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SNAPSHOT

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An expert review on 3D intracardiac echocardiography; biomimetic balloon-expandable THV in small aortic annuli; intra-annular TAVI in small aortic annuli; 5-year outcomes of transapical transcatheter mitral valve replacement; impact of coronary dominance on left main PCI prognosis; 5-year outcomes of the COMPARE trial; distal foot artery access compression; the retrieval of a stuck TAVI device; and more

Once again, EuroIntervention brings you an issue packed with study outcomes that not only push our thinking to evolve but help us to keep our patients at the centre of our decision-making.

3D ICE in structural heart disease

With the importance of three-dimensional intracardiac echocardiography (ICE) on the rise, **Sergio Berti, Ralph Stephan von Bardeleben and colleagues** review the most recent technical and procedural developments in a technology that is becoming integral to structural heart disease (SHD). This expert review covers the evolution of imaging in SHD, the current probes available for use, and training and workflow within different therapeutic subsets.

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Biomimetic balloon-expandable THV in small aortic annuli

Ole De Backer, Vinayak N. Bapat and colleagues report the 30-day procedural, clinical, and haemodynamic outcomes of the DurAVR transcatheter heart valve (THV) in patients with small aortic annuli. This novel balloon-expandable valve with a single-piece biomimetic leaflet design was associated with favourable haemodynamic outcomes and high technical and device success. This article is accompanied by an editorial from **Francesco Maisano.**

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Intra-annular TAVI in small aortic annuli

In a subanalysis of the NAVULTRA registry, **Stefano Cannata, Azeem Latib and colleagues** compare clinical outcomes and device performance of the self-expanding Navitor THV and the balloon-expandable SAPIEN 3 Ultra THV in patients with aortic stenosis and small aortic annuli undergoing transcatheter aortic valve implantation (TAVI). Despite comparable 1-year clinical outcomes, the Navitor demonstrated superior haemodynamic performance but higher rates of mild paravalvular leak and new permanent pacemaker implantation.

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Intrepid transapical TMVR 5-year outcomes

In examining the 5-year outcomes of the Intrepid transapical transcatheter mitral valve replacement (TMVR) system used in selected patients with symptomatic ≥moderate-severe mitral regurgitation (MR), **Gilbert H.L. Tang, Michael J. Reardon and colleagues** confirmed sustained MR elimination, durable haemodynamic valve performance, and improved functional status. **Marianna Adamo and Elisa Pezzola** contribute an editorial on this article.

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Also in this issue

Yingyang Geng, Lei Song and colleagues on the impact of coronary dominance on left main percutaneous coronary intervention (PCI) prognosis; **Tim Wittig, Sabine Steiner and colleagues** on the 5-year results of the COMPARE trial; **Róbert Bellavics, Zoltán Ruzsa and colleagues** on distal foot artery access compression in lower limb angioplasty; and more

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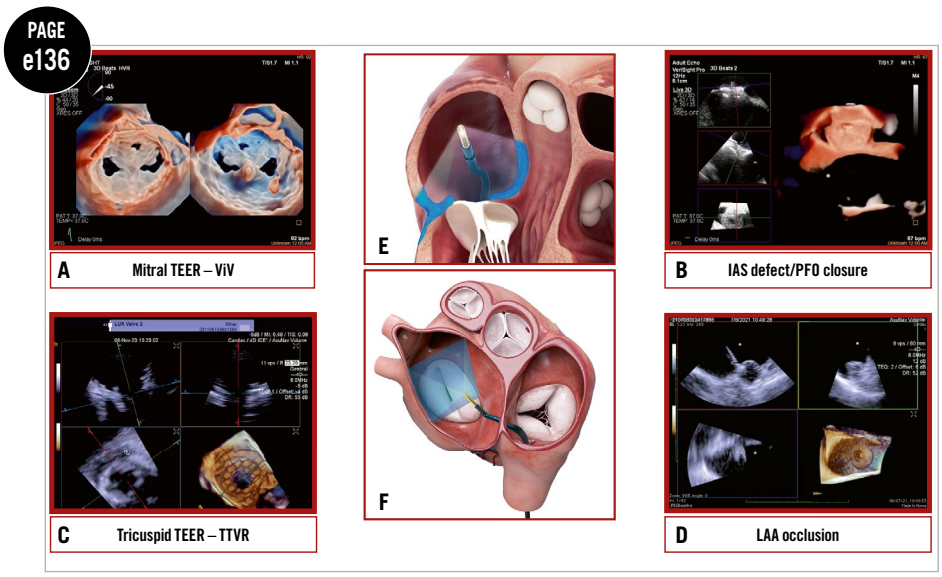

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Sergio Berti, Andreina D'Agostino, Ole De Backer, Edwin Ho, Felix Kreidel, Azeem Latib, Massimiliano Mariani, Fabien Praz, Nina C. Wunderlich, Ralph Stephan von Bardeleben
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EDITORIAL

From gradients to lifetime strategy: rethinking TAVI choice in small aortic roots

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Over the past two decades, transcatheter aortic valve implantation (TAVI) has transformed the management of aortic stenosis and has become the emblem of structural heart innovation. What started as a rescue option for inoperable patients is now a mainstream therapy across the entire risk spectrum[1]. With expanding indications, particularly in lower-risk patients with an expected survival well beyond 10 years, a natural question arises: is the innovation cycle in TAVI complete, or are we just entering a new phase? Can what has been transformational be further refined by incremental innovation?

In the early TAVI era, success meant crossing the valve, avoiding catastrophes and achieving an acceptable gradient. Today, this is no longer enough. For both TAVI and surgical aortic valve replacement (SAVR) operators, the index valve procedure must be planned as the first step of a lifelong strategy. Short-term safety still matters enormously and depends on three elements: patient anatomy and comorbidities, device selection, and operator performance. But current aortic interventions should be planned and performed with a long-term perspective: prosthesis durability, coronary access, feasibility and safety of redo-TAVI or surgical explant, and the impact of prosthesis-patient mismatch (PPM) or conduction disturbances on lifetime management. The device we choose today determines not only early haemodynamics but also what we will be able to offer when the valve inevitably degenerates.

This broader view is reinforced by changes both upstream (timely intervention) and downstream (better follow-up and management) of the procedure. In this continuum, device design remains crucial: it is not a technical detail; it is a major determinant of future options.

Interventions in small aortic annuli remain a challenge. SAVR in this setting frequently yields high postoperative gradients, small effective orifice areas, and a high rate of PPM, all associated with higher mortality, more heart failure hospitalisations, and accelerated bioprosthetic degeneration[2,3]. TAVI is not the final solution; in fact, small annuli magnify the trade-offs between different device platforms. A recent trial did not find different clinical outcomes between TAVI and SAVR in patients with small aortic annuli[4].

Registry and randomised data have consistently shown that in small annuli, supra-annular self-expanding valves (SEVs) tend to provide lower gradients and fewer PPM than intra-annular balloon-expandable valve (BEV) platforms but at the cost of more paravalvular leaks, and higher rates of permanent pacemaker implantation. The SMART trial[5] and TAVI-SMALL[6] registries have made many operators favour self-expanding valves in this anatomy when long-term haemodynamics and durability are perceived as the priority, particularly in younger patients. Conversely, BEVs are often preferred when paravalvular leak, coronary access, or precise positioning are the main concerns, accepting higher gradients as the price to pay.

In this issue of EuroIntervention, De Backer and colleagues[7] challenge the previous dichotomy, where, in small roots, the choice had been "better gradients" versus "more controlled implant and fewer pacemakers".

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The DurAVR transcatheter heart valve (Anteris Technologies) introduces two relevant concepts: a short-frame balloon-expandable platform and a single-piece biomimetic leaflet made from bovine pericardium treated with an anticalcification

process. The leaflet is moulded to mimic native aortic cusp geometry, with long coaptation and the promise of more physiological opening and closing, more laminar ascending aortic flow and, ultimately, better durability.

In their pooled analysis of 100 patients with small annuli treated with the "small" DurAVR size, the authors report Valve Academic Research Consortium 3 technical success of 93% overall, and 100% in the last 50 cases; with no deaths and 2% stroke at 30 days. Haemodynamic performance was outstanding with a mean gradient of 8.2±3.1 mmHg and a mean effective orifice area of 2.2±0.3 cm^2. This resulted in a moderate or severe PPM in only 3%. Such outcomes were achieved with a very reasonable permanent pacemaker rate of 6%.

For a balloon-expandable valve in a small annulus cohort, these figures are striking. The profile is SEV-like haemodynamics with BEV-like control and a low pacemaker rate. The short frame with large open cells and the possibility of commissural alignment may also help preserve coronary access and future TAVI-in-TAVI options. All these features are crucial in small roots, where the risk of sinus sequestration and coronary obstruction during redo procedures is intrinsically higher.

Of course, this is early, non-randomised, industry-sponsored evidence in a relatively small and highly selected population, with limited follow-up. But as a proof of concept, it suggests that thoughtful, "incremental" device innovation can soften, if not fully erase, the historical BEV-SEV trade-off.

A large number of new TAVI devices are entering the market, with unique features[8]. More options should reinforce an anatomy and lifetime-based decision algorithm rather than promote device enthusiasm. For older, frailer patients with limited life expectancy, well-established TAVI platforms (either SEV or BEV) already offer excellent outcomes, and the incremental benefits of a novel valve are less clear. On the other hand, there are several unmet needs including the management of small aortic roots, repeat procedures, longer durability, coronary access and several other challenges that will benefit from future innovation in the field. These results should push both surgeons and interventionalists to discuss lifetime management upfront: mechanical versus bioprosthetic choice, aortic root enlargement versus TAVI in very small roots, the likelihood and sequence of future redo procedures, and how each device option aligns with the patient's age, comorbidities and preferences.

Innovation in TAVI is far from finished: there is still a need for refinements in valve design and material science to improve durability and haemodynamics, along with the introduction of smart devices and advanced pharma integration to improve long-term clinical outcomes. Outcomes in the future can be improved by upstream strategies for early detection of disease and timely treatment, as well as innovative gene and ribonucleic acid therapies to delay or stop progression of the disease. Artificial intelligence in all its possible declinations, from big data management, real data online contributing to real-world decision-making, to robotics, automation, and real-time copiloting will flood our field and improve practice.

Incremental innovation will pursue the objective of better lifetime management: the key question is no longer "which valve gives the lowest gradient today?" but rather "which strategy keeps the most doors open for this patient over the next 20 or 30 years?" Innovative new devices like the biomimetic balloon-expandable DurAVR may become valuable tools in that strategy, provided we remain rigorous, cautious, and patient-centred as we test their promise.

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EDITORIAL

Durability of transcatheter mitral valve replacement: another step forward

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Transcatheter therapies for mitral regurgitation (MR) enable the treatment of patients who are unsuitable or at high risk for surgery. Transcatheter edge-to-edge repair (TEER) is the first-line therapy in patients with secondary ventricular MR, but it is also indicated for patients with primary MR and atrial secondary MR[1]. However, the use of TEER remains limited by some unfavourable anatomical characteristics (i.e., a very short posterior leaflet, small valve area, complex anatomies). Furthermore, suboptimal TEER results are known to be strongly related with worse clinical outcomes[2]. Thus, careful anatomical selection and availability of dedicated transcatheter mitral valve replacement (TMVR) systems are crucial in the management of high-risk patients with MR[2,3].

In the last decade, the development of TMVR has been slower than anticipated because of several challenges: delivery catheter sizing, anchoring design, risk of left ventricular outflow tract (LVOT) obstruction, thrombogenicity, and durability.

Today, we are finally turning the corner. Advances in technologies have led to the development of safe and effective devices. Currently, two prostheses are approved for commercial use in Europe (Tendyne [Abbott] and SAPIEN M3 [Edwards Lifesciences]), while several additional systems are under clinical evaluation for regulatory approval. Among these, the Intrepid valve (Medtronic) represents a promising TMVR technology.

In this issue of EuroIntervention, Tang and colleagues[4] report the 5-year outcomes from the Intrepid TMVR global Pilot Study, a multicentre, prospective, single-arm study including 95 patients who received the early-generation Intrepid transapical (TA) system between 2015 and 2019. These results are highly relevant, representing the longest follow-up currently available for any TMVR device.

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The study reported a 5-year all-cause mortality rate of 66.7% and a 5-year heart failure hospitalisation rate of 55.4%. These high rates of events can be easily explained by the TA access used and the comorbidity burden of the population included. The high rates of 30-day and 1-year mortality (18.9% and 31.9%, respectively) are in line with the Expanded Clinical Study of the Tendyne Mitral Valve System, which also utilised TA access, where 90-day and 1-year all-cause mortality rates were 16.2% and 31.8%, respectively[5]. The 5-year event rates are in line with randomised control trials and registries including patients with secondary MR undergoing TEER[6,7]. Indeed, the majority of patients had secondary MR (78.7%) and left ventricular dysfunction (70.2%). Results from the Intrepid TMVR Early Feasibility Study using the new transfemoral-transseptal delivery approach reported very low 30-day (0%) and 1-year (6.7%) all-cause mortality[8]. Similarly, the SAPIEN M3 system, the only transfemoral-transseptal TMVR device with a European Conformity (CE) mark, reported low 30-day and 1-year mortality rates in the ENCIRCLE Trial (0.7% and 13.9%, respectively)[9]. Interestingly, the populations included in the Intrepid TF and ENCIRCLE trials were slightly different compared with those included in the Intrepid TA and Tendyne studies (lower proportion of secondary MR and better left ventricular ejection fraction in the former two) **(Table 1)**. Thus, moving towards less invasive approaches and optimising patient selection for TMVR are crucial steps to improve clinical outcome. In addition, the adoption of

Table 1. Baseline characteristics and outcomes at the longest follow-up available after TMVR.

	INTREPID TA global Pilot Study[4]	INTREPID TF Early Feasibility Study[11]	TENDYNE Expanded Clinical Study[5,12]	SAPIEN M3 ENCIRCLE Trial[9]
Baseline characteristics				
Number of patients	95	33	191	299
Age, years	74.0±9.2	78.6±7.4	74.1±8.0	77 (70-82)
STS, %	6.5±4.8	5.3±2.8	7.7±6.6	6.6±4.1
NYHA III/IV	88.5 (84)	69.7 (23)	70.2 (134)	71 (213)
Secondary MR	78.7 (74)	39.4 (13)	88.5 (169)	58 (173)
LVEF, %	44.0 (36.0-55.0)	50.0 (45.0-60.9)	44.7±8.8	49.5 (38.7-58.1)
Longest available follow-up	**5 years**	**2 years**	**3 years**	**1 year**
All-cause mortality	66.7 (62)	16.8 (5)	51.3 (93)	13.9 (40)
CV mortality	51.6 (43)	10.2 (3)	45.6 (82)	8.9 (25)
Non-CV mortality	31.4 (19)	6.6 (2)	5.7 (11)	5.0 (15)
HFH	55.4 (37)	25.7 (7)	35.1 (67)	16.7 (47)
NYHA Class I/II	84.6 (26)	80 (16)	80.6 (54)	88 (205)
Valve thrombosis	12.2 (6)	7.4 (2)	5.8 (11)	6.7 (19)
Disabling stroke	9.1 (6)	0 (0)	4.7 (9)	3.9 (11)
Haemolysis	0 (0)	-	-	7.1 (21)
Endocarditis	4.6 (3)	3.4 (1)	6.3 (12)	1.5 (4)
Major bleeding events	32.5 (27)	35.1 (11)	27.7 (53)	18.5 (52)
No or mild residual MR	100 (21)	100 (20)	100 (60)	95.7 (222)
Mean MV gradient, mmHg	3.7 (3.0-4.7)	3.9 (3.1-5.5)	3.8±1.5	5.5
PVL	0 (0)	0 (0)	8.9 (17)	3.8 (11)
LVOT peak gradient, mmHg	6.0 (3.8-8.8)	8.4 (7.4-11.1)	-	-

Dichotomic variables are expressed as % (n). Continuous variables are expressed as mean±standard deviation or median (IQR). CV: cardiovascular; HFH: heart failure hospitalisation; IQR: interquartile range; LVEF: left ventricular ejection fraction; LVOT: left ventricular outflow tract; MR: mitral regurgitation; MV: mitral valve; NYHA: New York Heart Association; PVL: paravalvular leak; STS: Society of Thoracic Surgeons; TA: transapical; TF: transfemoral; TMVR: transcatheter mitral valve replacement

a holistic approach with the aim of reducing the residual risk of these complex patients may be helpful[1,2]. Notably, current European guidelines report TMVR as a possible therapeutic option only for patients deemed unsuitable for surgery or TEER, with primary MR or mixed mitral valve disease or mitral stenosis, but not in those with secondary MR[1].

Beyond patient selection and overall outcomes, a major result reported by Tang et al is the Intrepid valve performance at 5 years, since evidence on long-term durability for any TMVR technology remains limited to case reports[10].

The Intrepid TA TMVR system demonstrated sustained reduction of MR, durable valve function, and a low incidence of haemodynamic valve deterioration. Among 5-year survivors, all patients remained free from residual MR greater than mild (100%), with a mean transmitral gradient of 3.6 mmHg. No significant paravalvular leak (PVL) was observed. Of note, mitral annular calcification (MAC) was an exclusion criterion, and results from the MAC cohort of the APOLLO-EU study (ClinicalTrials.gov: NCT05496998) are awaited to confirm this low rate of PVL in more complex anatomies. The incidence of moderate haemodynamic valve deterioration was 1.4% (1/69), and no cases of severe deterioration were reported at 5 years. No other TMVR studies to date have provided such detailed information on long-term performance.

A stable LVOT peak gradient was maintained at follow-up (6 mmHg), likely facilitated by the lack of left ventricular reverse remodelling. Indeed, no significant changes in left ventricular dimensions or stroke volume were observed.

Device thrombosis with sequelae (heart failure hospitalisation or embolism) occurred in 1.95 per 100 patient-years (5 events in total, 2 within 1 year). These events were associated with echocardiographic evidence of mitral stenosis. Almost all of these patients received suboptimal antithrombotic therapy (clopidogrel or warfarin with no target international normalised ratio values) and were managed successfully by intensifying or initiating anticoagulation. Thus, as well stated by the authors, an appropriate anticoagulation regimen is of paramount importance to ensure a decreased risk of device thrombosis.

Endocarditis occurred in 1.17 per 100 patient-years, in line with data on transcatheter aortic valve interventions.

Unfortunately, it must be acknowledged that the number of 5-year survivors with available echocardiographic data was approximately 20, only slightly more than a case series. Thus, further data are needed to confirm the favourable long-term performance of Intrepid as well as to establish the durability of other platforms. However, as already stated, the results are unique; the events were centrally adjudicated and echocardiographic images centrally analysed; and last but

not least, the Intrepid TMVR device, both early and current generation, consists of the same valve design. It is a self-expanding nitinol dual-stent design: the inner stent frame houses a 27 mm trileaflet bovine pericardial valve, while the outer stent anchors the prosthesis to the native mitral anatomy. Therefore, durability outcomes from the early-generation study can reasonably be considered applicable to the current-generation device.

These preliminary data are promising and reassuring, and another step forward has definitely been taken towards increased knowledge in the TMVR field.

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EXPERT REVIEW

Three-dimensional intracardiac echocardiography in structural heart disease interventions

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ABSTRACT

Transcatheter heart interventions are expanding, and structural procedures are becoming more complex. This makes detailed visualisation and characterisation of cardiac anatomy and pathology increasingly important. As a result, there is a growing interest in interventional imaging for procedural guidance. Specifically, there is an increasing interest in using intracardiac echocardiography (ICE) as a complementary or alternative tool to transoesophageal echocardiography. Furthermore, new-generation three-dimensional matrix array ICE probes provide the possibility of obtaining multiplanar reconstruction imaging, playing a crucial role in structural heart interventions. To date, we still need guidelines that summarise the technical details of the most used ICE probes and that standardise procedure protocols. The purpose of this expert review is to provide an overview of ICE technology, describe the technical characteristics of the available probes, and present a review by a group of experts on their use in guiding structural heart interventions based on global clinical experience.

In recent years, indications for percutaneous structural heart disease (SHD) interventions have expanded significantly, and transcatheter procedures have become increasingly complex. Over the past decade, intraprocedural two-dimensional (2D) and three-dimensional (3D) transoesophageal echocardiography (TOE) have been widely used to assist in percutaneous SHD interventions. The increasing complexity of SHD procedures makes accurate visualisation and characterisation of the morphology and pathology of anatomical target structures mandatory for successful procedures. As a result, there is increasing interest in the use of new imaging techniques, particularly intracardiac echocardiography (ICE), for guiding procedures. With its high image resolution, close placement to the target area or device, and potential to perform procedures with local anaesthesia only, ICE is an intriguing alternative to TOE, which requires general sedation[1]. In high-volume centres, procedure duration and length of hospital stay also can be shortened by using ICE without significantly increasing the periprocedural complication rate[1-5]. With the introduction of 3D ICE probes, many of the limitations associated with conventional TOE can be overcome. These 3D capabilities allow for improved visualisation of dynamic cardiac structures and better positioning of catheters and devices during interventional procedures **(Central illustration)**. Data have shown that ICE can be safely used for guiding ablation of cardiac arrhythmias, atrial septal defect (ASD) closure, left atrial appendage occlusion (LAAO), transcatheter aortic valve implantation[6,7], mitral and tricuspid transcatheter edge-to-edge repair (M-TEER and T-TEER, respectively), transcatheter tricuspid valve replacement (TTVR), and percutaneous pulmonary valve replacement[1,8]. However, there is no universally accepted standard for ICE-guided imaging across different SHD interventions. This underscores the need for education and training to ensure optimal and effective use of ICE during transcatheter interventions. This expert review aims to present the latest technical developments of ICE probes and to provide standardised approaches for different transcatheter procedures based on current clinical experience.

KEYWORDS: 3D ICE; intracardiac echocardiography; intraprocedural imaging; structural heart disease; transcatheter intervention

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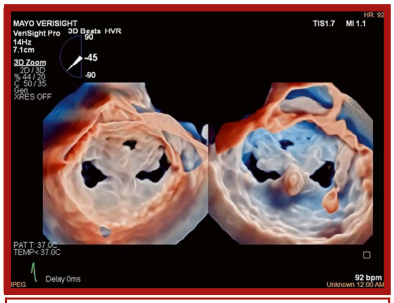
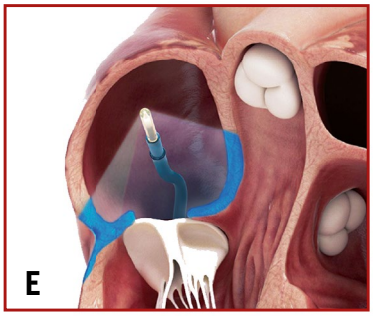
EuroIntervention — Central Illustration

Current landscapes on 3D ICE utilisation.



A Mitral TEER – ViV



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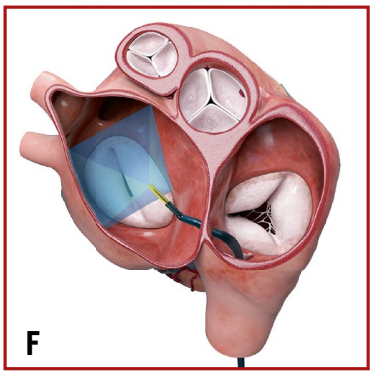

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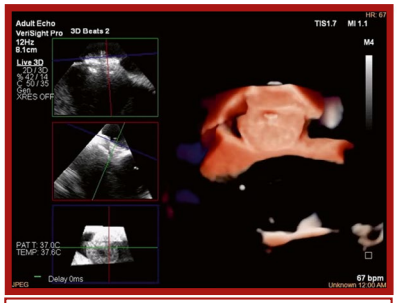
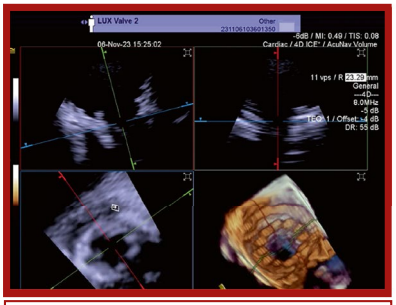
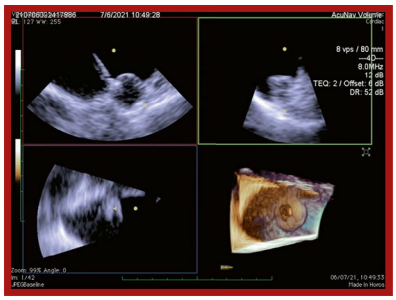


B IAS defect/PFO closure



C Tricuspid TEER – TTVR



D LAA occlusion

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An overview of the key structural heart interventions that increasingly utilise 3D ICE: (A) mitral TEER/ViV; (B) IAS defect/ PFO closure; (C) Tricuspid TEER/TTVR; (D) LAAO. E) An illustration of the ICE probe's position during imaging of the tricuspid valve. F) An illustration of the ICE probe's position during imaging of the mitral valve. 3D: three-dimensional; ICE: intracardiac echocardiography; IAS: interatrial septum; LAAO: left atrial appendage occlusion; TEER: transcatheter edge-to-edge repair; TTVR: transcatheter tricuspid valve replacement; ViV: valve-in-valve

Evolution of imaging for SHD interventions

TOE

Cardiovascular imaging modalities, such as TOE, are valuable tools for diagnosing and treating SHD[9]. The integration of 3D techniques, such as multiplane imaging, live multiplanar reconstruction (MPR), and photorealistic imaging in TOE, has been proven to be extremely beneficial[10]. Multiplane imaging uses simultaneous views of separate planes and unlimited combinations of tilting and rotation to visualise cardiac structures. Live 3D MPR enables real-time (RT) 3D visualisation of structures from multiple angles, which reduces parallax errors and provides views that are otherwise impossible to achieve with conventional 2D imaging. This enables a more precise and efficient analysis of the anatomical structures and their relationships with neighbouring structures. Despite these improvements in TOE technology, there are still some limitations. The posterior position of the TOE probe in the oesophagus may limit its ability to image far-field structures in the anterior heart and chest, such as the tricuspid valve (TV). Specifically,

Abbreviations

2D	two-dimensional	**MPR**	multiplanar reconstruction	**TEER**	transcatheter edge-to-edge repair
3D	three-dimensional	**MV**	mitral valve	**TOE**	transoesophageal echocardiography
ASD	atrial septal defect	**PFO**	patent foramen ovale	**TTVR**	transcatheter tricuspid valve replacement
ICE	intracardiac echocardiography	**PVL**	paravalvular leak	**TV**	tricuspid valve
LAA	left atrial appendage	**RT**	real time	**ViV**	valve-in-valve
LAAO	left atrial appendage occlusion	**SHD**	structural heart disease		

structures on the right side of the heart can be masked by shadowing from a prosthetic material (e.g, a mitral ring or an occluder in the interatrial septum) or calcification (e.g., aortic valve calcification) on the left side of the heart. In addition, the TOE probe also may interfere with the visualisation of structures on fluoroscopy. Furthermore, TOE requires the use of sedation or general anaesthesia to allow for oesophageal intubation for an extended time, increasing the risk of oesophageal injuries. Finally, some patients with oesophageal pathologies (achalasia, stricture, scleroderma, Mallory-Weiss tear or diverticulum), after oesophagus resection, inability to intubate (cervical and upper airway pathologies) or who are at increased risk of upper gastrointestinal bleeding (such as those with oesophageal varices) have absolute contraindications for a standard TOE probe[11]. Although the use of mini-TOE probes has been proposed in this scenario, ICE represents a potential alternative that may even allow performing the intervention under local anaesthesia only.

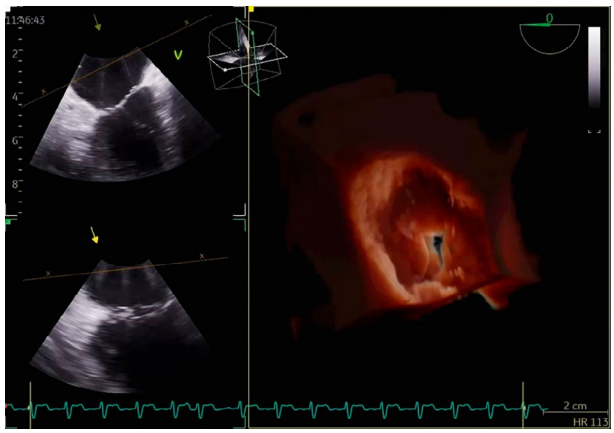

Figure 1. *Three-dimensional reconstruction of the atrial view of the tricuspid valve.*

3D ICE

In certain scenarios, integrating ICE, as opposed to TOE, into intraprocedural imaging guidance can notably streamline workflow[12,13]. For example, transcatheter LAAO, patent foramen ovale (PFO) closure, and mitral valve-in-valve (ViV) implantation can all be performed safely and effectively with local anaesthesia and 3D ICE guidance only. Advantages to this approach include more flexibility when planning procedures, eliminating the need for a general anaesthesia team, reduced burden on the intensive care unit, reduced turnover time in the cath lab, and the ability to perform TOE-free procedures (particularly in patients with absolute contraindications to this imaging technique)[4,14]. Furthermore, there is the potential for same-day discharge post-procedure, which could result in reduced overall costs and mitigate patient susceptibility to delirium or nosocomial infections in the intensive care unit[15].

For other procedures, such as transcatheter TV repair or replacement, 3D ICE is typically complementary to TOE[16]. TOE is the gold standard for TV imaging, but as previously noted, the posterior positioning of the probe relative to the valve can result in far-field tangential views with acoustic shadowing from other heart structures. Given its insertion via the femoral vein and ease of positioning within the right atrium (RA), the 3D ICE probe provides enhanced visualisation of the tricuspid leaflets and annulus **(Figure 1, Moving image 1)**. Nevertheless, it is important to note that despite these advantages, 3D ICE imaging cannot entirely replicate all TOE views, particularly the transgastric short- and long-axis views, underscoring the ongoing clinical utility of TOE in numerous scenarios[17]. However, this may change in the future, depending on the imaging needed for a specific TV prosthesis implant.

3D TOE VERSUS 3D ICE

3D TOE probes are equipped with larger matrix arrays, resulting in superior spatial and temporal resolution compared to 3D ICE probes. Furthermore, TOE offers a greater maximum 3D volume size. Compared to TOE, the spatial resolution of ICE 3D probes degrades along the axis perpendicular to the catheter's long axis (at a 90-degree omniplane angle) due to the physical limitations of the transducer array[18]. Hence, when utilising TOE, the quality of biplane imaging is superior across all angles relative to the transducer array. As a result, to achieve optimal biplane imaging on 3D ICE, it is essential that the imaging planes closely align with the diagonal across the matrix array. Initial experiences with three-/four-dimensional mini-TOE probes have recently been published, with promising results in terms of safety, feasibility and tolerability. However, there are currently no direct comparisons with 3D ICE[19]. Another significant factor to consider pertains to the cost-effectiveness ratio associated with using 3D ICE compared to 3D TOE. Currently, 3D ICE catheters are single-use devices and are more expensive than using TOE. However, this cost is partially offset by the potentially lower costs associated with a less invasive procedure and the ability to avoid general anaesthesia in some cases. Further studies are needed to understand better the impact of this factor on the widespread use of 3D ICE **(Table 1)**.

Basis of 2D ICE imaging

Understanding 3D intracardiac imaging requires knowledge of 2D imaging and its primary views. **Figure 2** schematises the main views of 2D ICE, presenting a drawing on the left and the corresponding echocardiographic image on the right. Beginning with venous access (either femoral or transjugular), the ICE probe is advanced to the RA, which allows for a step-by-step examination of various cardiac structures. Due to the limited ability to visualise structures of the left heart, particularly the left atrial appendage (LAA), from the RA, it has become common to position the ICE probe in the left atrium. The ability to guide transseptal puncture (TSP) using ICE and to position the ICE probe in the left heart sections has paved the way for percutaneous interventions on the mitral valve and atrial appendage with the assistance of ICE. A clear step-by-step approach is essential for safely and effectively performing a TSP at a specific location within the fossa ovalis. **Table 2** summarises the main steps of ICE-guided TSP.

