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State-of-the-Art

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A state-of-the-art on TAVI in biscuspid aortic stenosis; an expert consensus on transcatheter tricuspid valve interventions in patients with transvalvular right ventricular leads; the ACURATE platform discontinuation; coronary cannulation after transfemoral TAVI with the Evolut FX; HALT after TAVI with the SAPIEN Ultra RESILIA; impact of aortic annular size on long-term outcomes and valve durability; the TRICURE first-in-human study; 5-year follow-up of EVOQUE TTVR; and more

Davide Capodanno, *Editor-in-Chief*

And here we are again in November, opening a new issue full of articles on interventions for valvular heart disease, coinciding with another sparkling edition of PCR London Valves. This issue is special for us, and the fact that it is one of only four printed issues is the clearest proof. Perhaps we are a bit romantic – and in the digital era our kind is probably becoming extinct – but seeing conference attendees holding the printed copy, as a gift, is a real satisfaction.

I remember that, years ago, assembling this special issue was more complex. Given the nature of the conference, one would expect it to be full of articles on transcatheter aortic valve implantation (TAVI), mitral transcatheter edge-to-edge repair, and similar topics — and indeed, it always has been. However, filling an entire issue was not simple, especially in 2020, when most submissions were predominantly coronary-focused. At that time, we had to be resourceful, inviting renowned authors to contribute editorials, viewpoints, and reviews.

Now, the challenge is the opposite: we are fortunate to receive an abundance of high-quality submissions – likely reflecting the Journal's growth and rising impact factor. The task is no longer simply filling the issue, but selecting the most relevant articles, arranging them to ensure a coherent flow, and refining the production process to maximise both clarity and visual impact. Our aim is to attract trials, multicentre studies, and leading authors, always striving for excellence, even when the standard is already high.

In keeping with this commitment, and to celebrate the Journal's 20th anniversary, we are establishing a new tradition. For the first time, a prominent member of our cardiology community will receive the "Alain Cribier EuroIntervention" award. With the family Cribier's endorsement, the award will be presented in a plenary session by Hélène Eltchaninoff, honouring the academic and clinical contributions of a man whose invention, talent, and charisma have reshaped the management of valvular heart disease.

It is in this spirit of excellence and innovation that we present the current issue. Here, you will find a carefully curated selection of articles on TAVI and other interventions, each chosen to provide a comprehensive overview of the latest evidence, clinical insights, and emerging techniques. We hope this issue both informs and inspires, reflecting the dynamic progress in valvular heart disease management.

Let's turn to the articles:

We begin this issue with a state-of-the-art review on the transcatheter treatment of bicuspid aortic valve (BAV) stenosis from **Didier Tchétché, Ole De Backer and colleagues.** TAVI has expanded to include selected patients with BAV anatomies, but challenges, both technical and procedural, remain. The authors review the classifications of BAV disease and the current procedural techniques; they discuss what research has been done to date and what knowledge gaps remain to be filled.

In an expert consensus commissioned by the European Heart Rhythm Association and the European Association of Percutaneous Cardiovascular Interventions of the European Society of Cardiology, **Jean-Claude Deharo, Zachary Whinnett and colleagues** focus on the management of patients with transvalvular right ventricular leads undergoing transcatheter tricuspid valve interventions. Nearly one-third of patients referred for transcatheter tricuspid valve interventions have a pacemaker or implantable cardioverter-defibrillator lead, making communication between interventional cardiologists and electrophysiologists essential. This document relays the current scientific evidence available and is intended as a resource for Heart Teams in their decision-making and patient management.

The timing and impact of the ACURATE *neo2*/Prime transcatheter heart valve's (THV) discontinuation merit a nuanced discussion, according to **Won-Keun Kim and Helge Möllmann**. In this viewpoint, the authors discuss whether the platform's discontinuation really is the scientific reckoning that some claim, or whether other elements, such as registry design, device sizing and use, led to an underestimation of the device's potential.

To begin our original reseach section, **Kenichi Ishizu, Kentaro Hayashida and colleagues** examine the 30-day clinical incidence, predictors, and impact of hypoattenuated leaflet thickening (HALT) after TAVI with the latest-generation SAPIEN 3 Ultra RESILIA. The overall rates of HALT were found to be comparable with the previous-generation devices and the device's revised commissural leaflet suspension method that is specific to the smaller-sized

valves was not found to be associated with an increased risk of HALT. However, the prosthesis deformation index and asymmetric leaflet expansion were independently associated with an increased risk of HALT, regardless of THV size. **Jonathon A. Leipsic and John K. Khoo** comment in an accompanying editorial.

Our next original research articles asks whether a patient's baseline aortic annulus size is a predictor of long-term outcomes after TAVI with a balloon-expandable THV. **Masanori Yamamoto, Kentaro Hayashida and colleagues** tackle this question by dividing a large cohort of patients who underwent TAVI up to 7 years earlier by annular size in order to evaluate primary endpoints of all-cause mortality and stages of bioprosthetic valve failure. As annular size was not found to be associated with a long-term prognosis or valve durability, the authors suggest that other indicators need to be explored.

Then, we turn to whether optimal commissural and coronary alignment can be achieved using a tall-frame, supra-annular THV. **Yohei Ohno, Guilherme F. Attizzani and colleagues** evaluate the feasibility and timing of coronary cannulation post-TAVI with the new-generation Evolut FX device. The CANNULATE TAVR EXPANDED study had a 100% success rate in coronary cannulation of the left coronary artery and a 96.7% success rate for the right coronary artery. Misalignment was identified as a strong predictor for suboptimal coronary cannulation of both the left and right coronary arteries. In an accompanying editorial, **Ignacio J. Amat-Santos and Filippo Pensotti** discuss how these findings can help direct future research.

In this issue's final original research paper, **Emmanuel Teiger, Julien Dreyfus and colleagues** present the first-in-human TRICURE study which evaluated the safety and efficacy of the novel Topaz transcatheter tricuspid valve replacement system for the treatment of tricuspid regurgitation (TR). This dual-stent device, specifically designed for the tricuspid valve anatomy, was tested in 20 patients with outcomes including short procedure times, low complication rates, and substantial and sustained reduction of TR at 30 days. The authors include a case study of one patient at 6 months as well as a discussion about operator learning curves and screening criteria, in the hopes of paving the path for future studies.

And now, to the articles themselves.

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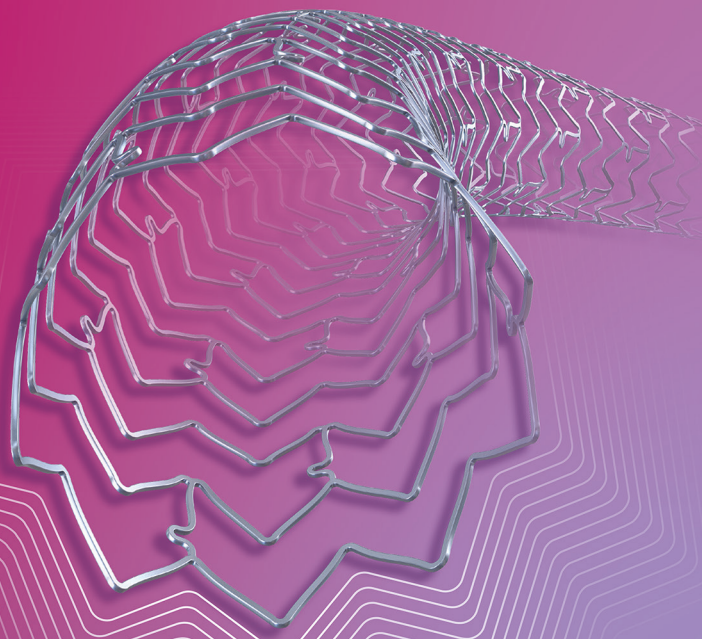

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1. Krone, RJ., et. al., Evaluation of the ACC/AHA and the SCAI Lesion Classification System in the Current Stent Era of Coronary Interventions (From the ACC NCDR), *The American Journal of Cardiology* Vol. 92 August 15, 2003. **2.** Zanchin, C., et al. *J Am Coll Cardiol Intv*. 2019;12(17):1665-1675. Serruys, P., et al. *N Engl J Med*. 2010;363:136-146. Shiomi, H., et al. *J Am Coll Cardiol Interv*. 2019;12:637-647. Kufner, S., et al. *Circulation*. 2019:139(3):325-333. Palmerini, T., et al. *Lancet*. 2013;379:1393-1402. Bangalore, S., et al. *Circ Cardiovasc Interv*. 2013;6(6):378-390. Pilgrim, T., et al. 2014;384:2111-2122. Pilgrim, T., et al. 2018;392:737-746.

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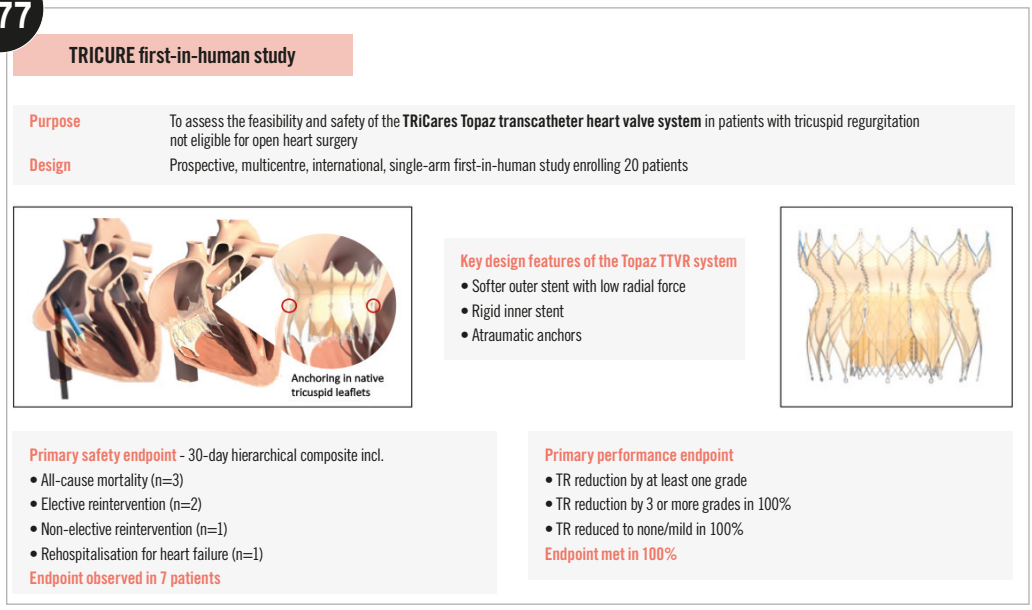

Image taken from the following paper printed in this issue:
TRICURE: first-in-human study of the Topaz transcatheter tricuspid heart valve system
Emmanuel Teiger, Mohammed Nejjari, Liesbeth Rosseel, Joëlle Kefer, Stefan Verheye, Patrizio Lancellotti, Léopold Oliver, Jean-François Obadia, Federico M. Asch, Philipp Blanke, Julien Dreyfus
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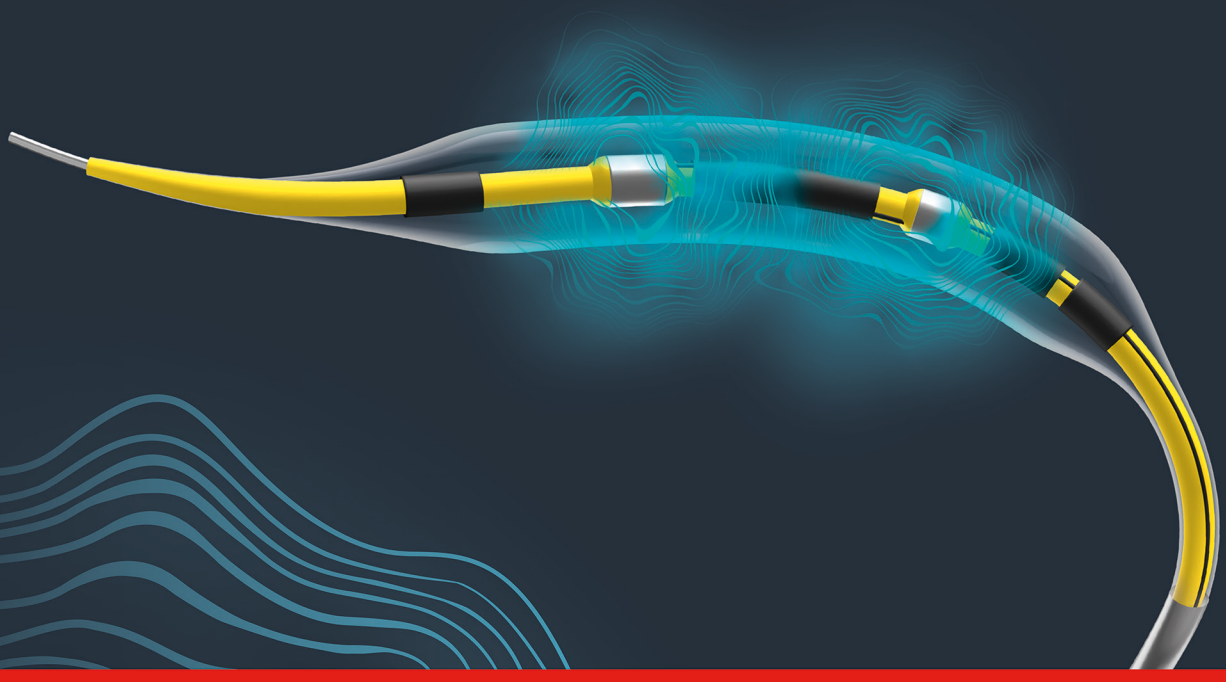

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EDITORIAL

HALT – an evolving understanding of the mechanisms of formation and clinical relevance

Jonathon A. Leipsic[1]*, MD; John K. Khoo[2], MBBS

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Since its initial description in 2015[1], hypoattenuating leaflet thickening (HALT) has been the subject of ongoing research. The incidence of HALT has been reported among all commonly used transcatheter heart valves (THVs) and various surgical bioprosthetic valves, based on data from nested registries of randomised trials as well as prospective and retrospective registries[2]. Its clinical significance is still under investigation. While the relationship of HALT with stroke and mortality is an area of question[3,4], there is growing evidence that HALT is associated with higher valve gradients and earlier valve degeneration[5,6]. Potential mechanisms of HALT development have been proposed, ranging from reduction of neosinus flow, asymmetric valve expansion, and biological mechanisms such as endothelial dysfunction[6]. Recognising this, it is generally accepted that valve design plays a potential role, and it is crucial not to assume that the incidence and mechanisms are the same across valve platforms[6].

Despite advancements in knowledge, there remain outstanding questions.

In this issue of EuroIntervention, Ishizu et al[7] look to provide answers. The authors took a subset of the OCEAN-TAVI registry to investigate the incidence, predictors, and clinical impact of HALT following transcatheter aortic valve implantation (TAVI) with the latest generation of the short frame, intra-annular and balloon-expandable SAPIEN 3 valve, the SAPIEN 3 Ultra RESILIA (S3UR; Edwards Lifesciences). This study is particularly important given the unique design of the S3UR valve with anticalcification treatment of the leaflets and modification of the commissural leaflet suspension method for the smaller-sized valves.

Article, see page 1338

The authors are commended for their thorough analysis. In addition to assessing HALT according to Valve Academic Research Consortium (VARC)-3 criteria[8], the study's independent core laboratory used four-dimensional cardiac computed tomography (CT) data acquired at 30 days to analyse THV geometry. This encompassed a host of thoughtfully defined variables including oversizing, expansion, canting, alignment, eccentricity, deformation index, and leaflet expansion. The analysis yielded noteworthy results.

The incidence of HALT in this study population was 21.3%, which is similar to prior reports for SAPIEN 3 valves[9]. Unique, though, to this analysis is the exploration of the relationship between HALT and the revised commissural leaflet suspension dedicated to the 20 mm and 23 mm THVs. Notably, these modifications were not associated with a signal for HALT, with a comparable incidence between THV sizes ≤23 mm and ≥26 mm (22.1% vs 20.2%).

Haemodynamic alterations were also assessed. The presence or absence of HALT did not show a significant association with increased gradients, consistent with findings from prior studies[9]. This relationship changed when assessing HALT according to severity. HALT when stratified by a 25% cutoff, by a 50% cutoff, and by involvement of more than one leaflet was significantly associated with higher post-implant gradients. HALT should therefore be considered along a spectrum of severity, rather than as a binary diagnosis.

The authors highlight that cross-sectional measures of valve deformation index and asymmetrical leaflet expansion were the two geometric variables independently associated with a higher incidence of HALT. A high deformation index indicates underexpansion and corresponds to the hourglass-shaped stent frame, while leaflet asymmetricity represents both underexpansion and uneven expansion[5]. Previous

studies also identified these variables as independent predictors of HALT in both balloon-expandable and self-expanding valves[9].

While providing valuable analyses, this study, like all such reports, leaves lingering questions. To start, the authors simply present 30-day data. Evaluating data out to one year and beyond would be valuable, and we hope the authors will pursue longer-term outcomes, including haemodynamic changes, survival, and treatment response. Also, although RESILIA leaflets did not prevent short-term HALT, this anticalcification technology may still be relevant to durability. Longer-term echocardiographic and CT data will demonstrate whether the S3UR reduces the incidence of valve degeneration. It would be good to explore this going forward, and it is helpful to provide evidence that supports and directs technological advancements.

Interestingly the authors opine that in patients with adverse root features and challenging sizing which would behove post-balloon dilatation, a supra-annular self-expanding valve might make more sense. The authors propose that underfilling would be associated with deformation and underexpansion and, in turn, HALT and therefore inform the recommendation for a different valve platform. While this is an intriguing idea, several variables must be considered, and further study is needed before making a confident recommendation.

In closing, we thank the authors for their thoughtful, involved, and important analysis. It represents the first investigation of HALT related to the RESILIA technology and the commissural modification in smaller S3UR valves. The findings overall align with prior such analyses of different valve platforms. While incremental and needed, we would advocate that the authors build on this work and continue this journey by undertaking intermediate and long-term analysis. This will inform the durability of the S3UR valve but also address unresolved issues regarding the relationship of HALT with long-term outcomes and valve degeneration.

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Conflict of interest statement

J.A. Leipsic discloses consulting fees from Circle CVI and HeartFlow; support for attending meetings and/or travel from Arineta; and stock or stock options from HeartFlow. J.K. Khoo has no conflicts of interest to declare.

References

1. Makkar RR, Fontana G, Jilaihawi H, Chakravarty T, Kofoed KF, De Backer O, Asch FM, Ruiz CE, Olsen NT, Trento A, Friedman J, Berman D, Cheng W, Kashif M, Jelnin V, Kliger CA, Guo H, Pichard AD, Weissman NJ, Kapadia S, Manasse E, Bhatt DL, Leon MB, Søndergaard L. Possible Subclinical Leaflet Thrombosis in Bioprosthetic Aortic Valves. *N Engl J Med*. 2015;373:2015-24.

2. Ahmad Y, Makkar R, Sondergaard L. Hypoattenuated leaflet thickening (HALT) and reduced leaflet motion (RELM) of aortic bioprostheses: An imaging finding or a complication? *Prog Cardiovasc Dis*. 2022;72:78-83.

3. Garcia S, Fukui M, Dworak MW, Okeson BK, Garberich R, Hashimoto G, Sato H, Cavalcante JL, Bapat VN, Lesser J, Cheng V, Newell MC, Goessl M, Elmariah S, Bradley SM, Sorajja P. Clinical Impact of Hypoattenuating Leaflet Thickening After Transcatheter Aortic Valve Replacement. *Circ Cardiovasc Interv*. 2022;15:e011480.

4. Choi Y, Ahn JM, Kang DY, Kim HJ, Kim H, Lee J, Kim M, Park J, Kim KW, Koo HJ, Yang DH, Jung SC, Kim B, Anthony Wong YT, Simon Lam CC, Yin WH, Wei J, Lee YT, Kao HL, Lin MS, Ko TY, Kim WJ, Kang SH, Lee SA, Kim DH, Lee JH, Park SJ, Park DW; ADAPT-TAVR Investigators. Frequency, Predictors, and Clinical Impact of Valvular and Perivalvular Thrombus After Transcatheter Aortic Valve Replacement. *JACC Cardiovasc Interv*. 2023;16:2967-81.

5. Fukui M, Cavalcante JL, Bapat VN. Deformation in transcatheter heart valves: Clinical implications and considerations. *J Cardiol*. 2024;83:351-8.

6. Samadzadeh Tabrizi N, Fishberger G, Musuku SR, Shapeton AD. Hypoattenuated Leaflet Thickening: A Comprehensive Review of Contemporary Data. *J Cardiothorac Vasc Anesth*. 2024;38:2761-9.

7. Ishizu K, Shirai S, Hayashi M, Morofuji T, Isotani A, Ohno N, Kakumoto S, Ando K, Yamamoto M, Ochiai T, Tsunaki T, Hioki H, Shimura T, Yashima F, Asami M, Yamanaka F, Ohno Y, Nakazawa G, Hachinohe D, Fuku Y, Otsuka T, Hayashida K; the OCEAN-TAVI investigators. Incidence, predictors, and clinical impact of hypoattenuating leaflet thickening following SAPIEN 3 Ultra RESILIA implantation. *EuroIntervention*. 2025;21:1338-49.

8. VARC-3 WRITING COMMITTEE; Généreux P, Piazza N, Alu MC, Nazif T, Hahn RT, Pibarot P, Bax JJ, Leipsic JA, Blanke P, Blackstone EH, Finn MT, Kapadia S, Linke A, Mack MJ, Makkar R, Mehran R, Popma JJ, Reardon M, Rodes-Cabau J, Van Mieghem NM, Webb JG, Cohen DJ, Leon MB. Valve Academic Research Consortium 3: Updated Endpoint Definitions for Aortic Valve Clinical Research. *J Am Coll Cardiol*. 2021;77:2717-46.

9. Fukui M, Bapat VN, Garcia S, Dworak MW, Hashimoto G, Sato H, Gössl M, Enriquez-Sarano M, Lesser JR, Cavalcante JL, Sorajja P. Deformation of Transcatheter Aortic Valve Prostheses: Implications for Hypoattenuating Leaflet Thickening and Clinical Outcomes. *Circulation*. 2022;146:480-93.

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EDITORIAL

Transcatheter aortic valve alignment: substantial progress, remaining gaps

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We are performing transcatheter aortic valve implantation (TAVI) procedures better than ever. Technical advancements and operator expertise have led to improved outcomes, and this, combined with growing evidence supporting TAVI durability, has accelerated its adoption in younger patients with longer life expectancy. But this progress comes with a caveat: longer post-TAVI survival means an increasing need for coronary angiography, percutaneous coronary intervention (PCI), and valve reintervention, all of which depend on reliable coronary cannulation (CC)[1].

In 2020, Barbanti et al[2] reported that selective coronary re-engagement was unsuccessful in 7.7% of patients after TAVI with the Evolut R/PRO valve (Medtronic), identifying implant depth and transcatheter heart valve (THV) oversizing relative to the sinus of Valsalva as predictors of failure. At that time, commissural and coronary alignment were rarely a concern during implantation. Subsequent studies recognised that misalignment might be a key driver of difficult CC, sparking device iterations and procedural refinements aimed at improving alignment – and, consequently, coronary access.

In this issue of EuroIntervention, the study by Ohno et al[3] confirms that these efforts are bearing fruit. Their multicentre prospective study demonstrates that commissural alignment, defined according to ALIGN-TAVR Consortium standards[4], was achieved in 86.4% of patients treated with the Evolut FX valve (Medtronic), while CC was successful in 100% of left coronary artery (LCA) cases and 96.7% of right coronary artery (RCA) cases. These are clear improvements over prior reports, including the contemporary CAvEAT Registry, where moderate or severe commissural misalignment was still seen in nearly one-third of cases[5].

Article, see page 1364

Ohno and colleagues deserve credit for their rigorous methodology, including systematic post-TAVI computed tomography and intraprocedural CC in all patients, and for using uniform definitions from ALIGN-TAVR[4]. Their results reflect a meaningful advancement in both technology and procedural practice. But despite these gains, several issues remain **(Figure 1)**.

First, while commissural alignment rates were high, coronary misalignment (moderate or severe) was still present in approximately 20% of patients. No strategies to improve coronary alignment *per se* are currently implemented in routine practice. Given that coronary alignment, rather than commissural alignment alone, is the most predictive factor for CC feasibility and efficiency, this remains a key unmet need.

Second, the focus of this and similar studies has been on CC after an index TAVI procedure, but redo-TAVI (transcatheter aortic valve [TAV]-in-TAV) will inevitably become more common as this younger TAVI population ages. In patients at risk for coronary obstruction during reintervention, coronary misalignment can preclude the use of leaflet modification techniques such as Bioprosthetic or native Aortic Scallop Intentional Laceration to prevent Iatrogenic Coronary Artery

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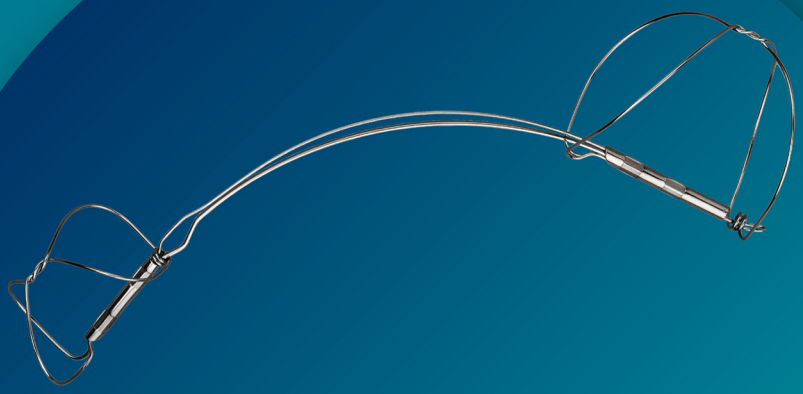

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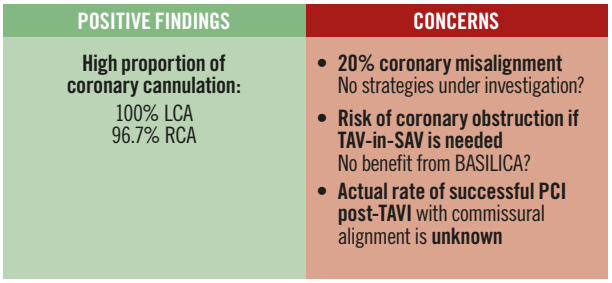

Figure 1. *Summary of the main findings and concerns regarding commissural and coronary alignment following TAVI with the Evolut transcatheter heart valve. BASILICA: Bioprosthetic or native Aortic Scallop Intentional Laceration to prevent Iatrogenic Coronary Artery obstruction; PCI: percutaneous coronary intervention; RCA: right coronary artery; SAV: surgical aortic valve; TAV: transcatheter aortic valve; TAVI: transcatheter aortic valve implantation*

obstruction (BASILICA)[6,7]. New dedicated leaflet laceration devices may help in patients with eccentric coronary ostia, but they are not yet commercially available.

Third, while successful CC is essential, it does not guarantee that PCI itself can be safely and effectively performed. Procedural support and equipment manipulation may be hampered even after successful ostial engagement. In a prior analysis by Won-Keun et al, nearly half of acute coronary syndromes post-TAVI remained untreated despite a high rate of CC[8]. Data on PCI success rates in patients with commissural alignment strategies are still lacking, but they will surely become a topic of intense investigation.

In sum, this study demonstrates that the combination of new-generation THV design and contemporary procedural practice has led to impressive CC success rates: 100% for the LCA and 96.7% for the RCA. This was achieved even before the introduction of the Evolut FX+ platform (Medtronic), which promises further facilitation of coronary access by incorporating enlarged frame cells. Yet, moderate-to-severe coronary misalignment remains frequent, highlighting a critical limitation of our current approach.

As TAVI expands further into younger populations, ensuring lifetime coronary access becomes an essential procedural goal. The field now requires a next step: dedicated procedural strategies or device designs specifically aimed at optimising coronary alignment, not just commissural alignment. Moreover, research should extend beyond CC feasibility to examine PCI success rates and procedural safety in these patients, including in the context of future TAV-in-TAV procedures.

While the achievements documented by Ohno et al represent substantial progress, they also expose the need for additional innovation. Our pursuit of perfection in TAVI alignment is not yet complete.

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Conflict of interest statement

I. J. Amat-Santos is a proctor for Boston Scientific, Medtronic, Meril Life Sciences, and Microport. F. Pensotti has no conflicts of interest to declare.

References

1. Vahanian A, Beyersdorf F, Praz F, Milojevic M, Baldus S, Bauersachs J, Capodanno D, Conradi L, De Bonis M, De Paulis R, Delgado V, Freemantle N, Haugaa KH, Jeppsson A, Jüni P, Pierard L, Prendergast BD, Sádaba JR, Tribouilloy C, Wojakowski W. 2021 ESC/EACTS Guidelines for the management of valvular heart disease. *EuroIntervention.* 2022;17:e1126-96.

2. Barbanti M, Costa G, Picci A, Criscione E, Reddavid C, Valvo R, Todaro D, Deste W, Condorelli A, Scalia M, Licciardello A, Politi G, De Luca G, Strazzieri O, Motta S, Garretto V, Veroux P, Giaquinta A, Giuffrida A, Sgroi C, Leon MB, Webb JG, Tamburino C. Coronary Cannulation After Transcatheter Aortic Valve Replacement: The RE-ACCESS Study. *JACC Cardiovasc Interv.* 2020;13:2542-55.

3. Ohno Y, Kamioka N, Miyamoto J, Omura R, Horinouchi H, Hashimoto K, Noda S, Murakami T, Ikari Y, Okada K, Frazzetto M, Raheja H, Lodi H, Rushing G, Ukaigwe A, Filby S, Yoon S, Feroze R, Dallan LAP, Attizzani GF; the CANNULATE TAVR EXPANDED investigators. Assessment of coronary cannulation after TAVI with the Evolut FX valve: the CANNULATE TAVR EXPANDED Study. *EuroIntervention.* 2025;21:1364-75.

4. Tang GHL, Amat-Santos IJ, De Backer O, Avvedimento M, Redondo A, Barbanti M, Costa G, Tchétché D, Eltchaninoff H, Kim WK, Zaid S, Tarantini G, Søndergaard L. Rationale, Definitions, Techniques, and Outcomes of Commissural Alignment in TAVR: From the ALIGN-TAVR Consortium. *JACC Cardiovasc Interv.* 2022;15:1497-518.

5. Tarantini G, Nai Fovino L, Belloni F, Barbierato M, Gallo F, Vercellino M, Trani C, Burzotta F, Asmarats Serra L, Petronio AS, Bedogni F, Berti S, Bertolini A, Fabris T, Tito A, Musto C, Giordano A, Corcione N, Maisano F, Medda M, Loi B, Cernetti C, Favero L, Di Lorenzo E, Gregori D, Lorenzoni G, Orzalkiewicz M, Esposito G, Saia F, Cardaioli F, Marchese A; CAvEAT Investigators and the Italian Society of Interventional Cardiology. The Coronary Access After TAVI (CAvEAT) Study: A Prospective Registry of CA After TAVR. *JACC Cardiovasc Interv.* 2025;18:1571-83.

6. Khan JM, Babaliaros VC, Greenbaum AB, Spies C, Daniels D, Depta JP, Oldemeyer JB, Whisenant B, McCabe JM, Muhammad KI, George I, Mahoney P, Lanz J, Laham RJ, Shah PB, Chhatriwalla A, Yazdani S, Hanzel G, Pershad A, Leonardi RA, Khalil R, Tang GHL, Herrmann HC, Agarwal S, Fail PS, Zhang M, Pop A, Lisko J, Perdoncin E, Koch RL, Ben-Dor I, Satler LF, Zhang C, Cohen JE, Lederman RJ, Waksman R, Rogers T. Preventing Coronary Obstruction During Transcatheter Aortic Valve Replacement: Results From the Multicenter International BASILICA Registry. *JACC Cardiovasc Interv.* 2021;14:941-8.

7. Redondo A, Baladrón Zorita C, Tchétché D, Santos-Martinez S, Delgado-Arana JR, Barrero A, Gutiérrez H, Serrador Frutos A, Ybarra Falcón C, Gómez MG, Carrasco Moraleja M, Sevilla T, Sanchez Lite I, Sanz E, San Román JA, Amat-Santos IJ. Commissural Versus Coronary Optimized Alignment During Transcatheter Aortic Valve Replacement. *JACC Cardiovasc Interv.* 2022;15:135-46.

8. Kim WK, Pellegrini C, Ludwig S, Möllmann H, Leuschner F, Makkar R, Leick J, Amat-Santos IJ, Dörr O, Breitbart P, Jimenez Diaz VA, Dabrowski M, Rudolph T, Avanzas P, Kaur J, Toggweiler S, Kerber S, Ranosch P, Regazzoli D, Frank D, Landes U, Webb J, Barbanti M, Purita P, Pilgrim T, Liska B, Tabata N, Rheude T, Seiffert M, Eckel C, Allali A, Valvo R, Yoon SH, Werner N, Nef H, Choi YH, Hamm CW, Sinning JM. Feasibility of Coronary Access in Patients With Acute Coronary Syndrome and Previous TAVR. *JACC Cardiovasc Interv.* 2021;14:1578-90.

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VIEWPOINT

Discontinuation of the ACURATE transcatheter heart valve platform: loss or reckoning?

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The self-expanding ACURATE transcatheter heart valve (Boston Scientific) received European Conformity (CE) mark approval in 2011 and has since progressed to its third-generation iteration, from "*neo*" to "*neo*2" to "Prime" **(Figure 1)**. Despite its successful use for over a decade, on 28 May 2025, Boston Scientific announced the discontinuation of the ACURATE platform. This decision is considered a consequential response to disappointing results in the randomised IDE trial with ACURATE *neo*2 (ClinicalTrials.gov: NCT03735667), which was preceded several years ago by negative outcomes in the SCOPE I (NCT03011346) and SCOPE II (NCT03192813) trials with the first-generation ACURATE *neo* valve **(Figure 1)**. Hence, critical voices may perceive this withdrawal as scientific reckoning, but this warrants a nuanced interpretation. The SCOPE trials lacked computed tomography core laboratory adjudication and centralised screening and included sites with limited experience using this platform. The outcomes in the IDE trial were largely driven by underexpansion – a procedural issue that was found to be preventable and correctable when adhering to the manufacturer's procedural recommendations, rather than being a device-inherent flaw[1]. Even though only hypothesis-generating, these insights have since contributed to the field's perception of valve underexpansion that can occur with all transcatheter aortic valve implantation (TAVI) platforms and will help to reinforce procedural best practices. It is worth mentioning that in the IDE trial, only a mean of 3 ACURATE implantations were performed per centre and year, with approximately 75% of operators performing fewer than five cases over the study period of four years. The main issue in the IDE trial, however, may have been that the balloon sizes for pre- and post-dilatation frequently were smaller than recommended by the screening committee.

In contrast to trial data, several large-scale European observational registries demonstrated non-inferior outcomes in experienced hands, suggesting that ACURATE's clinical potential may have been underestimated in the trials[2,3] – even though the inherently lower evidence level of observational studies should be taken into consideration. The platform offered several particularly advantageous features: intuitive deployment, haemodynamic stability during the deployment, reliable commissural alignment, preserved coronary access, minimal coronary obstruction risk, and low pacemaker rates. Furthermore, outcomes in the treatment of patients with pure aortic regurgitation, failed surgical valves, and redo-TAVI were promising[4]. These characteristics have become increasingly relevant in complex anatomical settings and for lifetime management considerations. As a matter of fact, the initial enthusiasm among competitors regarding increased market share may be tempered by the realisation that ACURATE had often been used in challenging anatomies – such as small annuli, horizontal aortas, short coronary heights, and tortuous vasculature – which may be more demanding when using alternative platforms.

