Scientific; speaker fees/honoraria from Biotronik, Boston Scientific, Elixir, and Abbott; participates in the advisory board of Elixir; and has a leadership or fiduciary role for Biotronik. G. Toth reports consulting fees from Biotronik, Medtronic, Abbott, and Terumo; and honoraria from Biotronik, Medtronic, Abbott, and Terumo. M. Joner reports

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Retrievable scaffold therapy before paclitaxel drug-coated balloon angioplasty in infrapopliteal arteries: one-year outcomes of the DEEPER OUS Study

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Percutaneous transluminal angioplasty (PTA) is a common treatment for infrapopliteal artery disease, but acute elastic recoil and restenosis limit its efficacy. While drug-coated balloons (DCBs) may reduce restenosis by delivering antiproliferative agents to the arterial wall, studies comparing DCBs to PTA have been inconclusive. Retrievable scaffold therapy (RST) utilises a spur stent with microspikes that create microchannels in the arterial wall to enhance DCB drug delivery. The prospective, multicentre, single-arm DEEPER OUS Study (ClinicalTrials.gov: NCT03807531) evaluated RST prior to paclitaxel DCB angioplasty for infrapopliteal disease.

Independent core laboratories evaluated duplex ultrasound and angiographic imaging. An independent clinical events committee adjudicated device-related adverse events, and an independent data safety monitoring board provided study oversight. The study enrolled adults with peripheral artery disease (Rutherford-Becker classification [RBC] 3-5) and infrapopliteal disease with lesion lengths of 30-150 mm and reference vessel diameters of 2.0-4.5 mm **(Supplementary Table 1)**. Patients were treated with RST (Spur Peripheral Retrievable Scaffold System [Reflow Medical]), a temporary self-expanding nitinol stent, prior to DCB angioplasty **(Supplementary Figure 1)**. The primary efficacy endpoint was primary patency at 6 months (duplex ultrasound patency and freedom from clinically driven target lesion revascularisation). The primary efficacy endpoint was compared to a 51% performance goal derived from an infrapopliteal PTA meta-analysis[1]. The primary safety endpoint was freedom from device- or procedure-related death up to 30 days.

Among 107 patients (mean age 76 years [range 49-98 years], 78% male, 69% RBC 5) enrolled at 10 centres between July 2019 and May 2022 **(Supplementary Table 2)**, 169 spur stents were deployed (mean treated length 90 mm) in 106 patients (1 delivery failure), with uncomplicated removal in all cases. Bailout treatment was performed in 2 (1.9%) patients: 1 received stent placement due to residual stenosis >30% in a heavily calcified lesion after DCB angioplasty and 1 received a dissection repair device for type B dissection following DCB angioplasty. Among 84 patients with duplex ultrasound imaging evaluated by the core laboratory at 6 months, primary patency was 85.7% (95% confidence interval: 78.2-93.2%; p<0.001 vs 51% performance goal), with no difference in patients with calcified (Peripheral Arterial Calcium Scoring System [PACSS] score 1-4) versus non-calcified (PACSS score 0) lesions (84.7% vs 88.0%; p=0.70). Freedom from device- or procedure-related death up to 30 days was 100%. Kaplan-Meier estimates at 1 year were 75.7% for primary patency **(Supplementary Figure 2)** (72.7% vs 76.9% in patients with calcified vs non-calcified lesions; p=0.69), 91.7% for freedom from clinically driven target lesion revascularisation **(Supplementary Figure 3)**, and 98.9% for freedom from major amputation. The mean RBC decreased from 4.5±0.8 at baseline to 1.9±2.1 at 1 year, with 69% of patients improving ≥2 categories. The ankle-brachial (0.75±0.28 to 0.94±0.31) and toe-brachial (0.45±0.24 to 0.58±0.24) indices both increased at 1 year (both p<0.001) **(Table 1)**. The composite Wound, Ischemia, foot Infection (WIfI) score decreased from 2.3±1.2 to 1.3±0.7: the wound score decreased from 1.3±0.6 to 0.6±0.6, the ischaemia score decreased from 1.4±0.9 to 0.6±0.9, and the foot infection score decreased from 0.5±0.8 to 0.1±0.4. The median wound area

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Table 1. Clinical outcomes up to 1 year.

Outcome	Baseline	1 month	3 months	6 months	1 year
Primary patency	-	98.9	93.5	85.7*	74.4
Freedom from CD-TLR	-	100	98.0	92.6	89.5
Freedom from major amputation	-	100	98.9	98.9	98.9
Freedom from all-cause death	-	100	98.1	95.3	91.6
Rutherford-Becker class	4.5±0.8	3.5±2.1†	2.7±2.3†	2.1±2.2†	1.9±2.1†
ABI	0.75±0.28	-	-	-	0.94±0.31†
TBI	0.45±0.24	-	-	-	0.58±0.24†

Values are mean±SD or percentages (derived from n/N). *The primary efficacy endpoint was met as the 95% confidence interval lower limit (78.2%) was significantly higher than the performance goal of 51%. †p<0.001 for change from baseline. ABI: ankle-brachial index; CD-TLR: clinically driven target lesion revascularisation; SD: standard deviation; TBI: toe-brachial index

decreased from 200 mm^2 to 2 mm^2, with complete wound healing in 59% of patients. Freedom from a device-related adverse event at 1 year was 95.3%, with only non-flow limiting dissection or vasospasm being reported.

