Volume 20 | Number 22 | November 2024
ISSN: 1774-024X (Print)
ISSN: 1969-6213 (Online)
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NOVEMBER 2024

VOLUME 20, Issue 22

EuroIntervention PCR London Valves Issue with: 2024 Core Curriculum on Percutaneous Valvular and Structural Heart Disease Interventions; a mini focus on redo-TAVI; outcomes of low-flow, low-gradient aortic stenosis after TAVI; worsening LVEF after M-TEER; the MitraCut procedure; referral trends in T-TEER; debating PCI for bystander CAD; news from the EAPCI; and more

Davide Capodanno, *Editor-in-Chief*

One thing I believe I've understood in publishing is that to simplify something is often harder than to make it more complicated. This issue coincides with the PCR London Valves Course, where, once again, there will be a strong focus on a minimalist approach to transcatheter valve disease treatment and, in keeping with the theme of simplification and minimalism, I'm pleased to announce that we've launched a new streamlined article submission process for our Journal.

Every author knows the frustration of dealing with complex submission systems, multiple forms to fill out, and formatting requirements for articles, tables, and figures. All that is now in the past for EuroIntervention. The submission system has been thoroughly revised to allow authors to complete the process in just a few minutes. We've removed unnecessary steps and questions and papers can essentially be submitted in the format of your choice. It's your paper – own the process.

Minimalism, however, does not mean oversimplification. Should your manuscript advance through to later stages, our editorial office will then request strict adherence to the Journal's submission guidelines. This seems like a fair compromise, focusing formatting efforts on only those manuscripts with the greatest chance of acceptance.

And, in keeping with this new and streamlined philosophy, we have redesigned the review submission process too, removing unnecessary steps to make life easier for our reviewers.

We hope all these changes will be well received by authors and reviewers alike, the people who are at the very core of EuroIntervention. These modifications came from your suggestions, and after some strategic planning, we've finally implemented them.

Let us know your thoughts. Meanwhile, let's focus on this special issue, aligned with the PCR London Valves tradition of special attention to valvular and structural topics.

And what better way to begin than with what we trust will lay the groundwork for future generations of interventionalists focused on treating structural, valvular, and non-valvular heart disease. **Rui Campante Teles, Dariusz Dudek and colleagues** present the 2024 Core Curriculum on Percutaneous Valvular and Structural Heart Disease Interventions, which represents the work of not only the European Association of Percutaneous Cardiovascular Interventions (EAPCI), but the European Association of Cardiovascular Imaging (EACVI) and the Cardiovascular Surgery Working Group (WG CVS) of the European Society of Cardiology (ESC) as well. This article provides an overview of the objectives, requirements and modules included in the EAPCI Structural Heart Disease Training and Certification, with full training in all competencies taking about 18 months. The Core Curriculum offers newly trained interventional cardiologists in ESC countries the chance to increase their knowledge and competence in structural heart disease interventions.

Turning next to original research, **Francesco Cardaioli, Giuseppe Tarantini and colleagues** probe whether the worse outcomes often associated with low-gradient aortic stenosis (AS) after transcatheter aortic valve implantation (TAVI) are due to the low-flow status alone, or if there are baseline characteristics that influence clinical outcomes. Using up to 10 years of follow-up data from three patient groups, classical low-flow, low-gradient AS, paradoxical low-flow, low-gradient AS, and high-gradient AS, they find that the higher mortality of the classical group seems to be associated more with the patient's risk profile than the low-flow status. This article is accompanied by an editorial from **John Webb and Sophie Offen**.

In this issue, we also have a mini focus on redo-TAVI, which, despite having emerged as a viable therapeutic option for many patients, remains fraught with complexities and knowledge gaps. **David Meier, Stephanie L. Sellers and colleagues** used *ex vivo* hydrodynamic testing to observe redo-TAVI using a SAPIEN 3 in failed calcified CoreValve/Evolut valves, evaluating the neoskirt height, leaflet overhang, frame expansion and the hydrodynamic performance of the SAPIEN 3 at three different implantation depths. Favourable haemodynamics were found with the SAPIEN 3 outflow positioned at node 5 of the degenerated valve, and the authors offer insights into patient selection and procedural planning.

Next in the mini focus, **Gintautas Bieliauskas, Ole De Backer and colleagues** look at the use of a SAPIEN 3 in a degenerated index ACURATE *neo2*, concluding that this is feasible in many patients, finding that a low implant position was associated with a lower risk for coronary flow compromise and coronary inaccessibility. A sinotubular

junction-to-aortic annulus mean diameter ratio <1.15 was a strong predictor that redo-TAVI was not feasible. The authors underline that meticulous preprocedural planning is imperative to determine the correct size and implant depth for an optimal result.

Wrapping up our redo-TAVI mini focus, **Ketina Arslani, Ole De Backer and colleagues** provide a research correspondence examining the coronary accessibility and feasibility of redo-TAVI with an Evolut valve in patients with bicuspid aortic stenosis. Using computed tomography data, they evaluate three different positions of a virtual SAPIEN 3 in an Evolut valve, finding that higher implantations were associated with an increased risk of coronary flow compromise and coronary inaccessibility.

To prevent left ventricular outflow tract (LVOT) obstruction in transapical transcatheter mitral valve replacement (TA-TMVR) patients, the MitraCut procedure uses beating heart transapical cannulation and standard endoscopic scissors to divide the anterior mitral leaflet. **Martin Andreas, Andrea Colli and colleagues** report on their multicentre experience using this procedure which they found to be effective, with low complication rates and having the advantage of not requiring specialised equipment.

Sachiyo Ono, Kentaro Hayashida and colleagues explore the predictors and clinical effects of left ventricular ejection fraction (LVEF) worsening after successful mitral transcatheter edge-to-edge repair (TEER). In a large-scale registry including both primary and secondary mitral regurgitation patients, nearly 30% of TEER patients had a worsened LVEF, found to be caused mainly by an increased left ventricular end-systolic volume. Predictors include patient-specific factors and baseline left ventricular volumes and the worsened LVEF was found to be temporary with no long-term clinical outcomes.

Have referral trends in tricuspid transcatheter edge-to-edge repair influenced outcomes? In this research correspondence, **Karl-Patrik Kresoja, Philipp Lurz and colleagues** investigate the baseline characteristics of patients referred for tricuspid transcatheter edge-to-edge repair (T-TEER) for tricuspid regurgitation (TR) from 2016 to 2022 and find a shift in patient profiles from ventricular TR phenotypes with a high systemic disease burden to atrial TR phenotypes with less systemic burden but earlier disease stages. These changes could impact the statistical power needed in clinical trials and merit consideration in future trial design.

Finally, we include a debate on the discrepancies between two randomised trials which have left us questioning whether TAVI patients with bystander coronary artery disease (CAD) should receive percutaneous coronary intervention (PCI). To begin to find an answer to this conundrum, we turn to four distinguished professionals. For **Josep Rodés-Cabau and Marisa Avvedimento**, revascularisation of bystander CAD in carefully selected patients can improve quality of life and prognosis, while **Tiffany Patterson and Benedict McDonaugh** ask which endpoint is the most important to the patient and the prognosis, favouring relief of aortic stenosis.

And now that you see what's at stake and what subjects you can choose from within this issue, to further simplify, we invite you to delve in and choose what interests you the most.

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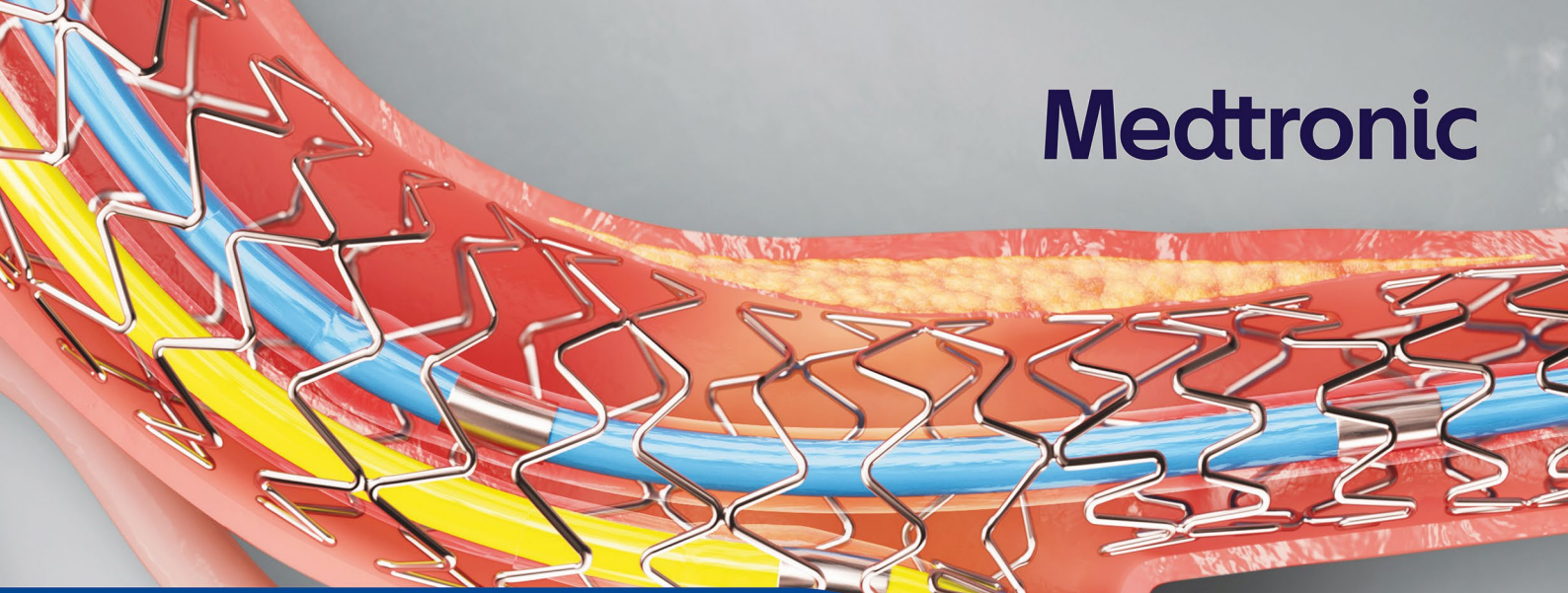
MINI FOCUS ON REDO-TAVI

ORIGINAL RESEARCH

RESEARCH CORRESPONDENCE

ORIGINAL RESEARCH



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RESEARCH CORRESPONDENCE

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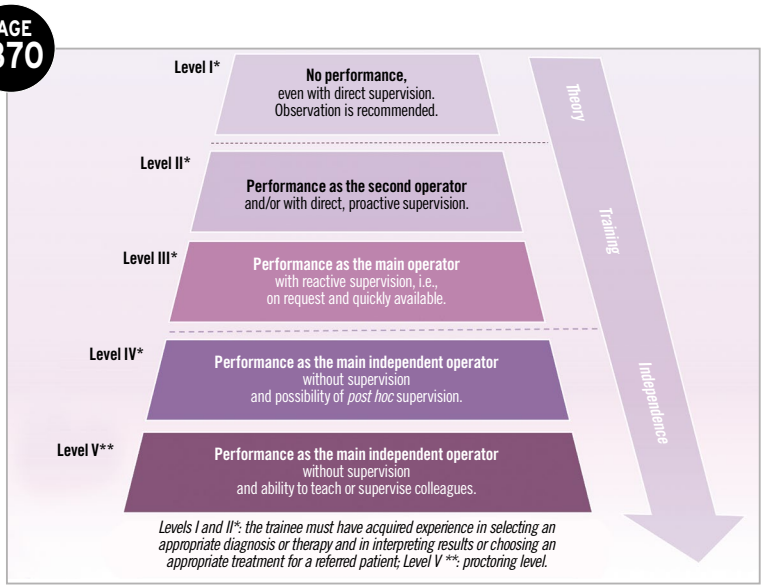

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Percutaneous Valvular and Structural Heart Disease Interventions. 2024 Core Curriculum of the European Association of Percutaneous Cardiovascular Interventions (EAPCI) of the ESC in collaboration with the European Association of Cardiovascular Imaging (EACVI) and the Cardiovascular Surgery Working Group (WG CVS) of the European Society of Cardiology
Rui Campante Teles, Eric Van Belle, Radoslaw Parma, Giuseppe Tarantini, Nicolas Van Mieghem, Darren Mylotte, Joana Delgado Silva, Stephen O'Connor, Lars Sondegaard, Andre Luz, Ignacio Jesus Amat-Santos, Dabit Arzamendi, Daniel Blackman, Ole De Backer, Vijay Kunadian, Gill Louise Buchanan, Phil MacCarthy, Philipp Lurz, Christopher Naber, Alaide Chieffo, Valeria Paradies, Martine Gilard, Flavien Vincent, Chiara Fraccaro, Julinda Mehilli, Cristina Giannini, Bruno Silva, Petra Poliacikova, Nicole Karam, Verena Veulemans, Holger Thiele, Thomas Pilgrim, Marleen van Wely, Stefan James, Michael Rahbek Schmidt, Anselm Uebing, Andreas Rück, Alexander Ghanem, Ziyad Ghazzal, Francis R. Joshi, Luca Favero, Renicus Hermanides, Vlasis Ninios, Luca Nai Fovino, Rutger-Jan Nuis, Pierre Deharo, Petr Kala, Gabby Elbaz-Greener, Didier Tchétché, Eustachio Agricola, Matthias Thielmann, Erwan Donal, Nikolaos Bonaros, Steven Droogmans, Martin Czerny, Andreas Baumbach, Emanuele Barbato, Dariusz Dudek, in collaboration with the European Association of Cardiovascular Imaging (EACVI) and the Cardiovascular Surgery Working Group (WG CVS) of the European Society of Cardiology
EuroIntervention 2024;20:1370-9.

EuroIntervention

EDITORIAL CONSULTANTS

EUROINTERVENTION
Publication : 24 numéros par an
Volume 20 - N°22 - Novembre 2024

Facteur d'impact : 7.6
2023 Journal Citation Reports®
(Clarivate Analytics, 2024)

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Groupe Composer : 2, impasse du Ramier des Catalans - CS 38503 - 31685 Toulouse Cedex 6 - France

Editeur
Frédéric Doncieux

Président : Marc Doncieux.
Principal actionnaire :
NOGA SAS

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

Imprimé en Espagne
par Soler T.G.
C/Enric Morera 15
08950 Esplugas de Llobregat España

EuroIntervention est édité par la Société Europa Group, SAS au capital de 1 080 704 euros, siège social : 19, allées Jean-Jaurès, 31000 Toulouse, France, RCS Toulouse 342 066 727, APE 8230 Z.

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

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

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2023 JOURNAL CITATION REPORTS® SCIENCE EDITION (CLARIVATE ANALYTICS, 2024)

Publication information
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EuroIntervention
2024;20:1364-1365
DOI: 10.4244/EIJ-E-24-00052

EDITORIAL

Low-flow, low-gradient aortic stenosis: an understanding is still a long way off

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Low-gradient (LG) aortic stenosis (AS) is estimated to account for at least one-third of all presentations in patients with suspected severe AS. Even though frequently encountered in clinical practice, patients with LG-AS are less likely to be referred for aortic valve replacement (AVR) compared to those with high-gradient (HG) AS, despite evidence to suggest a survival benefit with AVR over conservative management[1]. At least part of this therapeutic inertia is no doubt secondary to the ongoing diagnostic challenge associated with the correct adjudication of stenosis severity in patients presenting with discordant markers of AS severity on initial transthoracic echocardiography. Current society guidelines advocate a stepwise integrated approach for the diagnosis of LG-AS, utilising dobutamine stress echocardiography (DSE) and/or computed tomography calcium score, in patients with an aortic valve area <1 cm^2 and a mean gradient <40 mmHg[2]. These additional diagnostic modalities are intended to classify patients into 1 of 2 dominant patterns in LG-AS: classical low-flow, LG-AS (cLFLG-AS), in patients with a depressed left ventricular ejection fraction (LVEF; <50%), and paradoxical LFLG-AS (pLFLG-AS), in those with a normal LVEF but a low-flow state, as suggested by a reduction in the stroke volume index (<35 mL/m^2). However, DSE may be non-diagnostic in approximately 55% of patients with cLFLG-AS[3], and the utility of aortic valve calcium scoring in LG-AS has also recently been called into question[4]. It is therefore unsurprising that this patient population remains one of the more complex entities in valvular heart disease and, consequently, are often overlooked for appropriate intervention.

In this issue of EuroIntervention, Cardaioli et al[5] report on the long-term outcomes of patients with LG-AS undergoing transcatheter aortic valve implantation (TAVI). The authors performed a retrospective analysis of 574 consecutive patients at their institution, including 91 (15%) with pLFLG-AS, 64 (11%) with cLFLG-AS and 419 (73%) with HG-AS (>40 mmHg) who were followed for up to 12.3 years (median 4.8 years). The main findings of the study were as follows: (1) all-cause mortality was higher in patients with cLFLG-AS compared to both pLFLG-AS and HG-AS, which was most apparent in the first year following TAVI; (2) after adjustment for baseline covariates, including LVEF, the authors found no impact of flow status on long-term survival; and (3) LVEF improved by >10% in nearly two-thirds of patients with cLFLG-AS, and this was associated with improved survival. Cardaioli et al are to be commended for contributing important longer-term follow-up data on this still poorly understood group of patients with LG-AS.

Article, see page 1380

Consistent with previous studies and meta-analyses[1,6,7], a low-flow state was a powerful predictor of outcome, and patients with cLFLG-AS appeared to fare the worst (1-year Kaplan-Meier estimates: 75% for cLFLG-AS, 89% for pLFLG-AS, and 88% for HG-AS; p=0.009). Following adjustments for possible baseline confounders (including LVEF), however, the authors failed to find any significant differences in longer-term outcomes in patients with cLFLG-AS and HG-AS, leading them to surmise that it was the patients' comorbidities which had a greater impact on prognosis than the low-flow state itself. Arguably, this finding is not novel, with the comorbid nature of cLFLG-AS patients consistent with similar larger cohorts[6], and has been previously attributed to their poorer rates of survival following TAVI[8]. The degree of left ventricular (LV) impairment has also been shown to be a poor predictor of outcome in these patients[7]. The findings from the current study therefore reiterate that careful patient selection for

TAVI in patients with LG-AS is paramount, and likely more important than haemodynamics alone.

A degree of LV improvement following TAVI was also seen in nearly two-thirds of the current cohort with cLFLG-AS and was associated with an improvement in outcomes. This seems important and has frequently been reported in LG-AS (and HG-AS) cohorts[6-8]. Unfortunately, the authors did not have access to preprocedural DSE for the current cohort, with which they might have been able to compare the degree of contractile reserve, if any, with LV recovery. Previous studies have not, however, supported contractile reserve as a useful indicator of LV improvement over time[9]. Therefore the question remains as to how we predict those with the best likelihood for LVEF recovery and, thereby, clinical outcomes post-TAVI.

Patients with pLFLG-AS, on the other hand, have a normal LVEF and an impaired stroke volume due to a small LV cavity size and concentric remodelling leading to an intrinsic impairment in myocardial function. Contrary to the data presented in the current study, previous investigators have found higher rates of cardiovascular comorbidities also in patients with pLFLG-AS[6], raising the possibility that LG-AS may exist on a continuum, with cLFLG-AS an expression of a later stage of the same disease. Studies have described a poorer prognosis in pLFLG-AS compared to HG-AS, which is in contrast to the similar outcomes on unadjusted models presented in the current study. With only 64 patients included in this cohort, lack of an adequate sample size may contribute to this discrepancy.

In summary, the authors report on a topical group of patients with LG-AS, who remain underdiagnosed and undertreated in the cardiology community. They should be congratulated for contributing to the body of evidence that post-TAVI survival of these patients is comparable to those with HG-AS and is sustained in longer-term follow-up. Many of the findings presented, however, corroborate previous literature rather than move the needle forward to any great degree in our understanding of patients with LG-AS. Furthermore, the small patient cohort, particularly the number followed beyond 5 years, leaves significant unanswered questions regarding long-term outcomes of patients with LG-AS. Further studies are required to determine which patients with LG-AS, and at what timepoint, are most likely to benefit from valve replacement.

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Conflict of interest statement

J. Webb reports consulting fees from Edwards Lifesciences. S. Offen has no conflicts of interest to declare.

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EuroIntervention
2024;20:1366-1369
DOI: 10.4244/EIJ-E-24-00054

TAVI patients with bystander coronary artery disease should receive PCI: pros and cons

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The coexistence of coronary artery disease (CAD) and severe aortic stenosis is a frequent and complex clinical scenario, affecting up to 80% of patients undergoing transcatheter aortic valve implantation (TAVI). As the profile of TAVI candidates evolves – with younger patients and longer life expectancies – the prognostic implications of CAD become increasingly relevant. In addition, while aortic stenosis is a life-threatening condition requiring treatment to reduce overall mortality, the management of concomitant CAD is also crucial to improve symptoms. Treating significant CAD may undermine the benefits of TAVI, leading to persistent angina, adverse cardiac events over time, and reduced quality of life. However, stable CAD rarely necessitates urgent intervention, and percutaneous coronary intervention (PCI) carries potential risks (including bleeding, stroke, and acute kidney injury) without clear benefits in this setting. Although two randomised trials investigated this delicate issue, whether treating bystander CAD in patients undergoing TAVI is associated with favourable prognostic implications or merely adds procedural risks remains a matter of debate.

PROS

Josep Rodés-Cabau, MD, PhD; Marisa Avvedimento, MD

Due to the shared pathophysiology of aortic stenosis (AS) and atherosclerotic disease, more than half of patients with severe AS exhibit some degree of obstructive CAD, establishing coronary angiography as a routine examination to depict its presence before aortic valve replacement, whether surgical or transcatheter[1]. While obstructive CAD is routinely addressed at the time of surgical aortic valve replacement, the need for coronary revascularisation in TAVI candidates remains an unresolved issue. Three key points support the clinical benefit of PCI in TAVI recipients, with careful patient (and coronary anatomy) selection playing a pivotal role.

WHY? IMPACT OF SEVERE CAD ON ANGINA SYMPTOMS AND FUNCTIONAL STATUS

The primary goal of the TAVI procedure is not only to enhance survival but also functional status by relieving symptoms and ameliorating functional capacity. However, in TAVI candidates with severe, functionally significant coronary lesions, treating AS may extend life expectancy but may not sufficiently improve quality of life. Indeed, the coexistence of CAD is a strong contributing factor to persistent anginal symptoms, potentially hindering the overall benefit of the TAVI procedure[2,3]. In this context, addressing CAD can provide greater health benefits than performing TAVI alone, including improvements in angina relief, physical performance and quality of life.

WHEN? FAVOURABLE OUTCOMES OF PCI PRE-TAVI

PCI performed as part of the pre-TAVI work-up has consistently proven feasible and successful in most cases, even when addressing complex coronary lesions. Satisfactory midterm results have been reported, with low rates of target lesion failure (stent thrombosis and clinical restenosis at 2 years: 0.4% and 2.3%, respectively)[4]. These outcomes are comparable to those observed in all-comer PCI populations

outside the TAVI setting, providing reassuring evidence regarding the safety of combined PCI and TAVI procedures. Moreover, incomplete revascularisation and persistent angina after TAVI have been linked to poorer outcomes, including increased coronary events and cardiac death[1,3]. Performing PCI before TAVI may help to prevent coronary events stemming from untreated lesions and reduce the likelihood of unplanned revascularisation. Indeed, PCI failure rates increase in patients with prior TAVI, partly due to the interference between the transcatheter valve and the coronary ostia that can challenge or even preclude coronary revascularisation, which would likely have a negative impact on patient prognosis[1].

WHO? APPROPRIATE CORONARY ANATOMY SELECTION

To date, two randomised clinical trials have assessed the role of PCI in patients undergoing TAVI. In the PercutAneous Coronary inTervention prIor to transcatheter aortic VAlve implantaTION (ACTIVATION) trial, angiography-guided PCI pre-TAVI did not significantly reduce death or rehospitalisation rates at 1 year compared to medical treatment[5]. However, several limitations – such as premature enrolment termination, the exclusion of patients with more severe angina (Canadian Cardiovascular Society class III), lack of invasive physiology assessment, and an unrestricted CAD definition (stenosis ≥70%) – prevent firm conclusions. The third Nordic Aortic Valve Intervention (NOTION-3) trial constitutes the last and most valuable evidence in this scenario. In TAVI candidates with stable CAD, defined by a fractional flow reserve (FFR) ≤0.80 or a coronary stenosis of at least 90% as assessed by angiography, coronary revascularisation (PCI) was associated with a significant 29% reduction in all-cause mortality, myocardial infarction, or urgent revascularisation at a median follow-up of 2 years compared to conservative management[6]. Indeed, PCI decreased the risk of myocardial infarction by about 50%. This discrepancy with the ACTIVATION trial likely stems from coronary anatomy selection bias, as prior studies involving moderate or non-functionally significant lesions also failed to show clear benefits from routine revascularisation.

Revascularisation of bystander CAD in TAVI recipients can improve both prognosis and quality of life, provided that careful selection is performed. The decision to perform PCI should primarily be based on the angiographic degree of disease severity, with truly severe or physiologically significant stenoses located in the proximal-mid segments of major coronary arteries being the target of a default strategy. However, decisions should be also individualised according to the patient's age and comorbidities, functional status, and life expectancy, as well as bleeding risk.

Conflict of interest statement

J. Rodés-Cabau has received research grants and consultant/speaker fees from Edwards Lifesciences and Medtronic. M. Avvedimento reports no conflict of interest.

Cons

Tiffany Patterson, PhD; Benedict McDonaugh, MSc

Coronary artery disease coexists in a large proportion of patients with severe aortic stenosis (up to 80% in some series), the management of which continues to generate debate within Heart Teams across Europe and internationally[1]. Fundamentally, severe aortic stenosis is a life-threatening condition, whereas concomitant stable coronary artery disease is not. Therefore, the focus in these patients should always be relief of the aortic stenosis by TAVI. However, in the presence of bystander coronary disease, questions remain as to how best to minimise periprocedural risk and optimise longer-term outcomes.

There have been two recent randomised controlled trials comparing pre-TAVI PCI to a conservative approach, neither of which demonstrated an increase in periprocedural (TAVI) events in the control arm[5,6]. This could, in part, be due to the cohort of patients, who were younger and less comorbid than their counterparts 17 years ago, but also next-generation devices, delivery systems and operator experience with procedural risks, now quoted to be in the region of 2%.

Prior to the publication of the ACTIVATION trial results, practice was already changing: TAVI operators had moved away from performing routine pre-TAVI coronary angiography, to reduce hospital visits, and there had been a reduction in routine pre-TAVI PCI, in order to minimise stroke and acute kidney injury prior to TAVI **(Figure 1)**. With no demonstrable difference in the combined primary endpoint of death or rehospitalisation at 1 year and increased bleeding rates in the PCI arm post-randomisation, cardiologists were further deterred from performing pre-TAVI PCI.

The NOTION-3 Trial investigators present a different demographic of patients; in this refined cohort, patients with a low glomerular filtration rate were excluded, and patients exhibited a lower incidence of peripheral arterial disease, hence, the lower overall rates of bleeding in the PCI arm (although this was numerically higher compared to the conservative arm). Furthermore, fewer patients had prior myocardial infarction (MI), coronary artery bypass grafting or PCI in the trial cohort. The combined primary endpoint of death, MI and urgent revascularisation (predominantly non-ST-elevation MI [NSTEMI]) just reached statistical significance at 2 years, with a numerical difference of 21 events between the two groups for the primary endpoint despite the presence of significant coronary lesions (stenosis >90% on angiography and/or FFR <0.8) in all patients.

Post-TAVI coronary access is also a concern in these patients, and it is still prudent to select a valve with favourable coronary access in patients with concomitant coronary disease. However, the combination of refined device positioning, reduced stent-frame height, larger stent-frame cell size and commissural alignment increase the feasibility of successful coronary re-access[7].

Over the past two decades, numerous randomised trials have questioned the utility of PCI compared to medical therapy in patients with stable coronary disease. These have demonstrated that PCI does not reduce deaths or

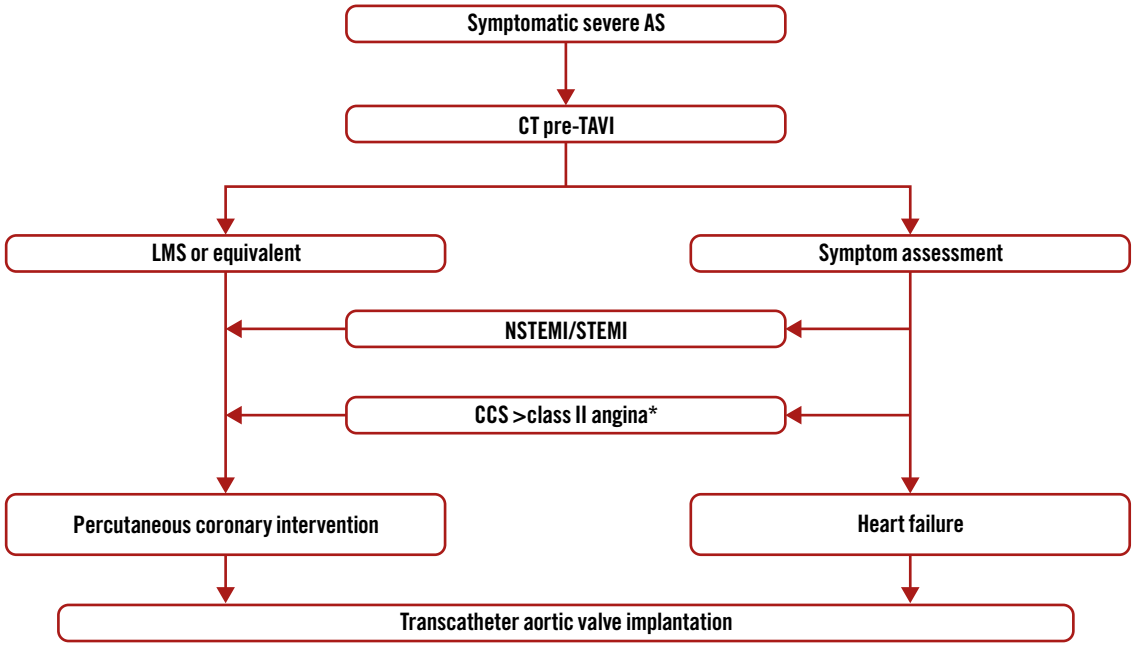

Figure 1. *Treatment of significant bystander coronary disease in patients awaiting transcatheter aortic valve implantation. All patients should be discussed in a Heart Team meeting, and the presence of significant frailty or advanced age would favour conservative management. *Considering FFR guidance whilst acknowledging the limitations in the presence of severe AS, it is reasonable to perform PCI before or after TAVI; if it is the latter, consideration should be given to valve choice. CCS: Canadian Cardiovascular Society; CT: computed tomography; FFR: fractional flow reserve; LMS: left main stem; NSTEMI: non-ST-elevation myocardial infarction; STEMI: ST-elevation myocardial infarction*

total MIs but does reduce unplanned revascularisation and spontaneous MI; in patients with significant angina, quality of life is improved with PCI. In patients over 75 years old, the SENIOR-RITA Trial[8] supports a conservative approach even in the presence of NSTEMI with no difference in outcomes when followed up to 4 years.

Extrapolation of these findings to our cohort of TAVI patients then raises the more important question of which endpoints matter to us and our patients, as large registries demonstrate a 1% incidence, at most, of unplanned PCI post-TAVI. Therefore, in the absence of severe left main stem disease or ST-elevation MI, it is sensible to conclude that the most significant lesion is in the aortic valve.

Conflict of interest statement

T. Patterson has no conflicts of interest to declare in relation to this article. B. McDonough has no conflicts of interest to declare in relation to this article.

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EuroIntervention
2024;20:1370-1379
published online ahead of print August 2024
DOI: 10.4244/EIJ-D-23-00983

Percutaneous Valvular and Structural Heart Disease Interventions. 2024 Core Curriculum of the European Association of Percutaneous Cardiovascular Interventions (EAPCI) of the ESC in collaboration with the European Association of Cardiovascular Imaging (EACVI) and the Cardiovascular Surgery Working Group (WG CVS) of the European Society of Cardiology

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ABSTRACT

The percutaneous treatment of structural, valvular, and non-valvular heart disease (SHD) is rapidly evolving. The Core Curriculum (CC) proposed by the EAPCI describes the knowledge, skills, and attitudes that define competency levels required by newly trained SHD interventional cardiologists (IC) and provides guidance for training centres. SHD ICs are cardiologists who have received complete interventional cardiology training. They are multidisciplinary team specialists who manage adult SHD patients from diagnosis to follow-up and perform percutaneous procedures in this area. They are competent in interpreting advanced imaging techniques and master planning software. The SHD ICs are expected to be proficient in the aortic, mitral, and tricuspid areas. They may have selective skills in either the aortic area or mitral/tricuspid areas. In this case, they must still have common transversal competencies in the aortic, mitral, and tricuspid areas. Additional SHD domain competencies are optional. Completing dedicated SHD training, aiming for full aortic, mitral, and tricuspid competencies, requires at least 18 months. For full training in the aortic area, with basic competencies in mitral/tricuspid areas, the training can be reduced to 1 year. The same is true for training in the mitral/tricuspid area, with competencies in the aortic area. The SHD IC CC promotes excellence and homogeneous training across Europe and is the cornerstone of future certifications and patient protection. It may be a reference for future CC for national associations and other SHD specialities, including imaging and cardiac surgery.

KEYWORDS: aortic stenosis; atrial fibrillation; hypertrophic cardiomyopathy; imaging modalities; mitral regurgitation; training and education

SUBMITTED ON 18/11/2023 - REVISION RECEIVED ON 1st 21/03/2024 / 2nd 08/07/2024 - ACCEPTED ON 08/07/2024

The treatment of structural, valvular, and non-valvular heart disease (SHD) has been revolutionised by the emergence and development of percutaneous techniques. Percutaneous treatment of adult SHD is now a mature field supported by robust scientific evidence developed in recent decades and has been associated with significant benefits for both individuals and populations. While it is expected by both regulation authorities and patients that physicians will have had guidance for individual training (cardiologists, imaging cardiologists, cardiac surgeons, and first use of interventional cardiologist) in managing patients suffering from SHD, such recommendations are still lacking. The current Core Curriculum (CC) for percutaneous SHD interventions has been designed by the European Association of Percutaneous Cardiovascular Interventions (EAPCI) as the first key step to filling this gap in interventional cardiology. This innovative document has been prepared in collaboration with the European Association of Cardiovascular Imaging (EACVI) and the Cardiovascular Surgery Working Group (WG CVS) of the European Society of Cardiology (ESC). It will stimulate future Core Curricula in other SHD specialities where EAPCI is available to offer support and expects to collaborate, including imaging and cardiac surgery.

This curriculum was organised to follow and complement the Core Curriculum for Percutaneous Cardiovascular Interventions (2020) by the EAPCI Training and Certification Committee (TCC)[1].

Introduction

The present SHD CC aims to support the educational requirements of an updated European consensus. It defines and standardises competency levels required for percutaneous SHD interventions to treat patients with heart failure and cardiac symptoms related to valve disease or to prevent complications of thromboembolic diseases **(Figure 1)**.

Methodology

The writing task force included members with substantial expertise in different aspects of SHD percutaneous interventions nominated by EAPCI. Detailed data on this document's preparation process are found in the "2023 EAPCI Core Curriculum for Percutaneous Structural Heart Disease Interventions Extended Version" and are available upon request to the corresponding authors **(Figure 2)**.

The 2023 EAPCI Core Curriculum for Percutaneous Structural Heart Disease Interventions Extended Version includes a comprehensive description of the specific components in 5 areas, organised into 114 chapters and subchapters. Each section includes statements on the objectives and is further subdivided into the required objectives, knowledge, skills, behaviours, ESC topic list, essential reading, and attitudes.

This manuscript aims to be a reference for future iterations that will occur under the auspices of the EAPCI **(Central illustration)**.

EAPCI Core Curriculum for Percutaneous Structural Heart Disease Interventions

THE CLINICAL FIELD OF PERCUTANEOUS STRUCTURAL HEART DISEASE INTERVENTIONS

A solid background in coronary interventions, peripheral artery disease, and management of any procedural complications is needed, requiring a level of competence in interventional cardiology that is equal to or above the EAPCI Interventional Cardiology Core Curriculum 2020[1-5].

The SHD CC differentiates between an "SHD IC" and a "Domain expert": the first chooses a comprehensive training in the Aortic (AOR) and/or Mitral/Tricuspid (MTC) modules. The latter is an IC whose differentiation is limited to particular areas: aortic, mitral, tricuspid, paravalvular regurgitation, septal ablation, adult congenital heart disease, ventricular septal defects, atrial septal defects, patent foramen ovale, left atrial appendage occlusions or pulmonary thromboembolism **(Figure 3)**.

GENERAL ASPECTS OF TRAINING IN PERCUTANEOUS SHD INTERVENTIONS

The candidates should be cardiologists licensed to practice IC in their country of training. A candidate should have completed a minimum of four years of training in general cardiology and two years of full-time training in IC. As part of the training in interventional cardiology, it is assumed that the IC has achieved all Level IV and Level V competencies described in the EAPCI IC CC[1].

The trainee should have had exposure to an appropriate mix of aortic and mitral/tricuspid as well as acute and elective cardiac care, including mandatory, strongly recommended or recommended elements, as described below in **Figure 4**[6-9].

LEARNING OBJECTIVES

The trainee's education should include the competency domains of interventional cardiology: knowledge, skills, and attitudes which are defined below and should be reinforced during ongoing training. This section describes the definition of EAPCI levels of competence (LoC) recommendations for procedural or non-procedural skills. Their ascending order is summarised in **Figure 5**.

REQUIREMENTS FOR TRAINING INSTITUTIONS, TRAINEES, AND TRAINERS

A percutaneous SHD training centre is an institution or healthcare network that performs SHD procedures and provides a structured training program for certified

Abbreviations

CC	Core Curriculum
EACVI	European Association of Cardiovascular Imaging
EAPCI	European Association of Percutaneous Cardiovascular Interventions
IC	interventional cardiologists/cardiology
LoC	levels of competence
SDAIC	Scientific Documents and Initiatives Committee
SHD	structural, valvular, and non-valvular heart disease
TCC	Training and Certification Committee
TF	Task Force
WG CVS	Cardiovascular Surgery Working Group

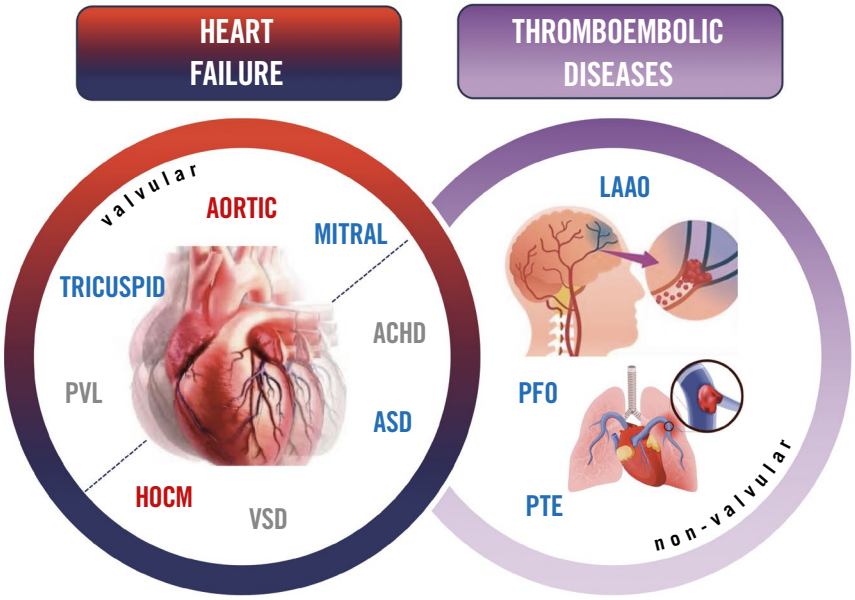


Figure 1. *The spectrum of cardiology areas treated by percutaneous structural heart disease interventions: valvular (aortic valve, mitral valve, tricuspid valves, paravalvular regurgitation) and non-valvular (hypertrophic obstructive cardiomyopathy septal ablation, ventricular septal defect, atrial septal defect, adult congenital heart disease, patent foramen ovale, left atrial appendage occlusion and pulmonary thromboembolism). These interventions can be used separately – or combined – to treat patients with thromboembolic diseases or heart failure. The colour code is consistent with the prevailing percutaneous treatment route, arterial (red), venous (blue) or mixed (red/blue). ACHD: adult congenital heart disease; ASD: atrial septal defect; HOCM: hypertrophic obstructive cardiomyopathy; LAAO: left atrial appendage occlusion; PFO: patent foramen ovale; PTE: pulmonary thromboembolism; PVL: paravalvular regurgitation; VSD: ventricular septal defect*

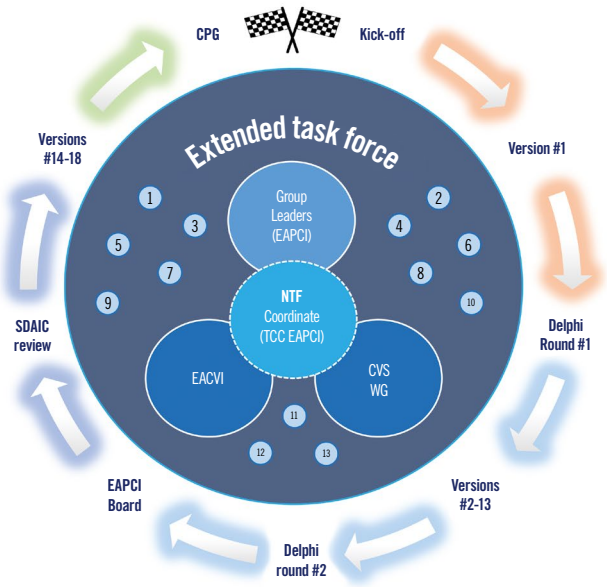
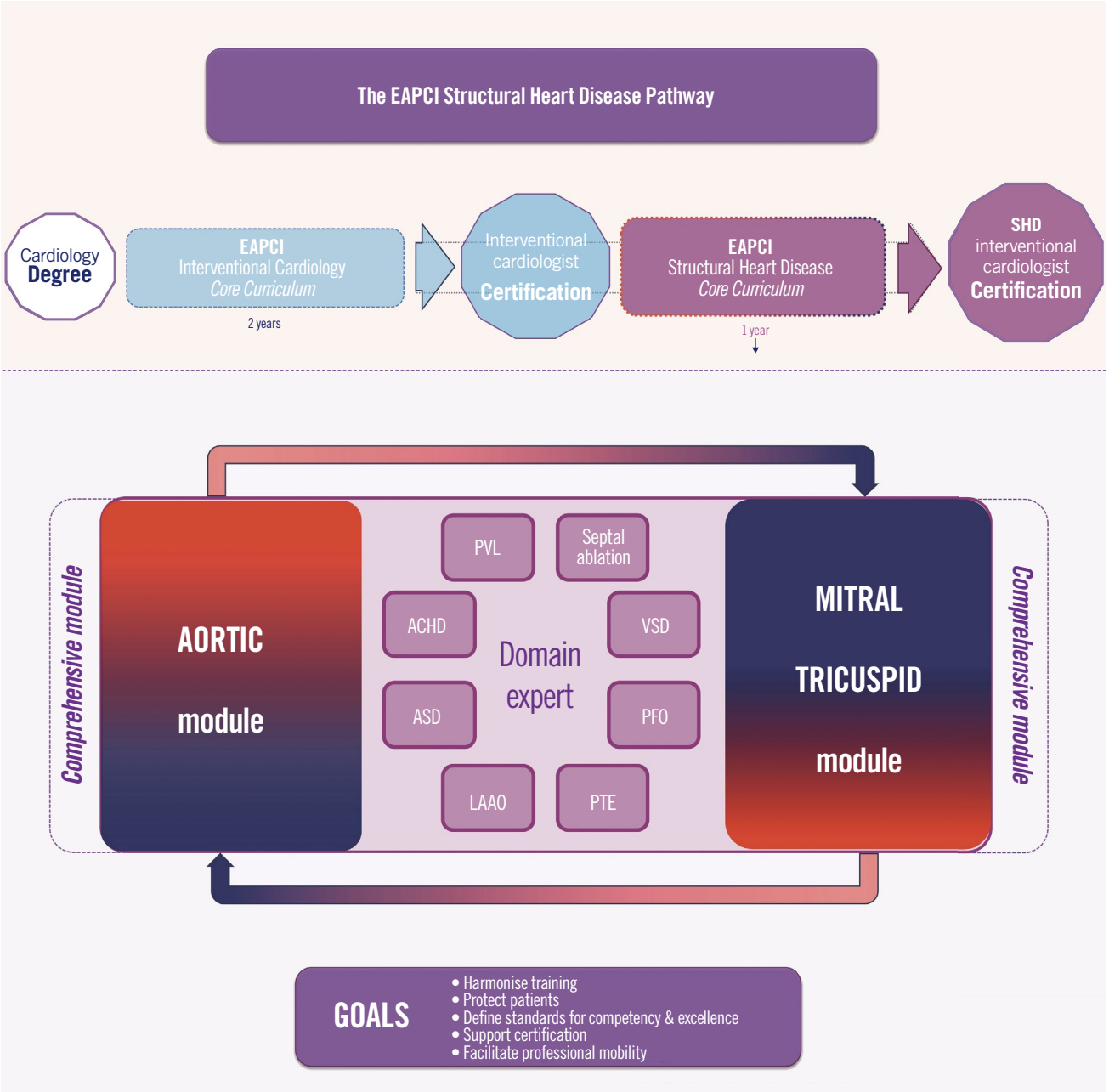


Figure 2. *Methodology of the European Association of Percutaneous Cardiovascular Interventions (EAPCI) Training and Certification Committee (TCC) Task Force (TF): the writing TF included three coordinating authors, a Nuclear Task Force (NTF) of 13 lead authors & group coordinators, and an Extended Task Force of 34 members, including the European Association of Cardiovascular Imaging (EACVI) and the Cardiovascular Surgery Working Group (WG CVS) of the European Society of Cardiology. The document was blindly revised by the EAPCI Scientific Documents and Initiatives Committee (SDAIC) and concluded after revision by the NTF and EAPCI Board. This version was circulated, revised, and approved by all authors. Finally, the Clinical Practice Guidelines (CPG) Committee formally approved the final version.*

EuroIntervention

Central **Illustration**

The EAPCI Structural Heart Disease Training and Certification Pathway.