Table 1. Comparison of TOE and ICE in the setting of SHD interventions.

	TOE	ICE
Procedure invasiveness	Semi-invasive	Invasive
Personnel requirements	Dedicated echocardiographer	Dedicated interventionalist and/or dedicated echocardiographer
Sedation requirements	General anaesthesia	Local anaesthesia
Integration in catheterisation laboratory	Requires additional equipment and space	Requires additional equipment and space Quick cath lab turnover
Imaging advantages	High-resolution imaging Biplane imaging/MPR Incremental value for 3D	High-resolution imaging Biplane imaging/MPR Incremental value for 3D Continuous imaging without interfering with fluoroscopy Advantages in specific settings (e.g., TV) limiting acoustic shadowing Superior right-sided cardiac imaging
Imaging disadvantages	Limited imaging of anterior structures (e.g., TV) Acoustic shadowing of prosthetic valves Mechanical traumatism on the oesophagus Limited access to oesophagus pathologies	Limited field of view Lower frame rate Lower volume of acquisition for certain technologies
Costs	Reasonable	High (limited reusability of the catheter)
Supportive data	Standard of care for most SHD interventions	Established utility for ASD/PFO closure and LAAO Emerging data on the feasibility of guidance of other SHD interventions

3D: three-dimensional; ASD: atrial septal defect; ICE: intracardiac echocardiography; LAAO: left atrial appendage occlusion; MPR: multiplanar reconstruction; PFO: patent foramen ovale; SHD: structural heart disease; TOE: transoesophageal echocardiography; TV: tricuspid valve

Evolution of 3D ICE catheter technology

There are currently two conceptually different ICE catheters available: rotational catheters and phased-array catheters[1]. The former are primarily used for electrophysiological procedures, while phased-array catheters are steerable and better suited for SHD interventions. They have a handle with three rows of knobs, which are used to manipulate the catheter and the 64-element phased-array ultrasonic transducer on its tip. These catheters can flex and be fixed in four directions (anterior/posterior, left/right). The technological evolution of phased-array catheters over the past decade has led to their progressive and increasingly important use in intraprocedural interventional SHD imaging. The ACUSON AcuNav V catheter (Siemens Healthineers) was the first commercially available ICE catheter with 3D imaging capabilities. It allows for 22° to 90° volumetric single-beat 3D imaging and can rotate the image in multiple planes. However, low frame rates and a narrow sector volume may limit full structural imaging[1,8]. The introduction of the full sample matrix array transducer represented a major step forward in 3D technology, significantly improving the spatial resolution of the transducer and its penetration[3,20]. However, this type of 3D imaging does not provide RT imaging, and the acquisition and reconstruction take a few minutes, which renders it unsuitable for a procedure. The fundamental innovation that made the use of 3D ICE routine in SHD procedures was the addition of the fourth dimension: time (or RT 3D imaging). The implementation of RT volumetric imaging enables MPR visualisation of target cardiac structures, thereby greatly expanding the potential of intracardiac imaging to guide percutaneous procedures. Currently, there are three available 3D ICE catheters: the ACUSON AcuNav Volume (Siemens Healthineers) **(Figure 3A)**, the VeriSight Pro (Philips) **(Figure 3B)**, and the NUVISION (Biosense Webster) **(Figure 3C)**. Each catheter has slightly distinctive features as noted in **Table 3**. All three catheters have multiple imaging modalities, including 2D imaging, colour-flow Doppler, RT 3D echocardiography, RT 3D colour-flow Doppler, spectral Doppler, and RT MPR.

SHD interventions and workflow recommendations

TRICUSPID THERAPY

Several factors can affect TOE imaging of the TV. These include its location in the anterior mediastinum with the left heart structures interposed between the probe and the TV, which results in beam widening and attenuation. The thin leaflets of the TV and the presence of other prosthetic valves or rings, atrial septal lipomatosis, and anatomical thoracic features, such as a horizontal heart axis, hiatal hernias, or additional thoracic/oesophageal pathology, can also contribute to these issues[21]. As previously noted, ICE has been used for intraprocedural guidance because it can accurately image the near-field and provide higher resolution of the cardiac structures. This helps to reduce shadowing and overcome the posterior position of the oesophagus within the mediastinum in case of TOE, which makes 3D ICE a promising complementary/replacement technique for TOE in transcatheter TV procedures. Although several approaches for guiding TV procedures have been described[22], the ICE imaging planes still need to be standardised.

TRICUSPID TEER

When performing a tricuspid TEER procedure (TriClip [Abbott], PASCAL [Edwards Lifesciences]), shadowing from mitral/aortic prostheses, septal hypertrophy, and other

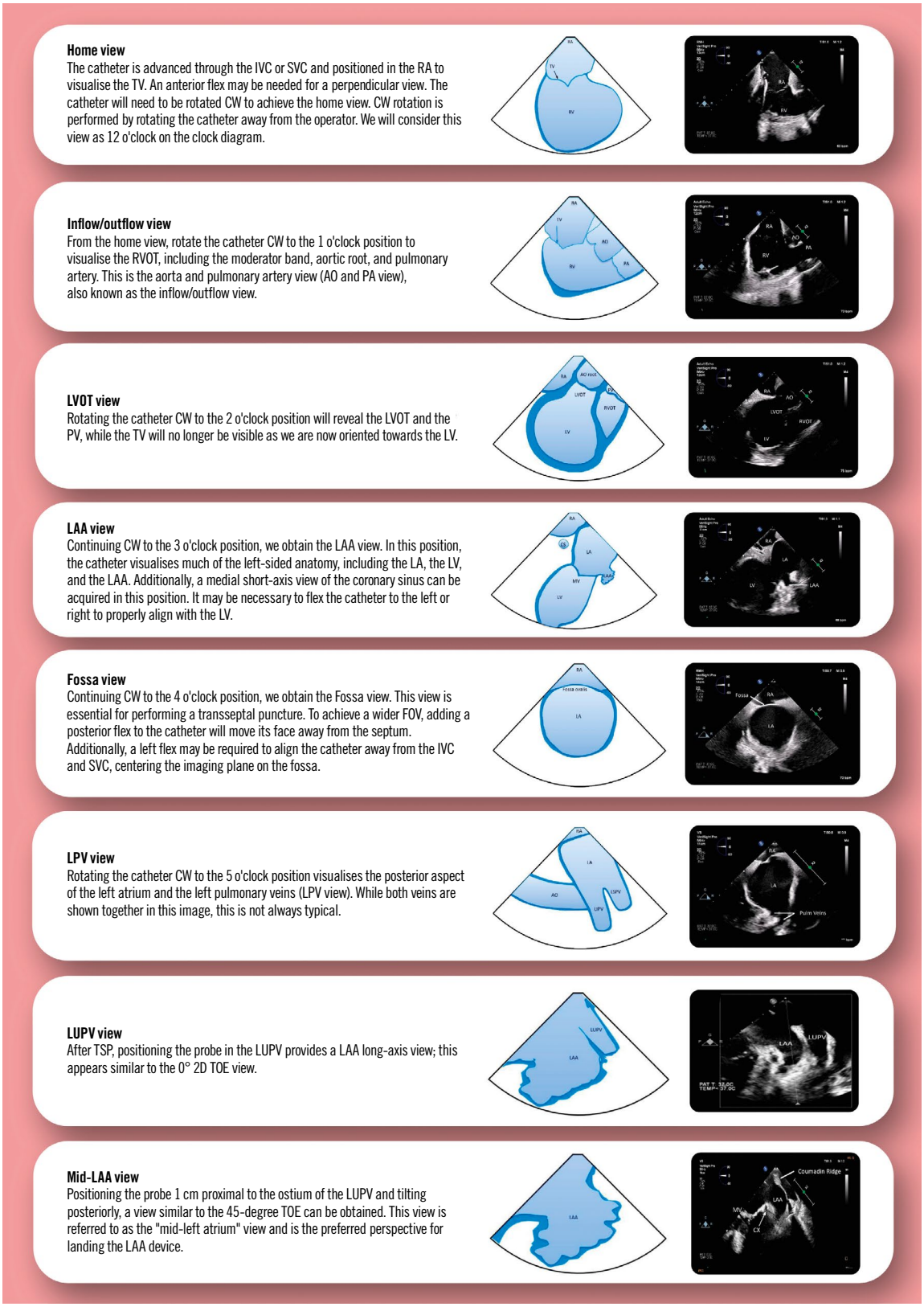

Figure 2. *Schematic representation of the main 2D ICE views. 2D: two-dimensional; AO: aorta; CW: clockwise; FOV: field of view; ICE: intracardiac echocardiography; IVC: inferior vena cava; LA: left atrium; LAA: left atrial appendage; LPV: left pulmonary vein; LUPV: left upper pulmonary vein; LV: left ventricle; LVOT: left ventricular outflow tract; PA: pulmonary artery; PV: pulmonary valve; RA: right atrium; RVOT: right ventricular outflow tract; SVC: superior vena cava; TOE: transoesophageal echocardiography; TSP: transeptal puncture; TV: tricuspid valve*

Table 2. Main steps of ICE-guided transseptal puncture.

ICE-guided transseptal puncture
The transseptal system is retracted from the SVC into the RA while the ICE maintains a view of the SVC.
From this view, the operator can easily confirm when the transseptal sheath enters the fossa ovalis. It also confirms tenting of the septum in the fossa ovalis and the superior-inferior position of the transseptal sheath.
Once the transseptal system is tenting the fossa ovalis, the anterior-posterior position of the transseptal needle can be visualised in two different ways: Clockwise rotation of the catheter moves the imaging plane to explore the posterior part of the septum (confirmed by identifying the LUPV) while counterclockwise rotation shows the anterior part of the septum (confirmed by identifying the aortic root) or Keep the transseptal system stable in this position and move the ICE probe to the "aortic view"
These two ICE views reveal if the tenting is located in the anterior or posterior fossa ovalis.
To achieve a more posterior position, the transseptal sheath should be rotated clockwise.
It is recommended to advance the needle using an anterior-posterior fluoroscopy view and to perform the puncture under both fluoroscopy and ICE guidance.

ICE: intracardiac echocardiography; LUPV: left upper pulmonary vein; RA: right atrium; SVC: superior vena cava

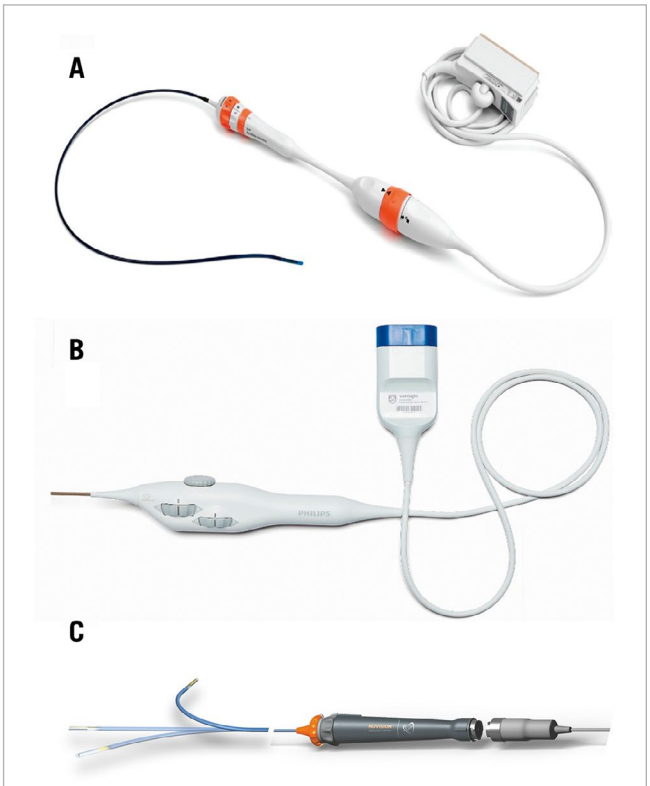

Figure 3. *Currently available 3D ICE catheters. A) The ACUSON AcuNav Volume ICE catheter (reproduced with permission from Siemens Healthineers); (B) the VeriSight Pro ICE catheter (reproduced with permission from Philips); (C) the NUVISION 3D ICE catheter (reproduced with permission from Biosense Webster).*

factors are particularly problematic when assessing for leaflet insertion. Three-dimensional ICE is a useful alternative for leaflet insertion in edge-to-edge repair. Starting from the home view (right ventricular inflow view), the use of biplane imaging creates a potential grasp view. Subsequently, a live 3D volume image can be obtained and used for a live 3D MPR[16]. Similar to TOE, 3D ICE also can be used for trajectory and alignment **(Figure 4, Moving image 2-Moving image 7)**.

TRANSCATHETER TRICUSPID VALVE REPLACEMENT

TTVR is a new technology used for tricuspid regurgitation (TR) treatment in patients not eligible for other percutaneous approaches[23]. The suitability for this treatment mainly depends on the annular dimensions, and unlike other treatment approaches, the imaging quality requirements are not very strict[24]. Three-dimensional ICE plays a crucial role in guiding the TTVR procedure, especially when TOE imaging is technically challenging. There are currently some cases described in the literature in which TTVR procedures are performed using combined 3D TOE-ICE imaging. Furthermore, there are only a limited number of centres with experience in ICE-guided TTVR[24], but considering the advantages of image quality, it could become the standard in the coming years. Typically, the ICE probe is inserted via transfemoral or transjugular access and positioned in the middle of the RA. By placing the 3D ICE probe directly in the RA, the problem of acoustic interference can be overcome. Furthermore, this position allows for stable visualisation of the TV and enables the acquisition of a 3D MPR by placing the region of interest over the TV annulus, creating a 3D *en face* view. The leaflet capture and the valve implantation can be guided stepwise with 3D MPR[25]. A dedicated echocardiographer is essential to create and optimise the imaging modalities (TOE and ICE). In fact, considering that intraprocedural echocardiographic guidance is essential for procedural success, the interventional imager plays a crucial role in guiding the implantation of the device. **Figure 5**, **Figure 6** and **Moving image 8** show a Cardiovalve case (Venus Medtech) and a LuX-Valve case (Jenscare Scientific).

MITRAL THERAPY

The use of ICE has been described for various mitral valve (MV) procedures, initially using 2D catheters and, more recently, RT 3D catheters, including mitral TEER with the MitraClip system[17] and PASCAL system, as well as transcatheter mitral ViV implantation. Because experienced TOE operators can accurately image the MV due to the proximity of the oesophagus and the left atrium, insufficient imaging quality is less common in patients with MV disease than in those with TV disease.

Imaging the MV with ICE implies crossing the interatrial septum and positioning the imaging catheter in the left atrium, a step that can be technically challenging. The TSP is performed using simultaneous biplane imaging with the ICE catheter positioned in the middle of the right atrium and retroflexed towards the septum **(Figure 7A)**. A preshaped stiff wire is carefully positioned into the upper left pulmonary vein under fluoroscopic and ICE guidance **(Figure 7B)**. Predilatation of the septum is required to facilitate the advancement of the

Table 3. Comparison of current 3D ICE catheters.

	ACUSON AcuNav Volume*	VeriSight Pro#	NUVISION§
Outer diameter	12.5 Fr	9 Fr	10 Fr
Working length	90 cm	90 cm	90 cm
Deflection range	160° (A/P, R/L)	120° (A/P, R/L)	120° (A/P, R/L) 360° (probe tip rotation)
Compatibility	ACUSON SC2000 Prime ultrasound system*	EPIQ 7C#, EPIQ CVx#, EPIQ CVxi#	GE Vivid E95¤, S70N Ultra Edition¤
Broadband frequency range	4-10 MHz	4-10 MHz	4-10 MHz
Type of array	Twisted linear	xMATRIX#	Array
Number of elements	128	840	840
Field of view	90°	90°	90°
Volume field of view	90° x 50°	90° x 90°	90° x 90°
Imaging modes			
2D imaging	Yes	Yes	Yes
Colour-flow Doppler	Yes	Yes	Yes
RT 3D echocardiography	Yes	Yes	Yes
RT 3D colour-flow Doppler	Yes	Yes	Yes
Pulsed-wave spectral Doppler	Yes	Yes	Yes
RT biplane imaging	Yes	Yes	Yes
Continuous-wave spectral Doppler	Yes	Yes	Yes
RT MPR imaging	Yes	Yes	Yes

*By Siemens Healthineers; #by Philips; §by Biosense Webster; ¤by GE HealthCare. 2D: two-dimensional; 3D: three-dimensional; A/P: anterior/posterior; ICE: intracardiac echocardiography; MPR: multiplanar reconstruction; R/L: right/left; RT: real-time

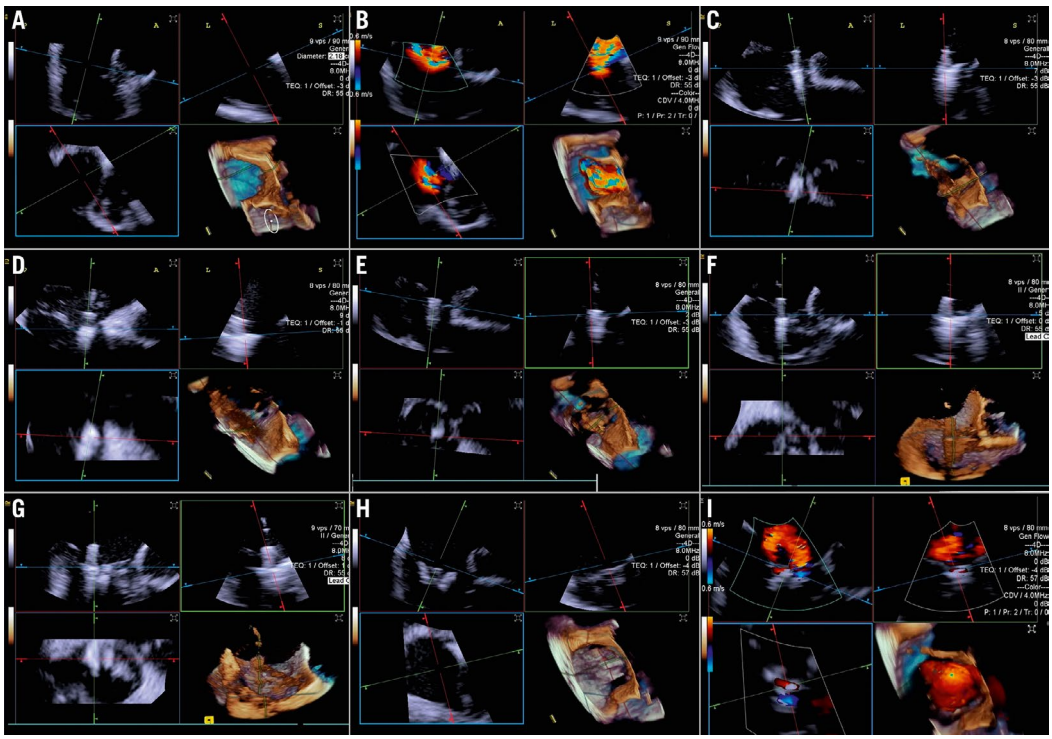

Figure 4. *Three-dimensional ICE-guided tricuspid transcatheter edge-to-edge repair. A) 3D MPR ICE imaging planes with posterior and anterior leaflets in the TV home view (top left), septal leaflet and anterior/lateral grasping view (top right). The blue plane (bottom left) represents the short-axis (atrial en face) view of the TV leaflets. Finally, the corresponding 3D volume (bottom right; the aorta is at 5 o'clock). B) 3D colour MPR ICE imaging shows severe tricuspid regurgitation, allowing assessment of the number of regurgitation jets and jet location. C-E) The first device is advanced under the tricuspid valve. Clip orientation is optimised to be orthogonal to the coaptation line while the clip position is fine-tuned to the target location, and independent leaflet grasping is performed. F) 3D MPR assessment of second device orientation and location. G) 3D MPR assessment of third device orientation and location. H, I) 3D MPR and colour-flow Doppler final assessment of the devices. 3D: three-dimensional; ICE: intracardiac echocardiography; MPR: multiplanar reconstruction; TV: tricuspid valve*

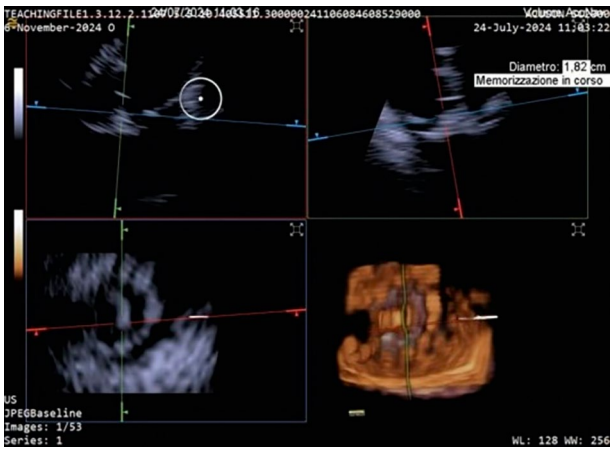

Figure 5. *3D MPR ICE imaging showing Cardiovalve device opening at the level of the tricuspid annulus. 3D: three-dimensional; ICE: intracardiac echocardiography; MPR: multiplanar reconstruction*

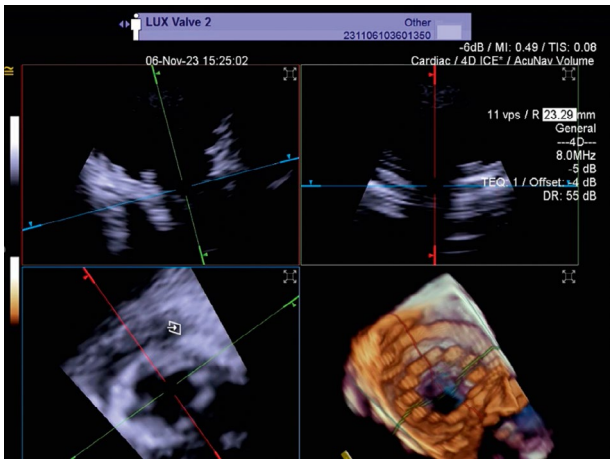

Figure 6. *Three-dimensional MPR views of the tricuspid valve after LuX-Valve deployment. The atrial en face view allows the evaluation of possible residual leakage. MPR: multiplanar reconstruction*

ICE catheter into the LA while tracking the trajectory of the wire **(Figure 7B)**. This can be done either by advancing and retracting the TEER-guiding catheter or through preparatory balloon septostomy using a 12-14 mm over-the-wire percutaneous transluminal angioplasty balloon. Once the ICE catheter has been placed successfully into the left atrium, it is followed by the guiding sheath, and the implant itself is then advanced towards the diseased MV **(Figure 7C)**. While the ICE catheter usually follows the curve of the delivery system, a position below it **(Figure 7D)** or the use of the right and left deflexion knob minimises shadowing artefacts and avoids direct interaction with the TEER device or any other catheter used for the intervention. The key advantage of RT 3D catheters is the ability to produce MPR that facilitates simultaneous optimisation of the trajectory and orientation in several planes and on the 3D view from the atrium **(Figure 8, Figure 9A-Figure 9C, Moving image 9-Moving image 11)**. At the end of the procedure, closure of the interatrial septum should be considered **(Figure 9D)**, since the defect is usually larger than after conventional TEER due to the manipulation of two catheters through the same access. Closure can be easily guided with the ICE catheter back to the right atrium **(Figure 9E)**. Mini-TOE or a paediatric probe (without 3D capabilities), as well as transthoracic echocardiography[26] are additional confirmatory imaging modalities that can be used in combination with ICE **(Figure 9F)**.

Similarly, ICE can also be used to guide transseptal transcatheter procedures for mitral ViV and valve-in-ring replacement under conscious sedation[27] **(Moving image 12-Moving image 13)**. A minimalistic approach may have several advantages, including early discharge (possibly within 24 hours)[28], and has been shown to offer similar safety compared to TOE guidance[27].

Paravalvular leak (PVL) closure has also been performed using ICE[29]. While imaging from the right atrium might be sufficient for medial PVL, septum crossing may be mandatory when lateral PVL is involved.

Non-valvular procedures

LAAO

In the majority of LAAO procedures, inferior and posterior transseptal punctures are needed to obtain coaxial alignment between the delivery system and the LAA central axis. When using 3D ICE, the probe is initially best positioned in the middle of the left atrium with a frontal view of the LAA. In comparison to the use of 2D ICE, 3D ICE enables reliable measurements of the LAA dimensions at a chosen depth by using the MPR function **(Figure 10)**. Once the measurements have been taken, the ICE catheter can be placed in the left upper pulmonary vein, with a good view of the LAA structures and the left circumflex artery. After the LAA occluder is deployed, ICE can be used to check its positioning, anchoring, size/device compression, and sealing. All of these items can be checked with 3D ICE using fewer positions than with 2D ICE **(Figure 11, Moving image 14-Moving image 17)**.

PFO/ASD CLOSURE

Although PFO/ASD procedures can be performed using a simple 2D ICE probe, in some more challenging anatomical settings (e.g., floppy interatrial septum [IAS], doubt about PFO/small ASD, particular PFO tunnel), 3D ICE can be of added value. When 3D ICE is used for PFO or ASD procedures, positioning within the right atrium is sufficient. With 3D ICE, the septal defect can be visualised in a 3D volume and typically only a catheter position is needed. When starting the procedure, the operator should screen patients for additional septal defects that may have been missed on the preprocedural imaging and determine whether there is a floppy interatrial septum (for PFO) and a sufficient superior and inferior rim (for ASD). Three-dimensional ICE allows us to determine the size of the septal defect (especially for an ASD closure), guide occluder deployment, verify placement post-deployment, and screen for residual shunts[1] **(Figure 12, Figure 13, Moving image 18-Moving image 22)**.

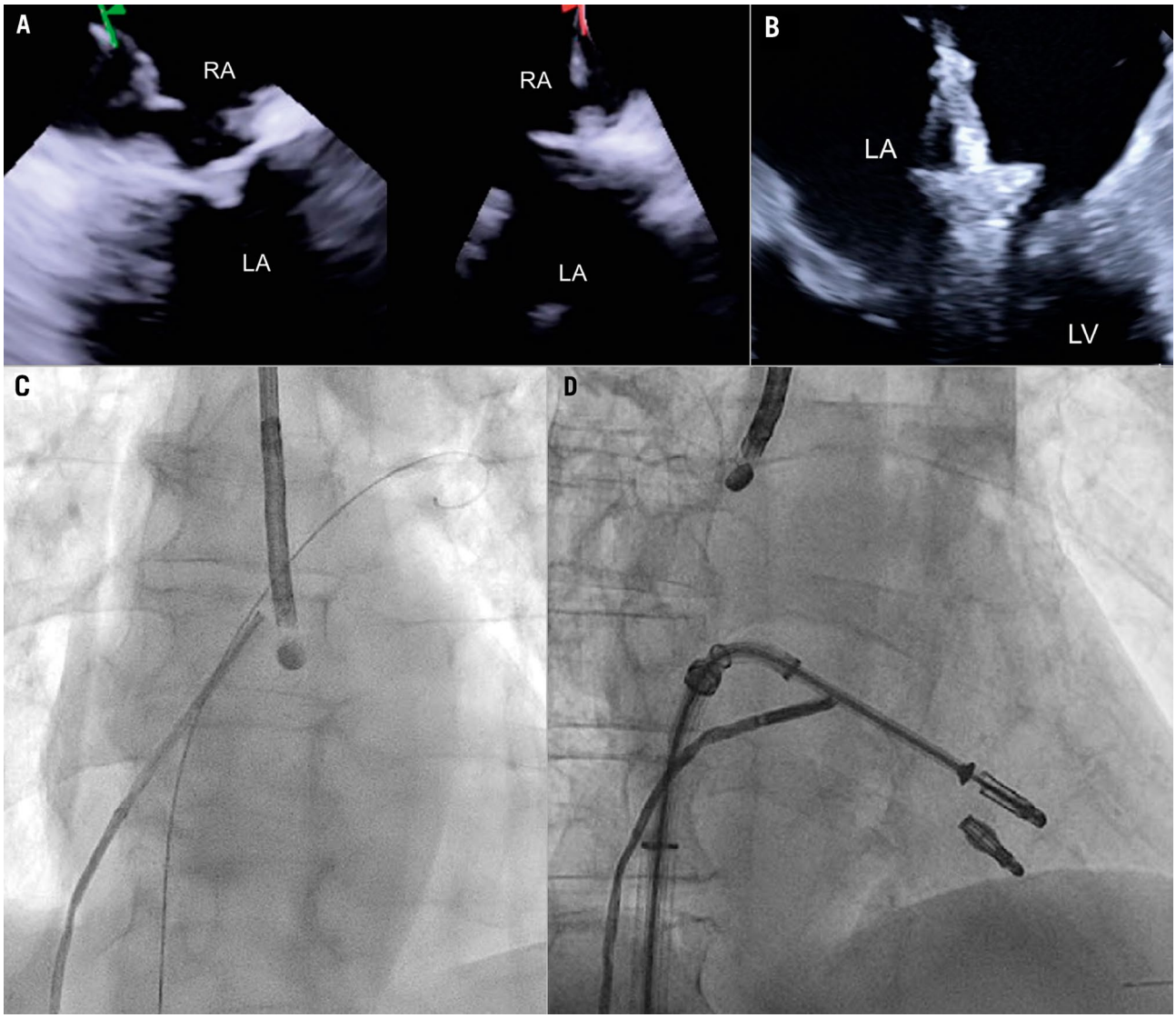

Figure 7. *ICE-guided transseptal puncture. A) Transseptal puncture using biplanar imaging with the ICE catheter retroflexed in the middle of the RA. Needle tenting is seen simultaneously in two dimensions. B) Position of the delivery catheter over the diseased mitral valve. C) After wire placement and septum predilatation, the ICE catheter is moved into the LA following the trajectory of the stiff wire. A paediatric TOE probe without 3D capacity is inserted into the oesophagus. D) Position of the ICE catheter below the TEER system to avoid shadowing artefacts. 3D: three-dimensional; ICE: intracardiac echocardiography; LA: left atrium; RA: right atrium; TEER: transcatheter edge-to-edge repair*

Training requirements

The manipulation of ICE catheters and the acquisition and interpretation of 3D ICE necessitate specialised training. To achieve these objectives, hands-on training using an animal model or a computer-based simulation tool is necessary to teach standard ICE positions and basic catheter movements inside the heart. Regardless of the training modality, standardised 3D ICE imaging protocols for each interventional procedure should be the foundation of these practical training events. Furthermore, clinical and procedural experience should be obtained under the direct supervision of expert physicians at high-volume centres. Finally, a case observation of an experienced interventionalist and imaging team can provide helpful insight into team dynamics, communication skills, and the shared vocabulary necessary for 3D ICE compared with TOE or 2D ICE. Operators should perform several simulated runs before using their skills in humans. The number of training sessions needed to achieve competence and confidence with 3D ICE technology is not established, and it is determined by the individual's interventional and imaging background. The 2019 American College of Cardiology/American Heart Association/American Society of Echocardiography paper suggests a minimum ICE volume of ≥10 cases for Level III structural heart echocardiography competency[30]. However, defining

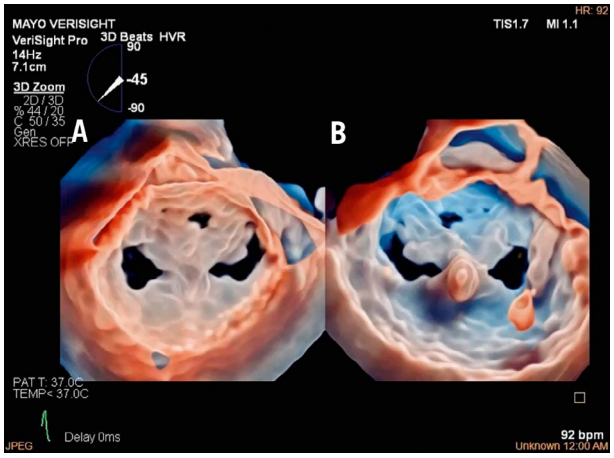

Figure 8. *Three-dimensional true surgical view and left ventricular view of the mitral valve after TEER. A) 3D true surgical view; (B) left ventricular view. 3D: three-dimensional; TEER: transcatheter edge-to-edge repair*

minimum requirements may become possible as more data on the learning curve for various procedures become available.