The DEEPER OUS Study demonstrated that RST prior to DCB angioplasty is a safe and effective strategy for treating infrapopliteal artery disease. The primary efficacy endpoint was met, with 6-month primary patency of 85.7% being statistically greater than the 51% performance goal. This outcome favourably compared to typical outcomes with PTA[1-3] or DCB[3,4] **(Supplementary Table 3)**. The sustained effectiveness of this treatment approach was demonstrated by low rates of clinically driven target lesion revascularisation and major amputation at 1 year, with significant improvements in RBC score, wound healing, and limb haemodynamics. Furthermore, a substudy of DEEPER OUS reported elastic recoil in 42.5% of lesions, compared to 97% recoil with PTA[5]. Thus, RST before DCB angioplasty may mitigate the negative impact of arterial recoil, improve intra-arterial drug delivery into complex lesions, and avoid complications associated with permanent metallic stents in infrapopliteal vessels.

Several limitations of this study warrant discussion. First, the 6-month primary patency results were compared to a historical PTA performance goal[1]; however, RST has not been directly compared to PTA or DCB alone in a clinical trial. Second, operators selected DCBs at their discretion, which complicates the evaluation of specific device combinations. Finally, the exclusion of patients with prior bypass surgery, lesion lengths of >150 mm, and severe calcification may limit the generalisability of the findings in these populations.

In conclusion, the DEEPER OUS Study demonstrates that RST prior to paclitaxel DCB angioplasty is a promising treatment strategy for patients with infrapopliteal artery disease. By addressing key limitations of existing endovascular therapies, such as acute vessel recoil and suboptimal drug delivery in calcified lesions, and leaving no permanent implant behind, this combination therapy may represent a significant advancement in the management of infrapopliteal artery disease.

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Conflict of interest statement

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Supplementary data

Supplementary Table 1. General and angiographic inclusion/exclusion criteria.

Supplementary Table 2. Patient and procedural characteristics.

Supplementary Table 3. Primary patency with retrievable scaffold therapy compared to meta-analysis-derived estimates with DCB and PTA in infrapopliteal arteries.

Supplementary Figure 1. Retrievable scaffold therapy.

Supplementary Figure 2. Kaplan-Meier estimate of target lesion primary patency up to 12 months.

Supplementary Figure 3. Kaplan-Meier estimate of freedom from clinically driven target lesion revascularisation up to 12 months.

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Carbon footprint of diagnostic coronary angiography

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Environmental concerns related to global warming impact all sectors of society, with healthcare contributing approximately 5% of global greenhouse gas (GHG) emissions – making it the 5th largest emitting entity on the planet. Annually, around 5 million cardiac catheterisation procedures are performed worldwide. Despite this, the healthcare sector is lagging in efforts to reduce GHG emissions, and there is a lack of detailed studies that accurately estimate the emissions generated by specific procedures[1]. Ditac et al reported that atrial fibrillation catheter ablation results in an average of 76.9 kg of carbon dioxide (CO_2)-equivalent (CO_2e) emissions, amounting to 125 tonnes of CO_2e released daily[2]. Unfortunately, no studies have evaluated the carbon footprint of coronary angiography procedures. This work aims to estimate the overall and detailed carbon footprint of a coronary angiography procedure, with the goal of raising awareness among healthcare professionals and industry partners to reduce the GHG emissions associated with these procedures.

To conduct this study, we exhaustively catalogued all the equipment and treatments used during a standardised diagnostic coronary angiography procedure at our centre. After this, we analysed each product, detailing its manufacturing material, country of origin, and primary packaging, while also measuring the weight of each item. We also considered the type of waste disposal (hazardous medical waste or general waste). The same process was applied to the treatments. Once the inventory was completed, all data were integrated into different calculators, which allowed us to establish the carbon footprint of each product. For medical devices, the calculator used was provided by the French Agency for Ecological Transition (ADEME) website. This calculator includes the entire lifecycle of a medical device, from the origin of all raw materials to the end-of-life of the device, including all transportation between different stages. We only considered the device and its primary packaging. For medications, the calculator used was provided by Ecovamed, which considers all stages of a medication's lifecycle (active ingredient, primary and secondary packaging, and end of life). The emission factor of the active ingredient was calculated based on the price of the active ingredient per kilogram, which was then multiplied by an economic emission factor depending on the country of production (EXIOBASE).

The total carbon footprint associated with the products used during a diagnostic coronary angiography procedure amounts to 8 kg of CO_2e. The total carbon waste for the treatment process, which includes the disposal and management of used materials, contributes an additional 4.48 kg of CO_2e (~35%) **(Supplementary Table 1)**. Energy consumption during a single procedure is estimated at 1.3 kWh, which corresponds to approximately 0.078 kg of CO_2e in France, where electricity generation is largely based on nuclear energy. Each intervention generates 2.869 kg of waste (621 g of packaging and 2,248 g of medical devices). An analysis of each procedural category reveals that most emissions arise from single-use consumables (31%) and surgical drapes/covers (40%), while medications, disinfection, and energy consumption play a comparatively smaller role **(Table 1)**.