Rui Campante Teles *et al.* • *EuroIntervention* 2024;20:1370-1379 • DOI: 10.4244/EIJ-D-23-00983

Starting with a general cardiology degree, the interventional cardiologist training follows the EAPCI Interventional Cardiology (IC) Core Curriculum to acquire the EAPCI Interventional Cardiology Certification. Sequentially, the same training path follows the EAPCI Core Curriculum for Percutaneous Structural Heart Disease (SHD) Interventions to acquire the SHD Certification. An overlap between IC and SHD-IC certifications is accepted, allowing the IC to be certified 30 months after starting the IC Certification. Within the SHD Certification, the same principle is envisaged. While a comprehensive aortic/mitral/tricuspid is recommended, further dedicated training using the aortic or the mitral/tricuspid module is also possible, allowing SHD training to be completed in 1 year. The additional domains can be acquired in parallel when conditions permit. ACHD: adult congenital heart disease; ASD: atrial septal defect; EAPCI: European Association of Percutaneous Cardiovascular Interventions; LAAO: left atrial appendage occlusion; PFO: patent foramen ovale; PTE: pulmonary thromboembolism; PVL: paravalvular regurgitation; VSD: ventricular septal defect

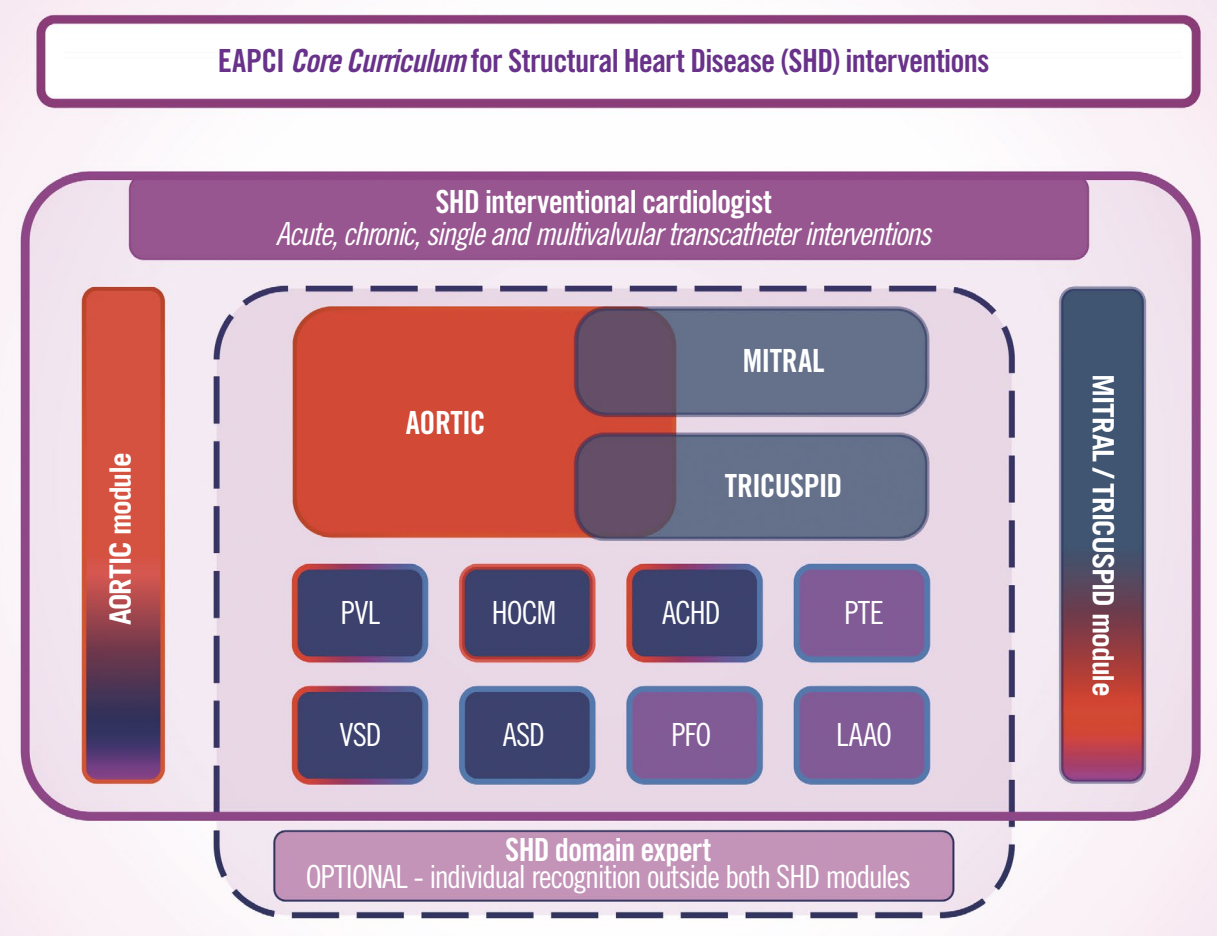


Figure 3. *The EAPCI Core Curriculum for Percutaneous SHD Interventions Training plan, modules, and domains: after the cardiology degree (minimum of 4 years of training) and interventional cardiologist (IC) certification (2 years) the trainee can engage in the comprehensive training module, the aortic/mitral/tricuspid (AoMTC), or choose between the aortic (AOR) and mitral/tricuspid (MTC) modules, respectively (red or light blue background, respectively). These modules are complementary, since each trainee involved in one module should still acquire minimal expertise from the other one. The recommended minimum duration of each of the two dedicated SHD IC training modules should be one year of training in SHD IC for each one of these areas, or 18 months when both are acquired in combination (AoMTC). In addition, as part of each module, the trainee will also have to acquire basic expertise in other specific SHD areas where full expertise can be acquired outside (or on top) of each SHD module* **(Figure 2)** *(dark blue or magenta backgrounds, that are related, respectively, with prevailing heart failure or thromboembolic disease). This optional "Domain expertise" recognition is designed to acknowledge the differentiation in any particular area included in the EAPCI SHD IC CC, without the requirement for transversal competencies as above: aortic intervention, mitral and tricuspid intervention, paravalvular regurgitation (PVL), septal ablation (HOCM), adult congenital heart disease (ACHD), ventricular septal defect (VSD), atrial septal defect (ASD), patent foramen ovale (PFO), left atrial appendage occlusion (LAAO) and pulmonary thromboembolism (PTE). Within the SHD Certification, practice overlap is possible to allow training in the Aortic, Mitral/Tricuspid modules, and any other domain can be acquired in parallel when conditions permit. The colour code is consistent with the prevailing disease: thromboembolic (magenta) or heart failure (red or blue background), and the competencies are delimited by different lines according to the usual percutaneous treatment route: arterial (red), venous (blue) or mixed (red/blue). SHD: structural heart disease*

interventional cardiologists aiming to achieve the required EAPCI SHD CC LoC in a favourable environment.

The technical portfolio, organisation, referral network, volume and performance of the SHD training centre define the extent and quality of training in SHD[10]. The institution and affiliates must comply with the requirements and recommendations of their national regulatory bodies first and follow the ESC recommendations and Heart Valve Centres concept, second[11]. An SHD training centre should have an established clinical, research and SHD training programme[12-20].

Trainers should be recognised IC specialists, trained and certified in SHD (where available), and actively involved in the clinical and research activities of the local Heart Team. Their number should always match or exceed the number of trainees. The LoCs that a trainee needs to achieve at the end of his training period are summarised in **Figure 6**. A more

AREA OF TRAINING	GENERAL ASPECTS OF TRAINING	REQUIREMENT
SUPERVISOR & MENTOR REQUIREMENTS	> 5 years dedicated to percutaneous cardiovascular interventions	M
CONTINUOUS MEDICAL EDUCATION	Structured learning under supervision	M
OUTPATIENT CLINIC	Diagnostic, pre- and postprocedural assessment	M
MULTIMODALITY IMAGING FOR CLINICAL EVALUATION	Comprehensive analysis of echocardiography, MSCT and CMR imaging	M
HEART TEAM	Active participation in regular meetings	M
CARDIAC SURGERY OR	Exposure to open heart procedures	R
MAIN STRUCTURAL INTERVENTIONS	Main exposure to aortic and/or to mitral/tricuspid areas (AOR or MTC or AoMTC modules)	M
OTHER STRUCTURAL INTERVENTIONS	Exposure to other structural domains	R+
PROCEDURAL IMAGING GUIDANCE	Imaging-based procedural planning software and interventional guidance	M
LARGE VASCULAR ACCESS	All aspects of management	M
PROCEDURAL SKILLS	Progress from cases with direct supervision to independent operator status (AORTIC or MITRAL module)	M
RESEARCH	Participation in research & critical appraisal of evidence	R
EVALUATION	Regular & formal LoC progress assessment and clinical audit program	M

M *Mandatory* R+ *Strongly recommended* R *Recommended*

Figure 4. *Summary of the structured requirements for percutaneous training programmes in structural heart disease. AOR: aortic; CMR: cardiac magnetic resonance; LoC: level of competence; MSCT: multislice computed tomography; MTC: mitral/tricuspid; OR: operating room*

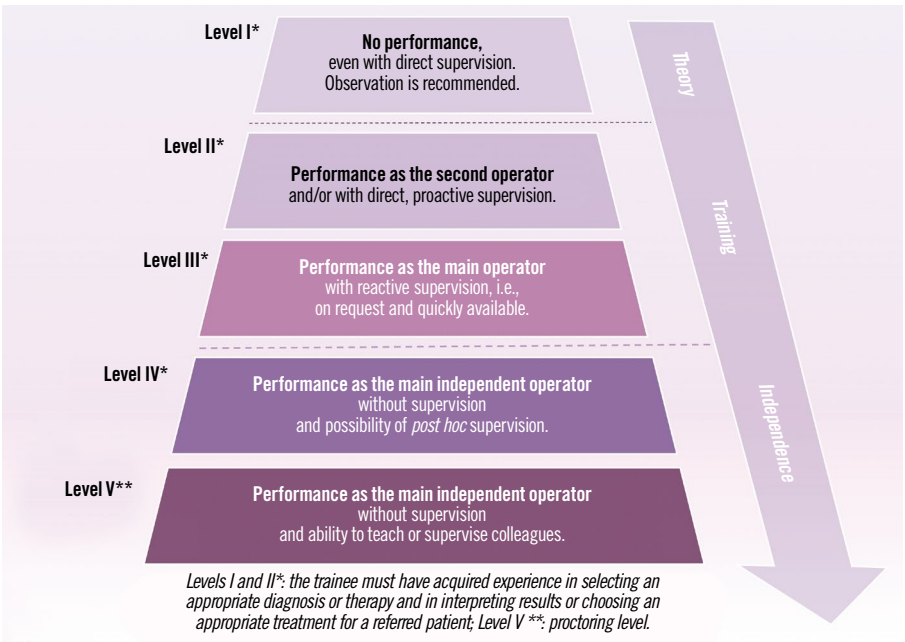


Figure 5. *Description of levels of competence (LoC) for non-procedural or procedural skills (adapted from Entrustable Professional Activities).*

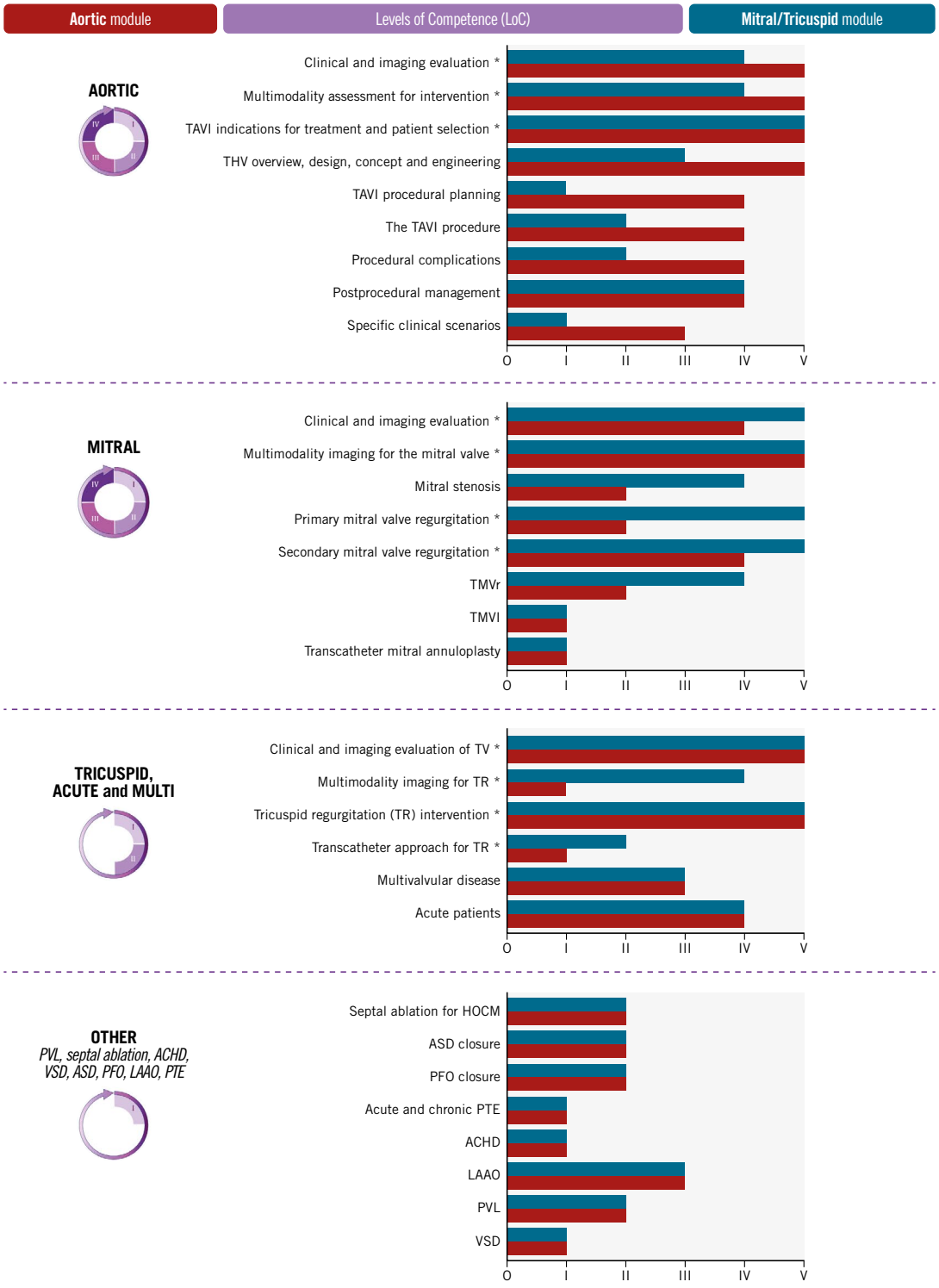


Figure 6. *Condensed comparison of the level of competence (LoC) for non-procedural (*) and procedural interventional cardiology skills in the AOR or MTC modules of the SHD IC (from I/1 to V/5). The AoMTC training requires, for any competence, the highest LoC of either AOR or MTC and is not presented to prevent confusion. The optional "Domain expert" recognition demands all theoretical requirements and a minimum LoC IV in all the domains of interventional cardiology, which are defined in their chapter or subchapter: aortic, mitral/tricuspid, septal ablation (HOCM), paravalvular leak (PVL), ventricular septal defect (VSD), atrial septal defect (ASD), adult congenital heart disease (ACHD), patent foramen ovale (PFO), left atrial appendage occlusion (LAAO) and pulmonary thromboembolism (PTE). HOCM: hypertrophic obstructive cardiomyopathy; TAVI: transcatheter aortic valve intervention; THV: transcather heart valve; TMVR: transcatheter mitral valve replacement; TMVI: transcatheter mitral valve intervention; TV: transcatheter valves*

detailed description of each area of training is provided in the extended version of the document. (https://www.escardio.org/Sub-specialty-communities/European-Association-of-Percutaneous-Cardiovascular-Interventions-(EAPCI)).

Conclusions

The Percutaneous Valvular and Structural Heart Disease Interventions Core Curriculum of the European Association of Percutaneous Cardiovascular Interventions (EAPCI) provides guidance for training centres and trainees.

It describes the knowledge, skills, and attitudes that define competency levels required from newly trained interventional cardiologists performing structural heart disease interventions. They should train within multidisciplinary teams, managing adult patients from diagnosis to follow-up, developing selective skills in either aortic and/or mitral/tricuspid areas. Their education may be complemented by competencies in other domains such as adult congenital heart disease, left atrial appendage occlusion, pulmonary thromboembolism, paravalvular regurgitation, septal ablation or septal defects.

The Core Curriculum promotes excellence and universal training in ESC countries, forming the cornerstone of future certifications for patient protection.

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Data availability statement

No new data were generated or analysed in support of this document.

Acknowledgements

The Clinical Practice Guidelines (CPG) Committee from the European Society of Cardiology formally approved the document.

Conflict of interest statement

E. Agricola has received speaker honoraria and compensation from GE HealthCare, outside the current topic. I.J. Amat-Santos has received speaker honoraria and advisory board compensation from Boston Scientific, Meril Life, Medtronic, and Abbott. A. Baumbach has received institutional research support from Biotronik; and honoraria from Faraday, Pi-Cardia and Meril Life. D. Blackman has acted as a consultant, advisory board member, and speaker for Abbott, Edwards Lifesciences, and Medtronic. N. Bonaros has received speaker honoraria from Edwards Lifesciences and Medtronic; as well as research grants from Edwards Lifesciences and Corcym. M. Czerny is consultant to Terumo Aortic, Medtronic, NEOS, and Endospan. O. De Backer has received research grants, speaker and consulting fees from Abbott, Boston Scientific, and Medtronic. P. Deharo has received honoraria from Boston Scientific, Abbott, Asahi, Medtronic and Novartis. P. Lurz has received institutional fees and research grants from Abbott, Edwards Lifesciences, and ReCor; honoraria from Edwards Lifesciences, Abbott, Innoventric, ReCor and Boehringer Ingelheim; and has stock options with Innoventric. R. Hermanides has received compensation from companies outside the current topic. S. James has received institutional research support from Edwards Lifesciences and Medtronic; and proctoring fees from Medtronic. F.R. Joshi has received honoraria and advisory board compensation from Boston Scientific; and travel support from Millbrook Medical. P. Kala declares that he has received consultant and speaker fees from Boston Scientific, Edwards Lifesciences, Sanofi, Novartis, and Servier; participated in advisory boards from Boston Scientific, Abbott, Novartis, and Servier; and received research support from Bayer, Novartis, and Amgen. N. Karam has received consultant fees from Abbott, Medtronic, Edwards Lifesciences, and Boston Scientific. A. Luz has received consultant fees from Abbott. J. Mehilli has received speaker honoraria and compensation from AstraZeneca, Boston Scientific, Daiichi Sankyo, and Shockwave. D. Mylotte has received research grants from Boston Scientific; and speaker honoraria/advisory board compensation from Medtronic, Microport, and Boston Scientific. R. Nuis has received research grant support from Vifor Pharma; and consulting fees from Edwards Lifesciences, Abbott, and Boston Scientific. V. Paradies declares research grants from Abbott to the institution; and speaker fees from Abbott and Boston Scientific. R. Parma has received speaker fees from Edwards Lifesciences. A. Rück declares institutional research and educational grants from Boston Scientific and Edwards Lifesciences; and personal speaker and consultancy fees from Boston Scientific, Abbott, Edwards Lifesciences, and Anteris. T. Pilgrim reports research, travel or educational grants to the institution without personal remuneration from Biotronik, Boston Scientific, and Edwards Lifesciences; and speaker fees and consultancy fees to the institution from Biotronik, Boston Scientific, Edwards Lifesciences, Abbott, Medtronic, Biosensors, and Highlife. G. Tarantini has received speaker honoraria/advisory board compensation from Edwards Lifesciences, Boston Scientific, Medtronic, Abbott, Philips, and Microport. D. Tchétché is consultant for Abbott, Boston Scientific, Edwards Lifesciences, and Medtronic. A. Uebing has received advisory board compensation from Medtronic. N. Van Mieghem has received research grant support from Abbott, Boston Scientific, Medtronic, AstraZeneca, and Daiichi Sankyo; and scientific advisory fees from Anteris, JenaValve, Amgen, Siemens, Pie Medical, Abbott, Boston Scientific, Medtronic, AstraZeneca, and Daiichi Sankyo. M. van Wely has received proctoring fees from Abbott; and speaker fees from Boston Scientific. V. Veulemans has received consulting fees, travel expenses, or study honoraria from Medtronic, Edwards Lifesciences, and Boston Scientific. The other authors have no conflicts of interest to declare.

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EuroIntervention
2024;20:1380-1389
DOI: 10.4244/EIJ-D-24-00442

ORIGINAL RESEARCH

Long-term survival after TAVI in low-flow, low-gradient aortic valve stenosis

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This paper also includes supplementary data published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-24-00442

ABSTRACT

BACKGROUND: In patients undergoing transcatheter aortic valve implantation (TAVI), the presence of a low-flow, low-gradient (LFLG) status has been associated with higher mortality at short-term follow-up.

AIMS: We aimed to evaluate long-term survival after TAVI in patients with classical (cLFLG) and paradoxical LFLG (pLFLG) aortic stenosis (AS) compared to high-gradient (HG)-AS.

METHODS: Patients undergoing TAVI at our centre with a hypothetical minimum 5-year follow-up were divided into 3 groups: (1) HG-AS (mean gradient [MG] >40 mmHg), (2) cLFLG-AS (MG <40 mmHg, ejection fraction [EF] <50%), and (3) pLFLG-AS (MG <40 mmHg, EF ≥50%). The primary endpoint of the study was all-cause mortality. Propensity score-weighted survival analysis was performed to adjust for possible baseline confounders.

RESULTS: A total of 574 subjects were included (73% HG-AS, 15% pLFLG-AS, 11% cLFLG-AS). The median survival time was 4.8 years, with a maximum of 12.3 years. Patients with cLFLG-AS presented the highest baseline cardiovascular risk. At unadjusted survival analysis, patients with cLFLG-AS showed the worst long-term prognosis, with a rapid decrease in survival within the first year, while pLFLG- and HG-AS patients presented similar survival rates (p=0.023). At weighted long-term analysis, cLFLG- and HG-AS had similar survival rates. Baseline EF was not related to long-term mortality, while patients with a post-TAVI left ventricular ejection fraction (LVEF) improvement >10% lived significantly longer (p=0.02).

CONCLUSIONS: Classical LFLG-AS patients had lower long-term survival rates as compared to pLFLG-AS and HG-AS patients. However, after adjustment for possible baseline confounders, a low-flow status *per se* did not have an impact on long-term mortality after TAVI. Post-TAVI LVEF recovery was associated with improved long-term outcome.

KEYWORDS: aortic stenosis; depressed left ventricular function; TAVI

SUBMITTED ON 10/05/2024 - REVISION RECEIVED ON 1st 12/07/2024 / 2nd 30/07/2024 - ACCEPTED ON 07/08/2024

Transcatheter aortic valve implantation (TAVI) has emerged as the preferred treatment for elderly patients with severe symptomatic aortic stenosis (AS)[1,2]. Up to one-third of patients with severe AS[3,4] exhibit a low-flow, low-gradient (LFLG) condition, characterised by an aortic valve area (AVA) <1 cm², a mean transvalvular gradient (MG) <40 mmHg, and a stroke volume index (SVi) <35 ml/m² [5]. Low-flow, low-gradient status can be further categorised into classical LFLG (cLFLG) when associated with a left ventricular ejection fraction (LVEF) <50% and paradoxical LFLG (pLFLG) when the LVEF is ≥50%[1]. Despite a clear benefit of TAVI over conservative treatment in patients with LFLG-AS[6-9], cLFLG status has been related to worse post-TAVI outcomes at midterm follow-up compared to high-gradient (HG)-AS[9-11]. Whether the worse outcome can be attributed to the low-flow status itself or is influenced by a more compromised baseline clinical condition remains a topic of debate[12,13]. However, it is reasonable to assume that multiple factors may contribute to the worse prognosis in cLFLG-AS patients, who are typically frailer and affected by various comorbidities[8,9,14]. On the contrary, patients with pLFLG-AS undergoing TAVI have shown survival rates at 1-year follow-up that are comparable to those of patients diagnosed with HG-AS[15,16]. Notwithstanding, data on the long-term outcomes of LFLG-AS patients treated with TAVI are lacking. The aim of our study was to assess the long-term survival (up to 10 years) following TAVI in patients with cLFLG- or pLFLG-AS compared to those with HG-AS.

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Impact on daily practice

While classical low-flow, low-gradient aortic stenosis (AS) patients exhibit lower survival rates compared to high-gradient AS patients at unadjusted analysis, this disparity diminishes when accounting for potential baseline confounders, suggesting that a patient's risk profile may play a more significant role than low-flow status alone. Thus, accurate patient selection during preprocedural planning might improve transcatheter valve implantation outcomes and could be useful to avoid futile interventions.

Methods

STUDY DESIGN

This study represents a retrospective analysis conducted using data from the Padua University REVALVing Experience (PUREVALVE) registry, which includes all consecutive patients who underwent TAVI for severe symptomatic AS (aortic valve area <1 cm² or <0.6 cm²/m² of body surface area) at our institution. For the purpose of the study, we included in the analysis all consecutive patients who underwent TAVI between June 2007 and December 2017. Indications for TAVI were based on a Heart Team decision. Patients were further divided into 3 different subgroups according to their baseline echocardiographic findings: (1) HG-AS: MG >40 mmHg; (2) cLFLG-AS: MG <40 mmHg, SVi <35 ml/m², LVEF <50%; and (3) pLFLG-AS: MG <40 mmHg, SVi <35 ml/m², LVEF ≥50%. We excluded from the current analysis (a) patients who underwent valve-in-valve interventions, (b) patients with preprocedural MG <40 mmHg associated with a normal SVi (>35 ml/m²), and (c) TAVI patients without technical success based on Valve Academic Research Consortium (VARC)-3 criteria[17]. Follow-up time was defined as the time from the procedure to the last documented contact with the patient (alive) or to the time of documented death. The primary endpoint was all-cause mortality. We also determined the percentage of patients who presented a significant improvement in LVEF within the first year after the procedure (>10%)[18,19]. All patients provided written informed consent for the procedure and data collection. The study was approved by the Institutional Ethics Committee and conforms to the principles outlined in the Declaration of Helsinki.

ECHOCARDIOGRAPHIC DATA

All patients underwent comprehensive baseline transthoracic echocardiography (TTE) by an experienced echocardiographer at our centre, in accordance with established guidelines[20,21]. Follow-up TTE was performed during the index hospitalisation and subsequently during follow-up, generally at 3, 6, and 12 months. LVEF was derived from left ventricular (LV) end-diastolic and end-systolic volumes measured on the apical 2- and 4-chamber views, using the Simpson method. Aortic valve area was calculated using the continuity equation. To confirm the severity of AS, dobutamine stress echocardiography was performed in patients with LFLG status and reduced LVEF (cLFLG-AS), while the aortic valve calcium score was evaluated at preprocedural multidetector computed tomography (CT) in case of pLFLG-AS[1].

DEVICE AND PROCEDURE

Transcatheter heart valve (THV) choice and TAVI access were based on a Heart Team decision. Five types of THV were implanted: (1) the balloon-expandable SAPIEN, SAPIEN XT and SAPIEN 3 (Edwards Lifesciences); (2) the mechanically expandable LOTUS Edge (Boston Scientific); (3) the self-expanding CoreValve, Evolut R and Evolut PRO (Medtronic); (4) the self-expanding ACURATE *neo* (Boston Scientific) and (5) the JenaValve Trilogy (JenaValve). Percutaneous coronary revascularisation was performed in case of severe coronary artery disease involving proximal vessel segments,

Abbreviations

AS	aortic stenosis	**LFLG**	low-flow, low-gradient	**SVi**	stroke volume index
AVA	aortic valve area	**LVEF**	left ventricular ejection fraction	**TAVI**	transcatheter aortic valve implantation
cLFLG	classical low-flow, low-gradient	**MG**	mean gradient	**THV**	transcatheter heart valve
HG	high-gradient	**pLFLG**	paradoxical low-flow, low-gradient	**TTE**	transthoracic echocardiography
KM	Kaplan-Meier	**PS**	propensity score		

and this approach was consistent over the study period[22,23]. In the presence of other severe valvular diseases, patients were managed in accordance with international guidelines following the TAVI procedure. In the absence of recent coronary intervention, discharge therapy consisted of dual antiplatelet therapy for 6 months, or a combination of an oral anticoagulant and aspirin (up to 6 months) if anticoagulation was clinically indicated[24]. All patients were treated with guideline-directed optimal medical therapy after discharge.

STATISTICAL ANALYSIS

Continuous variables are expressed as mean±standard deviation (SD) or median (interquartile range [IQR]) and were compared using the Student's t-test or the Mann-Whitney U test, as appropriate. Categorical variables are presented as counts (%) and were compared using the chi-square test or Fisher's exact test as appropriate. Survival curves with 95% confidence intervals (CI) were estimated for the 3 considered groups using the Kaplan-Meier (KM) method and compared with the log-rank test.

To account for potential confounders, we performed a propensity score (PS)-weighted analysis to estimate the average treatment effect (ATE). The covariates used for calculating the PS were chosen according to their clinical significance or previously reported independent impact on mortality among LFLG patients[10]. The following parameters were included in the PS model used to compare pLFLG-AS and HG-AS patients: LVEF, age, sex, body mass index, renal function, the presence of diabetes mellitus, atrial fibrillation, or chronic obstructive pulmonary disease, and the access route. On the contrary, LVEF was not included in the PS model used to compare cLFLG-AS and HG-AS patients, as LVEF determined patient classification into 1 of these 2 groups. Multivariable Cox regression analyses, including all variables included in the PS, were performed as sensitivity analyses. To adjust for the possible interaction between LVEF and survival, we subsequently performed a weighted multivariable Cox regression analysis including LVEF and cLFLG status. A Cox proportional hazards model, taking into account LVEF measured at multiple timepoints during the first year of follow-up, was employed to evaluate the association between longitudinally assessed LVEF and mortality risk. To account for within-patient correlation, robust covariance estimation was used. To avoid bias due to incomplete case analyses, missing data in baseline characteristics were handled with Multivariate Imputation via Chained Equations using the mice package (v3.13.0; van Buuren & Groothuis-Oudshoorn, 2011). For all the analyses, a 2-sided $p<0.05$ was considered to be significant. Statistical analyses were performed using R software, version 4.1.2 (R Foundation for Statistical Computing). "WeightIt" (version 0.12.0; Noah Greifer, 2021; method "npcbps" and "energy"), "Cobalt", "survival", "RISCA", "ggplot2", and "adjustedCurves" R packages were used for weight estimation, assessing balance on covariate distributions, estimating log-rank adjusted p-values and plotting adjusted KM curves.

Results

BASELINE CHARACTERISTICS AND PROCEDURAL DATA

Out of 681 patients who underwent TAVI at our institution, 574 subjects were included in the analysis **(Figure 1, Central illustration)**. Of these, 419 (73%) fulfilled the criteria for HG-AS, 91 (15%) for pLFLG-AS and 64 (11%) for cLFLG-AS. Baseline clinical, echocardiographic, and procedural characteristics are summarised in **Table 1**. Compared to patients diagnosed with HG-AS, those with cLFLG-AS were more often male (62.5% vs 46.8%; p=0.022), younger (77 vs 81 years old; p<0.001) and characterised by higher surgical risk (European System for Cardiac Operative Risk Evaluation [EuroSCORE] II 5.92% vs 3.87%; p<0.001; Society of Thoracic Surgeons Predicted Risk of Mortality [STS-PROM] score 5.42% vs 4.62%; p=0.321). Compared to those diagnosed with HG-AS,

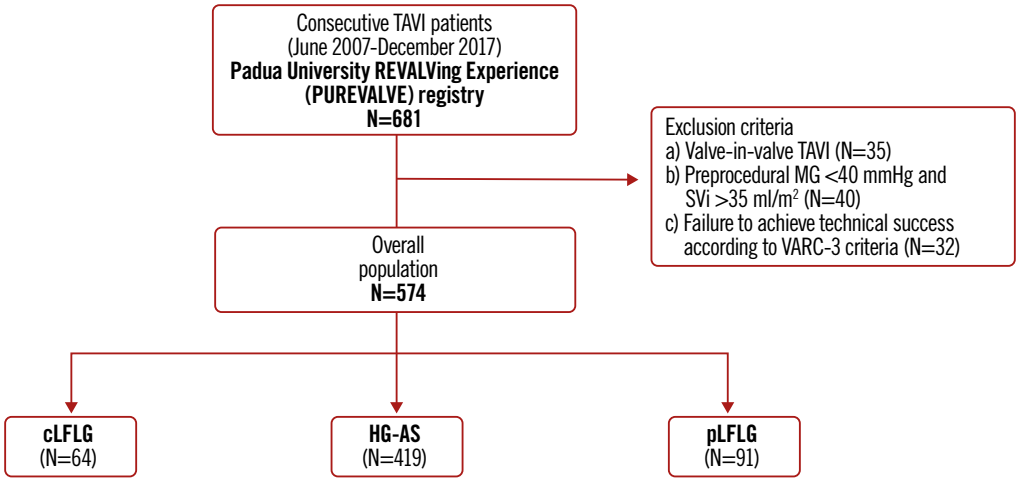


Figure 1. *Study flowchart. cLFLG: classical low-flow, low-gradient; HG-AS: high-gradient aortic stenosis; MG: mean gradient; pLFLG: paradoxical low-flow, low-gradient; SVi: stroke volume index; TAVI: transcatheter aortic valve implantation; VARC: Valve Academic Research Consortium*

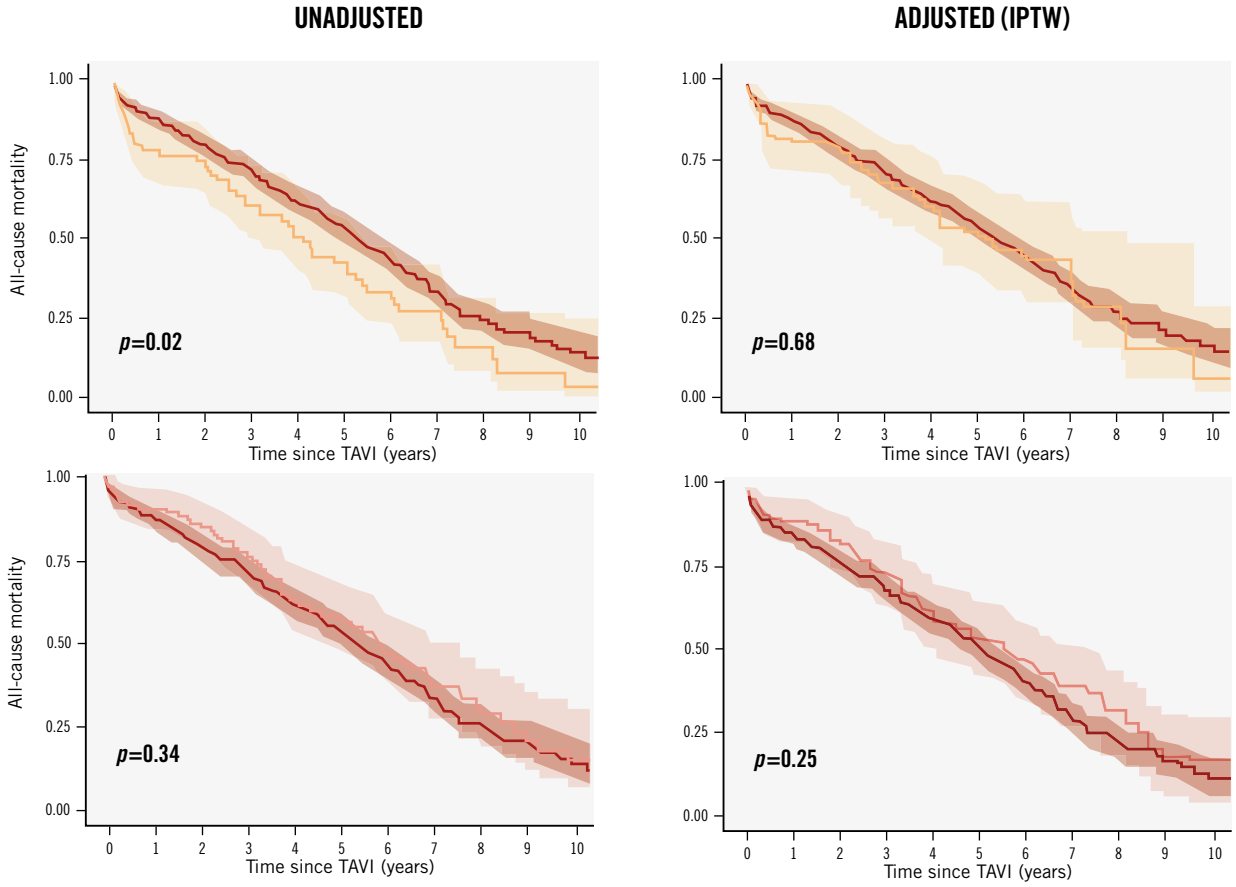
EuroIntervention Central **Illustration**

Long-term survival of patients with aortic stenosis undergoing TAVI according to valve flow status.

High gradient
(SVi >35 ml/m², MG >40 mmHg)
N=419

Classical LFLG
(SVi <35 ml/m², MG <40 mmHg, EF <50%)
N=64

Paradoxical LFLG
(SVi <35 ml/m², MG <40 mmHg, EF ≥50%)
N=91



Francesco Cardaioli *et al.* • *EuroIntervention* 2024;20:1380-1389 • DOI: 10.4244/EIJ-D-24-00442

Variables included in the propensity score models: age, sex, body mass index, renal function, diabetes mellitus, atrial fibrillation, chronic obstructive lung disease, access route and left ventricular ejection fraction (the latter only for paradoxical LFLG-AS vs HG-AS comparison). AS: aortic stenosis; EF: ejection fraction; HG: high-gradient; IPTW: inverse probability of treatment weighting; LFLG: low-flow, low-gradient; MG: mean gradient; SVi: stroke volume index; TAVI: transcatheter aortic valve implantation

patients with cLFLG-AS more often had concomitant coronary artery disease (68.8% vs 55.4%; p=0.049), previous myocardial infarction (26.6% vs 15.0%; p=0.003) and prior permanent pacemaker implantation (17.2% vs 6.7%; p=0.011). Conversely, pLFLG and HG-AS patients presented comparable baseline characteristics.