Future directions and potential technology advancements

While 3D ICE has effectively addressed several challenges encountered with 2D ICE during SHD interventions, there are various technical limitations associated with the currently available catheters. These include limited steerability and stability while manipulating the device, challenges when switching between ICE and TOE on the same machine, and lower image resolution compared with TOE, especially with full-volume 3D modalities. Implementation is also challenging because of the variability in individual anatomy. Structured training programmes for how to effectively use ICE currently do not exist, thus operator experience plays a crucial role in successful implementation. Looking ahead, one can anticipate the development of various iterations of catheters aimed at enhancing steerability, while sterile stands will enhance procedural stability. Larger catheters featuring expanded matrix arrays hold the potential to enhance image resolution and 3D volume size, thus enabling comprehensive imaging of the entire heart from the right heart cavities using appropriately sized catheters for venous access. Progress in hardware and software may further enhance imaging quality during RT 3D MPR, as well as refine colour Doppler capabilities, enable operators to save 3D MPR presets, and enhance measurement precision. Integration of ICE into fusion-imaging platforms could facilitate catheter orientation and navigation within the heart. However, the most significant impact on ICE is likely to arise from the integration of artificial intelligence for image recognition, potentially leveraging data from computed tomography images to predict optimal imaging angles, optimise device positioning, and enhance procedural guidance[31]. Moreover, the incorporation of artificial intelligence, alongside robotic solutions for controlling ICE catheter movements, may enable

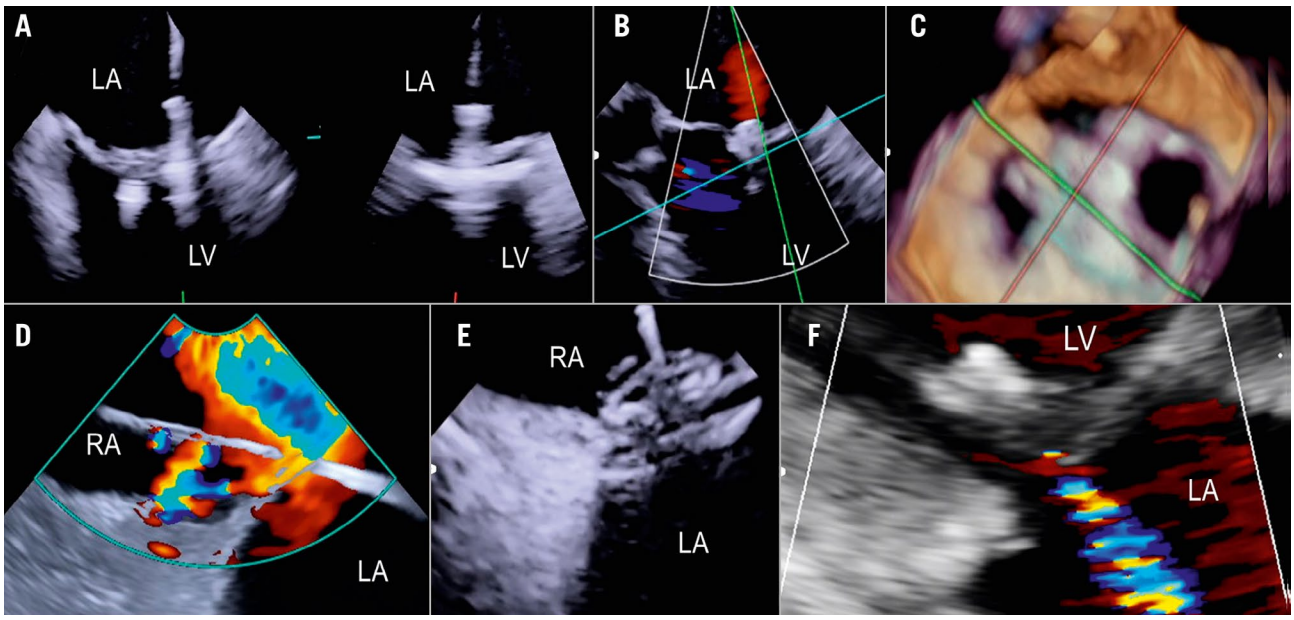

Figure 9. *ICE-guided mitral valve transcatheter edge-to-edge repair. A) Implantation of two clips and leaflet capture under ICE visualisation; (B) final result after implantation of two clips for correction of a posterior flail; (C) 3D ICE view of the MV after implantation of two clips; (D) large iatrogenic ASD visualised from the right atrium and crossed by a wire; (E) ASD closure using a 14 mm Amplatzer Septal Occluder under ICE guidance; (F) final result with mild residual MR as shown by transthoracic echocardiography at discharge. 3D: three-dimensional; ASD: atrial septal defect; ICE: intracardiac echocardiography; LA: left atrium; LV: left ventricle; MR: mitral regurgitation; MV: mitral valve; RA: right atrium; RV: right ventricle*

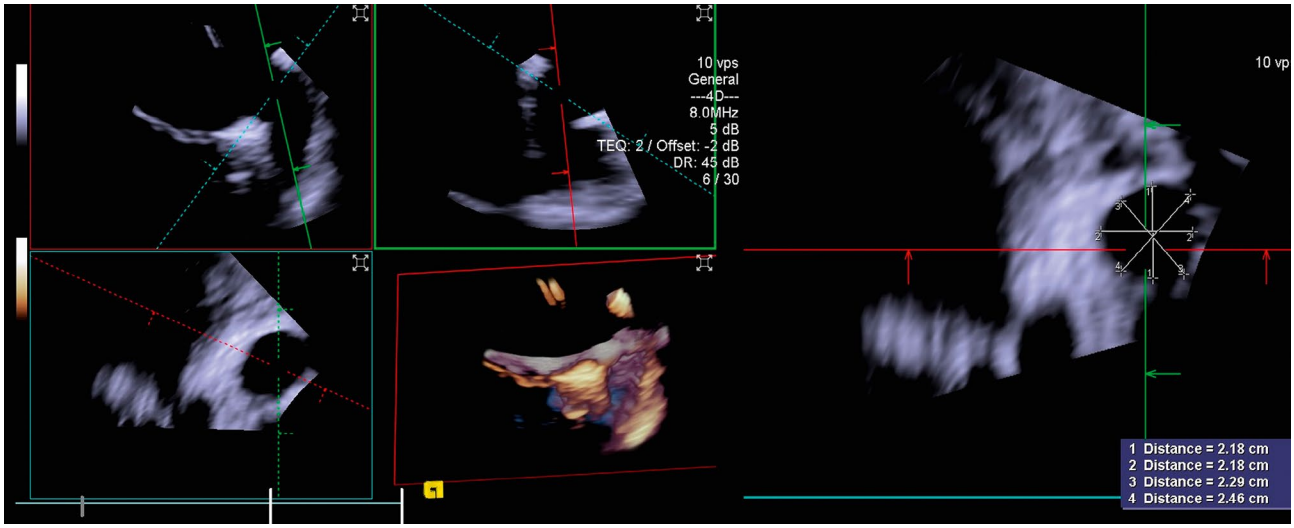

Figure 10. *Three-dimensional MPR views showing the LAA orifice with its measurements. LAA: left atrial appendage; MPR: multiplanar reconstruction*

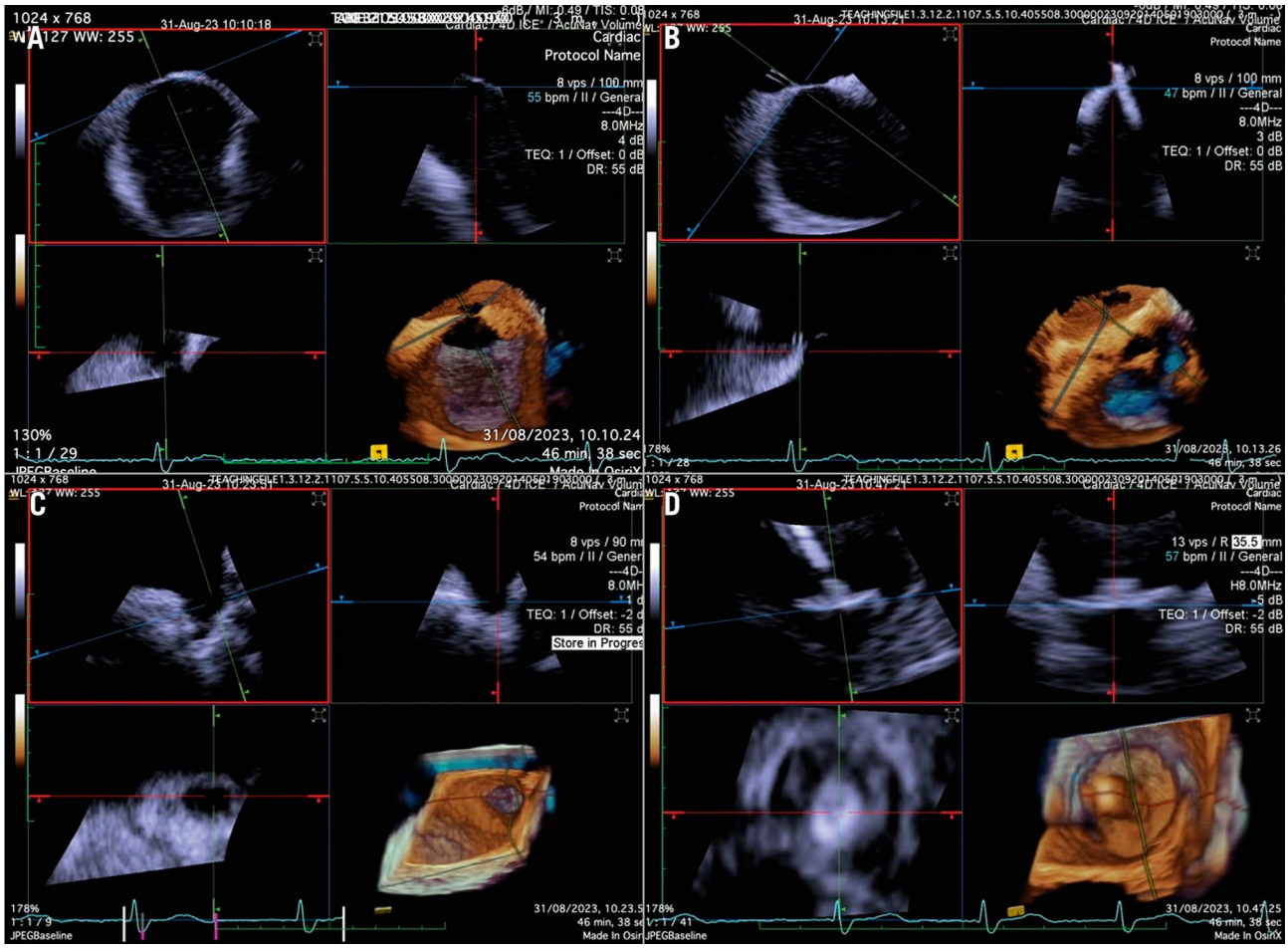

Figure 11. *Three-dimensional ICE-guided LAA occlusion. A) 3D MPR with probe in the right atrium to identify the best position of transseptal puncture. B) 3D MPR in real time to assess the catheter crossing the interatrial septum. C) 3D MPR to identify the shape and morphology of the LAA. D) 3D MPR in real time during deployment allows for precise positioning of the device and assessment of the position, anchor, size, and seal. 3D: three-dimensional; ICE: intracardiac echocardiography; LAA: left atrial appendage; MPR: multiplanar reconstruction*

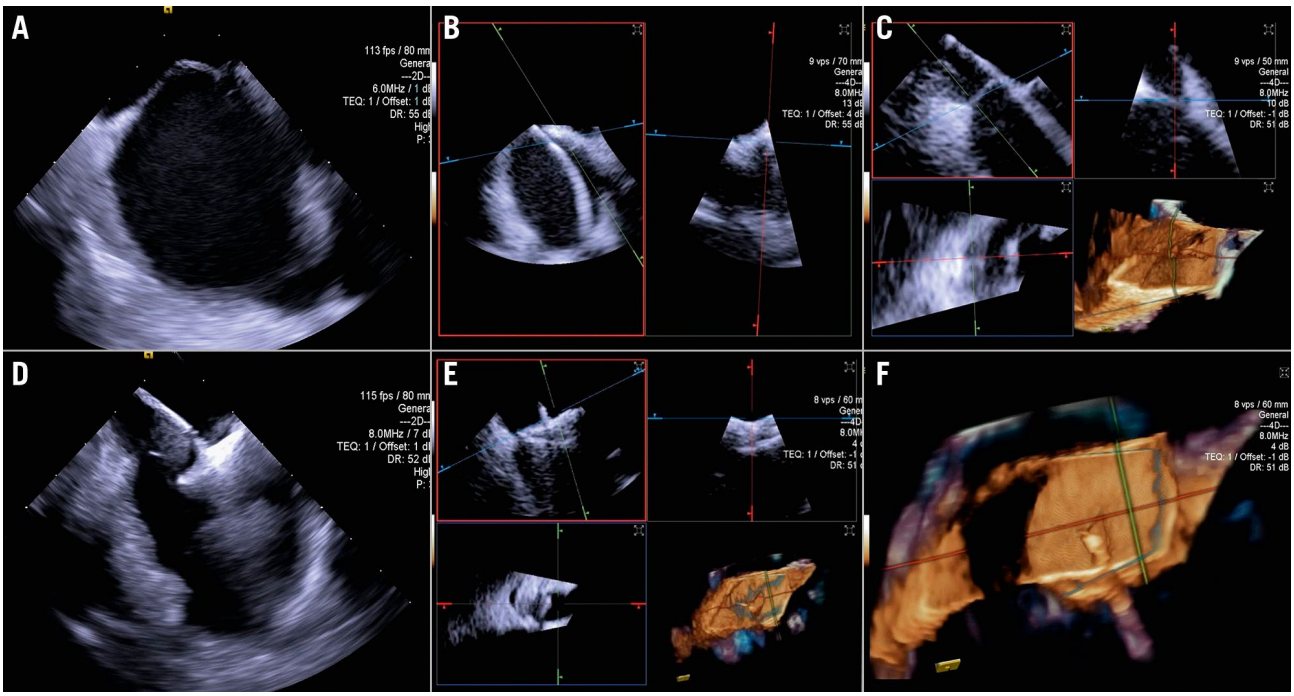

Figure 12. *Three-dimensional ICE-guided patent foramen ovale closure. A) 2D imaging allowing assessment of needle tenting in the middle of the fossa ovalis. B) Biplane imaging allowing assessment of the catheter after crossing the septum in the superior-inferior and anterior-posterior positions simultaneously. C) 3D multiplanar reconstruction (MPR) allowing assessment of the catheter after crossing the septum. D) 2D imaging showing the deployment of the right disc of the device. E) 3D MPR allowing simultaneous assessment in the lateral, axial, and azimuthal planes of the right disc of the device. F) 3D reconstruction of the device. 2D: two-dimensional; 3D: three-dimensional; ICE: intracardiac echocardiography*

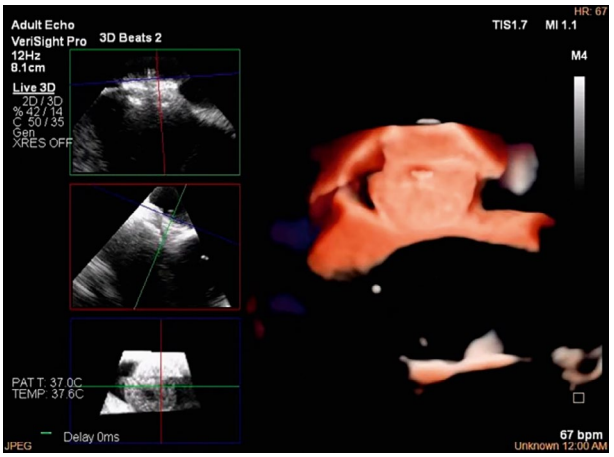

Figure 13. *Three-dimensional multiplanar reconstruction views of the device in the interatrial septum.*

precise and possibly independent catheter control through hand gestures and voice commands[32,33].

Conclusions

Three-dimensional ICE has become increasingly important in interventional cardiology, particularly for SHD, due to its unique ability to provide high-resolution images of the heart's internal structures. This capability offers several key advantages that make 3D ICE an essential tool for guiding and executing SHD interventions, especially in patients where TOE might be contraindicated or provide inadequate imaging due to anatomical constraints. This document outlines the most recent technical advancements in 3D ICE technology and provides strategies for different transcatheter procedures based on current clinical experience.

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Conflict of interest statement

S. Berti is a proctor for Edwards Lifesciences, Abbott, and Boston Scientific. O. De Backer received consultant fees from Abbott, Siemens, and Boston Scientific; and has received speaker honoraria from Abbott, Siemens, and Boston Scientific. E. Ho received consulting fees from Edwards Lifesciences, Medtronic, Abbott, Shifamed, GE HealthCare, Philips, NeoChord, and Valgen. F. Kreidel has received speaker honoraria from Philips, Siemens, and GE HealthCare. A. Latib received consultant fees from Medtronic, Philips, Abbott, Edwards Lifesciences, and Boston Scientific. M. Mariani received consultant fees and speaker honoraria from Edwards Lifesciences. F. Praz received support from attending meetings and/or travel from Abbott, Edwards Lifesciences, Medira, Siemens Healthineers, and inQB8 Medical Technologies; and he received grants from Abbott. N.C. Wunderlich is a proctor for Abbott, Edwards Lifesciences, and LifeTech Scientific Corporation; she has received speaker honoraria from Abbott, Edwards Lifesciences, GE HealthCare, Philips, and Boston Scientific. R.S. von Bardeleben has received speaker honoraria from Siemens, Philips, Abbott, and Edwards Lifesciences; he conducted trials (unpaid) for Abbott, Edwards Lifesciences, Medtronic, and Jenscare; and he received a fiduciary role on the board of directors of the Heart Valve Society USA (unpaid). A. D'Agostino has no conflicts of interest to declare.

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Supplementary data

Moving image 1. 3D reconstruction of the atrial view of the tricuspid valve.

Moving image 2. 3D RT MPR ICE imaging planes with the TV home view (top left), septo-lateral grasping view (top right), short axis (atrial *en face*) view of TV leaflets (bottom left) and the corresponding 3D volume (bottom right) with the aorta at 5 o'clock.

Moving image 3. 3D RT MPR ICE showing severe tricuspid regurgitation.

Moving image 4. 3D RT MPR views of independent leaflet grasping.

Moving image 5. 3D RT MPR views showing T-TEER device after grasping.

Moving image 6. 3D RT MPR assessment of stability after deployment of three T-TEER devices.

Moving image 7. 3D colour RT MPR result following T-TEER.

Moving image 8. 3D MPR views and 3D MPR colour of the TV after LuX-Valve deployment. The atrial *en face* view (bottom left) allows evaluation possible residual leakage.

Moving image 9. 3D True View surgical view and left ventricular view of mitral valve after TEER.

Moving image 10. Biplane imaging showing the long-axis view on the left and the bicommissural view on the right after M-TEER device release.

Moving image 11. Colour biplane imaging showing the long-axis view on the left and the bicommissural view on the right after M-TEER device release, with mild-to-moderate residual regurgitation.

Moving image 12. 3D mitral surgical view showing a degenerated bioprosthetic valve.

Moving image 13. 3D mitral surgical view after a mitral valve-in-valve procedure.

Moving image 14. 3D MPR with the probe in the RA to identify the best position for transseptal puncture.

Moving image 15. 3D RT MPR to assess the catheter crossing the interatrial septum.

Moving image 16. 3D RT MPR showing the structure of the LAA.

Moving image 17. 3D RT MPR during deployment allows for precise positioning of the device and assessment of its position, anchor, size, and seal.

Moving image 18. Biplane imaging allows assessment of the catheter after crossing the septum in superior-inferior and anterior-posterior positions simultaneously.

Moving image 19. 3D RT MPR allowing assessment of the catheter after crossing the septum.

Moving image 20. 3D MPR allowing the simultaneous assessment of the right disc of the device in the lateral, axial, and azimuthal planes.

Moving image 21. 3D MPR views of the device in the interatrial septum.

Moving image 22. Colour biplane imaging showing the device in the interatrial septum with no residual shunts.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-24-00868

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ORIGINAL RESEARCH

Thirty-day outcomes of a novel biomimetic balloon-expandable transcatheter heart valve in patients with small aortic annuli

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ABSTRACT

BACKGROUND: Transcatheter aortic valve implantation (TAVI) in patients with small aortic annuli (SAA) is associated with an increased risk of prosthesis-patient mismatch (PPM).

AIMS: This study assesses the 30-day performance of the novel balloon-expandable DurAVR transcatheter heart valve (THV), which features a unique single-piece biomimetic leaflet design, in patients with SAA.

METHODS: This pooled analysis derived from first-in-human and early feasibility studies includes all patients with SAA (defined as an aortic annular area from 346 mm^2 to 452 mm^2) treated with the small-sized DurAVR THV. The mean computed tomography (CT)-derived aortic annulus area was 404±37 mm^2, with a mean diameter of 22.7±1.0 mm. Outcomes at 30 days, including PPM, were evaluated per Valve Academic Research Consortium 3 criteria, with independent adjudication of clinical events and core laboratory analysis of post-implant transthoracic echocardiograms.

RESULTS: Amongst 100 patients (mean age 77.0±7.3 years; 78% female; mean Society of Thoracic Surgeons score 4.7±4.0%) treated with the DurAVR THV, the overall technical success rate was 93%. At 30 days, device success was achieved in 91% of patients, with no reported deaths and a stroke rate of 2%. Echocardiographic haemodynamic assessment showed a mean transprosthetic gradient of 8.2±3.1 mmHg, a mean effective orifice area of 2.2±0.3 cm^2, and a Doppler velocity index of 0.60±0.10. The incidence of moderate or greater PPM was 3%, and no patients experienced more than mild paravalvular leak. The rate of new permanent pacemaker implantation was 6%.

CONCLUSIONS: In patients with SAA, the DurAVR THV demonstrated promising clinical and echocardiographic outcomes at 30 days. Longer-term follow-up in larger cohorts is needed to confirm these encouraging early results.

KEYWORDS: biomimetic leaflets; early outcomes; small annulus; transcatheter aortic valve

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As transcatheter aortic valve implantation (TAVI) increasingly extends to younger patients with longer life expectancies, factors such as haemodynamic valve performance, valve durability, and the feasibility for reintervention become even more critical[1]. Patients with small aortic annuli (SAA) undergoing TAVI often encounter suboptimal results, including elevated transprosthetic gradients, increased prosthesis-patient mismatch (PPM), and early bioprosthetic valve failure (BVF)[2-5]. These outcomes can be influenced by the design of the transcatheter aortic valve (TAV), particularly differences in leaflet position, whether supra-annular or intra-annular, and leaflet design. However, existing data on this topic remain conflicting[5-11].

The DurAVR transcatheter heart valve (THV; Anteris Technologies) is a novel balloon-expandable valve featuring a unique first-of-its-kind single-piece biomimetic leaflet design. Early experience from first-in-human and early feasibility studies (EFS) have demonstrated promising results[12]. In this study, we report the procedural and 30-day clinical and haemodynamic outcomes for patients with SAA who underwent TAVI with the DurAVR THV.

Editorial, see page e131

Impact on daily practice

The DurAVR transcatheter heart valve (THV) is a balloon-expandable valve featuring a single-piece biomimetic leaflet design and was associated with favourable 30-day haemodynamic performance in patients with small aortic annuli. Ongoing randomised controlled trials will further evaluate DurAVR THV advantages compared to current-generation THVs and explore how its biomimetic design might improve patient outcomes.

Methods

STUDY COHORT

All patients with severe aortic stenosis and an SAA, defined as a computed tomography (CT)-based aortic annular area of 346-452 mm^2, who participated in the DurAVR: First-In-Human Study (EMBARK; ClinicalTrials.gov: NCT05182307), United States Early Feasibility Study (US-EFS; NCT05712161) and European Early Feasibility Study (EU-EFS; NCT06510855) were pooled together to constitute the study population for this analysis. The EMBARK First-in-Human study was a prospective, single-arm, single-centre study enrolling 90 patients from November 2021 to May 2025. The US-EFS was a prospective, single-arm study enrolling 15 patients across 4 sites between August and October 2023. The EU-EFS was a prospective, single-arm study enrolling 15 patients at a single centre between January and June 2025. The study protocols were approved by national regulatory authorities and the institutional ethical committees at the participating sites, and informed consent was obtained from all patients. Inclusion and exclusion criteria are detailed in **Supplementary Table 1**.

DEVICE DESCRIPTION

The DurAVR THV features a balloon-expandable stent frame encompassing a single piece of bovine pericardial tissue moulded into a trileaflet configuration to mimic native aortic valve geometry **(Figure 1)**. The bovine pericardium is treated with a proprietary ADAPT anticalcification tissue engineering process, which was developed to reduce the antigens responsible for inflammation and calcification[13]. This process enhances leaflet elasticity and strength, resulting in a valve performance comparable to healthy native leaflets[14]. The DurAVR stent frame consists of a top row of large open cells for ease of coronary access, radiopaque markers to facilitate valve positioning and commissural alignment, and a polyethylene terephthalate (PET) skirt to minimise paravalvular leak (PVL). The DurAVR THV is crimped onto a balloon-expandable catheter and delivered via the transfemoral ComASUR Delivery System (Anteris Technologies). The system comprises a flexible steering catheter and a commissural wheel that enables 1:1 rotational torque, facilitating patient-specific commissural alignment.

IMPLANT PROCEDURE

Patient eligibility for DurAVR THV implantation was determined by the respective Heart Teams at each site and the study screening committees. All patients received a small DurAVR THV, suitable for treatment of native aortic annuli with an area-derived diameter of 21-24 mm and aortic annulus area of 346-452 mm^2. The valve was deployed under fluoroscopic guidance during rapid pacing. Post-deployment assessments included stent frame expansion by fluoroscopy, haemodynamic function, and detection of aortic regurgitation. The overall procedural approach, including decisions regarding pre- or post-dilatation, use of cerebral embolic protection devices, vascular access closure methods, and postprocedural antiplatelet or antithrombotic therapy, was left to the discretion of the operator.

DATA COLLECTION

Prospective data on baseline demographics, procedural details, and 30-day follow-up results were collected. An independent clinical event committee verified all events in the EFS studies,

Abbreviations

AVA	aortic valve area	**EOA**	effective orifice area	**TAV**	transcatheter aortic valve
BMI	body mass index	**KCCQ**	Kansas City Cardiomyopathy Questionnaire	**TAVI**	transcatheter aortic valve implantation
BVF	bioprosthetic valve failure	**NYHA**	New York Health Association	**THV**	transcatheter heart valve
CT	computed tomography	**PPM**	prosthesis-patient mismatch	**TOE**	transoesophageal echocardiography
DVI	Doppler velocity index	**SAA**	small aortic annulus	**TTE**	transthoracic echocardiography
EFS	early feasibility study				

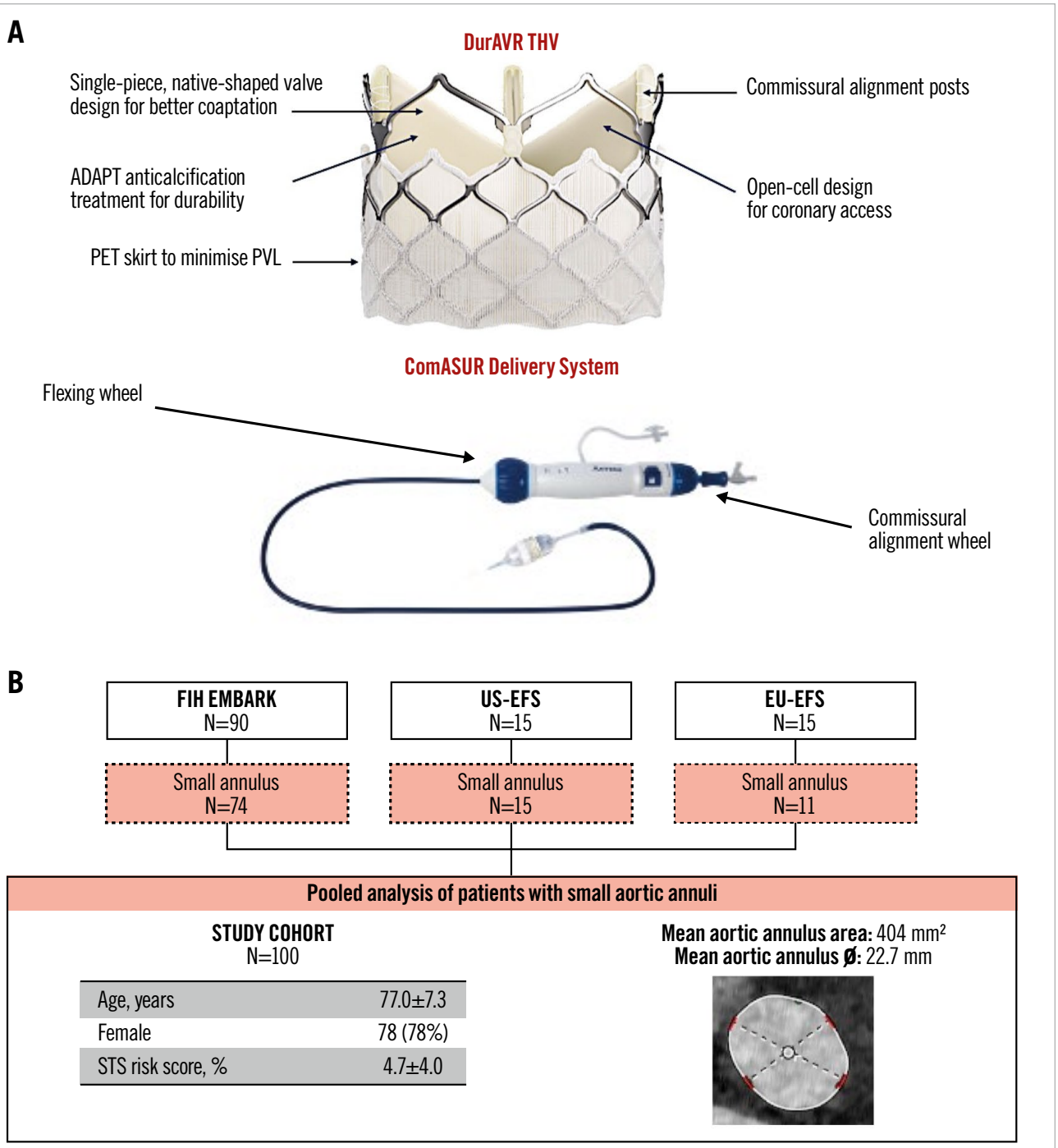


Figure 1. *DurAVR THV and study cohort. A) The DurAVR transcatheter heart valve (THV) is a short-frame, balloon-expandable valve featuring a novel single-leaflet, native-shaped biomimetic leaflet design that replicates native aortic valve leaflets. The valve is delivered using the dedicated ComASUR Delivery System, which permits active patient-specific commissural alignment. B) The study cohort comprises all patients with a small aortic annulus treated in the first-in-human and early feasibility studies. EFS: early feasibility study; EU: European; FIH: first-in-human; PET: polyethylene terephthalate; PVL: paravalvular leak; STS: Society of Thoracic Surgeons*

while independent physician adjudication was performed for the EMBARK study. Symptoms and quality of life were assessed at baseline and 30 days post-procedure using the New York Heart Association (NYHA) classification and the Kansas City Cardiomyopathy Questionnaire (KCCQ).