Unfortunately, the controversy surrounding the ACURATE platform will now remain unresolved. A definitive resolution would have required a robust trial design that ensured appropriate device use – incorporating core laboratory adjudication, proper sizing recommendations by an experienced screening committee, careful patient selection, and strict adherence to recommended procedural steps. This has been largely applied in the randomised DOUBLE-CHOICE

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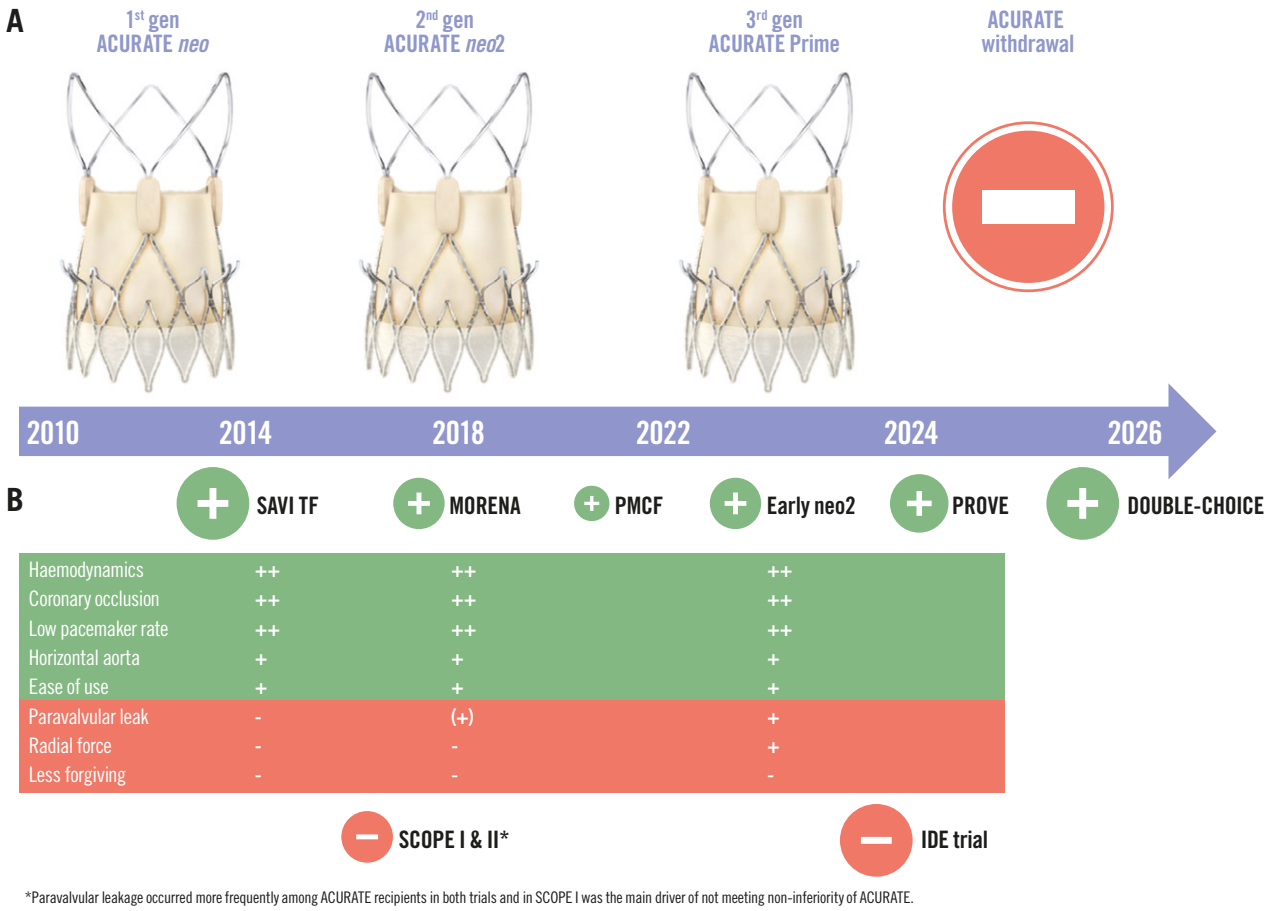

Figure 1. *Overview of the ACURATE platform. Timeline and iterations of the ACURATE transcatheter heart valve platform are shown in (A). The neo2 featured an extended sealing skirt, whereas the Prime was characterised by enhanced radial force and streamlined deployment. B) Available evidence, in circles sized according to the study size, with favourable studies in green and unfavourable studies in red. The table summarises strengths (highlighted in green) and weaknesses (highlighted in red) of the different iterations. -: unfavourable; (+): acceptable; +: good; ++: excellent; DOUBLE-CHOICE: ClinicalTrials.gov: NCT05036018; Early neo2 Registry, NCT04810195; MORENA: Multicenter Comparison of Novel Self-Expanding versus Balloon-Expandable Transcatheter Heart Valves; PMCF: Post Market Clinical Follow up Study, NCT04655248; PROVE: NCT05539573; SAVI TF: NCT02306226; SCOPE I: NCT03011346; SCOPE II: NCT03192813*

trial (Clinical Trials. gov: NCT05036018) where the primary combined endpoint at 30 days occurred in 15.4% among ACURATE *neo*2 recipients versus 30.4% among patients receiving Evolut valves (95% confidence interval: 9.1 to 20.7; p<0.001), albeit this difference was mainly driven by pacemaker implantations, and the more relevant 1-year outcomes are pending[5]. Admittedly, these very prerequisites – including the lack of long-term data – reflect the inherent limitation of the ACURATE platform, which may have been less forgiving than other valve types. Whether this represents an intrinsic device-specific issue or is merely related to the early-phase learning curve – similar to what we experienced with other platforms in the initial era of TAVI – remains an open question.

The imposed requirements by the notified body for an extension of the CE mark may have constituted the final death blow for ACURATE. According to Boston Scientific, a clinical follow-up of all European ACURATE recipients was demanded that was hardly viable and disproportionate, particularly in light of the risk-based principles outlined in the EU Medical Device Regulation. Have recent European data, including the 3-year results of SCOPE I – which showed similar outcomes, with event curves crossing at 3 years despite ACURATE failing to meet non-inferiority at 30 days – been ignored by the regulatory authorities[6]? Notably, the withdrawal of the ACURATE platform was driven by unfavourable outcomes associated with the earlier generation used in the IDE trial, the ACURATE *neo*2, without clear evidence that these limitations extend to the latest Prime iteration, which features enhanced radial force with a rapid and stable deployment and actually has demonstrated favourable results in a multicentre registry (Ruck, A. Early ACURATE prime: multicenter study to evaluate safety and effectiveness. EuroPCR 2025. 20-23 May 2025. Paris, France). While we can understand the decision of Boston Scientific leadership to discontinue ACURATE from a strategic perspective, we as implanting physicians are convinced that this platform would

have deserved a further chance – with a bit more perseverance, involvement of expert operators, and evaluation of more recent data that are expected soon in the decision process.

Most patients will remain well served by alternative devices. For some interventionalists, the discontinuation of ACURATE represents a meaningful loss, potentially limiting the ability to tailor valve selection in certain anatomical scenarios within contemporary TAVI practice.

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References

1. Makkar RR, Chakravarty T, Gupta A, Soliman O, Gnall E, Ramana RK, Ramlawi B, Diamantouros P, Potluri S, Kleiman NS, Samy S, Rassi A, Yadav P, Thourani V, Yakubov S, Frawley C, Patel D, Kapadia S, Chalekian A, Modolo R, Sathananthan J, Kim WK, Reardon MJ. Valve Underexpansion and Clinical Outcomes With ACURATE neo2: Findings From the ACURATE IDE Trial. *J Am Coll Cardiol.* 2025;86:225-38.

2. Kim WK, Pellegrini C, Eckel C, Renker M, Grothusen C, Choi YH, Charitos EI, Duesmann C, Blumenstein J, Rheude T, Sossalla S, Joner M, Möllmann H. 1-Year Outcomes of Transcatheter Aortic Valve Replacement Using a Self-Expanding vs Balloon-Expandable Transcatheter Aortic Valve. *JACC Cardiovasc Interv.* 2025;18:32-40.

3. Möllmann H, Noack T, Hilker M, Conradi L, Toggweiler S, Hofmann B, Joner M, Modolo R, Allocco DJ, Kim WK. Five-year outcomes of transcatheter aortic valve implantation with the ACURATE neo2 valve system. *EuroIntervention.* 2024;20:e951-3.

4. Kim WK, Seiffert M, Rück A, Leistner DM, Dreger H, Wienemann H, Adam M, Möllmann H, Blumenstein J, Eckel C, Buono A, Maffeo D, Messina A, Holzamer A, Sossalla S, Costa G, Barbanti M, Motta S, Tamburino C, von der Heide I, Glasmacher J, Sherif M, Seppelt P, Fichtlscherer S, Walther T, Castriota F, Nerla R, Frerker C, Schmidt T, Wolf A, Adamaszek MM, Giannini F, Vanhaverbeke M, Van de Walle S, Stammen F, Toggweiler S, Brunner S, Mangieri A, Gitto M, Kaleschke G, Ninios V, Ninios I, Hübner J, Xhepa E, Renker M, Charitos EI, Joner M, Rheude T. Comparison of two self-expanding transcatheter heart valves for degenerated surgical bioprostheses: the AVENGER multicentre registry. *EuroIntervention.* 2024;20:e363-75.

5. Feistritzer HJ, Ender J, Lauten P, Rudolph TK, Rudolph V, Geisler T, Massberg S, Adam M, Baldus S, Sossalla S, Joner M, Möllmann H, Wolf A, Kim WK, Borger MA, Noack T, Magunia H, von Dossow V, Sander M, Vigelius-Rauch U, Feuerecker M, Zakhary W, Boening A, Bleiziffer S, Hohenstein S, Hoesler N, Buske M, Desch S, Abdel-Wahab M, Thiele H; DOUBLE-CHOICE Investigators. Peri-interventional Anesthesia Strategies for Transcatheter Aortic Valve Implantation: A Multicenter, Randomized, Controlled, Non-inferiority Trial. *Circulation.* 2025 Aug 29. [Epub ahead of print].

6. Lanz J, Möllmann H, Kim WK, Burgdorf C, Linke A, Redwood S, Hilker M, Joner M, Thiele H, Conzelmann L, Conradi L, Kerber S, Thilo C, Toggweiler S, Prendergast B, Husser O, Stortecky S, Deckarm S, Künzi A, Heg D, Walther T, Windecker S, Pilgrim T; SCOPE I Investigators. Final 3-Year Outcomes of a Randomized Trial Comparing a Self-Expanding to a Balloon-Expandable Transcatheter Aortic Valve. *Circ Cardiovasc Interv.* 2023;16:e012873.

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State-of-the-Art
by EuroIntervention

Transcatheter treatment of bicuspid aortic valve stenosis

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ABSTRACT

Transcatheter aortic valve implantation (TAVI) has become an established treatment option for symptomatic patients suffering from aortic stenosis. A bicuspid aortic valve (BAV) is the most frequent congenital valvular abnormality. With the expansion of the indications for TAVI to patients at lower risk, including younger populations, a BAV is expected to be more frequently encountered. Several challenges are associated with BAVs, from diagnosis and classification to interventional or surgical treatment. Transcatheter prostheses, designed to treat tricuspid aortic valves, have shown promising results in BAV anatomies. However, technical limitations, such as underexpansion, ellipticity or procedural complications, have been identified. Several issues for transcatheter procedures are still a matter of discussion. In this state-of-the-art review, we explore the knowledge acquired about TAVI for BAVs, the sizing and technical specificities of interventional procedures, as well as the remaining evidence gaps and future perspectives.

A bicuspid aortic valve (BAV) is the most common congenital structural heart abnormality, affecting 0.5% to 2% of the general population and found in 5% to 20% of transcatheter aortic valve implantation (TAVI) populations in the Western world[1]. The epidemiology of BAV may be different in Asia, as approximately 50% of patients presenting for TAVI in China are reported to have a BAV morphology[2]. However, this may simply reflect the younger age of these populations, as the prevalence of a BAV is much higher in younger aortic stenosis (AS) patients compared to older patients. BAV anatomy predisposes to early valve degeneration, which may lead to severe AS and/or aortic regurgitation (AR) and a need for surgical aortic valve replacement (SAVR) at a young age[3]. Surgery has long been the gold-standard treatment for severe symptomatic bicuspid AS and remains the first-choice treatment for most young BAV patients with low surgical risk. For older BAV patients and those at high surgical risk, TAVI has become an accepted and appropriate treatment option. Contemporary TAVI in selected bicuspid AS patients has been reported to have similar clinical outcomes compared to TAVI in tricuspid AS patients[4,5]. However, due to relevant anatomical differences, BAVs may be associated with an increased risk of suboptimal procedural outcomes and complications in case of TAVI **(Central illustration)**, underscoring the need for careful patient selection and the use of patient-tailored TAVI strategies to achieve optimal outcomes[6]. This review article aims to give a state-of-the-art overview of our knowledge on TAVI in bicuspid AS and to discuss future directions.

Classification

Classification of BAV disease is essential for understanding its clinical presentation and guiding therapeutic strategies, particularly in the context of TAVI. Over the years, several classification systems have been proposed to categorise BAV anatomy based on cusp morphology, the presence of a raphe, and commissural orientation **(Figure 1)**.

The Sievers classification, based on the number of raphes, remains the most broadly adopted in daily clinical practice, although it does not cover the full complexity of BAV anatomy[7]. It divides BAVs into three phenotypes: type 0, when there is no raphe; type 1, when there is a raphe connecting two cusps; and type 2, when two raphes are identified. Sievers type 1 BAV, with a raphe between the right and left coronary cusps, is the most common phenotype in Western TAVI populations. Type 0 BAV seems to be more frequently encountered in Asian TAVI populations, while type 2 BAV is a rare phenotype worldwide and could more accurately be termed a unicuspid instead of a bicuspid aortic valve[1,7].

With the advent of multislice computed tomography (MSCT) imaging for TAVI procedural planning, Jilaihawi

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et al proposed another classification based on computed tomography (CT)-derived anatomical insights, categorising BAVs into bi- and tricommissural types[8]. Although it addresses some of the limitations of the Sievers classification and better evaluates supra-annular structures for TAVI planning, its adoption in daily clinical practice remains infrequent.

The International Consensus Statement, introduced in 2021, offers a more comprehensive and clinically relevant definition of a BAV, complementing the Sievers and Jilaihawi classifications[9]. It classifies BAV anatomy into three major phenotypes: two-sinus, fused, and partial-fusion types. The system further incorporates cusp symmetry, commissural angles, and the presence and characteristics of a raphe. For example, the fused BAV type, which is the most common, involves the fusion of two cusps – most frequently the right and left coronary cusps – with a raphe that may or may not be calcified. The International Consensus Statement enables a precise BAV classification, facilitating procedural TAVI planning. This classification also identifies a partial-fusion BAV and excludes unicuspid variants, unlike the Sievers classification. However, the concept of a fused BAV may be somewhat misleading because "developmentally" this phenotype is the result of incomplete cusp separation and must be distinguished from a fused commissure in tricuspid aortic valves.

Surgical treatment of BAV disease

SAVR remains the gold-standard treatment for patients with severe symptomatic BAV disease, in particular for patients less than 75 years of age and with no prohibitive surgical risk. Surgical intervention is also indicated for asymptomatic patients who have severe AS (aortic valve area <0.8 cm^2) or significant AR, especially if (1) there is evidence of left ventricular impairment (left ventricular ejection fraction <50% or significant ventricular dilation) or (2) the patient exhibits a rapid progression of their valve disease during follow-up. Both mechanical and bioprosthetic valves are options, depending on the patient's age, preferences, and anticoagulation considerations.

Combined procedures are decided based on the association with any aortopathy, concomitant mitral disease, coronary artery disease, or rhythm disturbance[10]. Individuals with a BAV are at a higher risk for aortopathy, including conditions such as aortic dilation and aneurysm. This risk is particularly pronounced in patients with associated connective tissue disorders, such as Marfan syndrome or Loeys-Dietz syndrome, in which structural abnormalities of the aortic wall exist[11]. The reported prevalence of aortic dilatation in BAV patients is approximately 50%, and the proposed mechanisms for aortic dilation are haemodynamic and/or genetic[12].

Both the European and US guidelines consider that concomitant aortic surgery is a reasonable approach (Class IIa) in BAV patients undergoing surgery for severe AS or AR with a dilated aortic root or ascending aorta of ≥45 mm, as this may prevent future complications such as aortic dissection or rupture. The latest ESC/EACTS guidelines broaden the indication for TAVI to include BAV patients who are at high surgical risk and have favourable anatomy, after thorough assessment at a Heart Valve Centre[13,14].

Recent data on TAVI in BAV disease

REGISTRY DATA

Technological advancements in devices, combined with a more comprehensive understanding of BAV anatomy, have enabled the application of transcatheter therapies to treat patients with BAV disease. Excluded from major randomised controlled trials (RCTs), patients with BAV stenosis have been predominantly studied in retrospective registries and only a few prospective studies. **Table 1** summarises the findings of the most important studies.

One of the first and largest multicentre retrospective studies was published in 2014[15]. Mylotte et al analysed the early and medium-term safety and efficacy outcomes of TAVI in a cohort of 139 patients with a BAV, using either self-expanding valves (SEVs) or balloon-expandable valves (BEVs). Most patients (63%) presented with a bicuspid Sievers type 1 morphology. At 30 days, the mortality rate was 5%, and the device success rate reached 90%, with no significant differences observed between the two prosthesis groups. At 1-year follow-up, Kaplan-Meier analysis indicated a mortality rate of 17.5%, with congestive heart failure as the primary cause of death. This initial registry demonstrated TAVI feasibility in BAV disease and highlighted the role of CT analysis as a potential factor for improving transcatheter aortic valve (TAV) prosthesis type and size selection and, consequently, patient outcomes.

Another multicentre registry exclusively utilising the balloon-expandable SAPIEN 3 TAV (Edwards Lifesciences) in a population of bicuspid AS patients demonstrated favourable valve performance and a minimal rate of paravalvular regurgitation (PVR) at 30-day follow-up[16]. The study enrolled a total of 51 patients (82% Sievers type 1). At the 30-day follow-up, no cases of moderate or severe PVR were reported, with two deaths (3.9%) and an overall device success rate of 98%. The authors underscored the low rate of PVR as one of the key findings of the study, attributing it to the technological

Abbreviations

AR	aortic regurgitation	**CT**	computed tomography	**RCT**	randomised controlled trial
AS	aortic stenosis	**ICD**	intercommissural distance	**SAVR**	surgical aortic valve replacement
AV	aortic valve	**LAO**	left anterior oblique	**SEV**	self-expanding valve
BAV	bicuspid aortic valve	**LIRA**	Level of Implantation at the RAphe	**STS**	Society of Thoracic Surgeons
BAVARD	Bicuspid Aortic Valve Anatomy and Relationship with Devices	**LVOT**	left ventricular outflow tract	**TAV**	transcatheter aortic valve
		MSCT	multislice computed tomography	**TAVI**	transcatheter aortic valve implantation
BEV	balloon-expandable valve	**PVR**	paravalvular regurgitation		

EuroIntervention — Central **Illustration**

TAVI to treat bicuspid aortic valve disease.

Bicuspid aortic valve disease:
- A frequent disease in the general population and in TAVI patients
- Prevalence: 5-15% in Western TAVI populations/up to 40% in Asian TAVI cohorts
- TAVI outcomes in this population are comparable with TAVI for tricuspid AV disease; however, there are **increased risks of procedural complications** and **worse clinical outcomes** in case of **excessively calcified leaflets** and/or a **calcified raphe**

Possible **anatomical differences** with tricuspid AV disease:
- Extra-large aortic annulus dimensions
- Severely calcified leaflets
- Presence of a (calcified) raphe
- Extra-large aortic root (sinuses of Valsalva, sinotubular junction)
- Coronary ostia: higher and more eccentric take-off
- Enlarged/dilated ascending aorta
- Coarctation of the aorta

TAVI in bicuspid aortic valve - associated with **increased risks** of:
- Paravalvular regurgitation
- Conduction disorders/permanent pacemaker
- Valve malpositioning
- Stroke risk
- Annulus rupture

- Valve stent frame underexpansion & non-circularity
- Limited valve durability

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Key features of TAVI in patients with bicuspid aortic valve disease, including anatomical differences with tricuspid aortic valve disease, and specific associated risks. AV: aortic valve; TAVI: transcatheter aortic valve implantation

features of the prosthesis, including the external sealing skirt on the inflow portion, as well as the improved valve delivery system, which enhanced accuracy during positioning. While the study demonstrated promising early results, these should be interpreted with caution given its retrospective design and the small sample size. A comparable outcome with the SAPIEN 3 valve was reported by Attinger-Toller et al in a multicentre study conducted some years later, with a median follow-up of 390 days[17].

Next, a retrospective propensity-matched analysis of 561 bicuspid and 4,546 tricuspid AS patients showed a higher frequency of conversion to surgery, a lower device success rate, and a higher incidence of moderate or greater PVR in the bicuspid cohort[18]. This study demonstrated that the outcomes were influenced by the generation of TAV being used: BAV patients treated with early-generation devices experienced more frequent aortic root injuries with BEVs and a higher incidence of moderate-to-severe PVR with SEVs.

Another multicentre registry explored the association and impact of BAV anatomical features on TAVI outcomes in 1,034 bicuspid AS patients[19]. The presence of a calcified raphe and excessive leaflet calcium was associated with worse clinical outcomes (higher 2-year all-cause mortality compared to patients with one or neither of these features [25.7% vs 9.5% vs 5.9%; p<0.001]). The role of BAV anatomical features was further highlighted in the AD HOC registry[20]. This study included 946 patients with bicuspid

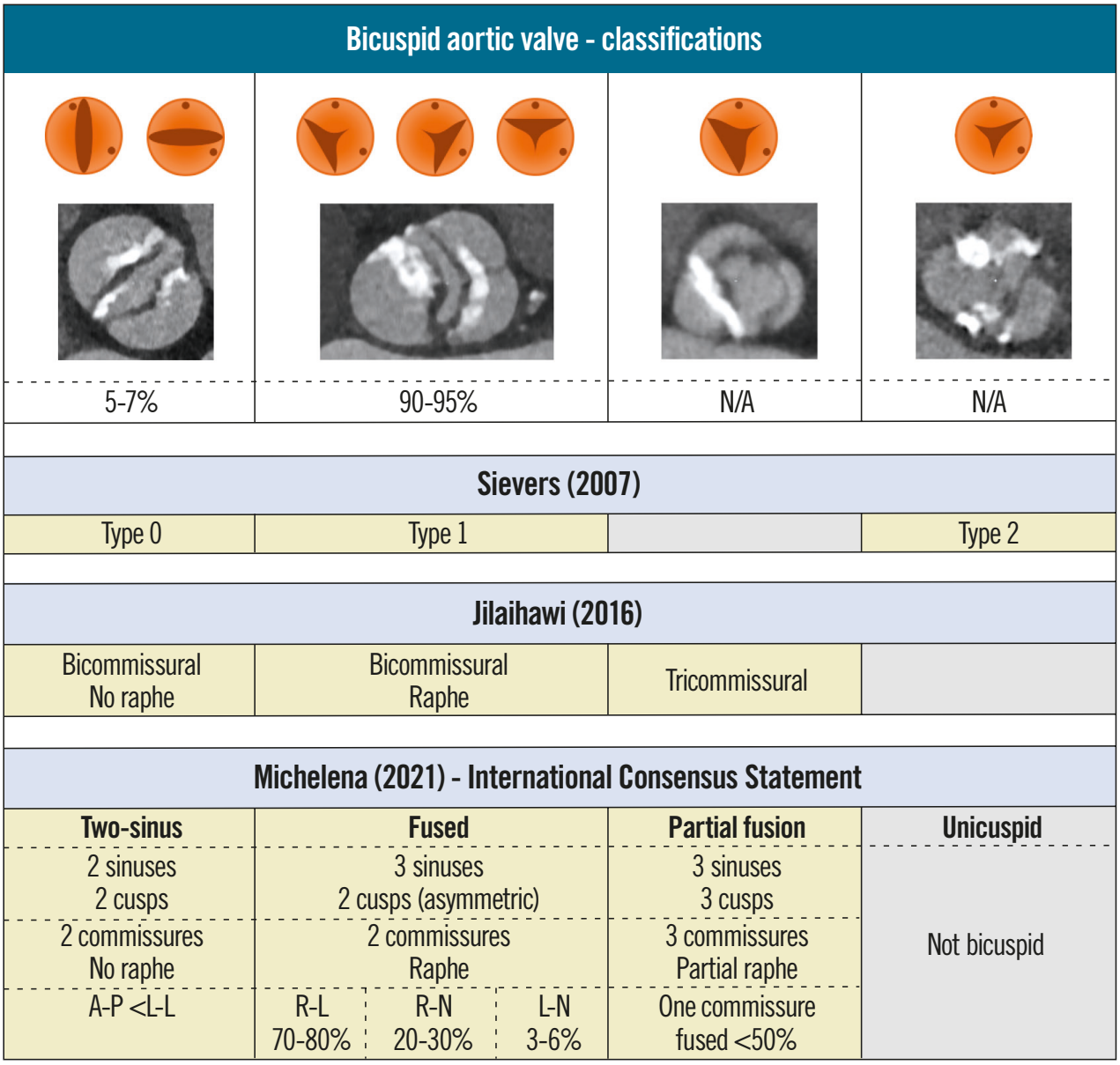


Figure 1. *Bicuspid aortic valve classifications. Different classification systems to categorise bicuspid aortic valve anatomy based on cusp morphology, the number of commissures, and the presence of a raphe. A-P: anterior-posterior; L-L: latero-lateral; L-N: left-non-cusp; N/A: not available; R-L: right-left cusp; R-N: right-non-cusp*

AS Sievers type 1. Independent predictors of PVR included a large virtual raphe ring perimeter, severe annular or left ventricular outflow tract (LVOT) calcification, use of a SEV, and intentional supra-annular TAV positioning. Although this study offered valuable insights, some important limitations should also be recognised, such as its retrospective study design, the inclusion of a variety of TAV devices, and the lack of a standardised sizing method.

IMPACT OF SIZING TECHNIQUE

The Bicuspid Aortic Stenosis With Evolut Platform International Experience (BIVOLUTX) study was a multicentre registry that aimed to assess the performance of the self-expanding, supra-annular Evolut PRO/XL valve (Medtronic) in 149 bicuspid AS patients (mean Society of Thoracic Surgeons Predicted Risk of Mortality [STS-PROM] score 2.6%) undergoing TAVI[21]. The CT analysis included various sizing methods, all of which were reviewed by a dedicated core lab. At 30 days, the cardiac death rate was 2.6%, with the valve demonstrating optimal haemodynamic performance. Moderate PVR was reported in 3 patients (2.8%), with no cases of severe regurgitation. At 1-year follow-up, valve haemodynamics remained consistent. Only 1 patient experienced moderate-to-severe PVR, and 3 patients had severe patient-prosthesis mismatch. Different CT-based sizing methods did not impact device or clinical outcomes. The BIVOLUTX study has limitations: 86.5% of all patients had a BAV of Sievers type 1. Consequently, the study findings should not be generalised to other BAV phenotypes,

Table 1. Main registries and trials exploring TAVI for bicuspid aortic valves.

Year, first author	Study design, sample size	Primary endpoint	Main conclusion(s)
2014, Mylotte D[15]	Registry N=139	Procedural and clinical (VARC)	TAVI in bicuspid AS is achievable with promising short- and medium-term clinical outcomes
2016, Perlman G[16]	Registry N=51	Procedural and clinical (VARC-2)	Promising early results with a device success rate of 98%
2017, Yoon SH[18]	Registry (PS-matched analysis) N=561	Procedural and clinical (VARC-2)	In comparison to TAVI in tricuspid AS: similar clinical outcomes, but a lower device success rate in the bicuspid cohort
2019, Waksman R[23]	Registry N=61	All-cause mortality at 30 days	No mortality at 30 days
2019, Attinger-Toller A[17]	Registry N=79	Procedural and clinical (VARC-2)	Favourable outcomes at 1 year and beyond, with a device success rate of 98%
2020, Yoon SH[19]	Registry N=1,034	All-cause mortality at 1 and 2 years	High-risk morphological features in BA influence outcome
2021, Makkar RR[24]	Registry (PS-matched analyses) N=37,660 (3,243 bicuspid and 34,417 tricuspid)	30-day and 1-year mortality and stroke	No significant difference between the groups
2021, Forrest JK[26]	Evolut Low Risk bicuspid study registry N=150	Incidence of all-cause mortality or disabling stroke at 30 days	Favourable 30-day outcome
2022, PARTNER 3 bicuspid registry, Williams MR[25]	Registry (PS-matched analyses) N=169 BA* vs 496 TA	1-year composite rate of death, stroke, and cardiovascular rehospitalisation	No significant difference between the groups
2022, Majmundar M[28]	Registry (PS-matched analyses) N=17,068 patients with a BAV (1,629 TAVI and 15,439 SAVR)	In-hospital mortality	TAVI is associated with reduced rates of in-hospital mortality
2023, BIVOLUTX, Tchétché D[21]	Registry N=149	Valve performance at 30 days	Favourable valve performance at 30 days
2024, Evolut Low Risk Bicuspid Study, 3-year follow-up, Zahr F[27]	Registry N=data available for 128 patients	Rates of all-cause mortality or disabling stroke	Low rates of all-cause mortality or disabling stroke
2024, AD HOC, Zito A[20]	Registry N=946	PVR incidence, MAE	Moderate or severe PVR occurred in about 4%; PVR ≥moderate was linked to an increased risk of MAE
2024, NOTION-2, Jørgensen TH[5]	Randomised trial (TAVI vs SAVR) N=370 randomised, 100 patients with a BA	Composite of all-cause mortality, stroke, or rehospitalisation at 12 months	In the BA cohort, the rate of the composite endpoint was significantly higher in patients undergoing TAVI

*Highly selected bicuspid anatomy; patients were excluded if presenting one of the following: left ventricular outflow tract or raphe calcification, aortic annulus diameter <16 mm or >28 mm, and ascending aorta diameter >40 mm. AS: aortic stenosis; BA: bicuspid anatomy; BAV: bicuspid aortic valve; BE: balloon-expandable; MAE: major adverse events (all-cause death, stroke, or hospitalisation for heart failure); PS: propensity score; PVR: paravalvular regurgitation; SAVR: surgical aortic valve replacement; SE: self-expanding; TA: tricuspid anatomy; TAVI: transcatheter aortic valve implantation; VARC: Valve Academic Research Consortium

and the limited sample size (for other BAV phenotypes) did not allow for comparisons between BAV phenotypes.

LOW-RISK PATIENTS

TAVI for low-risk patients was approved by the U.S. Food and Drug Administration (FDA) in 2019[22]. The Low Risk TAVR (LRT) study was the first to evaluate low-risk patients with bicuspid AS undergoing TAVI with either BEVs or SEVs[23]. At 30 days, there were no reported cases of mortality or ischaemic stroke. One patient experienced moderate PVR. Excellent clinical short-term results were reported in this low-risk population.

Another large propensity-matched study, including 3,168 pairs of low surgical risk bicuspid and tricuspid AS patients (mean age: 69 years) treated with the balloon-expandable SAPIEN 3 valve showed no significant difference in the primary endpoint of death and stroke at 30 days and 1 year[24]. Similar findings were observed in the PARTNER 3 bicuspid registry[25]. This study included 169 low surgical risk bicuspid AS patients (primarily Sievers type 1) with a mean age of 71.0 years.

A propensity score-matched analysis was also conducted comparing tricuspid AS patients treated in the Evolut Low Risk trial and bicuspid AS patients from the Evolut Low Risk bicuspid registry. No significant differences were observed between groups[26]. The 3-year follow-up data were recently published[27]. At 3-year follow-up, similar outcomes were observed in both groups regarding all-cause mortality or disabling stroke. This study represents the longest follow-up to date for low surgical risk bicuspid AS patients, offering

insights into the valve durability of this particular TAV prosthesis in this population.

TAVI VERSUS SAVR

Adjunctive data on outcomes for TAVI and SAVR in bicuspid AS were derived from a propensity score analysis of a cohort of 17,068 patients from the Nationwide Readmission Database (NRD), which generated 1,393 matched pairs[28]. The results showed that TAVI was associated with lower in-hospital mortality, with similar rates of major adverse cardiovascular events at 1 and 6 months. The favourable outcomes observed after TAVI in bicuspid AS should be interpreted with caution. This is because critical information was missing, such as valve anatomy and TAV prosthesis selection.

The Nordic Aortic Valve Intervention Trial 2 (NOTION-2) randomised 370 patients with severe AS and a mean age of 71.1 years at low surgical risk (median STS-PROM score 1.1%) to either TAVI or SAVR[5]. Among this cohort, 100 patients had a BAV, primarily Sievers type 1. At 1 year, the incidence of the primary endpoint – a composite of all-cause mortality, stroke, or rehospitalisation – was higher in bicuspid AS patients who underwent TAVI: 14.3% compared to 3.9% for SAVR (hazard ratio 3.8, 95% confidence interval: 0.8-18.5). The study included different BAV anatomical morphologies, complexities, and prostheses. This underscores the need for a properly sized randomised trial comparing TAVI and SAVR in bicuspid AS patients.

Sizing methods for TAVI in BAVs

Similar to TAVI in tricuspid AS, the gold standard for procedural planning of TAVI in BAVs consists of an in-depth analysis of MSCT images of the aortic valve (AV) complex and aortic root at different levels both above and below the virtual aortic annulus **(Figure 2)**.

The CT "scroll technique" offers a comprehensive overview of the anatomy during the mid-systolic phase of the cardiac cycle. This technique involves scrolling through the MSCT images from the level of the LVOT up to the ascending aorta to assess key anatomical features, such as BAV cusp morphology, calcium extent and distribution, raphe appearance and location, and coronary ostia location. In BAVs, these features can present very different challenges, each of which may impact TAV choice and procedural outcomes. Furthermore, it is important to evaluate the dimensions of the ascending aorta and aortic arch, as a BAV can be associated with dilatation of the ascending aorta and coarctation of the aorta **(Figure 2)**.

The choice of a correct TAV size is critical for safeguarding the procedural success of TAVI in BAVs while also minimising complications. The specific anatomical features of a BAV – including asymmetrical and excessive leaflet calcification and a (calcified) raphe – require tailored sizing methods in order to guarantee procedural success and reduce the risks of procedural complications. Several sizing methodologies have been proposed, each with its advantages and limitations **(Figure 3)**.

INTERCOMMISSURAL DISTANCE

The Bicuspid Aortic Valve Anatomy and Relationship with Devices (BAVARD) study was a multicentre registry study aimed at evaluating the anatomical characteristics of BAVs and their impact on TAVI outcomes[4]. When treating tricuspid AS with TAVI, the aortic annulus dimensions are considered for TAV size selection. However, the investigators realised that it is crucial to understand the configuration of the entire landing zone when treating bicuspid AS with TAVI. In an effort to achieve standardisation and according to the BAVARD sizing algorithm, measurement of the intercommissural distance (ICD) at 4 mm above the aortic annulus was introduced. Based on the comparison of the mean aortic annulus diameter and the ICD at 4 mm above the annulus, the BAV landing zone can be categorised as a tube, flared, or tapered. In case of a tube or flared configuration (85% of cases), standard TAV sizing based on the annular dimensions is recommended, whereas TAV "downsizing" is recommended in case of a tapered configuration of the landing zone (15% of cases) **(Figure 3A)**. This BAVARD sizing method has been validated in the BIVOLUTX study using the Evolut PRO/XL TAV and has been adopted in several high-volume centres in daily clinical practice thanks to its ease of use and reproducibility[21]. Of note, this sizing method is primarily validated for and applicable to TAVI with SEVs.

SUPRA-ANNULAR TRACING

Another approach to get a better insight and understanding of the BAV landing zone has been tracing the supra-annular orifice. In theory, these tracings can be performed at any level above the aortic annulus. However, sizing techniques for TAVI in BAVs relying on tracings of the supra-annular orifice have been described at specific, predefined levels above the virtual aortic annulus[4,20,29]. In parallel to the ICD measurement, the BAVARD investigators propose tracing the supra-annular orifice at 4 mm above the aortic annulus. The rationale behind this method is that the perimeter-derived mean diameter of the supra-annular tracing correlates strongly with the final mean TAV diameter and, as such, can assist in the final TAV size selection. On the other hand, the Level of Implantation at the RAphe (LIRA) sizing method relies on tracing the supra-annular orifice at the level of maximal raphe protrusion (approximately 10 mm above the annulus)[30,31]. However, the LIRA method is not widely adopted due to poor reproducibility and its applicability being limited to BAVs with a long, calcified raphe **(Figure 3B)**.