PROCEDURAL DATA AND PERIPROCEDURAL OUTCOMES

TAVI was performed through the transfemoral approach in 66.7% of the cases, without significant differences among groups. The balloon-expandable SAPIEN/SAPIEN XT/3 were the most frequently used prostheses, followed by the self-expanding CoreValve/Evolut R/PRO. Rates of device success

Table 1. Baseline characteristics and procedural data.

Variable	HG-AS (n=419)	cLFLG-AS (n=64)	*p*-value*	pLFLG-AS (n=91)	*p*-value#
Clinical characteristics					
Age, years	81.00±5.91	77.00±11.06	<0.001	81.00±4.80	0.359
Male sex	196 (46.8)	40 (62.5)	0.022	35 (38.5)	0.167
BMI, kg/m^2	25.82 [14.87-45.03]	24.50 [19.10-44.92]	0.048	26.04 [17.97-38.86]	0.973
Hypertension	381 (90.9)	55 (85.9)	0.254	82 (90.1)	0.690
Diabetes mellitus	117 (27.9)	23 (35.9)	0.187	29 (31.9)	0.445
Dyslipidaemia	257 (61.3)	44 (68.8)	0.271	54 (59.3)	0.638
Atrial fibrillation	126 (30.1)	26 (40.6)	0.111	34 (37.4)	0.218
Previous TIA/stroke	48 (11.5)	9 (14.8)	0.524	14 (15.4)	0.492
COPD	100 (23.9)	19 (29.7)	0.350	24 (26.4)	0.688
CKD (eGFR <60 ml/min/1.73 m^2)	239 (57.0)	39 (60.9)	0.589	48 (52.7)	0.357
Permanent PM	28 (6.7)	11 (17.2)	0.011	7 (7.7)	0.823
CAD	232 (55.4)	44 (68.8)	0.049	48 (52.7)	0.565
Previous PCI	72 (17.2)	13 (20.3)	0.597	22 (24.2)	0.136
Previous CABG	46 (11.0)	11 (17.2)	0.150	11 (12.1)	0.860
Previous AMI	64 (15.3)	17 (26.6)	0.003	19 (20.9)	0.216
EuroSCORE II, %	3.87 [0.91-32.67]	5.92 [0.99-50.07]	<0.001	4.41 [1.13-24.45]	0.232
STS-PROM, %	4.62 [0.70-47.10]	5.42 [1.03-57.20]	0.321	4.78 [1.23-37.00]	0.191
Echocardiographic characteristics					
LVEF, %	59.00 [22.72-78.00]	34.50 [19.00-49.00]	<0.001	60.00 [50.00-76.00]	0.002
Max transaortic gradient, mmHg	71.00 [57.00-132.00]	50.00 [32.00-75.00]	<0.001	48.00 [33.00-75.00]	<0.001
Mean transaortic gradient, mmHg	49.00 [42.00-109.00]	28.00 [6.00-39.00]	<0.001	34.00 [21.00-39.00]	<0.001
AVA, cm^2	0.74 [0.27-1.80]	0.82 [0.49-1.56]	0.003	0.84 [0.48-1.60]	<0.001
AVAi, cm^2/m^2	0.43 [0.11-0.90]	0.48 [0.26-1.03]	0.008	0.48 [0.23-0.87]	<0.001
LVEDVi, ml/m^2	59.0 [22.8-135.0]	68.0 [34.2-158.9]	0.002	61.3 [21.5-102.4]	0.189
Moderate or severe MR	10 (2.5)	3 (4.6)	0.213	5 (5.4)	0.092
Moderate or severe TR	13 (3.1)	2 (3.1)	0.742	3 (3.2)	0.453
Procedural data					
Type of anaesthesia			0.599		0.839
Deep sedation	272 (65.4)	37 (59.7)		62 (68.1)	
General anaesthesia	141 (33.9)	25 (40.3)		29 (31.9)	
Access site			0.054		0.981
Transfemoral	288 (68.7)	37 (57.8)		67 (73.6)	
Trans-subclavian	3 (0.7)	1 (1.6)		1 (1.1)	
Transapical	124 (29.6)	23 (35.9)		23 (25.3)	
Transaortic	4 (1.0)	3 (4.7)		0 (0)	
THV model			0.136		0.289
CoreValve/Evolut R/PRO[a]	64 (15.2)	12 (19.4)		11 (12.1)	
SAPIEN/SAPIEN XT/3[b]	287 (68.4)	45 (70.3)		71 (78.0)	
JenaValve Trilogy[c]	4 (1.0)	2 (3.2)		1 (1.1)	
LOTUS Edge[d]	47 (11.2)	3 (4.8)		4 (4.4)	
ACURATE *neo*[d]	17 (4.1)	0 (0)		4 (4.4)	
Early safety (at 30 days)	344 (82.3)	52 (81.4)	0.471	75 (82.4)	0.486
Device success (at 30 days)	404 (96.5)	61 (95.8)	0.204	88 (96.7)	0.332
Need for PM	54 (13.1)	9 (13.6)	0.231	12 (13.4)	0.763

Table 1. Baseline characteristics and procedural data (cont'd).

Variable	HG-AS (n=419)	cLFLG-AS (n=64)	*p*-value*	pLFLG-AS (n=91)	*p*-value#
Discharge medications					
Aspirin	350 (85.3)	55 (85.9)	0.658	80 (87.9)	0.376
Dual antiplatelet therapy	270 (64.4)	38 (59.3)	0.263	55 (60.4)	0.425
Oral anticoagulant	130 (31.0)	24 (37.5)	0.132	35 (38.4)	0.125
Beta blockers	356 (85.4)	57 (89.0)	0.114	80 (87.9)	0.274
ACE inhibitors/ARBs	314 (74.9)	46 (71.8)	0.165	69 (75.8)	0.723
MRA	260 (62.0)	55 (85.9)	0.064	53 (58.2)	0.521

Values are presented as mean±standard deviation, n (%) or median [interquartile range]. *P-value refers to the comparison between the NFHG-AS group and the cLFLG group. #P-value refers to the comparison between the NFHG-AS group and the pLFLG group. [a]By Medtronic; [b]by Edwards Lifesciences; [c]by JenaValve; [d]by Boston Scientific. ACE: angiotensin-converting enzyme; AMI: acute myocardial infarction; ARB: angiotensin II receptor blocker; AS: aortic stenosis; AVA: aortic valve area; AVAi: AVA index; BMI: body mass index; CABG: coronary artery bypass graft; CAD: coronary artery disease; CKD: chronic kidney disease; cLFLG: classical low-flow, low-gradient; COPD: chronic obstructive pulmonary disease; eGFR: estimated glomerular filtration rate; EuroSCORE: European System for Cardiac Operative Risk Evaluation; HG: high-gradient; LVEDVi: left ventricular end-diastolic volume index; LVEF: left ventricular ejection fraction; MR: mitral regurgitation; MRA: mineralocorticoid receptor antagonist; NF: no-flow; PCI: percutaneous coronary intervention; pLFLG: paradoxical low-flow, low-gradient; PM: pacemaker; STS-PROM: Society of Thoracic Surgeons Predicted Risk of Mortality; THV: transcatheter heart valve; TIA: transient ischaemic attack; TR: tricuspid regurgitation

and early safety at 30 days were similar among groups **(Table 1)**.

CLINICAL OUTCOMES

The median follow-up time was 4.8 years (IQR 2.3-6.2) with a maximum of 12.3 years. KM estimates for overall survival at 2, 4, 6, 8, and 10 years were 80% (95% CI: 77-83), 62% (95% CI: 58-66), 42% (95% CI: 38-46), 25% (95% CI: 21-30), and 12% (95% CI: 8-17), respectively. Unadjusted survival KM curves for the 3 groups are reported in **Figure 2**, **Figure 3A** and **Figure 4A**. Ten-year all-cause mortality was higher in patients with cLFLG-AS compared to those with HG-AS (p=0.02), while pLFLG-AS and HG-AS groups presented similar long-term survival (p=0.34). Among cLFLG-AS patients, the most significant decrease in mortality occurred within the first year after the procedure (KM estimates at 1 year: 75% [95% CI: 62-84] for cLFLG-AS, 89% [95% CI: 82-95] for pLFLG-AS, 88% [95% CI: 84-91] for HG-AS; p=0.009) **(Supplementary Figure 1)**, with similar unadjusted survival curves from the 1-year mark onwards (p=0.3) **(Supplementary Figure 2)**. Adjusted survival curves are reported in **Figure 3B** and **Figure 4B**. After performing propensity score weighting, no difference was found in terms of long-term mortality among the 3 different groups (the balance of covariates included in the PS analysis before and after the weighting is reported in **Supplementary Figure 3**). Classical LFLG status did not show a significant impact on weighted survival, even after adjusting for baseline LVEF **(Supplementary Table 1)**. A sensitivity analysis, consisting of 2 multivariable Cox regression models with all covariates included in the PS, confirmed the absence of a significant impact of either cLFLG or pLFLG status on long-term survival **(Supplementary Table 2, Supplementary Table 3)**.

LVEF IMPROVEMENT

Out of the 64 patients diagnosed with cLFLG-AS, echocardiographic follow-up throughout the first year after the procedure was available for 58 (91%) of them. Postprocedural improvement in LVEF >10% was common among patients

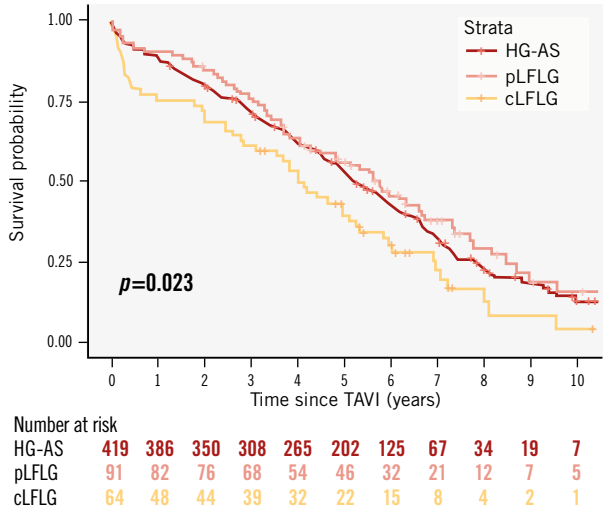


Figure 2. *Unadjusted KM survival curves. cLFLG: classical low-flow, low-gradient; HG-AS: high-gradient aortic stenosis; KM: Kaplan-Meier; pLFLG: paradoxical low-flow, low-gradient; TAVI: transcatheter aortic valve implantation*

with cLFLG-AS, occurring in approximately two-thirds of this subgroup (63%). As shown in **Supplementary Figure 4**, these patients experienced significantly longer survival compared to those with no or slighter (<10%) LVEF recovery (p=0.02). Moreover, by accounting for the longitudinal measures of LVEF throughout the first year of follow-up, the Cox proportional hazards model showed that an increase in LVEF during the follow-up period was associated with a lower likelihood of death (hazard ratio 0.9692, 95% CI: 0.9517-0.987; p<0.001).

Discussion

The main findings of our study – the first to examine long-term survival after TAVI in subjects with pLFLG- and cLFLG-AS

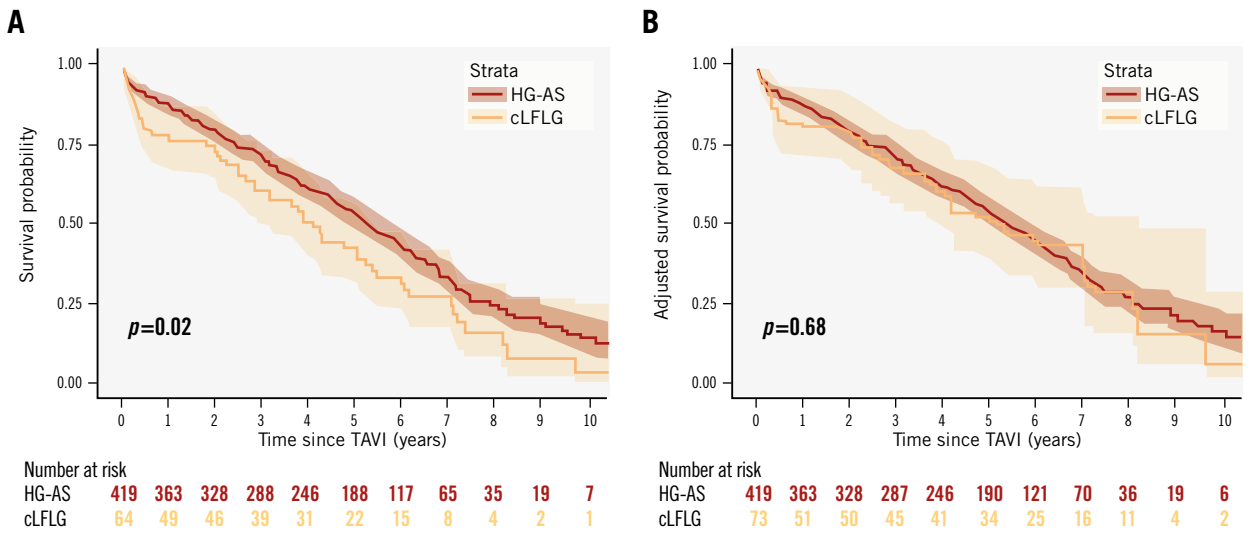


Figure 3. *KM survival curves for cLFLG- and HG-AS. A) Unadjusted survival curves, and (B) adjusted KM survival curves. cLFLG: classical low-flow, low gradient; HG-AS: high-gradient aortic stenosis; TAVI: transcatheter aortic valve implantation*

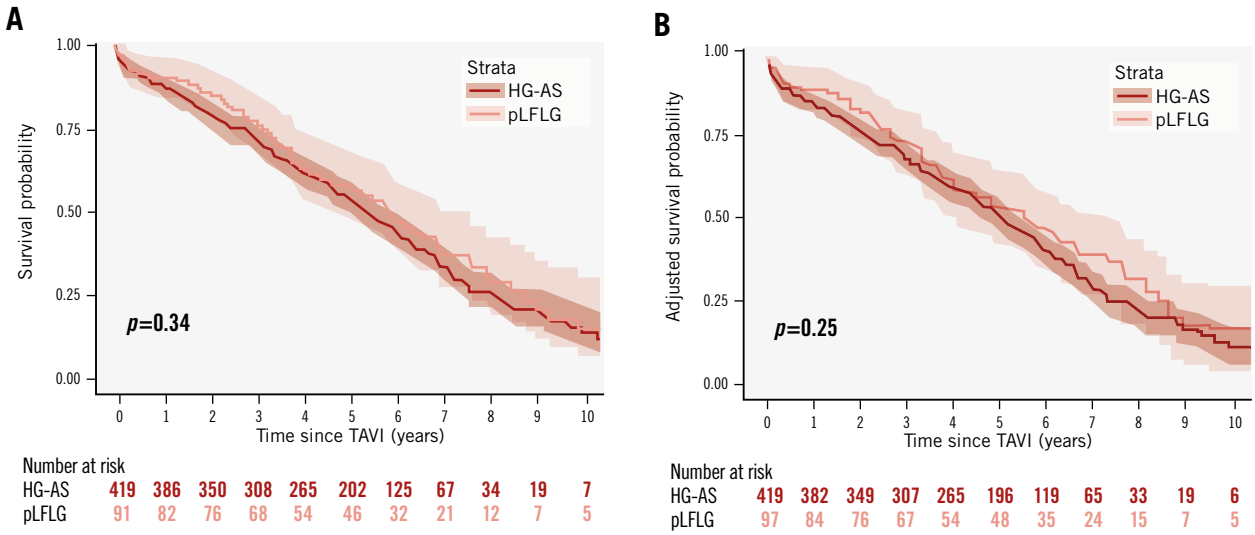


Figure 4. *KM survival curves for pLFLG- and HG-AS. A) Unadjusted survival curves, and (B) adjusted KM survival curves. HG-AS: high-gradient aortic stenosis; pLFLG: paradoxical low-flow, low gradient; TAVI: transcatheter aortic valve implantation*

versus HG-AS – can be summarised as follows: (1) patients with cLFLG-AS undergoing TAVI showed lower unadjusted 1-year survival rates as compared to those with pLFLG- or HG-AS, but no difference was observed from the 1-year mark onwards; (2) the worse long-term post-TAVI outcome of cLFLG-AS subjects seemed to be related more to the higher patient baseline risk rather than the low-flow status itself; (3) baseline LVEF did not appear to predict long-term survival in cLFLG-AS patients. Conversely, an early LVEF improvement post-TAVI, which was observed in two-thirds of cLFLG-AS subjects, yielded longer survival.

Low-flow, low-gradient status in the context of AS represents a challenging clinical setting both for diagnosis and therapeutical decision-making. As proven by a large amount of data in literature, TAVI has emerged as a suitable and effective treatment option also in this subset of patients[9,15,16]. Specifically, in keeping with previous reports[10], our patients with pLFLG-AS had similar post-TAVI outcomes at midterm follow-up compared to those with HG-AS. Furthermore, we extended these findings to a longer follow-up period. Conversely, subjects with cLFLG-AS have been shown to have the worst short-term post-TAVI survival among different AS flow statuses[5,9-11,15,25-29]. Our study confirms the worse 1-year survival after TAVI of cLFLG patients (75%), as compared to that of patients with either pLFLG- or HG-AS (89% and 88%), that has already been observed in smaller single-centre registries[5,10]. Furthermore, it extends these findings to a longer follow-up period, highlighting a time-dependent

mortality risk, which appeared to be concentrated in the first year after the procedure. Only one previous paper has reported on the outcomes of these patients beyond 1 year (with a median follow-up time of 3 years), observing lower post-TAVI survival rates in patients with cLFLG-AS[11]. However, the retrospective nature of the study along with the absence of a statistical adjustment to accommodate potential baseline confounders prevented further insights into the pathophysiological mechanism behind these findings. As in previous reports[11,15,19,30], our cLFLG-AS patients presented higher baseline cardiovascular and surgical risks (median EuroSCORE II 5.92% for cLFLG-AS vs 4.41% for pLFLG-AS vs 3.87% for HG-AS) due to concomitant comorbidities and frailty. We performed a propensity-weighted survival analysis to mitigate this underlying bias, and we found that a cLFLG status *per se* does not seem to carry an increased all-cause mortality risk after TAVI. This is in contrast with the findings of another previous single-centre registry with limited (1-year) follow-up, which reported lower survival rates of cLFLG patients even after adjustment for baseline clinical characteristics. Possible explanations for these conflicting results could be the longer follow-up of our study, the relatively lower surgical risk of our cLFLG patients (median STS-PROM score 5.4% vs 8.2% reported in the paper by Puls et al[11]), and the different covariates included in our PS model[10] (which did not include LVEF). Moreover, we could speculate that the similar outcome of pLFLG- and HG-AS patients (with similar baseline risk) supports the concept that the low-flow status itself might have a lesser impact on prognosis than a patient's comorbidities. The impact of baseline LVEF on TAVI outcomes has been a matter of debate. Our results confirm the lack of association between baseline LVEF and survival after TAVI in cLFLG patients, consistent with findings from previous studies in the field[11,19,31]. On the contrary, we found that an early post-TAVI increase in LVEF >10% yielded a 54% improvement in postprocedural median survival time (1,985 days vs 1,288 days)[18,19]. While the latter finding seems reasonable from a pathophysiological standpoint, it remains to be explained why the presence of contractile reserve at pre-TAVI dobutamine stress echocardiography has failed to show a significant survival benefit[32-34]. In conclusion, our results confirm the long-term efficacy and safety of TAVI in LFLG patients. Moreover, they suggest the importance of accurate preprocedural patient selection, in order to identify frailer patients for whom TAVI might be futile.

Limitations

This study is a single-centre, retrospective *post hoc* analysis of a prospective all-comers TAVI registry. The small sample size prevented further subanalyses to identify the subset of cLFLG patients who might demonstrate postprocedural LVEF improvement. Moreover, the small number of patients at risk beyond 5 years of follow-up prevents definite conclusions on post-TAVI outcomes in patients with LFLG-AS. In particular, due to the wide 95% CI obtained, we cannot definitively exclude the presence of a type II error. Nevertheless, our study population is one of the largest on the topic[5,11,35] and is the first to report preliminary results on the very late outcomes after TAVI in patients with LFLG-AS. Most of the patients had been referred to our centre after already completing preprocedural screening. Consequently, we were unable to provide data on preprocedural left ventricular contractile reserve. Patients who underwent surgical aortic valve replacement were not included in the study, preventing any inference on the interplay between the LFLG status and procedure type. Although the exams were performed by experienced certified operators, the absence of a core lab for standardised TTE acquisition and evaluation may have resulted in bias in image interpretation. We considered only all-cause death as the endpoint, not reporting data on cardiovascular mortality or other common postprocedural outcomes. Moreover, no specific quality-of-life questionnaire nor cognitive status assessment was routinely performed at follow-up.

Conclusions

Our findings suggest that the well-known higher mortality rates characterising patients with cLFLG-AS undergoing TAVI may be more related to their higher baseline cardiovascular risk than the low-flow status itself. Conversely, pLFLG patients represent a population similar to HG-AS subjects in terms of both baseline characteristics and long-term outcomes. Our study confirmed that LVEF recovery after TAVI is a common finding among patients affected by cLFLG-AS and correlates with postprocedural survival. While awaiting further studies and randomised data, performing TAVI in carefully selected patients with LFLG-AS seems to provide both safe and effective long-term results.

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Conflict of interest statement

G. Tarantini reports honoraria for lectures/consulting from Medtronic, Edwards Lifesciences, Boston Scientific, Abbott, GADA, MicroPort, and SMT. L. Nai Fovino reports honoraria for lectures from Edwards Lifesciences. G. Masiero reports honoraria for lectures/consulting from GE HealthCare. C. Fraccaro reports honoraria for lectures/consulting from Edwards Lifesciences. The other authors have no conflicts of interest to declare.

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Supplementary data

Supplementary Table 1. Multivariable weighted analysis on the impact of cLFLG status and baseline LVEF.

Supplementary Table 2. Sensitivity analysis (1).

Supplementary Table 3. Sensitivity analysis (2).

Supplementary Figure 1. Unadjusted 1-year Kaplan-Meier survival analysis.

Supplementary Figure 2. Unadjusted landmark survival analysis (1 year onward).

Supplementary Figure 3. Covariates balancing before and after propensity score weighting for cLFLG- and pLFLG-AS compared to HG-AS.

Supplementary Figure 4. Difference in postprocedural survival time between patients with and without EF improvement after TAVI.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-24-00442

EuroIntervention
2024;20:1390-1404
DOI: 10.4244/EIJ-D-24-00619

ORIGINAL RESEARCH

Redo-TAVI with the SAPIEN 3 valve in degenerated calcified CoreValve/Evolut explants

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This paper also includes supplementary data published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-24-00619

ABSTRACT

BACKGROUND: Redo-transcatheter aortic valve implantation (TAVI) is the treatment of choice for failed transcatheter aortic valves. Currently, implantation of a SAPIEN 3 (S3) is indicated for redo-TAVI in degenerated CoreValve/Evolut (CV/EV) transcatheter aortic valves (TAVs) but is not well understood.

AIMS: We aimed to evaluate S3 function following implantation in explanted calcified CV/EV TAVs and to assess the impact of CV/EV pathology on redo-TAVI outcomes.

METHODS: *Ex vivo* hydrodynamic testing was performed per the International Organization for Standardization (ISO) 5840-3 standard on 4 S3 TAVs implanted at node 5 in calcified CV/EV explants. The mean gradient (MG), effective orifice area (EOA), peak velocity, regurgitant fraction (RF), geometric orifice area (GOA), leaflet overhang, leaflet pinwheeling, neoskirt height, and frame deformation were evaluated.

RESULTS: CV/EV explants were calcified and stenotic. Following S3 implantation, the MG and peak velocity decreased. As per the ISO standard, all S3 implants showed adequate EOA, and 3 out of 4 had an RF within the accepted value (<20%). CV/EV leaflet overhang ranged from 25-37%. Calcified leaflets remained stationary throughout the cardiac cycle (difference <9%) and were not pinned in a manner that constrained S3 systolic flow or appeared to prevent selective frame cannulation. The downstream CV/EV GOA was larger than the upstream S3 GOA during systole. S3 frame underexpansion was seen, resulting in leaflet pinwheeling (range 13-30%). Above the neoskirt, calcium protrusion was observed in contact with the S3 leaflets.

CONCLUSIONS: S3 implantation at node 5 in calcified CV/EV valves resulted in satisfactory hydrodynamic performance in most configurations tested with stable leaflet overhang throughout the cardiac cycle. The long-term implications of S3 underexpansion, leaflet pinwheeling, and calcium protrusion require future studies.

KEYWORDS: aortic stenosis; TAVI; valve-in-valve

SUBMITTED ON 08/07/2024 - REVISION RECEIVED ON 23/08/2024 - ACCEPTED ON 16/09/2024

Transcatheter aortic valve implantation (TAVI) has been shown to be an effective therapy for patients with severe symptomatic aortic stenosis (AS) irrespective of surgical risk[1,2]. As TAVI is progressively utilised in lower-risk patients with the potential for longevity, transcatheter aortic valve (TAV) durability and the need for reintervention have become increasingly relevant[3-7]. A subset of younger, low-risk patients that are undergoing TAVI will eventually require repeat interventions due to structural valve deterioration (SVD), non-SVD, and/or other failure mechanisms.

Redo-TAVI has emerged as a viable therapeutic option for patients with a failed TAV. Redo-TAVI serves as a minimally invasive alternative to surgical TAV explant, which has been shown to be associated with high morbidity and mortality due to patient risk factors and technical challenges such as valve adherence, tissue ingrowth, and damage to surrounding structures[8-11]. However, redo-TAVI has many complexities and potential pitfalls. This procedure may not be feasible in all patients due to the risk of coronary obstruction and impaired coronary access, which requires careful consideration in procedural planning with respect to device combinations[12-18].

While clinical experience with redo-TAVI continues to grow, many critical knowledge gaps remain. *Ex vivo* bench testing can provide important insights when clinical experience is limited[14,19-21]. A recent study evaluated redo-TAVI for the self-expanding Evolut R (Medtronic) TAV following implantation of a balloon-expandable SAPIEN 3 (S3 [Edwards Lifesciences]) TAV[19]. The neoskirt height, leaflet overhang, Evolut R frame expansion, and S3 hydrodynamic performance were evaluated at different S3 implant depths. However, like all redo-TAVI bench testing to date, brand new index TAVs were used, thus, not accounting for the potential effect of index TAV leaflet degeneration and calcification on redo-TAVI. Given the features of TAV degeneration, such as leaflet thickening, stiffening and calcium nodule formation[22-24], consideration of these pathological features in bench models is key to further inform clinical practice regarding redo-TAVI. Therefore, this *ex vivo* benchtop study aimed to evaluate the functional performance of the S3 TAV following implantation within degenerated calcified CoreValve/Evolut (CV/EV) TAVs.

Impact on daily practice

Implantation of a SAPIEN 3 is indicated for redo-transcatheter aortic valve implantation (TAVI) in the setting of degenerated transcatheter aortic valves (TAVs) but has never been modelled in failed calcified CoreValve/Evolut TAVs. Redo-TAVI with the SAPIEN 3 outflow at node 5 of the degenerated calcified CoreValve/Evolut led to favourable haemodynamics in 3 of the 4 configurations tested, stable leaflet overhang, acceptable neoskirt heights, SAPIEN 3 underexpansion and pinwheeling, and some instances of index TAV calcium touching the SAPIEN 3 leaflets.

Methods

COREVALVE/EVOLUT TAVI EXPLANTS

A total of 4 CV/EV explants were used in this study as index TAVs: 23 mm Evolut R, 29 mm CoreValve, 29 mm Evolut PRO, and 34 mm Evolut R (all Medtronic devices). Two explants were obtained from the international, multicentre EXPLANT THV registry at St. Paul's Hospital (Vancouver, BC, Canada), with their study approved by the Providence Health Care Research Ethics Board. The remaining 2 TAV explants were acquired from clinical institutions and approved by local institutional review boards. Surgical explantation occurred for clinical indications as determined by local Heart Teams. Clinical and patient characteristics were obtained from each clinical institution, when available. This bench study did not involve animal participants. Additional details can be found in **Supplementary Appendix 1**.

SAPIEN 3 IN COREVALVE/EVOLUT REDO-TAVI

Redo-TAVI was performed on the bench using new S3 TAVs in the following combinations: 20 mm S3 within the 23 mm Evolut R, 26 mm S3 within the 29 mm CV, 26 mm S3 within the 29 mm Evolut PRO, and 29 mm S3 within the 34 mm Evolut R. The S3 TAVs were implanted with their outflow at CV/EV node 5 **(Figure 1A)**. Implant depth was chosen on the basis of prior bench testing and computed tomography (CT)-based simulation studies that evaluated the feasibility of coronary access at implantation depths between nodes 4-6 of the index CV/EV[12,18,19,25]. The S3 TAVs were implanted under fluoroscopy (ARTIS icono biplane C-arm system [Siemens Healthineers]) into the CV/EV TAVs using the manufacturer's standard delivery systems at a nominal volume. Balloon pre- and post-dilatation were not performed.

HYDRODYNAMIC BENCH TESTING

The HDTi-6000 heart valve pulse duplicator system (BDC Laboratories) was used to assess hydrodynamic performance before and after redo-TAVI in accordance with ISO 5840-3:2021 guidelines for *in vitro* pulsatile flow testing for heart valve substitutes implanted by transcatheter techniques **(Figure 1B)**. The mean gradient (MG; mmHg), effective orifice area (EOA; cm^2), peak velocity (m/s), and regurgitant fraction (RF; %) were quantified. An RF of >20% is considered significant in accordance with ISO guidelines. The EOA was derived from the continuity equation[26]. Additional details can be found in **Supplementary Appendix 1**.

MULTIMODALITY IMAGING ANALYSIS

Micro-CT imaging was used for calcium quantification of the index CV/EV leaflets, as previously described[22]. Briefly,

Abbreviations

AS	aortic stenosis	**GOA**	geometric orifice area	**SVD**	structural valve deterioration
CT	computed tomography	**MG**	mean gradient	**TAV**	transcatheter aortic valve
CV/EV	CoreValve/Evolut	**RF**	regurgitant fraction	**TAVI**	transcatheter aortic valve implantation
EOA	effective orifice area	**S3**	SAPIEN 3		

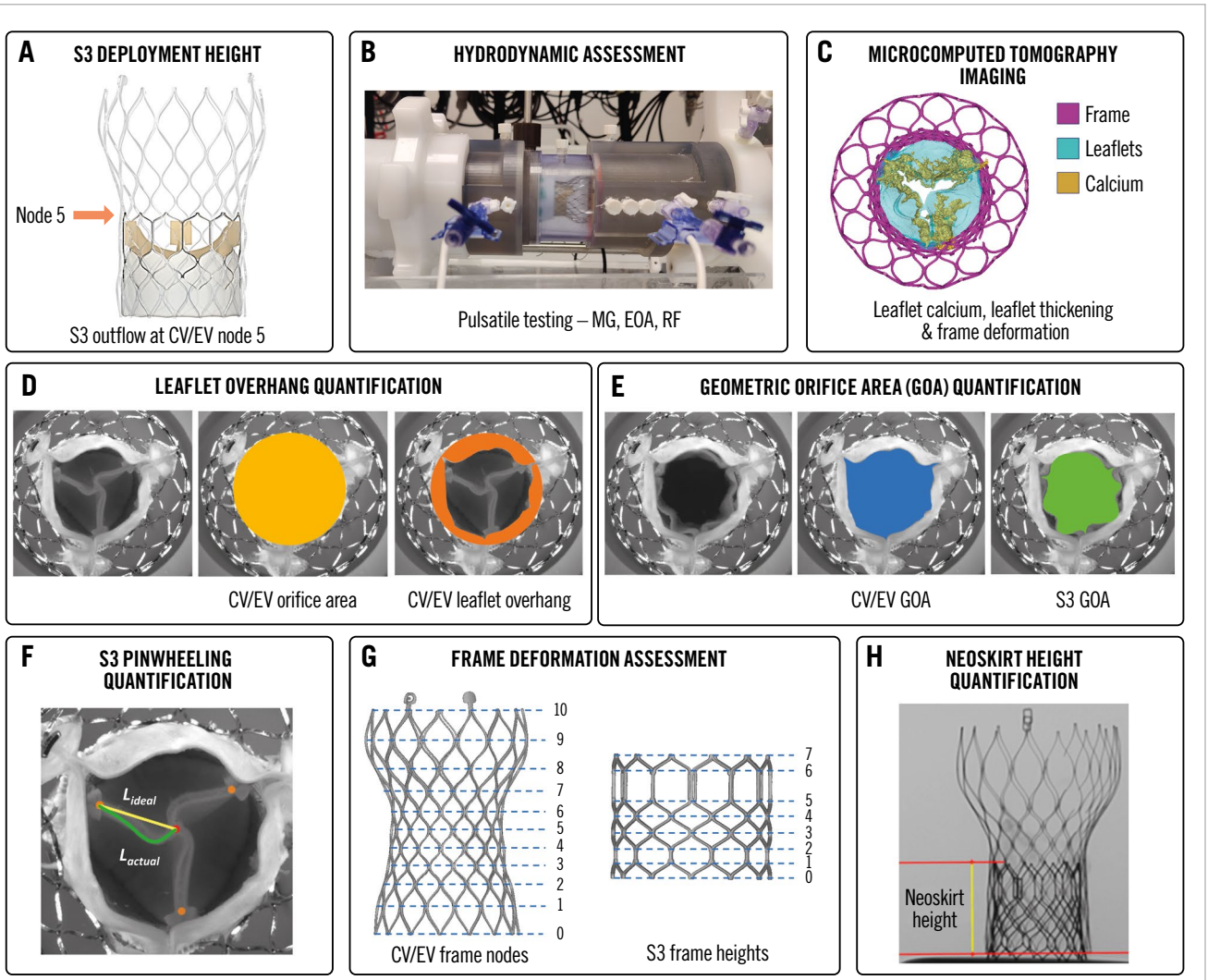


Figure 1. *Study methodology. A) Redo-TAVI with S3 outflow at node 5 (orange arrow) of CV/EV; (B) pulse duplicator; (C) microcomputed tomography imaging; (D) degree of leaflet overhang (%) of the stenotic CV/EV leaflets following S3 implant; (E) GOA of S3 and CV/EV; (F) S3 leaflet pinwheeling; (G) CV/EV frame nodes and S3 frame heights; (H) neoskirt height. CV/EV: CoreValve/Evolut; EOA: effective orifice area; L: leaflet; MG: mean gradient; RF: regurgitant fraction; S3: SAPIEN 3; TAVI: transcatheter aortic valve implantation*

calcification distribution on the CV/EV leaflets was assessed using volume measurement of the three-dimensionally (3D) reconstructed explanted TAVs. As shown in **Figure 1C**, segmentation and 3D reconstruction of the CV/EV frame (purple), leaflets (blue) and calcium burden (yellow) were performed in Mimics software, version 25.0 (Materialise). Calcium distribution analysis was performed in 3-matic software, version 17.0 (Materialise). Additional imaging details can be found in **Supplementary Appendix 1**.

LEAFLET FUNCTION ANALYSIS

COREVALVE/EVOLUT NEOSKIRT HEIGHT

The neoskirt height was defined as the distance from the CV/EV frame inflow to the pinned leaflet height at the S3 frame outflow[19] **(Figure 1H)**. Neoskirt height was measured by fluoroscopy at the level of the S3 outflow following visual confirmation that the degenerated index leaflets were subjected to overhang and not pinned in a manner that extended the functional neoskirt above the S3 frame outflow. Neoskirt values were derived from averaging 4 height measurements per redo-TAVI combination using the DICOM viewer software, version 3.9.5 (MicroDicom).

COREVALVE/EVOLUT LEAFLET OVERHANG

As shown in **Figure 1D**, leaflet overhang was defined as the percentage of orifice obstruction at the level of the index CV/EV commissure pad region (leaflet outflow) due to inward flexing of the unpinned portion of the CV/EV leaflets[19] **(Supplementary Appendix 1)**.

COREVALVE/EVOLUT AND SAPIEN 3 GEOMETRIC ORIFICE AREA

As shown in **Figure 1E**, the CV/EV geometric orifice area (GOA; blue) and S3 GOA (green) following redo-TAVI were measured and averaged from 3 still-frame systolic images

obtained from the high-speed videos using ImageJ software (ImageJ). The CV/EV GOA was compared to the S3 GOA at systole.

SAPIEN 3 PINWHEELING

Pinwheeling, defined as twisting of the TAV leaflet's free edge as a consequence of redundant leaflet tissue was assessed for the S3[27]. As shown in **Figure 1F**, pinwheeling – expressed as a percentage – was determined by tracing the contour of the length of the actual leaflet's free edge (L_{actual}) from the frame to the coaptation centre compared to the ideal configuration for the leaflet's free edge (straight line; L_{ideal}) **(Supplementary Appendix 1)**. Since pinwheeling might be difficult to measure in cases where major leaflet redundancy leads to a phenomenon of localised malcoaptation, regions where the leaflets' free edges failed to achieve full coaptation along their length were manually traced from images captured during diastole.

FRAME DEFORMATION ANALYSIS

As shown in **Figure 1G**, micro-CT imaging performed before and after redo-TAVI was used for measuring the CV/EV perimeter-derived outer frame diameter in each of the 11 frame node levels from inflow to outflow (nodes 0-10). Similarly, the S3 area-derived outer frame diameter was measured at the 8 frame heights from inflow to outflow (heights 0-7) following redo-TAVI. Diameter measurements were originally taken mid-strut followed by the addition of the frame thickness to obtain the outer frame diameter values. The reference S3 frame diameter before redo-TAVI was the nominal frame diameter per the instructions for use, which was assumed to be constant across the frame height. The change in radius for the CV/EV TAVs following redo-TAVI was also quantified.

STATISTICAL ANALYSIS

Continuous variables are presented as mean±standard deviation or median with interquartile range (IQR). Statistics were performed using Minitab software, version 20.1.3 (Minitab). Due to the small sample size, statistical comparisons between redo-TAVI configurations were not performed.

Results

COREVALVE/EVOLUT EXPLANTS CHARACTERISTICS

Clinical characteristics of the 4 CV/EV explants are provided in **Supplementary Table 1**. The median patient age at explant was 67 years (IQR 53-72 years), and 50% were female. The median time from index TAVI to explant was 4 years and 5 months (IQR 3 years and 1 month-4 years and 11 months). The degenerative mechanism responsible for explant in all cases was SVD, causing AS in 3 cases and mixed stenosis and concomitant regurgitation in 1 case.

Figure 2 and **Supplementary Table 1** show the calcium burden, leaflet thickness, morphological appearance, and leaflet kinematics of the 4 CV/EV explants before redo-TAVI. Leaflet kinematics were abnormal in all explants **(Moving image 1)**, and all explants were found to have leaflet calcification by micro-CT quantification (median 413 mm^3 [IQR 120-597 mm^3]). **Table 1** shows the hydrodynamic performance of the CV/EV explants. *Ex vivo* MG, EOA and peak velocity median values were 48.9 mmHg (IQR 34.9-71.5 mmHg), 0.84 cm^2 (IQR 0.70-1.04 cm^2) and 4.8 m/s (IQR 4.0-5.9 m/s), respectively.

SAPIEN 3 IN COREVALVE/EVOLUT HYDRODYNAMIC PERFORMANCE

Table 1 and **Figure 3** show the hydrodynamic performance and morphological appearance of the 4 redo-TAVI combinations. Following S3 implantation within the CV/EV at node 5 position, adequate S3 hydrodynamic function was achieved for 3 of the 4 redo-TAVI combinations per the ISO 5840-3 standard. The 29 mm S3 in 34 mm EV configuration showed an RF of 25.8%, above the 20% cutoff point defined by the standard. Further testing of this configuration was conducted by adding silicone sealant to the exterior surface of the 29 mm S3 to prevent inter-TAV leakage. Hydrodynamic retesting resulted in an RF of 21.7%, confirming the major contribution of central regurgitation to the high RF initially observed. The S3 in CV/EV redo-TAVI leaflet kinematics are presented in **Moving image 2**.

Hydrodynamic testing following redo-TAVI resulted in median MG, EOA and peak velocity measurements of 9.9 mmHg (IQR 7.6-23.9 mmHg), 2.1 cm^2 (IQR 1.4-2.4 cm^2) and 1.9 m/s (IQR 1.7-3.0 m/s), respectively **(Figure 3B, Table 1)**. As expected, the highest MG/peak velocity and smallest EOA were noted for the 20 mm S3 in 23 mm EV redo-TAVI combination.

REDO-TAVI LEAFLET MEASUREMENTS

As shown in **Table 2** and **Figure 3C**, the S3 in CV/EV redo-TAVI at node 5 position resulted in neoskirt heights ranging between 19.9-24.0 mm. The lowest neoskirt value was measured for the 20 mm S3 in 23 mm EV combination (19.9 mm), and the highest neoskirt was noted for the 26 mm S3 in 29 mm EV combination (24.0 mm). Of note, despite leaflet rigidity due to calcification, the neoskirt was not found to extend above the S3 frame. **Table 2** shows the degree of CV/EV leaflet overhang during diastole and systole. Leaflet overhang ranged from 24.8% to 37.3% across the 4 redo-TAVI combinations **(Figure 3B)**. Overall, index CV/EV leaflets were pinned open and remained stationary throughout the cardiac cycle, with a difference <9% in leaflet overhang between diastole and systole.

Index CV/EV GOA and S3 GOA were quantified for the 4 redo-TAVI combinations **(Table 2)**. The CV/EV GOA ranged from 3.2 cm^2 to 5.3 cm^2 across the 4 test combinations, while the S3 GOA ranged between 2.8 cm^2 and 4.2 cm^2. As shown in **Figure 4A**, during systole, the downstream opening orifice area (CV/EV GOA) was always larger than the upstream orifice area (S3 GOA), demonstrating that S3 systolic flow is not constrained by the overhanging leaflets. S3 EOA values are also presented in **Figure 4A**; however, directly comparing GOA to EOA measurements is inaccurate, because the former only considers the physical dimensions of the orifice, while the latter accounts for fluid flow characteristics.