Transthoracic echocardiography (TTE) was performed at baseline and 30 days after the procedure, with images analysed by dedicated core laboratories for the EMBARK (Acudoc Swedish Echo Core Lab, Acudoc Clinical Physiology Laboratories, Stockholm, Sweden) and US-EFS and EU-EFS

cohorts (Cardiovascular Research Foundation, New York, NY, USA). Aortic stenosis severity was determined using the mean gradient, peak velocity, and aortic valve area (AVA). Post-procedure valve haemodynamics included measurements of transprosthetic gradient, effective orifice area (EOA), and Doppler velocity index (DVI). PPM severity was classified according to Valve Academic Research Consortium 3 (VARC-3) criteria: in patients with a body mass index (BMI) <30 kg/m^2, moderate PPM was defined as an indexed EOA of 0.66-0.85 cm^2/m^2 and severe PPM was defined as ≤0.65 cm^2/m^2; in patients with a BMI ≥30 kg/m^2, moderate PPM was defined as an indexed EOA of 0.56-0.70 cm^2/m^2 and severe PPM was defined as ≤0.55 cm^2/m^2 [15]. Prosthetic aortic valve regurgitation (central and paravalvular) was graded per VARC-3 classification: none/trace, mild, moderate, or severe.

STUDY ENDPOINTS

All study endpoints were reported in accordance with VARC-3 criteria[15]. Technical success, assessed immediately upon exiting the procedure room, was defined as the absence of mortality, successful vascular access, proper delivery and deployment of the device, retrieval of the delivery system, correct positioning of a single prosthetic valve into the proper anatomical location, and absence of surgical or other interventions related to the device or major vascular, access-related, or cardiac structural complications. Safety endpoints were reported as per VARC-3 criteria. Clinical efficacy at 30 days was defined as the absence of all-cause mortality, stroke, hospitalisation related to the procedure or valve; a decline of less than 10 points in the overall KCCQ score from baseline; and no worsening of NYHA Class.

STATISTICAL ANALYSIS

Patient demographics, device performance, risk factors, and clinical outcomes are summarised using descriptive statistics. Continuous variables are expressed as means with standard deviations, while categorical variables are presented as counts and proportions. All analyses were performed using SPSS, version 30 (IBM).

Results

BASELINE CHARACTERISTICS

A total of 100 patients with SAA, derived from the EMBARK (n=74), US-EFS (n=15), and EU-EFS (n=11) cohorts, were included for analysis. Baseline characteristics are summarised in **Table 1**, with individual cohort details available in **Supplementary Table 2**. The mean age was 77.0±7.3 years, 78% were female, and the overall mean Society of Thoracic Surgeons (STS) risk score was 4.7±4.0%. A total of 91% of patients had a tricuspid aortic valve, and 9% had a type 1 bicuspid aortic valve phenotype (8 patients with left-right fusion and 1 patient with non-right fusion). The CT-based mean aortic annulus area was 404±37 mm^2, with a mean annulus diameter of 22.7±1.0 mm. The baseline mean aortic valve gradient was 48.1±17.0 mmHg and left ventricular ejection fraction (LVEF) was 58.0±7.0%.

PROCEDURAL OUTCOMES

Procedural data and outcomes are summarised in **Table 2** and **Supplementary Table 3**. In the initial EMBARK study, most procedures (69%) were performed under general anaesthesia with transoesophageal echocardiography (TOE) guidance. In contrast, in the more recent EU-EFS study, a minimalist approach using local anaesthesia and sedation was successfully adopted in 100% of procedures. The transfemoral access route was utilised for 94% of cases, while transaortic and transcarotid access routes were used in 5% and 1% of cases, respectively. Predilatation was performed in 57% of procedures, while post-dilatation was noted in 8% of procedures.

The overall VARC-3 defined technical success rate was 93%. Periprocedural complications were only encountered in

Table 1. Baseline characteristics.

	N=100
Clinical variables	
Age, years	77.0±7.3
Female	78 (78)
Body mass index, kg/m^2	28.6±5.1
Arterial hypertension	91 (91)
Diabetes mellitus	33 (33)
Coronary artery disease	60 (60)
Previous myocardial infarction	12 (12)
Previous PCI	36 (36)
Previous CABG	7 (7)
Peripheral arterial disease	2 (2)
Atrial fibrillation	12 (12)
Previous stroke	1 (1)
Renal insufficiency or failure	56 (56)
Chronic obstructive pulmonary disease	3 (3)
Previous pacemaker	6 (6)
STS risk score, %	4.7±4.0
NYHA Class III or IV	61 (61)
KCCQ overall summary score	40.7±20.4
Baseline echocardiographic data	
Left ventricular ejection fraction, %	58.0±7.0
Mean transvalvular gradient, mmHg	48.1±17.0
Peak transvalvular gradient, mmHg	78.3±26.8
Aortic valve area, cm^2	0.8±0.2
Aortic regurgitation ≥moderate, %	6/99 (6)
Mitral regurgitation ≥moderate, %	10/97 (11)
Baseline CT data	
Aortic annulus area, mm^2	404±37
Aortic annulus perimeter, mm	72.0±3.5
Aortic annulus mean diameter, mm	22.7±1.0
Sinotubular junction diameter, mm	27.3±2.6
Left coronary artery height, mm	13.2±2.8
Right coronary artery height, mm	16.4±2.8

Values are expressed as mean±SD, n (%) or n/N (%). CABG: coronary artery bypass grafting; CT: computed tomography; KCCQ: Kansas City Cardiomyopathy Questionnaire; NYHA: New York Heart Association; PCI: percutaneous coronary intervention; SD: standard deviation; STS: Society of Thoracic Surgeons

Table 2. Procedural characteristics and technical success.

	N=100
Procedural characteristics	
Anaesthesia type	
General anaesthesia	69 (69)
Conscious sedation/local anaesthesia	31 (31)
Transfemoral access and delivery	94 (94)
DurAVR THV small valve size	100 (100)
Predilatation	57 (57)
Post-dilatation	8/95 (8)
Cerebral embolic protection device	26 (26)
Procedural time, min	24.3±20.8
Fluoroscopy time, min	18.5±8.9
Use of contrast dye, mL	91.2±31.2
Technical success (VARC-3)	
Freedom from mortality	100 (100)
Successful access, delivery of the device, and retrieval of the delivery system	100 (100)
Correct positioning of a single THV into the proper anatomical location	98 (98)
Freedom from surgery or intervention related to the device or to a major vascular, access-related, or cardiac structural complication	95 (95)
Technical success at exit from procedure room	93 (93)
FIH-EMBARK cohort – early experience	67/74 (91)
US/EU-EFS cohort – later experience	26/26 (100)

Values are presented as mean±SD or, n (%). EFS: early feasibility study; FIH: first-in-human; SD: standard deviation; THV: transcatheter heart valve; VARC: Valve Academic Research Consortium

the EMBARK first-in-human cohort, reflecting early device and operator experience **(Supplementary Table 4)**. Subsequent refinements to the valve design, compliance of the inflation balloon, the delivery system, and the expandable sheath profile were implemented. In the last 50 consecutive implants, including the US-EFS and EU-EFS cohorts, no major periprocedural complications occurred, reflecting a technical success rate of 100% **(Table 2)**.

THIRTY-DAY CLINICAL OUTCOMES

Complete 30-day follow-up was achieved in all patients **(Figure 2)**. There were no deaths, and 2 patients experienced a stroke. Major vascular complications and bleeding (type 2-4) occurred in 5% and 7% of patients, respectively. Notably, none of these complications were observed in the US/EU-EFS cohorts. The overall rate of new permanent pacemaker implantation was 6%. Patients showed marked symptomatic improvement, with the KCCQ score increasing by 12 points from baseline. Additionally, 70% of patients reported an improvement in NYHA classification as early as 30 days.

VALVE PERFORMANCE

Device success per VARC-3 criteria was achieved in 91% of patients **(Figure 3)**. One patient developed a late external iliac artery thrombus requiring vascular intervention, and one other patient exhibited a residual mean transprosthetic gradient >20 mmHg, attributed to leaflet thrombosis detected on post-TAVI CT imaging. At 30 days, the mean transprosthetic gradient was 8.2±3.1 mmHg, with a mean EOA of 2.2±0.3 cm^2, and mean DVI of 0.60±0.10. The incidences of moderate and severe PPM were 2% and 1%, respectively. No patients had greater than mild PVL.

Discussion

This is the largest study to date reporting on clinical and echocardiographic outcomes following implantation of the novel biomimetic balloon-expandable DurAVR THV. Among 100 patients with SAA, we observed (1) a high rate of VARC-3-defined technical success (93%) and early clinical safety and efficacy; (2) favourable core-lab-assessed echocardiographic haemodynamic outcomes, including low mean transprosthetic gradients (8.2±3.1 mmHg), a large EOA (2.2±0.3 cm^2), only 3% of patients with moderate or greater PPM, and no cases of greater than mild PVL; and (3) a permanent pacemaker implantation rate of 6% **(Central illustration)**. It should be noted that these outcomes were derived from a mixed cohort, including first-in-human and early feasibility studies. In more recent US-EFS and EU-EFS cohorts, the DurAVR THV system demonstrated a 100% technical success rate, which compares favourably with current-generation TAVI systems when treating patients with SAA.

CHALLENGES OF SMALL AORTIC ANNULI

Surgical aortic valve replacement in patients with SAA often results in high postoperative mean transprosthetic gradients, small EOAs, and a high incidence of PPM, factors linked to increased all-cause and cardiovascular mortality, heart failure hospitalisations, and bioprosthetic valve degeneration

Early safety at 30 days (VARC-3)	
All-cause mortality	0
Stroke	2/100 (2%)
Disabling stroke	2/100 (2%)
Non-disabling stroke	0
Myocardial infarction	0
Vascular complication	
Minor	6/100 (6%)
Major	5/100 (5%)
Bleeding, type 2-4	7/100 (7%)
Acute kidney injury, stage 3-4	0
Permanent pacemaker implantation	6/100 (6%)
Surgery or intervention related to the device	0

Clinical efficacy at 30 days (VARC-3)§	
Freedom from all-cause mortality	100/100 (100%)
Freedom from stroke	98/100 (98%)
Freedom from procedure- or valve-related hospitalisation	96/100 (96%)
Freedom from KCCQ overall summary score decline from baseline of >10 points or worsening NYHA Class	94/98 (96%)

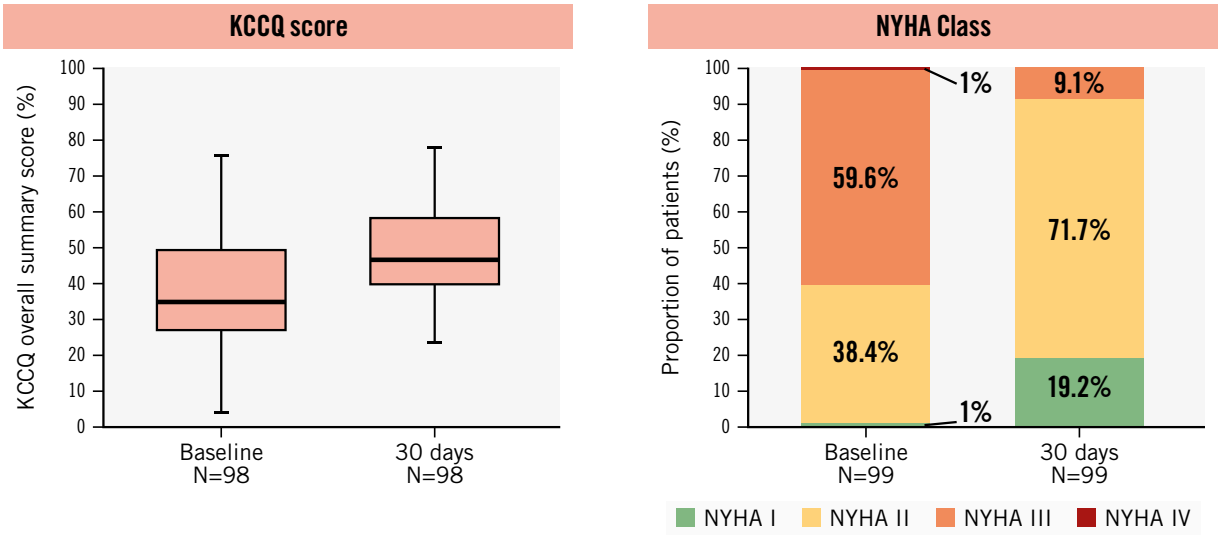


Figure 2. *Thirty-day clinical outcomes. High clinical safety, clinical efficacy, and improvement in symptoms were observed at 30 days following DurAVR THV implantation in patients with small aortic annuli. Paired analysis for KCCQ and NYHA scores. §Modified VARC-3 definition. KCCQ: Kansas City Cardiomyopathy Questionnaire; NYHA: New York Heart Association; THV: transcatheter heart valve; VARC: Valve Academic Research Consortium*

(BVD)[16-18]. Similarly, TAVI outcomes are affected by the presence of SAA, which are associated with higher residual gradients, increased PPM, and poorer clinical outcomes[6,19,20]. Data from the STS/ACC Transcatheter Valve Therapy (TVT) Registry showed that among 62,125 patients who underwent TAVI between 2014 and 2017, the incidences of moderate and severe PPM were 25% and 12%, respectively, and these were linked with increased mortality risk (hazard ratio [HR] 1.19, 95% confidence interval [CI]: 1.09-1.31; p<0.001) and heart failure hospitalisation (HR 1.12, 95% CI: 1.02-1.24; p<0.001) at 1-year follow-up[2]. Furthermore, the European Valve Durability TAVI Registry noted higher rates of structural valve deterioration (SVD) at a median follow-up of 6.1 years with smaller TAVs (HR 4.8, 95% CI: 2.42-9.60; p<0.001)[21].

IMPACT OF TRANSCATHETER AORTIC VALVE DESIGN

Not all TAVI devices perform equally in patients with SAA; outcomes vary significantly based on the valve design. The

Device success at 30 days (VARC-3)	
Device success (VARC-3)	91/100 (91%)
Technical success	93/100 (93%)
Freedom from mortality	100/100 (100%)
Freedom from surgery or intervention related to the device or to a major vascular, access-related, or cardiac structural complication	99/100 (99%)
Intended valve performance (mean gradient <20 mmHg, DVI ≥0.25, and paravalvular leak <moderate)	98/99 (99%)

Valve performance at 30 days (VARC-3)

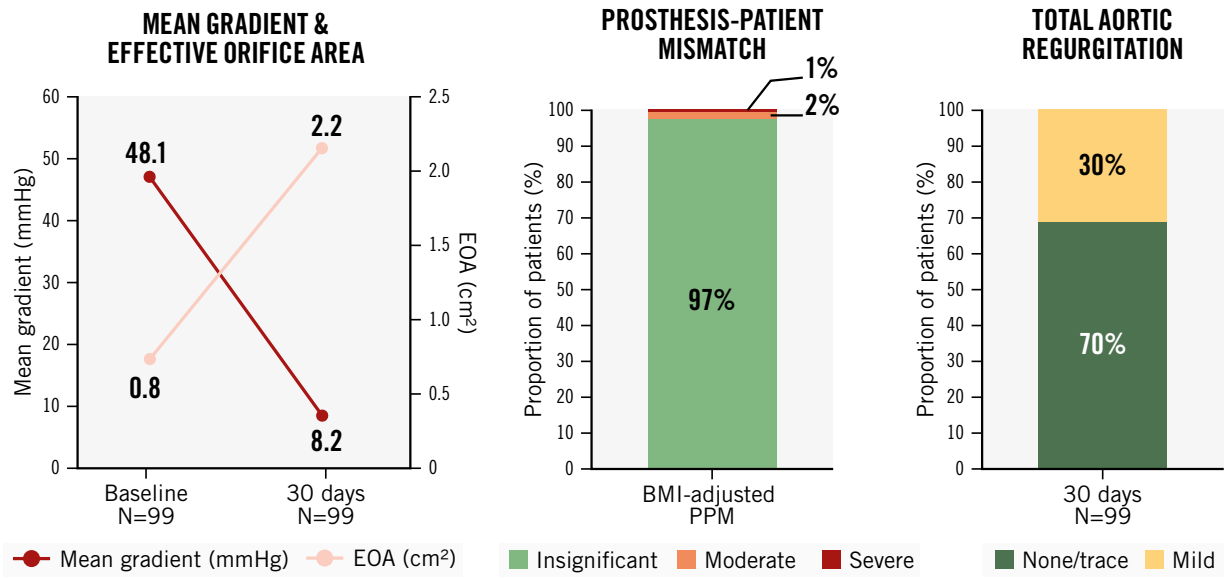


Figure 3. *Thirty-day device success and valve performance. The DurAVR THV demonstrated high device success and favourable haemodynamic outcomes at 30 days post-procedure in patients with small aortic annuli. BMI: body mass index; DVI: Doppler velocity index; EOA: effective orifice area; PPM: prosthesis-patient mismatch; THV: transcatheter heart valve; VARC: Valve Academic Research Consortium*

retrospective multicentre TAVI-SMALL 2 registry, involving 1,378 patients with SAA, reported that self-expanding valves (SEVs), compared to balloon-expandable valves (BEVs), were associated with lower mean transprosthetic gradients (8.0±4.1 mmHg vs 13.6±4.7 mmHg; p<0.001) and lower rates of PPM (4.6% vs 8.7%)[7]. Similarly, the Bern TAVI Registry, after propensity matching 723 patients with SAA, reported severe PPM in 19.7% with SEVs versus 51.8% with BEVs[9]. These findings have been consistent across studies involving both older- and newer-generation TAVs as well as in patients with extra-small annuli[8,11]. The SMART Trial, a randomised controlled trial comparing SAA patients receiving Evolut (SEV; Medtronic) or SAPIEN (BEV; Edwards Lifesciences) valves, demonstrated that SEV implantation was associated with a significantly lower incidence of mean transprosthetic gradients ≥20 mmHg (3.2% vs 32.2%), reduced moderate or greater PPM (11.2% vs 35.3%; p<0.001), and subsequently, lower rates of SVD (3.5% vs 32.8%) and BVD (10.2% vs 43.3%) at 1 year[5]. However, these haemodynamic advantages of SEVs come with trade-offs, including higher rates of PVL and permanent pacemaker implantation[7,9,11].

DURAVR THV FOR SMALL AORTIC ANNULI

In this study, we demonstrated that the balloon-expandable DurAVR THV exhibits favourable haemodynamic valve performance in patients with SAA. Specifically, low mean transprosthetic gradients (8.2±3.1 mmHg), high EOAs (2.2±0.3 cm²), and very low incidences of moderate (2%) and severe (1%) PPM were observed. Additionally, the rates of core-lab-assessed PVL were minimal, with no patients experiencing more than mild PVL. The need for new permanent pacemaker implantation was only 6%. This early experience suggests that the combination of BEV-like performance – characterised by high device success and low pacemaker implantation rates – alongside SEV-like haemodynamics makes the DurAVR THV an attractive new option for patients with SAA. The favourable haemodynamic profile may be attributed to its innovative biomimetic leaflet design. The DurAVR THV leaflets are made from a single piece of bovine pericardial tissue, treated with the proprietary ADAPT anticalcification tissue engineering process and shaped to mimic a native aortic valve. This design results in a longer leaflet coaptation length (~7 mm), allowing the valve to replicate the natural geometry and kinematics of a native

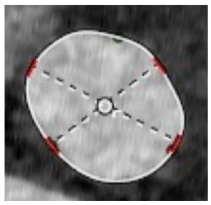
EuroIntervention — Central Illustration

Outcomes of the biomimetic balloon-expandable DurAVR THV in small aortic annuli.

Small DurAVR THV
Area: 346-452 mm²
Diameter: 21-24 mm

Patients with severe aortic stenosis and small aortic annuli

FIH EMBARK N=74	US-EFS N=15	EU-EFS N=11
Study cohort N=100	Age: 77.0±7.3 years; female: 78% STS risk score: 4.7±4.0%	



Study cohort
Mean area: 404 mm²
Mean Ø: 22.7 mm

Clinical outcomes at 30 days

Mortality	Stroke	Rehospitalisation§	Pacemaker
0%	2%	4%	6%

Valve performance at 30 days

Intended valve performance	99%
✓ Mean gradient <20 mmHg	
✓ Doppler velocity index ≥0.25	
✓ Paravalvular leak <moderate	

Prosthesis-patient mismatch	
• Moderate PPM	2%
• Severe PPM	1%
Moderate or severe PVL	**0%**

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VARC-3-defined clinical outcomes and valve performance at 30 days after DurAVR THV implantation in a patient population with small aortic annuli. §Procedure- and valve-related hospitalisations. PPM: prosthesis-patient mismatch; STS: Society of Thoracic Surgeons; THV: transcatheter heart valve; VARC: Valve Academic Research Consortium

aortic valve. In contrast, conventional TAVs have three separate leaflets sutured to the stent frame, often leading to smaller orifice areas and abnormal blood flow patterns in the ascending aorta[22].

Cardiac magnetic resonance flow studies support these findings, demonstrating that DurAVR THV restores near-normal laminar flow in the aorta, comparable to healthy valves[12]. Further research is needed to determine the impact that restoration of laminar flow can have on left ventricular mass regression, which is often impaired in SAA patients with PPM, and the risk of neosinus or leaflet thrombosis[23]. These factors could influence the long-term durability of the valve, especially as TAVI is increasingly used in younger patients with longer life expectancy, where considerations such as coronary reaccess and the feasibility of redo-TAVI are crucial for lifelong management. Patients with small aortic roots are at higher risk for challenging coronary access or redo interventions, and the short-frame design and ability to achieve patient-specific commissural alignment represent significant advantages of the DurAVR THV.

Limitations

Several limitations should be acknowledged. First, the small sample size included both very early first-in-human procedures and more recent implants, reflecting a learning curve and device improvements over time. This progression is evident in the better safety profile and technical success observed in the EFS cohorts compared to the EMBARK cohort. Second, this report describes haemodynamic performance at 30 days post-procedure; longer-term data are needed to confirm valve durability. Lastly, without a comparator group, it is difficult to directly compare DurAVR THV performance to that of other current-generation TAVs. However, this will be addressed in the upcoming PARADIGM randomised controlled trial (ClinicalTrials: NCT07194265), which will compare the DurAVR THV with commercially available TAV systems in a broad patient population with severe aortic stenosis.

Conclusions

The biomimetic balloon-expandable DurAVR THV demonstrated high rates of technical and device success, along with favourable haemodynamic outcomes at 30 days, including a low incidence of PPM in patients with SAA. Further studies are necessary to confirm its long-term durability.

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Conflict of interest statement

O. De Backer received institutional research grants and consulting fees from Abbott, Boston Scientific, and Medtronic. A.A. Khokhar received speaker fees/honoraria from Abbott, Boston Scientific, and Medtronic. G. Bieliauskas has received speaker honoraria and consulting fees from Abbott, Boston Scientific, Edwards Lifesciences, Medtronic, and Sahajanand Medical Technologies Ltd. A. Latib is a consultant for Medtronic; and received speaker honoraria from Medtronic and Biotronik. R. Puri is a consultant, speaker and proctor for Medtronic and Abbott; consults for Centerline Biomedical, Philips, Products & Features, Shockwave Medical, VDyne, VahatiCor, Advanced NanoTherapies, NuevoSono, TherOx, GE HealthCare, Anteris Technologies, T45 Labs, Pi-Cardia, Protembis, and Nyra Medical; and has equity interest in Centerline Biomedical, VahatiCor, and NuevoSono. A. Asgar has been a consultant for/on an advisory board for Medtronic and Abbott; and has been a consultant for Edwards Lifesciences. S.A. Garcia is supported by The Harold C. Schott Foundation Endowed Chair for Structural and Valvular Heart Disease; and is a proctor and steering committee member for Edwards Lifesciences. R.T. Hahn reports speaker fees from Abbott, Baylis Medical, Edwards Lifesciences, Medtronic, Philips, and Siemens Healthineers; institutional consulting contracts, for which she receives no direct compensation, with Abbott, Edwards Lifesciences, Medtronic, and Novartis; and she is Chief Scientific Officer for the Echocardiography Core Laboratory at the Cardiovascular Research Foundation for multiple industry-sponsored tricuspid valve trials, for which she receives no direct industry compensation. P. D. Mahoney is a consultant and proctor for Medtronic, Edwards Lifesciences, and Boston Scientific; is a consultant for Abbott; and has been awarded research grants from Edwards Lifesciences, Medtronic, Abbott, and Boston Scientific. T. Waggoner served as a consultant and received research grants from Abbott, Abiomed, Boston Scientific, Edwards Lifesciences, and Medtronic; received educational grants from Philips; and is a shareholder in Corstasis. S. Chetcuti reports personal fees from Medtronic; grants from Edwards Lifesciences, Boston Scientific, and JenaValve (paid to the institution) during the conduct of the study; and being on the advisory board for BioTrace and JenaValve, without remuneration. W.-K. Kim reports personal fees from Abbott, Anteris Technologies, Boston Scientific, Cardiawave, Edwards Lifesciences, Hi-D Imaging, JenaValve, Meril Life Sciences, and Products & Features; and institutional fees from Boston Scientific. J.L. Cavalcante has served on advisory boards for Abbott, Boston Scientific, and Medtronic; received consulting fees from 4C Medical Technologies, Anteris Technologies, Abbott, Aria CV, Boston Scientific, Edwards Lifesciences, JenaValve Technology, Medtronic, VDyne, W.L. Gore & Associates, and XyloCor; and received research/grant support from Abbott Northwestern Hospital Foundation and Abbott. K. Feldt has received consulting fees from Anteris Technologies and Alleviant Medical; payment or honoraria from AstraZeneca, Pfizer, and Abbott; and has participated on an advisory board at Amgen. C.U. Meduri is the CMO at Anteris Technologies; received grants/research support from Boston Scientific; and received honoraria/consultation fees from Abbott, Alleviant Medical, Boston Scientific, Cardiovalve, VDyne, and xDot Medical. D. Meier has received an institutional grant from Edwards Lifesciences; and is a consultant for Anteris Technologies and Abbott. J.J. Popma was a former employee of Medtronic (<24 months). S. Windecker reports research, travel and/or educational grants to the institution from Abbott, Abiomed, Alnylam, Amicus Therapeutics, Amgen, Anteris Technologies, AstraZeneca, Bayer, B. Braun, Bioanalytica, Biotronik, Boehringer Ingelheim, Boston Scientific, Bristol-Myers Squibb, Cordis Medical, CorFlow Therapeutics, CSL Behring, Daiichi Sankyo, Edwards Lifesciences, Fumedica, GE HealthCare, Guerbet, IACULIS, Inari Medical, Janssen AI, Johnson & Johnson, Medalliance, Medtronic, Merck Sharp & Dohme, Neovii Pharmaceuticals, Neutromedics AG, Novartis, Novo Nordisk, OM Pharma, Optimapharm, Orchestra BioMed, Pfizer, Philips AG, Sanofi-Aventis, Servier, Shockwave Medical, Siemens Healthineers, Sinomed, Sahajanand Medical Technologies, Vascular Medical, and V-Wave; and serves as an advisory board member and/or member of the steering/executive group of trials funded by Abbott, Amgen, Anteris Technologies, Abiomed, Edwards Lifesciences, EnCarda Inc., Medtronic, Novartis, and Sinomed, with payments to the institution but no personal payments; and he is also a member of the steering/

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Supplementary data

Supplementary Table 1. Inclusion and exclusion criteria for study cohorts.

Supplementary Table 2. Baseline characteristics.

Supplementary Table 3. Procedural characteristics and technical success for all study cohorts.

Supplementary Table 4. Summary of major periprocedural complications encountered.

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ORIGINAL RESEARCH

Intra-annular self-expanding or balloon-expandable TAVI in small annuli: the NAVULTRA registry

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ABSTRACT

BACKGROUND: Comparative data between self-expanding Navitor (NAV) and balloon-expandable SAPIEN 3 Ultra (ULTRA) transcatheter heart valves (THVs) in patients with small aortic annuli are lacking.

AIMS: This study sought to evaluate outcomes of transcatheter aortic valve implantation (TAVI) using the intra-annular NAV and the ULTRA THVs in severe aortic stenosis patients with small annuli.

METHODS: Patients with an aortic annulus area ≤430 mm^2 undergoing TAVI with either NAV or ULTRA from the NAVULTRA registry were included. Propensity-matched analysis was performed for adjustment. Primary endpoints included 1-year mortality, a composite endpoint (all-cause mortality, disabling stroke, or heart failure hospitalisation), and 30-day device-oriented outcomes (severe prosthesis-patient mismatch, moderate or greater paravalvular leak [PVL], mean gradient ≥20 mmHg).

RESULTS: Among 1,617 patients, 524 propensity score-matched pairs were analysed. At 1 year, all-cause mortality was 8.8% with NAV versus 9.0% with ULTRA (adjusted p=0.585), and the composite endpoint occurred in 11.3% versus 11.8%, respectively (adjusted p=0.149). The device-oriented endpoint favoured NAV compared to ULTRA (6.0% vs 29.3%; adjusted p<0.01), with a lower residual transvalvular gradient (7.3 mmHg vs 12.7 mmHg; adjusted p<0.01), and reduced incidence of any prosthesis-patient mismatch (odds ratio 0.27, 95% confidence interval: 0.18-0.43; adjusted p<0.01). However, NAV was associated with higher rates of mild paravalvular leak (NAV 33.5% vs ULTRA 23.2%; adjusted p<0.05) and permanent pacemaker implantation (PPI; NAV 20.1% vs 11.9% ULTRA; adjusted p<0.01).

CONCLUSIONS: In patients with small aortic annuli, TAVI with both NAV and ULTRA provided comparable 1-year clinical outcomes, but NAV showed better haemodynamic performance at the cost of higher rates of mild PVL and PPI.

KEYWORDS: intra-annular; Navitor; SAPIEN 3 Ultra; small aortic annuli; TAVI

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Over the past several years, transcatheter aortic valve implantation (TAVI) has become the standard treatment for elderly patients with severe aortic stenosis across a wide spectrum of surgical risk[1]. Different types of transcatheter heart valves (THVs) are now available, with supra-annular self-expanding (SE) valves demonstrating superior haemodynamic performance compared to balloon-expandable (BE) valves, possibly due to the supra-annular positioning of their leaflets[2,3]. These haemodynamic advantages are particularly important for patients with small annuli, who are at higher risk of residual elevated gradients, prosthesis-patient mismatch, and reduced exercise capacity[4,5]. The randomised SMART trial (Small Annuli Randomized to Evolut or SAPIEN Trial)[6] recently confirmed the superior haemodynamic performance of supra-annular self-expanding valves compared with intra-annular balloon-expandable valves in small annuli. However, data on the performance of intra-annular self-expanding valves in this population are scarce[7,8]. The aim of this study was therefore to evaluate, in real-world practice, the clinical outcomes and valve performance at 30 days and 1 year of the intra-annular self-expanding Navitor (NAV; Abbott) THV compared with the intra-annular balloon-expandable SAPIEN 3 Ultra (ULTRA; Edwards Lifesciences) THV in patients with small aortic valve (AV) anatomy.

Impact on daily practice

In this real-world, multicentre study, we found that the two transcatheter aortic valve implantation platforms, Navitor (NAV) and SAPIEN 3 Ultra, were associated with similar 1-year clinical outcomes, but the NAV device showed better haemodynamic performance and a lower incidence of moderate to severe prosthesis-patient mismatch, as well as higher rates of mild paravalvular leak and new permanent pacemaker implantation. Transprosthetic gradients were significantly lower in patients receiving NAV. Randomised clinical trials with longer follow-up are needed to explore the differences between the two devices, aiming for a patient-specific approach to ensure optimised patient outcomes in this challenging population.