CIRCLE METHOD

The "circle method" involves drawing concentric circles at the annulus and every 3 mm above the annulus on MSCT images to assess which valve size would best fit the anatomy. Therefore, it is of utmost importance to assess whether a chosen TAV size covers the commissures (at 4 mm above the annulus) and fits well within the supra-annular orifice at the level of the calcified leaflets and/or (calcified) raphe **(Figure 3C)**. Hence, the circle method integrates the BAVARD and supra-annular tracing methods into one comprehensive approach. Clearly, this sizing method offers simplicity and ease of use, allowing a straightforward visual assessment of the "valve fit" into a given anatomy. On the other hand, its performance depends heavily on operator experience, and it has only been validated for TAVI with BEVs[32]. However, when using dedicated CT analysis software such as 3mensio (Pie

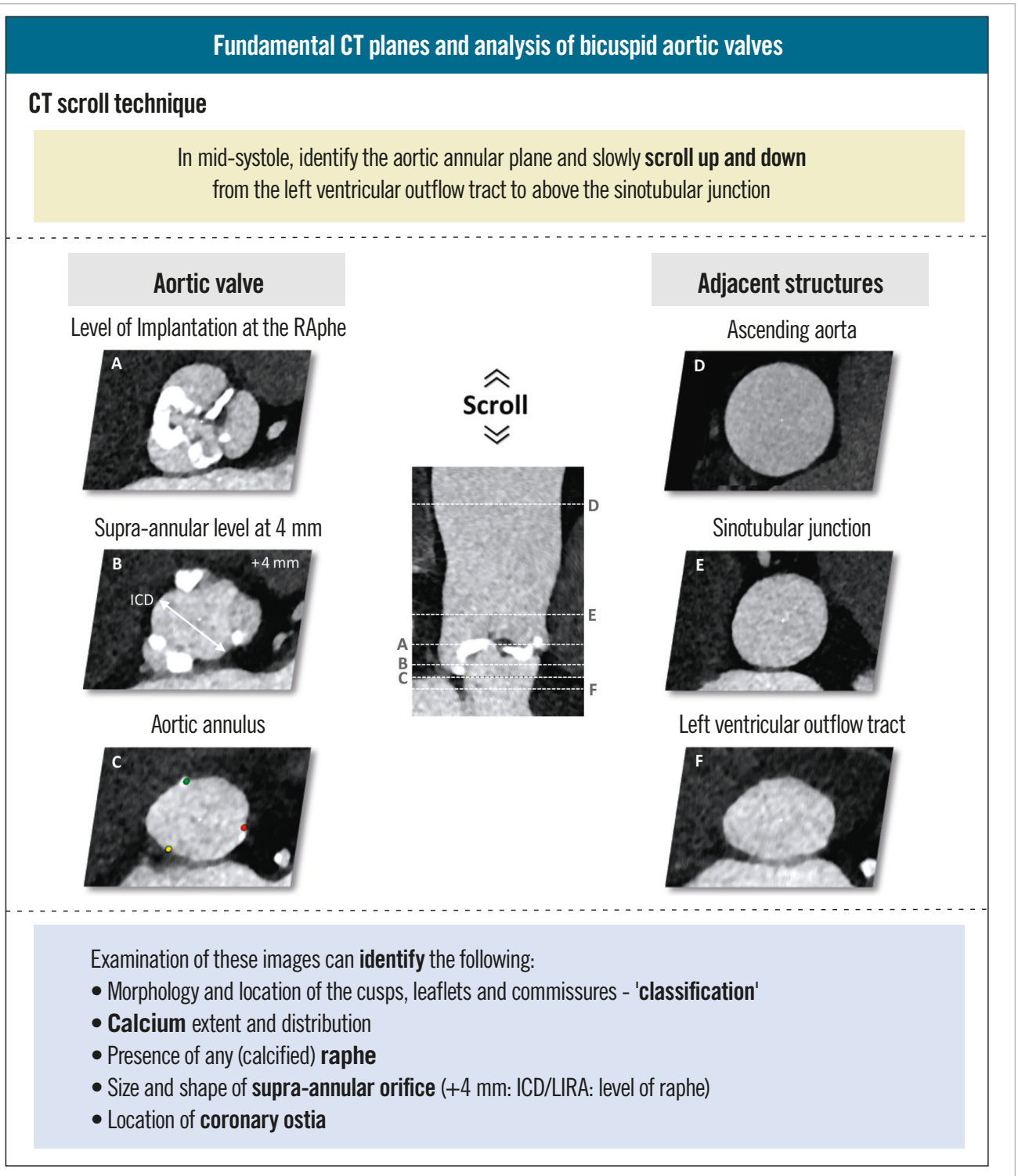


Figure 2. *Fundamentals of CT analysis of bicuspid aortic valves for TAVI treatment planning. The CT scroll technique ensures a comprehensive assessment of the aortic valve complex and aortic root. Precise measurements are made at different planes, including some specific planes to bicuspid aortic valve disease. CT: computed tomography; ICD: intercommissural distance; LIRA: Level of Implantation at the RAphe; TAVI: transcatheter aortic valve implantation*

Medical Imaging), a "virtual valve" with the exact dimensions of the chosen valve type and size can be superimposed onto the CT images and can offer this same visual assessment of "valve fit" into the anatomy for any TAV.

CASPER ALGORITHM

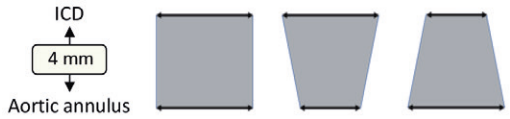
The Calcium Algorithm Sizing for bicusPid Evaluation with Raphe (CASPER) algorithm uses a formula starting with the aortic annular dimension and then subtracting 0.5-1 mm

TAV sizing for treatment of bicuspid aortic valves

A Intercommissural distance

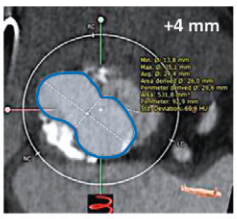
Based on the BAVARD sizing method

- Mostly used for **SEV sizing**
- Approx. 5% oversizing relative to the annulus Ø is sufficient
- It is key to understand the **landing zone configuration**

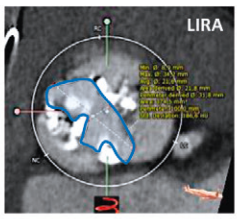


Sizing algorithm	Tube	Flared	Tapered
	Annular sizing 85%		ICD sizing 15%

B Supra-annular tracing



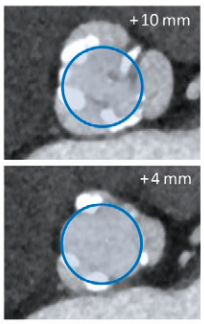
Supra-annular tracing at **4 mm** above the annulus

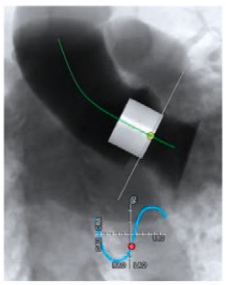


Supra-annular tracing at the **LIRA**

Anticipating the final TAV diameter
Perimeter-derived mean Ø of supra-annular orifice tracing at baseline CT correlates with the TAV mean Ø

C Circle method

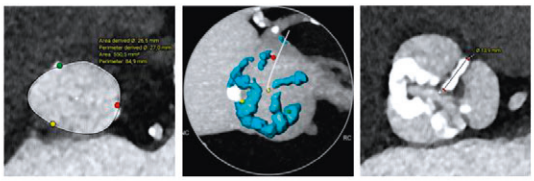




26 mm SAPIEN 3

- Mostly used for **BEV sizing**
- Can also be applied to SEV, taking into account the TAV design (tapering)

D CASPER algorithm



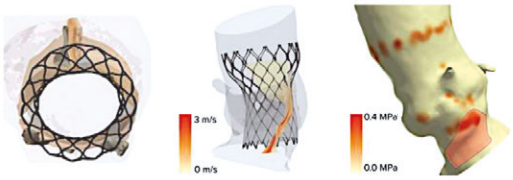
Annulus Ø 27.0 mm | *Calcium volume >300 mm³* | *Calcified raphe length 13.9 mm*

–1 mm | **–1.5 mm**

Perimeter/area-derived mean annulus Ø (in mm)

- –1 mm if leaflet calcium >300 mm³
- –1 mm if raphe length >50% of annulus Ø
- –0.5 mm if raphe is calcified

E Computational modelling

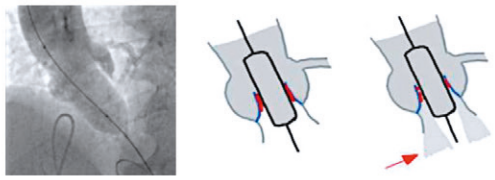


Regurgitant volume | *Contact pressure*

Patient-specific computational models predict:

- TAV stent frame deformation
- Risk of paravalvular regurgitation
- Risk of conduction disorder

F Balloon sizing



No leak | *Significant leak*

Aortic angiogram during predilatation:

- Visual assessment of leak/landing zone seal
- Balloon size that results in no leak
  - choice of TAV size based on sizing chart

Figure 3. *Different TAV sizing methodologies for the treatment of bicuspid aortic valves. A) Intercommissural distance, based on the BAVARD sizing method. B) Supra-annular tracing. C) Circle method. D) CASPER algorithm. E) Computational modelling. F) Balloon sizing. BAVARD: Bicuspid Aortic Valve Anatomy and Relationship with Devices; BEV: balloon-expandable valve; CASPER: Calcium Algorithm Sizing for bicusPid Evaluation with Raphe; CT: computed tomography; ICD: intercommissural distance; LIRA: Level of Implantation at the RAphe; SEV: self-expanding valve; TAV: transcatheter aortic valve*

based on factors such as calcium burden and raphe length to determine TAV size **(Figure 3D)**[33]. A strength of this sizing method is that it offers a standardised approach with high reproducibility. On the other hand, an important limitation of this method is that it has only been validated in small sample sizes using early-generation devices (including a mechanically expandable TAV, which is no longer available).

COMPUTATIONAL MODELLING

Computational modelling is a newer technology which relies on artificial intelligence-based simulations to predict TAV stent frame deformation, the risk of PVR, and potential conduction disorders for a specific TAV type and size in a patient-specific anatomy **(Figure 3E)**[34,35]. This highly individualised approach allows for meticulous procedural planning, including simulations with different TAV designs and sizes. While computational modelling has shown value when planning for TAVI in complex bicuspid cases, its reliance on specialised software and service providers has limited its accessibility in routine clinical practice. Computational modelling also shows promise with regard to the planning of redo-TAVI in younger bicuspid patients, with valuable insights into the risk of coronary occlusion and coronary inaccessibility in redo-TAVI scenarios.

BALLOON SIZING

The balloon-sizing method involves inflation of a balloon in the native aortic valve (predilatation) while performing an aorta angiogram to assess the presence of contrast leak into the left ventricle **(Figure 3F)**. In case of doubt between two TAV sizes, it is recommended to perform balloon sizing with a balloon diameter matching the smaller TAV size (for BEV) or one at the lower end of the aortic annulus range recommended for the smaller TAV size (for SEV). If no leak is detected, the balloon size is considered adequate, and the corresponding TAV size can be selected. While this method is straightforward and offers a real-time assessment of the valve's landing zone seal, a drawback of this sizing method is that it is performed intraprocedurally, thereby delaying TAV selection and loading. Additionally, the absence of contrast leak does not always guarantee optimal seal with the final valve implantation.

Procedural considerations

When performing TAVI in BAV patients, there are several considerations to address the specific anatomical complexities of BAVs **(Figure 4)**. A tailored approach is essential to maximise procedural success and reduce the risks of procedural complications, such as annulus rupture, sinus perforation, valve migration, PVR, and TAV underexpansion[9]. At each step in the procedure, patient-tailored modifications can be pivotal for achieving optimal outcomes. Of note, cerebral embolic protection may be considered when performing TAVI in BAV patients given the increased risk of procedural stroke in these patients[5,36].

CROSSING THE AORTIC VALVE

Wire crossing of BAVs can be difficult because of extensive leaflet calcification, a (calcified) raphe, and the presence of a wide and/or horizontal aortic root. Use of a predetermined patient-tailored fluoroscopic projection – the commissural view – derived from the preprocedural cardiac CT, can facilitate this step and is crucial throughout the entire procedure. The commissural view is a fluoroscopic projection on the aortic annulus S-curve, which is in line with the commissure, looking into it and distinguishing the calcified leaflets **(Figure 4A)**[37]. In case of the most common BAV phenotype – a BAV Sievers type 1 with right-left fused cusps – the commissural view corresponds to the classical right-left cusp-overlap view.

PREDILATATION

Predilatation is commonly performed when treating BAVs with TAVI, and it serves two primary purposes: facilitating the crossing of the native aortic valve with the TAVI delivery system and promoting optimal TAV expansion, thereby reducing the risk of TAV underexpansion **(Figure 4B)**. This step is particularly important for SEV platforms, where TAV underexpansion can lead to TAV infolding, migration, or even embolisation. The balloon size for predilatation should be carefully matched to the patient's anatomy, taking into account the anatomical size and extent of calcifications at the level of the aortic annulus, LVOT, and aortic root. A safe balloon size should be based on preprocedural CT planning using the circle method or the minimum annulus diameter. During predilatation, use of the commissural view allows for the assessment of balloon expansion and calcified leaflet modification. In case of severely calcified leaflets, a "double-tap" balloon inflation may be considered in order to maximally modify the leaflet calcifications. An aortic angiogram can also be performed during predilatation to assist with TAV sizing.

TAV IMPLANTATION

The choice of TAV type – either BEV or SEV – has implications for the implantation strategy when treating BAVs. For both types, higher implants are typically targeted in BAVs, because a deeper implant position increases the risks of supraskirt PVR and conduction disturbances **(Figure 4C-Figure 4D)**[4,38].

For BEVs, this higher TAV implant position corresponds to a 90/10% or even 100/0% supra-annular/infra-annular position, which can be achieved by deploying a SAPIEN valve (Edwards Lifesciences) with the radiopaque marker 3 mm above the annulus in the three-cusp coplanar view and/or with the radiolucent line at the annulus level in the right-left cusp-overlap view[39]. Moreover, when positioning BEVs in a BAV anatomy, it is important to verify that the outflow part of the BEV is positioned at least 1 mm above the dense leaflet calcifications; this to avoid TAV embolisation towards the left ventricle – this is a particular point of attention when using the shorter-frame Myval BEV (Meril Life Sciences) in bicuspid valves.

For SEVs, this higher TAV implant position corresponds to a 1 to 3 mm implant depth in relation to the aortic annulus. In case of implanting the Evolut platform, the right-left cusp-overlap view is typically used to guide initial TAV positioning, thereby keeping the 3 mm radiopaque marker just above the aortic annulus level during deployment to achieve a final depth of 1 to 3 mm below the annulus. Before final valve release, it is important to verify a minimum implant depth of 1 mm below the left coronary cusp; this can be done in

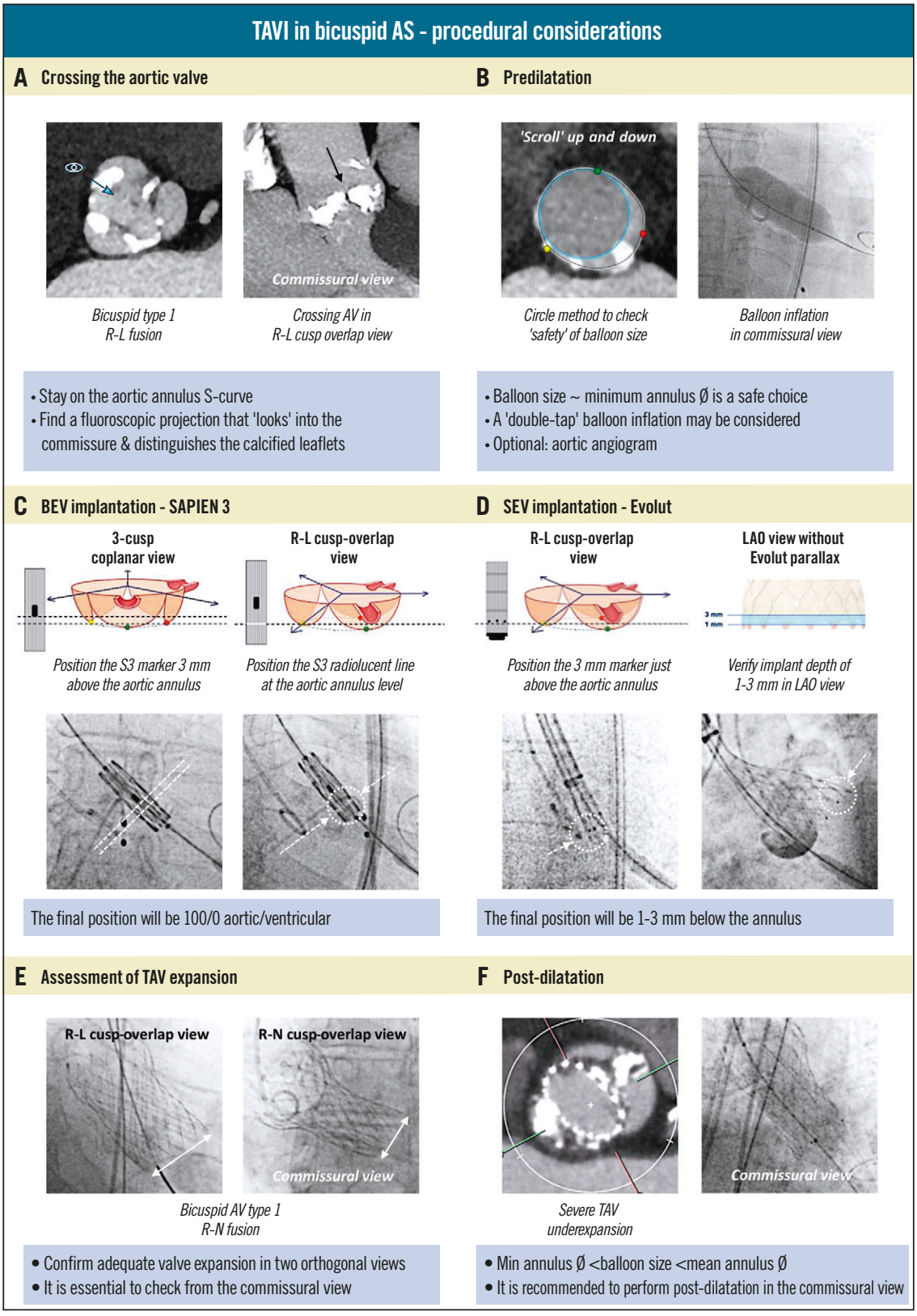


Figure 4. *Procedural considerations for TAVI in bicuspid aortic stenosis. A) Tailoring fluoroscopic projections for crossing the aortic valve. B) Aortic valve balloon predilatation. C, D) Positioning and implantation of a BEV or SEV in a bicuspid aortic valve stenosis. E) Assessment of post-implant TAV expansion. F) TAV balloon post-dilatation. AS: aortic stenosis; AV: aortic valve; BEV: balloon-expandable valve; LAO: left anterior oblique; R-L: right-left cusp; R-N: right-non-cusp; S3: SAPIEN 3; SEV: self-expanding valve; TAV: transcatheter aortic valve; TAVI: transcatheter aortic valve implantation*

a left anterior oblique (LAO) fluoroscopic projection with no parallax in the TAV.

Although targeting higher TAV implants improves procedural outcomes, it may compromise redo-TAVI options. In case of redo-TAVI, a high index TAV implant may result in a relatively high leaflet neoskirt, which could increase the risk of coronary artery occlusion (due to sinus sequestration) and coronary inaccessibility[40]. This is particularly relevant when planning for TAVI in bicuspid AS patients, as these patients are (on average) younger and have a longer life expectancy compared to tricuspid AS patients.

In very selected BAV cases with severe (right) coronary ostium eccentricity, it has been suggested by some operators to use the coronary ostia overlap fluoroscopic projection for SEV implantation; however, this may not be practically feasible and may complicate coronary access to the left coronary artery and jeopardise the benefits of commissural alignment[41].

ASSESSMENT OF TAV EXPANSION

Following implantation, assessing TAV expansion is crucial to ensure that the valve is well positioned and fully expanded. Therefore, it is essential to use two orthogonal fluoroscopic views, one LAO and one right anterior oblique fluoroscopic view, with one of these being the commissural view; this allows for a reliable evaluation of TAV symmetry and expansion **(Figure 4E)**. This is particularly relevant in BAVs with heavily calcified leaflets and/or a calcified raphe, which can make complete stent frame expansion challenging[19]. Importantly, there is increasing evidence that TAV underexpansion and eccentricity in BAVs can impact valve haemodynamics, the risk of leaflet thickening, and clinical outcomes[42]. Hence, this necessitates further intervention to optimise TAV performance.

POST-DILATATION

Post-dilatation can improve TAV expansion and circularity and enhance sealing, ensuring optimal valve function and reducing PVR, especially when heavy calcification has hindered full TAV expansion[4,19]. A balloon size 1 or 2 mm larger than the minimum annulus diameter – but smaller than the mean annulus diameter – can often be considered a safe and effective choice for post-dilatation. Extra caution and a more conservative balloon choice could be warranted for anatomies with subannular/LVOT calcification (consider a high balloon position) or a narrow and calcified sinotubular junction (consider a low balloon position), as studies with BEVs have linked this to an increased risk of aortic root injury[43]. Post-dilatation is best performed using the bicuspid "commissural view" for fluoroscopic guidance to assess balloon inflation and TAV stent frame expansion **(Figure 4F)**.

Missing evidence and perspectives

Despite the data on TAVI in BAV patients that have accumulated in recent years, there are remaining knowledge gaps to be filled in order to better understand the outcomes associated with TAVI in BAVs.

INDICATIONS AND PATIENT SELECTION

Although the European Society of Cardiology/European Association for Cardio-Thoracic Surgery (ESC/EACTS) Guidelines for the management of valvular heart disease formulate clear recommendations on indications for intervention in AS and the recommended mode of intervention, there is hardly any discussion on the role of TAVI in patients with BAV disease. The ESC/EACTS Guidelines state that "While several registries have reported excellent outcomes of TAVI in patients with a BAV who were unsuitable for surgery, SAVR remains more appropriate in patients with aortic stenosis affecting a bicuspid valve and in those with associated disease (e.g., aortic root dilatation, complex coronary artery disease, or severe mitral regurgitation) requiring a surgical approach." In the ACC/AHA Guidelines for the management of patients with valvular heart disease, a separate chapter has been dedicated to bicuspid aortic valves. However, the ACC/AHA Guidelines are also rather scarce with their comments on the role of TAVI to treat bicuspid AS and mention that "considerations are the younger age of patients with a BAV, for whom the risk-benefit ratio of TAVI versus SAVR needs careful consideration. Randomised controlled trials are needed to obtain full clarity on the optimal use of TAVI in this population, as well as long-term outcomes."

Besides this missing RCT evidence to support TAVI in BAV disease, there is an equally large gap in evidence on which BAV morphologies are suitable, less suitable, or absolutely not suitable for treatment with TAVI. Even an expert consensus document on the sizing and positioning of the SAPIEN 3/SAPIEN 3 Ultra (Edwards Lifesciences) in bicuspid AS did not address the topic of which BAV morphologies are most favourable or, conversely, should be avoided for TAVI and preferably referred to SAVR[32]. Clearly, a more granular risk stratification is necessary to guide our decision-making in daily clinical practice. Dedicated studies focusing on TAVI outcomes in different BAV morphologies or phenotypes (including BAV Sievers type 2 or unicuspid AV) are required in the future.

Finally, there is also missing evidence on what the mode of intervention should be in elderly patients with severe symptomatic AS and concomitant aortic root dilatation. A recent study reported that aortic root dilatation remained stable in 85% of patients at a median follow-up of 3 years after TAVI. In the 15% of patients with continuous aortic root dilatation, TAV stent frame geometry and function were identified as predictive factors of this continued dilatation after TAVI[44]. However, more evidence is needed on this topic.

DEDICATED TAV PROSTHESES

Although only the Evolut and SAPIEN platforms are European Conformity (CE) marked with an indication for TAVI in bicuspid AS, most contemporary balloon-expandable or self-expanding TAVs have been used to treat BAV morphologies; however, this has inherent constraints and weaknesses.

Newer-generation TAV devices, such as the Evolut FX+ (Medtronic) and SAPIEN 3 Ultra, have shown promise in optimising TAV positioning, promoting coronary access and preventing PVR in tricuspid AS[45,46]. Prospective studies exploring the performance of these newest-generation devices in bicuspid AS patients are also needed.

Importantly, TAV stent frame underexpansion and ellipticity in bicuspid AS could adversely impact valve haemodynamics and durability. Dedicated TAVI devices could be needed in the future to overcome the technical limitations of the current

TAVs, which are primarily designed for the treatment of tricuspid aortic valves.

PROCEDURAL REFINEMENTS

There may be significant differences in outcomes based on operator experience with TAVI in BAV patients. Training and the establishment of centres of excellence may help address these disparities. In the future, artificial intelligence could help integrate the bicuspid phenotype and calcium burden into the procedural decision algorithm, and robotic-assisted TAVI could improve the accuracy of TAV positioning and implantation.

Furthermore, as many procedural challenges and difficulties are related to the bicuspid configuration of the leaflets – resulting in TAV underexpansion and eccentricity – adjunctive therapies such as leaflet modification may play a role in the future. The ShortCut leaflet splitting device (Pi-Cardia) has shown promise for redo-TAVI procedures in degenerated surgical or transcatheter aortic bioprostheses[47]. Future studies should investigate whether "tricuspidalisation" of a bicuspid valve, by splitting the fused leaflet, is feasible, safe and effective and whether it might become an indispensable procedural refinement when treating bicuspid anatomies with TAVI.

LONG-TERM OUTCOMES

While several registries have reported excellent outcomes of TAVI in patients with a BAV, most existing evidence is derived from short- to medium-term follow-up studies. Taking into consideration that TAV underexpansion and eccentricity have been extensively documented in bicuspid anatomies, concerns have been raised that this could lead to impaired valve function and favour adverse outcomes such as leaflet thrombosis or valve deterioration[48]. Long-term outcomes with regard to valve haemodynamics, leaflet thrombosis, valve durability, and reintervention following TAVI in BAV patients are still underresearched and underreported. Understanding how different types of TAVs function over time in this specific anatomical setting is crucial. Larger cohorts of patients with extended follow-up, ideally up to 10 years, are needed to ensure that TAV durability is satisfactory when treating BAVs.

Lastly, there is a scarcity of data on patient-reported outcomes and on how TAVI impacts quality of life when treating younger, low-risk patients with a BAV, despite this being an important aspect of assessing treatment effectiveness. Aspects such as functional improvement and impact on quality of life should be considered equally important as valve durability in this group of patients.

NEED FOR COMPARATIVE STUDIES

When critically evaluating the data on TAVI in bicuspid AS (see section "Recent data on TAVI in BAV disease"), it is clear that most of the current evidence comes from (retrospective) single-arm registry studies. One of the obvious limitations of these registry studies is a strong patient selection bias. So far, there has been no RCT directly comparing TAVI with SAVR in BAV patients. Such studies are needed to determine the best treatment strategy for these patients. A future RCT comparing TAVI with SAVR in BAVs should attempt to enrol the broadest possible bicuspid AS population in the RCT arm, rather than in parallel TAVI or SAVR registry studies. However, it must be accepted that some BAV phenotypes, such as BAV Sievers type 2 or unicuspid aortic valves, will be excluded from the comparative study arm due to the unpredictable TAVI outcomes in these particular bicuspid AV phenotypes.

Finally, TAV type and design may also influence procedural and long-term outcomes after TAVI in BAVs. Various commercially available TAVI devices may perform differently in the context of BAVs. Head-to-head comparative studies, comparing TAVI devices in BAV patients are also needed to evaluate the safety and efficacy of different TAV designs in patients with bicuspid anatomy.

Conclusions

TAVI for bicuspid aortic valves has become a mature procedure with excellent clinical outcomes achieved in selected patients. We reviewed the classifications, challenges associated with bicuspid anatomies, and current knowledge and techniques for TAVI in this patient population, from the sizing to the procedure itself. Several remaining issues need to be addressed in future properly sized studies and randomised controlled trials.

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Conflict of interest statement

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References

1. Siu SC, Silversides CK. Bicuspid aortic valve disease. *J Am Coll Cardiol.* 2010;55:2789-800.

2. Jilaihawi H, Wu Y, Yang Y, Xu L, Chen M, Wang J, Kong X, Zhang R, Wang M, Lv B, Wang W, Xu B, Makkar RR, Sievert H, Gao R. Morphological characteristics of severe aortic stenosis in China: imaging corelab observations from the first Chinese transcatheter aortic valve trial. *Catheter Cardiovasc Interv.* 2015;85:752-61.

3. Fedak PW, Verma S, David TE, Leask RL, Weisel RD, Butany J. Clinical and pathophysiological implications of a bicuspid aortic valve. *Circulation.* 2002;106:900-4.

4. Tchetche D, de Biase C, van Gils L, Parma R, Ochala A, Lefevre T, Hovasse T, De Backer O, Sondergaard L, Bleiziffer S, Lange R, Kornowski R, Landes U, Norgaard BL, Biasco L, Philippart R, Molina-Martin de Nicolas J, Mylotte D, Lemee C, Dumonteil N, Van Mieghem NM. Bicuspid Aortic Valve Anatomy and Relationship With Devices: The BAVARD Multicenter Registry. *Circ Cardiovasc Interv.* 2019;12:e007107.

5. Jørgensen TH, Thyregod HGH, Savontaus M, Willemen Y, Bleie Ø, Tang M, Niemela M, Angerås O, Gudmundsdóttir IJ, Sartipy U, Dagnegaard H, Laine M, Rück A, Piuhola J, Petursson P, Christiansen EH, Malmberg M, Olsen PS, Haaverstad R, Sondergaard L, De Backer O; NOTION-2 investigators. Transcatheter aortic valve implantation in

low-risk tricuspid or bicuspid aortic stenosis: the NOTION-2 trial. *Eur Heart J*. 2024;45:3804-14.

6. Montalto C, Sticchi A, Crimi G, Laricchia A, Khokhar AA, Giannini F, Reimers B, Colombo A, Latib A, Waksman R, Mangieri A. Outcomes After Transcatheter Aortic Valve Replacement in Bicuspid Versus Tricuspid Anatomy: A Systematic Review and Meta-Analysis. *JACC Cardiovasc Interv*. 2021;14:2144-55.

7. Sievers HH, Schmidtke C. A classification system for the bicuspid aortic valve from 304 surgical specimens. *J Thorac Cardiovasc Surg*. 2007;133:1226-33.

8. Jilaihawi H, Chen M, Webb J, Himbert D, Ruiz CE, Rodés-Cabau J, Pache G, Colombo A, Nickenig G, Lee M, Tamburino C, Sievert H, Abramowitz Y, Tarantini G, Alqoofi F, Chakravarty T, Kashif M, Takahashi N, Kazuno Y, Maeno Y, Kawamori H, Chieffo A, Blanke P, Dvir D, Ribeiro HB, Feng Y, Zhao ZG, Sinning JM, Kliger C, Giustino G, Pajerski B, Imme S, Grube E, Leipsic J, Vahanian A, Michev I, Jelnin V, Latib A, Cheng W, Makkar R. A Bicuspid Aortic Valve Imaging Classification for the TAVR Era. *JACC Cardiovasc Imaging*. 2016;9:1145-58.

9. Michelena HI, Della Corte A, Evangelista A, Maleszewski JJ, Edwards WD, Roman MJ, Devereux RB, Fernández B, Asch FM, Barker AJ, Sierra-Galan LM, De Kerchove L, Fernandes SM, Fedak PWM, Girdauskas E, Delgado V, Abbara S, Lansac E, Prakash SK, Bissell MM, Popescu BA, Hope MD, Sitges M, Thourani VH, Pibarot P, Chandrasekaran K, Lancellotti P, Borger MA, Forrest JK, Webb J, Milewicz DM, Makkar R, Leon MB, Sanders SP, Markl M, Ferrari VA, Roberts WC, Song JK, Blanke P, White CS, Siu S, Svensson LG, Braverman AC, Bavaria J, Sundt TM, El Khoury G, De Paulis R, Enriquez-Sarano M, Bax JJ, Otto CM, Schäfers HJ; Endorsed by the Heart Valve Society (HVS), European Association of Cardiovascular Imaging (EACVI), Society of Thoracic Surgeons (STS), American Association for Thoracic Surgery (AATS), Society for Cardiovascular Magnetic Resonance (SCMR), Society of Cardiovascular Computed Tomography (SCCT), North American Society for Cardiovascular Imaging (NASCI) and the International Bicuspid Aortic Valve Consortium (BAVCon). International consensus statement on nomenclature and classification of the congenital bicuspid aortic valve and its aortopathy, for clinical, surgical, interventional and research purposes. *Eur J Cardiothorac Surg*. 2021;60:448-76.

10. Javadikasgari H, Roselli EE, Aftab M, Suri RM, Desai MY, Khosravi M, Cikach F, Isabella M, Idrees JJ, Raza S, Tappuni B, Griffin BP, Svensson LG, Gillinov AM. Combined aortic root replacement and mitral valve surgery: The quest to preserve both valves. *J Thorac Cardiovasc Surg*. 2017;153:1023-30.e1.

11. Tadros TM, Klein MD, Shapira OM. Ascending aortic dilatation associated with bicuspid aortic valve: pathophysiology, molecular biology, and clinical implications. *Circulation*. 2009;119:880-90.

12. Verma S, Siu SC. Aortic dilatation in patients with bicuspid aortic valve. *N Engl J Med*. 2014;370:1920-9.

13. Praz F, Borger MA, Lanz J, Marin-Cuartas M, Abreu A, Adamo M, Ajmone Marsan N, Barili F, Bonaros N, Cosyns B, De Paulis R, Gamra H, Jahangiri M, Jeppsson A, Klautz RJM, Mores B, Pérez-David E, Pöss J, Prendergast BD, Rocca B, Rossello X, Suzuki M, Thiele H, Tribouilloy CM, Wojakowski W. ESC/EACTS Scientific Document Group. 2025 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J*. 2025 Aug 29 [Epub ahead of print].

14. Otto CM, Nishimura RA, Bonow RO, Carabello BA, Erwin JP 3rd, Gentile F, Jneid H, Krieger EV, Mack M, McLeod C, O'Gara PT, Rigolin VH, Sundt TM 3rd, Thompson A, Toly C. 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: Executive Summary: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2021;143:e35-71.

15. Mylotte D, Lefevre T, Søndergaard L, Watanabe Y, Modine T, Dvir D, Bosmans J, Tchetche D, Kornowski R, Sinning JM, Thériault-Lauzier P, O'Sullivan CJ, Barbanti M, Debry N, Buithieu J, Codner P, Dorfmeister M, Martucci G, Nickenig G, Wenaweser P, Tamburino C, Grube E, Webb JG, Windecker S, Lange R, Piazza N. Transcatheter aortic valve replacement in bicuspid aortic valve disease. *J Am Coll Cardiol*. 2014;64:2330-9.

16. Perlman GY, Blanke P, Dvir D, Pache G, Modine T, Barbanti M, Holy EW, Treede H, Ruile P, Neumann FJ, Gandolfo C, Saia F, Tamburino C, Mak G, Thompson C, Wood D, Leipsic J, Webb JG. Bicuspid Aortic Valve Stenosis: Favorable Early Outcomes With a Next-Generation Transcatheter Heart Valve in a Multicenter Study. *JACC Cardiovasc Interv*. 2016;9:817-24.

17. Attinger-Toller A, Bhindi R, Perlman GY, Murdoch D, Weir-McCall J, Blanke P, Barbanti M, Sathananthan J, Ruile P, Gandolfo C, Saia F, Nietlispach F, Wood D, Leipsic J, Webb JG. Mid-term outcome in patients with bicuspid aortic valve stenosis following transcatheter aortic valve replacement with a current generation device: A multicenter study. *Catheter Cardiovasc Interv*. 2020;95:1186-92.