As shown in **Table 2**, S3 implanted within CV/EV resulted in average S3 pinwheeling values ranging from 12.5-29.8%. The largest degree of pinwheeling was noted for the 26 mm S3 in 29 mm EV combination. **Supplementary Table 2** shows the degree of pinwheeling for each pair of S3 leaflets. Pinwheeling also resulted in deficits in free-edge coaptation

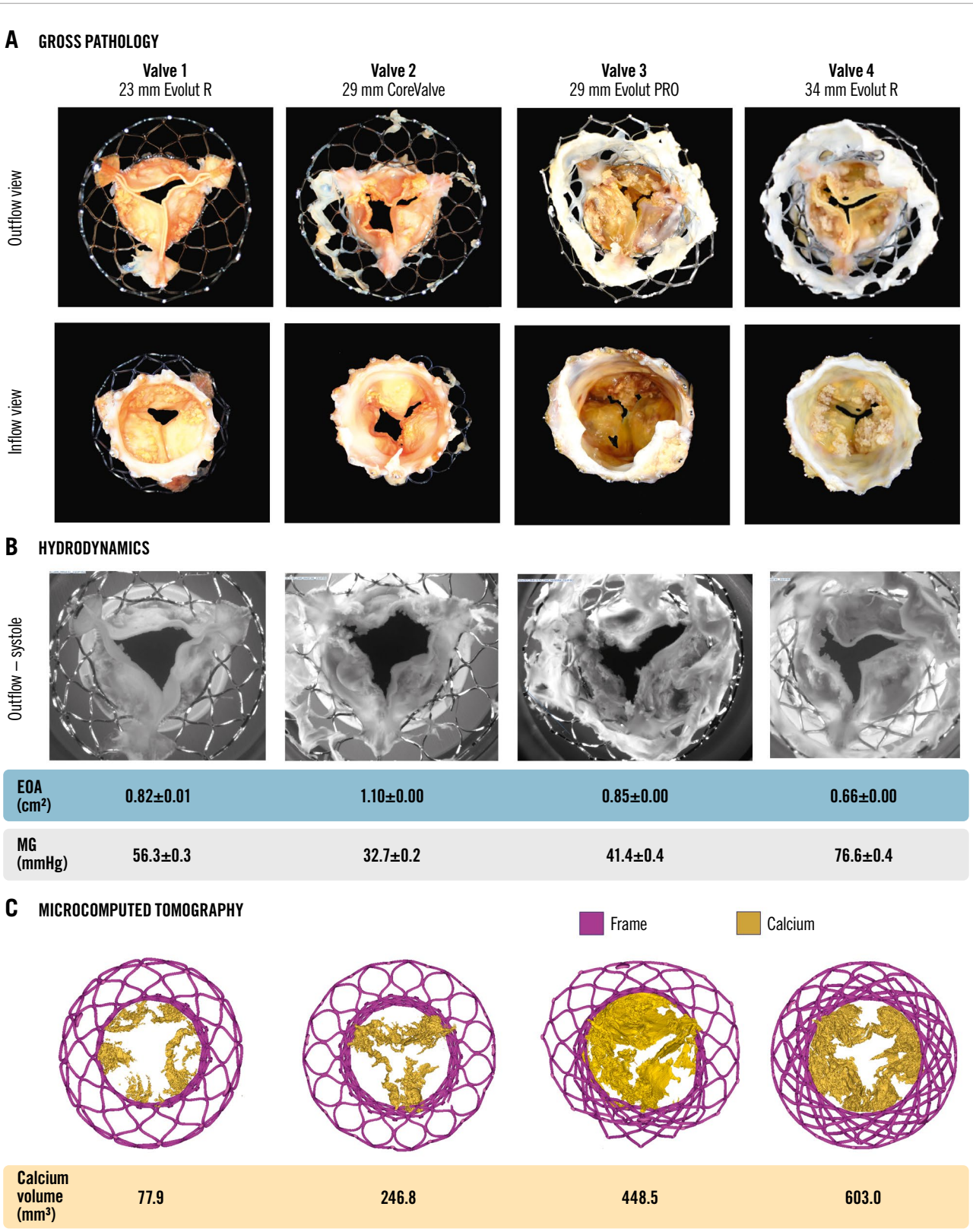


Figure 2. *Appearance, hydrodynamics and calcium of degenerated CoreValve/Evolut. A) Gross pathology of the explanted calcified CV/EV used in the study. B) Images of explants during systolic opening prior to redo-TAVI with corresponding MG and EOA. C) Micro-CT of explants (calcification=yellow) with calcium volume per valve. CT: computed tomography; CV/EV: CoreValve/Evolut; EOA: effective orifice area; MG: mean gradient; TAVI: transcatheter aortic valve implantation*

Table 1. Hydrodynamic performance before and after redo-TAVI.

	Mean gradient, mmHg		EOA, cm²			Peak velocity, m/s		Regurgitant fraction, %	
	Index CV/EV	Redo-TAVI	Index CV/EV	Redo-TAVI	ISO accepted	Index CV/EV	Redo-TAVI	Redo-TAVI	ISO accepted
VALVE 1 20 mm S3 in 23 mm Evolut R	56.3±0.3	28.5±0.2	0.82±0.01	1.17±0.00	0.95	5.0±0.0	3.4±0.0	7.9±0.6	20
VALVE 2 26 mm S3 in 29 mm CoreValve	32.7±0.2	9.5±0.1	1.10±0.00	2.16±0.02	1.60	3.8±0.0	1.9±0.0	18.9±0.4	
VALVE 3 26 mm S3 in 29 mm Evolut PRO	41.4±0.4	10.2±0.1	0.85±0.00	2.08±0.01	1.60	4.6±0.0	1.9±0.0	12.3±0.4	
VALVE 4 29 mm S3 in 34 mm Evolut R	76.6±0.4	7.0±0.1	0.66±0.00	2.54±0.02	2.10	6.2±0.1	1.6±0.0	25.8±0.3*	

Data presented as mean±standard deviation. *Subsequent hydrodynamic testing determined that central AR caused 21.7% of the total regurgitant fraction. AR: aortic regurgitation; CV/EV: CoreValve/Evolut; EOA: effective orifice area; ISO: International Organization for Standardization; S3: SAPIEN 3; TAVI: transcatheter aortic valve implantation

along the leaflet length. **Supplementary Figure 1** shows these areas highlighted in red where the free edges of each pair of leaflets did not meet.

COREVALVE/EVOLUT FRAME DEFORMATION FOLLOWING REDO-TAVI

Figure 4B presents the CV/EV outer frame diameter measurements at each node level before and after redo-TAVI. CV/EV frame expansion following redo-TAVI occurred more frequently closer to the waist and the functional leaflet region (nodes 4-7), and to a lesser extent at the inflow and outflow regions. CV/EV frame diameter measurements at each node level and change in radius following redo-TAVI are presented in **Supplementary Table 3**. The change in CV/EV radius was up to 1.7 mm across the tested combinations.

SAPIEN 3 FRAME EXPANSION FOLLOWING REDO-TAVI

Following redo-TAVI, S3 frame underexpansion was systematically observed to varying degrees along the frame height. **Figure 4C** shows the observed S3 frame diameter values compared to theoretical nominal expansion. In the case of the 20 mm S3 in 23 mm EV combination, the S3 showed a trumpet-like, "flared" frame geometry, with the highest frame underexpansion at the inflow and the lowest underexpansion at the outflow. In contrast, 2 of the remaining redo-TAVI combinations (valves 2 and 4) showed a funnel-like, "tapered" frame geometry, with the lowest frame underexpansion at the inflow and the highest underexpansion at the outflow, especially for the 29 mm S3 in 34 mm EV combination. The high S3 frame underexpansion observed for the 29 mm S3 in 34 mm EV combination appeared to have contributed to the high RF quantified for this configuration. The remaining redo-TAVI combination (valve 3) displayed a "dumbbell" geometry, with the midportion showing the highest degree of underexpansion. S3 frame underexpansion and degree of leaflet pinwheeling appears to be affected by redo-TAVI sizing and calcium location.

CALCIFICATION PATTERNS AND PROTRUSION

Calcification was observable on both the outflow and inflow surfaces of the CV/EV TAVs and protruded from the inflow and outflow surfaces **(Figure 5A)**. During hydrodynamic testing, CV/EV leaflet calcium protrusion from the inflow side through the S3 frame was observed for the 29 mm S3 in 34 mm EV combination, and to a lesser extent for the 26 mm S3 in 29 mm EV combination **(Figure 5B)**. During systole, this calcification could be seen in contact with the S3 leaflets **(Moving image 3)**. As shown in **Figure 5A**, this finding is in line with the substantial calcium burden and location identified by micro-CT at the inflow side of the 34 mm and 29 mm EV TAVs, which was deflected during redo-TAVI.

FRAME CANNULATION NEEDED FOR POTENTIAL CORONARY ACCESS FOLLOWING REDO-TAVI

Visually, *ex vivo* frame cannulation, which would be needed for coronary access, did not appear to be prevented by the positioning of the calcified CV/EV leaflets for all redo-TAVI combinations with the S3 outflow at node 5 **(Supplementary Figure 2A)**. **Supplementary Figure 2B** shows modelling of catheter access for the 20 mm S3 in 23 mm EV and the 29 mm S3 in 34 mm EV redo-TAVI combinations.

Discussion

Redo-TAVI is an increasingly common procedure, and the assessment of its feasibility plays a central role in the lifetime management of patients with AS. However, clinical evidence remains limited, and bench testing can provide valuable insight to help fill this knowledge gap[21,28-30]. In the context of redo-TAVI with an S3 for a failed calcified CV/EV, this study provides the following key insights: first, node 5 positioning of the S3 outflow within a stenotic calcified CV/EV resulted in favourable hydrodynamics in 3 of the 4 configurations tested. Second, leaflet overhang – which was originally described in pristine valves – was also observed in degenerated calcified samples but remained stable throughout the cardiac cycle. In the current short-term hydrodynamic testing, this

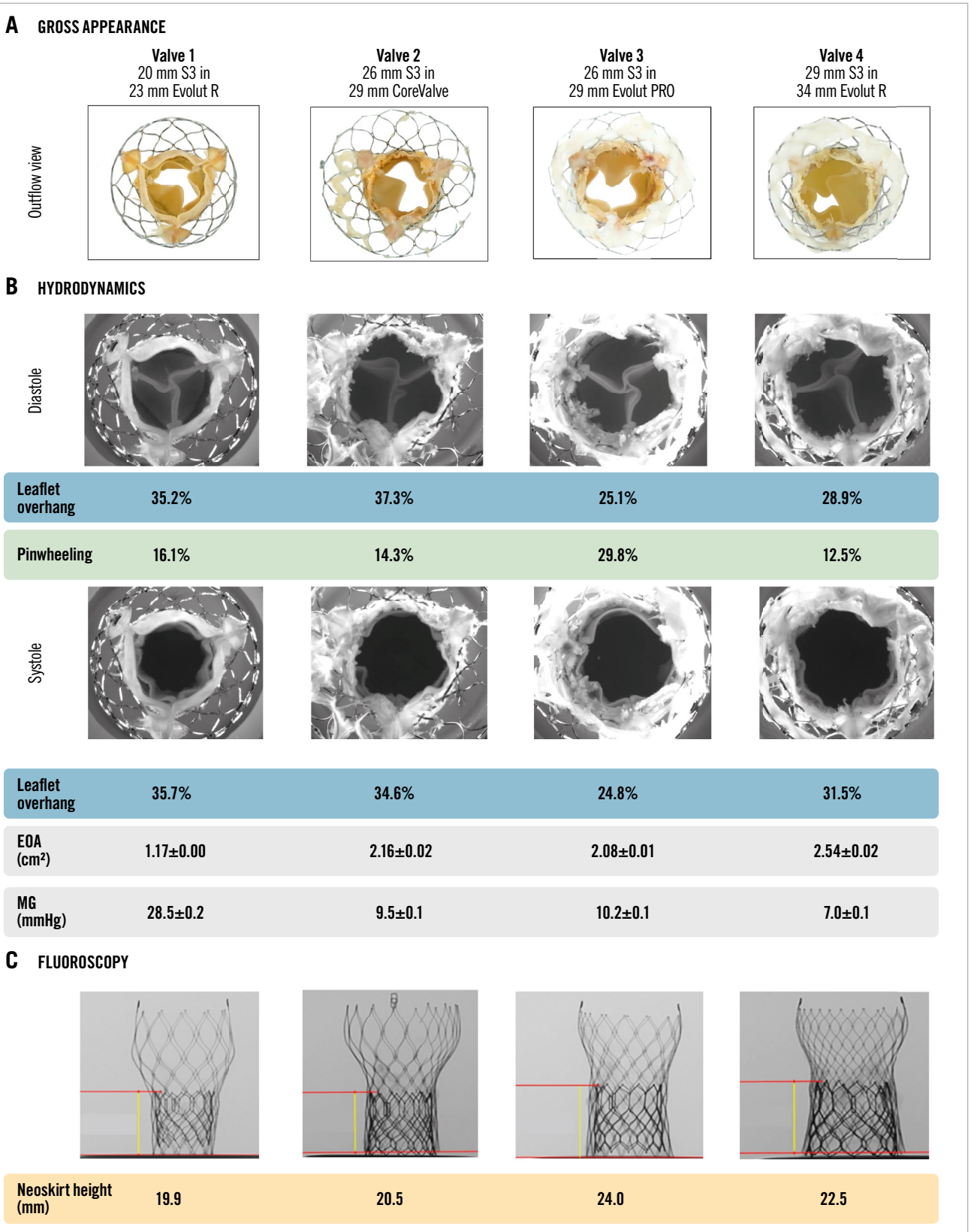


Figure 3. *Redo-TAVI with SAPIEN 3 in CoreValve/Evolut at node 5. A) Appearance of redo-TAVI combinations following S3 implant from the outflow perspective. B) Following redo-TAVI, images of confirmed leaflet opening (systole) and closing (diastole) during hydrodynamic testing with resulting EOA, MG, leaflet overhang and S3 pinwheeling. C) Fluoroscopy of redo-TAVI configuration noting neoskirt heights. EOA: effective orifice area; MG: mean gradient; S3: SAPIEN 3; TAVI: transcatheter aortic valve implantation*

Table 2. Neoskirt height, leaflet overhang, geometric orifice area, and pinwheeling following redo-TAVI.

	Neoskirt height, mm	Index CV/EV leaflet overhang, %			Index CV/EV GOA, cm²	S3 GOA, cm²	S3 pinwheeling, %
		Diastole	Systole	Difference			
VALVE 1 20 mm S3 in 23 mm Evolut R	19.9±0.1	35.2±0.6	35.7±0.4	1.4	3.22±0.03	2.81±0.02	16.1±5.7
VALVE 2 26 mm 3 in 29 mm CoreValve	20.5±0.4	37.3±0.8	34.6±0.2	7.5	4.08±0.02	3.67±0.05	14.3±10.5
VALVE 3 26 mm S3 in 29 mm Evolut PRO	24.0±0.5	25.1±1.0	24.8±1.4	1.2	5.11±0.05	3.76±0.01	29.8±9.3
VALVE 4 29 mm S3 in 34 mm Evolut R	22.5±0.3	28.9±0.3	31.5±0.6	8.6	5.26±0.02	4.19±0.04	12.5±3.6

Data presented as mean±standard deviation. CV/EV: CoreValve/Evolut; GOA: geometric orifice area; S3: SAPIEN 3; TAVI: transcatheter aortic valve implantation

phenomenon did not seem to have a significant impact on S3 hydrodynamic performance, since all combinations exhibited an EOA above the ISO-defined cutoff points and the GOA of CV/EV TAVs with overhanging leaflets always exceeded the GOA of S3 valves. Further, the ability to cannulate the frame on the bench did not appear to be affected by leaflet overhang. Third, considerable S3 frame underexpansion and leaflet pinwheeling were observed and may be affected by TAV sizing and calcium location. Fourth, in highly calcified CV/EV, calcium nodules from the inflow side can protrude through the S3 open cells and make contact with the S3 leaflets during systole. Fifth, we observed different patterns of S3 frame underexpansion geometry across the considered valves assessed.

The present study addresses some of the limitations of previous bench work on redo-TAVI with S3 in CV/EV[19]. Indeed, in the prior analysis, brand new CV/EV TAVs were used, which did not reproduce the challenges and outcomes of calcified stenotic CV/EV TAVs. Therefore, the present analysis offers a thorough examination of redo-TAVI in calcified CV/EV TAVs, assessing hydrodynamics, leaflet displacement and kinematics, frame deformation and expansion, and the impact of leaflet displacement and calcium burden on redo-TAVI functional outcomes.

The index TAVs used in our study demonstrated overt SVD consistent with previously documented modes of TAV degeneration, resulting in stenosis or mixed stenosis and regurgitation. These valves, while a selected subset, provide insight into the challenges faced in the setting of redo-TAVI across the different ranges of size combinations. Two of the 4 redo-TAVI combinations tested demonstrated overall satisfactory hydrodynamic performance per the ISO 5840-3 standard and clinical guidelines. However, the 29 mm S3 in 34 mm EV combination exhibited suboptimal RF, and the 20 mm S3 in 23 mm EV configuration showed a residual MG >20 mmHg. Interestingly, the 20 mm S3 in 23 mm EV combination also demonstrated a residual MG >20 mmHg when pristine valves were used[19].

These suboptimal results serve to highlight important clinical considerations for redo-TAVI. In the case of the high RF for the 29 mm S3 in 34 mm EV redo-TAVI, it was found that central leakage was the major contributor to the total RF initially observed. This was very likely secondary to S3 underexpansion, which was highest in this redo-TAVI combination, although it was observed in all redo-TAVI combinations. This observation is of utmost importance since the present study used a widely clinically accepted S3 sizing strategy of using an S3 that is one size smaller than the index CV/EV[25] and provides a comparison to previous bench studies using new TAVs and the same sizing strategy[19]. However, our findings underline the importance of TAV sizing based on the *in vivo* CT-based internal diameter of the index TAV, which may result in a smaller S3 implant with improved expansion and a potential reduction in the RF. This is in line with emerging data[13] and recent expert consensus from the freshly released Redo TAV app (KRUTSCH). Future redo-TAVI bench studies should consider the use of novel models that allow CT sizing. Our findings may also prove valuable for clinical studies on CT sizing. For example, current CT sizing does not incorporate aspects of TAV degeneration that may impact the internal diameter or the expansion of the index TAV. With respect to the high residual MG seen in the 20 mm S3 in 23 mm Evolut R configuration, this is in line with known complications of higher gradients in smaller TAVs, particularly when underexpanded, including the observation of gradients over 20 mmHg in the settings of index TAVI, valve-in-valve, and redo-TAVI with small S3 TAVs[15,31,32]. Thus, these findings bring important focus on the importance of optimising TAV type and size selection at the time of the index TAVI procedure in order to maximise the chances of successful redo-TAVI. Indeed, when considering the lifetime management of young patients, it is critical to consider the potential need for a subsequent intervention at the time of the index TAVI procedure.

We previously showed that the presence of calcification on the surface of failed TAVs provides insights into the underlying mechanisms of valve degeneration[22]. The current analysis now unveils a potential functional consequence of this in the context of redo-TAVI: protrusion of calcium from the inflow and outflow surfaces can interact with the second TAV. This can impact redo-TAVI functional outcomes

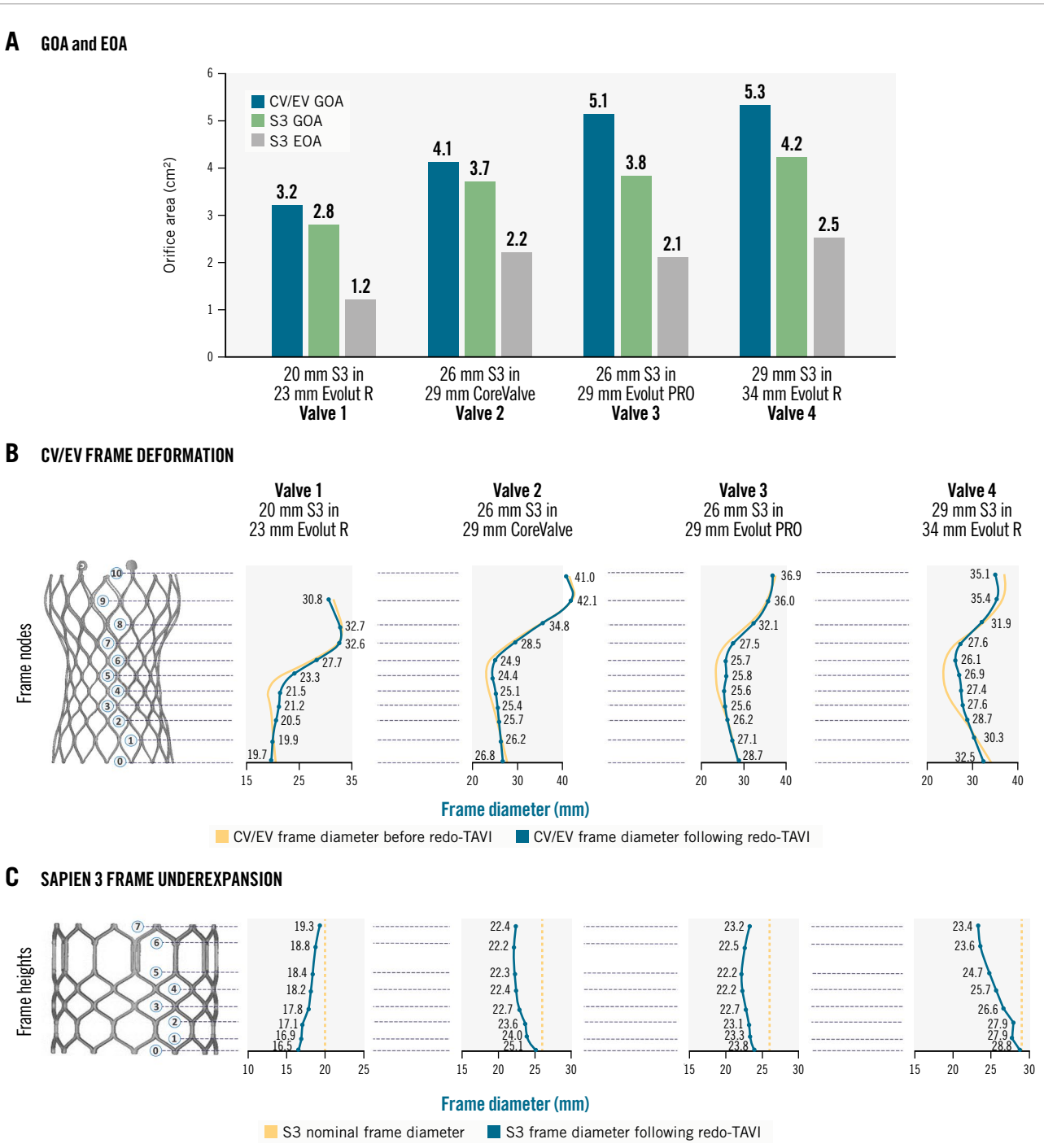


Figure 4. *CoreValve/Evolut and SAPIEN 3 orifice areas and frame deformation. A) Comparison of CV/EV GOA, S3 GOA and S3 EOA. B) CV/EV frame deformation at nodes 0 to 10 comparing frame diameter before (yellow) and after (blue) redo-TAVI. C) S3 frame expansion comparing observed S3 frame diameter at node heights 0 to 7 at nominal state (yellow) and after redo-TAVI (blue). The data points shown correspond to frame diameter values following redo-TAVI. CV/EV: CoreValve/Evolut; EOA: effective orifice area; GOA: geometric orifice area; S3: SAPIEN 3; TAVI: transcatheter aortic valve implantation*

in two potential ways. First, outflow surface calcium can become pinned between the two TAVs during redo-TAVI and thus, as a component of leaflet thickening, impact S3 expansion, as observed. Second, inflow surface calcium can be displaced through the S3 frame, leading to contact with the S3 leaflets during systole, as was seen in 2 of the 4 redo-TAVI configurations tested. The significant calcium burden identified by micro-CT imaging on the inflow side of explanted TAVs suggests a potential link between calcium location and the observed protrusion phenomenon. Moreover, future studies will need to consider how to characterise valve degeneration, including leaflet thickening and calcification

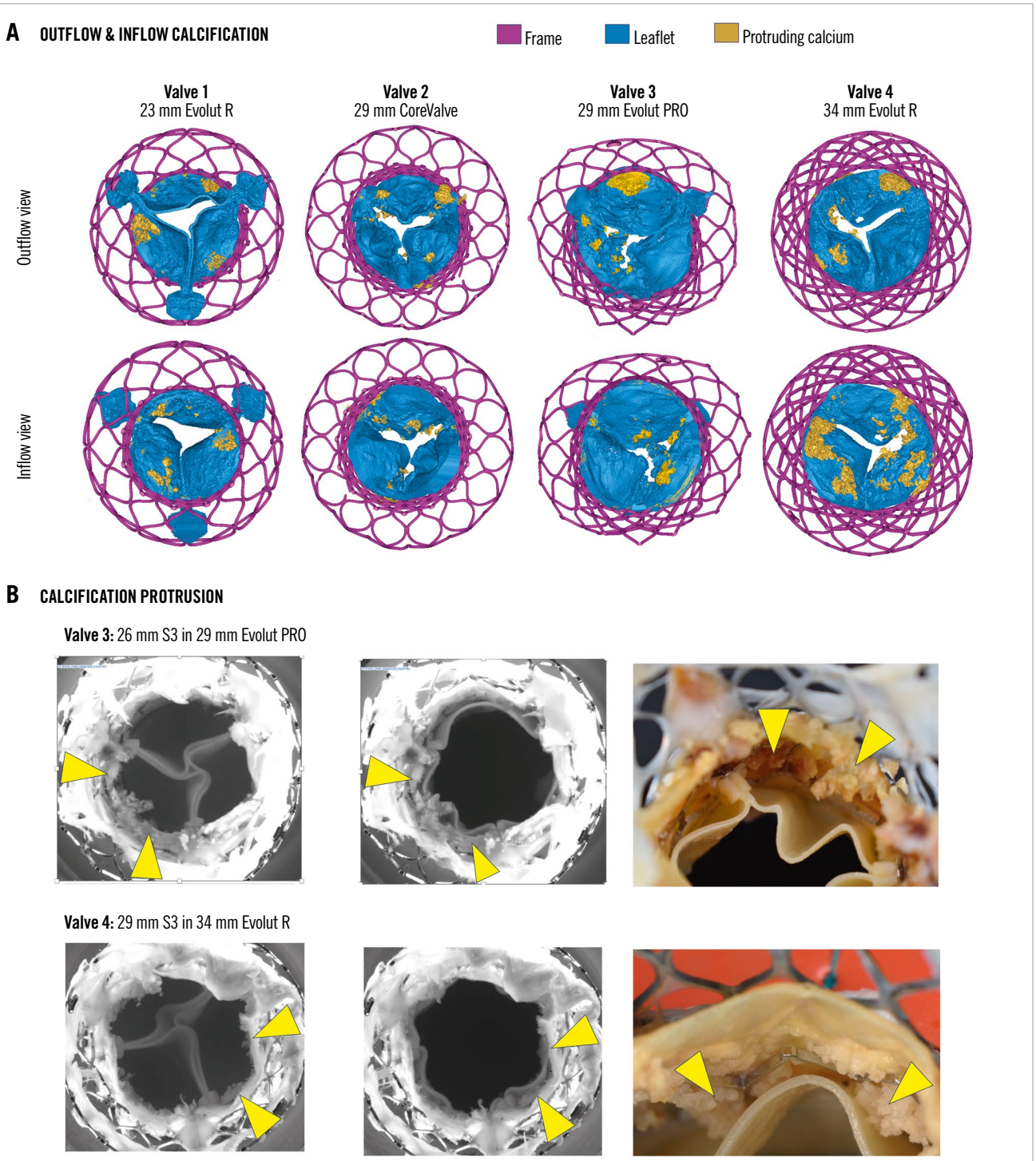


Figure 5. *CoreValve/Evolut calcification patterns and protrusion following redo-TAVI. A) CV/EV micro-CT showing patterns of inflow and outflow calcification protrusions from the surface of the TAV leaflet. B) Images from hydrodynamic testing showing protruding calcification from degenerated CV/EV in contact with the implanted S3 and high-resolution gross pathology images of areas of protrusion. The yellow arrowheads denote protruding calcification. CT: computed tomography; CV/EV: CoreValve/Evolut; S3: SAPIEN 3; TAV: transcatheter aortic valve; TAVI: transcatheter aortic valve implantation*

patterns, clinically in redo-TAVI. Indeed, even if the long-term consequences of repeated contact/friction with the calcium nodules are unknown, procedural planning to optimise sizing and minimise the risk of potential complications associated with calcium protrusion may be necessary.

This is also important when considering post-dilatation. While post-dilatation could improve S3 expansion, CV/EV deformation, and pinwheeling, there are potential concerns of damage to the S3 leaflets from protruding calcium, and further S3 expansion has implications for coronary flow

obstruction and the extent and stability of leaflet overhang. In the current study, post-dilatation was not performed, and this may have resulted in the notable S3 underexpansion, associated pinwheeling, and high RF observed in the 29 mm S3 in 34 mm EV configuration. Notably, S3 pinwheeling in the setting of considerable central leakage can be lower than expected, given the lack of central coaptation, which impacts the assessment of the length of the actual leaflet's free edge (L_{actual}). This can also be impacted by differences in the extent of coaptation along the length of the free edges of leaflet pairs, as leaflet redundancy is taken up by flexion of the leaflet in an axis that pinwheeling measurements are not able to assess. We highlight this in **Supplementary Figure 1**. Our findings regarding pinwheeling also suggest that factors such as differences in calcification volume and pattern may impact the extent of pinwheeling, likely related to differences in expansion geometry and central coaptation location.

Importantly, leaflet overhang, originally described on the bench using new TAVs[19], was still present in degenerated TAVs, although to a slightly lesser degree in some combinations. Furthermore, we showed that, in the presence of calcified leaflets, leaflet overhang is stable throughout the cardiac cycle with minimal difference between systole and diastole. While requiring more study, this may have implications for flow dynamics in the sinus, as an overhanging leaflet – whether stable or not – may contribute to turbulent flow, but how and the relative magnitude by which stable or unstable leaflet overhang impacts flow are unknown. The persistence of the leaflet overhang phenomenon in the presence of calcified leaflets has important clinical implications when considering redo-TAVI planning. Indeed, here we showed that leaflet overhang and neoskirt height findings are consistent: as the leaflets overhung and were not pinned straight or deflected outwards, the neoskirt was not found to extend above the S3 frame outflow. This is critical, since the neoskirt height is a key consideration for coronary access and assessment of risk of coronary obstruction. Thus, the fact that, on the bench, the neoskirt height can still be predicted by the level of the S3 outflow offers some reassuring elements in terms of the clinical predictability of procedural results. Current investigations have primarily focused on how leaflet overhang impacts the acute hydrodynamic function of redo-TAVI. However, future studies should explore other aspects of leaflet overhang and its effect on longer-term redo-TAVI outcomes, including evaluating how leaflet overhang and hydrodynamic function may change with implantation at higher or lower node positions. However, performing this in explants will always remain a significant challenge since implants in a degenerated CV/EV generally cause damage to the leaflets that preclude multiple S3 deployments.

Despite leaflet thickening and stiffness, and given the presence of leaflet overhang, we observed that these did not later prevent, at least on the bench, the ability to selectively cannulate the index TAV frame. This is of importance when considering the high prevalence of concomitant coronary artery disease in patients undergoing TAVI, especially when long-term survival is anticipated. However, given the patient-to-patient anatomical variation in aortic root dimensions, coronary height, and inconsistent rate of commissural alignment, selective coronary engagement might still remain extremely challenging in some cases, and further studies are required to better understand this issue.

Finally, we found that depending on the index TAV size and type, S3 frame expansion could follow several patterns. The smallest combination exhibited a "flared" frame geometry; 2 samples, particularly the largest configuration, displayed a "tapered" frame geometry, while one sample had a "dumbbell" geometry. This is of interest since S3 frame deformation has been shown to potentially impact outcomes such as risk for leaflet thrombosis[33]. While the current sample size does not allow for further characterisation of this phenomenon, future studies will need to look at the impact of parameters like degenerative changes of the index TAV or redo-TAVI sizing on patterns of expansion following redo-TAVI.

Limitations

There are limitations to be considered in this analysis. First, the *ex vivo* bench-testing setup may not reflect physiological conditions in clinical practice including the challenges of frame cannulation to achieve coronary access. *In vivo* expansion of the index and second TAVs may vary compared with a bench model, and the CV/EV holder used may not reflect patient anatomy but was in accordance with ISO 5840-3 guidance. Second, this is a limited redo-TAVI population which does not reflect all pathologies, patterns of calcification, size combinations, etc., but does reflect common challenges for failed CV/EV TAVs. Further, irreversible S3 frame deformation, risk of explanted CV/EV leaflet damage/tear during S3 removal, and CV/EV explant availability limited the assessment of additional redo-TAVI implant depth configurations. Third, sizing the S3 was based on recommendations of downsizing that did not consider CT sizing. Fourth, no balloon pre- or post-dilatation was performed, which may have impacted S3 frame expansion, CV/EV frame deformation, and S3 hydrodynamic performance. This gives insight into the standard nominal S3 deployment – a conservative approach that is used in clinical settings where the risk of coronary obstruction precludes the use of post-dilatation, which would further expand the CV/EV frame and increase the risk. However, this approach does not reflect the best-case scenario, where S3 nominal expansion can be achieved and where improved valve function could be expected. However, as mentioned earlier, it is also possible that aggressive post-dilatation could result in damage to the S3 leaflets from the calcium protrusion, and the issue of pre-/post-dilatation would warrant a full-scale future study considering method variations and outcomes of pre-/post-dilatation. Indeed, although 3 out of 4 redo-TAVI configurations had adequate hydrodynamic performance immediately after the procedure, S3 underexpansion, leaflet pinwheeling and calcium protrusion may have important longer-term clinical implications that were out of the scope of this study. While this study provides highly valuable insights, further validation using real-world clinical data on redo-TAVI is necessary.

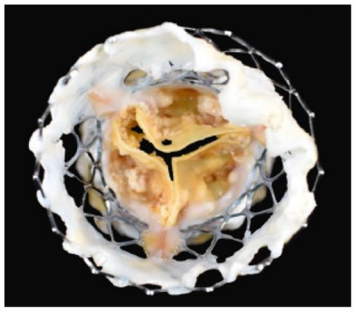
EuroIntervention — Central **Illustration**

Redo-TAVI with SAPIEN 3 outflow at node 5 of a degenerated calcified CoreValve/Evolut valve.

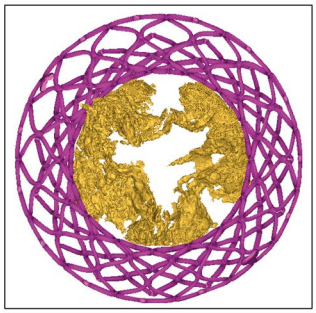
REDO-TAVI CONFIGURATION

S3 OUTFLOW AT CV/EV NODE 5

MORPHOLOGICAL APPEARANCE

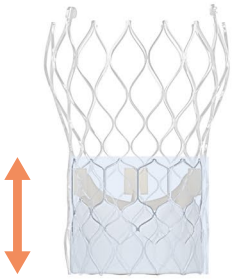


CALCIUM QUANTIFICATION



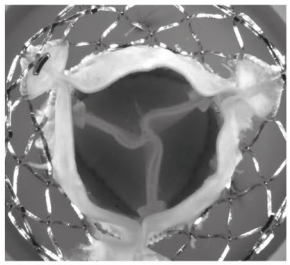
IMPLICATIONS OF SAPIEN 3 IMPLANT IN A STENOTIC CALCIFIED CV/EV

NEOSKIRT HEIGHT & CORONARY ACCESS



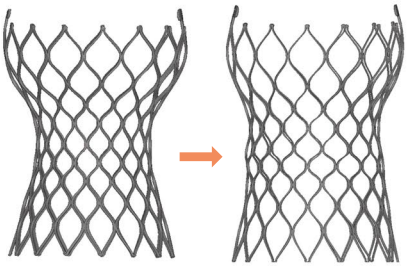
Node 5 positioning led to a neoskirt between 20 and 24 mm. Modelling of coronary access was feasible.

LEAFLET OVERHANG



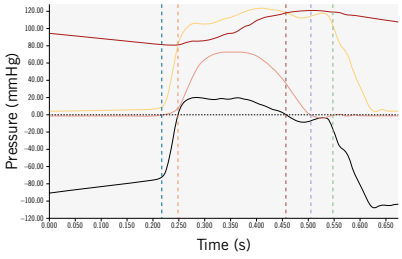
Leaflet overhang ranged from 25-37%, was stable throughout the cardiac cycle (<9% difference), and did not constrain systolic flow.

CV/EV DEFORMATION



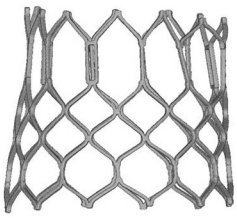
S3 implant caused CV/EV frame deformation. Change in radius by up to 1.7 mm.

HYDRODYNAMIC PERFORMANCE



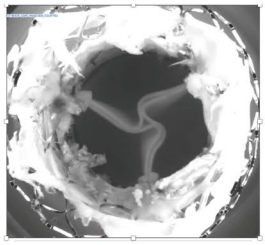
S3 hydrodynamic performance was adequate in 3 of the 4 configurations tested. The 29 mm S3 in 34 mm EV configuration led to a regurgitant fraction >20%.

S3 UNDEREXPANSION



S3 frame was found to be underexpanded in all cases following redo-TAVI.

CALCIUM PROTRUSION & S3 PINWHEELING



Calcium protrusion from the failed CV/EV was observed in contact with the S3 leaflets. S3 pinwheeling was detected.

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CV: CoreValve; EV: Evolut; S3: SAPIEN 3; TAVI: transcatheter aortic valve implantation

Conclusions

Redo-TAVI with the S3 outflow at node 5 of a calcified stenotic CV/EV resulted in adequate systolic hydrodynamic performance (EOA, MG, velocity) per the ISO standard in all combinations tested, while 3 out of 4 combinations had an RF within the accepted ISO range (RF <20%). On the bench, leaflet overhang did not seem to have a significant impact on S3 short-term hydrodynamic performance. CV/EV leaflets remained open and stationary throughout the cardiac cycle and were not pinned in a manner that constrained S3 systolic

flow or appeared to prevent selective frame cannulation on the bench. S3 frame underexpansion and leaflet pinwheeling, however, were observed. Overall, our findings contribute to the understanding of redo-TAVI in the context of failed CV/EV TAVs, offering valuable insights into patient selection, procedural planning with routine use of *in vivo* CT sizing, and optimisation of TAV performance. Further research and clinical studies are warranted to validate our findings and refine treatment strategies for patients requiring redo-TAVI, particularly in cases of valve degeneration and calcification.

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Acknowledgements

The authors wish to acknowledge that Amanda Tenhoff, PhD, an employee of Medtronic, provided technical input for the study. Andres Caballero, PhD, an employee of Medtronic, assisted in the preparation of the manuscript including drafting the methods and results sections, creating tables and figures, ensuring the accuracy of the data presented, and providing editorial support under the direction of the lead and senior authors.

Funding

This work was supported by Medtronic, USA, and the Cardiovascular Translational Laboratory at St. Paul's Hospital, Canada.

Conflict of interest statement

D. Meier has received an institutional grant from Edwards Lifesciences. A. Nigade, K. Dorman, and S. Javani are employees and shareholders of Medtronic. M. Akodad is a consultant to Edwards Lifesciences, Medtronic, and Abbott. D.A. Wood is a consultant and receives unrestricted grant support from Medtronic, Edwards Lifesciences, and Abbott. T. Rogers is a consultant to Edwards Lifesciences, Medtronic, Abbott, Anteris, and Boston Scientific; is an advisory board member to Medtronic and Boston Scientific; has equity in Transmural Systems; and is a co-inventor on patents, assigned to NIH, for transcatheter electrosurgery devices. R. Puri is a consultant, speaker and proctor for Medtronic and Abbott; consults for Centerline Biomedical, Philips, P+F Products + Features, Shockwave Medical, VDyne, VahatiCor, Advanced NanoTherapies, NuevoSono, TherOx, GE HealthCare, Anteris, T45 Labs, Pi-Cardia, Protembis, and Nyra Medical; and has equity interest in Centerline Biomedical, VahatiCor, and NuevoSono. K.B. Allen has received grant support, proctor and speaker bureau fees from Edwards Lifesciences, Medtronic, and Abbott, with no personal compensation. A.K. Chhatriwalla is a proctor for Edwards Lifesciences and Medtronic; is on the speakers bureau for Abbott, Edwards Lifesciences, and Medtronic; and has a research grant from Boston Scientific. M.J. Reardon has received fees to his institution from Medtronic for consulting and providing educational services. G.H.L. Tang has received speaker honoraria and served as a physician proctor, consultant, advisory board member, TAVI publications committee member, APOLLO trial screening committee member and IMPACT MR steering committee member for Medtronic; has received speaker honoraria and served as a physician proctor, consultant, advisory board member and TRILUMINATE trial anatomic eligibility and publications committee member for Abbott; has served as an advisory board member for Boston Scientific and JenaValve; a consultant and physician screening committee member for Shockwave Medical; a consultant for NeoChord, Shockwave Medical, Peija Medical, and Shenqi Medical Technology; and has received speaker honoraria from Siemens Healthineers. J.G. Webb is a consultant to and has received research funding from Edwards Lifesciences, Abbott, and ViVitro Labs. S. Fukuhara is a consultant for Medtronic, Terumo Aortic, and Artivion. S.L. Sellers is a consultant for Medtronic, Edwards Lifesciences, Excision Medical, and Anteris Technologies; has received research support from Medtronic, Edwards Lifesciences, Vivitro Labs, and HeartFlow; and has stock options in Excision Medical. V.N. Bapat is a consultant for Edwards Lifesciences, Medtronic, Abbott, Anteris Technologies, and Meril. The other authors have no conflicts of interest to declare.

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Supplementary data

Supplementary Appendix 1. Supplementary methods.

Supplementary Table 1. Characteristics of the four calcified transcatheter aortic valve explants.

Supplementary Table 2. SAPIEN 3 pinwheeling by leaflet pair.

Supplementary Table 3. CoreValve/Evolut frame diameter and change in frame radius following redo-TAVI.

Supplementary Figure 1. SAPIEN 3 coaptation deficit following redo-TAVI.

Supplementary Figure 2. Feasibility of frame cannulation needed for coronary access following redo-TAVI.

Moving image 1. Baseline CoreValve/Evolut explant function. Visualisation of valve kinematics during baseline hydrodynamic testing of explanted calcified CoreValve and Evolut TAVs.

Moving image 2. Hydrodynamic evaluation following redo-TAVI. Visualisation of valve kinematics, pinwheeling, and leaflet overhang following S3 in CV/EV redo-TAVI.