Methods

STUDY POPULATION

NAVULTRA is a multicentre, observational, investigator-initiated registry that enrolled consecutive patients with symptomatic severe aortic stenosis (AS) who underwent transfemoral TAVI using SE Navitor and BE SAPIEN 3 Ultra THVs at 16 high-volume centres across Europe and the United States. Details of the registry have been previously reported[9]. The present analysis included consecutive patients with an aortic valve annulus area of 430 mm^2 or less as determined on the pre-TAVI computed tomography (CT) scan. For the purposes of the present study, patients with a previous surgical aortic valve replacement, incomplete follow-up, missing THV identification (ID), or incomplete CT data were excluded **(Figure 1)**. The study was approved by the local ethics committee of the coordinating institution and was conducted in accordance with the Declaration of Helsinki.

DEFINITIONS AND STUDY OUTCOMES

A small aortic valve annulus was defined as an aortic valve area of 430 mm^2 or less as measured on computed tomography. The device-oriented endpoint was defined as haemodynamic structural valve dysfunction (HSVD) if the mean gradient was ≥20 mmHg or non-structural valve dysfunction (NSVD) if there was a severe prosthesis-patient mismatch (PPM) according to Valve Academic Research Consortium 3 (VARC-3) guidelines or the presence of moderate to severe paravalvular leak (PVL). The primary outcomes of this analysis were the rate of all-cause mortality, the composite of all-cause death, disabling stroke, and repeat hospitalisation for heart failure at 1 year, as well as the composite device-oriented endpoint of HSVD and NSVD. Secondary outcomes of interest were technical success, 30-day device success, and 30-day early safety. All clinical outcomes, procedural complications, and PPM were defined according to VARC-3 criteria[10].

STATISTICAL ANALYSIS

All continuous variables are expressed as the mean±standard deviation (SD) and compared using the unpaired Student's t-test. All categorical variables were compared using the chi-square test or Fisher's exact test. Missing baseline covariates were estimated using the multiple imputation by chained equations method (n=5)[11]. The propensity score (PS) was used to adjust for differences in baseline characteristics and potential confounders that may lead to biased estimates of treatment outcomes. A 1-to-1 nearest-neighbour matching algorithm without replacement (calliper=0.2) was performed to identify PS-matched pairs. This was done by means of a non-parsimonious multivariable logistic regression model including the following 38 covariates: age, sex, body mass index, hypertension, Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) score, New York Heart Association Functional Class III or IV, diabetes, chronic obstructive pulmonary disease, severe liver disease, atrial fibrillation, peripheral vascular disease, prior stroke, coronary artery disease, prior myocardial infarction, prior percutaneous coronary intervention, previous coronary artery bypass graft, other previous cardiac surgery, estimated glomerular filtration rate, dialysis, porcelain aorta, prior permanent pacemaker implantation (PPI), baseline left bundle branch block, baseline right bundle branch block,

Abbreviations

BE	balloon-expandable	**PVL**	paravalvular leak	**THV**	transcatheter heart valve
NAV	Navitor	**SE**	self-expanding	**ULTRA**	SAPIEN 3 Ultra
PPI	permanent pacemaker implantation	**TAVI**	transcatheter aortic valve implantation	**VARC-3**	Valve Academic Research Consortium 3

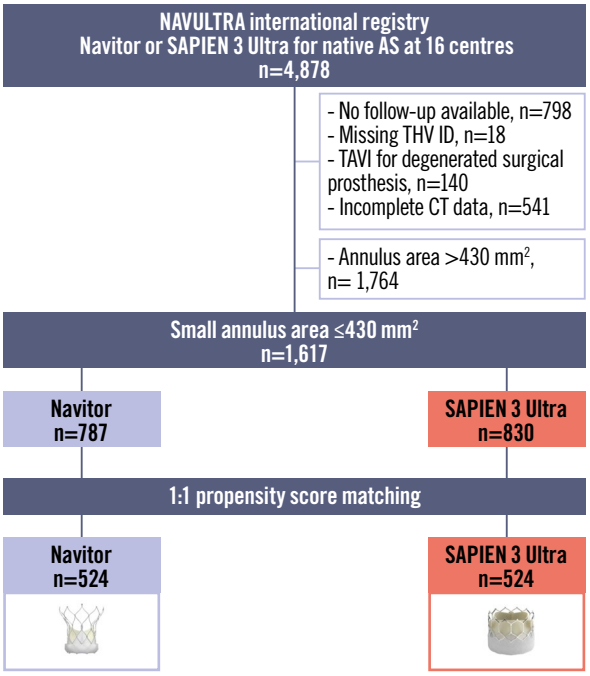


Figure 1. *Study flowchart. Study flowchart showing the derivation of unmatched and propensity-matched patient cohorts with small aortic annuli from the NAVULTRA registry. AS: aortic stenosis; CT: computed tomography; ID: identification; TAVI: transcatheter aortic valve implantation; THV: transcatheter heart valve*

baseline first-degree atrioventricular block, left ventricular ejection fraction, transaortic maximum gradient, transaortic mean gradient, aortic valve area, moderate to severe mitral regurgitation, moderate to severe tricuspid regurgitation, moderate to severe aortic regurgitation, severe pulmonary hypertension, anaesthesia type, aortic valve perimeter, sinus of Valsalva mean diameter, eccentric annulus index, left ventricular outflow tract (LVOT), and aortic valve calcium distribution at the pre-TAVI CT. Matching was performed within each imputed dataset using the observed and imputed covariate values. The balance in the matched datasets was assessed by computing the standardised mean difference for each covariate. Finally, the treatment effects estimated in each of the matched datasets were pooled together using Rubin's rules[12].

Prespecified primary and secondary outcomes were compared between the NAV and ULTRA valve groups in both the overall and PS-matched cohorts. The risk of adverse events 1 year after TAVI was compared for both cohorts using Cox proportional hazards regression and Kaplan-Meier analysis. The impact of the competing risk of death on disabling stroke incidence and heart failure (HF) rehospitalisation rates was assessed using cumulative incidence function analysis.

Interaction p-values between valve type and annulus size for clinical and echocardiographic outcomes were also calculated.

Statistical analysis was performed using R version 4.2.0 (R Foundation for Statistical Computing) and SPSS Statistics version 25 for Macintosh (IBM). Propensity score and matching procedures were conducted using the MatchThem package in R[12].

Results

STUDY POPULATION AND BASELINE CHARACTERISTICS

A total of 4,878 patients who underwent transfemoral TAVI were included in the NAVULTRA registry between November 2018 and April 2024; 1,617 patients with small annuli met the inclusion criteria and were analysed in the present study. Among these, 787 patients underwent TAVI with NAV and 830 with ULTRA **(Figure 1)**. The overall cohort was predominantly female (75.4%), with a mean age of 80.7 years and a mean STS-PROM score of 4.5%. The mean±SD aortic annulus area was 377±38 mm². Baseline characteristics of the unmatched population are reported in **Table 1** and **Supplementary Table 1**.

From the entire cohort, a 1-to-1 propensity score-matching analysis based on clinical and anatomical characteristics and anaesthesia type resulted in 524 matched pairs. There were no significant differences in baseline characteristics between the propensity score-matched NAV and ULTRA groups, including the mean aortic annular area, the degree of AV and LVOT calcification **(Supplementary Figure 1)**.

PROCEDURAL DETAILS, IN-HOSPITAL AND 30-DAY OUTCOMES

Procedural characteristics and in-hospital outcomes for the unadjusted and PS-matched populations are presented in **Table 2**, **Supplementary Table 2**, **Supplementary Table 3**, **Supplementary Figure 2**, and **Supplementary Figure 3**. In the PS-matched population, both predilatation and post-dilatation were more frequently performed with NAV compared with ULTRA (predilatation: odds ratio [OR] 17.32, 95% confidence interval [CI]: 10.98-27.31; p<0.01; post-dilatation: OR 3.09, 95% CI: 2.06-4.62; p<0.01). Procedural complications were rare with no significant differences between the two groups. The incidence of new left bundle branch block (OR 1.73, 95% CI: 1.18-2.56; p<0.01) and new permanent pacemaker implantation (OR 2.14, 95% CI: 1.40-3.25; p<0.01) were significantly higher in NAV recipients compared to those receiving ULTRA in both the unmatched and matched populations.

At 30 days, there were no significant differences between patients treated with the BE and SE valves in terms of all-cause mortality, disabling or non-disabling stroke, or rehospitalisation for heart failure. However, the incidence of new PPI was significantly higher in the SE group **(Supplementary Table 4)**.

STUDY ENDPOINTS

The study outcomes of both unadjusted and propensity score-matched populations are presented in **Table 3**. The rate of the coprimary composite endpoint of death from any cause, disabling stroke, or HF rehospitalisation at 1 year after the procedure was similar between the two groups (11.3% NAV vs 11.8% ULTRA; p=0.463) **(Central illustration)**. The estimates for each component of the clinical coprimary endpoint in the SE NAV and the BE ULTRA groups were as follows: the rates of death from any cause were 8.8% in patients receiving an

Table 1. Baseline characteristics of registry patients before PS matching.

	Missing data,%	Overall (n=1,617)	NAV (n=787)	ULTRA (n=830)	*p*-value
Age, years	-	80.7±6.7	81.0±6.0	80.0±7.3	<0.01
Female, n	-	1,219 (75.4)	635 (80.7)	584 (70.4)	<0.01
Body mass index, kg/m^2	1.4	26.80±5.22	26.20±4.58	27.36±5.70	<0.01
Body surface area, m^2	1.4	1.74±0.20	1.73±0.18	1.76±0.22	<0.01
STS-PROM score	25.3	4.55±3.29	4.98±3.54	4.34±3.14	0.01
NYHA Class III or IV	2.8	873 (55.5)	358 (46.0)	515 (65.0)	<0.01
Hypertension	-	1,294 (80.0)	638 (81.0)	656 (79.1)	0.330
Diabetes mellitus	-	530 (32.8)	239 (30.3)	291 (35.1)	0.04
COPD	0.1	233 (14.4)	126 (16.0)	107 (12.9)	0.076
Severe liver disease	1.7	22 (1.4)	8 (1.0)	14 (1.7)	0.235
Porcelain aorta	7.1	38 (2.0)	19 (2.8)	19 (2.3)	0.506
Atrial fibrillation	-	312 (19.2)	124 (15.7)	188 (22.6)	<0.01
Prior PCI	1.6	299 (18.8)	158 (20.0)	141 (17.6)	0.199
Peripheral vascular disease	0.5	180 (11.2)	91 (11.6)	89 (10.7)	0.566
Previous stroke	-	121 (7.5)	60 (7.6)	61 (7.3)	0.834
CAD	0.1	569 (35.2)	244 (31.0)	325 (39.2)	<0.01
Prior MI	0.1	200 (12.4)	85 (10.8)	115 (13.8)	0.06
Prior CABG	0.1	68 (4.2)	23 (2.9)	45 (5.4)	0.01
Other prior cardiac surgery	7.9	41 (2.7)	16 (2.1)	25 (3.4)	0.145
Dialysis	-	30 (1.8)	13 (1.6)	17 (2.0)	0.551
eGFR <30 mL/min/1.73m^2	2.8	151 (9.6)	58 (7.4)	93 (11.8)	0.03
eGFR, mL/min/1.73m^2	2.8	58.72±22.81	60.50±22.73	56.94±22.76	<0.01
Haemoglobin, g/dL	5.4	12.00±2.62	12.16±1.71	11.85±3.30	0.02
Severe pulmonary hypertension	22.5	119 (9.5)	61 (9.6)	58 (9.9)	0.657
Previous pacemaker	-	128 (7.9)	84 (10.7)	44 (5.3)	<0.01

Values are n, n (%), or mean±standard deviation. CABG: coronary artery bypass graft; CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; eGFR: estimated glomerular filtration rate; MI: myocardial infarction; NAV: Navitor; NYHA: New York Heart Association; PCI: percutaneous coronary intervention; PS: propensity score; STS-PROM: Society of Thoracic Surgeons Predicted Risk of Mortality; ULTRA: SAPIEN 3 Ultra

SE NAV and 9.0% in those with a BE ULTRA (p=0.449); the rates of disabling stroke were 1.3% for NAV and 1.6% for ULTRA (p=0.963); rehospitalisation for heart failure rates were, respectively, 3.9% and 3.0% (p=0.122) **(Supplementary Figure 4)**. These findings were consistent after accounting for the competing risk of all-cause death. The rate of a repeat procedure at 1 year was low and comparable between NAV and ULTRA groups, with only 1 and 2 cases, respectively.

The propensity-matched analysis confirmed that there were no significant differences in the rates of any death (hazard ratio [HR] 1.36, 95% CI: 0.89-2.08; p=0.152), cardiac death (HR 1.17, 95% CI: 0.70-1.98; p=0.543), disabling stroke (HR 1.20, 95% CI: 0.37-3.90; p=0.755), non-disabling stroke (HR 1.03, 95% CI: 0.33-3.21; p=0.961) or HF hospitalisation (HR 1.69, 95% CI: 0.84-3.38; p=0.137). However, the rate of new PPI at 1 year (HR 1.97, 95% CI: 1.36-2.85; p<0.01) was significantly higher in the NAV group compared with the ULTRA group in both unmatched and matched populations **(Table 3)**.

In the unadjusted population, the composite device-oriented endpoint **(Table 3, Central illustration)** occurred more frequently with the BE ULTRA (29.3%) than with SE NAV (6.0%; OR 0.15, 95% CI: 0.08-0.26; p<0.01). The rate of HSVD at 30 days was 0.6% with NAV and 10.4% with ULTRA (p<0.01). Similarly, NSVD was higher in the ULTRA group (4.4% NAV vs 19.6% ULTRA; p<0.01) **(Figure 2)**. The SE NAV yielded lower mean postprocedural aortic valve gradients than ULTRA (7.35 mmHg vs 12.71 mmHg, respectively; p<0.01) and larger effective orifice areas (EOAs; 2.09 cm^2 vs 1.64 cm^2; p<0.01). These differences corresponded to a significantly lower incidence of moderate PPM (NAV 11.9% vs ULTRA 30.8%; p<0.01) and severe PPM (NAV 2.5% vs ULTRA 18.8%; p<0.01) at 30 days in the NAV group. However, ULTRA more frequently achieved none/trace PVL compared to NAV (OR 0.63, 95% CI: 0.44-0.90; p=0.01), whereas the rate of mild PVL was higher in the NAV group (OR 1.63, 95% CI: 1.14-2.38; p<0.01) **(Figure 3)**.

In the propensity-matched analysis **(Table 3)**, the SE NAV confirmed having more favourable haemodynamic performance at 30 days (device-oriented endpoint: OR 0.34, 95% CI: 0.18-0.63; p<0.01) with lower residual mean gradients (mean difference: –5.03, 95% CI: –5.73 to 0.435; p<0.01), a larger effective orifice area (mean difference: 0.37, 95% CI: 0.24-0.50; p<0.01) and a lower incidence of any PPM, including moderate and severe (moderate: OR 0.45, 95% CI: 0.25-0.78; p<0.05; severe: OR 0.38, 95% CI:

Table 2. Procedural and in-hospital outcomes of unadjusted and propensity-matched cohorts.

	NAV (n=787)	ULTRA (n=830)	Unadjusted		Propensity-matched	
			Mean change/OR (95% CI)	*p*-value	Mean change/OR (95% CI)	*p*-value
General anaesthesia	47 (6.0)	130 (15.7)	0.34 (0.24-0.48)	<0.01	0.96 (0.58-1.49)	0.872
Predilatation	592/747 (79.2)	156/740 (21)	14.30 (11.17-18.41)	<0.01	17.32 (10.98-27.31)	<0.01
Post-dilatation	210/746 (28.1)	81/740 (10.9)	3.19 (2.42-4.24)	<0.01	3.09 (2.06-4.62)	<0.01
Contrast dye, mL	134±77	136±81	–2.23 (–11.33 to 6.77)	0.622	–4.10 (–14.19 to 5.99)	0.425
In-hospital death	3 (0.3)	8 (0.9)	0.30 (0.08-1.36)	0.169	1.28 (0.08-21.07)	0.858
Cardiac tamponade	2 (0.2)	4 (0.5)	0.71 (0.10-3.63)	0.689	0.61 (0.5-7.64)	0.690
Conversion to open-heart surgery	1 (0.1)	4 (0.5)	0.26 (0.01-1.78)	0.232	0.46 (0.04-5.17)	0.528
Second THV implanted	8 (1.0)	8 (0.9)	1.05 (0.39-2.88)	0.915	0.80 (0.22-2.91)	0.739
Major vascular complications	6 (0.8)	12 (1.4)	0.52 (0.18-1.35)	0.198	0.74 (0.17-1.74)	0.683
Major bleeding (type 2)	3 (0.4)	15 (1.8)	0.21 (0.05-0.63)	0.01	0.47 (0.10-2.20)	0.340
New pacemaker	138 (17.5)	76 (9.1)	2.10 (1.56-2.85)	<0.01	2.14 (1.40-3.25)	<0.01
New onset of AF	13 (1.6)	10 (1.2)	1.37 (0.60-3.24)	0.450	1.40 (0.44-4.52)	0.565
New LBBB	143/555 (25.8)	124/813 (15.2)	1.92 (1.47-2.52)	<0.01	1.73 (1.18-2.56)	<0.01
New dialysis	3 (0.4)	4 (0.5)	0.790 (0.15-3.59)	0.758	0.85 (0.03-22.46)	0.919
VARC-3 technical success	745 (94.7)	796 (95.9)	0.76 (0.47-1.20)	0.240	0.65 (0.31-1.37)	0.245
LOS, days	4.1±4.9	3.8±6.7	0.33 (–0.25 to 0.91)*	0.265	0.66 (–0.10 to 1.43)*	0.09

Values are n (%), n/N (%), or mean±standard deviation, unless otherwise indicated. *Indicates mean change. AF: atrial fibrillation; CI: confidence interval; LBBB: left bundle branch block; LOS: length of stay; NAV: Navitor; OR: odds ratio; THV: transcatheter heart valve; ULTRA: SAPIEN 3 Ultra; VARC-3: Valve Academic Research Consortium 3

0.18-0.80; p<0.05). The ULTRA remained associated with a lower incidence of PVL, both none/trace and mild (none/trace: OR 0.66, 95% CI: 0.50-0.94; p<0.05; mild: OR 1.56, 95% CI: 1.01-2.39; p<0.05) **(Figure 3, Supplementary Table 5)**. These results were consistent at 1 year post-procedure **(Supplementary Table 6)**.

Among the secondary outcomes **(Figure 4, Table 3)**, the rate of technical success was high and comparable between the two groups (94.7% for NAV vs 95.9% for ULTRA; p=0.240). The device success rate was also high in both groups, with a statistically significant difference favouring the NAV group (92.9% for NAV vs 84.7% for ULTRA; p<0.01). However, the rate of the early safety endpoint was significantly higher with the ULTRA THV (82.6%) compared to the NAV THV (75.6%; OR 0.65, 95% CI: 0.51-0.83; p<0.01).

INTERACTION ANALYSES

In the extended cohort, which also included patients with larger annuli (>430 mm^2), clinical and haemodynamic performance of the two devices was similar for both large and small annuli (all interaction p-values>0.05).

Discussion

The main findings of the present analysis comparing intra-annular SE Navitor and BE SAPIEN 3 Ultra THVs in an unselected real-world population with small annuli are as follows: (1) there were no significant differences between the SE and BE THVs in the rate of all-cause mortality or in the composite endpoint of death, disabling stroke, and repeat hospitalisation for heart failure at 1 year; (2) the SE device was superior to the BE platform with respect to the device-oriented composite endpoint of HSVD and NSVD; (3) the SE device demonstrated lower incidences of HSVD, NSVD, and any prosthesis-patient mismatch at 30 days owing to a lower mean residual transvalvular gradient and a larger EOA than with the BE device; (4) the VARC-3 technical success rate was achieved in >90% of patients for both devices, with no significant difference between groups; (5) the BE device had a lower rate of

Table 3. Study outcomes/endpoints of unadjusted and propensity-matched cohorts.

	Unadjusted				Propensity-matched	
	NAV	ULTRA	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Primary clinical endpoints	n=787	n=830				
All-cause death	50 (8.8)	54 (9.0)	1.13 (0.81-1.57)	0.449	1.36 (0.89-2.08)	0.152
Composite endpoint	66 (11.3)	72 (11.8)	1.11 (0.83-1.49)	0.463	1.33 (0.90-1.98)	0.149
Primary echocardiography endpoint	n=249	n=470				
Device-oriented endpoint at 30 days	15 (6.0)	138 (29.3)	0.15 (0.08-0.26)	<0.01	0.34 (0.18-0.63)	<0.01
Secondary endpoints						
30-day HSVD*	4 (0.6)	69 (10.4)	0.05 (0.02-0.13)	<0.01	0.11 (0.03-0.35)	<0.01
30-day NSVD*	11 (4.4)	87 (19.6)	0.19 (0.09-0.35)	<0.01	0.33 (0.21-0.52)	<0.01
30-day moderate PPM**	29 (11.9)	136 (30.8)	0.30 (0.19-0.45)	<0.01	0.45 (0.25-0.78)	0.01
30-day severe PPM**	6 (2.5)	83 (18.8)	0.08 (0.02-0.21)	<0.01	0.38 (0.18-0.80)	0.02
30-day any PPM**	35 (14.4)	219 (49.6)	0.17 (0.11-0.25)	<0.01	0.28 (0.18-0.43)	<0.01
VARC-3 technical success	745 (94.7)	796 (95.9)	0.76 (0.47-1.20)	0.240	0.64 (0.30-1.37)	0.245
VARC-3 device success	731 (92.9)	703 (84.7)	2.36 (1.70-3.30)	<0.01	1.88 (1.23-2.88)	<0.01
VARC-3 early safety	595 (75.6)	686 (82.6)	0.65 (0.51-0.83)	<0.01	0.61 (0.44-0.83)	<0.01
At 1 year						
Cardiac death	31 (5.5)	35 (5.7)	0.95 (0.63-1.44)	0.820	1.17 (0.70-1.98)	0.543
Disabling stroke	9 (1.3)	11 (1.6)	1.02 (0.45-2.32)	0.963	1.20 (0.37-3.90)	0.755
Non-disabling stroke	8 (1.1)	6 (0.8)	1.22 (0.44-3.38)	0.694	1.03 (0.33-3.21)	0.961
Hospitalisation for HF	23 (3.9)	17 (3.0)	1.54 (0.89-2.67)	0.122	1.69 (0.84-3.38)	0.137
New PPI	152 (20.1)	90 (11.2)	1.88 (1.45-2.44)	<0.01	1.97 (1.36-2.85)	<0.01

Values are n (%) unless otherwise indicated. Clinical outcomes are reported as Kaplan-Meier estimates at the specific timepoint. *Echo data were available for 641 patients with NAV and 662 with ULTRA. **Echo data were available for 243 with NAV and 444 with ULTRA. CI: confidence interval; HF: heart failure; HR: hazard ratio; HSVD: haemodynamic structural valve dysfunction; NAV: Navitor; NSVD: non-structural valve dysfunction; OR: odds ratio; PPI: permanent pacemaker implantation; PPM: prosthesis-patient mismatch; ULTRA: SAPIEN 3 Ultra; VARC-3: Valve Academic Research Consortium 3

VARC-3 device success, mainly due to a higher residual mean transprosthetic gradient; (6) the BE device was associated with a lower rate of PPI at 1 year and less occurrence of any PVL.

Patients with small annuli represent a challenging subset of aortic stenosis patients as they are at higher risk of residual elevated gradients and prosthesis-patient mismatch. These haemodynamic considerations may also have implications for clinical outcomes and valve durability[13,14].

In the present analysis from the unselected, real-world NAVULTRA registry, the rates of all-cause mortality and the composite endpoint at 1 year were similar between patients with small aortic annuli undergoing TAVI with intra-annular NAV and ULTRA THVs. Similarly, no significant differences were observed in the incidence of cardiac death, any stroke, disabling stroke, or repeat procedures between the two groups at 1 year. However, the rate of new PPI at 1 year was lower in the ULTRA group.

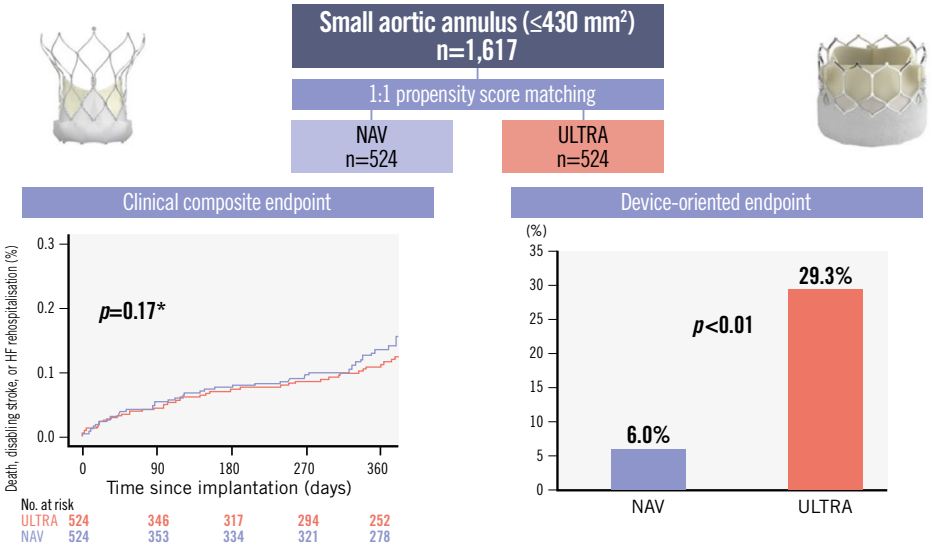
The SE NAV, despite its intra-annular design – which is often considered haemodynamically less favourable, particularly in patients with small aortic annuli – demonstrated superior haemodynamic performance compared with the intra-annular BE ULTRA due to the significantly lower rate of patients with mean residual transvalvular gradients ≥20 mmHg and less incidence of moderate or severe PPM. These outcomes are comparable to those reported for supra-annular self-expanding devices[15-17].

The clinical relevance of elevated residual gradients and moderate to severe PPM in patients with small aortic annuli undergoing TAVI remains a subject of debate. Data from the FRANCE-2 registry and the National Echo Database Australia demonstrated increased mortality at both 1 and 5 years among patients with persistently elevated transprosthetic gradients[18,19]. Previous studies have also shown increased risks of mortality and heart failure hospitalisation in patients with moderate to severe PPM following surgical aortic valve replacement and TAVI, particularly in those with severe PPM[5,20,21]. Conversely, other investigations have reported no significant association between severe PPM and clinical outcomes[14,22,23]. Few prospective, randomised studies comparing THV platforms have demonstrated superior haemodynamic performance of supra-annular self-expanding valves, yet they show no significant difference in clinical outcomes up to 5 years[3,4]. Most recently, the SMART randomised trial also confirmed that although supra-annular self-expanding valves offer improved haemodynamic performance in patients with small annuli, there was no difference in the composite clinical endpoint of death, stroke, and heart failure hospitalisation at 2 years[6]. This conflicting evidence on the impact of high residual gradients and PPM may reflect differences in study populations, definitions of PPM (measured EOA vs predicted EOA), and the variety of bioprostheses used across studies. Furthermore, echocardiographic assessment of gradients may be influenced

EuroIntervention — Central Illustration

Primary outcomes of TAVI with Navitor or SAPIEN 3 Ultra in patients with small aortic annuli.

The NAVULTRA multicentre, international registry: transfemoral TAVI with Navitor or SAPIEN 3 Ultra for severe native AS at 16 centres from 2018 to 2024



- NAV and ULTRA were associated with comparable rates of the composite endpoint of any death, disabling stroke, or rehospitalisation for heart failure at 1 year.
- The device-oriented composite endpoint of HSVD and NSVD occurred more frequently with ULTRA compared to NAV.
- NAV showed a lower mean transvalvular gradient and a larger EOA than ULTRA but higher rates of mild PVL and need for PPI.

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*Kaplan-Meier curves show the clinical composite endpoint at 1 year, and the device-oriented composite endpoint is presented in a bar chart. *The Kaplan-Meier curves in the figure are derived from a single imputed dataset and should be considered representative of the main results presented in the paper. AS: aortic stenosis; EOA: effective orifice area; HF: heart failure; HSVD: haemodynamic structural valve dysfunction; NAV: Navitor; NSVD: non-structural valve dysfunction; PPI: permanent pacemaker implantation; PVL: paravalvular leak; TAVI: transcatheter aortic valve implantation; ULTRA: SAPIEN 3 Ultra*

by factors such as Doppler misalignment, fluid viscosity, and the pressure recovery phenomenon. Notably, discordance between echocardiographic and invasive measurements for haemodynamic performance of bioprostheses has been shown in several studies[24,25], with higher transprosthetic gradients and smaller EOAs observed on echocardiography compared to catheter-based assessments.

In our study, the observed differences in residual mean gradients and rates of PPM did not appear to translate into differences in 1-year clinical outcomes between the two THV platforms. Specifically, there were no significant differences in mortality, heart failure rehospitalisation, any stroke, or reintervention at 1 year. However, impaired forward haemodynamics may become apparent in long-term outcomes, potentially accelerating bioprosthetic degeneration and the need for reintervention. Extended follow-up is therefore warranted.

In terms of paravalvular leak, the incidence of moderate or greater PVL was very low across both cohorts at 30 days and at 1 year. However, mild PVL was less frequent in patients treated with ULTRA compared to those treated with NAV. While the association between moderate PVL and increased mortality is well established, a recent meta-analysis has also suggested that even mild PVL may negatively affect mortality and rehospitalisation, regardless of the type of THV, although the data remain controversial[26,27].

Among the secondary outcomes, although VARC-3 technical success rates were high and comparable between groups, VARC-3 device success favoured NAV in our analysis, primarily due to the higher residual transprosthetic gradients observed in the ULTRA group. Conversely, the VARC-3 early safety composite endpoint significantly favoured ULTRA, driven by the higher incidence of new PPI in the NAV group. New PPI remains a concern following TAVI, as it has been associated with adverse clinical outcomes, including increased mortality and HF hospitalisations[28].

Of note, regarding in-hospital and 30-day outcomes, the rates of complications – including all-cause mortality, any

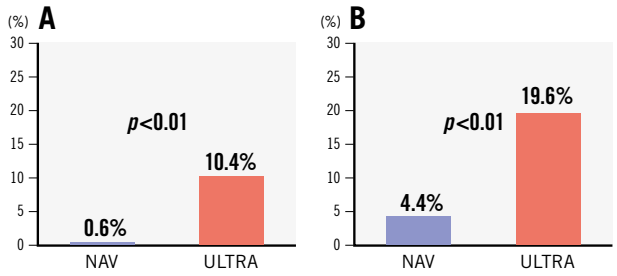

Figure 2. *Components of the device-oriented composite endpoint. The components of the device-oriented composite endpoint at 30 days post-procedure. A) Haemodynamic structural valve dysfunction (MG ≥20 mmHg). B) Non-structural valve dysfunction (severe PPM or PVL ≥2). MG: mean gradient; NAV: Navitor; PPM: prosthesis-patient mismatch; PVL: paravalvular leak; ULTRA: SAPIEN 3 Ultra*

stroke, annular rupture, or coronary occlusion – were very low for both devices, suggesting that both platforms are safe in patients with small aortic anatomy.

Finally, in the extended cohort, which included patients with larger annuli (>430 mm^2), clinical and haemodynamic performance between the two devices remained consistent across annulus sizes, with no significant heterogeneity in treatment effect observed.