18. Yoon SH, Bleiziffer S, De Backer O, Delgado V, Arai T, Ziegelmueller J, Barbanti M, Sharma R, Perlman GY, Khalique OK, Holy EW, Saraf S, Deuschl F, Fujita B, Ruile P, Neumann FJ, Pache G, Takahashi M, Kaneko H, Schmidt T, Ohno Y, Schofer N, Kong WKF, Tay E, Sugiyama D, Kawamori H, Maeno Y, Abramowitz Y, Chakravarty T, Nakamura M, Kuwata S, Yong G, Kao HL, Lee M, Kim HS, Modine T, Wong SC, Bedgoni F, Testa L, Teiger E, Butter C, Ensminger SM, Schaefer U, Dvir D, Blanke P, Leipsic J, Nietlispach F, Abdel-Wahab M, Chevalier B, Tamburino C, Hildick-Smith D, Whisenant BK, Park SJ, Colombo A, Latib A, Kodali SK, Bax JJ, Søndergaard L, Webb JG, Lefèvre T, Leon MB, Makkar R. Outcomes in Transcatheter Aortic Valve Replacement for Bicuspid Versus Tricuspid Aortic Valve Stenosis. *J Am Coll Cardiol*. 2017;69:2579-89.

19. Yoon SH, Kim WK, Dhoble A, Milhorini Pio S, Babaliaros V, Jilaihawi H, Pilgrim T, De Backer O, Bleiziffer S, Vincent F, Shmidt T, Butter C, Kamioka N, Eschenbach L, Renker M, Asami M, Lazkani M, Fujita B, Birs A, Barbanti M, Pershad A, Landes U, Oldemeyer B, Kitamura M, Oakley L, Ochiai T, Chakravarty T, Nakamura M, Ruile P, Deuschl F, Berman D, Modine T, Ensminger S, Kornowski R, Lange R, McCabe JM, Williams MR, Whisenant B, Delgado V, Windecker S, Van Belle E, Sondergaard L, Chevalier B, Mack M, Bax JJ, Leon MB, Makkar RR; Bicuspid Aortic Valve Stenosis Transcatheter Aortic Valve Replacement Registry Investigators. Bicuspid Aortic Valve Morphology and Outcomes After Transcatheter Aortic Valve Replacement. *J Am Coll Cardiol*. 2020;76:1018-30.

20. Zito A, Buono A, Scotti A, Kim WK, Fabris T, de Biase C, Bellamoli M, Montarello N, Costa G, Alfadhel M, Koren O, Fezzi S, Bellini B, Massussi M, Bai L, Costa G, Mazzapicchi A, Giacomin E, Gorla R, Hug K, Briguori C, Bettari L, Messina A, Villa E, Boiago M, Romagnoli E, Orbach A, Laterra G, Aurigemma C, De Carlo M, Renker M, Garcia Gomez M, Trani C, Ielasi A, Landes U, Rheude T, Testa L, Amat Santos I, Mangieri A, Saia F, Favero L, Chen M, Adamo M, Sonia Petronio A, Montorfano M, Makkar RR, Mylotte D, Blackman DJ, Barbanti M, De Backer O, Tchètchè D, Tarantini G, Latib A, Maffeo D, Burzotta F. Incidence, Predictors, and Outcomes of Paravalvular Regurgitation After TAVR in Sievers Type 1 Bicuspid Aortic Valves. *JACC Cardiovasc Interv*. 2024;17:1652-63.

21. Tchétché D, Ziviello F, De Biase C, De Backer O, Hovasse T, Leroux L, Petronio AS, Saint-Etienne C, Teles RC, Modine T, Sudre A, Teiger E, Mylotte D, Souteyrand G, Piazza N, Casassus F, Sondergaard L, Angelillis M, Nolasco T, Siddiqui S, Kardys I, Dumonteil N, Van Mieghem NM. Transcatheter aortic valve implantation with the Evolut platform for bicuspid aortic valve stenosis: the international, multicentre, prospective BIVOLUTX registry. *EuroIntervention*. 2023;19:502-11.

22. U.S. Food and Drug Administration. FDA expands indication for several transcatheter heart valves to patients at low risk for death or major complications associated with open-heart surgery. https://www.biospace.com/fda-expands-indication-for-several-transcatheter-heart-valves-to-patients-at-low-risk-for-death-or-major-complications-associated-with-open-heart-surgery. (Last accessed 15 August 2025).

23. Waksman R, Craig PE, Torguson R, Asch FM, Weissman G, Ruiz D, Gordon P, Ehsan A, Parikh P, Bilfinger T, Levitt R, Hahn C, Roberts D, Ingram M, Hanna N, Comas G, Zhang C, Ben-Dor I, Satler LF, Garcia-Garcia HM, Shults C, Rogers T. Transcatheter Aortic Valve Replacement in Low-Risk Patients With Symptomatic Severe Bicuspid Aortic Valve Stenosis. *JACC Cardiovasc Interv*. 2020;13:1019-27.

24. Makkar RR, Yoon SH, Chakravarty T, Kapadia SR, Krishnaswamy A, Shah PB, Kaneko T, Skipper ER, Rinaldi M, Babaliaros V, Vemulapalli S, Trento A, Cheng W, Kodali S, Mack MJ, Leon MB, Thourani VH. Association Between Transcatheter Aortic Valve Replacement for Bicuspid vs Tricuspid Aortic Stenosis and Mortality or Stroke Among Patients at Low Surgical Risk. *JAMA*. 2021;326:1034-44.

25. Williams MR, Jilaihawi H, Makkar R, O'Neill WW, Guyton R, Malaisrie SC, Brown DL, Blanke P, Leipsic JA, Pibarot P, Hahn RT,

Leon MB, Cohen DJ, Bax JJ, Kodali SK, Mack MJ, Lu M, Webb JG. The PARTNER 3 Bicuspid Registry for Transcatheter Aortic Valve Replacement in Low-Surgical-Risk Patients. *JACC Cardiovasc Interv.* 2022;15:523-32.

26. Forrest JK, Ramlawi B, Deeb GM, Zahr F, Song HK, Kleiman NS, Chetcuti SJ, Michelena HI, Mangi AA, Skiles JA, Huang J, Popma JJ, Reardon MJ. Transcatheter Aortic Valve Replacement in Low-risk Patients With Bicuspid Aortic Valve Stenosis. *JAMA Cardiol.* 2021;6:50-7.

27. Zahr F, Ramlawi B, Reardon MJ, Deeb GM, Yakubov SJ, Song HK, Kleiman NS, Chetcuti SJ, Gada H, Mumtaz M, Leung S, Merhi W, Rovin JD, DeFrain M, Muppala M, Kauten J, Rajagopal V, Huang J, Ito S, Forrest JK. 3-Year Outcomes From the Evolut Low Risk TAVR Bicuspid Study. *JACC Cardiovasc Interv.* 2024;17:1667-75.

28. Majmundar M, Kumar A, Doshi R, Shariff M, Krishnaswamy A, Reed GW, Brockett J, Lahorra JA, Svensson LG, Puri R, Kapadia SR, Kalra A. Early outcomes of transcatheter versus surgical aortic valve implantation in patients with bicuspid aortic valve stenosis. *EuroIntervention.* 2022;18: 23-32.

29. Kim WK, Renker M, Rolf A, Fischer-Rasokat U, Wiedemeyer J, Doss M, Möllmann H, Walther T, Nef H, Hamm CW, Liebetrau C. Annular versus supra-annular sizing for TAVI in bicuspid aortic valve stenosis. *EuroIntervention.* 2019;15:e231-8.

30. Iannopollo G, Romano V, Buzzatti N, De Backer O, Søndergaard L, Merkely B, Prendergast BD, Giannini F, Colombo A, Latib A, Granada JF, Chieffo A, Montorfano M. A novel supra-annular plane to predict TAVI prosthesis anchoring in raphe-type bicuspid aortic valve disease: the LIRA plane. *EuroIntervention.* 2020;16:259-61.

31. Iannopollo G, Romano V, Esposito A, Guazzoni G, Ancona M, Ferri L, Russo F, Bellini B, Buzzatti N, Curio J, Prendergast B, Montorfano M. Update on supra-annular sizing of transcatheter aortic valve prostheses in raphe-type bicuspid aortic valve disease according to the LIRA method. *Eur Heart J Suppl.* 2022;24:C233-42.

32. Blackman D, Gabbieri D, Del Blanco BG, Kempfert J, Laine M, Mascherbauer J, Parma R, Tchétché D. Expert Consensus on Sizing and Positioning of SAPIEN 3/Ultra in Bicuspid Aortic Valves. *Cardiol Ther.* 2021;10:277-88.

33. Petronio AS, Angelillis M, De Backer O, Giannini C, Costa G, Fiorina C, Castriota F, Bedogni F, Laborde JC, Søndergaard L. Bicuspid aortic valve sizing for transcatheter aortic valve implantation: Development and validation of an algorithm based on multi-slice computed tomography. *J Cardiovasc Comput Tomogr.* 2020;14:452-61.

34. Dowling C, Bavo AM, El Faquir N, Mortier P, de Jaegere P, De Backer O, Sondergaard L, Ruile P, Mylotte D, McConkey H, Rajani R, Laborde JC, Brecker SJ. Patient-Specific Computer Simulation of Transcatheter Aortic Valve Replacement in Bicuspid Aortic Valve Morphology. *Circ Cardiovasc Imaging.* 2019;12:e009178.

35. Hokken TW, Wienemann H, Dargan J, Ginkel DV, Dowling C, Unbehaun A, Bosmans J, Bader-Wolfe A, Gooley R, Swaans M, Brecker SJ, Adam M, Van Mieghem NM. Clinical value of CT-derived simulations of transcatheter-aortic-valve-implantation in challenging anatomies the PRECISE-TAVI trial. *Catheter Cardiovasc Interv.* 2023;102:1140-8.

36. Makkar RR, Yoon SH, Leon MB, Chakravarty T, Rinaldi M, Shah PB, Skipper ER, Thourani VH, Babaliaros V, Cheng W, Trento A, Vemulapalli S, Kapadia SR, Kodali S, Mack MJ, Tang GHL, Kaneko T. Association Between Transcatheter Aortic Valve Replacement for Bicuspid vs Tricuspid Aortic Stenosis and Mortality or Stroke. *JAMA.* 2019;321:2193-202.

37. Zgheib A, Campens L, Abualsaud A, Al Isma'ili A, Barbanti M, Dvir D, Gada H, Granada JF, Latib A, Leipsic J, Maisano F, Martucci G, Medina de Chazal HA, Modine T, Mylotte D, Prendergast B, Sawaya F, Spaziano M, Tang G, Theriault-Lauzier P, Tchetche D, van Mieghem N, Søndergaard L, De Backer O, Piazza N. Aortic Annulus S-Curve: Implications for Transcatheter Aortic Valve Replacement and Related Procedures, Part 1. *JACC Cardiovasc Interv.* 2022;15:2353-73.

38. Xiong TY, Ali WB, Feng Y, Hayashida K, Jilaihawi H, Latib A, Lee MK, Leon MB, Makkar RR, Modine T, Naber C, Peng Y, Piazza N, Reardon MJ, Redwood S, Seth A, Sondergaard L, Tay E, Tchetche D, Yin WH, Chen M, Prendergast B, Mylotte D. Transcatheter aortic valve implantation in patients with bicuspid valve morphology: a roadmap towards standardization. *Nat Rev Cardiol.* 2023;20:52-67.

39. Gutierrez L, Boiago M, De Biase C, Oliva O, Laforgia P, Feliachi S, Beneduce A, Dumonteil N, Tchetche D. Transcatheter Aortic Valve Implantation for Bicuspid Aortic Valve Disease: Procedural Planning and Clinical Outcomes. *J Clin Med.* 2023;12:7074.

40. Bapat VN, Fukui M, Zaid S, Okada A, Jilaihawi H, Rogers T, Khalique O, Cavalcante JL, Landes U, Sathananthan J, Tarantini G, Tang GHL, Blackman DJ, De Backer O, Mack MJ, Leon MB. A Guide to Transcatheter Aortic Valve Design and Systematic Planning for a Redo-TAV (TAV-in-TAV) Procedure. *JACC Cardiovasc Interv.* 2024;17:1631-51.

41. Wong I, Ho CB, Chui ASF, Chan AKC, Chan KT, Søndergaard L, Lee MK. Neo-Commissural Alignment During Transcatheter Aortic Valve Replacement: The LACRCO Algorithm. *JACC Cardiovasc Interv.* 2022;15:1582-4.

42. Fukui M, Bapat VN, Garcia S, Dworak MW, Hashimoto G, Sato H, Gössl M, Enriquez-Sarano M, Lesser JR, Cavalcante JL, Sorajja P. Deformation of Transcatheter Aortic Valve Prostheses: Implications for Hypoattenuating Leaflet Thickening and Clinical Outcomes. *Circulation.* 2022;146:480-93.

43. Barbanti M, Yang TH, Rodès Cabau J, Tamburino C, Wood DA, Jilaihawi H, Blanke P, Makkar RR, Latib A, Colombo A, Tarantini G, Raju R, Binder RK, Nguyen G, Freeman M, Ribeiro HB, Kapadia S, Min J, Feuchtner G, Gurtvich R, Alqoofi F, Pelletier M, Ussia GP, Napodano M, de Brito FS Jr, Kodali S, Norgaard BL, Hansson NC, Pache G, Canovas SJ, Zhang H, Leon MB, Webb JG, Leipsic J. Anatomical and procedural features associated with aortic root rupture during balloon-expandable transcatheter aortic valve replacement. *Circulation.* 2013;128:244-53.

44. Jia Y, Khokhar AA, Pilgrim T, Costa G, Mylotte D, Sammartino S, Tomii D, Fosbøl E, Tamburino C, Kofoed KF, Barbanti M, Windecker S, Chen M, De Backer O. Incidence and predictors of continued ascending aortic dilatation after TAVI in patients with bicuspid aortic stenosis. *Clin Res Cardiol.* 2025;114:375-84.

45. Nazif TM, Cahill TJ, Daniels D, McCabe JM, Reisman M, Chakravarty T, Makkar R, Krishnaswamy A, Kapadia S, Chehab BM, Wang J, Spies C, Rodriguez E, Kaneko T, Hahn RT, Leon MB, George I. Real-World Experience With the SAPIEN 3 Ultra Transcatheter Heart Valve: A Propensity-Matched Analysis From the United States. *Circ Cardiovasc Interv.* 2021;14:e010543.

46. Zaid S, Attizzani GF, Krishnamoorthy P, Yoon SH, Palma Dallan LA, Chetcuti S, Fukuhara S, Grossman PM, Goel SS, Atkins MD, Kleiman NS, Puri R, Bakhtadze B, Byrne T, Ibrahim AW, Grubb KJ, Tully A, Herrmann HC, Faggioni M, Ramlawi B, Khera S, Lerakis S, Dangas GD, Kini AS, Sharma SK, Reardon MJ, Tang GHL. First-in-Human Multicenter Experience of the Newest Generation Supra-Annular Self-Expanding Evolut FX TAVR System. *JACC Cardiovasc Interv.* 2023;16:1626-35.

47. Tchétché D, Kodali SK, Dvir D. First dedicated transcatheter leaflet splitting device: the ShortCut device. *EuroIntervention.* 2022;18:e428-9.

48. Cesario V, Oliva O, De Biase C, Beneduce A, Boiago M, Dumonteil N, Tchetche D. Who Lives Longer, the Valve or the Patient? The Dilemma of TAVI Durability and How to Optimize Patient Outcomes. *J Clin Med.* 2024;13:6123.

PODCAST

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TURNING POINT

ONE SCAN AWAY
FROM GREAT STORIES

EuroIntervention
2025;21:1317-1337
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EXPERT CONSENSUS

Management of patients with transvalvular right ventricular leads undergoing transcatheter tricuspid valve interventions: a scientific statement of the European Heart Rhythm Association and the European Association of Percutaneous Cardiovascular Interventions of the ESC endorsed by the Heart Rhythm Society, the Asian Pacific Heart Rhythm Society and the Canadian Heart Rhythm Society

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ABSTRACT

Up to one-third of patients referred for transcatheter tricuspid valve intervention (TTVI) have a transvalvular pacemaker (PPM) or implantable cardioverter-defibrillator (ICD) lead in place. Both the electrophysiology and interventional cardiology communities have been alerted to the complexity of decision-making in this situation due to potential interactions between the leads and the TTVI material, including the risk of jailing or damage to the leads. This document, commissioned by the European Heart Rhythm Association and the European Association of Percutaneous Cardiovascular Interventions of the ESC, reviews the scientific evidence to inform Heart Team discussions on the management of patients with a PPM or ICD who are scheduled for or have undergone TTVI. **Graphical abstract**.

KEYWORDS: Transcatheter tricuspid valve intervention; cardiac implantable electronic device lead; tricuspid regurgitation; lead jailing; lead extraction

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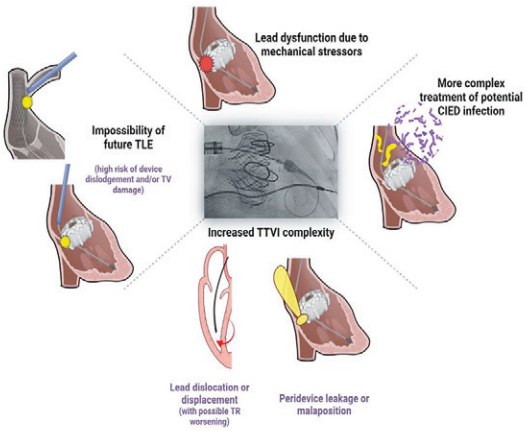
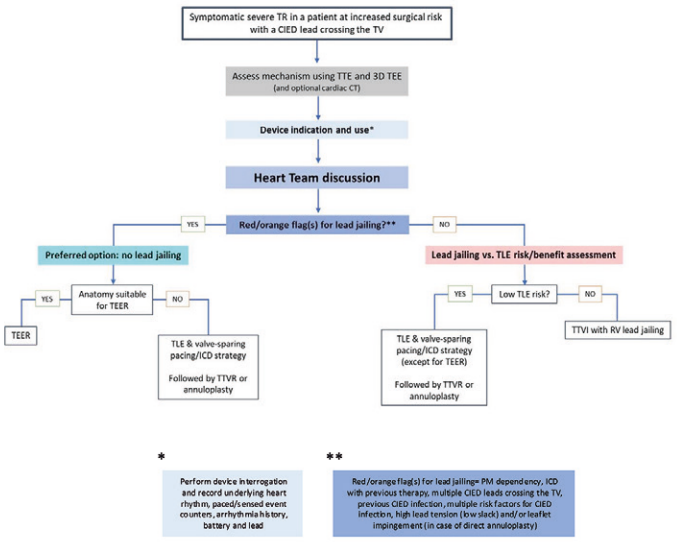


Proposed algorithm for the management in case of CIED lead crossing the tricuspid valve



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1. Introduction

The use of cardiac implantable electronic devices (CIED) has increased exponentially over the past two decades. According to data from the European Society of Cardiology (ESC), more than 600 permanent pacemakers (PPM), 100 implantable cardioverter defibrillators (ICDs), and 75 cardiac resynchronization therapy (CRT) devices are implanted per million inhabitants every year[1].

A growing body of evidence shows that patients with progressive tricuspid regurgitation (TR) have a poorer prognosis in various clinical scenarios, including left heart failure, multivalvular disease[3,4], and after CIED lead implantation[5]. Approximately one-third of patients referred for treatment of severe secondary TR have a transvalvular CIED lead implanted, which, in the majority of cases, is not the direct cause of TR (CIED-associated) but may interact during transcatheter tricuspid valve intervention (TTVI). A small but significant subgroup, representing approximately 5–7% of patients with relevant TR, has suspected CIED-related TR and requires specific diagnosis and management[6,7].

Both the electrophysiology and interventional cardiology communities have been alerted to the complexity of decision-making in practice when performing TTVI in patients with pacemaker or defibrillator lead(s) crossing the tricuspid valve (TV), due to potential interactions between the leads and TTVI material, including the risk of jailing or damaging the lead(s). At the same time, both communities are becoming increasingly aware of the potential role of CIED leads in the occurrence/ progression of TR.

Given the novelty of TTVI techniques, the European Heart Rhythm Association (EHRA) and the European Association of Percutaneous Cardiovascular Interventions (EAPCI) of the ESC have mandated this Task Force to create a Scientific Statement document highlighting the current scientific evidence regarding the increasingly common clinical problem of TTVI in patients with transvalvular CIED leads. The present document is intended to serve as a basis for multidisciplinary discussions between the different healthcare professionals involved in decision-making for the management of patients with CIED scheduled for or undergoing TTVI. It reviews the potential interactions between CIED leads, TV and TTVI materials focusing on the respective risks and benefits of lead jailing and elective lead extraction. Finally, it addresses the most common situations in clinical practice.

2. Interactions between transvalvular cardiac implantable electronic devices leads and the tricuspid valve

2.1. MECHANISMS

CIED-related TR is attributed to implantation-related, pacing-related, and device-related mechanisms. The incidence of TR worsening (by 1 or more grades) following CIED implantation vary from 10 to 39%[8,9]. Mechanisms are multiple, including: (i) Perforation and laceration of the TV[10], presumably occurring during direct introduction of the lead into the right ventricle (RV) rather than 'prolapsing' the lead; (ii) Entanglement of the valve or the chordae, particularly when using tined leads[11]; (iii) Impingement on a leaflet (most commonly the septal one)[12]; and (iv) Chronic dyssynchronous RV pacing, left ventricular dysfunction, and possibly RV dilatation. New flail leaflet may rarely be observed after implantation. Entanglement and impingement may later translate into fibrous adhesions between the lead and the TV/ subvalvular apparatus (**Figure 1** and **Moving images**), resulting in valve dysfunction[10,13]. In addition, following transvenous lead extraction (TLE), TR can be the consequence of leaflet avulsion or chordal rupture. Finally, the presence of a transvalvular lead may predispose to endocarditis, which in turn can worsen TR[14].

Procedural factors that impact the probability of valve damage include lead tip configuration[15,16], tined leads being more likely to become entangled or entrapped in the chordae tendinae, and valve crossing technique. Prolapsing may

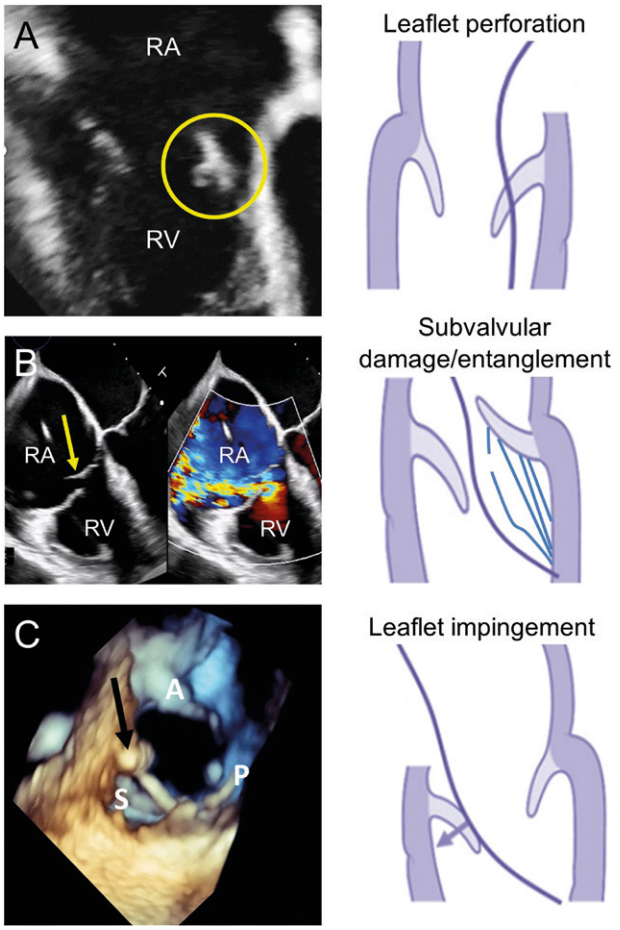

Figure 1. *Mechanisms of interaction between CIED lead and the tricuspid valve. (A) Example of leaflet perforation with the CIED lead piercing the septal leaflet (within the circle) and impairing its mobility. (B) Example of subvalvular apparatus damage during CIED lead positioning causing a flail septal leaflet (indicated by the arrow) due to chordal rupture and severe eccentric TR. (C) Example of impingement of the septal leaflet through a CIED lead (indicated by the arrow), limiting its systolic mobility and causing severe TR. A, anterior leaflet of the tricuspid valve; CIED, cardiac implantable electronic device; P, posterior leaflet of the tricuspid valve; RA, right atrium; RV, right ventricle; S, septal leaflet of the tricuspid valve; TR, tricuspid regurgitation.*

reduce the risk of perforation compared with 'direct crossing' because of less head on trauma to the TV leaflets and subvalvular apparatus[17]. Technical factors include the number, thickness, stiffness, and course of the lead across the valve.

2.2. ROLE OF TYPE OF LEAD, POSITION, AND PACING MODE

Studies failed to show clear differences between PPM and ICD leads regarding TV dysfunction despite the higher weight and rigidity of ICD leads[18-20]. Single-chamber RV pacing has been associated with TR progression[14,21–23], presumably due to changes in RV geometry[24], a risk that may be mitigated by the use of His bundle pacing[25]. Although investigated in a small patient population, His bundle pacing might reduce TR[25], which has not been observed with left bundle branch stimulation[26], especially in the case of a basal lead position[27]. Even without direct interaction with the TV leaflets, leadless cardiac pacemaker (LCPM) implantation may not fully exclude the occurrence of TR, which may be related to mechanical interference with the subvalvular apparatus[28] or to the pacing mode itself, as shown in an observational study including 53 patients followed up to 12 months[29]. However, a smaller study (N = 23) with shorter observation period failed to show significant changes in RV and TV structure, as well as their function 2 months after LCPM implantation operating in the VVIR mode[30].

2.3. DETECTION OF LEAD-RELATED TRICUSPID REGURGITATION

In CIED recipients, a pre-implant imaging assessment is recommended by the 2021 ESC guidelines on cardiac pacing and CRT[31] and it may detect pre-existing TR and help refine the pacing strategy according to TR grade. Although there is no prospective scientific evidence to support this statement, detailed echocardiographic assessment of TV function in the weeks following CIED implantation should be encouraged to diagnose acute damage or adverse interaction with the leaflets or subvalvular apparatus[6] and to identify new-onset severe TR that may benefit from early intervention. This applies in particular to patients with technical or clinical risk factor(s) contributing to TR development as summarized in **Table 1**. Appropriate decisions regarding potential treatment and/or subsequent follow-up may prevent the deterioration of RV function and heart failure symptoms over the long term. Baseline and follow-up information are also crucial, since they will guide decisions in case a TTVI is considered.

3. Transcatheter tricuspid valve interventions and potential lead issues

While open-heart surgery is the first-line option in low-risk patients, the high mortality associated with TV surgery in higher risk patients, mostly due to patient comorbidities, old age, and late referral[36], has encouraged the development of less invasive alternatives. Many TTVI procedures are still under investigation and numbers are expected to increase due to growing disease awareness and an ageing population.

Managing patients with CIED leads crossing the TV and causing CIED-related TR, or associated with TR, is challenging and warrants a thorough anatomic assessment before any TTVI. The magnitude of the problem is underscored by the consistently high number of patients with CIED reported in published studies, ranging from 11.8 to 36% **(Table 2)**, even though CIED leads crossing the TV may limit the feasibility of transcatheter repair, particularly when the lead is interacting with the valve leaflets[46,49-52]. There are currently four commercially available transcatheter therapies for TR treatment. Potential interactions of these therapies with CIED leads are illustrated in **Figure 2** and **Figure 3**.

Table 1. Risk factors for the development of significant tricuspid regurgitation in cardiac implantable electronic device recipients.

Technical factors: directly related to CIED lead(s)
Lead placement technique (prolapsing vs. direct crossing)
TV passage angle and leaflet interaction[32]
Multiple leads crossing the tricuspid valve[33]
Clinical factors associated with TR development: no direct relationship with current CIED lead(s)
High burden of RV pacing (>90%)[32]
Permanent AF[34]
Pre- and post-capillary pulmonary hypertension[34]
RV dilatation[34]
Previous cardiac surgery on left heart valves[34]
Previous transvenous lead extraction[35]

AF, atrial fibrillation; CIED, cardiac implantable electronic device; RV, right ventricle; TR, tricuspid regurgitation; TV, tricuspid valve.

(1) Transcatheter edge-to-edge repair (TEER): In analogy to its counterpart for the mitral valve, TEER aims to correct TR through leaflet approximation of the TV leaflets. Increasing evidence confirms the safety of tricuspid TEER and its efficacy to reduce TR using the two approved platforms, PASCAL[44] and TriClip[51] **(Figure 2A)**. A recently published randomized controlled trial (TRILUMINATE) showed that tricuspid TEER using the TriClip system significantly improves quality of life and reduces heart failure hospitalizations at 2 years compared with medical therapy alone. However, no significant change in terms of mortality was observed[49]. Further research is certainly needed, as this study was designed to include patients with favourable anatomic criteria for tricuspid TEER who appear to have less advanced disease than those included in other commercial and study cohorts[53]. Approximately 20–30% of TEER procedures are performed in the presence of a CIED lead crossing the TV[54]. There are two main scenarios[42]:

(a) The lead is an innocent bystander without a causative role in TR. In this scenario, the lead is usually far from the grasping zone and does not hamper leaflet coaptation and motion. Interaction with the lead during valve intervention is usually minimal and does not add risk of device detachment or damage.

(b) The lead has a causative role in TR. In this scenario, comprehensive imaging assessment is required to determine whether the lead is attached or fused to a valve leaflet. In case of intact lead mobility, TEER is likely to be successful and often implies displacing and/or fixing the lead into one of the commissures or between two clips **(Figure 3)**.

Irrespective of the strategy adopted, a too close interaction of any TEER catheter and a CIED lead should be avoided, in particular when the grippers are in open position. Penetration of the exposed grasping teeth into the lead coating may result in a potentially irreversible entanglement in addition to possible damage to the lead. Valve recrossing can be challenging depending on the number and location of the implants and necessitate echocardiographic guiding.

Table 2. Summary of published studies on transcatheter tricuspid valve interventions in patients with CIED leads.

Study reference	Patients (N)	Patients with transvenous leads (N)	System used for TTVI	TLE	Patients with jailed leads (N)	Lead complications	New Conduction disturbance	FU duration
FORMA[37]	19	3	FORMA	No	None	No issues reported	None reported	Mean 32 months (24– 36)
T-TEER in CIED patients[38]	102	33	MitraClip	No	12/33 clips close to RV lead	Slight increase in thresholds (1 RA, 1 LV, 1 RV)	None reported	1 day (0–188 days)
GATE[39]	5	1	NaviGate system	No	1	No change in threshold (died day 28)	1 temporary PPM and no definitive one	3–6 months
CAVI (Sapien)[40]	25	9	Sapien Single caval (IVC), N = 19 Bicaval, N = 6	No	Unknown (BiCaval + PPM unknown)	No issue reported	None reported	316 ± 453 days
VIVID Valve in valve registry[41]	329	128 with CIED 58 with transvenous leads 31 with leads crossing the TV	Sapien Melody Valve in previous surgical valve repair	3 before	28	Dislodgement: 1 Impedance and threshold increase: 1 Fracture M7: 1	None reported	Median 15.1 months
TriValve[42]	470	121	MitraClip (87%) CAVI FORMA Cardioband NaviGate Pascal	No	Not reported	No dislodgement No dysfunction	None reported	Median 7 months (1.15–20.00)
TRI-REPAIR[43]	30	4	Cardioband	No	Not reported	No issue reported	Conduction system disturbance: 2	2 years
PASTE[44]	235	72	PASCAL	No	Not reported	No lead issue reported; half of the SLDA occurred in patients with leads	None reported	Median follow-up of 173 days
1-year FU with EVOQUE system (compassionate use)[45]	27	9	EVOQUE	No	9	No dislodgement No dysfunction	–2 new PPM < day 3 –1 new PPM day 31	379 days (197–468)
TRISCEND I[46]	176	57	EVOQUE	No	57	No information	15 patients (13.3% of CIED-naïve patients) required new pacemaker implantation	1 year
TRICENTO[47]	21	3 + 1 extracted before and implanted with a Micra	Bicaval stent	No (1 before)	3	No issue reported	None reported	1 year
TRILUMINATE single arm[48]	98	14	TriClip	No	Not reported	No issue reported	2 patients received a new pacemaker within 3 years	3 years
TRILUMINATE RCT[49]	175 (170 received the device)	28	TriClip	No	Not reported	No issue reported	Not precisely reported (5 new CIEDs at 1 year)	12 months

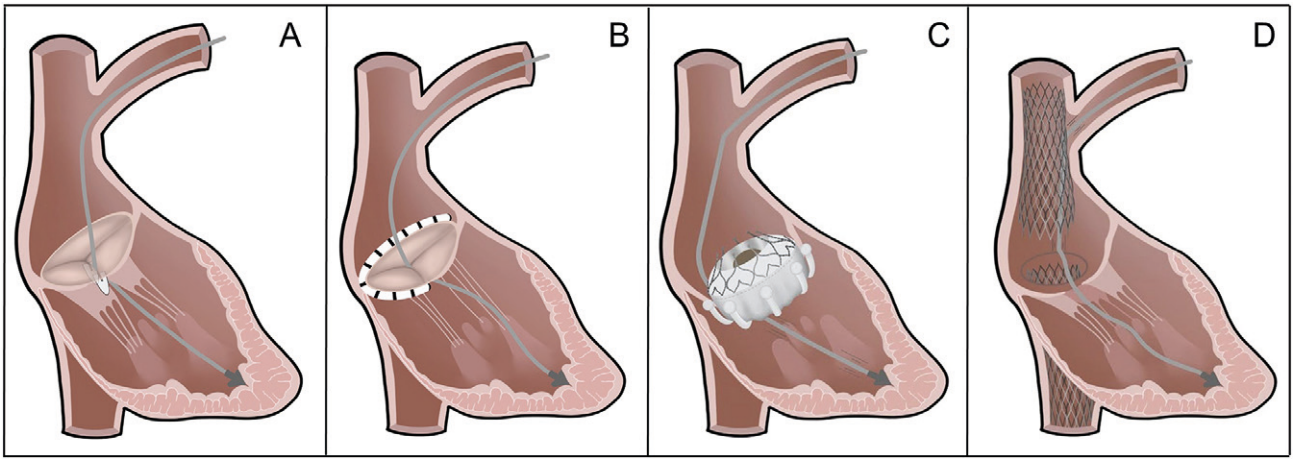

Figure 2. *Contemporary transcatheter treatment methods of tricuspid regurgitation and their interaction with CIED leads. (A) Transcatheter edge-to-edge repair; (B) Direct annuloplasty; (C) Transcatheter tricuspid valve replacement; (D) Heterotopic CAVI in both venae cavae.*

(2) Direct percutaneous annuloplasty: This procedure replicates the prosthetic surgical annuloplasty that addresses annular dilatation occurring in functional TR[43]. The Cardioband system has shown effective and durable TR reduction, along with substantial symptomatic improvement[55] **(Figure 2B)**. Combination with TEER may be needed to optimize TR reduction in patients with advanced disease or those with a persisting pseudo-prolapse. However, annuloplasty can be challenging in the presence of a lead close to the postero-septal or antero-septal area due to problematic visualization during the implant and lead jailing is occasionally unavoidable. This needs to be evaluated carefully since, in addition to lead injury, fixed leaflet impingement leading to TR worsening is sometimes observed. Lead insertion or extraction (if not jailed) after transcatheter annuloplasty is doable.

(3) Transcatheter tricuspid valve replacement (TTVR): This procedure aims to address TR through positioning of a transcatheter valve delivered from the femoral or jugular vein **(Figure 2C)**. In the TRISCEND II randomized controlled study investigating the EVOQUE system, 38.2% of the patients treated with TTVR had a CIED lead at baseline[56]. A new pacemaker (mainly LCPM) was implanted in 27.8% of the pacemaker-naïve patients within 1 year (17.4% of the whole cohort) after the procedure. In the presence of a pre-existing lead across the TV, the CIED is jailed between the annulus tissue and the self-expanding bioprosthesis precluding the option of subsequent lead extraction.

(4) Caval valve implantation (CAVI): Caval valve implantation represents a symptomatic treatment option for patients who cannot undergo valve repair or replacement. The goal of this therapy is to mitigate the consequences of TR backflow, improve renal congestion, and better control volume overload **(Figure 2D)**. Beside positive effects on symptoms, reverse RV remodelling has been observed in a prospective observational study. Approximately 22% of patients who receive CAVI have a CIED. Although the presence of leads does usually not mitigate the effectiveness of CAVI, it creates extensive entrapment in the superior vena cava of all intracardiac leads and (atrial) lead dislocation has been described[57]. Moreover, the presence of a valve that covers the brachiocephalic vein confluence may limit repeat lead implantation.