The total carbon impact of a coronary angiography procedure is estimated to be 12.56 kg of CO_2e. This highlights the significant environmental impact of such routine medical practices and underscores the importance

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Table 1. Carbon footprint summary by procedural category.

Category	Total carbon footprint (kg of CO_2e)	Waste management carbon footprint (kg of CO_2e)	% of total	Key reduction opportunity	
Medications & anaesthesia	3.10	0.03	~25%	Simplify agents	Policy, accreditation standards, and financial incentives
Consumables/tools	3.93	1.44	~31%	Switch to reusables or low-impact materials	
Disinfection	0.41	0.17	~3.3%	Use refillable packaging, low-impact agents	
Drapes & covers	5.04	2.84	~40%	Reduce drape use; bundle smarter packs	
Facility energy consumption	0.078		~0.6%	Energy efficient devices/ sustainable energy management/ reduce procedure duration	
Total	12.56	4.48			

of considering sustainability in healthcare procedures[3]. One area for improvement is the composition of the angiography kit provided. It would be beneficial to review the kit's contents to eliminate surplus devices that do not add value to the procedure but contribute significantly to the carbon footprint. Regarding iodine, using larger-volume vials that can be shared among multiple patients would not only reduce the carbon footprint but also provide an economic benefit to healthcare facilities. Attention must be given to the end-of-life management of all medications and medical devices. Establishing recycling pathways and collaborating with specialised waste management companies could significantly improve the environmental footprint. In addition to material and waste reduction, emerging strategies such as remote diagnostic approaches may further reduce the carbon footprint of cardiovascular procedures and warrant future investigation. Finally, regulatory and institutional frameworks – such as green procurement policies, sustainability-linked accreditation criteria, and reimbursement incentives – could play a pivotal role in encouraging hospitals to adopt low-carbon practices in procedural care.

This study presents some limitations. The calculations do not take into account the exact formulation or manufacturing processes for the medications, including factors such as yield or energy consumption in the production facilities. These data are not provided by pharmaceutical laboratories, making it impossible to incorporate them into the analysis. Similarly, for medical devices, the manufacturing process is not considered, as these details are subject to industrial confidentiality and are therefore unavailable for inclusion in the calculation. Some data were not available or not shared by the manufacturers. We chose not to include emissions from transportation and broader hospital logistics due to the significant variability of these factors depending on patient origin, staff travel modes, and institutional supply chains, which are often difficult to generalise across settings

The carbon footprint of a diagnostic coronary angiography procedure is estimated at 12.56 kg of CO_2e. This value is derived from various sources, including the use of medical materials, energy consumption and waste management. Several areas for improvement are identified, which could significantly reduce the carbon footprint of such cardiac procedures.

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Conflict of interest statement

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Supplementary data

Supplementary Table 1. Breakdown of the carbon footprint of a diagnostic coronary angiography procedure.

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A randomised controlled trial of the Cathpax AIR radioprotection cabin during cardiology procedures

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Ionising radiation is essential in interventional cardiology, but it is associated with occupational health hazards[1]. Personal protective equipment (PPE) is used to limit exposure to radiation, but because it is heavy and cumbersome, it may also have deleterious health effects[2]. New light radiation-attenuating materials can efficiently decrease scattered radiation originating from the patient. However, the increasing number and complexity of interventional cardiology procedures require a more global approach to minimise operator exposure to radiation. In collaboration with Lemer Pax, we designed and optimised the Cathpax AIR cabin to improve operator protection during structural procedures and also during coronary angiography and angioplasty. The feasibility of using the cabin during interventional cardiology procedures has been reported previously[3]. In the present prospective, randomised clinical study performed at Nantes University Hospital (France), we assessed the cabin's performance regarding radiation protection and ergonomics during structural and coronary angiography/angioplasty procedures (no trial registration exists).

All procedures were randomised daily to be performed with or without the Cathpax AIR cabin **(Supplementary Figure 1)**. The 4 participating interventional cardiologists (P. Guerin, J. Plessis, V. Letocart, and T. Manigold) wore their PPE equipped with thermoluminescent dosimeters for all procedures performed with or without the cabin. The left chest dosimeter provided the total dose received. A cumulative dose was collected over time for both groups of procedures. The primary and secondary endpoints were the differences with and without the cabin in total and individual body part radiation exposure, respectively. Medical team satisfaction with cabin ergonomics was assessed with a questionnaire **(Supplementary Figure 2)**. Additional method description is provided in **Supplementary Appendix 1**.