This study demonstrated that both intra-annular devices yielded comparable clinical outcomes at 1 year. However, the NAV device showed superior haemodynamic performance, with lower rates of PPM and residual high gradients, albeit at the cost of a higher incidence of mild paravalvular leak and need for PPI. As TAVI continues to expand to younger and lower-risk patient populations, haemodynamic performance becomes increasingly relevant, as it may influence long-term valve durability and the need for reintervention – particularly in patients with small aortic annuli, where reintervention poses technical challenges and is associated with increased

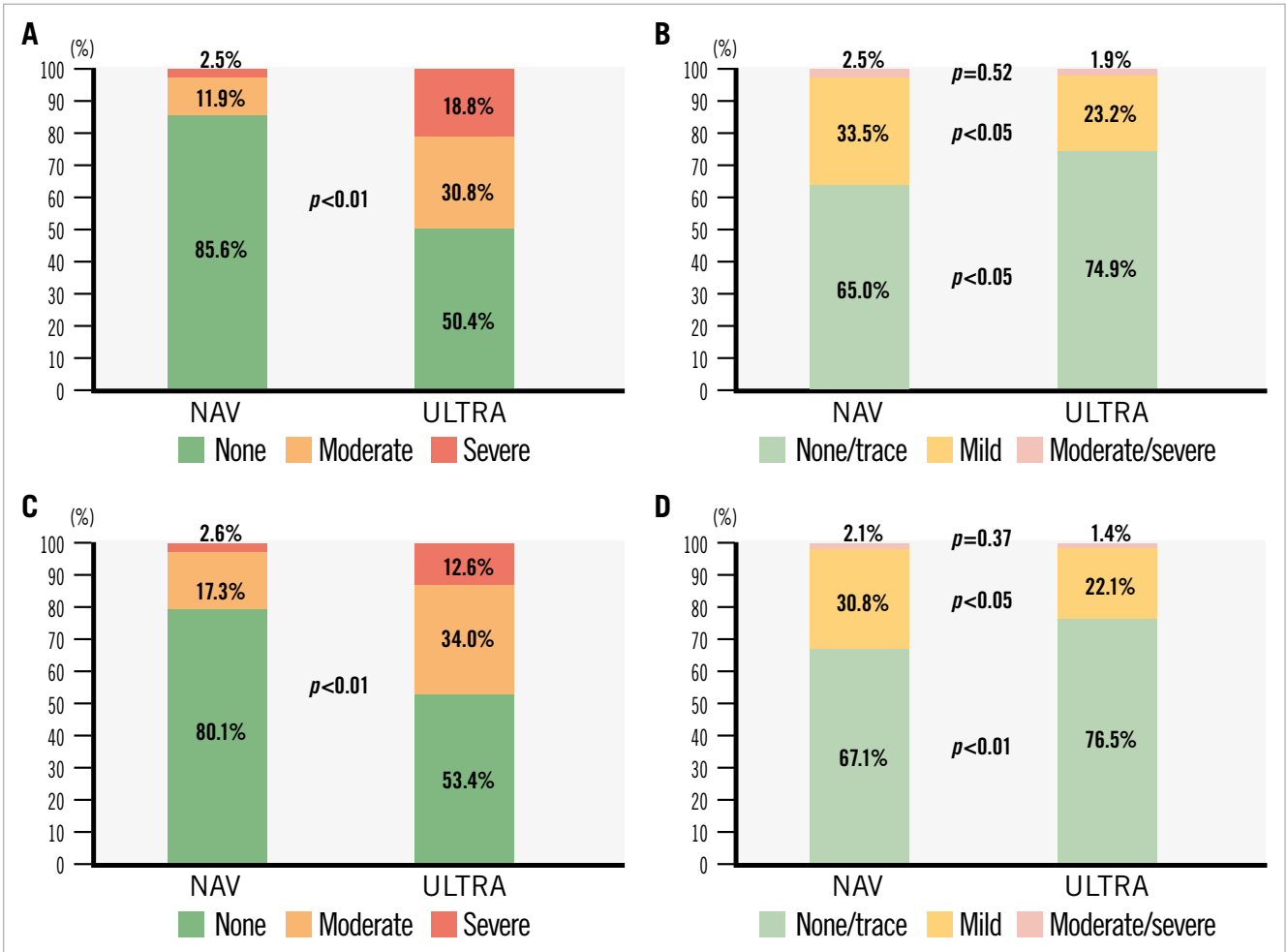

Figure 3. *Prosthesis-patient mismatch and paravalvular leak with Navitor and SAPIEN 3 Ultra in small aortic annuli. The bar charts represent the rates of prosthesis-patient mismatch and paravalvular leak at 30 days and 1 year in patients with small annuli undergoing TAVI with NAV and ULTRA: (A) prosthesis-patient mismatch at 30 days; (B) paravalvular leak at 30 days; (C) prosthesis-patient mismatch at 1 year; (D) paravalvular leak at 1 year. Echocardiographic data missing at 1 year were imputed using the last observation carried forward method. NAV: Navitor; TAVI: transcatheter aortic valve implantation; ULTRA: SAPIEN 3 Ultra*

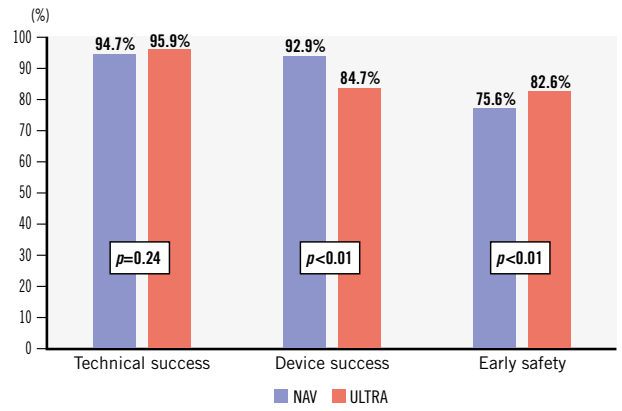

Figure 4. *Early VARC-3 endpoints comparing intra-annular self-expanding versus balloon-expandable transcatheter heart valves in small annuli. Comparison of VARC-3 early composite endpoints between intra-annular NAV and ULTRA devices in small annuli. NAV: Navitor; ULTRA: SAPIEN 3 Ultra; VARC-3: Valve Academic Research Consortium-3*

procedural risks such as coronary occlusion and sinus of Valsalva sequestration. Nevertheless, treatment decisions must also take into account other key clinical factors, including the risk of PVL, which is known to be associated with increased mortality and rehospitalisation for HF, along with the need for permanent pacemaker implantation, which may adversely affect long-term outcomes[28]. Therefore, transcatheter heart valve selection in patients with small aortic annuli should not rely solely on early haemodynamic parameters but rather be guided by a comprehensive, patient-specific approach including clinical and anatomical characteristics. This should incorporate life expectancy, body size, anatomical characteristics and calcium burden, risk of PVL and PPI, and the feasibility of future coronary access and repeat TAVI procedures. Further randomised investigations are warranted to compare different THV platforms in this challenging subset of patients with severe aortic stenosis.

Limitations

This study has the inherent limitations of non-randomised, observational, retrospective studies without an independent adjudication of clinical events or an independent core laboratory to assess PVL severity and transprosthetic gradients. Although a propensity-matched approach based on 38 variables was applied to overcome differences in baseline characteristics and potential confounders, residual confounding remains a source of bias that cannot be excluded. Moreover, including a large number of variables may have reduced the number of matched pairs and negatively impacted the precision of the estimates. Selection bias in THV choice should also be acknowledged. It should be recognised that some missing echocardiographic data may have increased the risk of a type II error; however, this appears unlikely given the significant differences observed in the device-oriented endpoint and rate of prosthesis-patient mismatch. Lastly, this analysis is limited to 1-year outcomes, whereas haemodynamic differences may have an impact on longer-term outcomes.

Conclusions

This subanalysis from the NAVULTRA registry demonstrated that, among patients with aortic stenosis and small annuli undergoing TAVI, the NAV and ULTRA devices were comparable with respect to the 1-year composite endpoint of mortality, heart failure rehospitalisation, or disabling stroke. However, the intra-annular NAV was associated with superior haemodynamic performance, showing a reduced risk of prosthesis-patient mismatch and residual high gradients, albeit with a higher rate of mild paravalvular leaks and PPI. These findings warrant further investigation and extended follow-up in dedicated randomised clinical trials directly comparing these intra-annular devices in this challenging patient population.

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Conflict of interest statement

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Supplementary data

Supplementary Table 1. Baseline electrocardiographic, echocardiographic, and computed tomography characteristics of registry patients before propensity score matching.

Supplementary Table 2. Valve sizes used in patients with small annuli.

Supplementary Table 3. Echocardiographic outcomes of unadjusted and propensity-matched populations at discharge.

Supplementary Table 4. Clinical outcomes of unadjusted and propensity-matched populations at 30 days.

Supplementary Table 5. Echocardiographic outcomes of unadjusted and propensity-matched populations at 30 days.

Supplementary Table 6. Echocardiographic outcomes of unadjusted and propensity-matched populations at 1 year.

Supplementary Figure 1. Covariate balance plot.

Supplementary Figure 2. Mean gradients at discharge.

Supplementary Figure 3. Paravalvular leak at discharge.

Supplementary Figure 4. One-year clinical outcomes between NAV and ULTRA THVs.

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ORIGINAL RESEARCH

Five-year outcomes of the early-generation Intrepid transapical transcatheter mitral valve replacement system

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ABSTRACT

BACKGROUND: Transcatheter mitral valve replacement (TMVR) offers a potential treatment option for select patients with mitral regurgitation (MR) deemed unsuitable for surgery or transcatheter repair, but data are limited on its long-term durability and performance.

AIMS: We evaluated 5-year outcomes from the global Pilot Study with the Intrepid transapical (TA) TMVR system.

METHODS: This multicentre, single-arm study evaluated the early-generation Intrepid TA system in patients with symptomatic ≥moderate-severe MR at high risk for mitral valve (MV) surgery. Echocardiograms and clinical events were independently adjudicated, and patients were followed for up to 5 years.

RESULTS: Ninety-five patients were enrolled at 21 sites between 2015 and 2019. The mean age was 74.0±9.2 years, 43.2% of patients were female, the mean Society of Thoracic Surgeons Predicted Risk of Mortality score was 6.5±4.8%, 57.9% had prior heart failure hospitalisation (HFH), and 88.4% were in New York Heart Association (NYHA) Functional Class III/IV. Secondary MR was present in 78.7%, and 76.6% had a left ventricular ejection fraction ≤50%. Up to 5 years, all-cause mortality was 66.7% and HFH was 55.4%, with one 30-day MV reintervention (1.1%). Haemodynamic valve deterioration occurred in 1.4%, the median MV mean gradient remained stable at 3.6 mmHg (first and third quartiles: 3.0, 4.8 mmHg), ≤mild MR was present in 100% of patients, and no patient experienced paravalvular leak. NYHA Functional Class I/II was maintained in 84.6%.

CONCLUSIONS: In this 5-year follow-up of the early-generation Intrepid TA TMVR system, we observed sustained MR reduction, durable haemodynamic valve performance, and improved functional status among survivors. The APOLLO (ClinicalTrials.gov: NCT03242642) and APOLLO-EU (NCT05496998) trials using the transfemoral Intrepid system will further determine the role of TMVR in managing this high-risk patient population. ClinicalTrials.gov: NCT02322840

KEYWORDS: durability; haemodynamic performance; long term; mitral regurgitation; TMVR; transapical

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Conventional surgical mitral valve (MV) repair or replacement improves longevity and quality of life for patients with MV disease. However, fewer than one-half of patients with ≥moderate-severe mitral regurgitation (MR) are referred for MV surgery, primarily due to high surgical risk[1,2]. The self-expanding Intrepid transcatheter mitral valve replacement (TMVR) system (Medtronic) is a less invasive investigational technology to treat MR. Data from the pooled analysis of the Pilot Study (ClinicalTrials.gov: NCT02322840) and the initial phase of the APOLLO trial (NCT03242642) using the early-generation transapical (TA) Intrepid system showed excellent device haemodynamics with the ability to eliminate MR up to 2 years[3]. The device performance data were further confirmed in the next-generation transfemoral system, which demonstrated improved safety outcomes up to 2 years in patients treated under an early feasibility study[4-6].

In order to treat severe MR in patients who are ineligible for conventional MV surgery or transcatheter MV repair, two TMVR devices are currently approved for commercial use in Europe (Tendyne [Abbott], SAPIEN M3 [Edwards Lifesciences]). Additionally, the Tendyne system recently received U.S. Food and Drug Administration approval for treating patients with symptomatic severe MV disease associated with severe mitral annular calcification. However, long-term data on device durability and clinical outcomes after TMVR beyond 3 years have not been reported[7]. The present Pilot Study aimed to evaluate the 5-year clinical and echocardiographic outcomes focused on device performance after TMVR with the Intrepid TA TMVR system.

Editorial, see page e133

Impact on daily practice

Intrepid transapical (TA) transcatheter mitral valve replacement (TMVR) was associated with long-term mitral regurgitation (MR) elimination, durable haemodynamic valve performance, and improved functional status among survivors up to 5 years in selected patients with symptomatic ≥moderate-severe MR. The 5-year clinical and echocardiographic outcomes will help Heart Teams in the decision-making process for MR treatment and underscore the need for optimal patient selection and heart failure therapies. With 5-year valve performance of the Intrepid TA TMVR system now available, future studies on transfemoral TMVR and comparison studies with transcatheter edge-to-edge repair will better define the role of TMVR in the management of high surgical risk patients with ≥moderate-severe MR.

Methods

STUDY DESIGN AND PATIENT POPULATION

The Intrepid TMVR global Pilot Study is a multicentre, prospective, non-randomised study evaluating the safety and performance of the Intrepid TA TMVR system in patients at high risk for conventional MV surgery. Patients were recruited from 21 hospitals in Australia, Europe, and the US **(Supplementary Table 1)**. Key eligibility criteria, study device, procedure-related details, and endpoints of the Pilot Study have been reported previously[3,8]. Briefly, inclusion criteria were age >18 years, symptomatic ≥moderate-severe MR (3-4+), no or minimal MV calcification, and a left ventricular ejection fraction (LVEF) ≥20%. Key exclusion criteria were severe pulmonary hypertension, need for coronary revascularisation, haemodynamic instability, need for other surgical valvular therapy, severe renal insufficiency, and prior MV surgery or intervention. The complete inclusion/exclusion criteria are listed in **Supplementary Table 2**. Institutional review board approval was obtained in all centres, and patients provided informed consent for study participation.

The early-generation Intrepid TMVR system comprised a self-expanding, nitinol dual-stent valve and a TA delivery system. A circular inner stent frame houses a 27 mm trileaflet bovine pericardial valve, and a conformable outer stent anchors to the native anatomy without leaflet capture. The valve is delivered transapically via a 35 Fr catheter access sheath. The early-generation system included valves with outer fixation ring diameters of 43, 46, and 50 mm, whereas 42 and 48 mm valves are used in current clinical trials[3,8].

Anatomical suitability for TA TMVR was determined using transoesophageal echocardiography and multidetector computed tomography (MDCT). Study eligibility was determined by local Heart Teams at the study sites (including, at the minimum, a cardiac surgeon, an interventional cardiologist, and an echocardiologist) and approved by an independent physician committee. An independent clinical events committee, which also served as the data and safety monitoring board (Stanford University, Stanford, CA, USA), adjudicated endpoint-related adverse events and reviewed the safety results. Echocardiographic endpoints were assessed by an independent echocardiographic core laboratory (Mayo Clinic, Rochester, MN, USA).

STUDY ENDPOINTS AND DEFINITIONS

Clinical and transthoracic echocardiography assessments were performed at discharge, 1 month, 3 months, 6 months, 12 months, and biannually thereafter for up to 5 years. Unscheduled echocardiograms were performed by sites if clinically indicated and reviewed by the echocardiographic core laboratory. The severity of MR was assessed according to American Society of Echocardiography criteria[9]. Moderate haemodynamic valve deterioration was defined according to the Heart Valve Collaboratory 2022 and Mitral Valve

Abbreviations

HFH	heart failure hospitalisation	**MV**	mitral valve	**TA**	transapical
LVEF	left ventricular ejection fraction	**MVARC**	Mitral Valve Academic Research Consortium	**TEER**	transcatheter edge-to-edge repair
MDCT	multidetector computed tomography			**TMVR**	transcatheter mitral valve replacement
MR	mitral regurgitation	**PVL**	paravalvular leak		

Academic Research Consortium (MVARC) 2015 criteria as an increase in the mean transmitral gradient of ≥5 mmHg from 30 days/discharge to the last available echocardiogram or transvalvular MR ≥moderate, while severe haemodynamic valve deterioration was defined as a mean transmitral gradient of ≥10 mmHg or MR ≥moderate-severe[10,11].

MDCT was collected per protocol at discharge and 1 year for patients enrolled at US sites. Quality of life was evaluated using the Minnesota Living with Heart Failure Questionnaire at baseline and 1 year, as previously reported[3]. New York Heart Association (NYHA) Functional Class was assessed from baseline to 5 years. Standard definitions for clinical events were used in accordance with the MVARC 2015 criteria[11], except for device thrombosis, as described in **Supplementary Appendix 1**. Post-procedure anticoagulation was prescribed per physician discretion but was recommended for at least 3-6 months post-implant, or longer unless there was a clinical indication to discontinue it.

STATISTICAL ANALYSIS

Continuous variables are summarised as mean±standard deviation, or median and first (Q1) and third quartiles (Q3), as appropriate. Categorical variables are reported as frequencies and percentages. Adverse event rates were estimated as Kaplan-Meier estimates and reported at 30 days, 1 year, and 5 years. Thrombosis and endocarditis events were also reported as linearised rates with 95% confidence intervals (CIs), expressed per 100 patient-years. All-cause, cardiovascular, and non-cardiovascular mortality were landmarked at 1 year post-procedure to assess the later impact of TMVR by excluding events potentially attributable to the TA approach. Paired echocardiographic analysis was performed using the Wilcoxon signed-rank test for continuous variables and McNemar's test for categorical variables. Change in NYHA Class from baseline was assessed using the Wilcoxon signed-rank test. A two-sided p-value<0.05 was considered statistically significant. Statistical analyses were performed by the sponsor using SAS software, version 9.4 (SAS Institute).

Results

BASELINE CHARACTERISTICS

The study cohort included 95 patients who had undergone TA TMVR between 2015 and 2019 and completed 5-year follow-up. Demographics, baseline characteristics, and medical history are presented in **Table 1**. The mean age was 74.0±9.2 years, 43.2% of patients were female, the Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) score for MV replacement was 6.5±4.8%, 57.9% had experienced a heart failure hospitalisation (HFH) within the year preceding enrolment, and 88.4% were in NYHA Class III/IV. The predominant mechanism of MR was secondary (78.7%), 70.2% had an LVEF ≤50%, and nearly all had ≥moderate-severe MR (95.8%). Four patients were initially treated for ≥moderate-severe MR based on the site echocardiogram reading but were later found to have lower MR severity after formal core lab review.

INTRAPROCEDURAL AND 30-DAY CLINICAL OUTCOMES

A summary of the patient flow is provided in **Figure 1**. The Intrepid valve was successfully implanted in 92 (96.8%) of 95 patients. In one patient, the procedure was aborted prior to valve deployment because of uncontrolled bleeding around the sutures at the apical incision site. The other two patients underwent conversion to surgical mitral valve replacement during the index procedure due to device malposition/migration. Clinical outcomes for the attempted implant cohort, reported as Kaplan-Meier estimates, are shown in **Table 2**. A total of 18 deaths (18.9%) occurred within 30 days post-procedure; the majority were attributed to cardiovascular causes (n=15, 15.8%).

Eight HFH events occurred within 30 days (9.6%), and 3 patients experienced a disabling ischaemic stroke (3.6%); one was procedure related, while two were both device and procedure related. A total of 20 patients experienced

Table 1. Baseline patient characteristics.

	(n=95)
Age, years	74.0±9.2
Sex	
Male	56.8 (54)
Female	43.2 (41)
STS-PROM score, %	6.5±4.8
NYHA III/IV	88.4 (84)
Diabetes	37.9 (36)
Hypertension	78.9 (75)
Prior MI	42.1 (40)
HFH within the past year	57.9 (55)
≥Moderate chronic lung disease	25.3 (24)
Peripheral artery disease	15.8 (15)
Prior stroke	13.7 (13)
Prior PCI	42.1 (40)
Prior cardiac surgery	47.4 (45)
Prior valve surgery	10.5 (10)
CABG	40.0 (38)
GFR <60 mL/min/1.73 m^2	57.4 (54/94)
Atrial fibrillation/atrial flutter	60.0 (57)
Prior ICD	28.4 (27)
Prior CRT	15.8 (15)
Aetiology of MR	
Primary MR	21.3 (20/94)
Secondary MR	78.7 (74/94)
≥Moderate-severe MR	95.8 (91)
LVEF, %	45.2±10.6
LVEF ≤30%	6.4 (6/94)
LVEF 30-50%	63.8 (60/94)
LVEF >50%	29.8 (28/94)
Valve size deployed	
43, 46, or 50 mm	94.7 (89/94)
42 or 48 mm	5.3 (5/94)

Data are presented as mean±standard deviation, % (no. of patients), or % (n/N). CABG: coronary artery bypass graft; CRT: cardiac resynchronisation therapy; GFR: glomerular filtration rate; HFH: heart failure hospitalisation; ICD: implantable cardioverter defibrillator; LVEF: left ventricular ejection fraction; MI: myocardial infarction; MR: mitral regurgitation; NYHA: New York Heart Association; PCI: percutaneous coronary intervention; STS-PROM: Society of Thoracic Surgeons Predicted Risk of Mortality

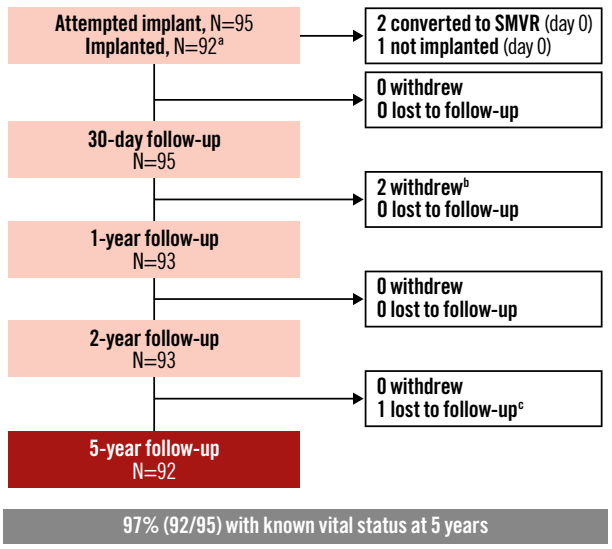


Figure 1. *Patient flowchart. Flowchart depicting the number of patients enrolled in the analysis cohort, number of successful implants, and number of patients with known vital status at follow-up. [a]The analysis of clinical outcomes is based on the attempted implant cohort, and the analysis of echocardiographic outcomes is based on the implanted cohort. [b]One patient who converted to SMVR at day 0 and one patient who converted to SMVR at day 1 were followed for 30 days then withdrew from the study. [c]One patient missed the 54- and 60-month visits and was considered lost to follow-up. Each follow-up includes patients who were evaluated, died prior to, or were observed alive at a later timepoint. SMVR: surgical mitral valve replacement*

life-threatening (n=16) or fatal bleeding events (n=4) due to access-related apical or intrathoracic bleedings. There was 1 MV (device-related) reintervention (1.1%) due to device malposition within 30 days, with successful percutaneous valve-in-valve implantation. No myocardial infarction, clinically significant device thrombosis, clinical haemolysis, or prosthetic MV endocarditis events were reported within the first 30 days.

ONE-YEAR CLINICAL OUTCOMES

All-cause mortality and HFH at 1 year were 31.9% and 26.0%, respectively **(Table 2)**. A total of 12 patients had their first HFH between 31 days and 1 year. No additional cases of disabling stroke occurred between 31 days and 1 year. Two cases of clinically significant device thrombosis with sequelae (3.0%) were diagnosed. At the time of diagnosis, the first patient was on warfarin but had a subtherapeutic international normalised ratio (INR) value, while the second patient was not on anticoagulation after completing the protocol-recommended 6-month period. In both cases, intensification or reinitiation of anticoagulation therapy led to resolution of thrombosis as confirmed by imaging.

There were 2 cases of MV endocarditis between 31 days and 1 year (observed on post-procedure days 84 and 167). The first resolved following antibiotic therapy, while the second case was fatal. Details on all device thrombosis and endocarditis events can be found in **Supplementary Table 3** and **Supplementary Table 4**, respectively. There were no new MV reinterventions or bleeding events between 31 days and 1 year.

FIVE-YEAR CLINICAL OUTCOMES

At 5 years, 62 patients were deceased, and 2 patients missed their follow-up visit. The remaining 28 patients that were still in contact completed their 5-year follow-up visit

Table 2. Clinical outcomes up to 5 years.

	30 days	1 year	5 years	New patients with events between 1 and 5 years
All-cause mortality	18.9 (18)	31.9 (30)	66.7 (62)	32
Cardiovascular mortality	15.8 (15)	26.1 (24)	51.6 (43)	19
Non-cardiovascular mortality	3.7 (3)	7.9 (6)	31.4 (19)	13
Disabling stroke	3.6 (3)	3.6 (3)	9.1 (6)	3
Myocardial infarction	0 (0)	0 (0)	22.9 (10)	10
Cardiovascular hospitalisation	12.1 (10)	48.2 (37)	79.0 (57)	20
Heart failure hospitalisation	9.6 (8)	26.0 (20)	55.4 (37)	17
Bleeding event ≥major (MVARC definition)	24.3 (23)	24.3 (23)	32.5 (27)	4
Fatal	4.2 (4)	4.2 (4)	4.2 (4)	0
Life-threatening	17.1 (16)	17.1 (16)	21.8 (18)	2
MV reintervention	1.1 (1)	1.1 (1)	1.1 (1)	0
Device thrombosis				
Clinically significant with sequelae	0 (0)	3.0 (2)	10.5 (5)	3
Clinically significant without sequelae	0 (0)	0 (0)	1.7 (1)	1
MV endocarditis	0 (0)	2.9 (2)	4.6 (3)	1
Haemolysis	0 (0)	0 (0)	0 (0)	0

Data are presented as Kaplan-Meier rates (no. of patients with the event). MV: mitral valve; MVARC: Mitral Valve Academic Research Consortium

(Table 2). The Kaplan-Meier rates for all-cause mortality, cardiovascular mortality, non-cardiovascular mortality, and HFH at 5 years were 66.7%, 51.6%, 31.4%, and 55.4%, respectively **(Central illustration A** and **B, Table 2)**. The composite rate of all-cause mortality or HFH at 5 years was 78.6%. Per the independent clinical events committee, a total of 5 deaths were attributed to the device. One death was deemed definitely related (endocarditis, as described previously), while four were considered possibly related (2 fatal strokes, 1 intracranial bleeding following a fall due to cardiac arrest, and 1 stroke followed by hospital-acquired pneumonia). One-year landmark analyses for all-cause, cardiovascular, and non-cardiovascular mortality are shown in **Supplementary Figure 1**. When excluding 1-year mortality, all-cause, cardiovascular, and non-cardiovascular mortality estimates up to 5 years were 51.2%, 34.5%, and 25.5%, respectively.

After 1 year, an additional 19 patients died due to cardiovascular causes **(Table 2)**. Worsening HF was the main cause of death among these patients (n=12), followed by sudden/unwitnessed death (n=3), death due to a neurological event (n=2), due to myocardial infarction (n=1), and of unknown cause (n=1). There were 17 patients that had their first HFH between 1 and 5 years. Among these, there were 4 patients with progression of other non-MV diseases that contributed to the advancement of HF (3 patients with severe aortic valve disease, and 1 patient with severe tricuspid regurgitation).

Between 1 and 5 years, myocardial infarction occurred in a total of 10 patients, all but two of whom had a history of prior myocardial infarction and/or revascularisation with percutaneous coronary intervention or coronary artery bypass grafting. Three additional patients experienced their first disabling stroke, with two of these events being device related. Additionally, no new fatal bleeds occurred between 1 and 5 years, while 2 patients had their first new life-threatening bleeding event. One life-threatening subdural haematoma occurred on day 1,185, associated with overanticoagulation (INR 9.6), and one life-threatening bleeding following postperipheral stenting occurred on day 1,545.

INTREPID VALVE FUNCTION UP TO 5 YEARS

The rate of significant device thrombosis per 100 patient-years with and without sequelae were 1.95 (95% CI: 0.81-4.69) and 0.39 (95% CI: 0.06-2.77), respectively. Three clinically significant device thrombosis events with sequelae and 1 event without sequelae occurred after 1 year **(Supplementary Table 3)**. At the time of the event, 2 patients were receiving warfarin (the INR was 2.1 in one patient and unknown in the other patient), and 2 patients were receiving clopidogrel. Management involved intensifying or adding anticoagulation therapy. Of these 4 cases, two completely resolved per follow-up imaging, one remained of unknown status, and one persisted in the setting of disseminated intravascular coagulation and a COVID-19 infection. Among the total of 6 cases of clinically significant device thrombosis up to 5 years of follow-up, the independent clinical events committee determined that none of the 5 subsequently occurring mortalities was caused by implant thrombosis.

The rate of MV endocarditis per 100 patient-years was 1.17 (95% CI: 0.38-3.63). There was one new case of MV endocarditis between 1 and 5 years (post-procedure day 500), which resolved following antibiotic therapy **(Supplementary Table 4)**. There was no new incidence of MV reinterventions between 1 and 5 years.

IMPROVEMENT IN FUNCTIONAL STATUS

At baseline, 88.4% of patients were in NYHA Class III/IV. Significant symptom improvement was observed following Intrepid TMVR, with 77.3%, 89.8%, and 84.6% of surviving patients in Class I/II at the 30-day, 1-, and 5-year follow-ups, respectively **(Central illustration C)**.

FIVE-YEAR ECHOCARDIOGRAPHIC OUTCOMES

Twenty-one of 28 patients (75%) with 5-year follow-up had transthoracic echocardiographic images for core lab evaluation of MR severity. Among survivors at 5 years, all patients were free from residual MR greater than mild in severity **(Figure 2A)**, and no patients had more than trace paravalvular leak (PVL) **(Figure 2B)**. Similar findings were observed in a paired MR analysis **(Central illustration D)**. A review of all available scheduled and clinically driven unscheduled echocardiograms revealed no MR or PVL greater than mild in severity in the study. The rate of moderate haemodynamic valve deterioration was 1.4% (1/69), while there was no evidence of severe haemodynamic deterioration during the 5 years of follow-up.