4. Potential risks due to lead jailing and device-lead interaction after transcatheter tricuspid valve intervention

The survival of patients with pre-existing CIED systems continues to improve, and the prevalence of both lead-related and lead-associated secondary TR will continue to rise[5]. This implies that the number of jailed leads is also expected to increase in the near future. The incidence of lead jailing during TTVI varies from 0 to 33% **(Table 2)**. Although major mechanical or electrical lead dysfunction has been rarely reported, the long-term risk has not been evaluated and is largely unknown. Importantly, no details regarding CIED, including pacing-dependency, lead type or defibrillation coils and indications for CIED therapy, are available in the majority of the studies **(Table 2)**.

In a large dataset of 329 patients undergoing tricuspid valve-in-valve or valve-in-ring procedures[41], a lead complication rate of 10.7% was observed over a median follow-up of 15.2 months in 28 patients who had jailed leads. Importantly, these patients had their lead jailed between two metallic structures (surgical valve or ring and the stent frame of the newly implanted transcatheter heart valve) and not between metal and tissue as it is the case for TTVI performed in native valves or CAVI. In the largest registry series of patients undergoing TEER, there were no reports of lead damage during short-term follow-up (median 6.2 months), although very limited information on lead type and function is available[58]. In a small number of patients treated with transcatheter TV annuloplasty, no adverse events related to jailed leads were reported[55]. At 1 year, no CIED-related complications were described in 9 patients with pre-existing CIED leads who underwent bicaval valve implantation[59].

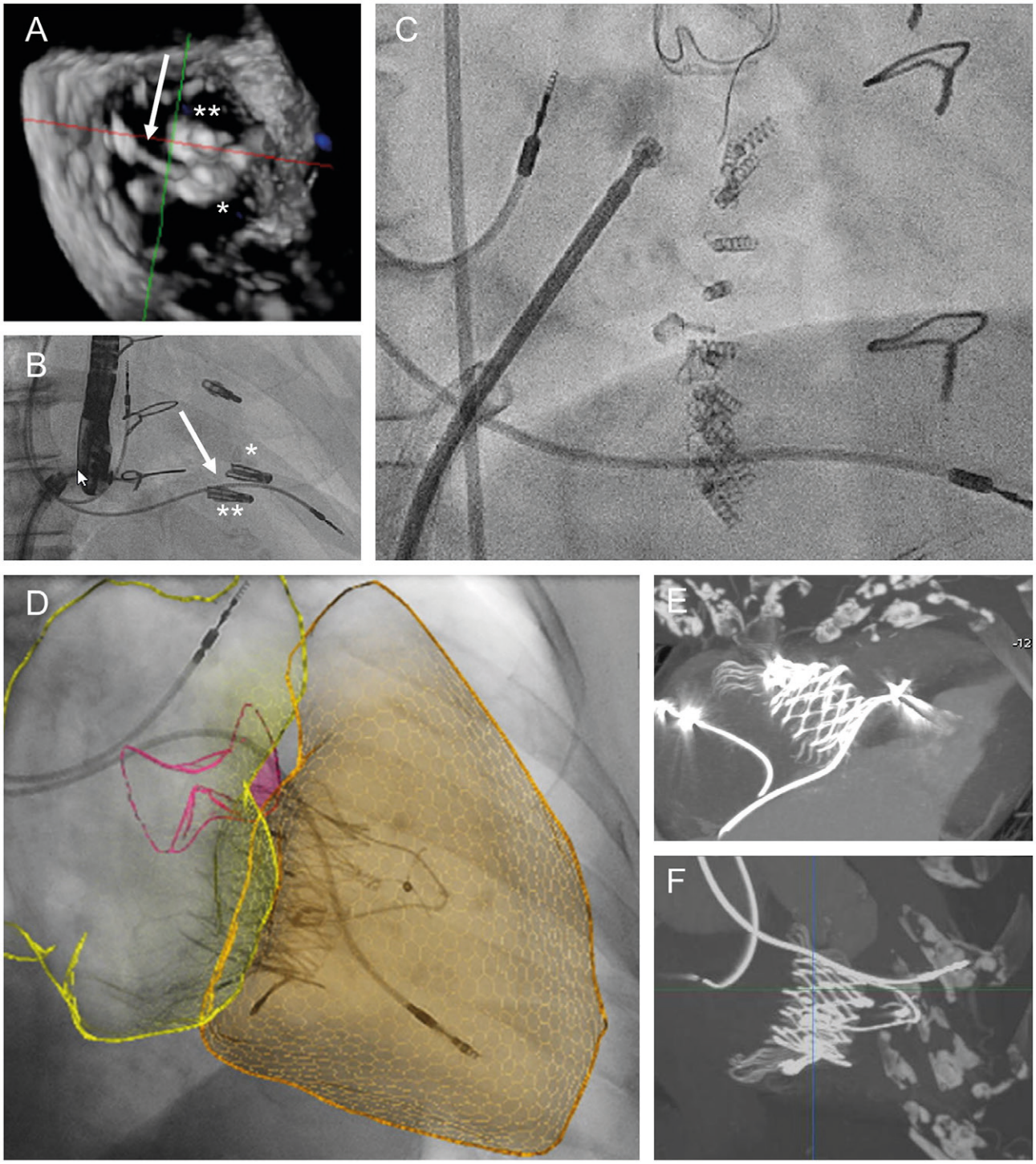

Figure 3. *Examples of interactions between tricuspid devices and CIED lead. (A–B) Implantation of 2 TriClips (*antero-septal coaptation line; **postero-septal coaptation line) with PM lead in-between (arrow); (C) Jailed PM lead after direct annuloplasty using the Edwards Cardioband system; (D–F) Interaction between the Lux valve and a jailed CIED RV lead as seen using echocardiography-fluoroscopy fusion imaging (D) and computed tomogram (E–F).*

The risks associated with CIED lead jailing are summarized in **Figure 4**. The overall risk of lead damage in this context remains unclear and is potentially related to the lead composition, dwell time and location, as well as the properties of the valve deployed. Transvenous leads are exposed to considerable mechanical and biological stressors within the vascular space, and any tricuspid prostheses jailing them is expected to have additional impact on subsequent lead performance. Lead dislodgement or damage may necessitate revision or replacement, which increases the

risk of venous occlusion, as well as infection. Extraction of jailed lead may not be feasible[60]. The reported rate of mid-term dysfunction is not negligible prompting careful patient and device evaluation before considering lead jailing. This includes patients with complete pacemaker dependency or prior use of ICD for treatment of arrhythmias, as well as those with previous CIED infection. In these situations, if doable, lead extraction may be preferred to avoid lead jailing **(Figure 5)**.

Only limited short-term lead safety data exists on leads jailed by stents in both the innominate vein and superior vena cava[61,62]. Case reports for both scenarios have been published at this early stage. Some report lead failure at 2 weeks[63], others freedom from failure at 1 year[59].

Another major concern is the risk of infection with need of lead extraction. The risk of CIED infection increases with re-interventions on the device, from around 1% after the first CIED implantation, and approximately doubling with each additional re-intervention[64]. Other risk factors for CIED infection are listed in **Table 3**. Cardiac implantable electronic devices infections are associated with increased mortality[66]. The number of CIED-infections is expected to increase with the growing pool of CIED-patients and the presence of TTVI material interacting with an infected CIED to complicate treatment. The risk of endocarditis associated with TTVI is not known and existing literature is very limited. There is agreement that CIED infection is best treated with complete CIED system removal[67], typically including TLE. One case report presented successful TLE of both a pacing and a defibrillator lead jailed around a surgical tricuspid bioprosthesis in a patient with CIED pocket infection[68]. However, both leads could be extracted without passing the TV with the extraction sheath. In another case of CIED pocket infection in a patient after TTVR, extraction of the jailed ICD lead was not attempted due to the risk of dislodging and embolizing the bioprosthesis[69]. We found no published reports on patients with indwelling RV pacing or defibrillator lead(s) who had received TEER and afterwards developed CIED infection with need for TLE.

Jailed leads often have long dwell-time and are adherent to the TV leaflets. Percutaneous extraction of jailed leads therefore carries a risk of TV laceration or damage and likely new TR in patients treated with TEER, as well as valve dislodgement after TTVR. There is no literature concerning the risk of TV endocarditis after TTVI in patients with CIED-infection. Case reports indicate that mitral valve endocarditis after transcatheter mitral valve repair has a deleterious prognosis, is best treated by surgery, whereas frequently the

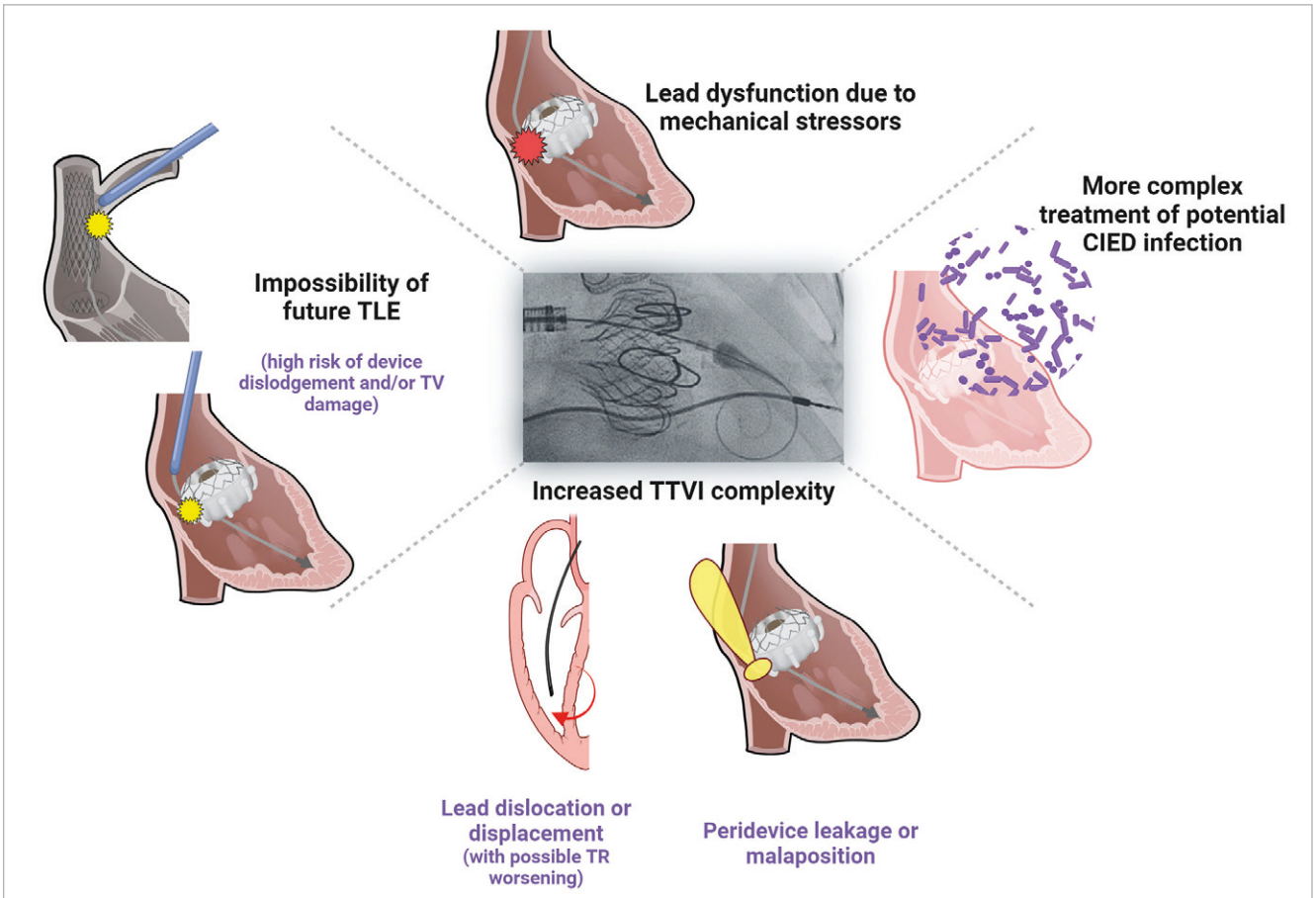

Figure 4. *Main risks associated with lead jailing during transcatheter tricuspid valve interventions. CIED, cardiac implantable electronic device; ICD, implantable cardiac defibrillator; TLE, transvenous lead extraction; TR, tricuspid regurgitation; TTVI, transcatheter tricuspid valve intervention; TV, tricuspid valve.*

alternative of long-lasting antibiotics must be chosen[70,71]. Similarly, extensive valve surgery may not be appropriate in elderly patients undergoing TTVI who will need to be managed conservatively.

5. Risks and benefits of transvenous lead extraction

Lead extraction needs to be carefully evaluated during the planning of TTVI through a multidisciplinary discussion taking into account individual risks of transvenous lead extraction (TLE) and a thorough evaluation of the mechanism and the anatomic relationship between the lead and the valve[6,72].

5.1. RISKS OF TRANSVENOUS LEAD EXTRACTION

TLE has evolved during the last 20 years and updated consensus documents with well-defined indications, definitions and outcomes are available[73,74]. It represents the cornerstone of the management of infected and malfunctioning CIED leads[75-77]. European Heart Rhythm Association surveys[78] and the ELECTRa (European Lead Extraction Controlled) Registry (N = 3510)[79] provided a snapshot of the clinical practices and physicians' attitudes towards TLE in Europe. Despite the development of different techniques[80-85] and approaches[86-88], TLE rarely leads to major complications (1.7%) and death (0.5%)[89-94]. Patient-related (age, sex, comorbidities, indications)[95-100] and lead-related factors (dwell time, lead and insulator type, design, fixation mechanisms, coil technologies,) may be associated with different risk profiles **(Table 4)**[101-111]. The factors with the highest risk are, in decreasing order, female sex, the number of leads to be extracted, the presence of coagulopathy, limited operator or centre experience, and low body mass index. A relationship has been suggested between operator and centre volumes and outcomes[112,113]. Educational pathways[73,114] have been advocated in order to minimize TLE related complications.

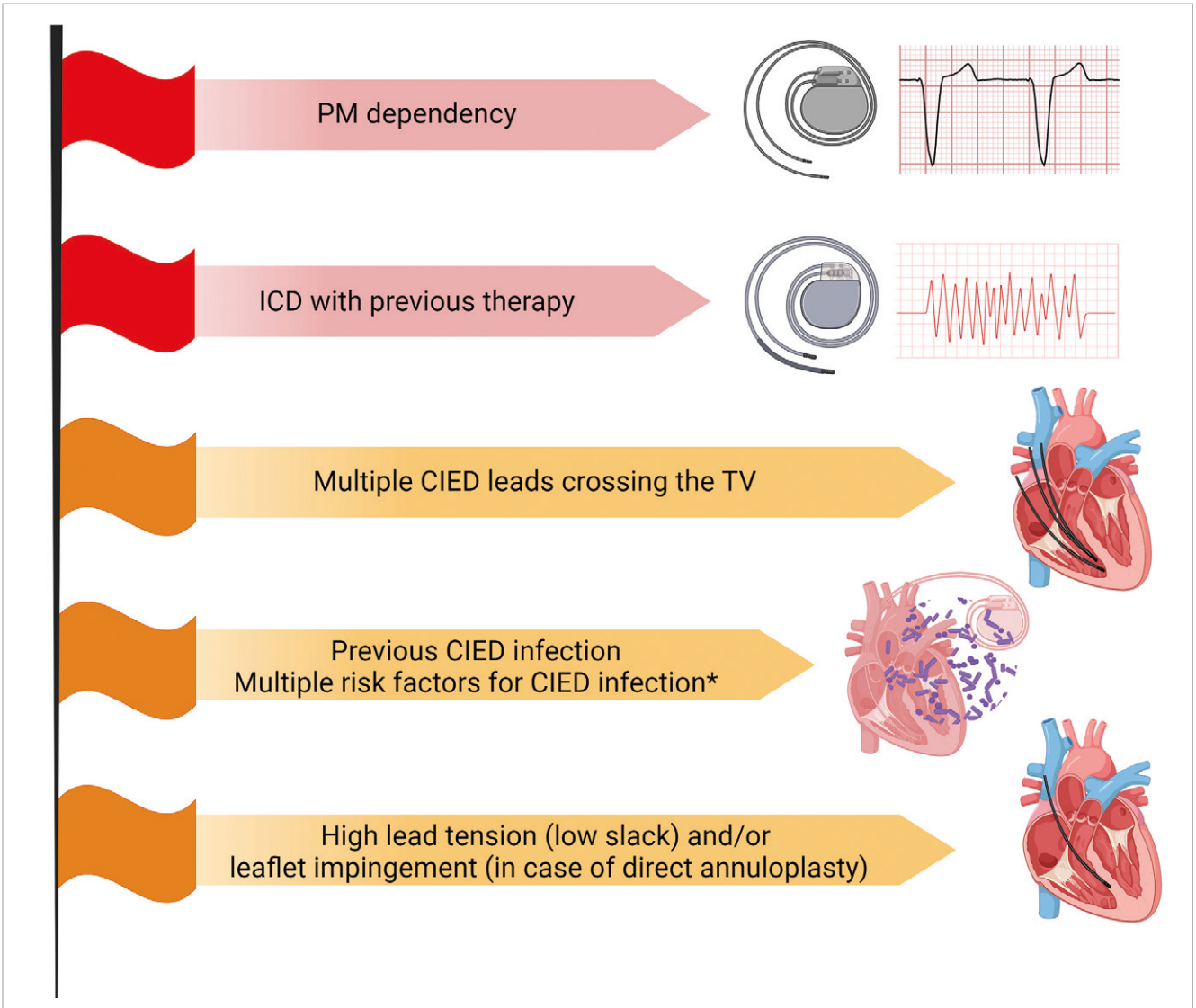

Figure 5. *A proposal to assist multidisciplinary discussion: red and orange flags for lead jailing—in these situations transvenous lead extraction requires careful multidisciplinary discussion before TTVI. (*see Table 3). CIED, cardiac implantable electronic device; ICD, implantable cardiac defibrillator; PM, pacemaker; TTVI, Transcatheter tricuspid valve intervention; TV, tricuspid valve.*

Procedure-related major complications including death were more frequent in women, in case of a dwell time >10 years and when powered sheaths or a femoral approach was used for TLE.

Several TLE risk stratification tools have been published so far but none is routinely used in clinical practice[115-120]. These scores show that the lead dwell time (>10 or 15 years for pacemaker leads and >5 or 10 years for defibrillator leads) and their number (increased risk for each lead beyond one) contribute most to the procedural risk. Machine learning may have an incremental value to predict adverse events, but has yet to be applied on large scale populations[119].

Age has been reported as a factor increasing the risk of complication during TLE, but this factor alone should not be considered a strict exclusion criteria. Indeed, according to a meta-analysis, octogenarians who are the main candidates for TTVI do not seem to have significantly higher mortality and major complications during or after TLE (RR 1.40 and 1.43, respectively, both not statistically significant)[121]. On the other hand, severe left ventricular dysfunction or advanced heart failure increase the risk of complications (by a factor of 2) and the risk of 30-day mortality (by a factor of 1.3–8.5)[75].

5.2. RISKS OF TRICUSPID VALVE DAMAGE DUE TO LEAD EXTRACTION

TLE is associated with a significant increase in the severity of TR in 3.5– 15% of the cases[35,122-128], which is likely explained by adherences between the leads and the TV apparatus[129]. This complication can occur irrespective of the type of the tools used for extraction (passive or mechanical sheath) and is usually due to a new flail leaflet[123]. The most important risk factors for worsening TR following TLE were longer lead dwell time and multiple leads crossing the TV. The use of several tools in the same patient has also been suggested as a potential cause, but is probably linked to the age of the lead and the complexity of adhesions. The medium-term prognosis of patients exposed to traumatic TR was shown to be changed, with new right-sided heart failure symptoms in a study of 208 patients[123], while it was not the case in another smaller study[126]. The risk of damaging the valvular/subvalvular tricuspid apparatus should be taken into consideration when planning TLE before TTVI. A traumatic lesion of the TV could compromise the effectiveness of subsequent TTVI or even render the patient unsuitable for any transcatheter treatment. It is therefore crucial to carefully reassess patients after TLE to confirm the feasibility of TTVI and the most adequate technique to use. As it is not possible to anticipate all technical difficulties, a TLE procedure may be interrupted if a risk of a serious TV damage is detected.

5.3. LEAD EXTRACTION TO REDUCE TRICUSPID REGURGITATION OR PREVENT JAILING

There is limited information on the use of TLE alone as a treatment of chronic lead-related TR. Polewczyk *et al.*[130] studied the effect of TLE in 119 patients with lead-related TR, which improved in only 35%. Results were similar in another series[131], and are even worse when there is coexisting TV annulus dilatation. In this respect, it makes sense that early detection of lead-related TR could allow TLE to be considered before annulus dilatation and extensive fibrosis occur.

For the indication of TLE, the exact mechanism of valve dysfunction must be analysed by 3D TEE and potentially CT[132,133], which also provide information regarding TLE access, in particular the presence of lead fibrosis and vein stenosis[132,134]. In the presence of acute TV dysfunction due to leaflet impingement after CIED implantation, timely TLE

Table 3. Risk factors for cardiac implantable electronic device lead infection.

Risk factors for CIED lead infection ordered from highest to lowest reported risk in each section (adapted from Blomstrom Lundqvist et al, Europace 2020)[65]
Patient-related factors
End stage renal disease
History of CIED infection
Fever prior to implant
Corticosteroid use
Renal failure
Chronic obstructive pulmonary disease
NYHA ≥ 2
Skin disorders
Malignancy
Diabetes mellitus
Heparin bridging
Chronic heart failure
Oral anticoagulants
Device-related factors
Abdominal pocket
≥2 leads
Dual chamber device

CIED, cardiac implantable electronic device; NYHA, New York Heart Association

Table 4. Risk factors for severe transvenous lead extraction complication.

Risk factors for severe TLE complication (adapted from Deharo et al, Europace 2012[73] and Kusumoto et al. Heart Rhythm 2017[75]
Patient-related factors
Low body mass index (<25 kg/m^2)
Female sex
Comorbidities, age, poor LV function, renal failure, coagulopathy, large vegetations
Occluded or severely stenosed venous access
Congenital heart disease with complex cardiac anatomy
Prior cardiac surgery lowers the risk of complications
Technical factors
Number of leads present or extracted
Passive fixation mechanism
Lead body geometry (non-isodiametric)
ICD lead
Dwell time greater than 1 year
Special/damaged/deficient leads
Limited operator and centre experience

LV, left ventricle; TLE, transvenous lead extraction; ICD, implantable cardioverter defibrillator

(within 6 months) seems appropriate in order to minimize the risk of complication and avoid leaflet scarring.

When a lead is anticipated to prevent effective repair with TEER, a multidisciplinary discussion should take place considering the risk and benefits of TLE to facilitate TEER. In cases of TTVR, TLE combined with valve sparing lead implantation, or rarely transvalvular implantation through the new valve, should be weighed against the potential risks associated with lead jailing. Given the uncertainties regarding long-term consequences of jailing, lead extraction should also be discussed before stent placement in the superior vena cava[75,135].

6. Valve-sparing pacing and implantable cardioverter-defibrillator strategies

Valve-sparing alternative pacing strategies have been proposed to mitigate lead-related TR and minimize interaction with implanted tricuspid devices **(Table 5)**[136]. Since many patients undergoing TTVI have chronic atrial fibrillation, atrial pacing plays a limited role. Options for long-term ventricular pacing include coronary sinus pacing, surgical epicardial lead placement, LCPM implantation. Coronary sinus pacing presents an appealing option as it avoids valve disturbances. However, challenges such as lead instability, phrenic nerve capture, and high capture thresholds limit its widespread adoption[137]. For safety, particularly in pacemaker-dependent patients, it may be appropriate to implant two leads in the coronary sinus and use quadripolar lead(s) (see **Figure 6**).

Table 5. Alternative pacing and implantable cardioverter defibrillator strategy in case of percutaneous tricuspid valve intervention.

Pacemaker alternatives	ICD alternatives
Ventricular pacing through coronary sinus	Subcutaneous-ICD (S-ICD™)
Epicardial pacing: may allow for dual chamber pacing or CRT	Subcutaneous-ICD (S-ICD™)
Leadless pacing (Micra™ or Aveir™): may allow for AV synchrony (Micra AV™) or dual chamber pacing (Aveir DR™)	S-ICD + leadless RV device for ATP and pacing (Empower™)
Left ventricular leadless pacing (WiSE-CRT™) Associated with Micra™ or Aveir™: allows for CRT	Transvenous ICD with lead coil in the middle cardiac vein or azygos vein and pace-sense lead in a coronary sinus branch (DF-1/IS-1 connection)

CRT, cardiac resynchronization therapy; AV, atrio-ventricular; ICD, implantable cardioverter defibrillator; S-ICD, subcutaneous implantable cardioverter defibrillator; RV, right ventricle; ATP, antitachycardia pacing.

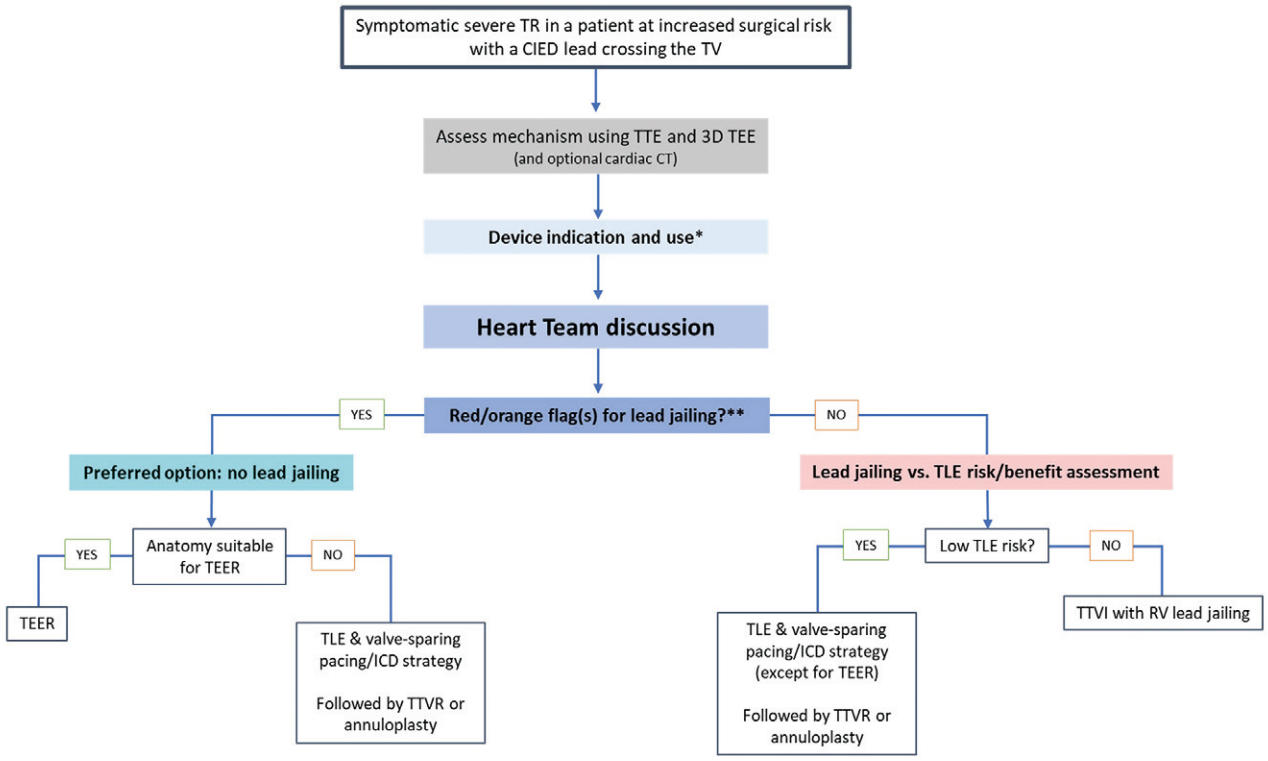

Figure 6. *Proposed algorithm for the management of TTVI candidates with symptomatic severe TR and a CIED lead crossing the TV. *Perform device interrogation and record underlying heart rhythm, paced/sensed event counters, arrhythmia history, battery and lead information (see also Table 6). **Red/orange flag(s) for lead jailing? PM dependency, ICD with previous therapy, multiple CIED leads crossing the TV, previous CIED infection, multiple risk factors for CIED infection, high lead tension (low slack) and/or leaflet impingement (in case of direct annuloplasty) (see also Figure 5). CIED, cardiac implantable electronic device; ICD, implantable cardiac defibrillator; RV, right ventricle; TLE, transvenous lead extraction; TR, tricuspid regurgitation; T-TEER, tricuspid transcatheter edge-to-edge repair; TTVI, transcatheter tricuspid valve intervention; TTVR, transcatheter tricuspid valve replacement; TV, tricuspid valve.*

Epicardial lead placement also avoids damage to endocardial structures but necessitates surgical access to the pericardium, which might be difficult in patients indicated for TTVI. In addition, it exhibits higher lead failure rates and often poorer electrical parameters for pacing/sensing compared with conventional transvenous leads and is often not ideal in case of previous heart surgery. Commercially available LCPM systems have low procedural and post-operative complication rates and can also be applied after TTVR **(Figure 6)**. Although unlikely, LCPM implantation does not necessarily exclude the apparition of TV dysfunction[29], in particular when implanted in septal position near the tricuspid valve annulus[28]. In an observational study of 54 patients receiving a LCPM, Arps et al.[138] found no alteration in TV function before and after implantation. In a small randomized study, Garweg et al.[139] compared 27 patients implanted with a Micra™ LCPM (Medtronic Inc., Minneapolis, MN, USA) to 24 other patients implanted with a conventional VVIR pacemaker and found no significant difference in TR between the two systems. Similarly, in a series of 23 patients implanted with a Micra™ VR or a Nanostim™ LCPM (Abbott Medical, Chicago, IL, USA), Salaun and colleagues reported no interaction of the devices with TV or RV function or anatomy[30]. Implanting physicians should be aware of potential interactions between RV LCPM and the material used for TTVI and adapt their implantation technique. A recent small series of patients implanted with LCPM following transcatheter or surgical TV repair or replacement confirms the feasibility and safety of such an approach. It also provides some technical guidance using fluoroscopic landmarks to implant the device at a site distant from the TV apparatus[140]. In case of the necessity of resynchronization, a total leadless CRT can be delivered with a combination of Micra™ or Aveir™ (Abbott Medical, Chicago, IL, USA) and WiSE-CRT™ (EBR Systems, Sunnyvale, CA, USA) systems[141].

His bundle pacing is another option, enabling a more physiologic electromechanical activation of the ventricles. Studies have shown no alteration of TV function with even TR reduction in some cases[25]. However, interactions with the TV cannot be ruled out with this technique and implantation may be difficult in case of previous TTVI. Additionally, His bundle pacing leads can be impacted by mechanical disturbances to the conduction system potentially caused by TTVR and will have to be monitored intra- and post-operatively. TV crossing to achieve left bundle branch area (LBBA) pacing (rather than conventional pacing) is an acceptable option in patients with high pacing need or those with reduced LVEF requiring resynchronization. Careful implantation (possibly under echocardiographic guidance) with assessment of valve function may help to overcome the challenges associated with this technique after TTVI[142]. In the future, LCPM allowing for LBBA pacing may become available. A very limited experience has been reported with the WiSE CRT system, which was not entirely leadless[143].

If an ICD is necessary, a subcutaneous (S-ICD) or extra-vascular ICD (EV-ICD) are good options. The S-ICD can also be associated with the Empower™ Leadless pacemaker (Boston Scientific, St. Paul, MN, USA), designed to be paired with the S-ICD to provide pacing or ATP therapies at the time they are needed[144]. However, this system is currently not commercially available. Transvenous ICD lead placement alternatives exist, including positioning of the defibrillation coil in the middle cardiac vein of the coronary sinus or in the azygos vein, and a coronary sinus lead for sensing and pacing in a coronary sinus branch.

Ideally, the options of valve-sparing pacing and ICD therapy should be discussed in CIED candidates with relevant TR who may benefit from TTVI in the future. In these patients, the Heart Team discussion will help selecting the best pacing strategy to avoid leads crossing the TV (i.e. ventricular pacing with a leadless pacemaker or with lead(s) in the coronary sinus branches, subcutaneous, or extravascular ICD therapy).

It is reasonable to schedule pacing system interventions such as generator replacement, lead revision, or upgrade procedures prior to the planned TTVI to reduce the risk of infection.

7. Lead management in cardiac implantable electronic devices patients with planned transcatheter tricuspid valve intervention

All CIED patients with transvalvular leads who are planned for TTVI should undergo evaluation by a Heart Team[6] consisting of a cardiologist with dedicated TTVI expertise, a cardiac surgeon, a lead extraction specialist and a cardiac imaging specialist **(Figure 7)**. The goal of the discussion is to answer the following questions:

(1) What is the aetiology of the valvular pathology? Is it lead-related?

(2) What is the risk associated with lead jailing depending on lead characteristics and use? Does the planned TTVI require prior TLE to facilitate the procedure and/or avoid lead jailing and what are the risks of such a TLE?

(3) Is there a need for urgent temporary pacing during the procedure?

(4) What are the options for valve-sparing pacing and ICD therapy?

Since TLE may be associated with damage to the leaflets or the sub-valvular apparatus of the TV, as well as serious disabling or life-threatening complications, multidisciplinary evaluation has to integrate a thorough risk-benefit-analysis taking into account life-expectancy, co-morbidities and valvular pathology of the individual patient.

In summary, the Heart Team should carefully weigh the risks and benefits of TLE. Examples of scenarios favouring TLE include patients with leads implanted for less than 10 years and those in whom advanced imaging has clearly demonstrated a lead-related TR mechanism.

7.1. ASSESS TR AETIOLOGY AND SUITABILITY FOR TRANCATHETER TRICUSPID VALVE INTERVENTION

Assessment of the mechanism of TR is essential in all patients considered for TTVI. This should be done using transthoracic and transoesophageal echocardiography in 2D and 3D modes, and CT if necessary.

A recent classification proposes a distinct aetiology group for patients with CIED-related TR, in addition to the traditional functional/ secondary and organic/primary TR categories[54,145]. However, determining whether TR is related to a CIED lead can be challenging. Advanced imaging techniques, such as 3D echocardiography and multiplanar

reconstructions, help to assess lead position, trajectory and interactions with anatomical structures in real time (**Figure 1** and **Moving images**)[146,147]. In advanced stages, differentiation between lead-related and lead-associated TR may be difficult due to RV remodelling. Cardiac CT, with its higher spatial resolution, can help diagnosing lead-leaflet interaction, measuring the annulus, assessing adjacent structures (e.g. right coronary artery) and anticipating the need for lead jailing[148]. Although less relevant for TEER[149], it is mandatory for the evaluation of valve replacement and annuloplasty.

In addition, it is critical to report the number and exact location of CIED leads, as this may influence the treatment strategy.

7.2. ASSESS CARDIAC IMPLANTABLE ELECTRONIC DEVICES FUNCTION BEFORE THE PROCEDURE

In a patient with a pacemaker or ICD lead, the main risks during TTVR are damaging the lead(s) mainly the ventricular one passing through the TV or dislodgment of the lead(s) related to the catheter manipulation. Damage of the leads may also occur late after the intervention.