Moving image 3. Calcium protrusion. Visualisation of S3 leaflet contact with protruding CV/EV calcification following redo-TAVI.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-24-00619

EuroIntervention
2024;20:1405-1415
DOI: 10.4244/EIJ-D-24-00367

ORIGINAL RESEARCH

Feasibility of redo-TAVI in the self-expanding ACURATE *neo*2 valve: a computed tomography study

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This paper also includes supplementary data published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-24-00367

ABSTRACT

BACKGROUND: Redo-transcatheter aortic valve implantation (TAVI) may be unfeasible because of the risk of compromising coronary flow or coronary access by the pinned back leaflets of the index transcatheter aortic valve.

AIMS: We aimed to evaluate the feasibility of redo-TAVI using the balloon-expandable SAPIEN 3 (S3) implanted within the self-expanding ACURATE *neo*2 (ACn2) valve and to identify predictors associated with a high risk of compromising coronary flow.

METHODS: A total of 153 post-ACn2 TAVI cardiac computed tomography scans were analysed. Redo-TAVI using an S3 was simulated in two positions: S3 outflow to the ACn2 upper crown (low implant) and S3 outflow to the base of the ACn2 commissural posts (high implant). The risk for coronary flow compromise and inaccessibility was determined by the height of the neoskirt created by the pinned back leaflets and the valve-to-aorta distances.

RESULTS: At a low S3 implant position, risk of coronary flow compromise was predicted in only 8% of patients and this increased to 60% with a high S3 position. In accordance, coronary access was predicted to be unrestricted in 52% versus 13% of patients with a low versus high S3 implantation. Female sex, a small aortic annular dimension and a sinotubular junction-to-aortic annulus mean diameter ratio <1.15 were independent predictors associated with a high risk for coronary flow compromise.

CONCLUSIONS: The feasibility of redo-TAVI with an S3 in an ACn2 depends on the implant depth of the S3 and the geometry of the surrounding aorta. A low S3 implant may reduce the risk of coronary flow compromise and inaccessibility.

KEYWORDS: aortic stenosis; computed tomography; lifetime management; reintervention; transcatheter aortic valve implantation

SUBMITTED ON 19/04/2024 - REVISION RECEIVED ON 1st 13/07/2024 / 2nd 06/08/2024 - ACCEPTED ON 14/08/2024

Globally, the median age of patients undergoing transcatheter aortic valve implantation (TAVI) is decreasing, and the long-term durability of transcatheter aortic valves (TAVs) remains unknown[1]. Therefore, an increasing proportion of younger patients are expected to outlive their index TAV[2]. For these patients, a redo-TAVI procedure compares favourably against surgical explantation[3-6].

Redo-TAVI is predicted to be unfeasible for a significant proportion of TAVI patients because of an increased risk of coronary obstruction or coronary inaccessibility[7-9]. Few data exist concerning the feasibility of redo-TAVI after failure of the self-expanding ACURATE *neo*2 (ACn2) TAV (Boston Scientific). *In vitro* studies[10,11] and isolated case reports[12,13] have confirmed the technical feasibility and favourable haemodynamic outcomes following implantation of the balloon-expandable SAPIEN 3 (S3) TAV (Edwards Lifesciences) to treat a degenerated ACn2; however, the subsequent impact on coronary flow and coronary access remains unknown.

In this study, we evaluated the feasibility of S3-in-ACn2 redo-TAVI, based on post-ACn2 TAVI computed tomography (CT) imaging and determined predictors associated with a high risk of compromising coronary flow and coronary access.

Impact on daily practice

This study investigated the feasibility of redo-transcatheter aortic valve implantation (TAVI) using a SAPIEN 3 (S3) to treat an index ACURATE *neo*2 valve. The risk of coronary flow compromise and coronary inaccessibility is highly dependent on the implant position of the S3, with a low position being the most favourable. A sinotubular junction-to-aortic annulus mean diameter ratio <1.15 is a strong predictor of redo-TAVI unfeasibility due to coronary issues. Careful preprocedural planning requires a detailed analysis of pre- and post-implant TAVI computed tomography scans to determine the optimal implant size and depth of the S3 to preserve coronary flow and future coronary access.

Methods

STUDY POPULATION

Amongst 1,024 patients who underwent TAVI with the ACn2 TAV in two centres in Germany and Denmark, 153 patients had high-quality post-implant cardiac CT scans, which were analysed for this study. Patients treated with an ACn2 TAV for a degenerated surgical bioprosthesis were excluded. All cardiac CT scans were electrocardiographically gated, contrast enhanced and had <1 mm slice thickness. CT analysis was performed using 3Mensio software (Pie Medical Imaging), and all measurements were performed and verified independently by two experienced physicians (G. Bieliauskas, Y. Kobari). Ethical approval for the study was granted by the local ethics committees, and written informed consent was obtained from all included patients.

SECOND TAV SIZING AND POSITIONING

The post-TAVI CT scans were used to implant the virtual S3 inside the ACn2 valves. Selection of the size of the S3 TAV for the simulation was based on the size and expansion of the index ACn2 as well as the native aortic annular dimensions derived from the pre-TAVI CT. The expected expansion of the redo-TAV complex was taken into consideration based on findings from previous bench-testing data and real-world case examples[11,13]. Accordingly, a 21 mm virtual S3 was implanted into a small ACn2 (ACn2 S), a 23 or 24 mm virtual S3 implanted into a medium ACn2 (ACn2 M), and a 25 mm virtual S3 into a large ACn2 (ACn2 L). The decision to use a 23 mm or 24 mm for the ACn2 M was based on the expansion of the index TAV and native aortic annular dimension **(Figure 1)**.

Two different implant positions of the S3 were evaluated: in case of a low S3 implant, the outflow of the S3 was positioned at the level of the upper crown of the ACn2. In case of a high S3 implant, the S3 outflow was positioned at the bottom of the commissural posts of the ACn2 **(Figure 1)** – these positions were based on prior bench test work.

The resulting height of the pinned-up leaflets, termed neoskirt, was defined as the distance from the ACn2 inflow to the outflow of the virtual S3, and this position was defined as the neoskirt plane (NSP). The residual leaflet length of the ACn2 above the outflow of the S3 or NSP was defined as leaflet overhang, and the extent of leaflet overhang was predicted based on data from bench testing[10,11].

DETERMINING THE RISK OF COMPROMISING CORONARY FLOW OR CORONARY ACCESS

In order to determine the risk of compromising coronary flow or access, two planes were identified: the NSP and the coronary risk plane (CRP). The neoskirt is the portion of the redo-TAV combination covered with the inner skirt and the pinned-open prosthetic leaflets of the index TAV – the NSP is defined as the plane at the top of the neoskirt[14,15]. The CRP is defined as the plane parallel with the aortic annulus at the base of the coronary ostium and was obtained for both the left and right coronary ostia. The relationship between the NSP and the CRP for each coronary ostium was noted.

Abbreviations

ACn2	ACURATE *neo*2	**S3**	SAPIEN 3	**TAVI**	transcatheter aortic valve implantation
CRP	coronary risk plane	**SoV**	sinus of Valsalva	**VTA**	valve-to-aorta
CT	computed tomography	**STJ**	sinotubular junction	**VTAoS**	valve-to-aortic sinus
LCA	left coronary artery	**STJ/AAØ**	sinotubular junction-to-aortic annulus mean diameter	**VTC**	valve-to-coronary
NSP	neoskirt plane	**TAV**	transcatheter aortic valve	**VTSTJ**	valve-to-STJ
RCA	right coronary artery				

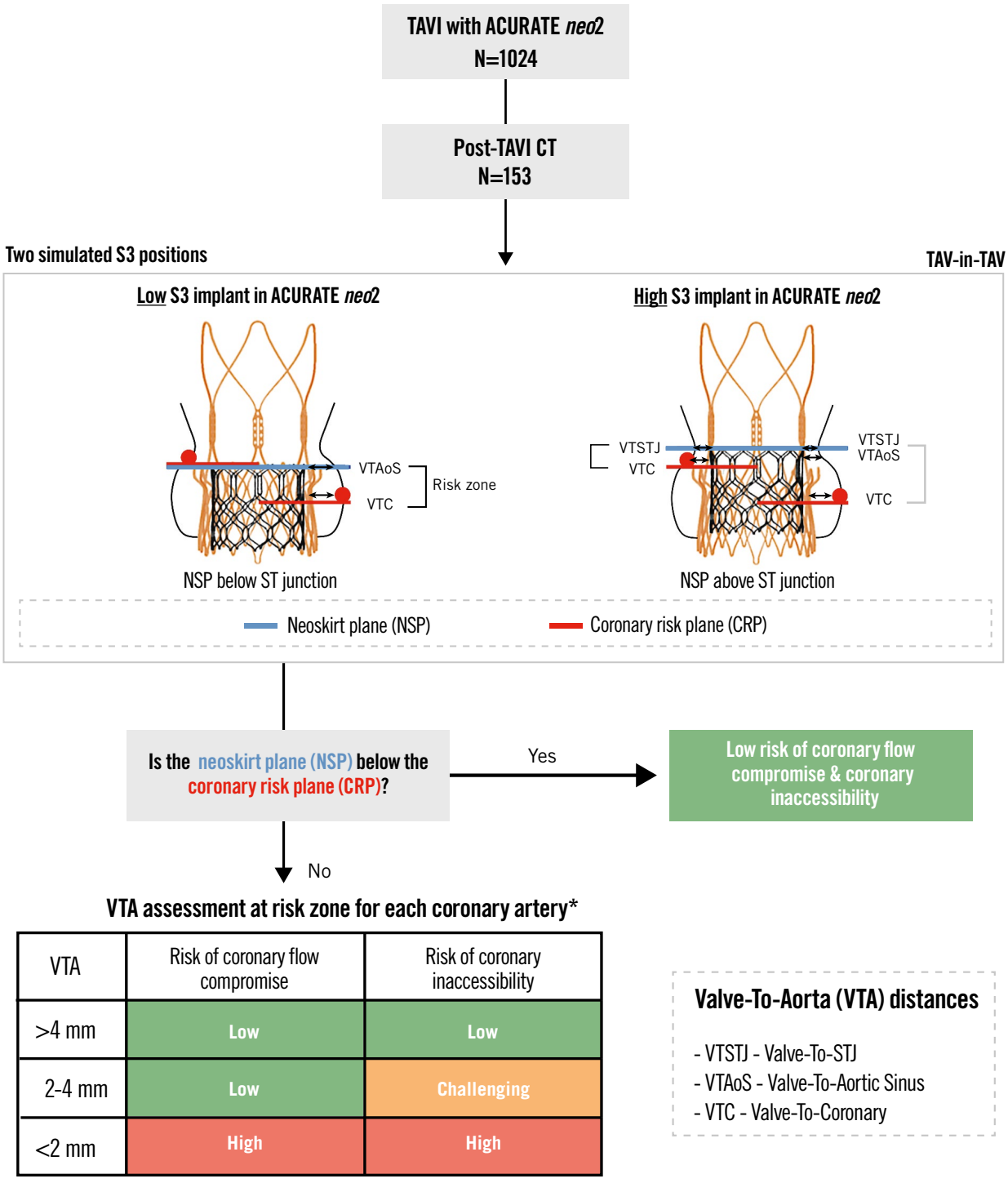


Figure 1. *Study concept and methodology. Methodology used to evaluate the risk of coronary flow compromise and coronary inaccessibility following virtual SAPIEN 3 (S3) implantation in an ACURATE neo2 (ACn2) index TAV using a post-index TAVI CT scan. Sizing of the virtual S3 was based on prior bench-testing data to account for predicted S3-in-ACn2 valve expansion. Definitions of the neoskirt plane and coronary risk plane can be found in the Methods section and on the redo TAV App (KRUTSCH). *Risk based on narrowest VTA measurement and simulated further (ACn2 expansion by S3 implantation – based on bench test data: 23 mm S3 in ACn2 S [21 mm]; 23 mm S3 in ACn2 M [23 mm]; 26 mm S3 in ACn2 M [24 mm]; 26 mm S3 in ACn2 L [25 mm]). CT: computed tomography; L: large; M: medium; S: small; S3: SAPIEN 3; ST: sinotubular; TAV: transcatheter aortic valve; TAVI: transcatheter aortic valve implantation*

In a short-axis view, the distance between the simulated redo-TAV complex (expanded ACn2 with a virtual S3) and the surrounding aortic wall was measured and termed the valve-to-aorta (VTA) distance. Considering the thickness of the stent frame and the blooming artefact on CT, the VTA distances were measured from the middle of the stent frame.

Depending on the patients' anatomy, the VTA distance can be evaluated at three different levels: (1) valve-to-coronary (VTC), (2) valve-to-aortic sinus (VTAoS), and (3) valve-to-sinotubular junction (VTSTJ). Each of these VTA measurements was performed for the left (LCA) and right coronary artery (RCA). Based on these measurements, the risk of compromising coronary flow or access was determined **(Figure 1)**.

Redo-TAV with an S3-in-ACn2 was deemed to be low risk for both coronary flow compromise and coronary inaccessibility if the NSP was below the CRP. If the NSP was above the CRP, then the narrowest of the three VTA measurements was used to further define the risk. The risk of coronary flow compromise was deemed to be low if the VTA was >2 mm; it was deemed high risk for compromise if the VTA was <2 mm. For coronary access, the risk of inaccessibility was deemed to be low if the VTA was >4 mm, challenging if the VTA was 2-4 mm, and high if the VTA was <2 mm. These evaluations were conducted for both the LCA and RCA. The higher risk for the two coronary arteries was determined as the overall risk level for each patient.

STATISTICAL ANALYSIS

Categorical variables are expressed as numbers (percentages) and continuous variables as medians (interquartile range). A stepwise uni- and multivariate logistic regression analysis was utilised in order to identify associated factors and independent predictors of coronary flow compromise in case of a high S3 implantation into an index ACn2 TAV. Clinical, cardiac CT and TAVI-specific variables were included in this analysis. Variables which were associated with a higher risk for coronary flow compromise in the univariate model (defined as $p<0.1$) were included in the multivariate model in order to identify independent predictors of coronary flow compromise. In case of similar variables (e.g., aortic annulus perimeter or area), only the variable with the highest statistical power was tested in the multivariate model in order to avoid multicollinearity issues. In case of a "ratio" variable with a p-value<0.1 in the univariate analysis, it was prespecified that the optimal cutoff value would be determined and tested in the multivariate analysis. A 2-sided p-value<0.05 was considered statistically significant. All statistical analyses were performed using SPSS, version 27.0 (IBM).

Results

For the purpose of this study, 153 patients with a post-TAVI cardiac CT following ACn2 TAV implantation were included. Baseline clinical, CT and procedural details are summarised in **Table 1**. The median age of the study cohort was 81 (77-84) years, 61% were female, and the median Society of Thoracic Surgeons risk score was 2.9% (2.2-4.6%). A small, medium, or large ACn2 was implanted in 30 (19.6%), 57 (37.3%),

Table 1. Baseline characteristics.

	N=153
Clinical variables	
Age, years	81 (77-84)
Female	94 (61.4)
Arterial hypertension	125 (81.7)
Diabetes mellitus	44 (28.8)
Coronary artery disease	75 (49.0)
Prior PCI	53 (34.6)
Prior CABG	14 (9.2)
Atrial fibrillation	47 (30.7)
Permanent pacemaker	13 (8.5)
Prior stroke	13 (8.5)
Peripheral arterial disease	16 (10.5)
Reduced renal function[§]	59 (38.6)
STS risk score, %	2.9 (2.2-4.6)
CT variables	
Aortic annulus perimeter, mm	74.7 (71.0-78.6)
Aortic annulus area, mm^2	432 (383-477)
Sinus of Valsalva mean diameter, mm	30.9 (28.8-33.5)
STJ mean diameter, mm	27.2 (25.6-29.4)
STJ height, mm	25.0 (22.7-28.0)
Left coronary artery height, mm	13.5 (12.0-15.8)
Right coronary artery height, mm	16.8 (14.5-18.6)
TAVI procedure	
ACURATE *neo2*	
Small, 23 mm	30 (19.6)
Medium, 25 mm	57 (37.3)
Large, 27 mm	66 (43.1)
Predilatation	148 (96.7)
Implant depth, mm	5.0 (4.0-5.6)
Post-dilatation	50 (32.7)
In-hospital outcomes	
Myocardial infarction	0
Stroke	4 (2.6)
Permanent pacemaker implantation	14 (9.2)
Predischarge echocardiographic outcomes	
Transprosthetic mean gradient, mmHg	8.0 (5.0-10.8)
Paravalvular regurgitation	
None-trace	71 (46.4)
Mild	77 (50.3)
Moderate or greater	5 (3.3)

Data are given as median (IQR) or n (%). [§]Reduced renal function is defined as estimated glomerular filtration rate <30 mL/min/1.73 m^2. CABG: coronary artery bypass graft; CT: computed tomography; IQR: interquartile range; PCI: percutaneous coronary intervention; STJ: sinotubular junction; STS: Society of Thoracic Surgeons; TAVI: transcatheter aortic valve implantation

and 66 (43.1%) of patients, respectively. Redo-TAVI was simulated using a virtual 21 mm S3 for all ACn2 S and a 25 mm S3 for all ACn2 L valves. For ACn2 M, a virtual 23 mm and 24 mm S3 were simulated in 44/57 and 13/57 of cases, respectively.

PREDICTED RISK OF CORONARY FLOW COMPROMISE

The predicted risk of coronary flow compromise was dependent on the implantation depth of the S3, with a greater risk seen with a higher implant of the S3 **(Figure 2)**. In case of a high S3 implant, 60% of patients were deemed to be at a high risk and 40% at a low risk of coronary flow compromise, whilst for a low S3 implant, only 8% were at a high risk and the remaining 92% at a low risk. Irrespective of the implant depth of the S3, the RCA was associated with a greater risk of coronary flow compromise compared to the LCA **(Figure 2)**.

PREDICTED RISK OF CORONARY INACCESSIBILITY

The risk of coronary inaccessibility was also greater with a higher implantation of the S3 TAV **(Figure 2)**. A total of 60% of patients would be at high risk for coronary inaccessibility to one or both coronary ostia with a high S3 implant, with a further 27% having challenging coronary access. Implanting the S3 lower would lead to only 8% of patients being at high risk for coronary inaccessibility, but 40% could still have challenging coronary access. A straightforward coronary access was predicted for 13% of patients with a high S3 implant; this increased to 52% with a low S3 implant. Again, the RCA was at an increased risk for coronary inaccessibility compared to the LCA.

PREDICTORS OF CORONARY FLOW COMPROMISE

The risk of coronary flow compromise is highest in case of a high S3 implant position. A list of clinical, CT and procedural variables was screened in order to identify variables associated with this increased risk. Besides female sex, coronary artery disease and atrial fibrillation, numerous CT variables reflecting a small aortic annulus, small aortic root and low coronary ostia were identified ($p<0.1$). None of the procedural variables were associated with a high risk of coronary flow compromise **(Table 2)**.

In the multivariate analysis, aortic annulus perimeter (odds ratio [OR] 0.91, 95% confidence interval [CI]: 0.83-0.99; p=0.035), female sex (OR 2.79, 95% CI: 1.29-6.10; p=0.01) and a sinotubular junction/aortic annulus mean diameter (STJ/AAØ) ratio <1.15 (OR 3.91, 95% CI: 1.55-9.88; $p<0.01$) were the only independent predictors of a high risk of coronary flow compromise following a high S3 implant **(Table 3)**; the latter variable being the strongest predictor.

The analysis to identify predictors of coronary inaccessibility (high risk) was, by definition, the same as reported in **Table 2** and **Table 3**. A separate analysis to identify variables associated with a high-intermediate risk (challenging access) of coronary inaccessibility resulted in similar findings and can be found in **Supplementary Table 1**.

Discussion

We used post-TAVI CT scans to determine the real-world feasibility of redo-TAVI for a degenerated ACn2 using an S3 valve at two different implant depths. The key conclusions are as follows: (1) redo-TAVI with an S3-in-ACn2 valve was potentially feasible for up to 92% of patients, (2) a low S3 implant position, in which the S3 outflow is aligned with the upper crown of the ACn2 valve, predicted a lower risk for coronary flow compromise and coronary inaccessibility, and (3) an STJ/AAØ ratio <1.15 was a strong independent predictor for high risk of coronary flow compromise in case of a high S3 implant position **(Central illustration)**.

OPTIMAL IMPLANT DEPTH OF S3

Implanting an S3 inside the supra-annular ACn2 valve pins back the leaflets of the index ACn2[11]. The outflow of the S3 determines the maximum height of the pinned back leaflets and is termed the NSP. One of the advantages of using a balloon-expandable TAV to revalve an ACn2 is that the operator can adjust the position of the S3, thereby impacting the NSP and subsequent risk for coronary issues[14]. However, the final position of a balloon-expandable TAV can be influenced by several procedural factors. In our study, 60% of patients were deemed high risk for coronary flow compromise or inaccessibility following a high implantation of the S3. In contrast, lowering the S3 implantation to match the S3 outflow at the level of the upper crown resulted in only 8% of patients having a high risk for coronary flow compromise or inaccessibility. The benefits of a low S3 implantation must be balanced against the potential impact of leaving residual leaflet tissue overhanging the S3. *In vitro* studies of S3-in-ACn2 demonstrated favourable haemodynamic outcomes associated with both tested S3 implant depths irrespective of the extent of leaflet overhang[11]. Still, it is not certain whether a low S3 position is sufficient to treat a degenerated ACn2 with stiff calcified leaflets, and the longer-term consequences remain unknown. As a result, we strongly advocate the study of real TAV-in-TAV cases and emphasise the need for future research to validate our findings and hypotheses.

Results from prior CT-based simulation studies evaluating S3 implantation in supra-annular TAVs are aligned with our findings. Analyses from pre- and post-TAVI CT scans from the Evolut Low Risk trial demonstrated that the risk of compromising coronary flow and access was lowest (20%) with the S3 implanted in the lower position (node 4). In case of a higher S3-in-Evolut (Medtronic) implant position (node 6), there was a high risk of coronary flow compromise reported in 75% of patients[9,16], which is a less favourable result as compared to the 60% of patients with a high risk of coronary flow compromise in case of a high S3-in-ACn2 implant. Taken together, these studies demonstrate that, although the absolute difference between a low and high S3 implant may only be 2-3 mm, the resulting consequences on coronary flow and access may be significant. This highlights the importance of adopting an individualised, systematic approach to preprocedural planning using cardiac CT to ensure optimal outcomes following redo-TAVI[13,15,17].

PREDICTING THE FEASIBILITY OF REDO-TAVI

Multiple anatomical and device-related factors can impact the feasibility of redo-TAVI[17,18]. In our study, following adjustment of clinical, CT-based and procedural variables, an STJ/AAØ ratio <1.15 proved to be the strongest independent predictor

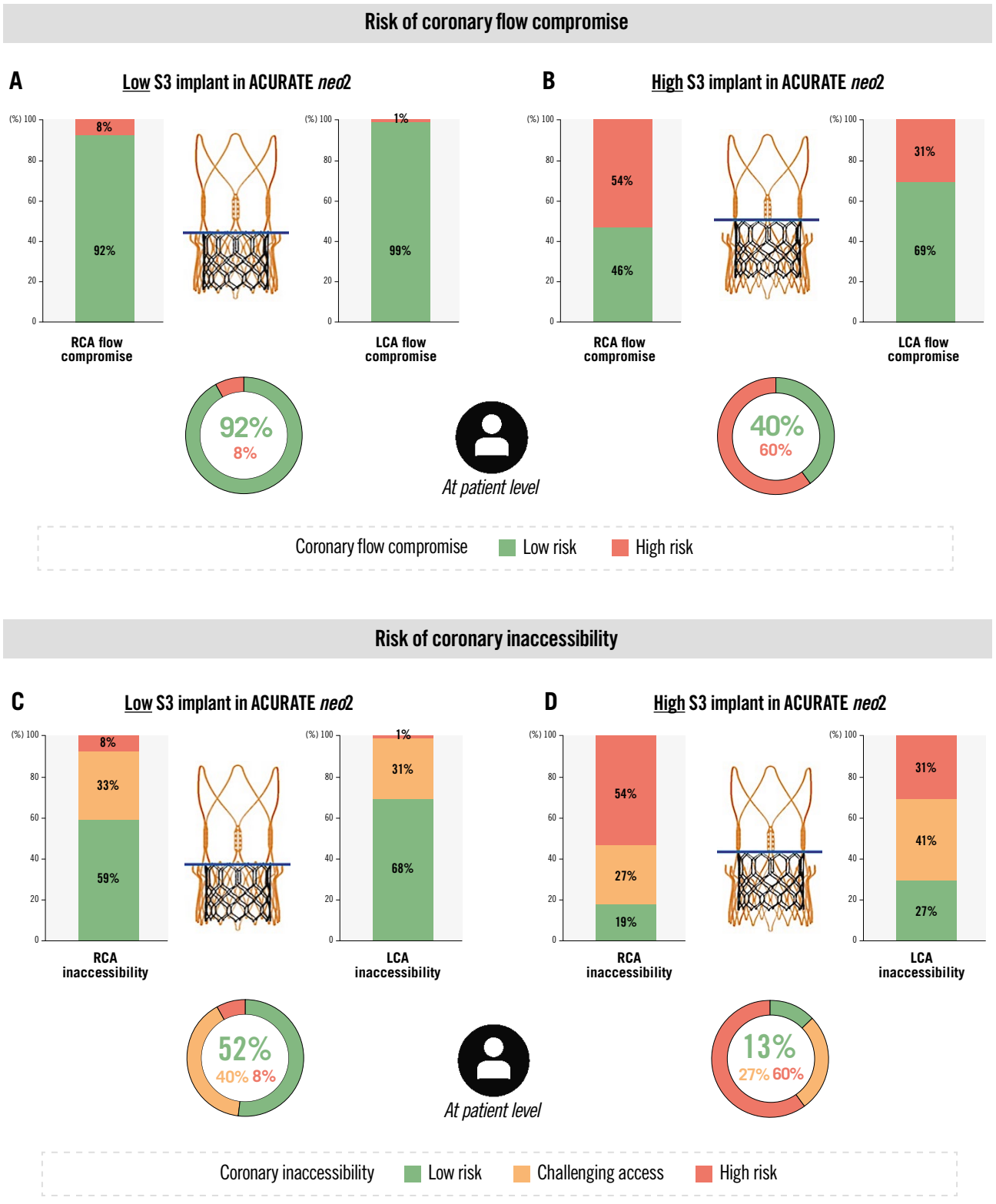


Figure 2. *CT-predicted risk of coronary flow compromise and coronary inaccessibility following redo-TAVI with S3-in-ACn2 TAV. A) The risk for coronary flow compromise was low (8%) with a low S3 implant position, aligning with the upper crown of the ACn2 and (B) relatively high (60%) with a high S3 implant position, aligning with the base of the ACn2 commissural posts. Similarly, the risk of a challenging coronary access or coronary inaccessibility was (C) low with a low S3 implant position and (D) higher with a high S3 position. ACn2: ACURATE neo2; CT: computed tomography; LCA: left coronary artery; RCA: right coronary artery; S3: SAPIEN 3; TAV: transcatheter aortic valve; TAVI: transcatheter aortic valve implantation*

Table 2. Characteristics and univariate analysis of a high risk of coronary flow compromise with a high S3 implant.

	Coronary flow compromise		Univariate model	
	High risk N=92	Low risk N=61	Odds ratio (95% CI)	*p*-value
Clinical variables				
Age, years	81 (77-84)	81 (78-86)	0.96 (0.91-1.02)	0.151
Female	68 (73.9)	26 (42.6)	3.81 (1.92-7.59)	<0.001*
Arterial hypertension	76 (82.6)	49 (80.3)	1.16 (0.51-2.67)	0.721
Diabetes mellitus	76 (82.6)	49 (80.3)	1.16 (0.51-2.67)	0.721
Coronary artery disease	39 (42.4)	36 (59.0)	0.51 (0.27-0.98)	0.045*
Prior PCI	29 (31.5)	24 (39.3)	0.71 (0.36-1.40)	0.320
Prior CABG	7 (7.6)	7 (11.5)	0.64 (0.21-1.91)	0.420
Atrial fibrillation	22 (23.9)	25 (41.0)	0.45 (0.23-0.91)	0.026*
Prior stroke	6 (6.5)	7 (11.5)	0.54 (0.17-1.69)	0.288
Peripheral arterial disease	8 (8.7)	8 (13.1)	0.63 (0.22-1.78)	0.385
CT variables				
Aortic annulus perimeter, mm	73.8 (70.4-77.0)	76.1 (72.1-79.4)	0.94 (0.88-1.00)	0.040*
Aortic annulus area, mm^2	417 (373-454)	445 (396-486)	0.99 (0.99-1.00)	0.041*
SoV-LCC, mm	30.3 (28.5-32.9)	33.4 (31.0-35.7)	0.75 (0.66-0.85)	<0.001*
SoV-RCC, mm	29.0 (27.3-31.0)	32.0 (30.3-33.9)	0.73 (0.65-0.83)	<0.001*
STJ mean diameter, mm	26.2 (24.6-27.8)	29.3 (27.7-31.3)	0.61 (0.51-0.73)	<0.001*
STJ/aortic annulus mean diameter ratio	1.12 (1.07-1.17)	1.22 (1.14-1.31)	0.39 (0.27-0.57)	<0.001*
STJ height, mm	24.0 (22.2-27.0)	26.8 (23.9-30.0)	0.89 (0.82-0.97)	0.005*
Left coronary ostium height, mm	13.0 (11.7-15.0)	14.0 (12.9-16.8)	0.84 (0.74-0.94)	0.003*
Right coronary ostium height, mm	16.0 (14.0-18.0)	17.5 (15.2-19.4)	0.83 (0.74-0.93)	0.002*
TAVI procedure				
ACURATE *neo2*				
Small, 23 mm	19 (20.7)	11 (18.0)	Reference	
Medium, 25 mm	38 (41.3)	19 (31.1)	1.16 (0.46-2.92)	0.756
Large, 27 mm	35 (38.0)	31 (50.8)	0.65 (0.27-1.59)	0.347
Predilatation	90 (97.8)	58 (95.1)	2.33 (0.38-14.6)	0.363
Post-dilatation	31 (33.7)	19 (31.1)	1.12 (0.56-2.25)	0.742
Commissural alignment	67 (72.8)	47 (77.0)	0.80 (0.38-1.70)	0.558

Data are given as median (IQR) or n (%). *P-value<0.10 for variable with the highest statistical power in case of multicollinearity. CABG: coronary artery bypass graft; CI: confidence interval; CT: computed tomography; IQR: interquartile range; LCC: left coronary cusp; PCI: percutaneous coronary intervention; RCC: right coronary cusp; S3: SAPIEN 3; SoV: sinus of Valsalva; STJ: sinotubular junction; TAVI: transcatheter aortic valve implantation

for a high risk of coronary flow compromise following a high S3 implant in an ACn2 index TAV.

Although aortic annulus and STJ dimensions are known to be positively correlated, variations in their relative dimensions can occur, with some individuals having a proportionally larger STJ relative to their aortic annulus dimensions, and vice versa[19,20]. The aortic annulus diameter dictates the size of the index ACn2 and the subsequent size of the implanted S3. The STJ/AAØ ratio encapsulates the geometric relationship between the S3-in-ACn2 redo-TAV complex with the surrounding aortic wall. Thus, for a given aortic annulus size, a proportionally smaller STJ may result in the redo-TAV complex being in closer proximity to the aortic wall, decreasing the VTA distances and increasing the risk of compromising coronary flow. A relatively high STJ above the aortic annulus plane may be beneficial and reduce the risk for coronary flow and/or access issues. Still, the STJ diameter will always dictate the overall VTA gap (VTSTJ and lower VTAoS) available for coronary flow or access after redo-TAVI, even when the STJ is above the projected functional neoskirt plane.

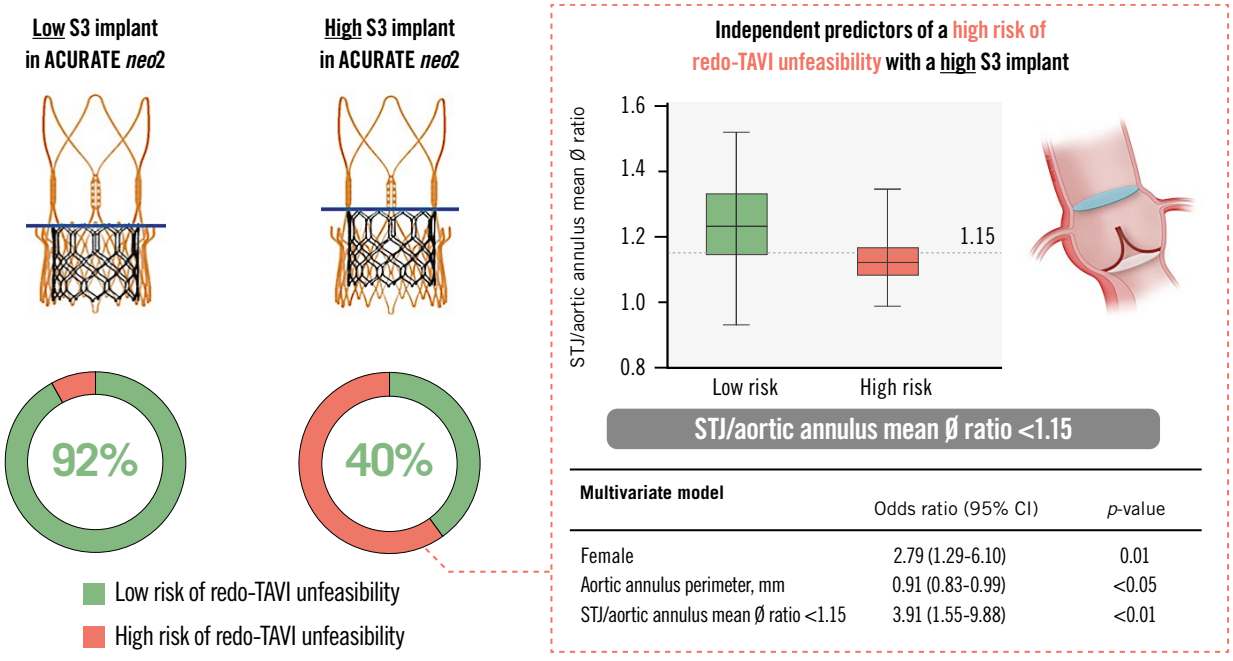
Table 3. Independent predictors of a high risk of coronary flow compromise for S3 implanted in a high position.

	Univariate model		Multivariate model	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Clinical variables				
Female	3.81 (1.92-7.59)	<0.001	2.79 (1.29-6.10)	0.010*
Coronary artery disease	0.51 (0.27-0.98)	0.045	0.62 (0.28-1.38)	0.242
Atrial fibrillation	0.45 (0.23-0.91)	0.026	0.51 (0.30-1.03)	0.114
CT variables				
Aortic annulus perimeter, mm	0.94 (0.88-1.00)	0.041	0.91 (0.83-0.99)	0.035*
SoV-LCC, mm	0.75 (0.66-0.85)	<0.001	0.99 (0.78-1.26)	0.959
SoV-RCC, mm	0.73 (0.65-0.83)	<0.001	0.85 (0.65-1.11)	0.220
STJ/aortic annulus mean diameter ratio <1.15	3.56 (2.05-6.20)	<0.001	3.91 (1.55-9.88)	0.004*
STJ height, mm	0.89 (0.82-0.97)	0.005	1.04 (0.93-1.16)	0.492
Left coronary ostium height, mm	0.84 (0.74-0.94)	0.003	0.95 (0.82-1.09)	0.439
Right coronary ostium height, mm	0.83 (0.74-0.93)	0.002	0.87 (0.74-1.02)	0.081

*P-value<0.05. CI: confidence interval; CT: computed tomography; LCC: left coronary cusp; OR: odds ratio; RCC: right coronary cusp; S3: SAPIEN 3; SoV: sinus of Valsalva; STJ: sinotubular junction

EuroIntervention — Central **Illustration**

Feasibility of redo-TAVI in ACURATE *neo2* valves: a CT analysis.



Multivariate model	Odds ratio (95% CI)	*p*-value
Female	2.79 (1.29-6.10)	0.01
Aortic annulus perimeter, mm	0.91 (0.83-0.99)	<0.05
STJ/aortic annulus mean Ø ratio <1.15	3.91 (1.55-9.88)	<0.01

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The risk of redo-TAVI unfeasibility is low (8%) in case of a low SAPIEN 3 (S3) implantation in an index ACURATE neo2; this risk increases to 60% in case of a high S3 implant. Independent predictors of a high risk of redo-TAVI unfeasibility in case of a high S3 implant are female sex, a small aortic annulus and an STJ/aortic annulus mean diameter ratio <1.15; the latter variable is the strongest predictor. CI: confidence interval; CT: computed tomography; STJ: sinotubular junction; TAVI: transcatheter aortic valve implantation

The STJ/AAØ ratio may have clinical utility when planning an index TAVI as well as a redo-TAVI procedure for S3-in-ACn2. If a ratio of <1.15 is noted, a lower S3 implant position could be pursued, if feasible, to reduce the risk of coronary flow compromise. Further clinical studies are required to validate the accuracy and reproducibility of this parameter as well as to determine its applicability to different combinations and configurations of redo-TAVI.

Finally, it is worth noting that in this study involving ACn2 valves, the risk of coronary flow compromise or inaccessibility following redo-TAVI was higher for the RCA than for the LCA, even though the RCA ostium is often a few millimetres higher than the LCA ostium. A clear explanation for this observation is lacking, although it can be hypothesised that the ACn2 implantation technique and final position – leaning more towards the outer aortic curvature – might be an explanation for this observation. Interestingly, this may indirectly also reduce the risk of coronary issues with the left main.

ADDITIONAL STRATEGIES TO IMPROVE REDO-TAVI FEASIBILITY

Despite a low S3 implantation, 8% of patients were still deemed to be at a high risk of coronary flow compromise and would not be suitable for redo-TAVI. For these patients, an alternative treatment strategy involving surgical explantation would carry a high risk of morbidity and mortality[5,6]. The potential benefit of adjunctive techniques such as leaflet modification merits evaluation. Techniques such as Bioprosthetic Aortic Scallop Intentional Laceration to prevent Iatrogenic Coronary Artery obstruction (BASILICA) may help to increase coronary flow by creating a splay in the pinned ACn2 leaflets[21,22]. Similarly, despite a low S3 implant, 40% of patients were still deemed to have a challenging coronary access. This highlights the importance of ensuring commissural alignment during index ACn2 implantation and the use of dedicated valve-specific cannulation techniques to facilitate coronary access[23-25], as well as not setting too high a threshold to consider leaflet modification in case of redo-TAVI.

Limitations

There are several limitations to note in this study. The patients did not undergo an actual redo-TAVI procedure; therefore the CT-based predictions may not fully reflect the physiological conditions in real-world practice. Our simulations may not fully capture the *in vivo* expansion of the ACn2 or S3 valves that may occur during redo-TAVI. Although we tried to account for the predicted S3 expansion, this was based on *in vitro* work using non-calcified, non-degenerated TAVs[11]. Previous studies did not consider this further expansion of the redo-TAV complex at all. Another limitation of this CT study is that it is impossible to predict what the impact will be of "overhanging" ACn2 leaflets in case of redo-TAVI with a low S3 implantation – both on coronary access and flow as well as on the haemodynamic valvular performance. Finally, a patient selection bias cannot be excluded, as only 153 of 1,024 patients treated with an ACURATE *neo*2 valve had a post-implant cardiac CT scan; these were most often performed in the context of studies investigating TAV leaflet thickening. Moreover, none of the patients in this study had a native bicuspid aortic valve anatomy – hence, extrapolation of the study results to this particular patient group should be avoided. Finally, the impact of leaflet modification on coronary flow and accessibility was not evaluated.

Conclusions

Post-TAVI CT analysis of the ACURATE *neo*2 valve confirmed that redo-TAVI using the short-frame balloon-expandable SAPIEN 3 valve is feasible. The lowest risk for coronary flow compromise and inaccessibility is observed when the S3 is implanted low. Clinical and anatomical factors may predict when a high S3 implant may be unfeasible to treat a degenerated ACURATE *neo*2, with an STJ-to-aortic annulus mean diameter ratio <1.15 being a strong predictor of redo-TAVI unfeasibility.

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Funding

An unrestricted grant was provided by Boston Scientific, USA.

Conflict of interest statement

G. Bieliauskas received institutional research grants and consulting fees from Boston Scientific. Y. Kobari has received financial support from the Japan Heart Foundation and Boston Scientific for his fellowship. A.A. Khokhar received speaker fees from Boston Scientific. M. Abdel-Wahab received consulting fees from Medtronic and Boston Scientific; and honoraria for lectures or advisory boards from Medtronic, Boston Scientific, and Edwards Lifesciences (paid to his institution). D. Dudek has received research funding from Boston Scientific. J. Cavalcante received consulting fees from 4C Medical, Abbott, Alleviant Medical, Anteris, Boston Scientific, Edwards Lifesciences, JenaValve, JC Medical, Medtronic, and Novo Nordisk; and has received research grant support from Abbott, Allina Health Foundation, JenaValve, and NIH/NHLBI. K. Hayashida is a clinical proctor for Edwards Lifesciences, Medtronic, and Abbott. G.H.L. Tang has received speaker honoraria and served as a physician proctor, consultant, advisory board member, TAVR publications committee member, APOLLO trial screening committee member and IMPACT MR steering committee member for Medtronic; has received speaker honoraria and served as a physician proctor, consultant, advisory board member and TRILUMINATE trial anatomic eligibility and publications committee member for Abbott; has served as an advisory board member for Boston Scientific and JenaValve;

a consultant and physician screening committee member for Shockwave Medical; a consultant for NeoChord, Peija Medical, and Shenqi Medical Technology; and has received speaker honoraria from Siemens Healthineers. D. Mylotte has been a consultant for Boston Scientific, Medtronic, and MicroPort. V.N. Bapat has received consulting fees from Abbott, Medtronic, Boston Scientific, and Edwards Lifesciences. O. De Backer received institutional research grants and consulting fees from Boston Scientific. The other authors have no conflicts of interest relevant to the contents of this paper to declare.