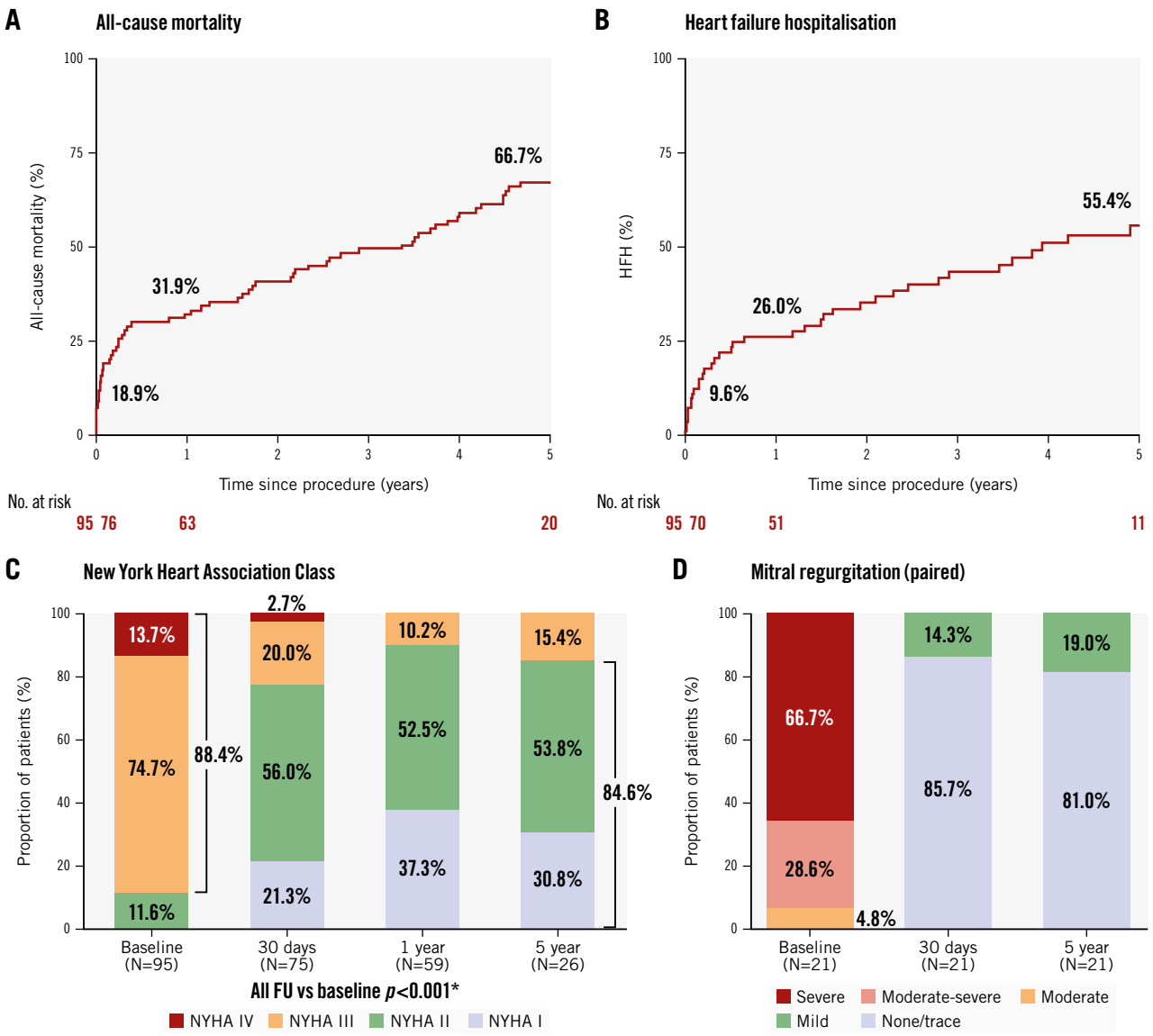
The median MV mean gradient at 5 years among survivors was 3.6 mmHg (Q1: 3.0 mmHg, Q3: 4.8 mmHg) **(Figure 3A)**, and the median left ventricular (LV) outflow tract peak gradient was 6.6 mmHg (Q1: 3.8 mmHg, Q3: 8.8 mmHg) **(Figure 3B)**. A paired comparison of echocardiographic outcomes at baseline and 5 years is shown in **Table 3**. There were no significant changes in the LV end-systolic diameter index, LV end-diastolic diameter index, cardiac output, or tricuspid regurgitation severity. The LVEF decreased from baseline to 5-year follow-up. Although not statistically significant, forward stroke volume increased, while pulmonary artery systolic pressure and right ventricular dysfunction decreased.

Discussion

The major findings in this study are as follows **(Central illustration)**: (1) Intrepid TA TMVR resulted in near-elimination of MR during 5-year follow-up among survivors, with durable haemodynamic valve performance and a low rate of haemodynamic valve deterioration; (2) there was one 30-day MV reintervention and none thereafter; (3) device-related complications (thrombosis and endocarditis) were infrequent during 5-year follow-up, with no apparent clustering of events and no cases of haemolysis; and (4) there was sustained improvement in functional status in survivors. In this high-risk patient population treated with the early-generation Intrepid TA TMVR system, 78.6% of the patients either died or were hospitalised for heart failure (HF) within 5 years. These findings highlight the complex comorbid patient population evaluated in this Pilot Study and the need for systematic optimisation of patient selection, guideline-directed medical therapy for HF, and a less invasive transfemoral delivery system.

EuroIntervention — Central Illustration

Five-year clinical outcomes with the Intrepid transapical TMVR system.



Five-year outcomes in the Pilot Study with the early-generation Intrepid TA TMVR system demonstrated the following in survivors:
- Sustained elimination of MR
- Durable haemodynamic valve performance
- One MV reintervention within 30 days, and none thereafter
- Low rates of thrombosis and endocarditis, and no cases of haemolysis
- Continued improvement in Functional Class

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*A) Kaplan-Meier estimate of all-cause mortality up to 5 years; (B) Kaplan-Meier estimate of heart failure hospitalisation up to 5 years; (C) symptom status (NYHA Functional Class) at baseline, 30 days, 1 year, and 5 years; *Wilcoxon signed-rank test; (D) mitral regurgitation severity over time (paired, N=21). FU: follow-up; HFH: heart failure hospitalisation; MR: mitral regurgitation; MV: mitral valve; NYHA: New York Heart Association; TA: transapical; TMVR: transcatheter mitral valve replacement*

DURABLE VALVE PERFORMANCE OF THE INTREPID TMVR SYSTEM

Building on previously published 2-year Intrepid TA TMVR data[3], the elimination of MR and low transvalvular gradients seen at 5 years are important factors when considering TMVR as an alternative treatment option to surgery or transcatheter repair. Despite an excellent safety profile, the Achilles' heel of transcatheter edge-to-edge repair (TEER) is residual or recurrent MR, as well as elevated transmitral gradients, both of which have been associated with adverse

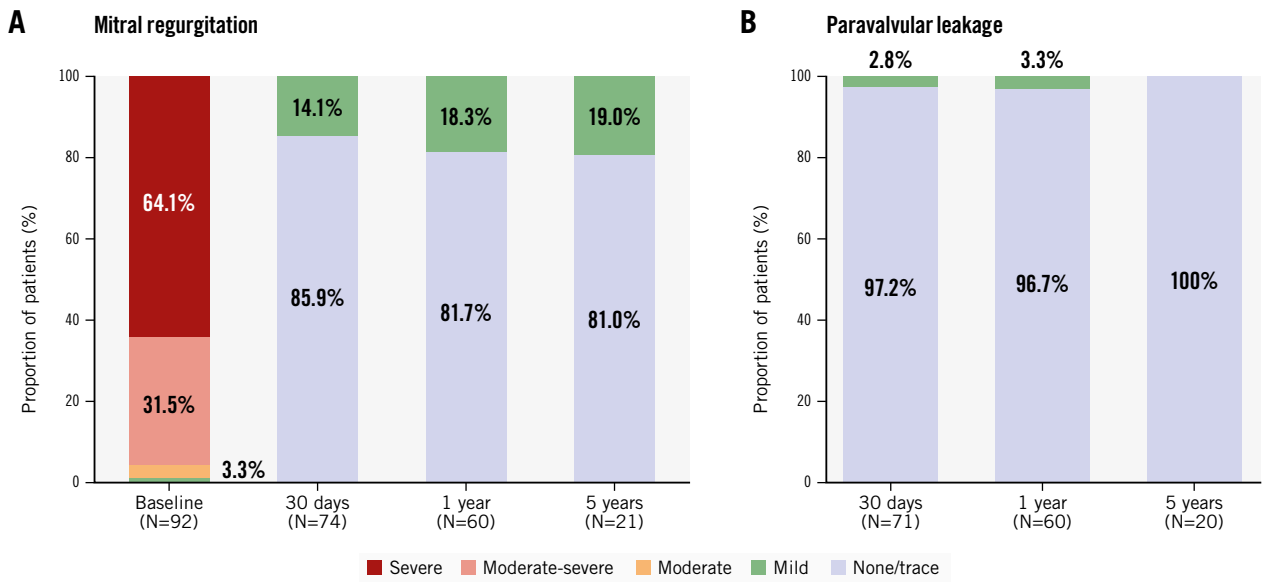

Figure 2. *Mitral regurgitation severity over time. A) Total mitral regurgitation from baseline to 5 years; (B) paravalvular leakage from 30 days to 5 years. Data are reported for the implanted cohort (N=92) in patients who were alive with evaluable echocardiograms at protocol-specific visits.*

clinical outcomes[12-17]. Similar to other Intrepid studies[5,6], the Pilot Study showed that among survivors, 100% had ≤mild MR and no PVL, with stable transmitral gradients for up to 5 years of follow-up. Clinically significant device thrombosis with sequelae, a concern for TMVR, was observed in this study, with no distinct pattern in the timing of events post-procedure, while MV endocarditis events remained infrequent (1.17 [95% CI: 0.38-3.6] per 100 patient-years). These findings align with other midterm TMVR[7] and conventional MV replacement studies[18,19] and reinforce the importance of valve performance as a key factor, supporting the continued use of the Intrepid TMVR system. Extending anticoagulation beyond 6 months after TMVR should be strongly considered in patients deemed at high risk for thrombosis (e.g., with a history of hypercoagulability, and/or severe left ventricular dysfunction) and at acceptable risk for bleeding. Further studies will be necessary to evaluate this hypothesis, given the balance between valve thrombosis and bleeding in this high-risk population.

TRANSFEMORAL FAVOURED OVER TRANSAPICAL APPROACH IN TMVR

TA transcatheter aortic valve implantation has largely been replaced by a transfemoral approach due to increased safety and better patient recovery[20,21]. Similarly, we have seen significant access site-related complications with TA TMVR, both with the Intrepid system and other systems[22,23]. However, there were almost no device-related events beyond the first year in the Pilot Study. The next-generation Intrepid transfemoral TMVR system has demonstrated improved procedural safety compared to the TA system reported in this study, with 0% 30-day and 6.7% 1-year mortality rates[5]. The most recent ENCIRCLE trial (ClinicalTrials.gov: NCT04153292) data on the SAPIEN M3 system further confirm the safety of transfemoral TMVR over a TA approach[24]. Transfemoral TMVR is now the only approach with the latest-generation 29 Fr Intrepid system in the APOLLO and APOLLO EU trials, with other TMVR systems also evolving to the transfemoral approach (e.g., Cephea [Abbott], InnoValve [Edwards Lifesciences], AltaValve [4C Medical]).

IMPACT OF PATIENT RISK PROFILE ON LONG-TERM OUTCOMES AFTER TMVR

This long-term study showed that both all-cause and cardiovascular mortality after TA TMVR were relatively high at 5 years, at 66.7% and 51.6%, respectively. The HFH rate was 55.4%. These findings paralleled those reported at 1 year in the TENDER registry with the Tendyne system[25], at 2 years with the CHOICE-MI registry with 11 different TMVR devices[26], at 3 years with other TA TMVR systems[7], and at 5 years with TEER[27,28]. Indeed, the Pilot Study population was a truly high-risk patient cohort: the mean STS-PROM score was 6.5% for MV replacement, nearly 50% had prior cardiac surgery, 28.4% had an implantable cardioverter defibrillator, 15.8% had an implantable cardiac resynchronisation therapy device, almost 80% had secondary MR, 70% had an LVEF ≤50%, and almost 60% had a prior HFH within the year preceding enrolment. Whether the high mortality rates relate to MR aetiology (primary MR vs secondary MR) remains unclear, given the relatively small sample sizes in the above studies and the limited ability to compare outcomes based on MR aetiology. However, TA TMVR with the Tendyne system had lower 1-year mortality in 2 real-world series with fewer secondary MR patients[25,29]. Results from the larger registries (e.g., ENCIRCLE, APOLLO, SUMMIT [ClinicalTrials.gov: NCT03433274]) will provide a more robust comparison in outcomes between primary and secondary MR patients undergoing TMVR.

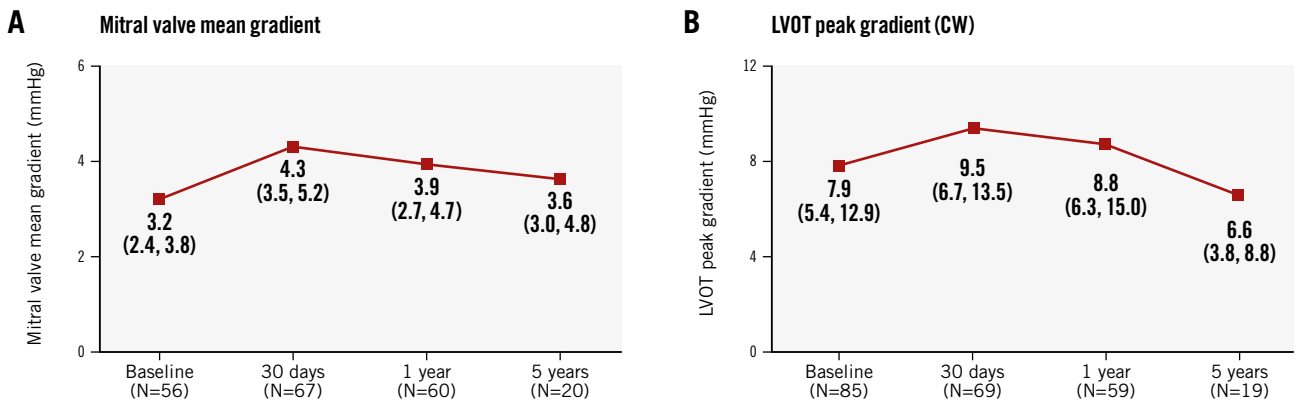

Figure 3. *Gradients over time. A) Mitral valve mean gradient over time; (B) left ventricular outflow tract peak gradient over time. Data are reported for the implanted cohort (N=92) in patients who were alive with evaluable echocardiograms at protocol-specific visits. Values are reported as median (Q1, Q3). CW: continuous wave; LVOT: left ventricular outflow tract; Q1: first quartile; Q3: third quartile*

With the TA TMVR system, the Kaplan-Meier analysis appeared to show an elevated risk of early mortality from day 0 to 6 months, followed by a plateau from 6 months to 1 year. After the first year, landmark analysis did reveal an ongoing mortality risk after TA TMVR, with 5-year cardiovascular and non-cardiovascular mortality rates of 34.5% and 25.5%, respectively. These findings suggest residual MR is not the main factor after TMVR with Intrepid; rather, mortality appears to be more influenced by patient comorbidities and progressive cardiomyopathy.

Interestingly, 5-year outcomes after TEER in the COAPT Trial were also sobering, with all-cause mortality, cardiovascular mortality, and HFH at 57.3%, 49.0%, and 61.0%, respectively[27]. The 5-year results of the EuroSMR registry showed a similar all-cause mortality of 65% in patients with secondary MR[28]. These similar findings, regardless of whether MR reduction or elimination was successful, suggest that we are treating a patient population with severe illness and advanced heart disease. This holds true despite the fact that the two study groups come from different patient populations and time periods. Interestingly, two recent propensity-matched studies between TA TMVR with Tendyne and surgical MV replacement showed no significant outcome differences, but TMVR patients had fewer blood transfusions and shorter hospital stays[29,30]. A less invasive strategy to eliminate MR may be beneficial in this high-risk population. Nevertheless, implementing a more precise patient selection strategy and optimising HF medical therapy after a successful procedure will be crucial to better address this high-risk patient group beyond just treating their MR.

FUNCTIONAL IMPROVEMENT OVER TIME IN TA TMVR SURVIVORS

Despite a relatively high early mortality after TA TMVR with the Intrepid system, patients who survived to 5 years did exhibit sustained functional improvement, with 84.6% remaining at NYHA Class I/II. This is consistent with the sustained improvements observed with other TMVR systems[7]. Although left ventricular dimensions and cardiac output were unchanged over time in this 5-year study, similar to other midterm TMVR series[31], forward stroke volume, right ventricular dysfunction, and pulmonary arterial systolic pressure showed improvements following Intrepid TA TMVR, consistent with the improvements observed in the early feasibility study using a transfemoral approach[6]. The Intrepid APOLLO and APOLLO EU trials will show whether improvements in these cardiac function metrics are observed in a larger patient cohort.

By paired analysis, LVEF numerically declined from 44% at baseline to 40% at 5 years in this study; however, it is unclear whether this decrease is clinically meaningful. Given that approximately 40% of our patients had a history of coronary artery bypass grafting, percutaneous coronary intervention, and myocardial infarction, underlying myocardial dysfunction could be a contributing factor. A similar postprocedural decline in LVEF has been reported with surgery[32,33], TEER[27,34], and TA TMVR[31,35]. It is likely that outcomes may continue to improve with the routine use of a transfemoral approach, device iterations, and procedural maturity in TMVR. Seeing durable valve performance at 5 years, even with this early-generation Intrepid system, is important information for discussing treatment options with patients with symptomatic MR at high risk for open surgery.

Limitations

The current work describes the longest follow-up of patients treated to date by TA TMVR. Nonetheless, it remains a relatively small, single-arm study of the early experience with a new TMVR device using a TA approach and may reflect the initial learning curve associated with the procedure and site experience. The lack of a control group limits conclusions with regard to the comparison to other MR therapies. Although clinical follow-up was comprehensive in surviving patients, echocardiograms were not obtained in all patients at all timepoints. Thus, paired comparisons of parameters of cardiac function could only be performed for a subset of patients. Furthermore, results are limited by the competing risk of mortality and reflect outcomes in a minority of surviving patients. Kansas City Cardiomyopathy

Table 3. Paired comparison of echocardiographic outcomes at 5 years.

	n	Baseline	5 years	*p*-value
MV mean gradient, mmHg	14	3.2 (2.3, 3.9)	3.7 (3.0, 4.7)	0.08
LVOT peak gradient, mmHg	17	6.1 (4.5, 6.6)	6.0 (3.8, 8.8)	0.94
LVESD index	7	2.4 (2.1, 2.9)	2.3 (1.9, 3.1)	0.84
LVEDD index	15	3.1 (2.9, 3.4)	3.1 (2.7, 3.5)	0.46
LVEF, %	20	44.0 (36.0, 55.0)	39.5 (26.5, 46.5)	0.008
Forward stroke volume, mL	14	56.1 (47.4, 65.1)	64.5 (47.4, 69.1)	0.15
Cardiac output, L/min	14	4.7 (3.2, 4.7)	4.4 (3.9, 5.1)	0.33
RV dysfunction ≥mild	17	76.5 (13/17)	47.1 (8/17)	0.06
PASP, mmHg	11	46.0 (33.0, 59.0)	39.0 (32.0, 54.0)	0.42
TR ≥moderate	21	38.1 (8/21)	38.1 (8/21)	>0.99

Data are presented as median (Q1, Q3) or % (n/N). Paired comparisons were made using the Wilcoxon signed-rank test for continuous variables and McNemar's test for categorical variables. LVEDD: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; LVESD: left ventricular end-systolic diameter; LVOT: left ventricular outflow tract; MV: mitral valve; PASP: pulmonary artery systolic pressure; Q1: first quartile; Q3: third quartile; RV: right ventricular; TR: tricuspid regurgitation

Questionnaire assessment was not collected in the Pilot Study, which restricts our ability to assess patient-reported quality-of-life outcomes. Anticoagulation therapy was recommended for at least 3-6 months, but the rates of continuation or discontinuation were unknown. Perioperative management of this high-risk population and long-term medical therapy were not captured by the study protocol. Rigorous and intensive medical therapy with input from HF specialists might have led to improved longer-term outcomes.

Conclusions

In the longest follow-up series of TA TMVR using the early-generation Intrepid system in a high-risk patient population, we observed 5 years of sustained MR elimination and durable valve performance, along with sustained functional improvement among survivors, despite predictable mortality and HFH. Ongoing clinical trials using the less invasive transfemoral approach will help define the patient population most likely to benefit from TMVR.

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Conflict of interest statement

G.H.L. Tang has received speaker honoraria from and served as a physician proctor, consultant, advisory board member, TAVR publications committee member, RESTORE study steering and screening committee member, APOLLO trial screening committee member, and IMPACT MR steering committee member for Medtronic; has received speaker honoraria from and served as a physician proctor, consultant, advisory board member, ENVISION trial screening committee member, and TRILUMINATE trial anatomical eligibility and publications committee member for Abbott; has served as an advisory board member for Boston Scientific; a consultant for Shockwave Medical, Anteris, Philips, Edwards Lifesciences, Peija Medical, and Shenqi Medical Technology; and has received speaker honoraria from Siemens Healthineers. V. Rajagopal has received personal fees for speaking from Medtronic, Boston Scientific, and Abbott; is on the screening committee for the APOLLO trial sponsored by Medtronic; and has equity stake in and is Chief Medical Officer of Opus Medical Therapies. P. Sorajja has served as a consultant for Medtronic, 4C Medical, Abbott, Adona, Arcos, Boston Scientific, ConKay, Coramaze, CroiValve, Cultiv8, Edwards Lifesciences, Egg Medical, Evolution-Med, Foldax, GE HealthCare, Haemonetics, inQB8, Laguna Tech, Laza Medical, Mirus, Philips, Polares, Tricares, W.L. Gore & Associates, VDyne, Unorthodox Ventures, Valcare, and xDot. T. Bajwa has received personal and institutional consulting fees from Medtronic. R. Gooley has received consulting fees from Medtronic, Boston Scientific, Abbott, and Teleflex. A. Walton

has served as a physician proctor and an advisory board member for and has received institutional research grant support from Medtronic, Edwards Lifesciences, and Abbott. T. Modine is a consultant for Abbott, Boston Scientific, Cephea, Edwards Lifesciences, GE HealthCare, Medtronic, and MicroPort; and is a proctor for and receives speaker fees from Medtronic. M.K. Ng has received institutional grant support from and is a proctor for Edwards Lifesciences and Abbott. A. Zajarias is a consultant for Medtronic, Edwards Lifesciences, and Anteris. D. Hildick-Smith has received speaker honoraria from and served as a physician proctor for Medtronic, Edwards Lifesciences, Terumo, Abbott, and Boston Scientific. D. Tchétché has served as a consultant for Medtronic, Abbott, Boston Scientific, and Edwards Lifesciences. K. Spargias has served as a physician proctor and consultant for Medtronic, Edwards Lifesciences, and Abbott. V.N. Bapat is a consultant for Medtronic, Edwards Lifesciences, Abbott, and Reniva. O. De Backer has received institutional research grant support and consulting fees from Medtronic, Abbott, and Boston Scientific. D. Blackman is a consultant and proctor for Medtronic and JenaValve Technology; is a consultant and speaker for Abbott; and has received institutional research grant support from Medtronic. P. McCarthy has received speaker fees and royalties from Edwards Lifesciences; speaker fees from Atricure; served on the advisory board for Arthrex; received royalties from Genesee; served as the surgical primary investigator for the REPAIR-MR trial (unpaid); and served on the advisory board for Abbott. R. Jain is a consultant for Medtronic, Edwards Lifesciences, Philips Healthcare, and GE HealthCare; and is an advisory board member for Medtronic. R. Martin is on the executive steering committee for the APOLLO trial sponsored by Medtronic; and on the steering committee of REPAIR MR sponsored by Abbott. J.J. Thaden reports research support for the echocardiographic core laboratory from Medtronic. N.A. Marka is an employee and shareholder of Medtronic. M. Mack is on the executive board for the APOLLO trial sponsored by Medtronic; and is co-principal investigator for the PARTNER 3 and COAPT trials sponsored by Edwards Lifesciences and Abbott. D.H. Adams has served as the national co-principal investigator of the Medtronic APOLLO Food and Drug Administration pivotal trial, the NeoChord ReChord Food and Drug Administration pivotal trial, the Medtronic CoreValve US pivotal trial, and the Abbott TRILUMINATE pivotal trial. M.B. Leon has received personal and institutional grant support from Abbott, Boston Scientific, Edwards Lifesciences, and Medtronic. M.J. Reardon reports receiving personal consulting fees from Abbott, Boston Scientific, W.L. Gore & Associates, and Medtronic, outside of the submitted work. The other authors have no conflicts of interest to declare.

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Supplementary data

Supplementary Appendix 1. Study definitions.

Supplementary Table 1. Participating investigators, sites, and personnel.

Supplementary Table 2. Inclusion and exclusion criteria.

Supplementary Table 3. Summary of clinically significant device thrombosis up to 5 years.

Supplementary Table 4. Summary of mitral valve endocarditis up to 5 years.

Supplementary Figure 1. Landmark analysis at 1 year.

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Impact of coronary dominance on long-term outcomes in patients undergoing left main coronary artery percutaneous coronary intervention

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Coronary dominance patterns are associated with the prevalence and severity of obstructive coronary artery disease (CAD), as well as with prognosis following percutaneous coronary intervention (PCI)[1]. The left main (LM) coronary artery supplies 75% to 100% of the left ventricular myocardium, placing the left ventricle at considerable risk in cases of significant LM stenosis, particularly in patients with left dominance[2]. Studies have indicated that left coronary dominance is associated with worse outcomes compared to right dominance in CAD populations; however, these studies are either outdated or lack sufficient statistical power[3]. Current clinical guidelines for LM PCI focus on assessment of the lesion complexity and intravascular imaging guidance to optimise stent implantation[4], without explicitly considering coronary dominance as an independent factor. This study aims to evaluate the influence of coronary dominance on long-term prognosis among a large cohort of LM PCI patients.

We analysed the relationship between coronary dominance and outcomes in consecutive patients with obstructive LM disease who underwent PCI between January 2004 and December 2016 at Fuwai Hospital, Beijing, China. The primary endpoint was 3-year major adverse cardiac events (MACE), a composite of cardiac death, myocardial infarction (MI), and target vessel revascularisation (TVR). Statistical analyses were carried out using SPSS Statistics, version 26.0 (IBM), and a two-sided p-value<0.05 was considered statistically significant.

Among 4,625 LM PCI patients, 166 (3.6%) had left dominance **(Figure 1A)**. These patients had a lower prevalence of hypertension and prior PCI and a higher incidence of isolated LM lesions, a shorter lesion length, a larger reference vessel diameter, and lower SYNTAX scores **(Supplementary Table 1, Supplementary Table 2)**. Multivariable Cox regression analyses demonstrated that age, left dominance, and incomplete revascularisation were associated with an increased risk of MACE, whereas successful lesion revascularisation was associated with a reduced risk. Additionally, left dominance and diabetes mellitus were linked to a higher risk of TVR, while successful lesion revascularisation was associated with a lower risk **(Figure 1B)**. After propensity score matching, the 3-year incidence of MACE was higher in patients with left coronary dominance compared to those without (adjusted hazard ratio [HR] 1.73; 95% confidence interval [CI]: 1.01-2.95; p=0.04), primarily driven by a higher rate of TVR (adjusted HR 3.25; 95% CI: 1.53-6.90; p=0.001) **(Figure 1C)**. The rates of all-cause death, cardiac death, and MI were comparable between the two groups **(Supplementary Table 3)**. After accounting for the competing risk of non-cardiac death, the risk of MACE in the left dominance group remained higher than that in the non-left dominance group, but the difference did not reach statistical significance **(Supplementary Figure 1)**. According to the subgroup analysis of MACE, the higher risk associated with left dominance was more significant among patients with LM bifurcation lesions and those with a residual SYNTAX score >0 **(Figure 1D)**.

Our findings demonstrate that (1) the proportion of left dominance among patients undergoing LM PCI is low, and these patients generally present with lower anatomical complexity; (2) left dominance in LM PCI patients is associated

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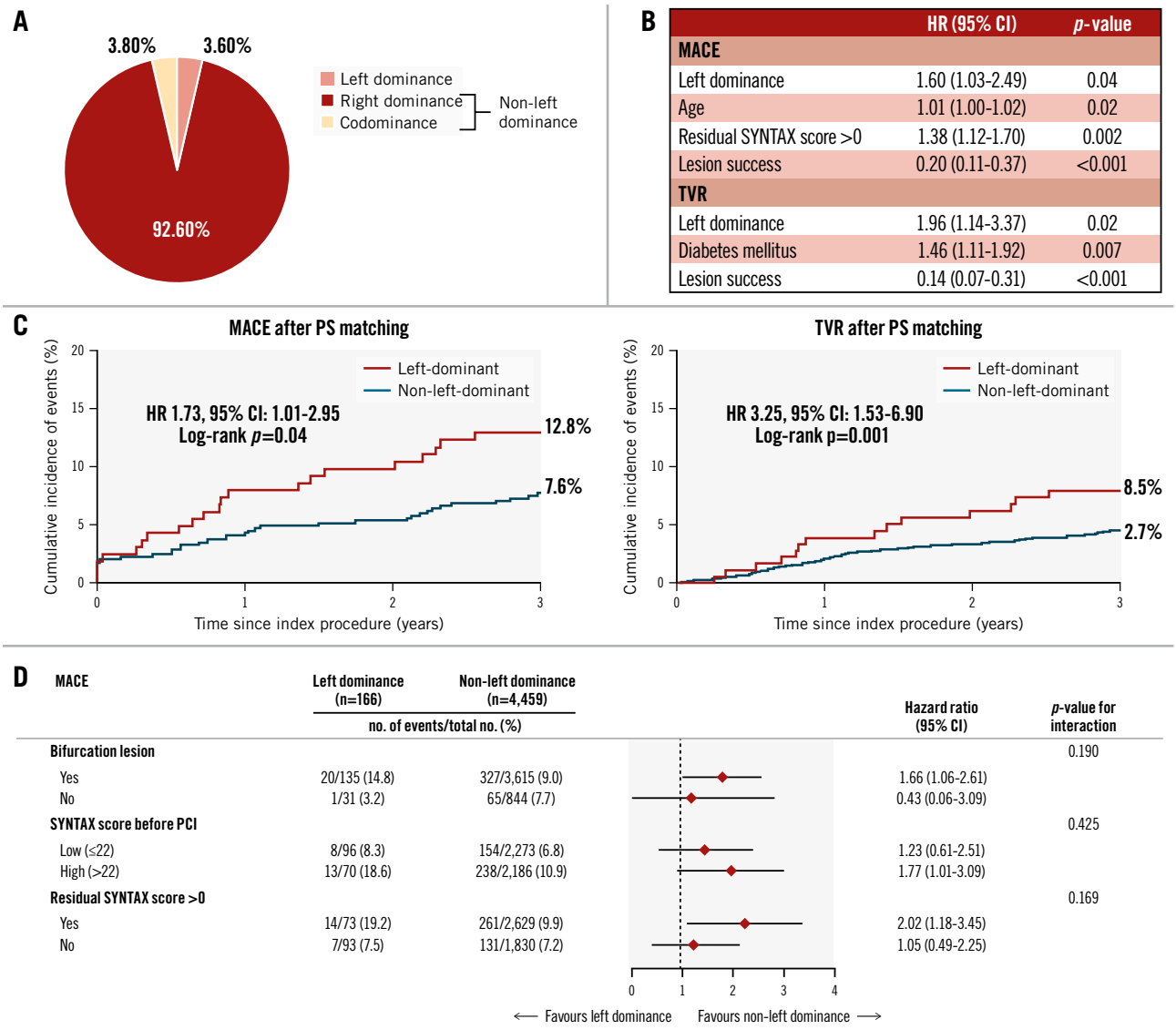

	HR (95% CI)	*p*-value
MACE		
Left dominance	1.60 (1.03-2.49)	0.04
Age	1.01 (1.00-1.02)	0.02
Residual SYNTAX score >0	1.38 (1.12-1.70)	0.002
Lesion success	0.20 (0.11-0.37)	<0.001
TVR		
Left dominance	1.96 (1.14-3.37)	0.02
Diabetes mellitus	1.46 (1.11-1.92)	0.007
Lesion success	0.14 (0.07-0.31)	<0.001

MACE	Left dominance (n=166)	Non-left dominance (n=4,459)	Hazard ratio (95% CI)	*p*-value for interaction
	no. of events/total no. (%)			
Bifurcation lesion				0.190
Yes	20/135 (14.8)	327/3,615 (9.0)	1.66 (1.06-2.61)	
No	1/31 (3.2)	65/844 (7.7)	0.43 (0.06-3.09)	
SYNTAX score before PCI				0.425
Low (≤22)	8/96 (8.3)	154/2,273 (6.8)	1.23 (0.61-2.51)	
High (>22)	13/70 (18.6)	238/2,186 (10.9)	1.77 (1.01-3.09)	
Residual SYNTAX score >0				0.169
Yes	14/73 (19.2)	261/2,629 (9.9)	2.02 (1.18-3.45)	
No	7/93 (7.5)	131/1,830 (7.2)	1.05 (0.49-2.25)	

Figure 1. *Coronary dominance distribution and clinical outcomes in left main patients. A) Coronary dominance distribution; (B) multivariable Cox regression models for MACE and TVR; (C) propensity score matching-adjusted Kaplan-Meier cumulative event curves for MACE and TVR; (D) subgroup analyses of 3-year MACE. MACE was defined as a composite of cardiac death, MI, and TVR. Propensity score matching variables: age, sex, hypertension, hyperlipidaemia, diabetes mellitus, family history of CAD, creatinine clearance rate before PCI, prior PCI, prior MI, ACS, LVEF, isolated left main, LM lesion length, residual SYNTAX score. ACS: acute coronary syndrome; CAD: coronary artery disease; CI: confidence interval; HR: hazard ratio; IVUS: intravascular ultrasound; LM: left main; LVEF: left ventricular ejection fraction; MACE: major adverse cardiac events; MI: myocardial infarction; PCI: percutaneous coronary intervention; PS: propensity score; TVR: target vessel revascularisation*

with a higher risk of long-term adverse events – particularly TVR – compared to non-left dominance patients; and (3) this increased risk may be more pronounced in patients with higher lesion complexity or incomplete revascularisation.