This study included 63 structural procedures and 92 angiography/angioplasty procedures performed between March 2021 and January 2022. Patient demographics and procedure characteristics were similar in the groups with and without the cabin **(Supplementary Table 1)**. Use of the cabin reduced the total radiation dose by 63% – from 490 µSv without the cabin (n=31) to 180 µSv with the cabin (n=32) – for the structural procedures, and by 58% – from 810 µSv without the cabin (n=50) to 340 µSv with the cabin (n=42) – for the angiography/angioplasty procedures **(Figure 1)**. The most important benefit provided by the cabin was the protection of the eyes and brain, which had an exposure below the detection limit (<10 µSv) regardless of the procedure **(Figure 1)**. The extremities were also protected by the cabin, with a dose reduction of more than 70% for the left wrist. The questionnaire indicated that cabin installation and physical burden were the major points of dissatisfaction, while accessibility, visibility and communication were satisfactory **(Supplementary Figure 3, Supplementary Figure 4)**.

This study showed an improvement in radiation protection when using the Cathpax AIR cabin during various structural procedures and angiography/angioplasty with no increase in procedure duration or radiation exposure despite some procedures being lengthy and complex. Based on our results, an interventional cardiologist performing 10 structural and 30 angiography/angioplasty procedures per month would receive an annual dose of approximately 3.6 mSv when

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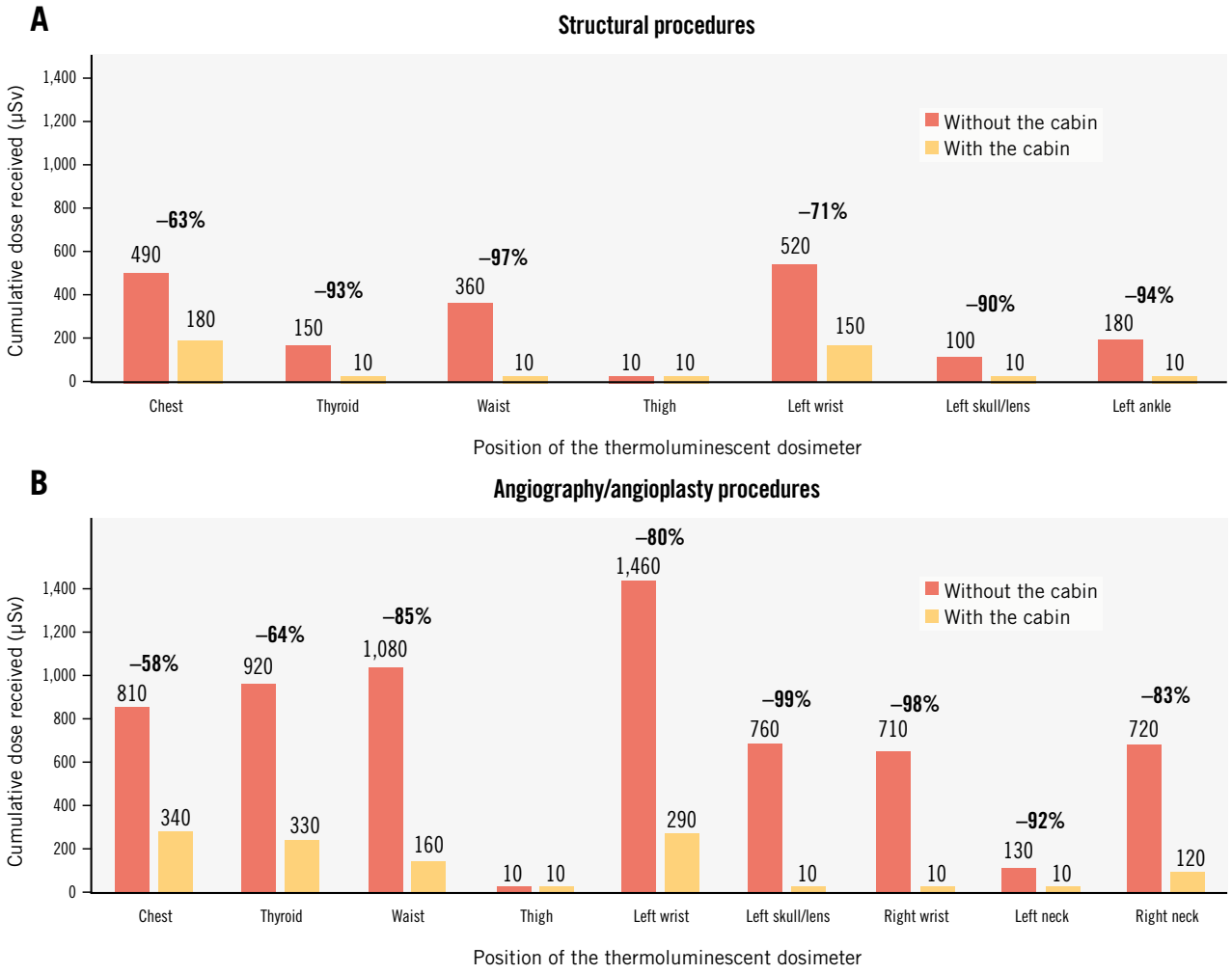