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Supplementary data

Supplementary Table 1. Characteristics and univariate analysis of a high-intermediate risk of coronary inaccessibility with a high S3 implant.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-24-00367

EuroIntervention
2024;20:1416-1418
DOI: 10.4244/EIJ-D-24-00702

Redo-TAVI feasibility and coronary accessibility following index TAVI with the Evolut valve in patients with bicuspid aortic valve stenosis

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With an increasing choice of transcatheter aortic valve implantation (TAVI) to treat younger aortic valve stenosis (AS) patients, it can be anticipated that (1) TAVI will be used more often to treat bicuspid AS, as the latter is more often encountered in young patients, and (2) there will be an increasing need for redo-TAVI in the future. In general, there is more limited evidence on the performance of TAVI in bicuspid AS, as this has been kept out of the large randomised trials. Still, there are relatively good registry data on the safety and efficacy of TAVI with the balloon-expandable SAPIEN (Edwards Lifesciences) and self-expanding Evolut (Medtronic) transcatheter aortic valves (TAVs) to treat severe bicuspid AS[1,2]. Unfortunately, there are no data available on redo-TAVI feasibility in patients with bicuspid AS. Redo-TAVI in the self-expanding Evolut can present challenges because of the supra-annular leaflet position, which may result in a higher functional neoskirt in case of redo-TAVI. This study aimed to assess redo-TAVI feasibility and coronary accessibility following index TAVI with an Evolut TAV in patients with bicuspid AS using post-TAVI computed tomography (CT) data.

In this retrospective analysis, we included 175 patients with native bicuspid AS who were treated with an Evolut TAV in 10 centres in Europe between March 2017 and February 2023; it was necessary for the patients to have a post-TAVI CT available in order to be eligible for this study. Of these patients, 105 were prospectively enrolled in the BIVOLUTX trial and the additional 70 patients were retrospectively added to this cohort. For the redo-TAVI simulations, virtual SAPIEN 3 (S3) TAVs were implanted at 3 different positions in the functional leaflet region of the Evolut, namely with the S3 outflow positioned at Evolut nodes 4, 5 and 6. The virtual implantation of the S3 within the Evolut used the expanded Evolut diameters published in a recent *in vitro* redo-TAVI study[3]. The risks of coronary flow compromise (low, high) and coronary inaccessibility (low, challenging, high) were assessed for each coronary artery, according to the previously published algorithm by Grubb et al[4]. The CT images were analysed with 3Mensio software (Pie Medical Imaging).

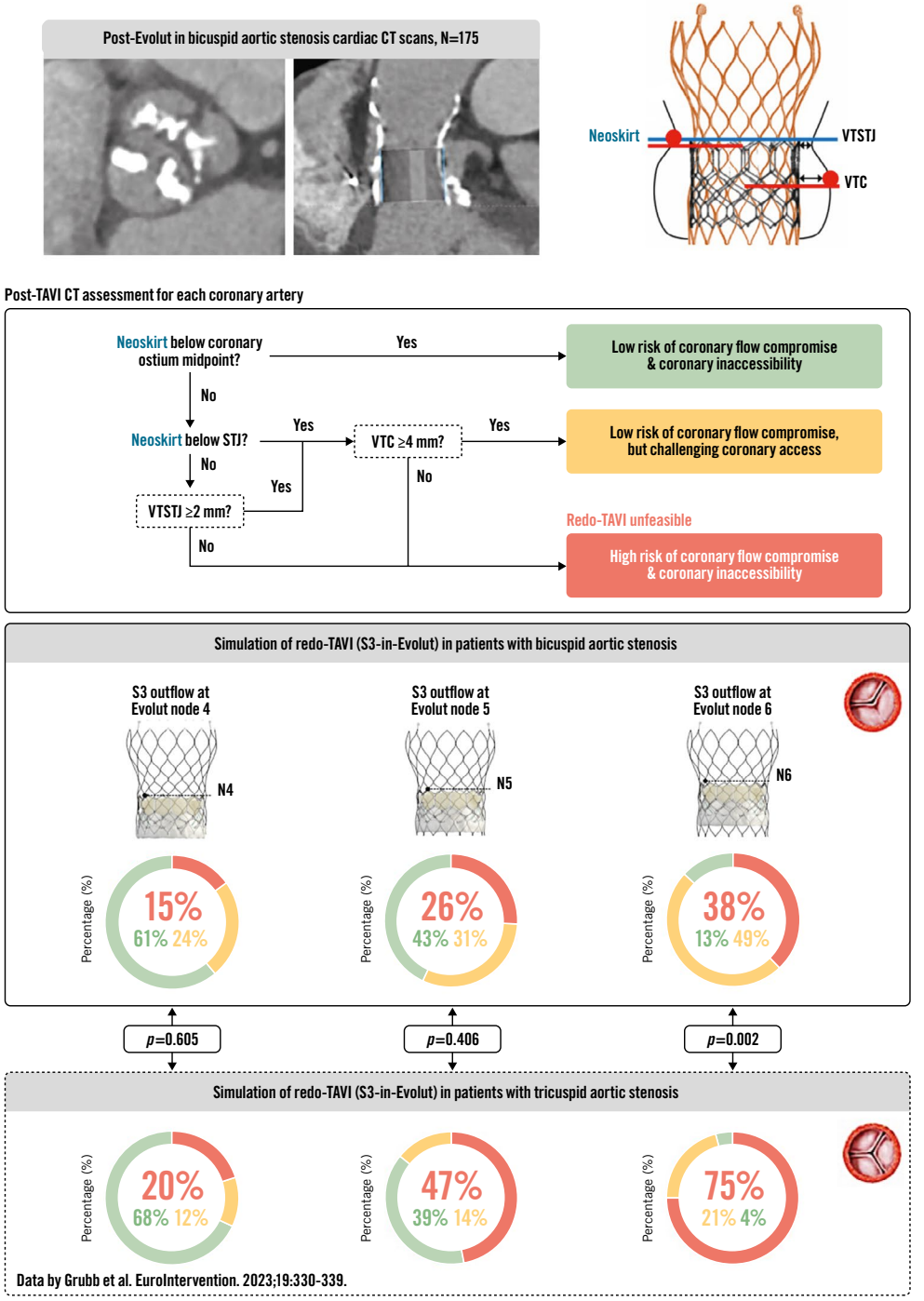
The study population mainly included type 1 bicuspid aortic valves (93%) with a mean aortic annulus diameter of 26.0±2.4 mm, a sinotubular junction (STJ) diameter of 32.2±3.9 mm and a left and right coronary artery height of 16.8±3.8 mm and 18.3±3.8 mm, respectively. The predicted risk of coronary flow compromise (high risk: red; low risk: green) and coronary inaccessibility (high risk: red; challenging access: yellow; low risk: green) are shown in the **Central illustration**. As expected, the simulations showed that an increasingly higher S3 implantation is associated with an increasing risk of coronary flow compromise and coronary inaccessibility. Based on our CT analysis and simulations, redo-TAVI would be unfeasible in 15%, 26% and 38% of all Evolut-in-bicuspid AS cases with an S3 outflow implantation at nodes 4, 5 and 6, respectively. In comparison, Grubb et al previously assessed redo-TAVI to be unfeasible in 20%, 47% and 75% of all Evolut-in-tricuspid AS cases with similar S3 outflow simulations at nodes 4, 5 and 6[4].

Clearly, multiple factors will determine these risks in case of redo-TAVI: (1) the underlying anatomy, (2) the choice of the first TAV type, size and implant depth, (3) the choice of

SUBMITTED ON 31/07/2024 - REVISION RECEIVED ON 1st 25/08/2024 / 2nd 16/09/2024 - ACCEPTED ON 20/09/2024

EuroIntervention — Central **Illustration**

Redo-TAVI feasibility and coronary accessibility following index TAVI with Evolut in bicuspid AS.



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For the redo-TAVI simulations, virtual SAPIEN 3 (S3) TAVs were implanted at 3 different positions in the index Evolut TAV, namely with the S3 outflow at Evolut nodes 4, 5 and 6. The risks of coronary flow compromise and inaccessibility following redo-TAVI in our 175 bicuspid AS patients were assessed and compared with the risks of redo-TAVI in tricuspid AS, as previously reported by Grubb et al[4]. Statistical comparisons for redo-TAVI unfeasibility (red) were performed for all three S3 positions using a chi-square test. AS: aortic stenosis; CT: computed tomography; N: node; TAV: transcatheter aortic valve; TAVI: transcatheter aortic valve implantation; VTC: valve-to-coronary distance; VTSTJ: valve-to-sinotubular junction distance

the second TAV type, size and implant depth, and (4) the possible use of leaflet modification techniques (although the latter would not be useful in case of severe commissural misalignment, i.e., 24.8% of cases in this cohort).

The explanation for the better redo-TAVI feasibility outcomes in this study as compared to Grubb et al[4] lies in the fact that native bicuspid AS is often associated with a larger aortic root and, consequently, larger valve-to-aorta distances (STJ/aortic annulus diameter ratio: 1.24 in this bicuspid study versus 1.14 in the tricuspid study by Grubb et al). In addition, a calcified raphe in type 1 bicuspid AS may act as a barrier and hold the TAV stent frame at a distance from the coronary ostium (average raphe length: 13.2 mm vs 11.4 mm for patients in the green/yellow versus red risk category, respectively). On the other hand, TAVI operators may aim for a slightly higher Evolut implant position in bicuspid AS (mean implant depth 3.8 mm in this cohort) and sometimes "downsize" the Evolut TAV in excessively calcified anatomies. All these aspects should be weighed against each other when planning (redo-) TAVI in a young patient with an anticipated long(er) life expectancy. As bicuspid AS is more prevalent in young patients, these study results are encouraging when considering TAVI expansion to these younger patients. More data on the durability of TAVs in bicuspid AS are still pending.

In conclusion, redo-TAVI feasibility and coronary accessibility following index TAVI with an Evolut valve are more favourable in patients with bicuspid AS compared to tricuspid AS. The most favourable outcome regarding redo-TAVI feasibility was obtained with a low(er) S3 implantation.

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Conflict of interest statement

K. Arslani has received a research grant from the Swiss Academy of Medical Sciences, the Gottfried and Julia Bangerter-Rhyner Foundation and the Swiss National Science Foundation (P500PM_202963), Switzerland, outside of the submitted work. O. De Backer received institutional research grants and consulting fees from Abbott, Boston Scientific, and Medtronic. G.H.L. Tang has received speaker honoraria and served as a physician proctor, consultant, advisory board member, TAVR publications committee member, RESTORE study steering committee member, APOLLO trial screening committee member and IMPACT MR steering committee member for Medtronic; has received speaker honoraria and served as a physician proctor, consultant, advisory board member and TRILUMINATE trial anatomic eligibility and publications committee member for Abbott; has served as an advisory board member for Boston Scientific and JenaValve; a consultant and physician screening committee member for Shockwave Medical; a consultant for NeoChord, Peija Medical, and Shenqi Medical Technology; and has received speaker honoraria from Siemens Healthineers. K.J Grubb is a consultant for or has received an honorarium from Medtronic, Abbott, Boston Scientific, Ancora, 4C Medical, and OpSens. N.M. Van Mieghem has received research grant support from Abbott, Boston Scientific, Medtronic, Edwards Lifesciences, Teleflex, and PulseCath BV; also advisory fees from Antares, JenaValve, Polares Medical, Siemens, Abbott, Boston Scientific, Medtronic, Teleflex, and PulseCath BV. D. Mylotte is a consultant for Medtronic, Boston Scientific, and MicroPort; and received institutional research grants from Boston Scientific. D. Tchétché is a consultant for Abbott Vascular, Edwards Lifesciences, Medtronic, Boston Scientific, T-Heart, and Caranx Medical. V.N. Bapat is a consultant for Abbott Structural, Medtronic, Boston Scientific, and Edwards Lifesciences. L. Leroux is a proctor for Medtronic. G. Tirado-Conte has no conflicts of interest to declare.

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EuroIntervention
2024;20:1419-1429
DOI: 10.4244/EIJ-D-24-00490

ORIGINAL RESEARCH

Prevention of left ventricular outflow tract obstruction in transapical mitral valve replacement: the MitraCut procedure

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This paper also includes supplementary data published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-24-00490

ABSTRACT

BACKGROUND: The MitraCut procedure employs beating heart transapical (TA) cannulation and endoscopic scissors for dividing the anterior mitral leaflet (AML) to prevent left ventricular outflow tract (LVOT) obstruction in transapical transcatheter mitral valve replacement (TA-TMVR).

AIMS: We present the first multicentre experience of the MitraCut procedure prior to TA-TMVR to prevent LVOT obstruction.

METHODS: In 6 European centres, the clinical outcomes of all 13 high-risk patients who had undergone the MitraCut procedure during TA-TMVR procedures were retrospectively reviewed regarding technical success, procedural details and outcome.

RESULTS: The MitraCut procedure was successfully completed in 11 patients with 1 cutting attempt, while 2 patients had 2 cutting attempts, with an average procedure duration of 9.0±5.4 min. No patient demonstrated postoperative LVOT obstruction, and all mitral valve (MV) prostheses were competent throughout the follow-up period. However, 1 patient developed a MitraCut-related paravalvular leak (PVL; technical success rate: 12/13). The mean LVOT gradient was 3.9±4.4 mmHg directly after valve expansion and 3.6±3.1 mmHg at follow-up. In-hospital and 30-day mortality were 0%. One patient experiencing MitraCut-related PVL was successfully treated by interventional PVL closure (reintervention rate: n=1). One patient died at 47 days due to cardiac arrhythmia, unrelated to the AML-directed procedure. The mean follow-up at the time of data analysis was 52±34 days.

CONCLUSIONS: The MitraCut procedure was effective and reproducible for preventing potential LVOT obstruction in TA-TMVR patients during its initial exploration in 6 European hospitals. Considerations regarding the scissors' characteristics, their handling and cut length are mandatory for safe performance of the procedure.

KEYWORDS: interventional mitral valve replacement; left ventricular outflow tract obstruction; mitral valve disease; transcatheter mitral valve replacement

SUBMITTED ON 27/05/2024 - REVISION RECEIVED ON 1st 03/07/2024 / 2nd 12/07/2024 / 3rd 22/07/2024 - ACCEPTED ON 25/07/2024

Severe mitral valve (MV) disease is associated with high mortality rates when untreated[1]. In patients presenting as frail or with multiple comorbidities preventing conventional MV surgery, several transcatheter interventional approaches have emerged as potentially valuable therapeutic options[2]. The decision by the Heart Team between interventional MV repair or replacement (TMVR) remains challenging. Many of the evaluated patients do not meet the inclusion criteria of market-release TMVR studies[3-6]. While interventional repair techniques continue to expand to patients with complex MV pathologies[4], various anatomical predictors indicate unfavourable outcomes of transcatheter edge-to-edge repair; such poor prognostic indicators include mitral annular calcification (MAC)[7], restricted leaflet motion of the posterior MV leaflet[8], a small MV opening area[9], and a high baseline MV mean pressure gradient (MPG)[7].

Because of expected unsatisfactory outcomes and/or contraindications for interventional repair (e.g., stenotic MV disease), there is a trend towards liberal screening for TMVR[6]. Though TMVR has been shown to be highly effective in reducing mitral regurgitation (MR)[1,6,10], up to 69% of the screened patients are considered anatomically ineligible for TMVR, mainly due to unsuitable annular dimensions and unacceptably high risk for left ventricular outflow tract (LVOT) obstruction[1]. Despite specific screening processes, including assessment of the neo-LVOT by cardiac multislice detector computed tomography (MDCT), LVOT obstruction may occur in >10% of patients[11]. Further, (dynamic) LVOT obstruction has been reported with the Tendyne (Abbott) valve system even in presence of an acceptable neo-LVOT[6,12] above 250 mm^2.

While transseptal electrosurgical techniques for splitting the anterior mitral leaflet (AML), including laceration of the anterior mitral leaflet to prevent outflow tract obstruction (LAMPOON), have been shown to be effective for avoiding systolic anterior movement of the AML and obstruction of the LVOT by the subvalvular portion of the prosthesis stent frame, such techniques can be difficult to perform[13-15]. The MitraCut procedure in TA-TMVR opens new paths to address the AML, as this leaflet can be easily reached by endoscopic scissors without requiring an additional access site or expensive equipment. Based on the success of previous published case reports of the novel MitraCut procedure from different centres[16-19], this retrospective study describes the relative safety and efficacy of the MitraCut procedure prior to TMVR across a larger study population within this first European, multicentre experience.

Impact on daily practice

The MitraCut procedure may improve results after transapical transcatheter mitral valve replacement (TA-TMVR) and increase the rate of patients successfully screened for TA-TVMR by reducing the risk of left ventricular outflow tract obstruction.

Methods

This is a retrospective report of a European, multicentre evaluation regarding the early surgical results of the beating heart MitraCut procedure incorporating a transapical large-bore sheath to enable scissor-mediated AML division. To our best knowledge, all European centres applying this technique prior to TA-TMVR in the initial period (11/2022-05/2023) were invited to participate. Finally, patients from 6 heart centres in Austria, Germany, Italy, and Spain were included. Each centre followed the standards of the local ethical boards. Data collection was performed according to Mitral Valve Academic Research Consortium (MVARC) criteria.

MITRACUT PROCEDURE

The Heart Team elected to perform the MitraCut procedure in patients with a small predicted LVOT (but above the cutoff for Tendyne implantation), in patients with a long anterior mitral valve leaflet or if a potential risk for fixed or dynamic LVOT obstruction based on preoperative or intraoperative imaging was perceived **(Supplementary Table 1)**. The MitraCut procedure was performed using endoscopic shafted scissors and a manually shortened large-bore sheath **(Moving image 1)**. The diameter and the length of the sheath were chosen based on the size and length of the endoscopic scissors' shaft; the sheath was typically shortened to a length of between 10 and 15 cm. After carefully flushing the shortened sheath, the endoscopic scissors were introduced inside the sheath to check the length **(Figure 1A)**.

After performing a standard apical access, heparinisation, and "flossing" manoeuvre to exclude any entanglement of the guidewire in the subvalvular apparatus[20], the modified sheath and its indwelling dilator were passed through the apical myocardium into the left ventricle while maintaining the guidewire tip's position in the pulmonary vein. This dilator was later replaced by the scissors through the sheath. The sheath was advanced into the left atrium to approximately 2 cm above the MV plane **(Figure 1B)**. The tip of the scissors was pushed out of the sheath and opened to demonstrate appropriate alignment under three-dimensional

Abbreviations

AML	anterior mitral leaflet	**MDCT**	multislice detector computed tomography	**TA**	transapical
ASA	alcohol septal ablation	**MPG**	mean pressure gradient	**TA-TMVR**	transapical transcatheter mitral valve replacement
LAMPOON	laceration of the anterior mitral leaflet to prevent outflow tract obstruction	**MR**	mitral regurgitation	**TMVR**	transcatheter mitral valve replacement
		MV	mitral valve		
LVOT	left ventricular outflow tract	**NYHA**	New York Heart Association	**TOE**	transoesophageal echocardiography
MAC	mitral annular calcification	**PVL**	paravalvular leakage		

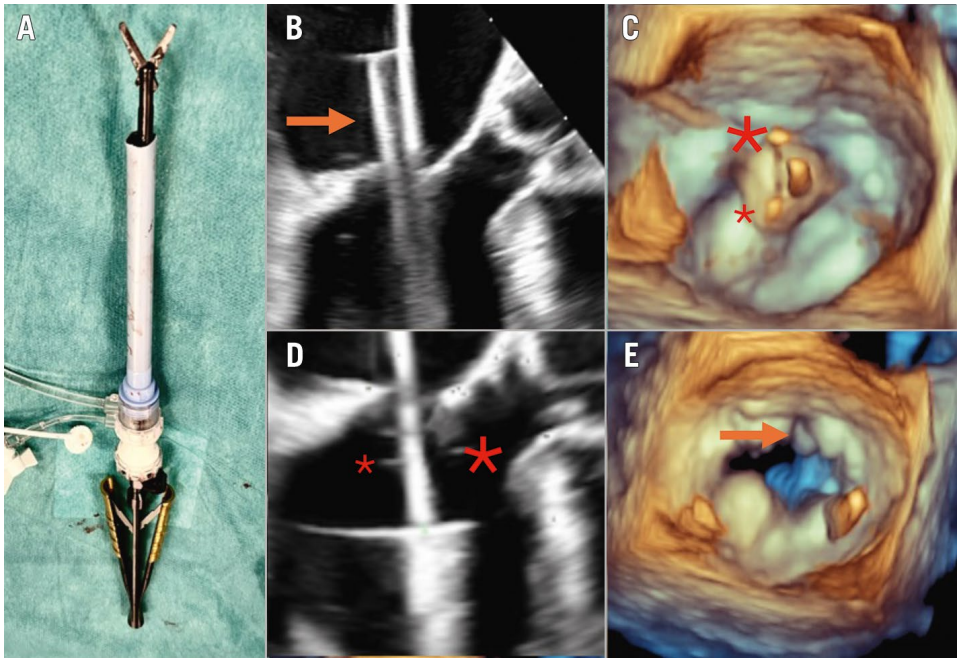


Figure 1. *The MitraCut procedure. Illustration of the off-table preparation after manual shortening of the large-bore sheath and insertion of the endoscopic scissors (A). The sheath and the covered scissors (orange arrow) are inserted up to approximately 2 cm above the MV plane (B), followed by alignment of the scissors (C; big asterisk above the AML, small asterisk above the posterior leaflet). The scissors together with the sheath are carefully retracted into the left ventricle, enabling the grasping of the AML (D). The post-MitraCut three-dimensional en-face view demonstrates successful AML division (E). Adapted and changed from Andreas et al*[16]*. AML: anterior mitral leaflet; MV: mitral valve*

(3D) echocardiography **(Figure 1C)**. Once correct alignment in the centre of the MV was achieved, the open scissors and the sheath were simultaneously retracted into the left ventricle. Guided by an X-plane view of the left ventricle (intercommissural view, LVOT view), the AML was trapped between the scissor blades and sharply transected in the A2 segment **(Central illustration, Figure 1D)**. The effectiveness of the transection was assessed based on a 3D en-face view of the MV **(Figure 1E)**. After the cuts were complete, the scissors were retracted into the sheath, facilitating their removal without risk of tissue damage. The MitraCut procedure was followed by TMVR with the Tendyne valve system, as previously described in detail[5,20].

ECHOCARDIOGRAPHIC ASSESSMENT

The LVOT gradients were measured directly after complete valve expansion in the operating room by transoesophageal echocardiography (TOE) and at follow-up by transthoracic echocardiography. Prosthetic mitral valve function (MV MPG and paravalvular leakage [PVL]) was assessed according to the recommendations of the American Society of Echocardiography[21,22].

MDCT CALCULATIONS

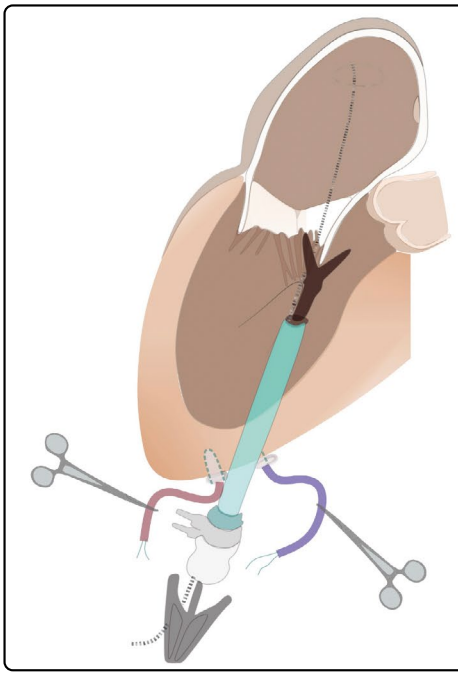
The calculations from the screening MDCT scan were conducted using the commercially available MV workflow of 3mensio, version 10.3 (Pie Medical Imaging). The standard triangle language file of the respective Tendyne valve was snapped to the mitral annulus to achieve a coaxial alignment. The narrowest part between the simulated valve and the LVOT was traced (neo-LVOT) in end-systole and end-diastole **(Figure 2A, Figure 2B)**. Additionally, the distance between the stent frame and the LVOT/interventricular septum (AML clearance in end-systole and end-diastole) **(Figure 2C, Figure 2D)** as well as the length of the AML were measured in an LVOT view **(Figure 2E)**. MAC was graded according to Guerrero et al **(Figure 2F)**[23].

ENDPOINTS

The primary endpoint was the technical success of the MitraCut procedure, which was defined as successful insertion and removal of the sheath and scissors, an echocardiographically confirmed division of the AML, successful valve implantation without LVOT obstruction, freedom from clinically significant PVL related to the AML cutting and embolic events, freedom from apical access and bleeding complications with a need for reintervention and/or haemodynamic instability, as well as periprocedural death. The number of AML cutting attempts, the time from skin incision to closure (procedural time), insertion and removal of the sheath for the MitraCut and the time from AML division to complete valve expansion were recorded. Secondary endpoints within the index hospitalisation and the last available follow-up were reported according to the criteria defined by the MVARC[24].

Numerical and categorical data were reported as mean±standard deviation and number (%), respectively. Descriptive statistics were applied using SPSS Statistics, version 29.0 (IBM) and Excel for Mac (Microsoft).

Multicentre experience with a novel surgical technique to prevent LVOT obstruction in TMVR: the MitraCut procedure.



13 patients at assumed risk for LVOT obstruction following TA Tendyne TMVR	
Endpoints	
Technical success	12/13
MitraCut time, min	9.0±5.4
LVOT obstruction	0/13
LVOT MPG, mmHg - Operating room - Last follow-up (50±38 days)	 3.9±4.4 3.6±3.1
Reintervention rate	1/13
In-hospital/30-day mortality	0/13

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LVOT: left ventricular outflow tract; MPG: mean pressure gradient; TA: transapical; TMVR: transcatheter mitral valve replacement

Results

Thirteen patients who underwent the MitraCut procedure prior to TA-TMVR to prevent LVOT obstruction were included in this analysis. The Heart Team decision against conventional surgery was determined based on age, frailty or cardiac cachexia (n=6), immobility (n=1), severely reduced left ventricular systolic function (n=1), prior cardiac surgery (n=4), and previous thoracic endovascular aortic repair hindering aortic clamping (n=1) **(Supplementary Table 1)**. Two patients were enrolled for valve-in-ring TMVR due to recurrent MR after surgical annuloplasty. The reasons for rejecting transcatheter MV repair are depicted in **Figure 3**.

BASELINE DATA

The multiple comorbidities of this patient cohort are reflected within the demographic data **(Table 1)**. All patients were symptomatic and had been previously hospitalised due to heart failure prior to TMVR (mean count of heart failure hospitalisations: 1.4±0.9). Nine patients were treated for primary MV disease. In 12 patients, MR was the leading pathology, while 1 patient underwent TMVR due to severe calcific mitral stenosis (MPG 12 mmHg). The left ventricular ejection fraction ranged from 30% to 70%. Septal hypertrophy (>11 mm) was evident in 8 of 13 patients. Four patients had concomitant severe tricuspid regurgitation. The advanced heart failure status was reflected by the elevated mean systolic pulmonary artery pressure (59±18 mmHg).

Moderate or severe MAC was evident in 5 patients **(Table 2)**. The median neo-LVOT were 358±77 mm^2 and 405±156 mm^2 in end-systole and end-diastole, respectively, and decreased in 12/13 patients during systole. The AML length ranged from 20 mm to 29 mm. The end-systolic distance from the sealing-body of the prosthesis to the interventricular septum was <6 mm in 2/13 patients, <8 mm in 5/13 patients, <10 mm in 8/13 patients and ≥10 mm in 5/13 patients. The surgeon's reasons for the AML-directed procedure are given for each patient in **Supplementary Table 1**.

The median procedure time was 111±44 min, of which 9.0±5.4 min were attributed to the MitraCut procedure. The labelled diameter of the manually shortened, transapically inserted sheaths were 20 Fr (n=1), 24 Fr (n=3), and 26 Fr (n=9). The size of the sheath was based on the size of the endoscopic scissors used at each centre (Ceramo HCR, MRT-2 [Fehling Surgical Instruments]; CLICKLINE no 33151 [KARL STORZ]; ValveGate PRO [Geister]; ValveGate classic line 15° with 25 cm working length [Geister]; AdTec mini [Aesculap/B. Braun]). The AML division was achieved after 1 (n=11) or 2 cutting attempts (n=2) in the 13 treated patients. The technical success rate of the MitraCut procedure was 92%. One patient experienced significant

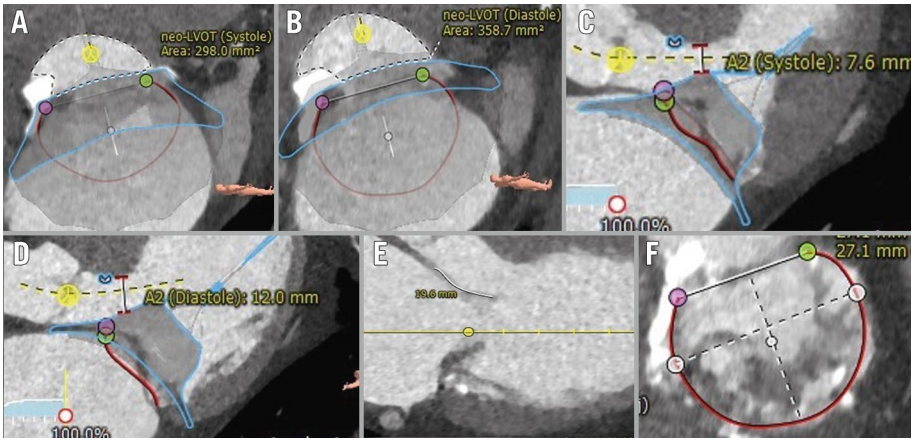

Figure 2. *MDCT-derived assessment. Calculation of the neo-LVOT and the distance between the stent frame and the interventricular septum (A2 clearance) in end-systole (A,C), and end-diastole (B,D), respectively. Further, the anterior length on an LVOT view (E), as well as the degree of mitral annular calcification on an en-face view (F), were determined. Adapted and changed from Andreas et al[16]. LVOT: left ventricular outflow tract; MDCT: multislice detector computed tomography*

PVL in the anterior portion of the AML, most likely related to a MitraCut extending into the aortomitral continuity due to excessive scissor blade length or too high pressure during the AML cut. The increase in MR after cutting the AML prior to prosthetic placement was well tolerated by all patients, with no haemodynamical instability nor need for circulatory support. Sheath removal, insertion of the Tendyne valve system, and complete valve expansion took a total of 7.0±7.4 min. There was no evidence of LVOT obstruction, as demonstrated by the patients' LVOT MPG of 3.9±4.4 mmHg directly after complete valve expansion.

All patients were free from procedural and in-hospital mortality. One patient had a prolonged in-hospital stay (43 days; 20 days in the intensive care unit), which might have been related to the high surgical risk (European System for Cardiac Operative Risk Evaluation [EuroSCORE] II 15.8%) and postprocedural acute kidney injury. The prosthesis showed mild PVL, unrelated to the AML cut, and an MPG of 7 mmHg. One bleeding complication, not related to the MitraCut procedure, without indication for intervention/surgery, was recorded. Further endpoints during the index hospitalisation are summarised in **Table 3**. The mean clinical

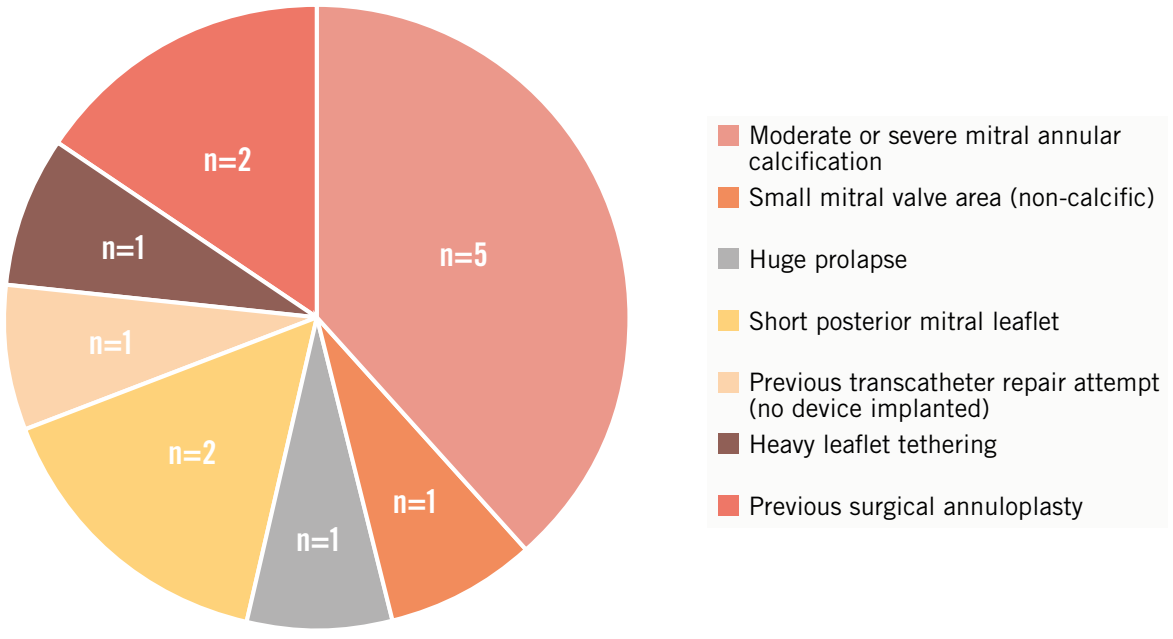

Figure 3. *Reasons against transseptal transcatheter mitral valve repair. Seven patients were anatomically ineligible for repair. One patient had a previous repair attempt with an unsatisfactory interventional result and abandonment of the procedure. In 5 patients, an inadequate repair result was expected because of moderate or severe mitral annular calcification.*

Table 1. Baseline subject characteristics.

	Study population (n=13)
Age, years	77.1±11.4
Female	6 (46)
Body mass index, kg/m^2	25.6±5.5
EuroSCORE II, %	6.1±4.7
STS-PROM score, %	5.1±2.7
NYHA Class ≥III	13 (100)
Previous HFH	13 (100)
NT-proBNP, ng/dL	4,230±5,295
Atrial fibrillation or flutter	8 (62)
Glomerular filtration rate, ml/min/1.73 m^2	62.4±20.8
COPD	2 (15)
Stroke	2 (15)
Coronary artery disease	7 (54)
Previous myocardial infarction	4 (31)
Previous PCI	2 (15)
Previous CABG	1 (8)
Previous TAVI	1 (8)
Previous SAVR	1 (8)
Previous MV intervention	1 (8)
Previous MV surgery	2 (15)
Valve-in-ring TMVR	2 (15)
Valve-in-MAC TMVR*	5 (39)
Pacemaker	1 (8)
Heart failure medication	
ACE inhibitor/ARB	9 (69)
Beta blocker	10 (77)
SGLT2 inhibitor	3 (23)
Diuretics	12 (92)
CRT	0 (0)
Echocardiographic characteristics	
Mitral valve disease aetiology	
Primary	9 (69)
Secondary	4 (31)
Mitral regurgitation ≥3+	12 (92)
Stenotic mitral valve disease	4 (31)
Mitral valve mean pressure gradient, mmHg	4.2±3.1
LVEF, %	56.0±10.3
LVEDD, mm	51.5±6.4
Interventricular septum, mm	11.5±2.7
TAPSE, mm	17.8±5.9
Tricuspid regurgitation ≥3	4 (31)
sPAP, mmHg	58.7±17.8

Numerical data are given as n (%), and metric variables are given as mean±standard deviation. *MAC ≥moderate according to Guerrero et al[23]. ACE: angiotensin-converting enzyme; ARB: angiotensin II receptor blocker; CABG: coronary artery bypass grafting; COPD: chronic obstructive pulmonary disease; CRT: cardiac resynchronisation therapy; EuroSCORE: European System for Cardiac Operative Risk Evaluation; HFH: heart failure hospitalisation; LVEDD: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; MAC: mitral annular calcification; MV: mitral valve; NT-proBNP: N-terminal pro-brain natriuretic peptide; NYHA: New York Heart Association; PCI: percutaneous coronary intervention; SAVR: surgical aortic valve replacement; SGLT: sodium-glucose linked transporter; sPAP: systolic pulmonary artery pressure; STS-PROM: Society of Thoracic Surgeons Predicted Risk of Mortality; TAPSE: tricuspid annular plane systolic excursion; TAVI: transcatheter aortic valve implantation; TMVR: transcatheter mitral valve replacement

Table 2. Computed tomography-derived measurements.

	Study population (n=13)
End-systolic neo-LVOT, mm^2	358±77
End-diastolic neo-LVOT, mm^2	405±156
AML length, mm	23.6±2.4
End-systolic AML clearance, mm	9.2±3.0
End-diastolic AML clearance, mm	11.8±2.3
Mitral annular calcification	
None	7 (54)
Mild	1 (8)
Moderate	4 (31)
Severe	1 (8)
AML calcification	1 (8)

Numerical data are given as n (%), and metric variables are given as mean±standard deviation. AML: anterior mitral leaflet; LVOT: left ventricular outflow tract

and echocardiographic follow-up periods were 52±34 days and 50±38 days, respectively. The patient who experienced the prolonged and complicated postoperative course died 47 days after the procedure due to cardiac arrhythmia, without evidence of LVOT obstruction. All other patients were free from mortality during the follow-up period.

The patient with the MitraCut-related PVL (n=1), which was graded as mild immediately after TMVR, required hospitalisation because of heart failure within the 30-day follow-up period. Subsequent imaging and clinical assessment detected an increase of the PVL to severe with significant haemolysis. This patient's PVL was successfully addressed by 3 interventional PVL closure devices, reducing the PVL to mild 28 days after the index procedure. Accordingly, this study cohort had a reintervention rate of 8% within the follow-up period. All patients were otherwise free from residual MR ≥1+ and improved by at least 1 New York Heart Association (NYHA) Class at the last clinical follow-up compared to baseline **(Table 4)**.

While the average gradient in the LVOT remained low (MPG: 3.6±3.1 mmHg, peak pressure gradient: 5.9±5.8 mmHg), 4 patients had an MV MPG ≥5 mmHg (MV MPG 5-7 mmHg), which appears attributable to the use of low-profile valves (prosthesis area 2.2 cm^2).

Discussion

This report describes the first successful multicentre experience of the MitraCut procedure for surgical division of the AML to prevent LVOT obstruction in patients undergoing TA-TMVR. Our initial clinical MitraCut experience can be summarised as effective, with no consecutive LVOT obstruction after TMVR, a fast procedure time, and a low complication rate based on this early clinical experience.

The MitraCut procedure does not require any specialised technology. It can be conducted using standard shafted endoscopic scissors inserted through a large-bore sheath. Though we are currently exploring more optimised options, each surgeon in this early experience manually shortened the sheaths to accommodate the endoscopic scissors.

Table 3. Procedural and in-hospital outcomes.

	Study population (n=13)
Procedural time, min	111.4±44.4
Total MitraCut time, min	9.0±5.4
AML division attempts	
n=1	11 (85)
n=2	2 (15)
Technical success of MitraCut	12 (92)
Time from MitraCut to valve expansion, min	7.0±7.4
Technical success according to MVARC criteria	12 (92)
Use of neuroprotection device*	2 (15)
Low-profile valve	13 (100)
LVOT obstruction	0 (0)
LVOT gradient directly after valve expansion, mmHg	3.9±4.4
Postprocedural PVL	2 (15)
Postprocedural MitraCut-related PVL†	1 (8)
Valve retrieval	0 (0)
Major cardiac structural complication at the apex	0 (0)
Conversion to full sternotomy	0 (0)
Heart-lung machine/ECMO	0 (0)
Intraprocedural death	0 (0)
In-hospital adverse events	
In-hospital death	0 (0)
Reintervention related to access	0 (0)
Bleeding complication	1 (8)
BARC 3a	1 (8)
Transfusion of packed red blood cells, units	1.0±1.2
Myocardial infarction	0 (0)
Stroke	0 (0)
Acute kidney injury	1 (8)
Dialysis	0 (0)
Sepsis	0 (0)
In-hospital stay, days	12.2±9.7
Time in intensive care unit, days	2.8±5.4
Discharge location	
Home	11 (85)
Other hospital	1 (8)
Rehabilitation centre	1 (8)

Numerical data are given as n (%), and metric variables are given as mean±standard deviation. *Neuroprotection also covering the left vertebral artery was used in both patients. †MitraCut-related PVL was graded mild immediately after TMVR in the operating room but increased to severe with an indication for interventional PVL closure within 30 days after the procedure. AML: anterior mitral leaflet; BARC: Bleeding Academic Research Consortium; ECMO: extracorporeal membrane oxygenation; LVOT: left ventricular outflow tract; MVARC: Mitral Valve Academic Research Consortium; PVL: paravalvular leakage; TMVR: transcatheter mitral valve replacement

The modification of this equipment required special considerations (further discussed in **Moving image 1**). The necessary sheath length is determined by the distance from the left ventricular apex access to approximately 2 cm above the MV; this distance will vary between patients and can be accurately assessed by segmentation of the screening MDCT scan **(Figure 4)**. It is important to note that the sheaths used clinically so far include a spiral wire along their length. When cutting the sheath for the MitraCut procedure, the surgeon must ensure that the sharp wire is not protruding from the cut sheath tip. This consideration is one reason why we are evaluating alternative options **(Supplementary Figure 1)**.

The endoscopic scissors used for the MitraCut procedure must have a working length greater than the length of the sheath to enable the division of the AML **(Figure 1D)**. While inserting the endoscopic scissors through the apex, left ventricle, and MV, the scissors remain securely retracted within the sheath to avoid injury to delicate tissue structures. Most important for safe performance of the MitraCut is adequate TOE imaging quality, because the grasping of the AML and estimation of the cut length is performed under precise X-plane LVOT view guidance. Care must be taken to avoid folding of the AML between the scissor blades, which is an indicator of too much push with the scissors towards the aortomitral continuity, and to account for the guidewire to prevent guidewire transection by the scissors. For safe performance of the procedure, especially for scissor positioning, specific training and proctoring is advised. In the reported MitraCut-related PVL, too much push on the scissors and/or use of scissors with scissor blades that were too long relative to the AML was suggested. Subsequently, we inferred empirically a maximal cut length of one-half of the TOE-derived leaflet length, controllable by the choice of the scissors and push during the cut towards the AML hinge point. This threshold should be sufficient to prevent LVOT obstruction, as part of the anterior leaflet is covered by the Tendyne outer stent graft anyway. Further simulations may investigate if there is a cut length-dependent effect of the MitraCut. Independent of the length of the AML cut, the anaesthesiologist should be prepared for an acute increase in MR following division of the AML, and therefore, close communication between the surgeon and the anaesthesiology staff must be maintained.

In our first experience, a single cut was sufficient in 11/13 patients. Even though no thromboembolic event was recorded in our first multicentre experience, multiple cuts may theoretically increase the thromboembolic risk due to potential cutting of free parts of the leaflets or chords. A relatively high portion of patients (5/13) were treated for calcific (≥moderate MAC) MV disease. Neuroprotection devices also covering the left vertebral artery were used in the only patient with AML calcification and in one patient with severe MAC. Complete neuroprotection is strongly recommended particularly in the presence of AML calcification and should be considered in patients with extensive MAC.