Before any TTVI, complete details of the implanted system must be available **(Figure 7)**. For ICD, the type and frequency of therapy use should be recorded. **Figure 5** highlights the two main periprocedural concerns: pacemaker dependency and the presence of an ICD with prior therapy. In case of full pacemaker

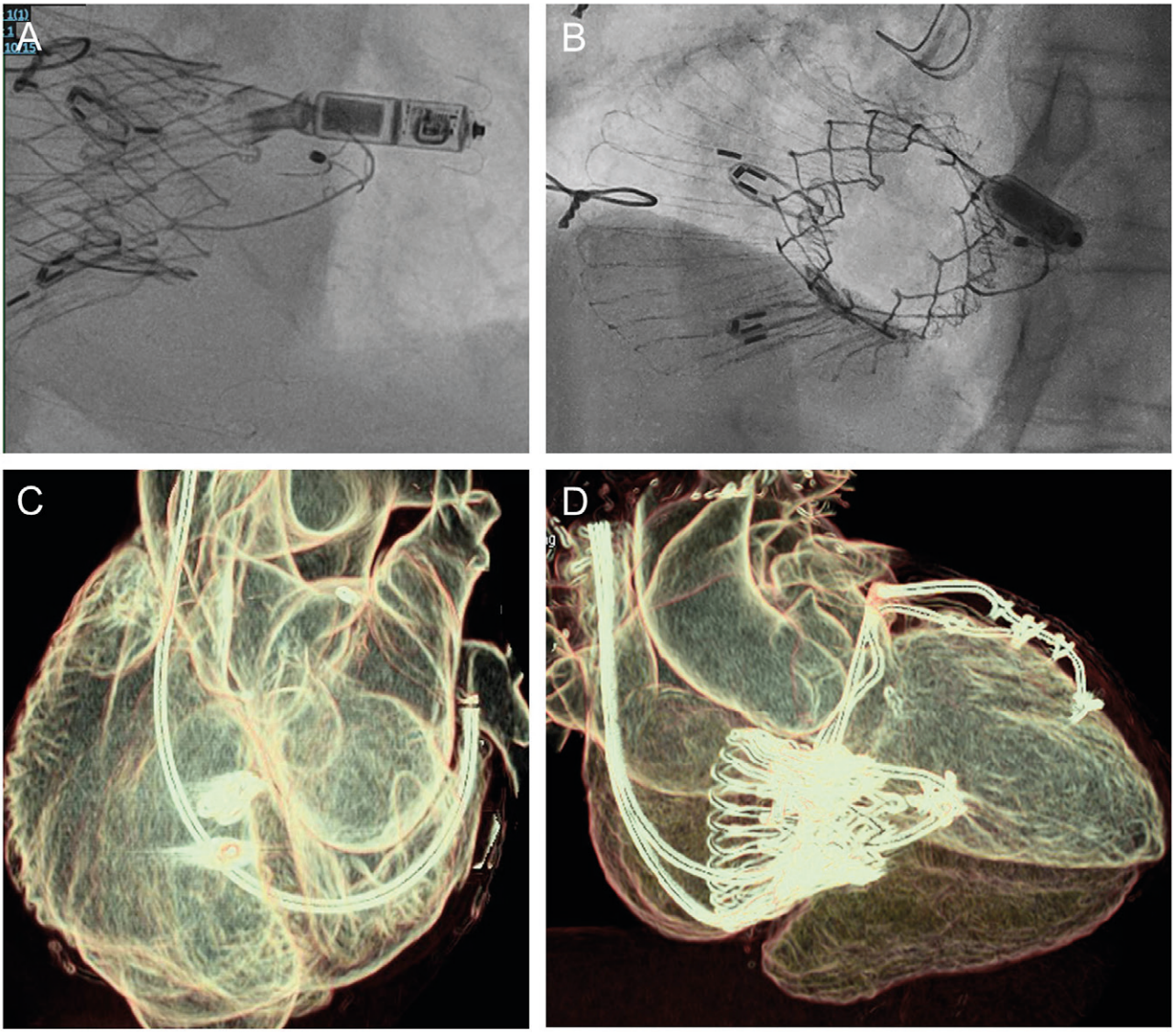

Figure 7. *Example of valve-sparing implantation techniques after transcatheter tricuspid valve interventions. (A) Implantation of a LCPM after TTVR with delivery tool crossing the transcatheter transjugular LUX valve system (RAO). (B) Definitive position of the LCPM in the same case (not shown in this LAO projection, the LCPM is implanted away from the LUX valve system). (C) A pacing lead implanted in a coronary sinus branch after TEER. (D) Two pacing leads implanted in two distinct coronary sinus branches (PPM-dependent patient) after TTVR with the LUX valve system. LAO, left anterior oblique view; LCPM, leadless cardiac pacemaker; RAO, right anterior oblique view; TEER, transcatheter edge-to-edge repair; TTVR, transcatheter tricuspid valve replacement.*

dependency, an asynchronous mode can be programmed just before the intervention to avoid sensing interferences. The need for temporary pacing should be anticipated (see specific section).

Reassessment of the electrical parameters has to be performed immediately after the procedure, and compared with the pre-operative measurements to detect potential lead(s) dysfunction.

Ideally, as the damage of the leads may occur late after the intervention (even if the probability is largely unknown), a remote monitoring follow-up is the preferred option to detect late lead dysfunction.

7.3. EVALUATE THE NEED FOR (URGENT) TEMPORARY PACING DURING TRANSCATHETER TRICUSPID VALVE INTERVENTION

Based on device interrogation, in particular if the patient is pacing dependent (i.e. has inadequate or even absent intrinsic rhythm and therefore can suffer significant symptoms or cardiac arrest after cessation of pacing) the risks of lead dislodgement or damage during TTVI should be carefully anticipated[150]. In general, it seems reasonable to ensure the stability of electrical parameters after CIED implantation whenever possible, if TTVI is planned.

After TTVI, new conduction disturbances have been reported **(Table 2)** and are much more frequent after valve replacement[45]. Therefore, risk anticipation and preventive measures need to be integrated into pre-procedural planning.

In patients considered high risk, i.e. those who are pacemaker-dependent or may become pacemaker-dependent, the interventional team should be prepared to install preventive or bailout temporary pacing strategies that preferably do not cross the TV. This includes preemptive coronary sinus lead placement, as well as emergency pacing options like LV or RV wire pacing[6]. RV temporary pacing leads should be avoided during TTVR, since lead positioning and retrieval can be challenging. In case of temporary pacing failure, transient patch pacing may be required, but can be generally avoided with adequate planning.

8. Management of a patient with a jailed lead

8.1. ORGANIZE MULTIDISCIPLINARY FOLLOW-UP (INFORM PATIENT AND CAREGIVERS)

All CIED patients with jailed lead(s) after TTVI should be evaluated by an electrophysiologist with specific cardiac device expertise, in addition to the interventional cardiologist with TTVI expertise. The multidisciplinary follow-up should focus on:

(1) The TTVI material jailing the lead(s), including all details of potential interactions between this material and the implanted lead(s)

(2) The indication for CIED implantation and the current underlying cardiac rhythm (i.e. pacemaker dependence or not) and device use (percentage of pacing in each cavity and previous arrhythmia and therapy delivered by the device in the case of an ICD).

The team in charge of the follow-up should ensure that the patient and his caregivers are properly informed about potential lead failure[75] and/or device infection[65]. Due to the risks associated with CIED infection, all CIED procedures should be performed using all available preventive measures[67]. Appropriate follow-up of the CIED and TTVI devices should be planned (see following section) with particular attention to signs of lead failure and interactions between the TTVI material and lead(s) **(Figure 8)**.

8.2. PLANNING FOR CARDIAC IMPLANTABLE ELECTRONIC DEVICES FOLLOW-UP

An immediate peri-procedural interrogation of the CIED is indicated to detect damage to hardware **(Table 6)**. The 2021 ESC guidelines on earlier detection of technical issues in pacemaker and CRT patients, particularly those at increased risk[31]. The 2022 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death recommend remote monitoring also for patients with ICD to reduce inappropriate ICD-therapy[151]. Follow-up of a patient with jailed lead(s) is comparable to a patient with a lead under alert/recall[152]. In cases where acoustic or vibration-based device alerts are available, they should be activated, and patients instructed accordingly. If alerts and remote follow-up are not available, frequent (every 3 months) outpatient visits are required **(Figure 8)**. Close follow-up is especially relevant in cases of pacing or ICD dependency.

Regular echocardiographic exams are required to assess the function of the repaired or replaced TV and whether the jailed lead(s) may affect long-term treatment efficacy **(Table 6)**.

8.3. MANAGEMENT AND TREATMENT OF DEVICE-RELATED INFECTION

There is currently insufficient data to guide the management of patients with infectious complications after TTVI. As shown in **Figure 8**, in this highly concerning situation therapeutic decisions should be taken in a multidisciplinary way and rely on patient status and preferences, as well as the type of infection, which may be limited to the pocket or a bloodstream infection with lead or valve endocarditis.

As a first step, the extent of a desired treatment should be defined according to the patient's preference, especially since the population qualifying for TTVI is elderly and at high surgical risk with multiple co-morbidities **(Figure 8)**.

With regard to the management of jailed leads in patients with transcatheter TV devices, when TLE must be performed due to infection, two different scenarios need to be differentiated: infection without TV involvement vs. infection with TV involvement (i.e. TV endocarditis).

In patients without signs of involvement of the TV device, an approach with explantation of all parts of the system including transvenous extraction of all leads including jailed leads and preservation of the TV device may be attempted, although challenging[68]. In patients with infection involving the TV, a curative treatment concept consists of surgical explant of the TV device and surgical TV repair or replacement, as well as CIED explant including extraction of all leads[153].

In both scenarios, adequate antibiotic therapy is started and maintained, ideally and if possible guided by infectious disease specialists. If CIED reimplantation is needed, valve-sparing reimplantation techniques should be preferred **(Figure 8)**.

In patients deemed too frail or unwilling to undergo a TLE attempt (likely a high proportion of the patients undergoing TTVI), long-term suppressive antibiotic treatment can be offered, considering the less favourable infectious prognosis

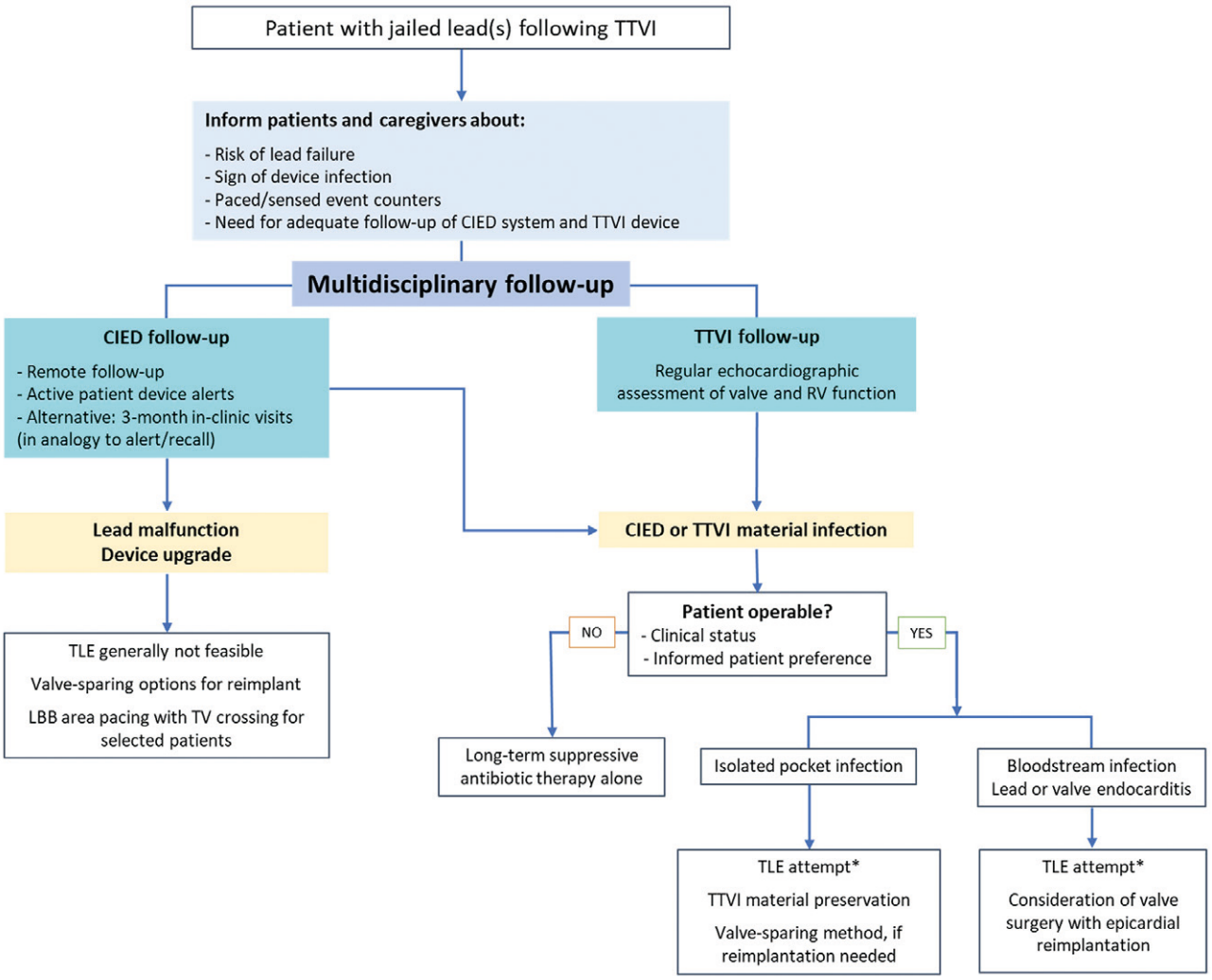

Figure 8. *Proposed algorithm for the management of patients with a jailed RV CIED lead. CIED, cardiac implantable electronic device; LBB, left bundle branch; TTVR, transcatheter valve replacement; RV, right ventricle; TLE, transvenous lead extraction; TTVI, transcatheter tricuspid valve intervention.*

associated with such a strategy[153-155]. Local ultra-high dose antibiotic administration has been proposed, but the Task Force considers it investigational at this time[156].

8.4. MANAGEMENT OF MALFUNCTIONING JAILED LEADS AND UPGRADE PROCEDURES

In case of lead malfunction, an electrophysiologist with specific device expertise should take the most appropriate decision, depending on patient clinical status and the type of lead malfunction, most likely to replace the lead. However, removal of jailed leads is generally not an option and the reimplantation or upgrade (i.e. from conventional pacing to CRT or to ICD therapy) should favour a valve-sparing option (see specific section). For example, for CRT, a coronary sinus lead is preferred to an LBBA pacing lead. For defibrillation, extravascular or coronary sinus/azygous vein options are preferred over endovascular RV defibrillation lead implantation. In the event of vein occlusion and the need for a new lead, venoplasty or implantation of a contralateral lead is mandatory, as TLE is not an option to achieve vein patency.

Table 6. CIED follow-up in patients with TTVI and jailed leads.

CIED interrogation	Pacing threshold
	Lead impedance
	Sensing value
	Pacing/sensing percentages
	ICD therapies
	Oversensing issues
	Risk of asystole due to pacing inhibition
	Risk of inappropriate ICD therapy
Fluoroscopy	In case CIED interrogation shows abnormalities
Echocardiography	Function of the repaired or replaced TV

CIED, cardiac implantable electronic device; ICD, implantable cardioverter defibrillator; TV, tricuspid valve.

9. Conclusion

This scientific statement document emphasizes the importance of the Heart Team management and decision-making of TTVI candidates for the treatment of symptomatic severe TR and a lead crossing the TV. Specific scientific data on lead dysfunction, infectious risk and durability of outcomes after TTVI are still scarce and could be improved through dedicated registries. However, "red flags" that may indicate a higher risk of adverse events following lead jailing need to be considered in pre-interventional discussions and alternatives evaluated. TLE before TTVI remains a viable option, integrating the higher risk in this fragile, often elderly patient population. In situations where leads are jailed, frequent monitoring is desirable, particularly in patients who are pacemaker-dependent or who have an ICD indication for secondary prevention.

10. Summary position

Scientific evidence concerning TTVI in patients with CIED leads is scarce and comes from observational studies or first-in-human reports.

CIED-related tricuspid regurgitation: Interactions between transvalvular CIED leads and the TV may result into CIED-related TR and predisposing factors have been identified. Physician awareness around this complication and echocardiographic follow-up of patients at risk are needed to allow for early detection and management of CIED-related TR.

Potential CIED lead issues with transcatheter tricuspid valve interventions: between 11.8 and 36% of candidates for TTVI have transvenous CIED leads. Attitudes towards lead management in TTVI are heterogeneous due to the lack of scientific evidence. So far, experience with lead jailing is limited but lead failure or dislodgement have been reported and are a matter of concern. High risk situations for lead jailing and the general patient clinical condition should be taken into consideration before final decision.

Due to the novelty of the technique, there are very few reports of CIED-related infections in patients with jailed leads and management is uncertain in this high-risk population. The consensual management of CIED infections applies to patients who have had TTVI but the approach must be adapted on a case-by-case basis, particularly in the event of jailed leads.

Transvenous lead extraction to prepare for transcatheter tricuspid valve intervention: contemporary data show that complications of transvenous lead extraction are rare but can occur. Peri-procedural mortality is reported at 0.5% and major complications at 1.7%. TR reduction following TLE is unlikely and the TV can be damaged by TLE. Risk factors for complicated TLE need to be taken into account for individualized Heart Team decision-making. Safe and feasible valve-sparing PPM/ICD techniques have been extensively studied out of TTVI. Small series emphasize their role in patients with TTVI.

Heart Team discussion and patient engagement: due to the above-mentioned lack of strong scientific evidence in this area, we believe that a Heart Team case-by-case discussion is essential for each patient with a CIED who is scheduled for TTVI. Follow-up of a patient with jailed lead(s) after TTVI needs particular care and dedicated expertise to assess both TTVI result and lead integrity, as well as to manage complications. Due to the novelty and lack of knowledge, CIED patients who are candidates for TTVI should be informed about the benefits and risks of each approach.

Need for increased evidence: prospective systematic collection of CIED data in patients included in TTVI studies is encouraged. Reporting of longer-term systematic CIED follow-up data is desirable.

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Supplementary data

Moving images

References

1. https://eatlas.escardio.org/Atlas/ESC-Atlas-of-Cardiology.
2. Defaye P, Biffi M, El-Chami M, Boveda S, Glikson M, Piccini J et al. Cardiac pacing and lead devices management: 25 years of research at EP Europace journal. *Europace*. 2023; 25:euad202.
3. Tribouilloy C, Bohbot Y, Kubala M, Ruschitzka F, Popescu B, Wendler O et al. Characteristics, management, and outcomes of patients with multiple native valvular heart disease: a substudy of the EURObservational Research Programme Valvular Heart Disease II Survey. *Eur Heart J*. 2022;43: 2756–66.
4. d'Arcy JL, Coffey S, Loudon MA, Kennedy A, Pearson-Stuttard J, Birks J et al. Large-scale community echocardiographic screening reveals a major burden of undiagnosed valvular heart disease in older people: the OxVALVE Population Cohort Study. *Eur Heart J*. 2016;37:3515–22.
5. Offen S, Strange G, Playford D, Celermajer DS, Stewart S. Prevalence and prognostic impact of tricuspid regurgitation in patients with cardiac implantable electronic devices: from the national echocardiography database of Australia. *Intern J Cardiol*. 2023;370:338–44.
6. Andreas M, Burri H, Praz F, Soliman O, Badano L, Barreiro M et al. Tricuspid valve disease and cardiac implantable electronic devices. *Eur Heart J*. 2024;45:346–65.
7. Van De Heyning CM, Elbarasi E, Masiero S, Brambatti M, Ghazal S, Al-Maashani S et al. Prospective study of tricuspid regurgitation associated with permanent leads after cardiac rhythm device implantation. *Can J Cardiol*. 2019;35:389–95.
8. Paniagua D, Aldrich HR, Lieberman EH, Lamas GA, Agatston AS. Increased prevalence of significant tricuspid regurgitation in patients with transvenous pacemakers leads. *Am J Cardiol*. 1998;82:1130–2.
9. Barclay JL, Cross SJ, Leslie SJ. Entanglement of passive fix ventricular lead in tricuspid valve. *Pacing Clin Electrophysiol*. 2008;31;138.
10. Novak M, Dvorak P, Kamaryt P, Slana B, Lipoldova J. Autopsy and clinical context in deceased patients with implanted pacemakers and defibrillators: intracardiac findings near their leads and electrodes. *Europace*. 2009;11: 1510–6.
11. Schilling RJ. Pacing lead entanglement in the tricuspid valve appartus during implantation. *Europace*. 1999;1:201.
12. Rothschild DP, Goldstein JA, Kerner N, Abbas AE, Patel M, Wong WS. Pacemaker-induced tricuspid regurgitation is uncommon immediately post-implantation. *J Interv Card Electrophysiol*. 2017;49:281–7.
13. Lin G, Nishimura RA, Connolly HM, Dearani JA, Sundt TM, Hayes DL. Severe symptomatic tricuspid valve regurgitation due to permanent pacemaker or implantable cardioverter-defibrillator leads. *J Am Coll Cardiol*. 2005;45:1672–5.
14. Chang JD, Manning WJ, Ebrille E, Zimetbaum PJ. Tricuspid valve dysfunction following pacemaker or cardioverter-defibrillator implantation. *J Am Coll Cardiol*. 2017;69:2331–41.
15. Res JC, De Cock CC, Van Rossum AC, Schreuder J. Entrapment of tined leads. *Pacing Clin Electrophysiol*. 1989;12:1583–5.
16. Fürstenberg S, Bluhm G, Olin C. Entrapment of an atrial tined pacemaker electrode in the tricuspid valve—a case report. *Pacing Clin Electrophysiol*. 1984;7:760–2.
17. Rajappan K. Permanent pacemaker implantation technique: part II. *Heart*. 2009;95:334–42.
18. Schleifer JW, Pislaru SV, Lin G, Powell BD, Espinosa R, Koestler C et al. Effect of ventricular pacing lead position on tricuspid regurgitation: a randomized prospective trial. *Heart Rhythm*. 2018;15:1009–16.
19. Tatum R, Maynes EJ, Wood CT, Deb AK, Austin MA, O'Malley TJ et al. Tricuspid regurgitation associated with implantable electrical device insertion: a systematic review and meta-analysis. *Pacing Clin Electrophysiol*. 2021;44:1297–302.
20. Anvardeen K, Rao R, Hazra S, Hay K, Dai H, Stoyanov N et al. Lead-specific features predisposing to the development of tricuspid regurgitation after endocardial lead implantation. *CJC Open*. 2019;1:316–23.
21. Al-Bawardy R, Krishnaswamy A, Bhargava M, Dunn J, Wazni O, Tuzcu EM et al. Tricuspid regurgitation in patients with pacemakers and implantable cardiac defibrillators: a comprehensive review. *Clin Cardiol*. 2013;36: 249–54.
22. Lee RC, Friedman SE, Kono AT, Greenberg ML, Palac RT. Tricuspid regurgitation following implantation of endocardial leads: incidence and predictors. *Pacing Clin Electrophysiol*. 2015;38:1267–74.
23. Fanari Z, Hammami S, Hammami MB, Hammami S, Shuraih M. The effects of right ventricular apical pacing with transvenous pacemaker and implantable cardioverter defibrillator on mitral and tricuspid regurgitation. *J Electrocardiol*. 2015;48:791–7.
24. Vaturi M, Kusniec J, Shapira Y, Nevzorov R, Yedidya I, Weisenberg D et al. Right ventricular pacing increases tricuspid regurgitation grade regardless of the mechanical interference to the valve by the electrode. *Eur J Echocardiogr*. 2010;11:550–3.
25. Zaidi SMJ, Sohail H, Satti DI, Sami A, Anwar M, Malik J et al. Tricuspid regurgitation in his bundle pacing: a systematic review. *Ann Noninvasive Electrocardiol*. 2022;27:e12986.
26. Li X, Zhu H, Fan X, Wang Q, Wang Z, Li H et al. Tricuspid regurgitation outcomes in left bundle branch area pacing and comparison with right ventricular septal pacing. *Heart Rhythm*. 2022;19:1202–3.
27. Bednarek A, Kielbasa G, Moskal P, Ostrowska A, Bednarski A, Sondej T et al. Left bundle branch area pacing improves right ventricular function and synchrony. *Heart Rhythm*. 2024;21:2234–41.
28. Hai JJ, Mao Y, Zhen Z, Fang J, Wong CK, Siu CW et al. Close proximity of leadless pacemaker to tricuspid annulus predicts worse tricuspid regurgitation following septal implantation. *Circ Arrhythm Electrophysiol*. 2021;14:e009530.
29. Beurskens NEG, Tjong FVY, de Bruin-Bon RHA, Dasselaar KJ, Kuijt WJ, Wilde AAM et al. Impact of leadless pacemaker therapy on cardiac and atrioventricular valve function through 12 months of follow-up. *Circ Arrhythm Electrophysiol*. 2019;12:e007124.
30. Salaun E, Tovmassian L, Simonnet B, Giorgi R, Franceschi F, Koutbi-Franceschi L et al. Right ventricular and tricuspid valve function in patients chronically implanted with leadless pacemakers. *Europace*. 2018;20: 823–8.
31. Glikson M, Nielsen JC, Kronborg MB, Michowitz Y, Auricchio A, Barbash IM et al. 2021 ESC guidelines on cardiac pacing and cardiac resynchronization therapy. *Eur Heart J*. 2021;42:3427–520.
32. Yu YJ, Chen Y, Lau CP, Liu YX, Wu MZ, Chen YY et al. Nonapical right ventricular pacing is associated with less tricuspid valve interference and long-term progress of tricuspid regurgitation. *J Am Soc Echocardiogr*. 2020;33:1375–83.

33. De Cock CC, Vinkers M, Van Campe LC, Verhorst PM, Visser GA. Long-term outcome of patients with multiple (≥3) noninfected transvenous leads: a clinical and echocardiographic study. *Pacing Clin Electrophysiol.* 2000;23:423–6.

34. Wang TKM, Akyuz K, Mentias A, Kirincich J, Duran Crane A, Xu S et al. Contemporary etiologies, outcomes, and novel risk score for isolated tricuspid regurgitation. *JACC Cardiovasc Imaging.* 2022;15:731–44.

35. Park S-J, Gentry JL, Varma N, Wazni O, Tarakji KG, Mehta A et al. Transvenous extraction of pacemaker and defibrillator leads and the risk of tricuspid valve regurgitation. *JACC Clin Electrophysiol.* 2018;4:1421–8.

36. Dreyfus J, Audureau E, Bohbot Y, Coisne A, Lavie-Badie Y, Bouchery M et al. TRI-SCORE: a new risk score for in-hospital mortality prediction after isolated tricuspid valve surgery. *Eur Heart J.* 2022;43:654–62.

37. Asmarats L, Perlman G, Praz F, Hensey M, Chrissoheris MP, Philippon F et al. Long-term outcomes of the FORMA transcatheter tricuspid valve repair system for the treatment of severe tricuspid regurgitation: insights from the first-in-human experience. *JACC Cardiovasc Interv.* 2019;12:1438–47.

38. Lurz J, Rommel KP, Unterhuber M, Besler C, Noack T, Borger M et al. Safety and efficacy of transcatheter edge-to-edge repair of the tricuspid valve in patients with cardiac implantable electronic device leads. *JACC Cardiovasc Interv.* 2019;12:2114–6.

39. Hahn RT, George I, Kodali SK, Nazif T, Khalique OK, Akkoc D et al. Early single-site experience with transcatheter tricuspid valve replacement. *JACC Cardiovasc Imaging.* 2019;12:416–29.

40. Lauten A, Figulla HR, Unbehaun A, Fam N, Schofer J, Doenst T et al. Interventional treatment of severe tricuspid regurgitation: early clinical experience in a multicenter, observational, first-in-man study. *Circ Cardiovasc Interv.* 2018;11:e006061.

41. Anderson JH, McElhinney DB, Aboulhosn J, Zhang Y, Ribichini F, Eicken A et al. Management and outcomes of transvenous pacing leads in patients undergoing transcatheter tricuspid valve replacement. *JACC Cardiovasc Interv.* 2020;13:2012–20.

42. Taramasso M, Gavazzoni M, Pozzoli A, Alessandrini H, Latib A, Attinger-Toller A et al. Outcomes of TTVI in patients with pacemaker or defibrillator leads: data from the TriValve registry. *JACC Cardiovasc Interv.* 2020;13:554–64.

43. Nickenig G, Weber M, Schueler R, Hausleiter J, Näbauer M, von Bardeleben RS et al. 6-Month outcomes of tricuspid valve reconstruction for patients with severe tricuspid regurgitation. *J Am Coll Cardiol.* 2019;73:1905–15.

44. Wild MG, Löw K, Rosch S, Gerçek M, Higuchi S, Massberg S et al. Multicenter experience with the transcatheter leaflet repair system for symptomatic tricuspid regurgitation. *JACC Cardiovasc Interv.* 2022;15:1352–63.

45. Webb JG, Chuang AM, Meier D, von Bardeleben RS, Kodali SK, Smith RL et al. Transcatheter tricuspid valve replacement with the EVOQUE system: 1-year outcomes of a multicenter, first-in-human experience. *JACC Cardiovasc Interv.* 2022;15:481–91.

46. Kodali S, Hahn RT, Makkar R, Makar M, Davidson CJ, Puthumana JJ et al. Transfemoral tricuspid valve replacement and one-year outcomes: the TRISCEND study. *Eur Heart J.* 2023;44:4862–73.

47. Wild MG, Lubos E, Cruz-Gonzalez I, Amat-Santos I, Ancona M, Andreas M et al. Early clinical experience with the TRICENTO bicaval valved stent for treatment of symptomatic severe tricuspid regurgitation: a multicenter registry. *Circ Cardiovasc Interv.* 2022;15:e011302.

48. Nickenig G, Lurz P, Sorajja P, von Bardeleben RS, Sitges M, Tang GHL et al. Percutaneous edge-to-edge repair for tricuspid regurgitation: 3-year outcomes from the TRILUMINATE study. *JACC Cardiovasc Interv.* 2024;17:2113–22.

49. Sorajja P, Whisenant B, Hamid N, Naik H, Makkar R, Tadros P et al. Transcatheter repair for patients with tricuspid regurgitation. *N Engl J Med.* 2023;388:1833–42.

50. Taramasso M, Benfari G, van der Bijl P, Alessandrini H, Attinger-Toller A, Biasco L et al. Transcatheter versus medical treatment of patients with symptomatic severe tricuspid regurgitation. *J Am Coll Cardiol.* 2019;74:2998–3008.

51. Lurz P, Besler C, Schmitz T, Bekeredjian R, Nickenig G, Möllmann H et al. Short-term outcomes of tricuspid edge-to-edge repair in clinical practice. *J Am Coll Cardiol.* 2023;82:281–91.

52. Dreyfus J, Galloo X, Taramasso M, Heitzinger G, Benfari G, Kresoja KP et al. TRI-SCORE and benefit of intervention in patients with severe tricuspid regurgitation. *Eur Heart J.* 2023;45:586–97.

53. Maisano F, Hahn R, Sorajja P, Praz F, Lurz P. Transcatheter treatment of the tricuspid valve: current status and perspectives. *Eur Heart J.* 2024;45:876–94.

54. Praz F, Muraru D, Kreidel F, Lurz P, Hahn RT, Delgado V et al. Transcatheter treatment for tricuspid valve disease. *EuroIntervention.* 2021;17:791–808.

55. Nickenig G, Weber M, Schuler R, Hausleiter J, Nabauer M, von Bardeleben RS et al. Tricuspid valve repair with the Cardioband system: two-year outcomes of the multicentre, prospective TRI-REPAIR study. *EuroIntervention.* 2021;16:e1264–71.

56. Hahn RT, Makkar R, Thourani VH, Makar M, Sharma RP, Haeffele C et al. Transcatheter valve replacement in severe tricuspid regurgitation. *N Engl J Med.* 2025;392:115–26.

57. Chen M, Moschovitis A, Taramasso M. Pacemaker lead dislocation during TricValve procedure with an extremely small superior vena cava. *Int J Cardiovasc Imaging.* 2024;40:1149–51.

58. Mehr M, Taramasso M, Besler C, Ruf T, Connelly KA, Weber M et al. 1-Year outcomes after edge-to-edge valve repair for symptomatic tricuspid regurgitation: results from the TriValve registry. *JACC Cardiovasc Interv.* 2019;12:1451–61.

59. Blasco-Turrión S, Briedis K, Estévez-Loureiro R, Sánchez-Recalde A, Cruz-González I, Pascual I et al. Bicaval TricValve implantation in patients with severe symptomatic tricuspid regurgitation: 1-year follow-up outcomes. *JACC Cardiovasc Interv.* 2024;17:60–72.

60. Gabriels JK, Schaller RD, Koss E, Rutkin BJ, Carrillo RG, Epstein LM. Lead management in patients undergoing percutaneous tricuspid valve replacement or repair: a 'heart team' approach. *Europace.* 2023;25:euad300.

61. Slonim SM, Semba CP, Sze DY, Dake MD. Placement of SVC stents over pacemaker wires for the treatment of SVC syndrome. *J Vasc Interv Radiol.* 2000;11:215–9.

62. Saad TF, Myers GR, Cicone J. Central vein stenosis or occlusion associated with cardiac rhythm management device leads in hemodialysis patients with ipsilateral arteriovenous access: a retrospective study of treatment using stents or stent-grafts. *J Vasc Access.* 2010;11:293–302.

63. Plant A, Stewart F, Hooks D. Implantable cardioverter-defibrillator lead failure and revision following transcutaneous bicaval valve (TricValve(R)) implantation. *J Cardiovasc Electrophysiol.* 2024;35:1050–4.

64. Olsen T, Jørgensen OD, Nielsen JC, Thogersen AM, Philbert BT, Johansen JB. Incidence of device-related infection in 97 750 patients: clinical data from the complete Danish device-cohort (1982–2018). *Eur Heart J.* 2019;40:1862–9.

65. Blomström-Lundqvist C, Traykov V, Erba PA, Burri H, Nielsen JC, Bongiorni MG et al. European Heart Rhythm Association (EHRA) international consensus document on how to prevent, diagnose, and treat cardiac implantable electronic device infections-endorsed by the Heart Rhythm Society (HRS), the Asia Pacific Heart Rhythm Society (APHRS), the Latin American Heart Rhythm Society (LAHRS), International Society for Cardiovascular Infectious Diseases (ISCVID) and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). *Europace.* 2020;22:515–49.

66. Wilkoff BL, Boriani G, Mittal S, Poole JE, Kennergren C, Corey GR et al. Impact of cardiac implantable electronic device infection: a clinical and economic analysis of the WRAP-IT trial. *Circ Arrhythm Electrophysiol.* 2020;13:e008280.

67. Blomström-Lundqvist C, Traykov V, Erba PA, Burri H, Nielsen JC, Bongiorni MG et al. European Heart Rhythm Association (EHRA) international consensus document on how to prevent, diagnose, and treat cardiac implantable electronic device infections-endorsed by the Heart Rhythm Society (HRS), the Asia Pacific Heart Rhythm Society (APHRS), the Latin American Heart Rhythm Society (LAHRS), International Society for Cardiovascular Infectious Diseases (ISCVID) and the European Society of

Clinical Microbiology and Infectious Diseases (ESCMID) in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). *Eur J Cardiothorac Surg*. 2020;57:E1–E31.

68. Sheldon SH, Joyce LD, Friedman PA. Transvenous extraction of right ventricular leads jailed by a bioprosthetic tricuspid valve. *J Innov Card Rhythm Manag*. 2013;4:1209–12.

69. Paz Rios LH, Alsaad AA, Guerrero M, Metzl MD. Tricuspid valve-in-valve jailing right ventricular lead is not free of risk. *Catheter Cardiovasc Interv*. 2020;96:E758–60.

70. Chourdakis E, Koniari I, Osman N, Kounis N, Hahalis G, Werner N. Late infective endocarditis after transcatheter mitral valve reconstruction (MitraClip): a case report and a review of the literature. *Angiology*. 2023;74:205–15.

71. Yokoyama H, Ochiai T, Saito S. Infective endocarditis after transcatheter edge-to-edge repair for severe mitral regurgitation; a case report and a systematic review. *Catheter Cardiovasc Interv*. 2023;102:367–74.

72. Gabriels JK, Schaller RD, Koss E, Rutkin BJ, Carrillo RG, Epstein LM. Lead management in patients undergoing percutaneous tricuspid valve replacement or repair: a 'heart team' approach. *Europace*. 2023;25:euad300.

73. Deharo JC, Bongiorni M, Rozkovec A, Bracke F, Defaye P, Fernandez-Lozano I et al. Pathways for training and accreditation for transvenous lead extraction: a European Heart Rhythm Association position paper. *Europace*. 2012;14:124–34.

74. Bongiorni MG, Blomström-Lundqvist C, Kennergren C, Dagres N, Pison L, Svendsen JH et al. Current practice in transvenous lead extraction: a European Heart Rhythm Association EP Network survey. *Europace*. 2012;14:783–6.

75. Kusumoto FM, Schoenfeld MH, Wilkoff BL, Berul CI, Birgersdotter-Green UM, Carrillo R et al. 2017 HRS expert consensus statement on cardiovascular implantable electronic device lead management and extraction. *Heart Rhythm*. 2017;14:e503–51.