Figure 1. *Cumulative dose received by the operator with and without the cabin. Cumulative dose received by the operator during structural (A) and angiography/angioplasty (B) procedures, with and without the radioprotection cabin. The study included 63 structural and 92 coronary angiography/angioplasty procedures. The left chest dosimeter provided the total dose received by the primary operator (study primary endpoint).*

using the radioprotection cabin, which is below the 5 mSv/year value reported with PPE[1]. The eyes and brain were particularly protected. This is an advantage of the cabin over radiation protection goggles, which are efficacious[4] but not systematically worn because of their weight and the discomfort created. Regarding hand protection, the cabin was superior to PPE, given the lack of reliability of protective gloves[5]. However, the level of radioprotection reported in this real-life study was not as high as anticipated. Further improvement could be achieved by abandoning the local practice of installing the cabin after performing the vascular approach with fluoroscopic guidance, as was the case for 8 structural procedures. In emergency situations (e.g., external cardiac massage), the cabin would have to be rapidly removed. In that respect, the cabin ergonomics need improvement, as the physical burden associated with cabin handling was described as high. Nevertheless, after set-up, the additional strain induced by the cabin during routine work was acceptable. We did not investigate the safety-related aspects of the cabin, but a review of hospital reports in the early post-intervention phase did not indicate any major complication related to cabin use.

One limitation of our study is the small number of procedures, which, given the low irradiation doses perceived behind the cabin, did not always allow for a precise assessment of benefits. The challenge was to collect a sufficient number of coronary angiography or angioplasty procedures using a cabin, which explains the long inclusion period. Also, the wide range of procedures performed led to significant variability in the use of fluoroscopy, but the study was designed to be representative of daily practice. We evaluated the cabin performance on top of PPE, and an additional study would be necessary to assess the combined radiation protection impact of the cabin and PPE.

In summary, the Cathpax AIR cabin reduces radiation exposure during various routine interventional cardiology procedures. The improvement in radiation protection with the cabin is particularly significant for areas of the body insufficiently protected by standard equipment, such as the skull, the eyes, and the extremities.

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Conflict of interest statement

P. Guerin is the initiator of the cabin and has been involved in its creation, design, and optimisation; he has a consultancy agreement with Lemer Pax. The other authors have no conflicts of interest to declare.

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Supplementary data

Supplementary Appendix 1. Additional methods.
Supplementary Table 1. Procedure and patient characteristics.
Supplementary Figure 1. The Cathpax AIR radioprotection cabin.
Supplementary Figure 2. The satisfaction questionnaire.
Supplementary Figure 3. Overall satisfaction of the interventional cardiologist and paramedic team with the cabin.
Supplementary Figure 4. Evaluation of the strain and physical burden associated with the use of the cabin.

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Erosion-like plaque image during coronary vasospasm

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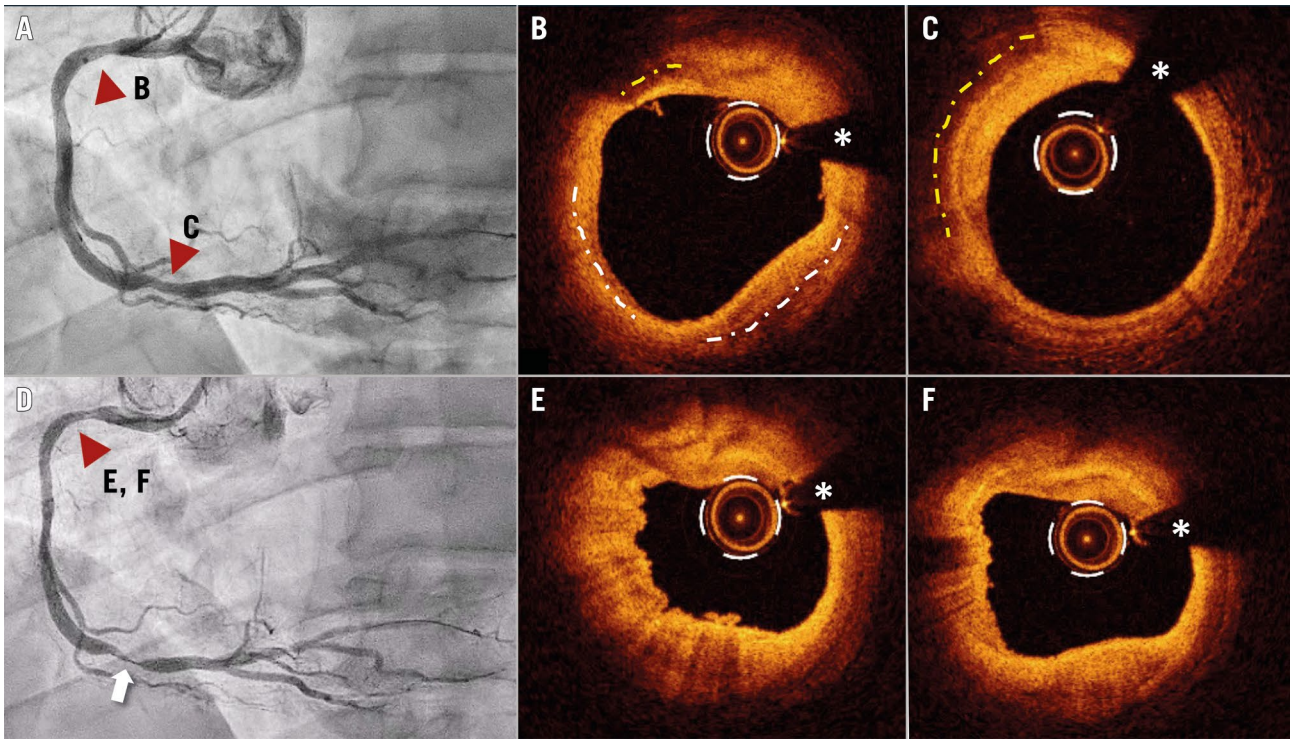