Time is a valuable resource in hybrid operating rooms, and it has been reported that shorter anaesthesia times for comorbid patients may confer additional benefits[25]. Even in this first multicentre experience report, the time required for the MitraCut procedure and the time from dividing the AML to complete valve expansion were remarkably low: 9.0±5.4 min and 7.0±7.4 min, respectively. The LAMPOON technique is primarily utilised in transseptal TMVR[13,14,26], but the technique has also been employed prior to TA-TMVR[27]. In TA-TMVR, the MitraCut procedure

Table 4. Short-term follow-up.

	Study population (n=13)
Follow-up (follow-up time: 52±34 days)	
30-day mortality	0 (0)
Overall mortality	1 (8)
Heart failure hospitalisation	3 (23)
NYHA Class*	
≤II	11 (85)
Reintervention†	1 (8)
Bleeding event between discharge and follow-up	0 (0)
Haemolysis	1 (8)
Valve thrombosis	0 (0)
Valve migration or embolisation	0 (0)
Myocardial infarction	0 (0)
Stroke	0 (0)
Echo (follow-up time: 50±38 days)	
LVEF, %	53.5±6.5
LVEDD, mm	46.9±6.3
LVOT obstruction	0 (0)
LVOT mean pressure gradient, mmHg	3.6±3.1
LVOT peak pressure gradient, mmHg	5.9±5.8
Mitral regurgitation	
None	10 (77)
Mild	3 (23)
No PVL	11 (85)
Mild PVL	2 (15)
Mitral valve mean pressure gradient, mmHg	4.5±1.5
Mitral valve peak pressure gradient, mmHg	13.2±4.1

Numerical data are given as n (%), and metric variables are given as mean±standard deviation. *Only assessed in the survivors (n=12). †Interventional treatment of severe paravalvular leakage (haemolysis) using 3 closure devices. LVEDD: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; LVOT: left ventricular outflow tract; NYHA: New York Heart Association; PVL: paravalvular leakage

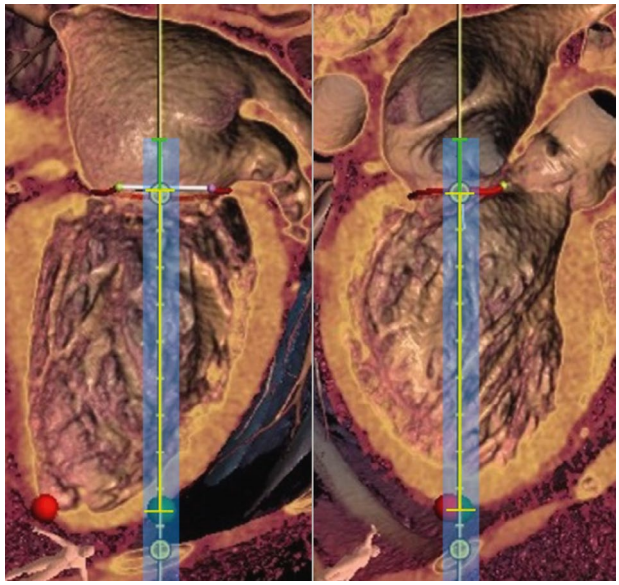

Figure 4. *Assessment of the length of the large-bore sheath by segmentation of the cardiac computed tomography scan (left: intercommissural view, right: LVOT view). The length of the sheath is calculated from the distance between the target access (green dot) and MV plane (yellow bracket) plus approximately 2 cm (green bracket). This is important to enable complete covering of the scissors during the insertion to avoid structural cardiac damage with the sharp scissor tips. Red dot: true apex. LVOT: left ventricular outflow tract; MV: mitral valve*

appears to offer advantages for dividing the AML due to its straightforward TA approach with no need for additional femoral access. Compared to European real-world data with the Tendyne prosthesis, our early experience with the MitraCut procedure did not demonstrate an increase in the incidence of bleeding complications (Bleeding Academic Research Consortium class 2, 3, 4: 11% without MitraCut in the real-world data vs 8% in our experience)[6].

Alcohol septal ablation (ASA) represents an effective strategy to prevent LVOT obstruction, primarily in patients with septal hypertrophy[28,29]. However, in patients without severe septal hypertrophy, we favour an AML-directed prevention strategy. Unlike with the MitraCut procedure, patients require at least a 1-month recovery period between ASA and TMVR. In addition to the physical, psychological, and economic burden of multiple hospitalisations, this waiting period is a significant delay in treating an ill patient's MV disease. ASA prior to TMVR has also been associated with a significant incidence of complete heart block and need for pacemaker implantation of up to 35%[29]. Techniques that address the AML likely avoid this potential complication. The BATMAN technique, a balloon-mediated rupturing of the AML to facilitate transseptal or TA-TMVR, represents a further AML-directed transcatheter technique to prevent LVOT obstruction[30,31]. We agree with Denti et al that this technique should be restricted to the in valve-in-ring setting due to the unpredictable tissue damage of the ballooning[30]. Notably, we propose the MitraCut procedure in TA-TMVR, but transseptal LVOT obstruction preventive techniques should be employed in transseptal TMVR to avoid unnecessary access.

In our MitraCut procedure patients undergoing TA-TMVR with the Tendyne valve system, the MDCT-derived neo-LVOT areas were significantly higher than those reported for patients receiving LAMPOON and ASA prior to TMVR with the SAPIEN 3 (S3) valve (Edwards Lifesciences)[13,14,26,28,29]. The neo-LVOT was not below 250 mm² in any of our patients[32]. However, a potential risk for LVOT obstruction was assumed in all patients, as summarised in **Supplementary Table 1**. Importantly, the acceptable burden of the neo-LVOT for TA-TMVR with the Tendyne valve has to be larger than for the S3 valve[33], as the subvalvular component of the Tendyne valve stent frame is covered by the pericardium, which limits the potential effect of leaflet cutting compared to the open stent frame which is present in the S3 valve. Thus, the concept of the "skirt" neo-LVOT is not applicable. Further, dynamic variables throughout the entire cardiac cycle, for example, leaflet tethering, should also be taken into account within the procedural planning

because of experiences with dynamic LVOT obstruction, especially in case of poor AML tethering[12]. While balloon-expandable valve implantation depth can be readily controlled, the position of the self-expanding Tendyne valve with its sealing body is influenced by the pull on the tether in addition to the position of the apical access. An unintended deviation of the calculated apical target access anteriorly may further push the sealing body into the LVOT, with a subsequent increased risk of LVOT obstruction. Importantly, even if systolic anterior motion occurs in an anterior mitral valve leaflet previously cut in the A2 segment, LVOT obstruction may be avoided due to the cut.

Kohli et al showed the beneficial haemodynamic effect of AML division with the LAMPOON technique prior to TMVR in a silicon model; this beneficial effect on the haemodynamics increased with a smaller predicted neo-LVOT[34]. A similarly designed study for assessing the haemodynamic effect of AML division prior to Tendyne valve implantation is necessary. Such a study would help to define the anatomical characteristics of patients who could benefit from AML division to prevent complete or dynamic LVOT obstruction and to determine the smallest acceptable neo-LVOT for the Tendyne system. This might help to reduce the screening failure rate related to risk for LVOT obstruction. Further clinical evaluation of haemodynamics and short- to intermediate-term outcomes in matched left ventricular and mitral anatomies between patients with and without additional MitraCut are awaited.

The MitraCut procedure is technically straightforward. In addition, it appears to be effective and time efficient in our early experience. However, simulator-based surgical training and proctoring is advised for the first cases. A dedicated device to address the AML transapically, which was originally designed to prevent coronary obstruction in valve-in-valve transcatheter aortic valve replacement, mimics the effect of the MitraCut but is restricted for use in a few centres in the context of clinical evaluation studies and might be more expensive[35].

Limitations

Due to the novelty of the MitraCut procedure, the sample size of this study was limited to 13 patients. Risk assessment for LVOT obstruction is not standardised yet, and a composite of MDCT-derived measurements and TOE-acquired AML imaging mainly focusing on AML length and tethering was used. Therefore, the indication to perform MitraCut was an individual decision made based on expert opinion without a control group. The study is limited by its retrospective study design.

Conclusions

This initial multicentre experience evaluating the effectiveness and reliability of the MitraCut procedure showed promising results regarding LVOT obstruction avoidance in TA-TMVR. The procedure was technically straightforward and did not require specialised equipment. We believe that it has the potential for widespread applicability to lower LVOT obstruction risk in TA-TMVR.

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Funding

Preclinical imaging for this work was funded by the Christian Doppler Society (Laboratory for Microinvasive Heart Surgery at the Medical University of Vienna), supported by the Austrian Federal Ministry of Labour and Economy and the National Foundation for Research, Technology and Development. The authors have no funding relevant to the contents of this multicentre experience to disclose.

Conflict of interest statement

M. Andreas is a proctor/consultant/speaker for Edwards Lifesciences, Abbott, Medtronic, Boston Scientific, Zoll, and B. Braun; and received institutional research grants from Edwards Lifesciences, Abbott, Medtronic, and LSI. T. Kerbel received speaker honoraria from Abbott. M. Mach has received institutional grants, research support, speaker honoraria, and travel compensation from Edwards Lifesciences, Symetis SA, JenaValve, Boston Scientific, Medtronic, Abbott, and Novartis. A. Zierer serves as a proctor for Tendyne; and received speaker fees and educational grants from Abbott. H. Ruge is an Abbott board member and serves as a physician proctor and speaker for Abbott and Edwards Lifesciences. A. Colli is a proctor/consultant for Abbott. E. Kuhn is a proctor for Medtronic and Abbott. J.S. Sauer is President and CEO of LSI Solutions. A. Regueiro is a proctor and consultant for Abbott.

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Supplementary data

Supplementary Table 1. Patient-specific decision-making about the interventional approach and risk assessment regarding left ventricular outflow tract obstruction.

Supplementary Figure 1. Alternative MitraCut procedure equipment currently being evaluated.

Moving image 1. Step-by-step explanation of the MitraCut procedure prior to transapical transcatheter mitral valve replacement.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-24-00490

EuroIntervention
2024;20:1430-1441
DOI: 10.4244/EIJ-D-23-01092

ORIGINAL RESEARCH

Predictors and clinical impact of worsening left ventricular ejection fraction after mitral transcatheter edge-to-edge repair

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This paper also includes supplementary data published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-23-01092

ABSTRACT

BACKGROUND: Little is known about the effects of left ventricular ejection fraction (LVEF) worsening after transcatheter edge-to-edge valve repair (TEER) for mitral regurgitation (MR).

AIMS: This study investigated the predictors and clinical impact of LVEF worsening after TEER for primary MR (PMR) and secondary MR (SMR).

METHODS: This study included 2,019 patients (493 with PMR and 1,526 with SMR) undergoing successful TEER (postprocedural MR grade ≤2+) in the OCEAN-Mitral registry. The patients were categorised into worsened LVEF (wEF), defined as a relative decrease of >12.9% in LVEF at discharge, and preserved LVEF (pEF). The serial changes in left ventricular (LV) function at 1 year were also evaluated.

RESULTS: Following TEER, 657 (32%) patients demonstrated wEF. The pEF group demonstrated both decreased left ventricular end-diastolic volumes (LVEDV) and end-systolic volumes (LVESV), and the wEF group showed significantly increased LVESV at discharge. Higher LVEF, larger LVEDV, higher B-type natriuretic peptide levels, and moderate/severe aortic regurgitation predicted wEF. Compared with baseline, the wEF group still demonstrated lower LVEF (46% to 43%; p<0.001) but significantly increased stroke volume (48 mL to 53 mL; p=0.001) at 1 year. The incidence of death or heart failure hospitalisation was similar between the wEF and pEF groups (hazard ratio 1.14, 95% confidence interval: 0.72-1.80; p=0.84) and also in patients with PMR and SMR.

CONCLUSIONS: LVEF worsening after TEER was not uncommon and was caused by the increased LVESV. LV volumes and some patient-specific factors predicted worsened LVEF which was not associated with long-term clinical outcomes. OCEAN-Mitral registry: UMIN-CTR ID: UMIN000023653.

KEYWORDS: clinical research; mitral valve repair; non-invasive imaging; transthoracic echocardiogram

SUBMITTED ON 25/12/2023 - REVISION RECEIVED ON 1st 25/02/2024 / 2nd 11/04/2024 / 3rd 22/05/2024/ 4th 10/07/2024 - ACCEPTED ON 11/07/2024

Transcatheter edge-to-edge repair (TEER) for mitral regurgitation (MR) is becoming a popular and promising alternative for treating primary MR (PMR) and secondary MR (SMR) in high surgical risk patients. Moderate or severe MR progressively reduces left ventricular (LV) function and causes congestive heart failure[1]. A persistent imbalance in preload and afterload due to MR may lead to LV remodelling and poor long-term prognosis[2]. LV ejection fraction (LVEF) worsens immediately following surgical mitral valve repair and has increased postoperative mortality[3,4]. Several factors can cause LV systolic dysfunction, including open-heart surgery, cardiopulmonary bypass, and cardioplegic arrest. In patients undergoing mitral valve surgery, pulmonary hypertension, atrial fibrillation, low preoperative LVEF, and large LV have been reported to predict a reduced postoperative LVEF[4-6]. In contrast, in patients undergoing TEER, a procedure that does not require open-heart surgery or cardiac arrest, myocardial damage due to increased afterload after MR reduction may be the only factor leading to reduced LVEF. Several studies have reported postinterventional changes in LVEF after TEER, but their predictors have not been investigated[7-11]. A few studies with limited sample sizes reported the clinical outcomes of patients who experienced LVEF reduction, but the clinical impact of worsened LVEF in patients with PMR and SMR remains unclear.

This study aimed to investigate the predictors and clinical impact of LVEF worsening after successful MR reduction with TEER from a large-scale registry and evaluate them in PMR and SMR separately.

Impact on daily practice

The OCEAN-Mitral registry observed worsened left ventricular ejection fraction (LVEF) after transcatheter edge-to-edge repair (TEER) in approximately 30% of patients with mitral regurgitation (MR) mainly because of the increased left ventricular (LV) end-systolic volume. Worsened LVEF was predicted by baseline LV volume and patient-specific factors, and was not associated with long-term clinical outcomes regardless of MR aetiology. Worsened LVEF after TEER was temporary and did not affect the outcomes, and thus, TEER can be safely and effectively performed even when LVEF is reduced after TEER.

Methods

STUDY POPULATION

The Optimized CathEter vAlvular iNtervention (OCEAN)-Mitral registry is an ongoing, prospective, investigator-initiated, multicentre registry assessing the safety and efficacy of TEER for patients with significant MR. This registry included 21 Japanese institutions. Acute and 1-year outcomes have previously been reported[12,13]. From April 2018 to June 2021, 2,150 consecutive patients with symptomatic MR underwent TEER with the MitraClip (Abbott) device. The multidisciplinary local Heart Team, consisting of an interventional cardiologist, a cardiothoracic surgeon, and an echocardiologist, reviewed patient data. This study excluded 131 patients due to unsuccessful TEER procedures (postprocedural MR ≥3; n=97), early surgical mitral valve interventions (n=8), or inadequate echocardiographic images at baseline and at discharge follow-up (n=26). Therefore, the analysis included 2,019 patients. This study was registered with the University Hospital Medical Information Network Clinical Trials Registry, as accepted by the International Committee of Medical Journal Editors (UMIN000023653). The institutional review board of each institution approved the study protocol. This study was conducted under the provisions of the Declaration of Helsinki and the guidelines for epidemiological studies issued by the Ministry of Health, Labour, and Welfare of Japan.

TEER PROCEDURE

TEER with the MitraClip device was performed under general anaesthesia with fluoroscopic and transoesophageal echocardiographic guidance as previously described[1]. After transseptal puncture through femoral vein access, a 24 Fr guiding catheter is advanced into the left atrium. The clip delivery system is inserted above the MR jet origin and then advanced into the LV. The mitral leaflets are grasped, and the clip is closed to approximate the leaflets. If adequate MR reduction is obtained without relevant mitral stenosis, assessed by transmitral mean pressure gradient, the clip is released. If further reduction of MR is necessary, a second clip implantation is considered.

ECHOCARDIOGRAPHIC EVALUATION

All echocardiographic examinations were carried out by trained sonographers using high-quality cardiovascular ultrasound systems at baseline, discharge, and 1 year. MR severity was graded according to the American Society of Echocardiography guidelines based on a validated multi-integrative method[14]. Both qualitative (colour flow mapping) as well as quantitative measurements (proximal velocity surface area whenever feasible) were used to grade the MR severity from grades 0 to 4 (grade 0: no/trace; grade 1: mild; grade 2: moderate; grade 3: moderate to severe; grade 4:

Abbreviations

LV	left ventricle
LVEDV	left ventricular end-diastolic volume
LVEF	left ventricular ejection fraction
LVESV	left ventricular end-systolic volume
MR	mitral regurgitation
M-TEER	mitral transcatheter edge-to-edge repair
PMR	primary mitral regurgitation
SMR	secondary mitral regurgitation
SV	stroke volume
TEER	transcatheter edge-to-edge repair

severe). LV end-diastolic and end-systolic diameters were measured using two-dimensional images. The LV outflow tract velocity time integral values were measured at the timing of the most averaged RR interval on the electrocardiogram. Patients were categorised into two groups according to the occurrence of LVEF worsening as either worsened LVEF (wEF) or preserved LVEF (pEF). The change in LVEF was assessed by calculating the percentage of changes as follows: (early postinterventional LVEF–preinterventional LVEF)/preoperative LVEF. This study defined wEF as a >12.9% decrease in LVEF, which represented the median value of LVEF reduction and was considered the threshold to determine LVEF worsening. Further, the changes in LVEF, LV end-diastolic volume (LVEDV), LV end-systolic volume (LVESV), and stroke volume (SV) were assessed at 1 year, and these changes were compared between the wEF and pEF groups. The biplane Simpson disk method, from the apical 4- and 2-chamber views, was used to calculate LVEF, LVEDV, and LVESV. SV was calculated non-invasively by measuring the Doppler-derived velocity time integral of the left ventricular outflow tract. The degree of MR reduction was calculated based on the difference in the MR grade between pre- and post-TEER (preinterventional grade–postinterventional grade).

CLINICAL FOLLOW-UP

The primary study endpoint includes a composite of all-cause death and hospitalisation for heart failure. The secondary endpoint includes all-cause death, hospitalisation for heart failure, and the New York Heart Association (NYHA) Functional Class at 1 year. Information on survival status and clinical events was obtained from patient records or telephone calls with the patient, the patient's family, or family physicians.

STATISTICAL ANALYSIS

Categorical variables are reported as numbers with relative percentages and were compared using the chi-square test or Fisher's exact test. Continuous variables are presented as mean±standard deviation or median [interquartile range]. Paired and unpaired Student's t-tests were used to compare continuous variables with a normal distribution, and the Mann-Whitney U test or Wilcoxon signed-rank test was used to compare those without a normal distribution. The Bonferroni correction was used for *post hoc* analysis. The Kaplan-Meier method was used to estimate the cumulative incidences of clinical events, and the log-rank test was used to assess differences. The multivariate logistic regression analysis was used to calculate independent predictors of worsened LVEF, and a multivariable Cox proportional hazard model was used to obtain the hazard ratio (HR) of wEF for the primary and secondary endpoints. The multivariate model included statistically significant variables ($p<0.05$) from the univariate analysis. The results were expressed as odds ratios (OR) and HR with associated 95% confidence intervals (CI). In addition, a restricted cubic spline with 5 knots was used to show a continuous relationship between the rate of change in LVEF and adjusted HR for the primary endpoint. The locations of the 5 knots were determined as the 5th, 27.5th, 50th, 72.5th, and 95th percentiles of the distribution of the change in LVEF. The reference value for the rate of change in LVEF was set at –12.9%, which was the median value of LVEF reduction in the study population. The HR was adjusted for statistically significant variables for the primary endpoint in univariate analysis. JMP (version 10.0 for Windows [SAS Institute]) or Stata 17 (StataCorp) were used for all statistical analyses.

Results

BASELINE PATIENT CHARACTERISTICS AND PERIPROCEDURAL RESULTS

Among the 2,019 patients of this study, 657 (32%) demonstrated >12.9% decrease in LVEF. Therefore, there were 657 patients in the wEF group and 1,362 patients in the pEF group. **Table 1** shows the baseline clinical characteristics. Compared with the pEF group, the wEF group showed more history of ventricular tachycardia or fibrillation and cardiac resynchronisation therapy. Diuretics were more commonly used in the wEF group. The atrial fibrillation prevalence was lower in the wEF group. **Table 2** summarises the echocardiographic findings. The wEF group included 184 of the total 493 patients with PMR (37%) and 473 of the 1,526 patients with SMR (31%). The wEF group had a higher PMR prevalence, more severe MR, more pulmonary hypertension, and more moderate or severe aortic and tricuspid regurgitation. Additionally, the wEF group demonstrated larger LVEDV, larger LVESV, larger left atrial volume index, and lower SV. **Table 3** presents the periprocedural results. The wEF group had a higher prevalence of multiple clip implantation and a longer procedure time. The echocardiographic results at discharge showed lower LVEF and larger LV volumes in the wEF group. **Figure 1** shows the degree of MR reduction in the wEF and pEF groups. The degree of MR reduction was greater in the wEF group than in the pEF group, and the patients with wEF were more likely to have an MR grade reduction ≥3 **(Table 3)**. This trend was similarly observed in both SMR and PMR (SMR: wEF 49.9% vs pEF 44.2%; p=0.04; PMR: wEF 72.3% vs pEF 60.8%; p=0.01). The residual MR grade did not differ between the two groups, but SV was significantly lower in the wEF group.

PREDICTORS OF WORSENED LVEF

Table 4 and the **Central illustration** show predictors of wEF in multivariable analysis. Higher baseline LVEF (OR 1.01, 95% CI: 1.00-1.01; p<0.0001), larger baseline LVEDV (OR 1.05, 95% CI: 1.03-1.06; p<0.0001), higher baseline B-type natriuretic peptide (BNP) levels (OR 1.00, 95% CI: 1.00-1.00; p=0.02), and moderate or severe aortic regurgitation (OR 1.65, 95% CI: 1.01-2.72; p=0.04) were independently associated with wEF after TEER in the total cohort. Larger baseline LVEDV, smaller baseline LVESV, higher baseline BNP levels, previous cardiac resynchronisation therapy, and longer procedural time were independently associated with wEF in patients with SMR. Higher baseline LVEF, larger LVEDV, a degree of MR reduction ≥3, and lower SV were independently associated with wEF in patients with PMR.

CHANGES IN LVEF, LV VOLUME, SV, AND CLINICAL OUTCOME

Figure 2 and the **Central illustration** show the serial changes in LVEF, SV, and LV volumes for 1 year. In the pEF group,

Table 1. Baseline demographic and clinical characteristics.

	Total n=2,019	wEF n=657	pEF n=1,362	*p*-value
Clinical				
Male	1,127 (55.8)	374 (56.9)	753 (55.3)	0.50
Age, years	78.3±9.5	78.2±9.4	78.4±9.5	0.68
Body surface area, m^2	1.5±0.2	1.5±0.2	1.5±0.2	0.27
Hypertension	1,363 (67.5)	434 (66.1)	929 (68.2)	0.33
Dyslipidaemia	1,041 (51.6)	338 (51.5)	703 (51.6)	0.96
Diabetes	552 (27.3)	188 (27.3)	364 (26.7)	0.39
Smokers	687 (34.0)	237 (36.1)	450 (33.0)	0.19
Bleeding	130 (6.5)	49 (7.5)	81 (6.0)	0.21
Atrial fibrillation	1,281 (63.5)	393 (59.8)	888 (65.2)	0.02
Ventricular tachycardia or fibrillation	212 (10.5)	87 (13.2)	125 (9.2)	0.007
Previous coronary artery disease	731 (36.2)	235 (35.8)	496 (36.4)	0.80
Prior stroke	231 (11.4)	69 (10.5)	162 (11.9)	0.37
Open-heart surgery	224 (11.1)	63 (9.6)	161 (11.8)	0.15
Peripheral vascular disease	208 (10.3)	73 (11.1)	135 (9.9)	0.41
Chronic obstructive pulmonary disease	199 (9.9)	67 (10.3)	132 (9.7)	0.75
Dialysis dependent	103 (5.1)	33 (5.0)	70 (5.1)	1.00
STS score for mitral valve repair, %	6.3 [3.6-10.1]	6.6 [3.6-10.3]	6.2 [3.6-10.1]	0.62
EuroSCORE II, %	4.7 [3.0-8.0]	4.6 [2.7-8.0]	4.8 [8.1-3.1]	0.15
Haemoglobin, g/dL	11.7±1.9	11.7±1.9	11.7±1.9	0.42
eGFR, mL/min/1.73 m^2	39.5±19.2	39.4±19.3	39.6±19.2	0.90
BNP, pg/mL	336.8 [168.7-675.0]	405.2 [200.1-785.9]	309.1 [160.9-627.3]	0.001
Related to heart failure				
NYHA Functional Class				0.03
I	44 (2.2)	16 (2.4)	28 (2.1)	
II	703 (34.8)	210 (32.0)	493 (36.2)	
III	993 (49.2)	320 (48.7)	673 (49.4)	
IV	279 (13.8)	111 (16.9)	168 (12.3)	
NYHA Functional Class ≥III	1,272 (63.0)	431 (65.6)	841 (61.8)	0.09
Hospitalisation for heart failure within the previous 1 year	1,455 (72.3)	469 (71.4)	986 (72.7)	0.56
Previous cardiac resynchronisation therapy	207 (10.3)	85 (12.9)	122 (9.0)	0.01
Previous implantation of a defibrillator	283 (14.0)	101 (15.4)	182 (13.4)	0.24
Medications at baseline				
Beta blocker	1,519 (75.2)	481 (73.2)	1,038 (76.2)	0.15
ACEI, ARB or ARNI	1,255 (62.2)	395 (60.1)	860 (63.1)	0.20
Mineralocorticoid receptor antagonist	1,109 (54.9)	376 (57.2)	733 (53.8)	0.15
SGLT-2 inhibitors	204 (10.1)	67 (10.2)	137 (10.1)	0.94
Diuretic	1,760 (87.2)	592 (90.1)	1,168 (85.8)	0.01
Oral anticoagulant agent	1,296 (64.2)	412 (62.7)	884 (64.9)	0.35
Oral antiplatelet agent	823 (40.8)	273 (41.6)	550 (40.4)	0.63

Data are presented as the mean value±standard deviation, median [interquartile range], or as a proportion, n (%). ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; ARNI: angiotensin receptor-neprilysin inhibitor; BNP: B-type natriuretic peptide; eGFR: estimated glomerular filtration rate; EuroSCORE: European System for Cardiac Operative Risk Evaluation; NYHA: New York Heart Association; pEF: preserved left ventricular ejection fraction; SGLT-2: sodium-glucose cotransporter 2; STS: Society of Thoracic Surgeons; wEF: worsened left ventricular ejection fraction

LVEF and SV consistently increased and LV volumes decreased from baseline to 1 year. In the wEF group, LVEF and LVESV showed a biphasic pattern: LVEF decreased and LVESV increased after the procedure, but LVEF increased and LVESV decreased at 1 year. Further, LVEDV decreased and SV increased from baseline to 1 year. LVEF remained lower

Table 2. Baseline echocardiographic parameters.

	Total n=2,019	wEF n=657	pEF n=1,362	*p*-value
Severity of MR				
≤Moderate, ≤grade 2+	263 (13.0)	54 (8.2)	209 (15.3)	<0.0001
Moderate to severe, grade 3+	522 (25.9)	137 (20.9)	385 (28.3)	0.0003
Severe, grade 4+	1,234 (61.1)	466 (70.9)	768 (56.4)	<0.0001
Cause of MR				0.01
Primary	493 (24.4)	184 (28.0)	309 (22.7)	
Secondary	1,526 (75.6)	473 (72.0)	1,053 (77.3)	
Ischaemic MR	454 (29.8)	151 (31.9)	303 (28.8)	0.23
EROA, cm^2	0.39±0.25	0.43±0.24	0.37±0.25	<0.0001
Regurgitant volume, mL/beat	55.9±25.8	59.9±28.4	54.0±24.4	<0.0001
Mitral valve orifice area, cm^2	5.3±1.6	5.4±1.6	5.3±1.6	0.12
Transmitral mean pressure gradient, mmHg	1.8±1.2	1.9±1.1	1.7±1.2	0.07
LVDs, mm	44.3±13.2	45.7±13.8	43.7±13.0	0.002
LVDd, mm	57.2±10.2	58.8±10.4	56.4±10.0	<0.0001
LVESV, mL	90.0±63.3	92.2±63.6	88.9±63.2	0.29
LVEDV, mL	150.3±72.1	159.4±72.6	146.0±71.9	<0.0001
LVEF, %	43 [31-60]	44 [33-62]	42 [30-59]	0.001
Left atrial volume index, mL/m^2	87.3±44.3	90.6±42.9	85.7±45.0	0.01
LVOT VTI, cm	14.1±4.7	13.7±4.5	14.4±4.9	0.006
Stroke volume, mL	48.8±16.3	47.7±15.9	49.3±16.5	0.05
Moderate or severe aortic stenosis	59 (2.9)	19 (2.9)	40 (2.9)	1.00
Moderate or severe aortic regurgitation	181 (9.0)	78 (11.9)	103 (7.6)	0.002
Moderate or severe tricuspid regurgitation	711 (35.3)	253 (38.6)	458 (33.7)	0.03
RVFAC, %	36.6±10.7	36.2±10.8	36.7±10.6	0.38
Tricuspid regurgitation peak gradient, mmHg	35.1±14.0	36.7±14.7	34.3±13.6	0.0004
Right ventricular systolic pressure, mmHg	41.3±15.7	43.1±16.2	40.5±15.4	0.002

Data are presented as the mean value±standard deviation, median [interquartile range], or as a proportion, n (%). EROA: effective regurgitant orifice area; LVDd: left ventricular end-diastolic dimension; LVDs: left ventricular end-systolic dimension; LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; LVESV: left ventricular end-systolic volume; LVOT VTI: left ventricular outflow tract velocity time integral; MR: mitral regurgitation; pEF: preserved left ventricular ejection fraction; RVFAC: right ventricular fractional area change; wEF: worsened left ventricular ejection fraction

Table 3. Procedural and echocardiographic parameters at discharge.

	Total n=2,019	wEF n=657	pEF n=1,362	*p*-value
Procedure				
Number of MitraClip* devices implanted ≥2	781 (38.7)	296 (45.1)	485 (35.6)	<0.0001
Total procedure time, min	95.7±46.5	100.2±45.6	93.6±46.7	0.005
Discharge				
Mitral regurgitation at discharge				0.29
None-trivial, grade 0	386 (19.1)	121 (18.4)	152 (23.1)	
Mild, grade 1+	1,207 (59.8)	384 (58.5)	823 (60.4)	
Moderate, grade 2+	426 (21.1)	152 (23.1)	274 (20.1)	
Degree of MR reduction ≥3	1,022 (50.6)	369 (56.2)	653 (47.9)	0.0006
Transmitral mean pressure gradient, mmHg	3.0±1.6	3.0±1.6	3.0±1.5	0.77
Mitral valve orifice area, cm^2	2.7±1.0	2.7±1.0	2.8±1.0	0.11
LVDs, mm	44.0±13.5	46.2±13.9	42.9±13.3	<0.0001
LVDd, mm	55.3±10.7	56.6±11.2	54.6±10.5	0.0002
LVESV, mL	90.3±62.9	101.0±66.9	85.0±60.9	<0.0001
LVEDV, mL	141.9±72.0	146.6±73.9	139.7±71.0	0.046
LVEF, %	40 (29-55)	34 (25-48)	44 (32-58)	<0.0001
Rate of change in LVEF, %	–5.5±15.9	–24.3±10.0	3.6±18.0	<0.0001
LVOT VTI, cm	14.9±5.1	14.0±4.7	15.4±5.3	<0.0001
Stroke volume, mL	51.6±16.3	49.1±15.8	52.9±16.5	<0.0001
Tricuspid regurgitation peak gradient, mmHg	30.3±10.0	29.8±9.8	30.6±10.1	0.11
RVFAC, %	39.3±10.1	38.4±10.5	39.7±10.0	0.041
Left atrial volume index, mL/m^2	80.4±38.5	80.6±37.1	80.3±39.2	0.84
Moderate or severe tricuspid regurgitation	569 (28.2)	203 (30.9)	366 (27.0)	0.07

Data are presented as the mean value±standard deviation, median [interquartile range], or as a proportion, n (%). *By Abbott. LVDd: left ventricular end-diastolic dimension; LVDs: left ventricular end-systolic dimension; LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; LVESV: left ventricular end-systolic volume; LVOT VTI: left ventricular outflow tract velocity time integral; MR: mitral regurgitation; pEF: preserved left ventricular ejection fraction; RVFAC: right ventricular fractional area change; wEF: worsened left ventricular ejection fraction

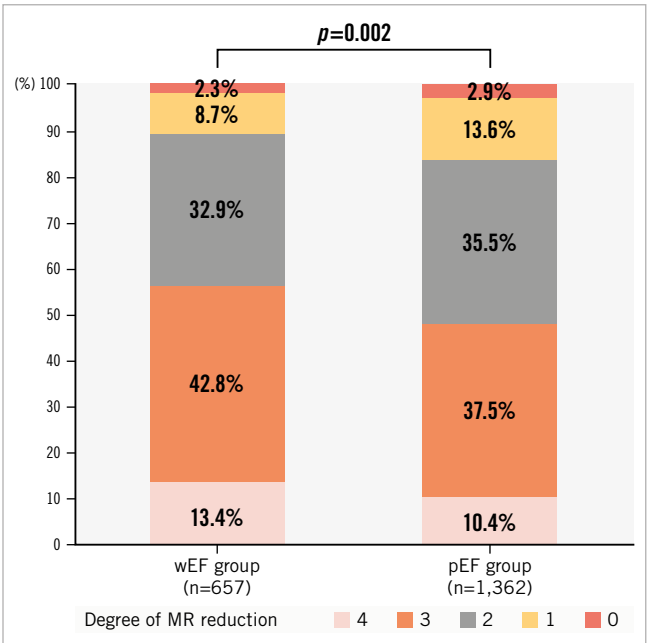


Figure 1. *The degree of MR reduction in wEF and pEF groups. LVEF: left ventricular ejection fraction; MR: mitral regurgitation; pEF: patients with preserved LVEF; wEF: patients with worsened LVEF*

at 1 year than at baseline (from 46% to 43%; p<0.001), but SV significantly increased at 1 year (from 48 mL to 53 mL; p=0.001). Both SMR and PMR demonstrated similar trends **(Supplementary Figure 1, Supplementary Figure 2)**.

Over a follow-up period of 436 days (range: 369-744), 380 deaths and 366 hospitalisations for heart failure were recorded in the total population. There were no significant differences in the primary endpoint between the wEF and pEF groups (HR 1.14, 95% CI: 0.72-1.80; p=0.84) **(Figure 3A, Central illustration)**. The incidences of all-cause death (HR 1.03, 95% CI: 0.57-1.76; p=0.19) and hospitalisation for heart failure (HR 0.73, 95% CI: 0.41-1.29; p=0.49) were also similar between the two groups **(Figure 3B, Figure 3C, Central illustration)**. An improvement of NYHA Functional Class was observed in both the wEF (n=343; p<0.0001) and pEF (n=718; p<0.0001) groups **(Figure 4)**. NYHA Functional Class at baseline was higher in the wEF group than in the pEF group (p=0.03), but there was no significant difference between the two groups at 1 year (p=0.34) **(Figure 4)**. In both SMR and PMR patients, the incidence of the primary endpoint was similar between the wEF and pEF groups (SMR: HR 0.80, 95% CI: 0.48-1.35; p=0.41, PMR: HR 0.58, 95% CI: 0.17-1.99; p=0.58). In addition, the impact of wEF on the primary endpoint was not significant in patients with baseline LVEF <30% (n=400, HR 1.13, 95% CI: 0.57-2.23; p=0.73) or ≥30% (n=1,619, HR 1.03, 95% CI: 0.62-1.70; p=0.91).

The effect of changes in LVEF on the primary endpoint was further investigated. The ratio of changes in LVEF from baseline to discharge was also similar between patients who met and did not meet the primary endpoint (–5.0±22.4% vs –5.7±19.7%; p=0.50). Neither absolute (HR 0.99, 95% CI: 0.95-1.03; p=0.66) nor relative (HR 0.99, 95% CI: 0.97-1.01; p=0.38) changes in LVEF as a continuous variable were associated with the primary endpoint. In a restrictive cubic spline curve, a greater reduction in LVEF did not increase the risk of the primary endpoint **(Supplementary Figure 3)**. These results indicated that the risk of death or heart failure hospitalisation cannot be predicted by greater LVEF reduction.

Discussion

The main study results include (1) worsened LVEF was identified in approximately 30% of patients with MR undergoing TEER, caused by the increased LVESV after TEER; (2) predictors of wEF were LVEDV in both SMR and PMR; LVESV, BNP levels, previous cardiac resynchronisation therapy, and procedural time in SMR; and LVEF, SV, and the degree of MR reduction being ≥3 in PMR; and (3) SV and LVEF improved over time in the wEF group, and wEF after TEER was temporary and unrelated to prognosis.

Previous studies emphasised that the increased afterload due to the MR correction caused a dramatic decrease in LVEF after open-heart surgery[3,15]. This phenomenon reflects that mitral valve surgery unmasks the decreased myocardial contractility, and the SV forwardly ejects into the high impedance of the aorta. The acute change in loading conditions without any effects of intraoperative myocardial injury associated with cardiopulmonary bypass or cardiopulmonary arrest caused the decrease in LVEF in patients undergoing TEER. LVESV was used to determine the afterload and cardiac contractility as previously reported[16]. In this study, whereas the pEF group showed a decrease in both LVEDV and LVESV after TEER, LVESV significantly increased in the wEF group regardless of MR aetiology. This indicates that the worsened LVEF due to afterload changes post-TEER is generated by changes in LVESV in both PMR and SMR.

This study revealed larger LVEDV at baseline as a wEF predictor in both SMR and PMR. Conversely, a higher LVEF at baseline predicted wEF only in PMR. Increased preload and decreased afterload due to MR often keep LVEF within normal limits and sometimes cause hyperkinetic contraction to maintain SV in patients with PMR. Previous studies revealed that preload and afterload normalised and LVEF decreased after mitral valve surgery, revealing myocardial dysfunction[17]. The degree of systolic contractility can be a risk of worsened LVEF, because the hyperkinetic LV indicates the presence of myocardial disorder in PMR. LV volumes, not LVEF, predicted wEF in SMR. These data indicate that LV volumes were more important factors for worsened LVEF after TEER than baseline LVEF, and concerns about wEF due to TEER may not be a reason to exclude patients with low LVEF as candidates for TEER. In our study, an MR grade reduction ≥3 was an independent predictor of wEF in patients with PMR. A greater MR reduction can cause wEF in patients with PMR, but this had no prognostic impact in our study. Therefore, maximum MR reduction should be achieved in order to allow the reduction in LVEF after the procedure. Higher BNP levels at baseline were identified as a factor of wEF in SMR. High BNP levels are induced by increased preload and afterload.

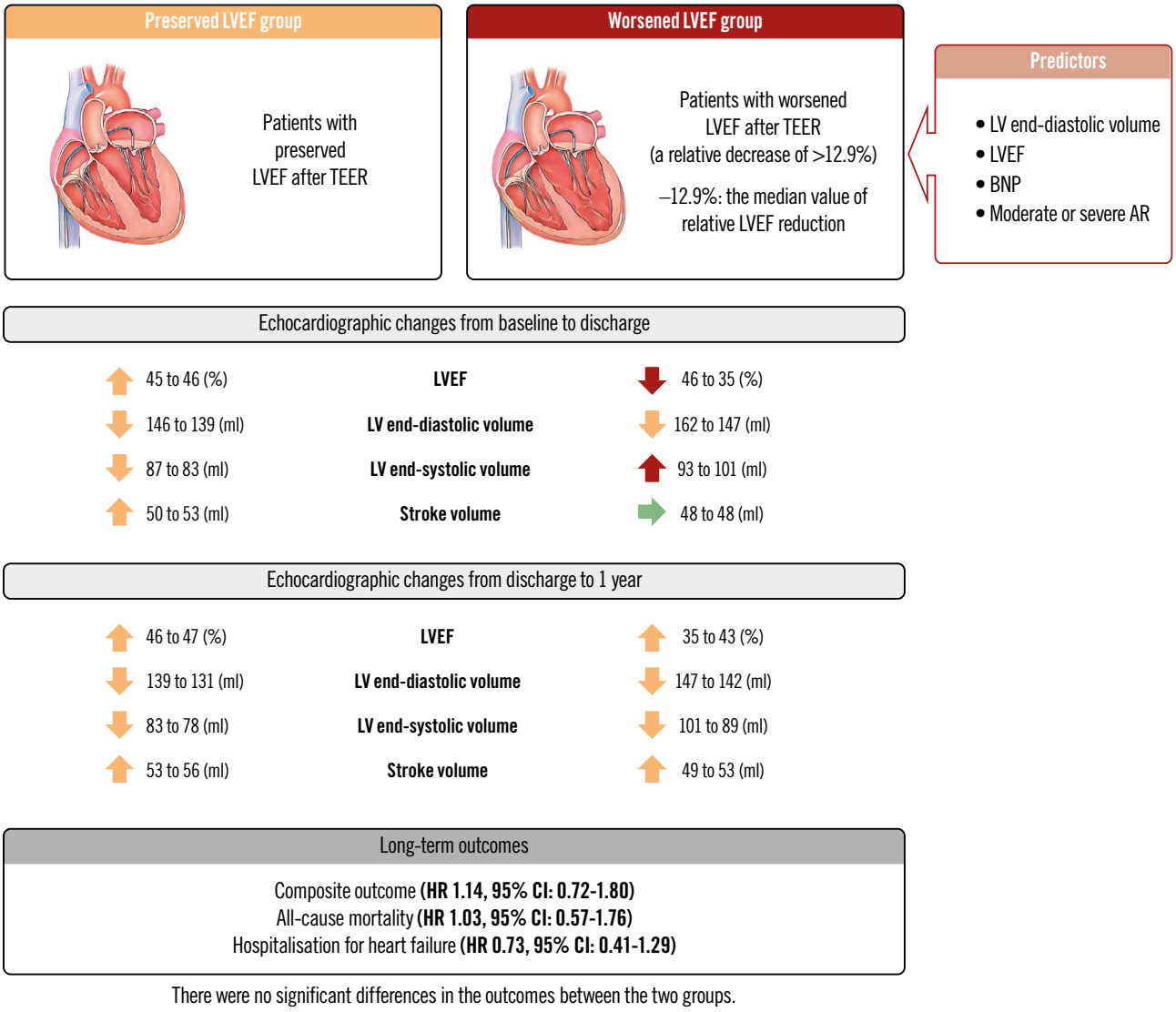
Table 4. Independent predictors of worsened LVEF.