76. Bongiorni MG, Burri H, Deharo JC, Starck C, Kennergren C, Saghy L et al. 2018 EHRA expert consensus statement on lead extraction: recommendations on definitions, endpoints, research trial design, and data collection requirements for clinical scientific studies and registries: endorsed by APHRS/HRS/LAHRS. *Europace*. 2018;20:1217.

77. Wilkoff BL, Love CJ, Byrd CL, Bongiorni MG, Carrillo RG, Crossley GH et al. Transvenous lead extraction: Heart Rhythm Society expert consensus on facilities, training, indications, and patient management: this document was endorsed by the American Heart Association (AHA). *Heart Rhythm*. 2009;6:1085–104.

78. Bongiorni MG, Marinskis G, Lip GY, Svendsen JH, Dobreanu D, Blomström-Lundqvist C et al. How European centres diagnose, treat, and prevent CIED infections: results of an European Heart Rhythm Association survey. *Europace*. 2012;14:1666–9.

79. Bongiorni MG, Kennergren C, Butter C, Deharo JC, Kutarski A, Rinaldi CA et al. The European lead extraction controlled (ELECTRa) study: a European heart rhythm association (EHRA) registry of transvenous lead extraction outcomes. *Eur Heart J*. 2017;38:2995–3005.

80. Bongiorni MG, Soldati E, Zucchelli G, Di Cori A, Segreti L, De Lucia R et al. Transvenous removal of pacing and implantable cardiac defibrillating leads using single sheath mechanical dilatation and multiple venous approaches: high success rate and safety in more than 2000 leads. *Eur Heart J*. 2008;29:2886–93.

81. Wazni O, Epstein LM, Carrillo RG, Love C, Adler SW, Riggio DW et al. Lead extraction in the contemporary setting: the LExICon study: an observational retrospective study of consecutive laser lead extractions. *J Am Coll Cardiol*. 2010;55:579–86.

82. Byrd CL, Wilkoff BL, Love CJ, Sellers TD, Reiser C. Clinical study of the laser sheath for lead extraction: the total experience in the United States. *Pacing Clin Electrophysiol*. 2002;25:804–8.

83. Neuzil P, Taborsky M, Rezek Z, Vopalka R, Sediva L, Niederle P et al. Pacemaker and ICD lead extraction with electrosurgical dissection sheaths and standard transvenous extraction systems: results of a randomized trial. *Europace*. 2007;9:98–104.

84. Scott PA, Chow W, Ellis E, Morgan JM, Roberts PR. Extraction of pacemaker and implantable cardioverter defibrillator leads: a single-centre study of electrosurgical and laser extraction. *Europace*. 2009;11:1501–4.

85. Mazzone P, Tsiachris D, Marzi A, Ciconte G, Paglino G, Sora N et al. Advanced techniques for chronic lead extraction: heading from the laser towards the evolution system. *Europace*. 2013;15:1771–6.

86. Bongiorni MG, Segreti L, Di Cori A, Zucchelli G, Viani S, Paperini L et al. Safety and efficacy of internal transjugular approach for transvenous extraction of implantable cardioverter defibrillator leads. *Europace*. 2014;16:1356–62.

87. Koneru JN, Ellenbogen KA. High-risk lead extraction using a hybrid approach: the blade and the lightsaber. *J Cardiovasc Electrophysiol*. 2014;25:622–3.

88. Fischer A, Love B, Hansalia R, Mehta D. Transfemoral snaring and stabilization of pacemaker and defibrillator leads to maintain vascular access during lead extraction. *Pacing Clin Electrophysiol*. 2009;32:336–9.

89. Hamid S, Arujuna A, Ginks M, McPhail M, Patel N, Bucknall C et al. Pacemaker and defibrillator lead extraction: predictors of mortality during follow-up. *Pacing Clin Electrophysiol*. 2010;33:209–16.

90. Brunner MP, Cronin EM, Wazni O, Baranowski B, Saliba WI, Sabik JF et al. Outcomes of patients requiring emergent surgical or endovascular intervention for catastrophic complications during transvenous lead extraction. *Heart Rhythm*. 2014;11:419–25.

91. Zucchelli G, Di Cori A, Segreti L, Laroche C, Blomstrom-Lundqvist C, Kutarski A et al. Major cardiac and vascular complications after transvenous lead extraction: acute outcome and predictive factors from the ESC-EHRA ELECTRa (European Lead Extraction ConTRolled) registry. *Europace*. 2019;21:771–80.

92. Diemberger I, Mazzotti A, Biffi M, Massaro G, Martignani C, Ziacchi M et al. From lead management to implanted patient management: systematic review and meta-analysis of the last 15 years of experience in lead extraction. *Expert Rev Med Devices*. 2013;10:551–73.

93. Akhtar Z, Kontogiannis C, Georgiopoulos G, Starck CT, Leung LWM, Lee SY et al. Comparison of non-laser and laser transvenous lead extraction: a systematic review and meta-analysis. *Europace*. 2023;25:euad316.

94. Rinaldi CA, Diemberger I, Biffi M, Gao YR, Sizto E, Jin N et al. Safety and success of transvenous lead extraction using excimer laser sheaths: a meta-analysis of over 1700 patients. *Europace*. 2023;25:euad298.

95. Cecchin F, Atallah J, Walsh EP, Triedman JK, Alexander ME, Berul CI. Lead extraction in pediatric and congenital heart disease patients. *Circ Arrhythm Electrophysiol*. 2010;3: 437–44.

96. Giannotti Santoro M, Segreti L, Zucchelli G, Barletta V, Fiorentini F, Di Cori A et al. Transvenous lead extraction: efficacy and safety of the procedure in octogenarian patients. *Pacing Clin Electrophysiol*. 2020;43: 382–7.

97. Diemberger I, Segreti L, Rinaldi CA, Svendsen JH, Kutarski A, Younis A et al. Transvenous lead extraction in patients with cardiac implantable device: the impact of systemic and local infection on clinical outcomes—an ESC-EHRA ELECTRa (European lead extraction controlled) registry substudy. *Biology (Basel)*. 2022;11:615.

98. Polewczyk A, Rinaldi CA, Sohal M, Golzio P-G, Claridge S, Cano O et al. Transvenous lead extraction procedures in women based on ESC-EHRA EORP European Lead Extraction ConTRolled ELECTRa registry: is female sex a predictor of complications? *Europace*. 2019;21:1890–9.

99. Segreti L, Bongiorni MG, Barletta V, Parollo M, Di Cori A, Fiorentini F et al. Transvenous lead extraction: efficacy and safety of the procedure in female patients. *Heart Rhythm O2*. 2023;4:625–31.

100. Di Cori A, Auricchio A, Regoli F, Blomström-Lundqvist C, Butter C, Dagres N et al. Clinical impact of antithrombotic therapy in transvenous lead extraction complications: a sub-analysis from the ESC-EORP EHRA ELECTRa (European Lead Extraction ConTRolled) registry. *Europace*. 2019;21:1096–105.

101. Segreti L, Rinaldi CA, Claridge S, Svendsen JH, Blomstrom-Lundqvist C, Auricchio A et al. Procedural outcomes associated with transvenous lead extraction in patients with abandoned leads: an ESC-EHRA ELECTRa (European Lead Extraction ConTRolled) registry sub-analysis. *Europace*. 2019;21:645–54.

102. Regoli F, Auricchio A, Di Cori A, Segreti L, Blomström-Lunqvist C, Butter C et al. Impact of anticoagulation therapy on outcomes in patients with cardiac implantable resynchronization devices undergoing transvenous lead extraction: a substudy of the ESC-EHRA EORP ELECTRa (European

Lead Extraction ConTRolled) registry. *J Cardiovasc Electrophysiol.* 2019;30: 1086–95.

103. Segreti L, Di Cori A, Soldati E, Zucchelli G, Viani S, Paperini L et al. Major predictors of fibrous adherences in transvenous implantable cardioverter-defibrillator lead extraction. *Heart Rhythm.* 2014;11:2196–201.

104. Di Cori A, Bongiorni MG, Zucchelli G, Segreti L, Viani S, De Lucia R et al. Large, single-center experience in transvenous coronary sinus lead extraction: procedural outcomes and predictors for mechanical dilatation. *Pacing Clin Electrophysiol.* 2012;35: 215–22.

105. Di Cori A, Bongiorni MG, Zucchelli G, Lilli A, Coluccia G, Fabiani I et al. Short-term extraction profile of cardiac pacing leads with hybrid silicone-polyurethane insulator: a pilot study. *Int J Cardiol.* 2013;168:4432–3.

106. Di Cori A, Bongiorni MG, Zucchelli G, Segreti L, Viani S, Paperini L et al. Transvenous extraction performance of expanded polytetrafluoroethylene covered ICD leads in comparison to traditional ICD leads in humans. *Pacing Clin Electrophysiol.* 2010;33: 1376–81.

107. Bongiorni MG, Di Cori A, Segreti L, Zucchelli G, Viani S, Paperini L et al. Transvenous extraction profile of Riata leads: procedural outcomes and technical complexity of mechanical removal. *Heart Rhythm.* 2015;12: 580–7.

108. Maytin M, Carrillo RG, Baltodano P, Schaerf RH, Bongiorni MG, Di Cori A et al. Multicenter experience with transvenous lead extraction of active fixation coronary sinus leads. *Pacing Clin Electrophysiol.* 2012;35:641–7.

109. Gabriels JK, Kim BS, Shoda M, Birgersdotter-Green U, Di Cori A, Zucchelli G et al. International experience with transvenous lead extractions of an active-fixation coronary sinus pacing lead. *Heart Rhythm.* 2024;21: 686–7.

110. Sidhu BS, Gould J, Bunce C, Elliott M, Mehta V, Kennergren C et al. The effect of centre volume and procedure location on major complications and mortality from transvenous lead extraction: an ESC EHRA EORP European Lead Extraction ConTRolled ELECTRa registry subanalysis. *Europace.* 2020;22:1718–28.

111. Racine H-P, Jacques F, Philippon F. The effect of centre volume and procedure location on major complications and mortality from transvenous lead extraction: an ESC EHRA EORP European Lead Extraction ConTRolled ELECTRa registry subanalysis. *Europace.* 2021;23:1149.

112. Agarwal SK, Kamireddy S, Nemec J, Voigt A, Saba S. Predictors of complications of endovascular chronic lead extractions from pacemakers and defibrillators: a single-operator experience. *J Cardiovasc Electrophysiol.* 2009;20:171–5.

113. Fu HX, Huang XM, Zhong L, Osborn MJ, Asirvatham SJ, Espinosa RE et al. Outcomes and complications of lead removal: can we establish a risk stratification schema for a collaborative and effective approach? *Pacing Clin Electrophysiol.* 2015;38:1439–47.

114. Bongiorni MG, Segreti L, Di Cori A, Zucchelli G, Paperini L, Viani S et al. Overcoming the current issues surrounding device leads: reducing the complications during extraction. *Expert Rev Med Devices.* 2017;14:469–80.

115. Bontempi L, Vassanelli F, Cerini M, D'Aloia A, Vizzardi E, Gargaro A et al. Predicting the difficulty of a lead extraction procedure: the LED index. *J Cardiovasc Med (Hagerstown).* 2014;15:668–73.

116. Kancharla K, Acker NG, Li Z, Samineni S, Cai C, Espinosa RE et al. Efficacy and safety of transvenous lead extraction in the device laboratory and operating room guided by a novel risk stratification scheme. *JACC Clin Electrophysiol.* 2019;5:174–82.

117. Jacheć W, Polewczyk A, Polewczyk M, Tomasik A, Kutarski A. Transvenous lead extraction SAFeTY score for risk stratification and proper patient selection for removal procedures using mechanical tools. *J Clin Med.* 2020;9:361.

118. Sidhu BS, Ayis S, Gould J, Elliott MK, Mehta V, Kennergren C et al. Risk stratification of patients undergoing transvenous lead extraction with the ELECTRa Registry Outcome Score (EROS): an ESC EHRA EORP European lead extraction ConTRolled ELECTRa registry analysis. *Europace.* 2021;23:1462–71.

119. Mehta VS, O'Brien H, Elliott MK, Wijesuriya N, Auricchio A, Ayis S et al. Machine learning-derived major adverse event prediction of patients undergoing transvenous lead extraction: using the ESC EHRA EORP European lead extraction ConTRolled ELECTRa registry. *Heart Rhythm.* 2022;19:885–93.

120. Mehta VS, Ma Y, Wijesuriya N, DeVere F, Howell S, Elliott MK et al. Enhancing transvenous lead extraction risk prediction: integrating imaging biomarkers into machine learning models. *Heart Rhythm.* 2024;21: 919–28.

121. Lin AY, Lupercio F, Ho G, Pollema T, Pretorius V, Birgersdotter-Green U. Safety and efficacy of cardiovascular implantable electronic device extraction in elderly patients: a meta-analysis and systematic review. *Heart Rhythm O2.* 2020;1:250–8.

122. Roeffel S, Bracke F, Meijer A, Van Gelder B, Van Dantzig JM, Botman CJ et al. Transesophageal echocardiographic evaluation of tricuspid valve regurgitation during pacemaker and implantable cardioverter defibrillator lead extraction. *Pacing Clin Electrophysiol.* 2002;25:1583–6.

123. Franceschi F, Thuny F, Giorgi R, Sanaa I, Peyrouse E, Assouan X et al. Incidence, risk factors, and outcome of traumatic tricuspid regurgitation after percutaneous ventricular lead removal. *J Am Coll Cardiol.* 2009;53:2168–74.

124. Glover B, Watkins S, Mariani J, Yap S, Asta J, Cusimano R et al. Prevalence of tricuspid regurgitation and pericardial effusions following pacemaker and defibrillator lead extraction. *Int J Cardiol.* 2010;145:593–4.

125. Coffey JO, Sager SJ, Gangireddy S, Levine A, Viles-Gonzalez JF, Fischer A. The impact of transvenous lead extraction on tricuspid valve function. *Pacing Clin Electrophysiol.* 2014;37:19–24.

126. Givon A, Vedernikova N, Luria D, Vatury O, Kuperstein R, Feinberg MS et al. Tricuspid regurgitation following lead extraction: risk factors and clinical course. *Isr Med Assoc J.* 2016;18:18–22.

127. Rodriguez Y, Mesa J, Arguelles E, Carrillo RG. Tricuspid insufficiency after laser lead extraction. *Pacing Clin Electrophysiol.* 2013;36:939–44.

128. Migliore F, Pittorru R, De Lazzari M, Dall'Aglio PB, Cecchetto A, Previtero M et al. Evaluation of tricuspid valve regurgitation following transvenous rotational mechanical lead extraction. *Europace.* 2024;26:euae191.

129. Candinas R, Duru F, Schneider J, Lüscher TF, Stokes K. Postmortem analysis of encapsulation around long-term ventricular endocardial pacing leads. *Mayo Clin Proc.* 1999; 74:120–5.

130. Polewczyk A, Jacheć W, Nowosielecka D, Tomaszewski A, Brzozowski W, Szczęśniak-Stańczyk D et al. Lead dependent tricuspid valve dysfunction-risk factors, improvement after transvenous lead extraction and long-term prognosis. *J Clin Med.* 2021;11:89.

131. Nazmul MN, Cha YM, Lin G, Asirvatham SJ, Powell BD. Percutaneous pacemaker or implantable cardioverter-defibrillator lead removal in an attempt to improve symptomatic tricuspid regurgitation. *Europace.* 2013;15:409–13.

132. Patel D, Vatterott P, Piccini J, Epstein LM, Hakmi S, Syed I et al. Prospective evaluation of the correlation between gated cardiac computed tomography detected vascular fibrosis and ease of transvenous lead extraction. *Circ Arrhythm Electrophysiol.* 2022;15: e010779.

133. Tułecki L, Polewczyk A, Jacheć W, Nowosielecka D, Tomków K, Stefańczyk P et al. Analysis of risk factors for major complications of 1500 transvenous lead extraction procedures with especial attention to tricuspid valve damage. *Int J Environ Res Public Health.* 2021;18:9100.

134. Svennberg E, Jacobs K, McVeigh E, Pretorius V, Birgersdotter-Green U. Computed tomography-guided risk assessment in percutaneous lead extraction. *JACC Clin Electrophysiol.* 2019;5:1439–46.

135. Saad TF, Hentschel DM, Koplan B, Wasse H, Asif A, Patel DV et al. Cardiovascular implantable electronic device leads in CKD and ESRD patients: review and recommendations for practice. *Semin Dial.* 2013;26:114–23.

136. Schaller RD, Giri J, Epstein AE. Entrapped leads after transcatheter tricuspid valve replacement. *JACC Cardiovasc Interv.* 2021;14:715–6.

137. Noheria A, Van Zyl M, Scott LR, Srivathsan K, Madhavan M, Asirvatham SJ et al. Single-site ventricular pacing via the coronary sinus in patients with tricuspid valve disease. *Europace.* 2018;20:636–42.

138. Arps K, Li B, Allen JC Jr, Alenezi F, Frazier-Mills C, Al-Khatib SM et al. Association of leadless pacing with ventricular and valvular function. *J Cardiovasc Electrophysiol.* 2023; 34:2233–42.

139. Garweg C, Duchenne J, Vandenberk B, Mao Y, Ector J, Haemers P et al. Evolution of ventricular and valve function in patients with right ventricular pacing–A randomized controlled trial comparing leadless and conventional pacing. *Pacing Clin Electrophysiol.* 2023;46:1455–64.

140. Fink T, Eitz T, Sciacca V, Rudolph V, Sohns C, Sommer P et al. Transfemoral leadless pacemaker implantation after interventional or surgical tricuspid valve repair. *Europace.* 2024;26:euae111.

141. Carabelli A, Jabeur M, Jacon P, Rinaldi CA, Leclercq C, Rovaris G et al. European experience with a first totally leadless cardiac resynchronization therapy pacemaker system. *Europace.* 2021;23:740–7.

142. Torres-Quintero L, Molina-Lerma M, Cabrera-Borrego E, García-Orta R, Tercedor-Sánchez L, Álvarez M. His-bundle pacing from the right atrium in a patient with tetralogy of Fallot and a prosthetic tricuspid valve. *JACC Clin Electrophysiol.* 2020;6:745–6.

143. Elliott MK, Vergara P, Wijesuriya N, Mehta VS, Bosco P, Jacon P et al. Feasibility of leadless left ventricular septal pacing with the WiSE-CRT system to target the left bundle branch area: a porcine model and multicenter patient experience. *Heart Rhythm.* 2022;19:1974–83.

144. Knops RE, Lloyd MS, Roberts PR, Wright DJ, Boersma LVA, Doshi R et al. A modular communicative leadless pacing-defibrillator system. *N Engl J Med.* 2024;391:1402–12.

145. Lancellotti P, Pibarot P, Chambers J, La Canna G, Pepi M, Dulgheru R et al. Multi-modality imaging assessment of native valvular regurgitation: an EACVI and ESC council of valvular heart disease position paper. *Eur Heart J Cardiovasc Imaging.* 2022;23:e171–232.

146. Mediratta A, Addetia K, Yamat M, Moss JD, Nayak HM, Burke MC et al. 3D echocardiographic location of implantable device leads and mechanism of associated tricuspid regurgitation. *JACC Cardiovasc Imaging.* 2014;7:337–47.

147. Nucifora G, Badano LP, Allocca G, Gianfagna P, Proclemer A, Cinello M et al. Severe tricuspid regurgitation due to entrapment of the anterior leaflet of the valve by a permanent pacemaker lead: role of real time three-dimensional echocardiography. *Echocardiography.* 2007;24:649–52.

148. Hell MM, Emrich T, Kreidel F, Kreitner KF, Schoepf UJ, Münzel T et al. Computed tomography imaging needs for novel transcatheter tricuspid valve repair and replacement therapies. *Eur Heart J Cardiovasc Imaging.* 2021;22:601–10.

149. Bartkowiak J, Vivekanantham H, Kassar M, Dernektsi C, Agarwal V, Lebehn M et al. Computed tomography anatomic predictors of outcomes in patients undergoing tricuspid transcatheter edge-to-edge repair. *J Cardiovasc Comput Tomogr.* 2024;18:259–66.

150. Korantzopoulos P, Letsas KP, Grekas G, Goudevenos JA. Pacemaker dependency after implantation of electrophysiological devices. *Europace.* 2009;11:1151–5.

151. Zeppenfeld K, Tfelt-Hansen J, de Riva M, Winkel BG, Behr ER, Blom NA et al. 2022 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart J.* 2022;43:3997–4126.

152. Ferrick AM, Raj SR, Deneke T, Kojodjojo P, Lopez-Cabanillas N, Abe H et al. 2023 HRS/EHRA/APHRS/LAHRS expert consensus statement on practical management of the remote device clinic. *Europace.* 2023;25:euad123.

153. Delgado V, Ajmone Marsan N, de Waha S, Bonaros N, Brida M, Burri H et al. 2023 ESC guidelines for the management of endocarditis: developed by the task force on the management of endocarditis of the European Society of Cardiology (ESC) endorsed by the European Association for Cardio-Thoracic Surgery (EACTS) and the European Association of Nuclear Medicine (EANM). *Eur Heart J.* 2023;44:3948–4042.

154. Tan EM, DeSimone DC, Sohail MR, Baddour LM, Wilson WR, Steckelberg JM et al. Outcomes in patients with cardiovascular implantable electronic device infection managed with chronic antibiotic suppression. *Clin Infect Dis.* 2017;64:1516–21.

155. Peacock JE Jr, Stafford JM, Le K, Sohail MR, Baddour LM, Prutkin JM et al. Attempted salvage of infected cardiovascular implantable electronic devices: are there clinical factors that predict success? *Pacing Clin Electrophysiol.* 2018;41:524–31.

156. Topaz M, Chorin E, Schwartz AL, Hochstadt A, Shotan A, Ashkenazi I et al. Regional antibiotic delivery for implanted cardiovascular electronic device infections. *J Am Coll Cardiol.* 2023;81:119–33.

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ORIGINAL RESEARCH

Incidence, predictors, and clinical impact of hypoattenuating leaflet thickening following SAPIEN 3 Ultra RESILIA implantation

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ABSTRACT

BACKGROUND: The latest-generation SAPIEN 3 Ultra RESILIA (S3UR) transcatheter heart valve (THV) incorporates several changes in leaflet design, including an improved anticalcification coating and modified commissural attachment. There are no established data on hypoattenuating leaflet thickening (HALT) following transcatheter aortic valve implantation (TAVI) using the S3UR.

AIMS: Our study aimed to elucidate the clinical features of HALT following S3UR implantation.

METHODS: As a subset of the OCEAN (Optimized CathEter vAlvular INtervention)-TAVI registry, we prospectively assessed patients who underwent cardiac computed tomography (CT) 30 days after S3UR implantation. HALT and potentially relevant THV geometry were analysed using four-dimensional CT data by an independent core laboratory.

RESULTS: Of the 445 patients studied, HALT was detected in 95 patients (21.3%) 30 days after TAVI. The modification of the commissural attachment specific to the 20 mm and 23 mm S3UR THVs did not affect the incidence of HALT (22.1% for ≤23 mm; 20.2% for ≥26 mm; p=0.636). The hourglass-shaped THV frame (p<0.001) and asymmetricity of THV leaflets (p=0.002) were independently associated with HALT development. A trend toward higher mean aortic gradients at 30 days with greater degrees of HALT (HALT >25% vs HALT ≤25%: 10.3 [interquartile range {IQR} 7.0-13.0] mmHg vs 8.6 [IQR 6.3-11.6] mmHg; p=0.007; HALT >50% vs HALT ≤50%: 11.5 [IQR 7.0-14.3] mmHg vs 8.9 [IQR 6.3-11.9] mmHg; p=0.002) was noted.

CONCLUSIONS: The incidence of HALT for the S3UR was comparable with the already reported incidences for the previous-generation SAPIEN 3 THV. Given the haemodynamic impact of HALT severity and multiplicity, strategic planning to avoid deformation of the implanted THV might be required. (Clinical trial registration: UMIN000020423)

KEYWORDS: aortic stenosis; computed tomography; hypoattenuating leaflet thickening; transcatheter aortic valve implantation

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In the past decades, recommendations for transcatheter aortic valve implantation (TAVI), which was established as a therapeutic alternative to surgical aortic valve replacement for inoperable or high-risk patients with severe aortic stenosis (AS), have expanded to include low-risk patients. Despite significant advances in transcatheter heart valve (THV) technologies and increased operator experience, there have been concerns about hypoattenuating leaflet thickening (HALT) with or without reduced leaflet motion (RLM), which potentially increases the risk of systemic embolisation and affects prosthesis function or durability[1-3]. In patients who received the previous-generation balloon-expandable SAPIEN 3 (S3) THV (Edwards Lifesciences), the incidence of HALT was reported to be 13-21%, and non-uniform expansion of the THV, including frame deformation and asymmetric leaflet, has been identified as a strong predictor of HALT[4-7]. The latest-generation balloon-expandable SAPIEN 3 Ultra RESILIA (S3UR) THV (Edwards Lifesciences), with new features such as dry tissue storage in combination with the anticalcification technology of RESILIA tissue and the alteration in the leaflet attachment method at the commissural posts specific to smaller 20 mm and 23 mm THV sizes, has been in clinical use for several years. Although recent papers have reported the significantly better valve performance of the S3UR[8,9], no data on its HALT have been established. Therefore, this study aimed to investigate the incidence, predictors, and clinical impact of HALT following TAVI with the S3UR using Japanese multicentre prospective registry data.

Editorial, see page 1293

Impact on daily practice

The 30-day incidence of hypoattenuating leaflet thickening (HALT) in patients who were treated with the SAPIEN 3 Ultra RESILIA (S3UR) transcatheter heart valve (THV) was 21.3%, which was comparable with recently reported incidences for the previous-generation SAPIEN 3 THV. The revised commissural leaflet suspension method specific to the 20 mm and 23 mm S3UR THVs was not associated with an increased risk of HALT, whereas the prosthesis deformation index and asymmetric leaflet expansion were independently associated with an increased risk of HALT development regardless of the S3UR THV size. Both greater degrees (>25%) and multiplicity (≥2 leaflets) of HALT were associated with a higher mean aortic gradient after transcatheter aortic valve implantation.

Methods

STUDY POPULATION AND DESIGN

As a subset of the ongoing, prospective, Japanese multicentre Optimized CathEter vAlvular INtervention (OCEAN)-TAVI registry, beginning on April 2023, we prospectively performed an electrocardiogram (ECG)-gated, contrast-enhanced cardiac computed tomography (CT) scan 30 days following TAVI to detect HALT and RLM and assess the feasibility of future redo-TAVI, unless medical or social contraindication precluded contrast administration. This study included all patients who underwent such CT examinations following S3UR implantation at 12 institutions in Japan between April 2023 and March 2024. Patients with transfemoral and non-transfemoral approaches were included. To evaluate the clinical characteristics of HALT and RLM for the S3UR, patients with previous aortic bioprosthetic valves, a second THV implantation for bailout, or inadequate CT image quality for leaflet assessment were excluded from the analysis.

The decision to proceed with TAVI and the selection of the THV type and size were made with the consensus of a dedicated Heart Team at each site. During TAVI, an activated clotting time of ≥250 s was achieved by intravenous administration of unfractionated heparin. After the procedure, the recommended antithrombotic regimen was dual antiplatelet therapy (DAPT) consisting of aspirin and thienopyridine for 6 months, followed by lifelong aspirin therapy, as per the Japanese guidelines[10]; however, single antiplatelet therapy (SAPT) or no antiplatelet therapy (NAPT) was selected for patients deemed to be at high bleeding risk. A single oral anticoagulant without antithrombotic agents was selected when long-term anticoagulation was indicated because of pre-existing atrial fibrillation or deep vein thrombosis.

The study protocol of the OCEAN-TAVI registry was approved by the local institutional review board of each participating centre and registered with the University Hospital Medical Information Network (UMIN000020423). All the patients provided written informed consent before undergoing TAVI. Data collection was conducted as shown in **Supplementary Appendix 1**.

CT IMAGE ACQUISITION AND INTERPRETATION

For both the baseline and 30-day assessments, an ECG-gated, contrast-enhanced cardiac CT scan was performed based on a pre-established protocol **(Supplementary Appendix 2)**. Centralised core laboratory assessment of the CT data using 3mensio Valves software, version 8.0 (Pie Medical Imaging) was performed at Toyohashi, Nagoya, and Gifu Heart Centers by experienced imaging specialists who were not aware of all clinical results. Baseline variables were assessed using pre-TAVI CT with standard definitions[11]. Post-TAVI CT data were analysed using multiplanar reformats aligned with the short- and long-axis dimensions of the THV. HALT and RLM were meticulously evaluated using the entire cardiac cycle data, whereas the other variables, such as prosthesis expansion, implantation depth, and commissural alignment, were assessed in one phase of mid-diastole (70-80% of the R-R interval).

Abbreviations

CT	computed tomography	**PPM**	prosthesis-patient mismatch	**S3UR**	SAPIEN 3 Ultra RESILIA
HALT	hypoattenuating leaflet thickening	**RLM**	reduced leaflet motion	**TAVI**	transcatheter aortic valve implantation
ICC	intraclass correlation coefficient	**SOV**	sinus of Valsalva	**THV**	transcatheter heart valve
NCC	non-coronary cusp	**S3**	SAPIEN 3		

ASSESSMENT OF THE IMPLANTED THV USING POST-TAVI CT

PROSTHETIC LEAFLET ABNORMALITIES

HALT and RLM were assessed per leaflet according to the Valve Academic Research Consortium (VARC)-3 criteria **(Supplementary Figure 1)**[12]. HALT was defined as a visually identified increased leaflet thickness with a typically meniscal appearance on long-axis views. The extent of leaflet thickening was semiquantitatively graded on long-axis views carefully aligned with the leaflet centre, focusing on involvement along the curvilinear leaflet beginning at the base, using a 5-tier grading scale: none, ≤25%, >25% to ≤50%, >50% to ≤75%, and >75%. If HALT was identified, the presence of RLM throughout the entire systolic phase was also evaluated using a 4-tier grading scale along the curvilinear leaflet beginning at the base: none, <50%, ≥50% to <100%, and immobile (100%). The location of HALT was also evaluated with regard to which of the 3 leaflets of a THV was involved. Among the 3 leaflets of a THV, the one facing more than half of the native non-coronary cusp (NCC) on the THV short-axis CT image was defined as the NCC-side leaflet. Subsequently, based on the location of the NCC-side leaflet, the left coronary cusp (LCC)-side leaflet and right coronary cusp (RCC)-side leaflet were determined. The Valsalva thrombus was defined as a low-density space without contrast enhancement between the native sinus of Valsalva (SOV) and the implanted THV stent frame.

THV STENT FRAME DEFORMATION

The geometry of the THV stent frame was assessed for orthogonal major and minor diameters and expansion area at 3 levels of the prosthesis: leaflet inflow (i.e., the nadir of the prosthesis leaflets), prosthesis waist, and leaflet outflow (i.e., the top of the 3 commissural tabs) levels **(Supplementary Figure 2)**[5]. To minimise measurement errors due to blooming artefacts, these stent frame measurements were obtained by tracing or connecting the middle of the stent struts at a window width of 3,000 and a window level of 2,000. The THV implantation depth was defined as the mean of the distances from the inflow of the THV to the SOV floor, measured at each coronary cusp, as previously described[13,14]. The degree of canting was calculated as the difference between the maximum and minimum THV implantation depths. The postprocedural native annulus level was defined as the plane with a mean THV implantation depth above the THV frame inflow level.

Post-implant THV oversizing (%) was calculated as follows: (measured THV area at the native annulus level/native annulus area – 1) × 100. THV expansion (%) was calculated as follows: (measured THV area/nominal THV area) × 100. The nominal THV areas of the S3UR valves used in the above calculations were 300 mm^2, 390 mm^2, 503 mm^2, and 621 mm^2 for 20 mm, 23 mm, 26 mm, and 29 mm THVs, respectively, consistent with the previous paper where the nominal CT-derived area was measured by tracing the centre of the stent frame[15]. The prosthesis deformation index was calculated as follows: (THV area at the leaflet inflow level + THV area at the leaflet outflow level) / (2 × THV area at the prosthesis waist level)[5]. THV eccentricity (%) was calculated as follows: $\sqrt{\{1 - (\text{minor diameter})^2/(\text{major diameter})^2\}} \times 100$.

ASYMMETRIC LEAFLET EXPANSION

The expansion of each prosthetic valve leaflet was evaluated by measuring the angle (°) formed by the border stent struts corresponding to each prosthetic valve leaflet and the THV centre point at the coaptation level **(Supplementary Figure 2)**. Assuming that the full expansion of each leaflet would be 120°, the asymmetric leaflet expansion was calculated as the sum of the difference between 120° and each measured leaflet angle.

AREA RATIO OF THE THV TO THE SOV

To assess the extent to which the THV occupied the SOV, the SOV and THV areas were measured at the level where the SOV area was visually the largest **(Supplementary Figure 3)**. The area ratio (%) of the THV to the SOV was calculated[16].

OVERLAP BETWEEN THE THV COMMISSURES AND CORONARY OSTIA

The angle between the THV commissure and each coronary ostium was measured, as previously reported[13]. Briefly, the positions of the THV commissures were identified and marked at the cross-sectional level of the THV leaflet coaptation, and the ostium of each coronary artery was identified in a cross-section perpendicular to the axis of the aorta. Subsequently, the two angles through the centre of the aorta were measured: one from the left coronary artery ostium to the nearest THV commissure, and the other from the right coronary artery ostium to the nearest of the THV commissures. The severity of the overlap between the THV commissures and coronary ostia was defined as follows: severe (0-20°), moderate (21-35°), and mild/no (36-60°) overlap[17].

STATISTICAL ANALYSIS

Categorical variables are described as numbers and percentages and were compared using the chi-square or Fisher's exact test, as appropriate. Continuous variables, whose normality of distribution was assessed using the Shapiro-Wilk test, are described as means±standard deviations or medians (interquartile ranges [IQRs]) and were compared using the unpaired Student's t-test or Wilcoxon rank-sum test based on their distributions. To determine the risk factors for HALT 30 days after S3UR implantation, logistic regression analyses were conducted. Variables deemed to be clinically relevant to HALT were included in the multivariable model. Odds ratios (ORs) were reported with corresponding 95% confidence intervals (CIs). The variance inflation factor was used to check for multicollinearity for each variable, and the obtained variance inflation factor value was between 1 and 2. Receiver operating characteristic curves were utilised to illustrate and assess the predictive performance of the variables for HALT. Furthermore, the c-statistics between the potential predictors were compared using the method of DeLong et al[18]. Linear mixed models were used to identify independent predictors of the prosthesis deformation index and asymmetric leaflet expansion. Variables with p-values<0.10 in the univariate analysis were considered eligible for inclusion in the multivariable model. Regarding the post-TAVI CT analysis, intraobserver (2-week interval) and interobserver agreements were evaluated using the intraclass correlation coefficient (ICC) in 20 patients who were randomly selected.

All statistical analyses were performed using JMP, version 14.2.0 (SAS Institute) and R, version 4.0.2 (R Foundation for Statistical Computing). A 2-tailed p-value of 0.05 was used for significance testing.

Results

STUDY POPULATION AND INCIDENCE OF HALT AND RLM

A total of 481 patients undergoing TAVI using the S3UR at 12 participating institutions between April 2023 and March 2024 were enrolled in this post-TAVI CT study. After exclusion of 36 patients due to a previous aortic bioprosthetic valve (n=3), second THV requirement for bailout (n=1), or inadequate CT image quality for leaflet assessment (n=32), 445 patients were included in the final analysis. The median age of the patients was 84 years, and 40% of them were male.

Of these patients, 95 (21.3%) with HALT were identified at the 30-day post-TAVI CT **(Central illustration)**. The incidence of HALT was statistically comparable between the four S3UR sizes, albeit with a relatively lower incidence for the 20 mm valve **(Figure 1)**. Although the unique modification of the S3UR in the sawing manoeuvres for commissures is applied only in the 20 mm and 23 mm valves, this modification did not affect the incidence of HALT (22.1% for 20 mm and 23 mm valves, 20.2% for 26 mm and 29 mm valves; p=0.636) **(Central illustration)**. Overall, 45 patients (10.1%) showed HALT involving multiple leaflets. A leaflet-level analysis revealed that HALT was detected in 13.5%, 10.5%, and 11.9% of the leaflets on the NCC, LCC, and RCC sides, respectively (p=0.406). All leaflets with >25% HALT exhibited signs of RLM, whereas no RLM was identified in 56 (83.6%) of 67 leaflets with ≤25% HALT **(Supplementary Table 1)**.