Figure 1. *Coronary angiography and OCT images. A) Coronary angiography of the baseline RCA shows no significant lesions in the proximal or distal segments (red arrowheads). B,C) OCT images of the proximal and distal segments demonstrate fibrolipidic plaques with macrophage infiltration (yellow dotted line) and no evidence of rupture or thrombus but findings suggestive of layered plaque (white dotted line). D) Coronary angiography after intracoronary acetylcholine administration reveals the development of a severe lesion in the distal segment (white arrow) and moderate obstruction in the proximal segment (red arrowhead). E,F) OCT images of the proximal segment show features resembling a typical erosion image during coronary vasospasm. White asterisks denote wire artefacts. OCT: optical coherence tomography; RCA: right coronary artery*

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A 58-year-old male with hypertension, diabetes mellitus, and a history of smoking was admitted following a four-week history of oppressive chest pain at rest, with episodes lasting up to 20 minutes. His electrocardiogram and serial cardiac biomarkers were within normal limits. However, transthoracic echocardiography revealed hypokinesia in the basal septal and inferior wall regions. Coronary angiography showed mild atheromatosis in the left coronary artery without significant lesions. The right coronary artery (RCA) **(Figure 1A, Moving image 1)** demonstrated mild irregularities, along with a moderate lesion in the distal segment. Optical coherence tomography (OCT) revealed a fibrolipidic plaque without evidence of rupture or thrombus formation but with macrophage infiltration and images suggestive of layered plaque **(Figure 1B, Figure 1C, Moving image 1)**. A vasospasm test with acetylcholine was subsequently performed. Following the administration of 20 µg of intracoronary acetylcholine, the patient experienced angina with ST-segment elevation, accompanied by the development of a significant stenosis in the distal RCA and an intermediate stenosis in the proximal segment **(Figure 1D, Moving image 2)**. OCT of the proximal RCA during vasospasm confirmed a reduced intraluminal area and revealed an irregular endothelial surface with dorsal shadowing that was suggestive of thrombus, resembling the appearance of plaque erosion **(Figure 1E, Figure 1F)**. Symptoms and ST-segment changes resolved completely after intracoronary nitroglycerine administration. A repeat coronary angiogram and OCT evaluation showed findings identical to the baseline **(Moving image 3)**. The patient was treated with aspirin, ticagrelor and calcium-channel blockers, with an uneventful clinical course.

The typical OCT findings during coronary vasospasm include medial thickening and a "bumping" appearance of the intimal layer caused by muscular contraction of the media[1]. Intracoronary thrombus is a relatively common finding when evaluating coronary vasospasm sites with OCT[2]. Furthermore, laminar thrombus layered on the intima has been described in cases of recurrent coronary vasospasm[3] and is proposed as the mechanism underlying the higher frequency of layered healing plaques observed in coronary arteries with positive vasospasm tests[4].

In this case, the findings can be explained by a combination of these phenomena: a pre-existing layered thrombus adherent to the intima, resulting from recurrent vasospasm episodes, that was then externally compressed by medial contraction during a subsequent vasospastic event. The most intriguing aspect is the erosion-like image observed on OCT, which was transient and resolved after nitroglycerine administration. To the best of our knowledge, this phenomenon has not been previously reported and could have significant implications for intracoronary imaging interpretation and diagnosis.

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Conflict of interest statement

The authors have no conflicts of interest to declare.

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Supplementary data

Moving image 1. Baseline co-registration angio and optical coherence tomography images.
Moving image 2. After acetylcholine administration: co-registration angio and optical coherence tomography images.
Moving image 3. After nitroglycerine administration: co-registration angio and optical coherence tomography images.

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Letter: Complex PCI in severe aortic stenosis: high risk, low reward?

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We read with great interest the recent publication by Montalto et al, "Outcomes of complex, high-risk percutaneous coronary intervention in patients with severe aortic stenosis: the ASCoP registry"[1]. The authors are to be congratulated for addressing such a critical and emerging clinical challenge, complex percutaneous coronary intervention (PCI) in patients with severe aortic stenosis (AS). However, certain aspects of the study findings warrant further discussion.