	OR (95% CI)	*p*-value
Overall		
LVEF	1.01 (1.00-1.01)	<0.0001
LVEDV	1.05 (1.03-1.06)	<0.0001
BNP	1.00 (1.00-1.00)	0.02
Moderate or severe aortic regurgitation	1.65 (1.01-2.72)	0.04
Diuretic	1.55 (0.96-2.49)	0.07
Moderate or severe tricuspid regurgitation	1.35 (0.97-1.87)	0.08
Previous cardiac resynchronisation therapy	1.53 (0.93-2.52)	0.09
Atrial fibrillation	0.76 (0.56-1.04)	0.10
Procedural time	1.00 (1.00-1.01)	0.10
Tricuspid regurgitation peak gradient	0.99 (0.98-1.00)	0.10
Stroke volume	0.99 (0.98-1.00)	0.12
Ventricular tachycardia or fibrillation	1.35 (0.84-2.18)	0.22
Number of implanted clips ≥2	1.19 (0.86-1.66)	0.29
Degree of MR reduction ≥3	1.14 (0.84-1.53)	0.40
EROA	1.22 (0.70-2.13)	0.49
Degenerative MR	1.09 (0.71-1.68)	0.69
Left atrial volume index	1.00 (1.00-1.00)	0.84
SMR		
LVEDV	1.03 (1.02-1.05)	<0.0001
LVESV	0.96 (0.94-0.98)	<0.0001
BNP	1.00 (1.00-1.00)	0.009
Previous cardiac resynchronisation therapy	1.87 (1.15-3.03)	0.01
Procedural time	1.00 (1.00-1.01)	0.04
Mineralocorticoid receptor antagonist	1.41 (0.99-2.00)	0.06
Moderate or severe aortic regurgitation	1.68 (0.97-2.92)	0.06
Atrial fibrillation	0.74 (0.51-1.06)	0.10
Stroke volume	0.99 (0.98-1.00)	0.11
Diuretic	1.46 (0.80-2.64)	0.21
EROA	1.75 (0.70-4.39)	0.23
Ventricular tachycardia or fibrillation	1.22 (0.77-1.94)	0.40
LVEF	0.99 (0.96-1.02)	0.55
Tricuspid regurgitation peak gradient	1.00 (0.98-1.01)	0.57
Number of implanted clips ≥2	0.99 (0.67-1.46)	0.94
Degree of MR reduction ≥3	1.01 (0.72-1.41)	0.97
PMR		
LVEF	1.01 (1.00-1.02)	0.0002
LVEDV	0.98 (0.96-1.00)	0.006
Degree of MR reduction ≥3	2.06 (1.15-3.66)	0.01
Stroke volume	0.98 (0.96-1.00)	0.03
Left atrial volume index	1.01 (1.00-1.01)	0.07
Chronic obstructive pulmonary disease	1.97 (0.89-4.39)	0.09
ACEI/ARB/ARNI	0.69 (0.41-1.15)	0.16
Number of implanted clips ≥2	1.30 (0.79-2.15)	0.30
Regurgitant volume	1.00 (0.99-1.01)	0.62
Moderate or severe tricuspid regurgitation	1.13 (0.65-1.97)	0.66
BNP	1.00 (0.99-1.01)	1.00

ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; ARNI: angiotensin receptor-neprilysin inhibitor; BNP: B-type natriuretic peptide; CI: confidence interval; EROA: effective regurgitant orifice area; LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; LVESV: left ventricular end-systolic volume; MR: mitral regurgitation; OR: odds ratio; PMR: primary mitral regurgitation; SMR: secondary mitral regurgitation

EuroIntervention — Central Illustration

Outcomes of patients undergoing TEER according to LVEF change: predictors and clinical impact of LVEF worsening.



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The OCEAN-Mitral registry observed worsened LVEF after TEER in approximately 30% of patients with MR mainly due to the increased LV end-systolic volume, but LVEF tended to improve after 1 year with reverse remodelling (the red, orange, and green arrows indicate adverse change, positive change, and no change in the left ventricle, respectively). Worsened LVEF was predicted by LV volume and patient-specific factors, and was not associated with long-term outcomes regardless of MR aetiology. AR: aortic regurgitation; BNP: B-type natriuretic peptide; CI: confidence interval; HR: hazard ratio; LV: left ventricular; LVEF: left ventricular ejection fraction; MR: mitral regurgitation; TEER: transcatheter edge-to-edge valve repair

Patients with high BNP levels have a severe haemodynamic status with both increased preload and afterload. Because MR reduction by TEER generally increases afterload further, the effect of TEER on the LV might be greater in patients with high BNP levels. A previous study reported that BNP activation in MR was more prominent in SMR and linked with LV remodelling[18]. Therefore, high BNP levels in SMR may be associated with increased LVESV and decreased contractility after MR reduction.

Previous studies reported that reduced LVEF after surgery or TEER indicates irreversible LV remodelling and a risk of adverse events[4,19,20]. The current study revealed that LVEF improved, SV increased, and LV volumes became smaller at 1 year in patients with worsened LVEF compared to those

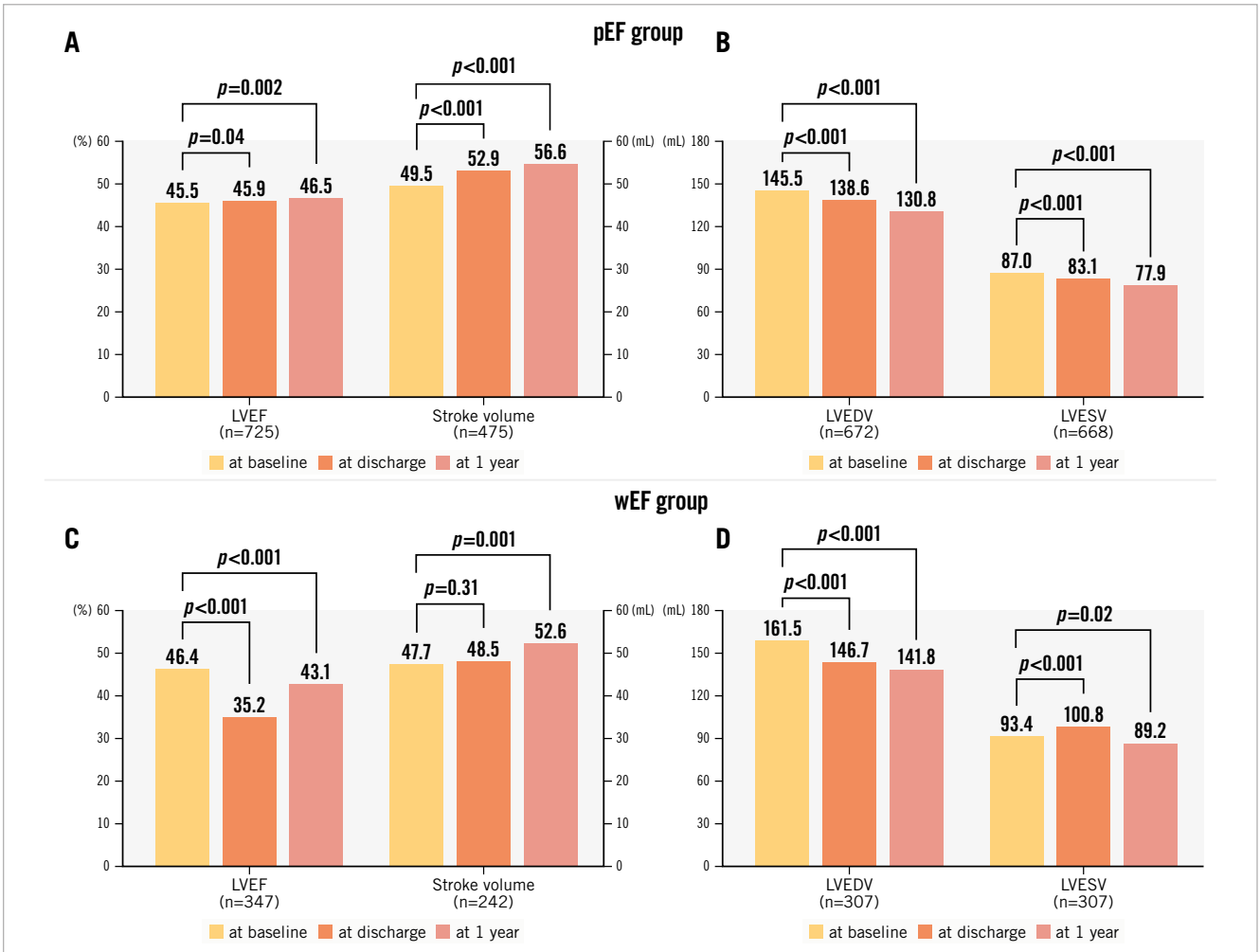

Figure 2. *Serial changes in LVEF, stroke volume, and LV volumes. LVEF, stroke volume, LVEDV, and LVESV at baseline, discharge, and 1 year in the pEF groups (A,B) and wEF (C,D). LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; LVESV: left ventricular end-systolic volume; pEF: patients with preserved LVEF; wEF: patients with worsened LVEF*

at discharge in both PMR and SMR, indicating LV reverse remodelling for 1 year after discharge. These data indicate that worsened LVEF after MR reduction with TEER is temporary and does not necessarily mean "irreversible myocardial damage". Additionally, the benefits of increased SV and reverse remodelling after TEER seem to be significant.

Previous studies have shown that wEF after surgery or TEER is associated with worse outcomes[4,21]. Additionally, a recent large cohort study demonstrated that wEF (>15% postinterventional LVEF reduction) in PMR was associated with a worse prognosis at 1 year[22]. However, our study revealed that wEF is not related to long-term prognosis in either SMR or PMR. Also, no apparent linear relationship of greater reduction in LVEF with adverse events was demonstrated. The positive effects of reverse remodelling, increased stroke volume, and improved ejection fraction over time by MR reduction may outweigh the temporary worsening in LVEF after TEER. The benefit of TEER is currently controversial for patients with advanced heart failure and a very low LVEF of <20%[23,24]. However, our data indicate that TEER is safe and effective even when LVEF is worsened after TEER in patients with reduced LVEF.

Limitations

First, this is a retrospective, observational study, and concomitant factors may have affected the results. Second, echocardiographic data were not analysed in an independent core laboratory. To standardise the measurement, we developed a consensus document on the periprocedural echocardiographic assessment before and after TEER based on the guidelines and shared it with the participating institutions before enrolment. Additionally, several echocardiographic examinations for valvular heart disease had already been performed by experienced echocardiographers at the participating institutions when they started their TEER programmes. Third, the exclusion of 26 patients due to inadequate imaging data potentially introduces bias into our results. However, the low proportion of excluded patients means

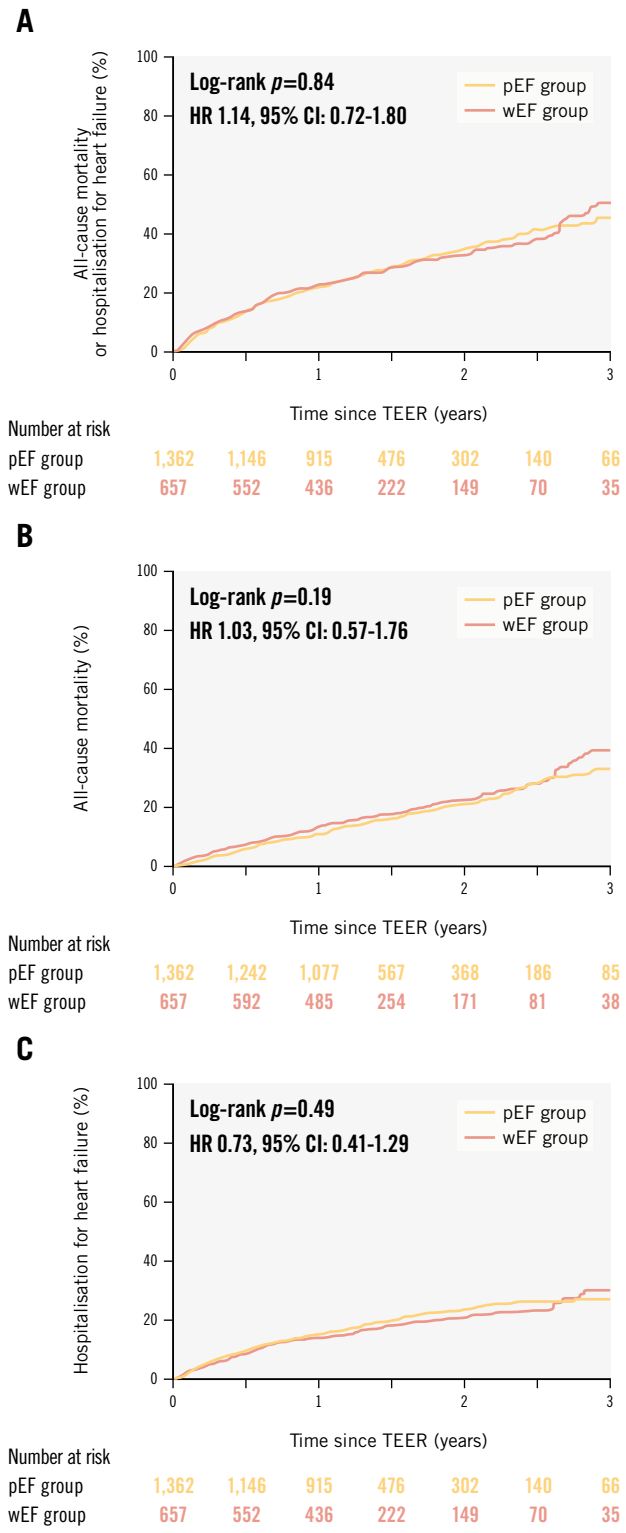

Figure 3. *Time-to-first event curves for the primary and secondary endpoints. Kaplan-Meier curves of (A) all-cause mortality or hospitalisation for heart failure, (B) all-cause mortality, and (C) hospitalisation for heart failure, stratified according to LVEF changes after TEER. CI: confidence interval; HR: hazard ratio; LVEF: left ventricular ejection fraction; pEF: patients with preserved LVEF; TEER: transcatheter edge-to-edge repair; wEF: patients with worsened LVEF*

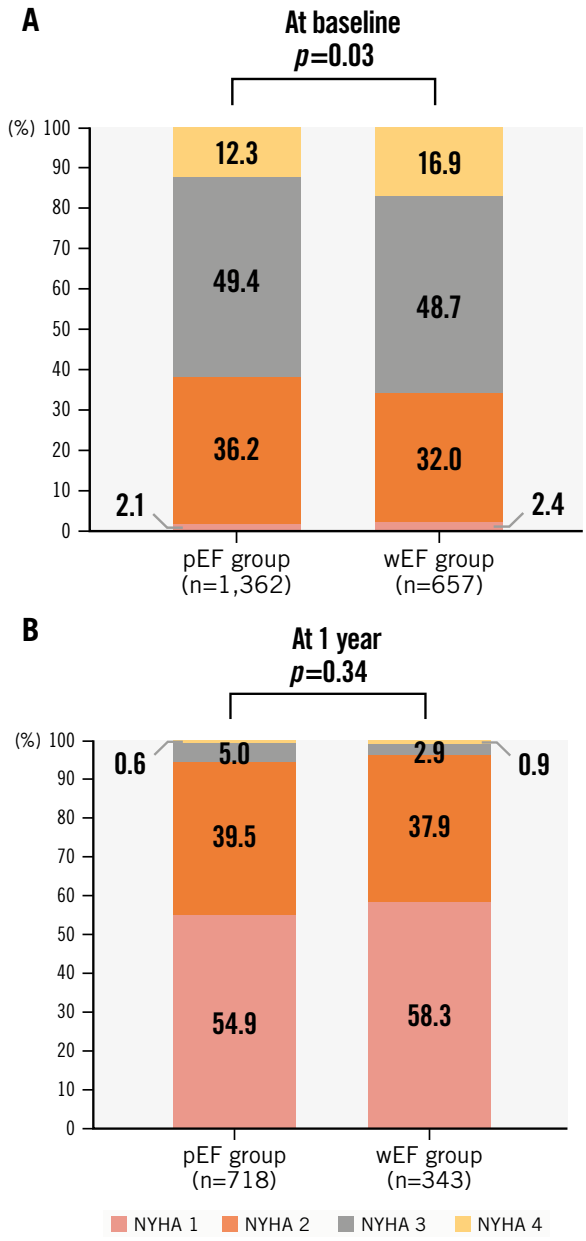

Figure 4. *NYHA Functional Class at baseline and 1 year. NYHA Functional Class at baseline (A) and 1 year (B) in the wEF and pEF groups. LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; pEF: patients with preserved LVEF; wEF: patients with worsened LVEF*

the effect of this bias on results may be limited. Fourth, it was difficult to eliminate the effects of certain variables, such as haemodynamic conditions, volume status, aortic regurgitation, and LV outflow tract obstruction on SV in transthoracic echocardiography (TTE). In addition, heart rate and blood pressure during TTE are not available in this registry. Fifth, detailed information on invasive haemodynamics and medical therapy at follow-up was not available in this study. Therefore, this study did not investigate the effects of periprocedural haemodynamic and postinterventional heart failure drugs. Sixth, wEF

was defined based on the median values of the decrease in LVEF, and this value was used in both SMR and PMR. While the relative decrease in LVEF of 12.9% represents a greater absolute decrease in LVEF in patients with PMR, this value represents a smaller absolute decrease in patients with SMR. However, when the clinical effect of an absolute decrease of ≥10% after TEER on the primary endpoint was evaluated in patients with baseline LVEF ≤40%, an absolute decrease of ≥10% was not associated with the incidence of the primary endpoint (58.2% vs 47.2%, HR 0.94, 95% CI: 0.61-1.47; p=0.80). Finally, postinterventional LVEF is measured until discharge, and it does not accurately reflect the immediate postinterventional LVEF.

Conclusions

The OCEAN-Mitral registry observed wEF after TEER in approximately 30% of patients with MR mainly due to their increased LVESV. LVEDV in both SMR and PMR; LVESV, higher BNP levels, longer procedural time, and previous cardiac resynchronisation therapy in SMR; and LVEF, an MR reduction ≥3 grades, and SV in PMR were wEF predictors. LVEF in patients with wEF tended to improve after 1 year with reverse remodelling, and wEF after TEER was not associated with long-term outcomes regardless of MR aetiology.

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Acknowledgements

The authors thank all investigators participating in this registry.

Funding

The OCEAN-Mitral registry, which is part of the OCEAN-SHD registry, is supported by Edwards Lifesciences, Medtronic Japan, Boston Scientific, Abbott Medical Japan, and Daiichi Sankyo.

Conflict of interest statement

S. Kubo, M. Saji, M. Izumo, Y. Watanabe, M. Amaki, Y. Nakajima, Y. Enta, S. Shirai, S. Mizuno, H. Bota, and M. Yamamoto are clinical proctors of transcatheter edge-to-edge repair for Abbott; and have received speaker fees from Abbott. M. Asami and K. Kodama have received speaker fees from Abbott. J. Yamaguchi is a clinical proctor of transcatheter edge-to-edge repair for Abbott; and has received a lecture fee and a scholarship donation from Abbott. Y. Ohno has received consultant, advisor, and speaker fees from Abbott. The other authors have no conflicts of interest relevant to the content of this article to declare.

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Supplementary data

Supplementary Figure 1. Serial changes in LVEF, stroke volume, and LV volumes in patients with secondary MR.

Supplementary Figure 2. Serial changes in LVEF, stroke volume, and LV volumes in patients with primary MR.

Supplementary Figure 3. Spline curve analysis of the primary endpoint according to worsening LVEF.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-23-01092

EuroIntervention
2024;20:1442-1446
DOI: 10.4244/EIJ-D-24-00158

Temporal trends in characteristics of patients undergoing transcatheter tricuspid edge-to-edge repair for tricuspid regurgitation

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This paper also includes supplementary data published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-24-00158

In the last decade, the management of tricuspid regurgitation (TR) has significantly changed owing to the emergence of novel interventional treatment approaches that have allowed safe and effective treatment of TR. While retrospective studies suggested a survival benefit of interventional TR treatment as compared to patients treated conservatively[1,2], the first randomised clinical trial that compared tricuspid transcatheter edge-to-edge repair (T-TEER) to optimal medical treatment, the TRILUMINATE Pivotal Trial, showed no differences at 1 year with regards to mortality or heart failure hospitalisation, albeit meeting its primary endpoint[3]. A possible explanation for this discrepancy might be attributable to a change in the characteristics of patients who are referred for T-TEER therapy nowadays, as compared to initial treatment experiences. Therefore, the aim of this study was to evaluate changes in the characteristics of patients referred for T-TEER and investigate their influence on outcomes.

Patients from the European Registry of Transcatheter Repair for Tricuspid Regurgitation (EuroTR) who underwent interventional therapy for symptomatic TR from 2016 until 2022 at 12 European study sites (Germany, Italy, Switzerland, Spain, France, and Sweden) were included, and a complete list of investigators can be found in **Supplementary Appendix 1**. T-TEER was performed using either the PASCAL device (Edwards Lifesciences) or the MitraClip/TriClip system (Abbott).

Data are given as median and corresponding interquartile range (IQR). Continuous variables were compared with the Kruskal-Wallis test. Categorical variables were compared using Fisher's exact test. Kaplan-Meier analyses were used to compare the survival in different subgroups; the log-rank test was used to test for differences. Patients were split into 3 time periods: (a) 2016 to 2018, (b) 2019 to 2020, and (c) 2021 to 2022.

The analysis comprised 1,031 patients, of whom 157 (15%) underwent T-TEER between 2016 and 2018, 386 (37%) between 2019 and 2020, and 488 (47%) between 2021 and 2022 **(Table 1)**. The rate of atrial fibrillation and/or flutter increased over time (p=0.017). Patients treated in the earlier time periods of T-TEER were younger (p<0.001), more symptomatic with a worse New York Heart Association Class (p=0.010), had higher rates of pleural effusion (p=0.028), and more ascites (p=0.081). The TRI-SCORE was lower in patients treated at later time periods (p=0.019). Biomarkers of organ function showed that renal function was comparable over different time periods, while markers of impaired liver function and congestion, as well as N-terminal pro-brain natriuretic peptide levels, were worse among patients treated in the earlier time periods.

All patients demonstrated at least moderate functional TR on echocardiography **(Central illustration)**, and TR severity increased over the specified time periods. In the later time periods, TR

SUBMITTED ON 17/02/2024 - REVISION RECEIVED ON 1st 19/05/2024 / 2nd 28/06/2024 / 3rd 04/08/2024 - ACCEPTED ON 06/08/2024

Table 1. Baseline characteristics.

Variables	Overall n=1,031	2016 to 2018 n=157	2019 to 2020 n=386	2021 to 2022 n=488	*p*-value
Age, years	80 (76, 83)	78 (75, 82)	79 (75, 82)	81 (77, 83)	<0.001
Female sex	533 (52)	80 (51)	193 (50)	260 (53)	0.6
BMI, kg/m^2	26 (23, 29) (n=1,020)	25 (23, 28)	26 (23, 29) (n=381)	26 (23, 29) (n=482)	0.6
Signs & symptoms					
NYHA Class					0.010
II	134 (13)	19 (12)	48 (12)	67 (14)	
III	753 (73)	102 (65)	290 (75)	361 (74)	
IV	142 (14) (n=1,029)	36 (23)	48 (12)	58 (12) (n=486)	
Ascites	152 (15) (n=1,025)	31 (20)	60 (16) (n=385)	61 (13) (n=483)	0.081
Pleural effusion	234 (28) (n=844)	56 (36)	81 (24) (n=336)	97 (28) (n=345)	0.028
Risk scores					
EuroSCORE II, %	4.8 (2.8, 8.1) (n=1,024)	4.8 (3.3, 7.9) (n=156)	4.6 (2.7, 8.4)	4.9 (2.7, 7.7) (n=482)	0.6
TRI-SCORE, points	6.0 (4.0, 7.0) (n=616)	6.0 (5.0, 7.0) (n=123)	6.0 (4.0, 7.0) (n=240)	5.0 (4.0, 7.0) (n=253)	0.019
Past medical history					
Chronic dialysis	41 (4.9) (n=845)	11 (7.0)	12 (3.6) (n=336)	18 (5.1) (n=352)	0.2
Diabetes	233 (28) (n=845)	45 (29)	97 (29) (n=336)	91 (26) (n=352)	0.6
Previous cardiac surgery	337 (33) (n=1,027)	53 (34)	131 (34) (n=385)	153 (32) (n=485)	0.7
Previous tricuspid valve surgery	7 (1.2) (n=576)	1 (1.2) (n=81)	4 (2.3) (n=173)	2 (0.6) (n=322)	0.2
Transtricuspid lead	299 (29)	42 (27)	123 (32)	134 (27)	0.3
Atrial fibrillation or flutter	917 (89) (n=1,029)	134 (85)	335 (87) (n=385)	448 (92) (n=487)	0.017
Lab charts					
Estimated glomerular filtration rate, ml/min/1.73 m^2	45 (33, 58) (n=1,027)	45 (32, 60) (n=156)	43 (33, 58) (n=384)	45 (32, 58) (n=487)	0.7
Bilirubin, mg/dl	0.83 (0.60, 1.29) (n=830)	0.99 (0.63, 1.30) (n=139)	0.80 (0.59, 1.20) (n=296)	0.80 (0.60, 1.33) (n=395)	0.079
AST, U/l	27 (22, 34) (n=954)	29 (24, 37) (n=153)	27 (23, 35) (n=369)	26 (20, 33) (n=432)	<0.001
ALT, U/l	18 (13, 25) (n=879)	19 (15, 26) (n=148)	19 (14, 25) (n=327)	17 (11, 23) (n=404)	<0.001
GGT, U/l	95 (50, 189) (n=875)	98 (67, 196) (n=143)	104 (55, 194) (n=347)	88 (44, 179) (n=385)	0.014
NT-proBNP, pg/ml	2,268 (1,247, 4,606) (n=971)	3,038 (1,471, 6,258) (n=145)	2,082 (1,213, 4,553) (n=371)	2,350 (1,231, 4,085) (n=455)	0.008
Echocardiography					
LVEF, %	55 (47, 60) (n=979)	56 (46, 63)	55 (47, 60) (n=379)	55 (48, 60) (n=443)	0.5
TR EROA, cm^2	0.54 (0.40, 0.75) (n=888)	0.50 (0.40, 0.70) (n=156)	0.50 (0.40, 0.70) (n=342)	0.59 (0.41, 0.80) (n= 390)	<0.001
TR regurgitant volume, ml	45 (35, 59) (n=847)	42 (32, 54) (n=154)	42 (33, 54) (n=325)	49 (38, 66) (n=368)	<0.001
TR vena contracta, mm	10.0 (8.0, 14.0) (n=939)	9.0 (8.0, 12.0)	10.0 (7.9, 12.0) (n=371)	11.0 (8.0, 14.0) (n=411)	<0.001
RV mid-ventricular diameter, mm	41 (36, 47) (n=810)	42 (37, 47) (n=149)	43 (37, 49) (n=295)	39 (33, 45) (n=366)	<0.001
TV annular diameter, mm	44 (39, 50) (n=912)	46 (43, 51) (n=153)	46 (41, 51) (n=340)	42 (37, 48) (n=419)	<0.001

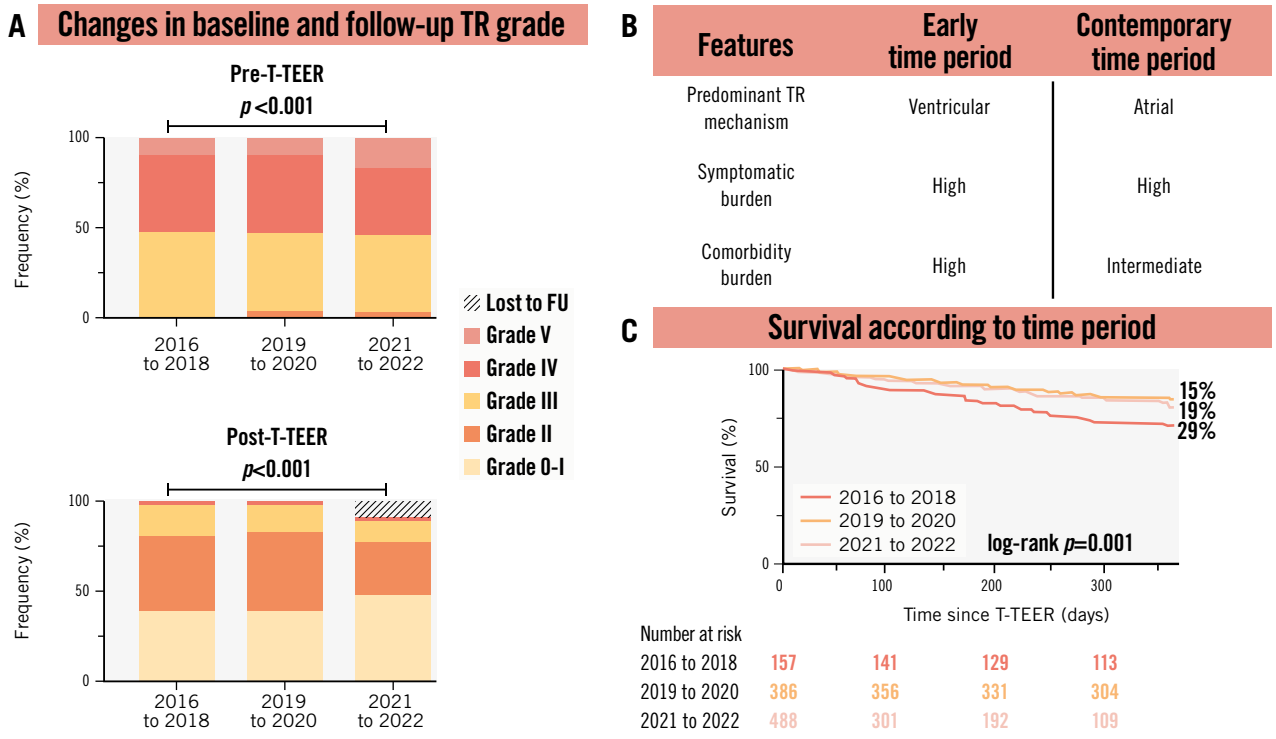
Table 1. Baseline characteristics (cont'd).

Variables	Overall n=1,031	2016 to 2018 n=157	2019 to 2020 n=386	2021 to 2022 n=488	*p*-value
TAPSE, mm	17.0 (14.0, 20.0) (n=967)	16.0 (13.0, 21.0)	17.0 (14.0, 20.0) (n=374)	17.0 (14.0, 20.0) (n=436)	0.15
Estimated pulmonary artery pressure, mmHg	41 (33, 51) (n=958)	45 (34, 54)	41 (34, 52) (n=376)	41 (32, 49) (n=425)	0.013
TAPSE/sPAP, mm/mmHg	0.41 (0.31, 0.52) (n=937)	0.39 (0.29, 0.47)	0.40 (0.30, 0.50) (n=367)	0.43 (0.32, 0.56) (n=413)	0.002
Coaptation gap, mm	6.0 (4.0, 8.0) (n=692)	5.0 (4.0, 7.0) (n=140)	6.2 (4.5, 8.5) (n=252)	5.3 (4.0, 7.0) (n=300)	<0.001
TV tenting height, mm	7.0 (6.0, 10.0) (n=522)	9.0 (7.0, 11.9) (n=94)	7.0 (5.0, 9.0) (n=182)	7.0 (5.8, 9.0) (n=246)	<0.001
TV tenting area, cm²	1.70 (1.20, 2.40) (n=472)	2.00 (1.30, 2.86) (n=93)	1.60 (1.15, 2.14) (n=156)	1.72 (1.26, 2.52) (n=223)	0.015
Atrial TR	445 (47) (n=942)	62 (40) (n=157)	167 (45) (n=369)	216 (52) (n=416)	0.018

Data are given as median (IQR) or n (%). In case of missing variables, the number of patients with available data is given in parentheses. ALT: alanine transaminase; AST: aspartate aminotransferase; BMI: body mass index; EROA: effective regurgitant orifice area; EuroSCORE: European System for Cardiac Operative Risk Evaluation; GGT: gamma-glutamyl tranferase; IQR: interquartile range; LVEF: left ventricular ejection fraction; NT-proBNP: N-terminal pro-brain natriuretic peptide; NYHA: New York Heart Association; RV: right ventricular; sPAP: systolic pulmonary artery pressure; TAPSE: tricuspid annular plane systolic excursion; TR: tricuspid regurgitation; TV: tricuspid valve

EuroIntervention — Central Illustration

Temporal trends in characteristics of patients undergoing tricuspid transcatheter edge-to-edge repair for tricuspid regurgitation.



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A) Changes in tricuspid regurgitation grades according to the timepoint of treatment, where pre-T-TEER refers to TR grades immediately before T-TEER, and post-T-TEER refers to TR grades after T-TEER. Kruskal-Wallis test for pre- and postprocedural TR grade: p<0.001 and p=0.001, respectively. B) Comparison of TR features between early and contemporary time periods. C) Changes in survival rates according to the timepoint of treatment. FU: follow-up; TR: tricuspid regurgitation; T-TEER: tricuspid transcatheter edge-to-edge repair

effective regurgitant orifice area (p<0.001), regurgitant volume (p<0.001), and vena contracta (p<0.001) were higher, while right ventricular and tricuspid annulus dimension parameters were smaller (p<0.001). The size of the coaptation gap increased in patients treated at later timepoints (p<0.001), but interestingly markers of tricuspid leaflet displacement, like tenting height and area, were smaller in these patients (p<0.001 for both). In line with this, the incidence of atrial TR, as previously defined[4], increased over the included time periods.

The intraprocedural success rates of the procedures (50% MitraClip/TriClip, 50% PASCAL), according to the Tricuspid Valve Academic Research Consortium criteria[5], did not significantly differ between the time periods (a: 82% vs b: 83% vs c: 85%; p=0.36). Patients treated in the earliest period had a higher mean number of devices (2.1±0.7) compared to those treated in 2019 to 2020 (1.8±0.6) and 2021 to 2022 (1.9±0.7) (p<0.001).

During the 1-year follow-up (median follow-up 308 [IQR 126 to 365] days), 149 patients (15%) died. Mortality significantly decreased over time and was highest in patients treated between 2016 and 2018 (Kaplan-Meier curve estimated 1-year mortality 29%). Outcomes were comparable for patients treated from 2019 to 2020 and 2021 to 2022 (Kaplan-Meier curve estimated 1-year mortality of 15% and 19%, respectively; log-rank p=0.001) **(Central illustration)**.

This is the first study that has investigated changes in the baseline characteristics of patients undergoing T-TEER in over 1,000 patients since the establishment of the treatment in 2016 until 2022. The main findings of the study were that there has been a significant shift in the baseline characteristics of patients undergoing T-TEER, with patients presenting with fewer symptoms and less systemic involvement in recent years. Despite this, TR severity has increased over time, but 1-year mortality rates have decreased.

TR has been considered to be associated with an adverse prognosis, with high 1-year mortality rates ranging from 10-20%, in T-TEER patients[1,2,6]. This was put into question by one of the lowest ever reported 1-year mortality rates for TR in the TRILUMINATE Pivotal study of 9.4%. Our study also observed a decrease in mortality from 29% to 15-19% over time, despite increased TR severity. This improvement might be attributable to greater awareness of and earlier intervention for TR. Further technological advances have successfully pushed the boundaries for the treatment of more severe TR. The shift from a ventricular to an atrial phenotype of TR over time, which is indicated by more severe TR with concomitant decreases in tethering area and height, might also have contributed to better outcomes[4,6].

In summary, T-TEER patient profiles have shifted over time from a ventricular TR phenotype with high systemic disease burden to an atrial TR phenotype with higher TR severity but fewer systemic issues and possibly earlier disease stage. This shift should be considered in clinical trials, as decreasing 1-year mortality rates in recent TR cohorts could impact the statistical power needed to show treatment differences in clinical endpoints.

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Conflict of interest statement

K.-P. Kresoja reports travel expenses from Edwards Lifesciences. L. Stolz received speaker honoraria from Edwards Lifesciences. W. Rottbauer received speaker honoraria from Edwards Lifesciences and Abbott. P. Denti served as a consultant for InnovHeart, Pi-Cardia, HVR Cardio, and Approxima; and received speaker honoraria from Abbott and Edwards Lifesciences. T. Rassaf received speaker honoraria and consulting fees from AstraZeneca, Bayer, Pfizer, and Daiichi Sankyo. M. Barreiro-Perez received speaker fees from Abbott, Edwards Lifesciences, and Venus Medtech. M. Adamo has received consulting fees in the last three years from Abbott and Edwards Lifesciences. R.-S. von Bardeleben has received institutional grants and served as speaker to Abbott and Edwards Lifesciences. S. Toggweiler has received personal honoraria from Medtronic, Boston Scientific, Biosensors, Abbott, Medira, Shockwave Medical, Teleflex, atHeart Medical, Cardiac Dimensions, Polares Medical, Amarin, Sanofi, AstraZeneca, ReCor Medical, and Daiichi Sankyo; has received institutional research grants from Edwards Lifesciences, Boston Scientific, Fumedica, Novartis, and Boehringer Ingelheim; and holds equity in Hi-D Imaging. M. Metra has received consulting fees in the last three

years from Abbott, AstraZeneca, Bayer, Boehringer Ingelheim, Edwards Lifesciences, and Roche Diagnostics. T. Geisler received speaker honoraria/research grants from AstraZeneca, Bayer, Bristol-Myers Squibb/Pfizer, Ferrer/Chiesi, Medtronic, and Edwards Lifesciences, but none of these were related to this study. R. Estévez-Loureiro received speaker fees from Abbott, Edwards Lifesciences, Boston Scientific, and Venus Medtech. P. Luedike received speaker honoraria and consulting fees from AstraZeneca, Bayer, Pfizer, and Edwards Lifesciences; and research honoraria from Edwards Lifesciences. F. Maisano received grant and/or research institutional support from Abbott, Medtronic, Edwards Lifesciences, Biotronik, Boston Scientific, NVT, Terumo, and Venus Medtech; consulting fees, honoraria personal and institutional from Abbott, Medtronic, Edwards Lifesciences, Xeltis, Cardiovalve, Occlufit, Simulands, Mtex, Venus Medtech, Squadra, and Valgen; royalty income/IP rights from Edwards Lifesciences; and is a shareholder (including share options) of Magenta, Transseptal Solutions, and 4Tech. F. Praz received travel expenses from Edwards Lifesciences, Abbott, Polares Medical, Medira, and Siemens Healthineers. M. Kessler received speaker honoraria from Edwards Lifesciences and Abbott. D. Kalbacher has received personal fees from Abbott, Edwards Lifesciences, and Pi-Cardia. V. Rudolph received research grants from Abbott, Boston Scientific, and Edwards Lifesciences. C. Iliadis received consultant fees and travel expenses from Abbott and Edwards Lifesciences. J. Hausleiter reports research grant support and speaker honoraria from Edwards Lifesciences. P. Lurz received institutional grants from Edwards Lifesciences and honoraria from Innoventric. The other authors have no relevant conflicts of interest to declare.

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Supplementary data

Supplementary Appendix 1. Investigators.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-24-00158

EAPCI at PCR London Valves 2024

PCR London Valves – an official course of the EAPCI – is the largest worldwide course focusing on the care of patients with valvular heart disease and percutaneous valvular intervention. The programme is innovative, hands on and designed for the entire Heart Team: interventional cardiologists, cardiac surgeons, interventional imagers, nurses and allied professionals.

PCR London Valves 2024 will take place in November, marking the first anniversary of the new EAPCI membership. If you have any doubts regarding your member status, please drop by the EAPCI stand to update your membership and learn about the many benefits associated with being an EAPCI member. EAPCI members benefit from preferential registration fees for EuroPCR and PCR London Valves, receive a discount on the print version of *EuroIntervention* journal which includes free access to the online version, plus a discount on the *PCR-EAPCI Textbook*. Being a member of the EAPCI community opens up many opportunities to become involved in EAPCI activities, including scientific documents, journal clubs, webinars and a new educational path we are designing for our members. Membership also opens up the opportunity to apply for fellowship grants, along with coaching and mentoring programmes.

At PCR London Valves, many EAPCI members are involved in presenting cases, participating in sessions and presenting abstracts. An EAPCI session chaired by EAPCI President Alaide Chieffo and President-Elect Martine Gilard – entitled "How to implement a successful structural intervention programme" – will take place on Tuesday, 26 November from 08:30 to 09:30. This session is dedicated to the presentation and discussion of the recently published "Percutaneous Valvular and Structural Heart Disease Interventions. 2024 Core Curriculum of the European Association of Percutaneous Cardiovascular Interventions (EAPCI) of the ESC in collaboration with the European Association of Cardiovascular Imaging (EACVI) and the Cardiovascular Surgery Working Group (WG CVS) of the European Society of Cardiology." Using a case-based discussion format, this promises to be a lively and interactive session, highlighting the requirements and challenges of developing a high-quality, standardised training programme in structural and valvular interventions and maintaining optimal patient care. There are also numerous sessions dedicated to nurses and allied professionals, the hands-on learning and simulation sessions always being well received.

Finally, young interventional cardiologists will be awarded their EAPCI Fellowship Grants at a ceremony in the main arena. The EAPCI Fellowship Grants support interventional cardiology fellows to undergo a year-long period of training outside of their own country. The opportunity to train in high-volume centres using techniques and equipment not necessarily available in the recipients' home countries allows them to gain key skills to take back to their home countries and improve clinical care in the future. These grants require collaboration with industry; companies that provide economic support are contributing to shaping the future of cardiovascular interventions, predominantly in countries with limited training opportunities. Congratulations to the awardees.

The 2024 edition of PCR London Valves will undoubtedly be a highly educational event which will provide our community with an opportunity to come together, share opinions and learn from each other. We look forward to seeing those of you attending in person.

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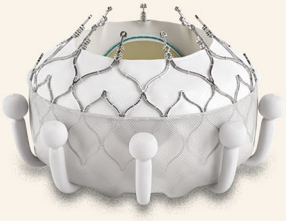

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