In this study, the prevalence of left dominance among patients undergoing LM PCI was slightly lower than the previously reported 8% to 12% in CAD patients undergoing coronary angiography[5]. Additionally, patients with left dominance in the present LM PCI cohort demonstrated less complex demographic and anatomical characteristics compared with non-left dominance patients. This observation likely reflects the influence of patient selection in real-world clinical practices. Given the extensive myocardial territory supplied by the LM artery in left-dominant patients, interventional cardiologists tend to avoid PCI in patients with more complex anatomy within this high-risk group.

According to this observational study, the data highlight two critical aspects: first, compared with non-left-dominant patients, those with left dominance exhibited a greater need for sustained blood flow restoration and experienced a higher

rate of repeat revascularisation; and second, the risk of acute ischaemic damage was comparable between the two groups once adequate blood flow was restored. Notably, the risk in left-dominant patients was not significant among those with lower anatomical complexity, such as low SYNTAX scores or absence of LM bifurcation. Moreover, achieving complete revascularisation is particularly important, as the relatively small size and limited perfusion capacity of the right coronary artery make the maintenance of a non-stenotic left coronary artery essential. In summary, careful patient selection, optimal treatment strategies, and the achievement of satisfactory acute outcomes are crucial for effective PCI management in this population.

This study has several limitations. First, as a retrospective, single-centre analysis including only Chinese patients, it is susceptible to selection bias. Second, intravascular imaging was not mandatory during the study period, leading to limited utilisation, which might have influenced long-term outcomes. Third, variations in operator experience and technique had the potential to impact outcomes. Future large-scale, prospective studies are needed to further elucidate the influence of coronary artery dominance on the long-term prognosis of LM patients.

In this large-scale retrospective study, LM patients with left dominance undergoing PCI were associated with a significantly higher risk of long-term adverse events, particularly for TVR. Among patients with a higher lesion complexity and incomplete revascularisation, this risk may be further increased.

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Conflict of interest statement

The authors have no conflicts of interest to declare.

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Supplementary data

Supplementary Table 1. Baseline characteristics.
Supplementary Table 2. Lesion and procedural characteristics.
Supplementary Table 3. Clinical outcomes up to 3 years.
Supplementary Figure 1. Competing risks analysis of MACE.

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Low-dose versus high-dose drug-coated balloons for femoropopliteal lesions: 5-year results from the prospective, randomised COMPARE trial

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Drug-coated balloons have become a first-line treatment for femoropopliteal lesions in patients with lower limb peripheral artery disease (LLPAD), offering improved patency compared to plain old balloon angioplasty (POBA)[1]. Drug-coated balloons vary in drug composition, dosage, excipients, and coating techniques, influencing drug release kinetics and transfer to the target lesion. The COMPARE trial was the first randomised study comparing the long-term outcomes of low-dose (2.0 µg/mm²) versus high-dose (3.5 µg/mm²) paclitaxel-coated balloons (PCBs) in complex femoropopliteal lesions, reflecting real-world clinical scenarios. Non-inferiority was met for both primary efficacy and safety endpoints after 1 year, and comparable treatment effects were reported after 2 years[2,3]. Given ongoing concerns about the long-term mortality signal of PCBs, follow-up was extended to 5 years[4].

The COMPARE trial was an investigator-initiated, prospective, multicentre trial that enrolled patients with symptomatic LLPAD across 15 sites in Germany (ClinicalTrials.gov: NCT02701543). The study protocol, population, endpoints, and statistical analyses have been described in depth in prior publications[2,3]. Briefly, patients with symptomatic lesions (Rutherford 2-4) of the native non-stented superficial femoral and/or proximal popliteal artery with a length of up to 30 cm and a stenosis of ≥70% were included. Participants were randomised in a 1:1 ratio to receive treatment either with the low-dose Ranger PCB (Boston Scientific) or the high-dose IN.PACT Admiral or Pacific PCB (Medtronic). Stratification by lesion length (≤10 cm, >10 and ≤20 cm, >20 cm and ≤30 cm) was applied to ensure a balanced allocation of short, intermediate, and long lesions between treatment arms. The primary efficacy endpoint was primary patency, defined as freedom from clinically driven target lesion revascularisation (CD-TLR) or binary restenosis at 12 months, and the primary safety endpoint included the absence of device- or procedure-related death within 30 days and the absence of major adverse events (target limb major amputation and CD-TLR) over 12 months. Extended follow-up endpoints assessed all-cause mortality, major target limb amputation, and CD-TLR. Patients were followed through in-person visits at 6, 12, and 24 months and via structured telephone interviews at 36, 48, and 60 months.

Out of 414 enrolled patients, vital status at 5 years was available for 130/207 (62.8%) patients in the high-dose group and 146/207 (70.5%) patients in the low-dose group. Lesion characteristics were similar across groups, with a mean lesion length of approximately 12.5 cm and over 40% classified as chronic total occlusions. At 5 years, Kaplan-Meier (KM) estimates showed no significant difference in freedom from CD-TLR, with 75.2±3.6% in the high-dose group and 67.1±3.7% in the low-dose group (log-rank p=0.1) **(Figure 1)**. Stratification by lesion length showed consistent results, with the best patency observed for short lesions in both groups **(Supplementary Figure 1)**. A total of 96 first target lesion revascularisations (TLRs) were performed across both groups. Subsequently, 27 second TLRs and 7 third TLRs were recorded. One

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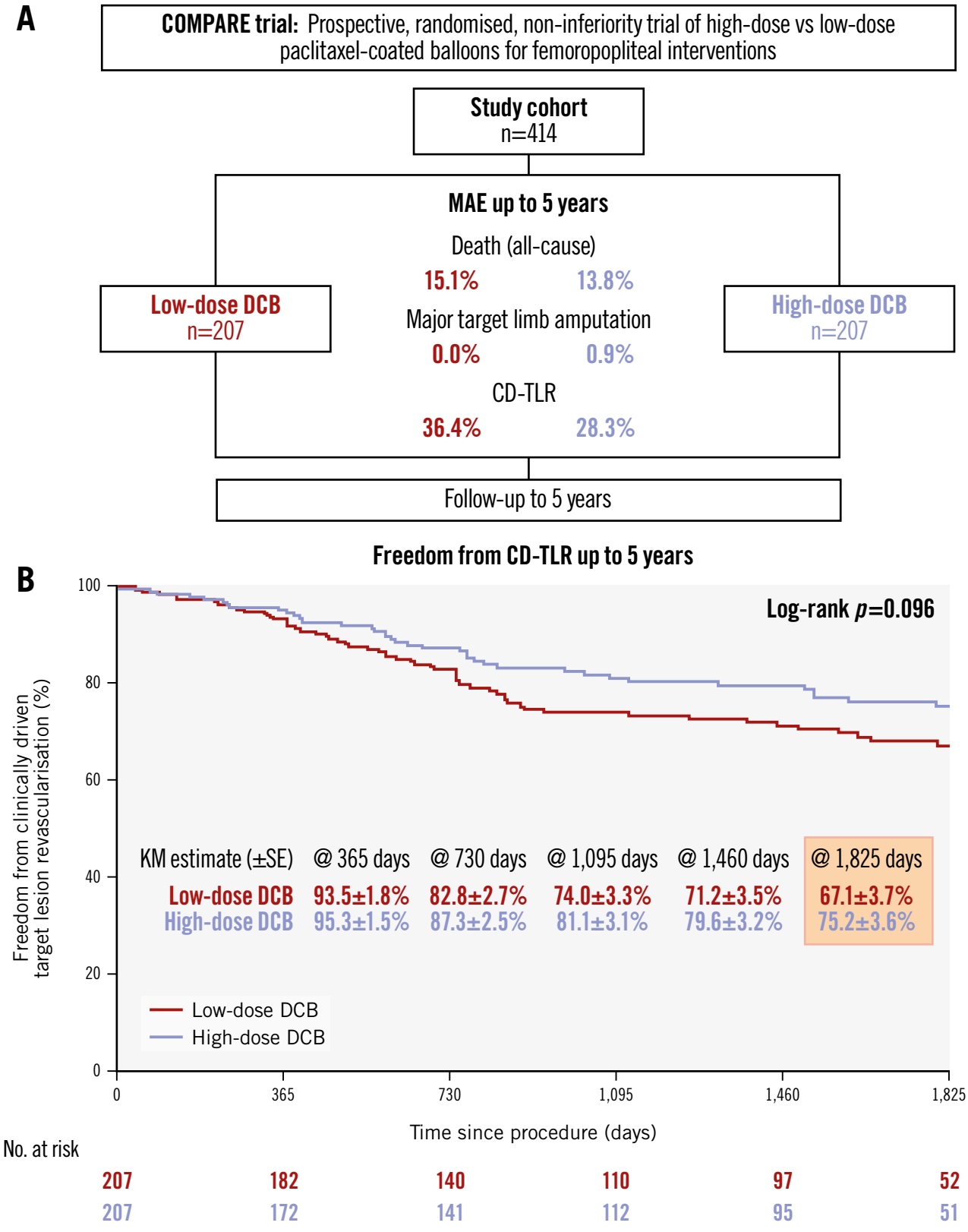

Figure 1. *Study design and 5-year outcomes. A) Study design; (B) Kaplan-Meier estimates showing freedom from clinically driven target lesion revascularisation for low-dose (red curve) and high-dose (blue curve) paclitaxel-coated balloons, with the corresponding number of patients at risk. CD-TLR: clinically driven target lesion revascularisation; DCB: drug-coated balloon; KM: Kaplan-Meier; MAE: major adverse events; SE: standard error*

patient in the low-dose group underwent a total of 6 TLR procedures. The median time to TLR was 677.3±442.5 days (high-dose group: 692.1±463.4 days vs low-dose group: 667.3±431.4 days; p=0.8), with reocclusions observed in 36.5% of target vessels (high-dose group: 38.5% vs low-dose group: 35.7%; p=0.5). Reinterventions were predominantly endovascular (96.8%). All-cause mortality was 13.8% (18/130) in the high-dose group and 15.1% (22/146) in the low-dose group (p=0.9), with no significant difference in KM survival estimates (87.1±2.9% vs 87.5±2.6%; p=0.8) **(Supplementary Figure 2)**. One major target limb amputation was reported after 615 days in the high-dose group.

At 5 years, similar treatment effects between high-dose and low-dose PCB angioplasty were observed, indicating comparable long-term efficacy. Survival analysis revealed an early, non-significant separation of the curves between treatment arms up to 2 years, which remained stable over time. However, the patency curves remained almost overlapping during this period, indicating that the observed difference is likely attributable to chance, particularly given the low event rate. Despite the inclusion of long and complex lesions, including a high proportion of total occlusions, reintervention rates were generally moderate, and similar long-term patency rates after PCB treatment have been published previously[5]. The final results of the COMPARE trial demonstrate no evidence of increased mortality or major target limb amputation in either treatment arm.

Study limitations include that operator blinding was not feasible because of visible device differences. However, core laboratory personnel and members of the clinical events committee were blinded to the treatment assignments. Furthermore, extending the study's follow-up after enrolment had begun may have impacted retention rates. Loss to follow-up rates were high, with a higher rate in the high-dose group, possibly introducing bias.

In conclusion, the 5-year results from the COMPARE trial suggest a comparable efficacy of low-dose PCB angioplasty to the high-dose alternative. Additionally, the trial demonstrated the safety of both PCBs, supporting their long-term viability as treatment options. These results reinforce the superior long-term patency of PCBs over POBA and provide valuable evidence for their continued use in managing challenging LLPAD cases.

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Conflict of interest statement

S. Steiner has been a consultant or advisory board member for Angiodynamics, Biotronik, Boston Scientific, Cook Medical, and iThera Medical. A. Schmidt has been a consultant for Abbott, BD, Boston Scientific, Cook Medical, Reflow Medical, and Upstream Peripheral Technologies. T. Zeller has received consulting fees from Boston Scientific, W.L. Gore & Associates, Medtronic, Shockwave Medical, VentureMed, Veryan, and Reflow Medica; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Acotec, BD Bard, Biotronik, Boston Scientific, Cook Medical, Cordis, Medtronic, and Veryan; and has stock or stock options in ANT. G. Tepe is on the advisory board for Medtronic and Philips; and has received study support from Bard, Bayer, B. Braun, Biotronik, Boston Scientific, Cardiovascular Systems, Gore Medical, Veryan, and Shockwave Medical. E. Blessing has received honoraria from Abbott, B. Braun, Biotronik, Boston Scientific, Cook Medical, W. L. Gore & Associates, Medtronic, Philips-Spectranetics, and Shockwave Medical; and is a consultant for Boston Scientific, Medtronic, and Bayer. R. Langhoff has received consulting and speaker honoraria from Boston Scientific, Biotronik, Abbott, Contego Medical, Terumo, Cardinal Health, Alvimedica, B. Braun, and Kardionet; and has received speaker honoraria from Bard, and Bayer. N. Weiss has received speaker honoraria or research funding from Bard, Terumo, Optimed, Amgen, Bayer, Esperion, Pfizer, Pluristem, and TICEBA. D. Scheinert is a consultant for Abbott, Acotec, Boston Scientific, Concept Medical, Medtronic, Upstream Peripheral Technologies, Penumbra, Philips, and Reflow Medical. M. Thieme has received consulting and speaker honoraria from Reflow Medical, Bristol-Myers Squibb, and Pfizer. The other authors have no conflicts of interest to declare relevant to the contents of this paper.

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Supplementary data

Supplementary Figure 1. Survival curve for freedom from clinically driven target lesion revascularisation stratified according to lesion length.

Supplementary Figure 2. All-cause mortality up to 5 years.

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Balloon compression or haemostatic patch after distal foot arterial access for lower limb angioplasty: the PED-PRESS trial

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Traditionally, lower-limb endovascular interventions have used transfemoral or transbrachial access. Alternative approaches such as transradial and distal foot artery (DFA) access are now, however, increasingly adopted[1,2]. DFA access (distal anterior tibial/dorsalis pedis, distal posterior tibial, and distal peroneal/perforator arteries) offers a smaller-calibre, superficial, and easily compressible artery, lowering access site bleeding complications[2]. Given the DFA's small size, intravascular closure devices cannot be used; haemostasis relies on external compression. The standard method is manual compression, but dedicated devices are often employed for convenience. Two devices are commonly used: a balloon compression device (TR Band [Terumo]) originally designed for radial artery haemostasis[3], and a topical haemostatic patch (StatSeal [Biolife]). StatSeal utilises a hydrophilic polymer that dehydrates blood and absorbs exudate, while its potassium ferrate-induced low pH aggregates proteins and promotes seal formation. StatSeal has demonstrated efficacy in reducing transradial access haemostasis time[4]. The PED-PRESS trial presented herein compared DFA access site complications utilising these two closure devices.

This prospective, randomised trial enrolled 150 patients. The procedures used ultrasound-guided DFA access. Patients were randomised to TR Band or StatSeal closure devices post-sheath removal. If retrograde crossing failed, proximal femoral access was used. The primary endpoints were major (requiring surgical/interventional treatment, e.g., large haematoma needing transfusion, pseudoaneurysm needing thrombin injection, or access site occlusion) and minor (self-limiting bleeding or haematoma <5 cm requiring no therapy)[5]. Group comparisons used chi-square or Fisher's exact tests for categorical variables, with $p<0.05$ considered significant.

Patients classified in Rutherford categories 2-5 (from claudication to chronic limb-threatening ischaemia, e.g., ischaemic rest pain, crural ulcer, pedal gangrene) were included. Those in Rutherford categories 0-1 (asymptomatic to mild claudication) were excluded.

Inaccessible DFA arteries (e.g., complete occlusion, severe calcification, anatomical variations), non-viable lower limbs, contraindications to dual antiplatelet therapy for ≥1 month, heart failure (ejection fraction <35%), significant valvular disease, age >85 years, severe renal dysfunction (glomerular filtration rate <30 mL/kg/min), ongoing sepsis, or life expectancy <3 years. Of the screened patients, 30% were excluded, mainly due to non-viable limbs (25 patients), antiplatelet contraindications (20 patients), or severe comorbidities (15 patients).

A postoperative vascular ultrasound assessed DFA artery patency and puncture-related haematomas on day 1.

Patients received preprocedural aspirin (325 mg) and clopidogrel (300 mg), with dual antiplatelet therapy (aspirin 100 mg, clopidogrel 75 mg) for two months after stenting or lifelong aspirin after balloon angioplasty. Heparin (100 IU/kg) and nitroglycerine (250 mcg) were administered via the DFA sheath.

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For access, a 4 Fr Terumo transradial sheath, a HI-TORQUE PROGRESS 40 0.14" guidewire (Abbott) and CXI Support 0.35" catheter (Cook Medical) were used. Stenting was performed for flow-limiting dissections, with sheath upsizing to 6 Fr in 66% of cases.

Percutaneous transluminal angioplasty was performed in all 150 patients using DFA access. Secondary femoral access was required in 89 patients (59.3%) due to retrograde crossing failure. Access sites comprised the anterior tibial/dorsalis pedis arteries in 115/150 (76.7%), the distal posterior tibial artery in 21/150 (14.0%), and the peroneal artery in 14/150 (9.3%). Baseline characteristics were balanced between groups **(Supplementary Table 1)**, and procedural characteristics are provided in **Supplementary Table 2**.

Major DFA access-site complications occurred in 6.7% (5/75) of patients in the TR Band group versus 5.3% (4/75) with StatSeal (p=1.00). Minor complications occurred in 4/75 (5.3%) versus 3/75 (4.0%), for TR Band and StatSeal, respectively (p=1.00). Combined DFA access site complications (major and minor) occurred in 9/75 (12.0%) TR Band patients versus 6/75 (8.0%) StatSeal patients (p=0.60). Component events were the following, for TR Band and StatSeal patients, respectively: haematomas <5 cm: 4/75 (5.3%) versus 3/75 (4.0%); major bleeding: 1/75 (1.3%) versus 0/75 (0%); pseudoaneurysm: 1/75 (1.3%) versus 1/75 (1.3%); arteriovenous fistula 1/75 (1.3%) versus 0/75 (0%); and tibial occlusions 1/75 (1.3%) versus 1/75 (1.3%). Per-artery, per-device data are shown in **Supplementary Table 3**. No infections, acute limb ischaemia, nor compartment syndrome occurred. Next-day vascular ultrasound confirmed DFA patency was 74/75 (98.6%) in TR Band vs 72/75 (96.0%) in StatSeal (p=1.00). **Figure 1** summarises DFA access site complication rates.

This is the first randomised trial comparing TR Band and StatSeal for DFA access site closure after endovascular intervention. Complication rates were similar (any: 12.0% TR Band vs 8.0% StatSeal; p=0.60; major: 6.7% TR Band vs 5.3% StatSeal; p=1.00; minor: 5.3% TR Band vs 4.0% StatSeal; p=1.00). The study was not powered to detect small between-group differences; therefore, numerical differences should be interpreted cautiously. Compared to prior studies, our results align with the low bleeding complication rates reported for DFA access[3,4].

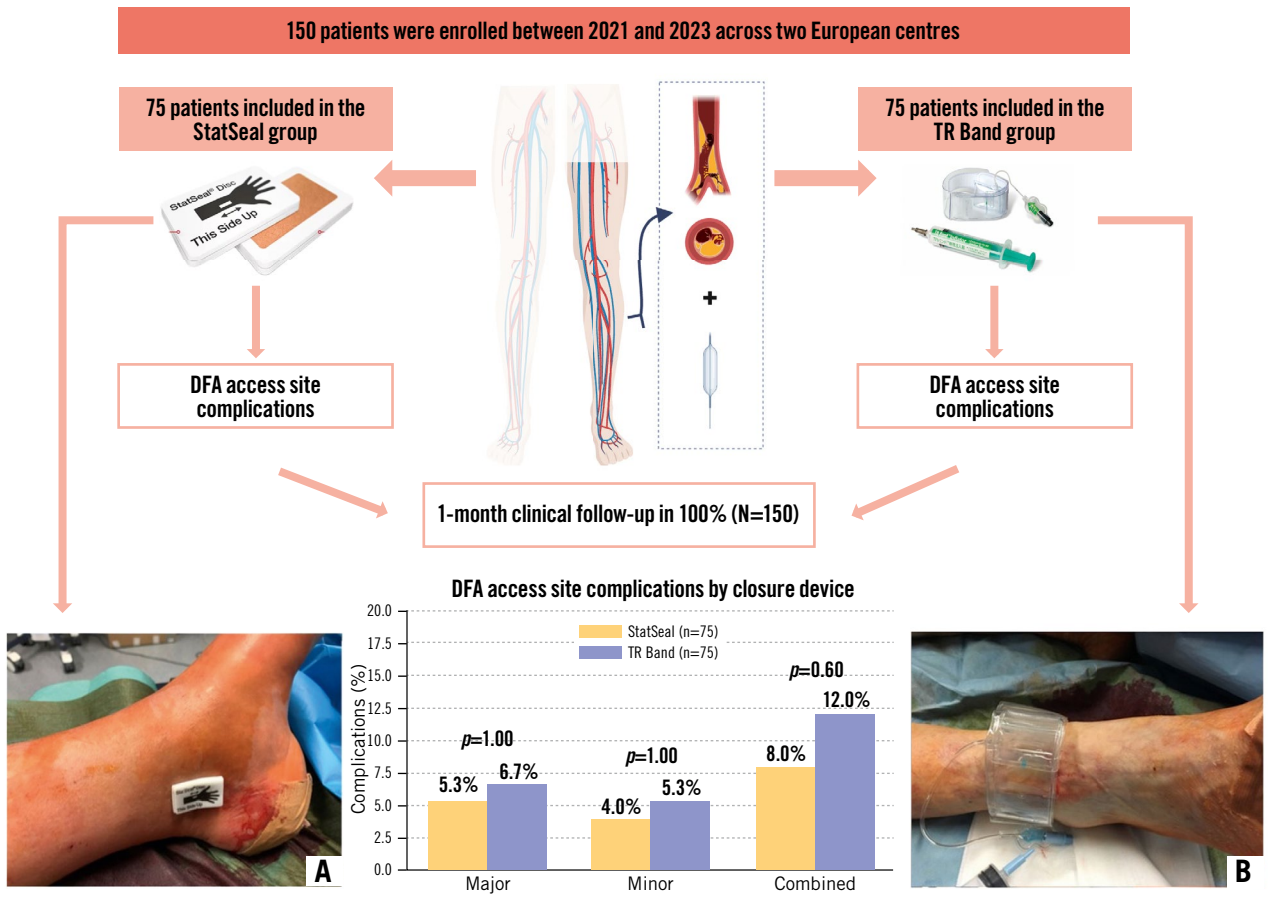

Figure 1. *PED-PRESS study design and outcomes. Study design showing 150 patients enrolled (2021-2023) across two European centres, randomised to StatSeal (n=75) or TR Band (n=75) for distal foot artery access site closure. The bar chart displays distal foot artery access site complications: major (6.7% TR Band vs 5.3% StatSeal; p=1.00), minor (5.3% vs 4.0%; p=1.00), and combined (12.0% vs 8.0%; p=0.60). An illustration of device applications is provided for (A) StatSeal and (B) TR Band. Created with BioRender.com.*

Both devices provided reliable DFA haemostasis. Limitations include the modest sample size and absence of a manual compression arm, of patient-reported outcomes, and of cost analyses. Peroneal access (~10% of cases) had one event overall (7.1%; StatSeal) and was not analysed separately due to low counts. Larger trials are warranted.

Distal foot artery access for lower limb interventions has low access site complication rates. Both TR Band and StatSeal closure devices are safe and effective, with no significant differences in access site complication rates. While closure device choice may not significantly impact overall success and complication rates, further research is needed to optimise closure strategies.

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Conflict of interest statement

The authors have no conflicts of interest to declare.

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Supplementary data

Supplementary Table 1. Baseline patient characteristics.
Supplementary Table 2. 30-day procedural outcome data.
Supplementary Table 3. Per-artery and per-device DFA access site complications (combined).

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Retrieval of a stuck transcatheter aortic valve device via left ventricular apex and transapical implantation

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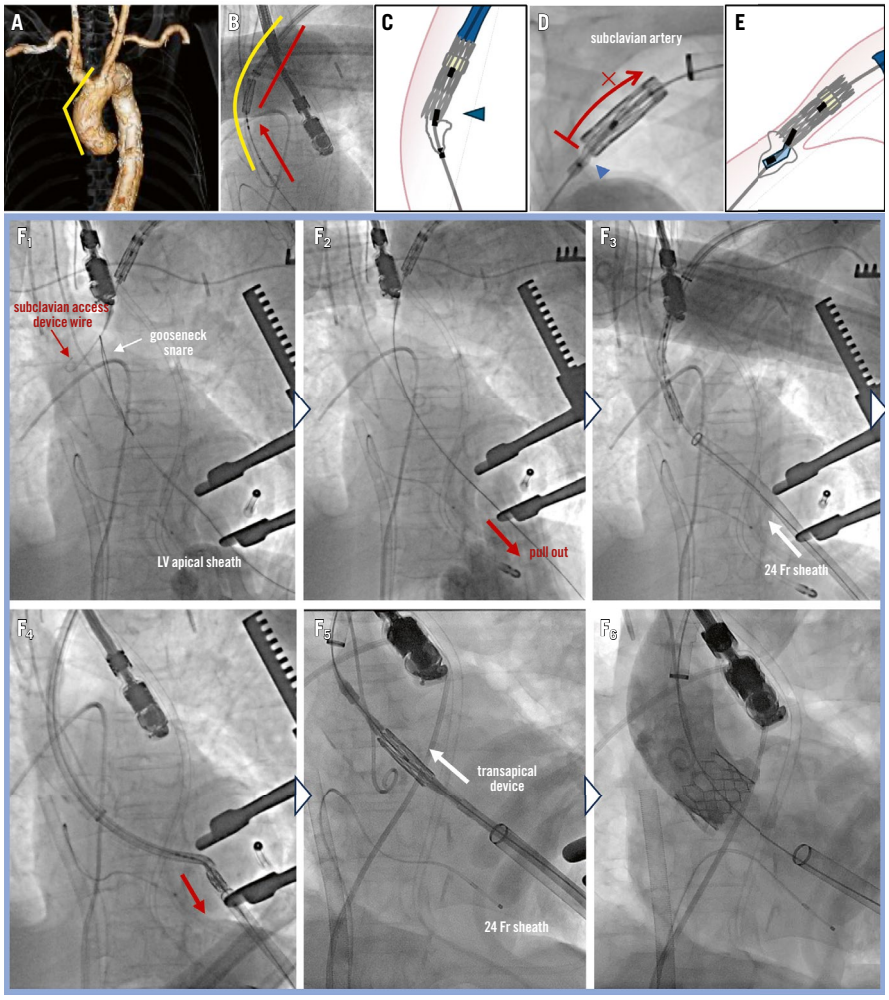

Figure 1. *Procedural image of the stuck prosthesis caused by balloon alignment failure and its removal via the left ventricular apex. A) Angle of the aortic arch and ascending aorta. B) Balloon-valve alignment performed in the ascending aorta. C) Balloon injury occurred due to alignment in a curved segment, resulting in failed positioning. D, E) The deformed balloon, indicated by the blue arrowheads, could not be withdrawn via the subclavian artery. F1) The stiff wire was folded using a 10 mm gooseneck snare from the LV apical sheath. F2) The wire was pulled through. F3, F4) The SAPIEN 3 delivery system was extracted from the LV along with the 24 Fr sheath. F5) A new 24 Fr sheath was reinserted via the apical site over the stiff wire. F6) A second 26 mm SAPIEN 3 valve was deployed through the 24 Fr sheath using a transapical device. LV: left ventricle*

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A 71-year-old male with schizophrenia and chronic subdural haematoma was transferred to our hospital in cardiogenic shock. Cardiopulmonary resuscitation combined with extracorporeal membrane oxygenation (ECMO) and an intra-aortic balloon pump (IABP) was initiated via the bifemoral artery and vein, leading to return of spontaneous circulation. Transthoracic echocardiography showed a severely stenotic, calcified aortic valve with an area of 0.6 cm^2 and a mean pressure gradient of 23 mmHg. The stroke volume index was 18.5 mL/m^2 and the left ventricular (LV) ejection fraction was 20%. Computed tomography confirmed severe calcification (calcium score of 3,310 Agatston units), consistent with low-flow, low-gradient severe aortic stenosis.

Given the patient's comorbidities and haemodynamic instability, the Heart Team opted for urgent transcatheter aortic valve implantation (TAVI) using a 26 mm SAPIEN 3 valve (Edwards Lifesciences). Left subclavian access was chosen because both femoral arteries were occupied by ECMO and IABP devices. With a vessel diameter of >6 mm, aortic arch angle of 120°, and ascending aorta length of 74 mm, the left subclavian route was deemed feasible **(Figure 1A)**. An 18 Fr sheath was inserted into the aortic arch over a SAFARI XS wire (Boston Scientific). The prosthetic valve with its delivery system was advanced into the ascending aorta, and prosthesis-balloon alignment was attempted, notably near the aortic arch **(Figure 1B)**. However, strong resistance disrupted alignment at the balloon's midportion, preventing withdrawal to the warning marker. The balloon could only mount two-thirds of the valve, and fracture of the unretractable distal balloon shaft was confirmed **(Figure 1C, Moving image 1)**. Blood return from the inflation device indicated balloon rupture. Removal via the subclavian artery was impossible because of the deformed balloon obstructing passage (**Figure 1D**, **Figure 1E**).

Ultimately, the stuck prosthesis and delivery system were retrieved via the LV apex. After LV apex puncture via a standard transapical approach, the stiff wire of the SAPIEN delivery system was folded using a 10 mm gooseneck snare from the LV apical sheath **(Figure 1F1)** and pulled through the LV apex sheath **(Figure 1F2)**. The distal end of the delivery system combined with the 24 Fr sheath was extracted via the left ventricle **(Figure 1F3, Figure 1F4, Moving image 2)**. After cutting the delivery system at the balloon shaft, a new 24 Fr sheath was immediately reinserted via the apex over the stiff wire **(Figure 1F5)**. A second 26 mm SAPIEN 3 valve was successfully deployed via the transapical route **(Figure 1F6)**. Haemodynamic assist devices were successfully removed after TAVI with an improved LV ejection fraction of 40%. The patient was transferred to a rehabilitation hospital 1 month later.

Prosthesis-balloon alignment failure and balloon rupture during TAVI are rare, mostly reported in cases with femoral access. With left subclavian access, the limited straight segment may contribute to such complications. To prevent this, alignment should occur in a straight portion, a stiffer wire should be used, and a Certitude system (Edwards Lifesciences) should be considered. Transoesophageal echocardiography also aids in identifying causes. The bailout technique described here is not standard; access site selection and avoidance of balloon alignment near bends are crucial.

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Conflict of interest statement

G. Nakazawa serves as a proctor for Edwards Lifesciences. The other authors have no conflicts of interest to declare.

Supplementary data

Moving image 1. Prosthesis-balloon alignment failure and balloon rupture.

Moving image 2. Retrieval of the stuck prosthesis via LV apex and transapical implantation.

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