Firstly, the study highlights substantial adverse event rates associated with complex/high-risk PCI in patients with severe AS, irrespective of whether PCI was performed concomitantly or staged with transcatheter aortic valve implantation (TAVI). Notably, early safety occurred in 55.9% of cases overall, device success in 74.8% of cases overall, and major adverse cardiac and cerebrovascular events (MACCE) remained considerable with a percentage of 19.8%. These outcomes stand in contrast to both data from randomised trials and real-world studies, which reported device success rates of about 90% and 87% and early safety rates of about 75% and 76%, respectively, with fewer MACCE[2,3].

These findings raise fundamental questions regarding the overall benefit-risk ratio of performing complex PCI in this fragile population. The procedural risks appear disproportionately high when weighed against the uncertain incremental clinical benefits, particularly in a cohort marked by severe baseline frailty and often limited life expectancy. Notably, a large majority of patients in this study (N=440/519, 84.8%) underwent PCI for chronic coronary syndrome (CCS) – a subgroup in which contemporary evidence increasingly supports conservative management[4]. Thus, while revascularisation prior to TAVI may be justified in the presence of critical coronary anatomy (e.g., unprotected left main or severe proximal lesions), the threshold for intervention – particularly for non-left main, non-culprit lesions – should be reconsidered, favouring a more conservative, physiology-guided approach.

Secondly, an interesting finding was the relatively low usage of radial artery access for both staged and concomitant PCI in the registry (N=293/519, 56.6% overall). This contrasts with current evidence supporting radial access as the first-line approach in PCI, even in patients undergoing high-risk or complex PCI, or with acute coronary syndrome as the indication in high-risk and complex cases. For instance, the MATRIX trial (ClinicalTrials.gov: NCT01433627) demonstrated that radial access significantly reduces major bleeding and mortality, without increasing ischaemic complications or compromising procedural success, and the Color trial confirmed that even large-bore complex PCI can be performed safely and effectively via transradial access, with a dramatic reduction in access site complications compared to via femoral access[5].

Considering that vascular complications and major bleeding were among the leading adverse events observed in the ASCoP registry, it could be considered that a wider adoption of radial access as the first-line vascular access could have improved the safety and the outcomes.

In conclusion, Montalto et al have provided real-world data that should encourage reconsideration of both the value of complex PCI in patients with CCS and severe AS and the preferable vascular access in such patients.

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Reply: Complex PCI in severe aortic stenosis: high risk, low reward?

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We sincerely appreciate the interest in our article "Outcomes of complex, high-risk percutaneous coronary intervention in patients with severe aortic stenosis: the ASCoP registry"[1] shown in the Letter to the Editor by Ktenopoulos et al[2]. We agree with the authors about the need to balance the procedural risk of these patients against the anticipated clinical benefit that could be achieved after percutaneous coronary intervention (PCI). Patients who have severe aortic stenosis and concomitant coronary artery disease often present more comorbidities and challenging vascular access that translate into a higher risk of complications during transcatheter aortic valve implantation (TAVI) and/or PCI. Data from randomised trials and real-world registries considering this high-risk population reported a high rate of events (particularly bleeding, vascular complications, and acute kidney injury), with a significant increase in their incidence if TAVI and PCI were both performed[3-5]. The results of our registry, considering an even higher-risk population, confirmed previous evidence.

As is correctly pointed out by Ktenopoulos et al, one of the reasons that might justify the high rate of adverse events (vascular complications and major bleeding) observed in the ASCoP registry is the low use of radial artery access for PCI (56.6% overall). PCI from the radial artery was more commonly performed in patients undergoing staged than concomitant procedures (69.4% vs 25.7%). Moreover, while the use of radial access increased over time in the staged-strategy group (44.5% in 2013-2014 to 84% in 2022-2023), its use in the concomitant-strategy group remained unchanged over the years (18.5% in 2013-2014 to 27.5% in 2022-2023). The rate and the trend over time of the use of radial artery access observed in patients undergoing PCI before or after TAVI are in line with real-world experiences on complex/high-risk PCI[6]. On the other hand, the high usage of the femoral artery access in the concomitant-strategy group might be explained by the possibility to perform complex/high-risk PCI and TAVI from the same large-bore arterial access. As a result, periprocedural complications occurred more frequently in the concomitant than in the staged group (vascular complications: concomitant 16.7% vs staged 9.4%; major bleeding: concomitant 10.9% vs staged 3.9%).

In conclusion, clinical presentation (acute or chronic coronary syndrome), coronary anatomy and subtended global myocardial ischaemia, angiographic and/or functional severity of coronary lesions and patients' frailty and comorbidities should guide selection of candidates who will benefit the most from revascularisation, independently of TAVI, while timing (concomitant vs staged) should be tailored individually to minimise the overall procedural risk. This is especially true in cases of complex/high-risk PCI, when higher rates of adverse events are expected, but should not hamper clinical decision-making *per se*.

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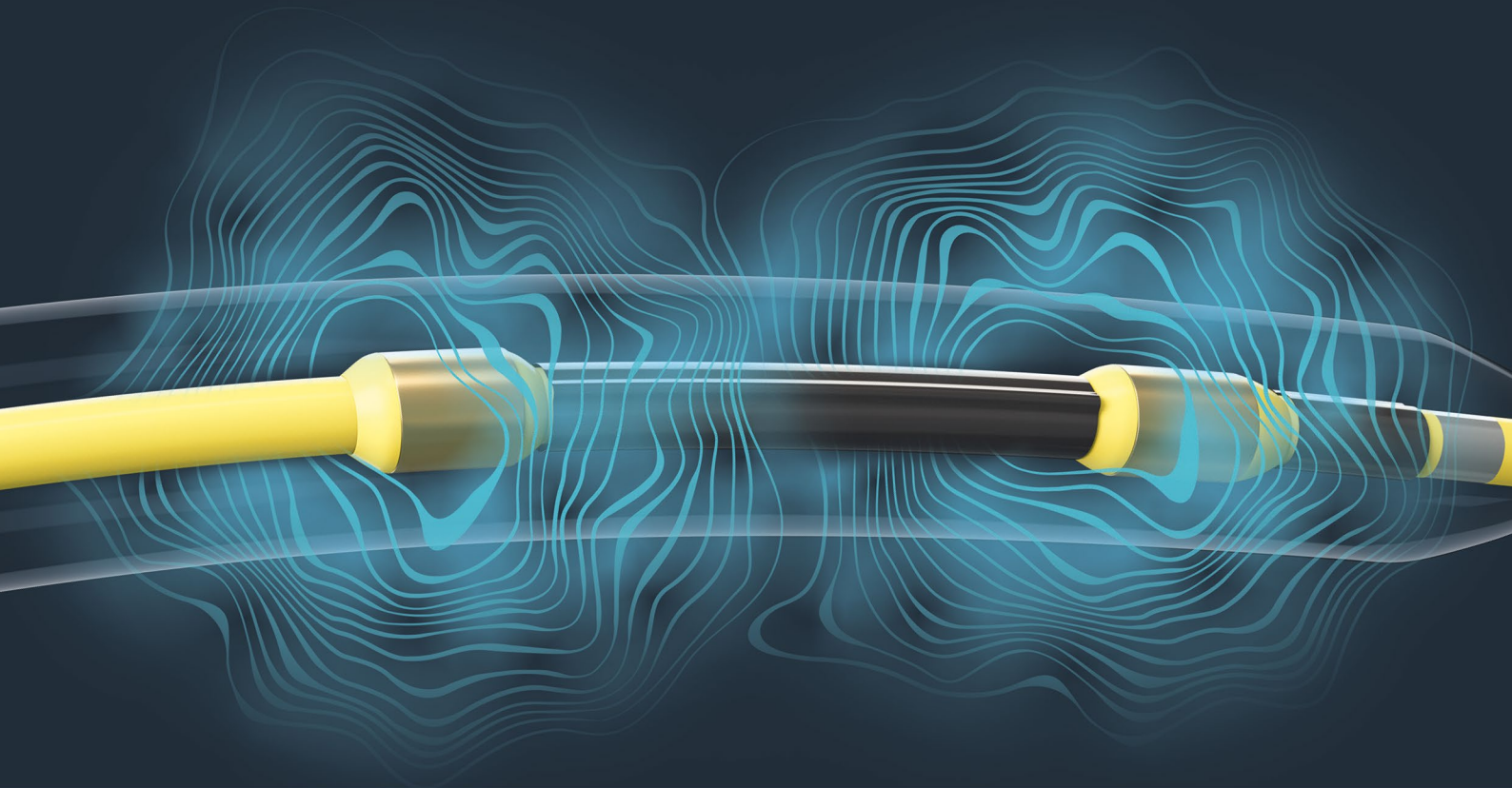

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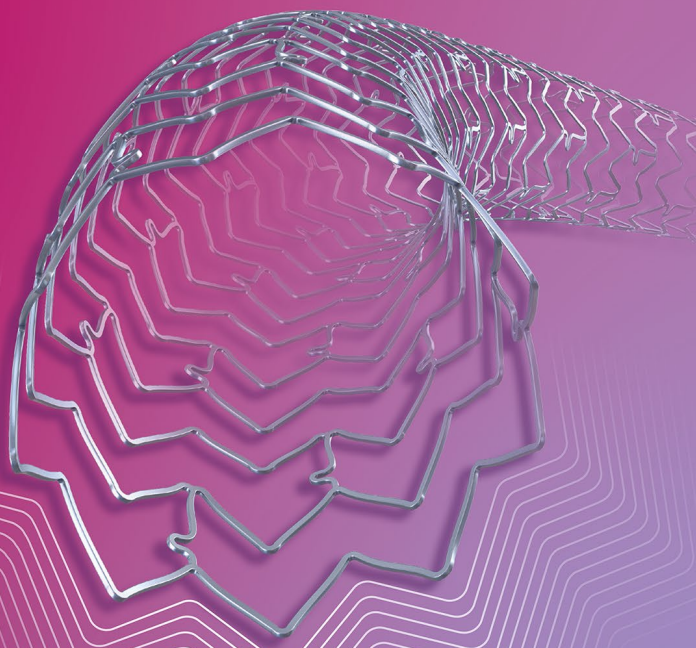

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