Baseline and procedural characteristics were comparable between patients with and without HALT, except for the prevalence of atrial fibrillation (10.5% vs 21.4%; p=0.011) and usage of anticoagulant therapy at discharge (13.7% vs 23.4%; p=0.033) **(Table 1)**. In a subanalysis focusing on 350 patients without anticoagulation therapy at discharge, DAPT was associated with a significantly decreased risk of HALT occurrence as compared with SAPT and NAPT (8.7% vs 25.3% vs 26.7%; p=0.021). Meanwhile, in 95 patients with anticoagulant therapy at discharge, the incidence of HALT was comparable between those taking oral vitamin K antagonists and those taking direct oral anticoagulants (17.7% vs 12.8%; p=0.697) **(Supplementary Figure 4)**.

POSTPROCEDURAL ECHOCARDIOGRAPHIC DATA

Compared with patients without HALT, those with HALT had a numerically higher mean aortic gradient; however, the difference was not significant. The degree of paravalvular leakage was also not associated with HALT development **(Table 2)**. A greater proportion of patients with HALT fulfilled the VARC-3 criteria for prosthesis-patient mismatch (PPM) compared to those without HALT (15.8% vs 8.6%; p=0.049).

An additional sensitivity analysis according to the degree of HALT showed significant differences in the mean aortic gradient on setting 25% or 50% as the cutoff for HALT severity (HALT >25% vs HALT ≤25%: 10.3 [IQR 7.0-13.0] mmHg vs 8.6 [IQR 6.3-11.6] mmHg; p=0.007; HALT >50% vs HALT ≤50%: 11.5 [IQR 7.0-14.3] mmHg vs 8.9 [IQR 6.3-11.9] mmHg; p=0.002). The presence of multiple HALT involving two or three leaflets was also associated with a higher mean aortic gradient (multiple HALT >0% or not: 11.0 [IQR 7.5-14.9] mmHg vs 8.6 [IQR 6.3-11.6] mmHg; p=0.001; multiple HALT >25% or not: 14.0 [IQR 8.9-17.5] mmHg vs 9.0 [IQR 6.3-11.9] mmHg; p=0.025) **(Central illustration)**.

IMPLANTED THV ASSESSMENT USING POST-TAVI CT

Compared with the nominal THV areas offered by the manufacturer, underexpansion of the implanted THV was observed at all levels of the S3UR frame in post-TAVI CT **(Table 3)**. Regardless of the presence or absence of HALT, the expansion area percentage of the THV was the smallest at the prosthesis waist level with a median prosthesis deformation index of 1.06, indicating an hourglass-shaped implantation of the THV. However, patients with HALT had a larger prosthesis deformation index than those without HALT (1.11 [IQR 1.09-1.13] vs 1.06 [IQR 1.04-1.07]; p<0.001), and this difference was observed for all THV sizes **(Figure 2A)**. THV eccentricity, ranging from 0.29 to 0.35 at each level of the THV, was comparable between the two groups at all levels, whereas asymmetric leaflet expansion was associated with HALT development (16° [IQR 9-22°] vs 8° [IQR 6-12°]; p=0.001). Larger asymmetric leaflet expansion in patients with HALT was also identified for all THV sizes **(Figure 2B)**. The intra- and interobserver agreement was acceptable for the prosthesis deformation index (intraobserver ICC=0.94; interobserver ICC=0.91) and the asymmetric leaflet expansion (intraobserver ICC=0.95; interobserver ICC=0.91).

PREDICTORS OF HALT FOLLOWING S3UR IMPLANTATION

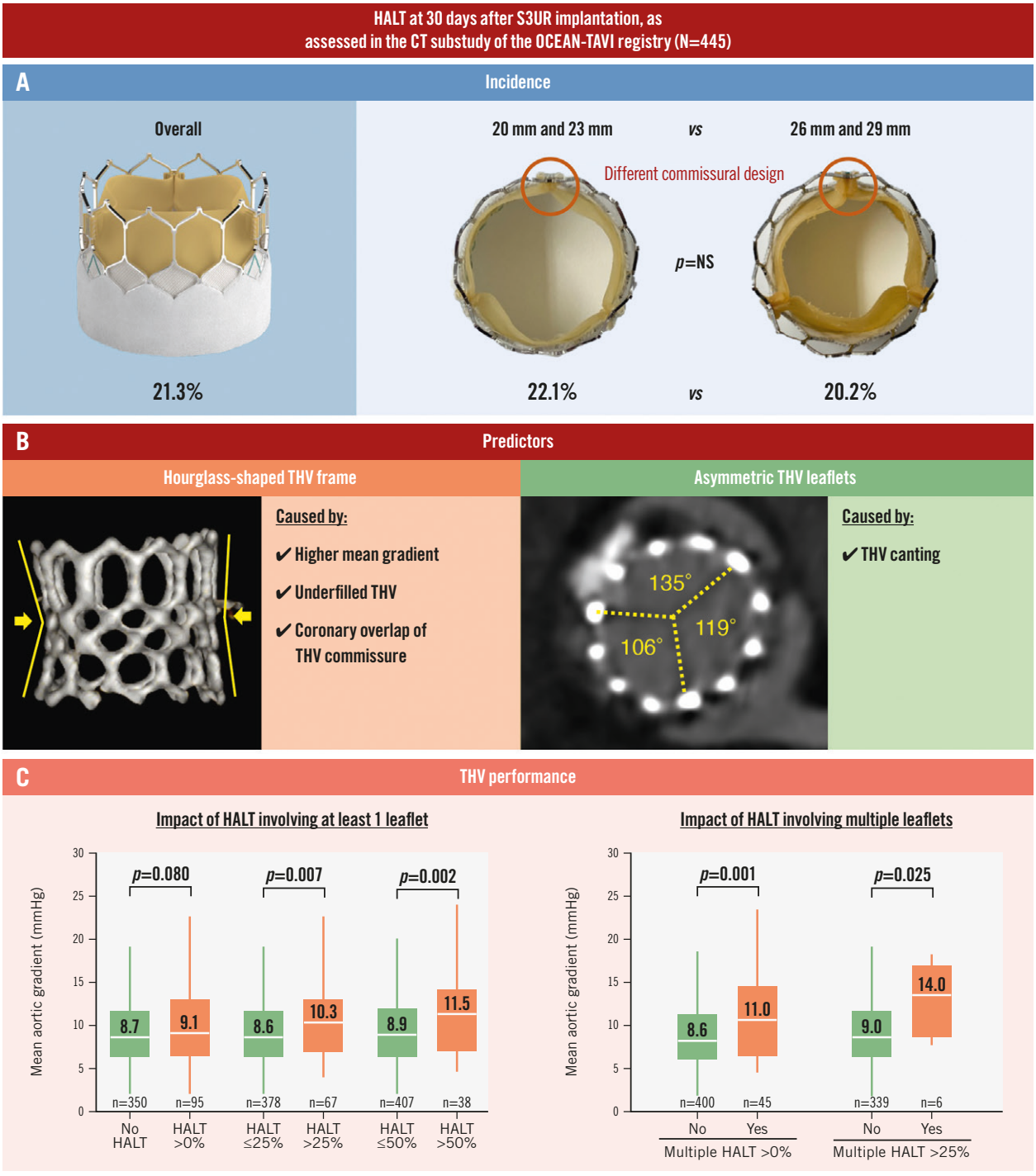
Logistic regression analysis was utilised to determine the predictors of HALT in patients who received S3UR implantation **(Supplementary Table 2, Table 4)**. The multivariable model showed that the prosthesis deformation index (OR 2.87 per 0.01 increase, 95% CI: 2.23-3.70; p<0.001) and asymmetric leaflet expansion (OR 1.10 per 1° increase, 95% CI: 1.03-1.18; p=0.004) were independently associated with HALT development. Anticoagulant therapy at discharge and moderate or severe overlap between the THV commissure and either coronary artery exhibited significance in the univariate analysis, but not in the multivariable analysis.

A comparative analysis assessing the discrimination values of these factors is shown in **Figure 3**. The prosthesis deformation index was more predictive of HALT than asymmetric leaflet expansion, although asymmetric leaflet expansion also had a relatively high discriminatory value (c-statistic: 0.88 vs 0.77; p=0.001). The best discriminatory cutoffs of the prosthesis deformation index and asymmetric leaflet expansion were 1.08 and 14°.

FACTORS ASSOCIATED WITH THV DEFORMATION

Linear regression analyses were applied to identify the factors associated with THV deformation **(Supplementary Table 3)**. In the multivariable models, a greater mean aortic gradient at baseline, underfilling implantation of the THV, and moderate or severe overlap between THV commissures were independently related to a larger prosthesis deformation

HALT following S3UR implantation.



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A) Thirty-day incidence of HALT for the S3UR. B) The two independent predictors of HALT and the risk factors for these variables. C) Box plots of postprocedural mean aortic gradient according to the degree and multiplicity of HALT. The white horizontal lines within the boxes denote the median, and the bottom and top edges of the boxes represent the 25th and 75th percentiles, respectively. The whiskers extend from the edges of the boxes to the lowest and highest values within 1.5 times the interquartile range. CT: computed tomography; HALT: hypoattenuating leaflet thickening; NS: non-significant; S3UR: SAPIEN 3 Ultra RESILIA; THV: transcatheter heart valve

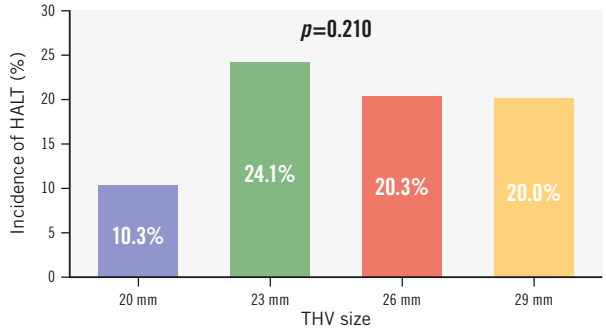


Figure 1. *Incidence of HALT for each THV size. Bar graph showing the incidence of HALT for each size of the SAPIEN 3 Ultra RESILIA prosthesis. HALT: hypoattenuating leaflet thickening; THV: transcatheter heart valve*

index, whereas only the canting degree of the THV was an independent predictor of a larger asymmetric leaflet expansion.

Discussion

To the best of our knowledge, this is the first multicentre study evaluating the clinical characteristics of HALT for the latest-generation balloon-expandable S3UR THV. The main findings of this study are summarised as follows: (i) HALT was detected in 21.3% of the patients in this cohort; (ii) the revised commissural leaflet suspension method specific to the 20 mm and 23 mm THVs to maximise the leaflet opening was not associated with an increased risk of HALT; (iii) the degree and multiplicity of HALT were associated with a higher postprocedural mean aortic gradient; and (iv) the prosthesis deformation index and asymmetric leaflet expansion were independently associated with an increased risk of HALT development.

With the expansion of TAVI indications for lower risk profiles of severe AS, the occurrence of HALT, which may be related to impaired prosthesis function and durability[2,3], has been recognised as a serious concern. Regarding the previous-generation balloon-expandable S3 THV, two prospective CT studies have investigated the clinical characteristics of HALT in detail. The first is an imaging substudy (n=221) of the Placement of Aortic Transcatheter Valves (PARTNER) 3 trial, showing that the incidence of HALT for the S3 increased from 13.3% at 30 days to 27.5% at 1 year[4]. The second is a single-centre but large study that analysed the prospectively acquired CT data of 352 patients treated with the S3, elucidating that the 30-day incidence of HALT was 20.7%[5]. In the present study evaluating 445 patients treated with the latest-generation balloon-expandable S3UR THV, the incidence of HALT at 30 days following TAVI was 21.3%, suggesting that the introduction of this newer device was not associated with an increased risk of HALT development. Fundamentally, RESILIA technology is designed to prevent calcification rather than thrombosis. However, the lack of a significant difference in the incidence of HALT between RESILIA and non-RESILIA leaflets is noteworthy, particularly given prior histological evidence suggesting a progression from thrombosis to fibrosis and then to calcification[19]. The susceptibility of a leaflet thrombus to organisation should be assessed in future studies with longer-term follow-up and repeated CT examinations. Furthermore, although we had been concerned about the potential effect of the revised commissural leaflet suspension method specific to the 20 mm and 23 mm S3UR THVs on HALT occurrence, the present study found a comparable incidence of HALT between THV sizes ≤23 mm and ≥26 mm (22.1% vs 20.2%).

HALT development includes a multifactorial process involving foreign body materials and patient-specific blood chemistry. However, previous studies with *in vitro* models have indicated local blood flow stagnation on the THV leaflets, particularly at the basal neosinus, which is consistent with the region where HALT has been detected clinically[20]. In this context, an intra-annular THV may be somewhat disadvantaged because its neosinus is surrounded by both its inner skirt and native leaflets and is structurally larger than that of a supra-annular THV. In fact, some studies have suggested a greater incidence of HALT in balloon-expandable THVs compared with self-expanding THVs[1,21]. Therefore, detecting modifiable risk factors for HALT in patients who are treated with balloon-expandable THVs is quite important. Although some previous studies have identified that the non-uniform expansion of the previous-generation S3 THV is strongly related to the development of HALT, no data on HALT for the latest-generation S3UR THV have been established. Our study successfully validated the robust association between HALT development and THV deformation, including an hourglass-shaped frame and leaflet eccentricity, in a larger, independent cohort that exclusively included patients treated with the S3UR. As *in vitro* simulation studies showed that such THV distortion can alter the flow characteristics and increase the shear stress of leaflets[22], the highly predictive performance of those factors for HALT development is mechanistically understandable.

Linear regression analyses were also performed for implanted THV deformation, identifying baseline mean aortic gradient, underfilling implantation, coronary malalignment, and THV canting as risk factors. These insights shed light on critical aspects that could inform clinical decision-making and preprocedural planning, such as THV type, size, and position. From a practical aspect, post-dilatation would be useful to mitigate the risk of THV deformation; however, this strategy entails a trade-off with the risk of procedural complications, including aortic root injury, conduction disturbances, and THV leaflet damage. In other words, in cases where the underfilling implantation of the S3UR is likely to be required because of severe calcification, other THVs with supra-annular leaflets may be a reasonable choice.

The impact of HALT on THV haemodynamic status is not well established and varies across studies, which can be attributed to the heterogeneity in the severity of HALT included in those studies. Theoretically, the haemodynamic impact of the THV is likely to differ depending on the severity of HALT, but prior studies with a relatively small number of patients may not have possessed the statistical power to perform severity-specific analyses. Our study, taking advantage of its larger cohort, successfully

Table 1. Baseline clinical and procedural characteristics.

	Overall (N=445)	HALT		*p*-value
		Yes (N=95)	No (N=350)	
Demographics				
Age, years	84 (80-87)	84 (80-86)	84 (80-88)	0.753
Male	178 (40.0)	36 (37.9)	142 (40.6)	0.636
BSA, m^2	1.48 (1.35-1.61)	1.47 (1.34-1.64)	1.48 (1.35-1.60)	0.843
Clinical Frailty Scale ≥4	189 (41.5)	39 (41.1)	150 (42.9)	0.773
NYHA Functional Class III/IV	80 (18.0)	21 (22.1)	59 (16.9)	0.247
STS-PROM score, %	6.0 (3.8-9.5)	5.1 (3.5-7.6)	6.2 (4.0-9.8)	0.062
Comorbidities				
Hypertension	325 (73.0)	70 (73.7)	255 (72.9)	0.872
Dyslipidaemia	222 (50.0)	45 (47.4)	177 (50.6)	0.580
Diabetes	147 (33.0)	29 (30.5)	118 (33.7)	0.556
Atrial fibrillation	85 (19.1)	10 (10.5)	75 (21.4)	0.011
CAD	161 (36.2)	29 (30.5)	132 (37.7)	0.192
Previous CABG	19 (4.3)	5 (5.3)	14 (4.0)	0.598
PAD	53 (11.9)	11 (11.6)	42 (12.0)	0.910
CKD: eGFR <60 mL/min/1.73 m^2	316 (71.0)	67 (70.5)	249 (71.1)	0.907
Haemodialysis	78 (17.5)	15 (15.8)	63 (18.0)	0.612
COPD	28 (6.3)	4 (4.2)	24 (6.9)	0.325
Previous stroke/TIA	41 (9.2)	6 (6.3)	35 (10.0)	0.252
Previous pacemaker	23 (5.2)	4 (4.2)	19 (5.4)	0.627
Echocardiographic data				
AVA, cm^2	0.71 (0.59-0.82)	0.73 (0.62-0.84)	0.70 (0.58-0.81)	0.492
Mean aortic gradient, mmHg	41.0 (35.0-48.8)	40.0 (33.3-47.2)	41.0 (35.1-49.3)	0.245
LVEF, %	63.5 (57.6-68.4)	63.3 (58.4-69.6)	63.7 (56.3-68.0)	0.662
Preprocedural CT data				
Bicuspid aortic valve	15 (3.4)	4 (4.2)	11 (3.1)	0.618
Annulus area, mm^2	413.0 (365.0-472.0)	402.0 (357.0-457.0)	409.9 (359.6-470.2)	0.464
LVOT calcification	40 (10.8)	12 (12.6)	36 (10.3)	0.520
Procedural variables				
Transfemoral access	425 (95.7)	91 (95.8)	334 (95.7)	0.970
Predilatation	34 (7.7)	12 (12.6)	22 (6.3)	0.052
Post-dilatation	59 (13.3)	14 (14.7)	45 (12.9)	0.643
THV size				0.210
20 mm	39 (8.8)	4 (4.2)	35 (10.0)	
23 mm	228 (51.2)	55 (57.9)	173 (49.4)	
26 mm	148 (33.3)	30 (31.6)	118 (33.7)	
29 mm	30 (6.7)	6 (6.3)	24 (6.9)	
Area oversizing for THV, %	9.8 (2.1-15.7)	11.7 (4.4-17.3)	9.4 (1.4-15.2)	0.121
Medications at discharge				
Antiplatelet therapy	287 (64.5)	62 (65.3)	225 (64.3)	0.860
Anticoagulant therapy	95 (21.4)	13 (13.7)	82 (23.4)	0.033

Values are n (%) or median (interquartile range). AVA: aortic valve area; BSA: body surface area; CABG: coronary artery bypass grafting; CAD: coronary artery disease; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; CT: computed tomography; eGFR: estimated glomerular filtration rate; HALT: hypoattenuating leaflet thickening; LVEF: left ventricular ejection fraction; LVOT: left ventricular outflow tract; NYHA: New York Heart Association; PAD: peripheral artery disease; STS-PROM: Society of Thoracic Surgeons Predicted Risk of Mortality; THV: transcatheter heart valve; TIA: transient ischaemic attack

Table 2. Postprocedural echocardiographic data.

	Overall (N=445)	HALT		*p*-value
		Yes (N=95)	No (N=350)	
EOA, cm^2	1.77 (1.47-2.11)	1.72 (1.32-2.10)	1.79 (1.48-2.11)	0.207
Indexed EOA, cm^2/m^2	1.18 (1.01-1.44)	1.14 (0.94-1.44)	1.19 (1.03-1.43)	0.123
Mean aortic gradient, mmHg	9.0 (6.4-12.0)	9.1 (6.5-13.0)	8.7 (6.3-11.6)	0.080
PVL				0.433
None-to-trivial PVL	381 (85.6)	78 (82.1)	303 (86.6)	
Mild PVL	62 (13.9)	16 (16.8)	46 (13.1)	
Moderate-to-severe PVL	2 (0.5)	1 (1.1)	1 (0.3)	
MR ≥moderate	30 (6.7)	4 (4.2)	26 (7.4)	0.358
TR ≥moderate	47 (10.6)	10 (10.5)	37 (10.6)	0.990
SPAP, mmHg	29.0 (24.0-35.0)	27.0 (22.5-32.5)	29.2 (24.4-36.0)	0.038

Values are n (%) or median (interquartile range). EOA: effective orifice area; HALT: hypoattenuating leaflet thickening; MR: mitral regurgitation; PVL: paravalvular leakage; SPAP: systolic pulmonary artery pressure; TR: tricuspid regurgitation

Table 3. Post-TAVI CT data.

	Overall (N=445)	HALT		*p*-value
		Yes (N=95)	No (N=350)	
Measured oversizing, %	–7.5 (–12.4 to –2.3)	–7.6 (–12.7 to –1.9)	–7.5 (–12.4 to –2.5)	0.740
Expansion area of THV, %				
Leaflet inflow	85.6 (82.2-89.5)	87.0 (82.2-89.7)	85.4 (82.2-89.4)	0.279
Prosthesis waist	82.8 (78.7-86.7)	80.6 (76.2-83.4)	83.8 (79.8-87.1)	<0.001
Leaflet outflow	91.1 (86.9-94.4)	91.2 (88.6-95.0)	91.0 (86.2-94.3)	0.179
THV eccentricity				
Leaflet inflow	0.32 (0.26-0.37)	0.31 (0.24-0.36)	0.32 (0.27-0.37)	0.104
Prosthesis waist	0.31 (0.26-0.36)	0.30 (0.23-0.35)	0.32 (0.27-0.36)	0.143
Leaflet outflow	0.29 (0.24-0.34)	0.28 (0.22-0.33)	0.29 (0.25-0.35)	0.154
Prosthesis deformation index	1.06 (1.05-1.08)	1.11 (1.09-1.13)	1.06 (1.04-1.07)	<0.001
Asymmetric leaflet expansion, degrees	10 (6-12)	16 (9-22)	8 (6-12)	<0.001
Implantation depth, mm	2.3 (1.7-3.5)	2.4 (1.7-3.7)	2.3 (1.6-3.4)	0.785
Canting, mm	2.0 (1.3-3.0)	2.3 (1.5-3.1)	2.0 (1.2-2.9)	0.115
Area ratio of THV to SOV, %	47.6 (43.5-51.3)	47.6 (42.6-51.3)	47.6 (43.6-51.3)	0.646
Overlap between THV commissure and LCA				0.452
Severe	144 (32.4)	32 (33.7)	112 (32.0)	
Moderate	123 (27.6)	30 (31.6)	93 (26.6)	
Mild/none	178 (40.0)	33 (34.7)	145 (41.4)	
Overlap between THV commissure and RCA				0.638
Severe	141 (31.7)	28 (29.5)	113 (32.3)	
Moderate	110 (24.7)	27 (28.4)	83 (23.7)	
Mild/none	194 (43.6)	40 (42.1)	154 (44.0)	
Moderate or severe overlap between THV commissure and either coronary artery	341 (76.6)	80 (84.2)	15 (14.4)	0.042
SOV thrombus	102 (22.9)	34 (35.8)	68 (19.4)	0.001

Values are n (%) or median (interquartile range). CT: computed tomography; HALT: hypoattenuating leaflet thickening; LCA: left coronary artery; RCA: right coronary artery; SOV: sinus of Valsalva; TAVI: transcatheter aortic valve implantation; THV: transcatheter heart valve

showed that greater degrees (>25%) and/or multiplicity (≥2 leaflets) of HALT were associated with a higher mean aortic gradient **(Central illustration)**, which may be clinically relevant. Although further study is needed to determine whether these small increases (3-4 mmHg) noted at 30 days will be amplified over time and cause structural valve deterioration, an elevated aortic gradient detected during clinical follow-up may indicate the occurrence of extensive

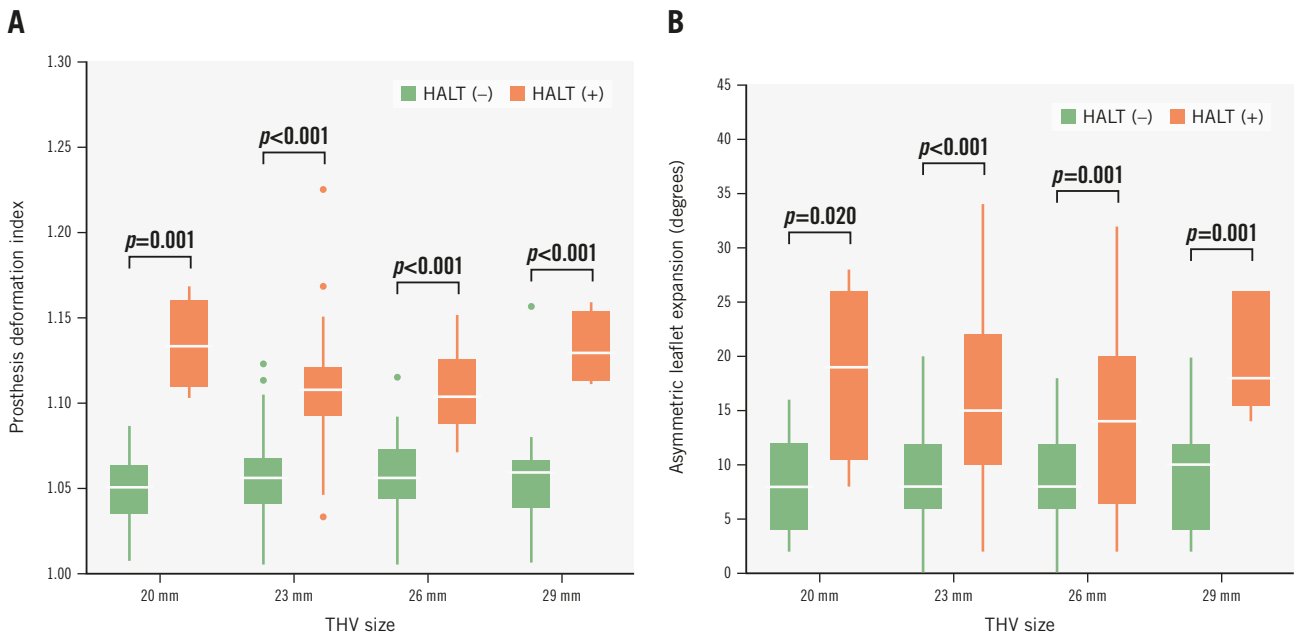


Figure 2. *Implanted THV deformation and HALT by THV size. Box plots of prosthesis deformation index (A) and asymmetric leaflet expansion (B) according to THV size. The white horizontal lines within the boxes denote the median, and the bottom and top edges of the boxes represent the 25th and 75th percentiles, respectively. The whiskers extend from the edges of boxes to the lowest and highest values within 1.5 times the interquartile range. The dots outside the whiskers represent the outliers. HALT: hypoattenuating leaflet thickening; THV: transcatheter heart valve*

HALT, which should probably be confirmed by cardiac CT. We also showed a higher incidence of fulfilling the criteria for PPM in patients with HALT; however, the incidence of PPM in relation to HALT should be carefully interpreted because PPM is essentially a subtype of non-structural valve dysfunction and should be evaluated after excluding HALT. Although numerous studies have investigated the impact of PPM following TAVI[23,24], the majority of them have not evaluated HALT for patients with PPM, potentially influencing the true incidence and prognostic effect of PPM.

The possible sequelae of subclinical leaflet thrombosis include central and systemic thromboembolism, progressive valve stenosis, and a negative impact on long-term valve durability. However, leaflet thrombosis involves a dynamic process that may develop and resolve spontaneously with or without anticoagulant use and may pose challenges in diagnosis and treatment[4,25]. Thus, the routine use of preventive anticoagulants or follow-up cardiac CT screenings following TAVI remains debatable. On the other hand, the growing evidence regarding the negative impact of a major burden of HALT (>50%) on long-term THV outcomes is of great interest[26]. Considering this finding in conjunction with a recent histological study suggesting that the organisation of leaflet thrombus to pannus begins within a year, earlier initiation of anticoagulation could be more effective[19]. Our study only evaluated the 30-day clinical characteristics of HALT for the S3UR, and a longer-term follow-up is warranted to assess the full effect of HALT on THV performance and structural valve dysfunction.

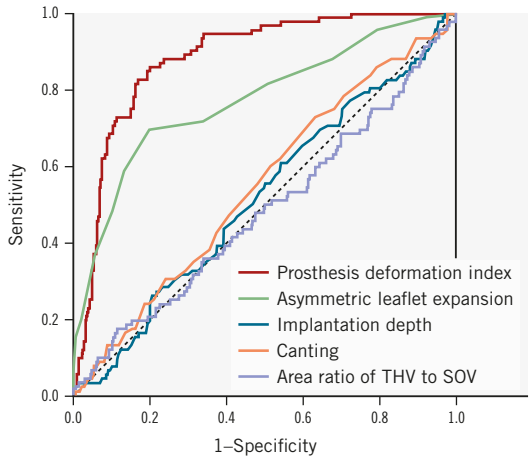
Limitations

This study has several limitations. First, this study has inherent limitations as it is based on a retrospective analysis of prospectively registered dataset. However, the participation of several institutions in the study may have attenuated the potential selection and ascertainment biases. Second, this study only examined the 30-day clinical features of HALT for the S3UR despite the transient and dynamic nature of HALT. Future studies with longer-term follow-up and detailed antithrombotic regimens are needed to assess the full clinical impact of HALT. In addition, the single-arm design that enrolled only patients who received an S3UR precluded direct comparison with those who received a previous-generation S3. Third, CT analyses were performed by an independent core laboratory blinded to clinical outcomes, but the presence or absence of HALT as a primary outcome measure would be apparent on CT images to the reviewers, resulting in some inevitable measurement biases. Fourth, among a total of 481 patients, 32 patients (6.7%) were excluded from our analysis because of poor image quality caused by beam artefacts. Although the CT acquisition protocol of this study adopted a tube voltage of 100-120 kV based on previous studies, the aggressive use of a higher tube voltage (~140 kV) could have mitigated such artefacts[27]. Finally, the information on baseline oral anticoagulant, such as dose, regimens, and targeted international normalised ratios for warfarin users, was unavailable, which could have affected the outcomes.

Table 4. Multivariable logistic regression analysis for predictors of HALT.

Variables	Adjusted OR	95% CI	*p*-value
Age (per 1-year increase)	0.95	0.89-1.02	0.194
Male sex	1.55	0.58-4.15	0.379
Anticoagulant therapy at discharge	0.39	0.13-1.20	0.105
THV size ≤23 mm	1.25	0.49-3.23	0.640
Prosthesis deformation index (per 0.01 increase)	2.87	2.23-3.70	<0.001
Asymmetric leaflet expansion (per 1° increase)	1.10	1.03-1.18	0.004
Implantation depth (per 1 mm increase)	0.97	0.75-1.26	0.839
Canting (per 1 mm increase)	0.96	0.71-1.32	0.816
Area ratio of THV to SOV (per 5% increase)	1.03	0.79-1.35	0.790
Moderate or severe overlap between THV commissure and either coronary artery	1.49	0.49-4.58	0.478

CI: confidence interval; HALT: hypoattenuating leaflet thickening; OR: odds ratio; SOV: sinus of Valsalva; THV: transcatheter heart valve



Predictors	Cutoff point	Sensitivity, %	Specificity, %	PPV, %	NPV, %	C-statistic (95% CI)
Prosthesis deformation index (A)	1.08	85.0	79.7	53.3	95.2	0.88 (0.84-0.91)
Asymmetric leaflet expansion (B)	14°	70.0	80.2	48.5	90.8	0.77 (0.71-0.83)
Implantation depth (C)	3.7 mm	26.3	80.2	25.5	79.7	0.52 (0.45-0.58)
Canting (D)	1.6 mm	73.7	36.6	24.0	83.7	0.55 (0.48-0.61)
Area ratio of THV to SOV (E)	54.1%	17.9	88.3	29.3	79.8	0.48 (0.41-0.55)
Comparison	**A vs B**	**A vs C**	**A vs D**	**A vs E**		**B vs C**
Difference	0.108	0.365	0.334	0.400		0.257
p-value	0.001	<0.001	<0.001	<0.001		<0.001
Comparison	**B vs D**	**B vs E**	**C vs D**	**C vs E**		**D vs E**
Difference	0.226	0.292	–0.031	0.035		0.066
p-value	<0.001	<0.001	0.423	0.423		0.172

Figure 3. *Predictive ability of implanted THV geometry for HALT. Receiver operating characteristic curves with comparative analyses of the predictability of prosthesis deformation index (A), asymmetric leaflet expansion (B), implantation depth (C), canting (D), and area ratio of THV to SOV (E) for HALT. CI: confidence interval; HALT: hypoattenuating leaflet thickening; NPV: negative predictive value; PPV: positive predictive value; SOV: sinus of Valsalva; THV: transcatheter heart valve*

Conclusions

On 30-day CT, HALT was detected in 21.3% of the patients who were treated with the latest-generation balloon-expandable S3UR THV. The modified commissural leaflet suspension method specific to the 20 mm and 23 mm S3UR THVs was not associated with an increased risk of HALT, whereas the prosthesis deformation index and asymmetric leaflet expansion were independently associated with an increased risk of HALT development regardless of the THV size. These findings may shed light on important aspects that could inform clinical decision-making, preprocedural planning, and amelioration of THV designs.

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Conflict of interest statement

F. Yashima and Y. Ohno are clinical proctors for Medtronic. M. Asami is a clinical proctor for Abbott and Medtronic. Y. Fuku is a clinical proctor for Edwards Lifesciences and Medtronic. G. Nakazawa is a clinical proctor for Edwards Lifesciences and Abbott. M. Yamamoto, S. Shirai, D. Hachinohe, and K. Hayashida are clinical proctors for Edwards Lifesciences, Abbott, and Medtronic. The other authors have no conflicts of interest to declare.

References

1. Chakravarty T, Søndergaard L, Friedman J, De Backer O, Berman D, Kofoed KF, Jilaihawi H, Shiota T, Abramowitz Y, Jørgensen TH, Rami T, Israr S, Fontana G, de Knegt M, Fuchs A, Lyden P, Trento A, Bhatt DL, Leon MB, Makkar RR; RESOLVE; SAVORY Investigators. Subclinical leaflet thrombosis in surgical and transcatheter bioprosthetic aortic valves: an observational study. *Lancet*. 2017;389:2383-92.

2. Sellers SL, Turner CT, Sathananthan J, Cartlidge TRG, Sin F, Bouchareb R, Mooney J, Nørgaard BL, Bax JJ, Bernatchez PN, Dweck MR, Granville DJ, Newby DE, Lauck S, Webb JG, Payne GW, Pibarot P, Blanke P, Seidman MA, Leipsic JA. Transcatheter Aortic Heart Valves: Histological Analysis Providing Insight to Leaflet Thickening and Structural Valve Degeneration. *JACC Cardiovasc Imaging*. 2019;12:135-45.

3. Cartlidge TRG, Doris MK, Sellers SL, Pawade TA, White AC, Pessotto R, Kwiecinski J, Fletcher A, Alcaide C, Lucatelli C, Densem C, Rudd JHF, van Beek EJR, Tavares A, Virmani R, Berman D, Leipsic JA, Newby DE, Dweck MR. Detection and Prediction of Bioprosthetic Aortic Valve Degeneration. *J Am Coll Cardiol*. 2019;73:1107-19.

4. Makkar RR, Blanke P, Leipsic J, Thourani V, Chakravarty T, Brown D, Trento A, Guyton R, Babaliaros V, Williams M, Jilaihawi H, Kodali S, George I, Lu M, McCabe JM, Friedman J, Smalling R, Wong SC, Yazdani S, Bhatt DL, Bax J, Kapadia S, Herrmann HC, Mack M, Leon MB. Subclinical Leaflet Thrombosis in Transcatheter and Surgical Bioprosthetic Valves: PARTNER 3 Cardiac Computed Tomography Substudy. *J Am Coll Cardiol*. 2020;75:3003-15.

5. Fukui M, Bapat VN, Garcia S, Dworak MW, Hashimoto G, Sato H, Gössl M, Enriquez-Sarano M, Lesser JR, Cavalcante JL, Sorajja P. Deformation of Transcatheter Aortic Valve Prostheses: Implications for Hypoattenuating Leaflet Thickening and Clinical Outcomes. *Circulation*. 2022;146:480-93.

6. Yanagisawa R, Tanaka M, Yashima F, Arai T, Jinzaki M, Shimizu H, Fukuda K, Watanabe Y, Naganuma T, Higashimori A, Mizutani K, Araki M, Tada N, Yamanaka F, Otsuka T, Yamamoto M, Hayashida K. Early and Late Leaflet Thrombosis After Transcatheter Aortic Valve Replacement. *Circ Cardiovasc Interv*. 2019;12:e007349.

7. Khan JM, Rogers T, Waksman R, Torguson R, Weissman G, Medvedofsky D, Craig PE, Zhang C, Gordon P, Ehsan A, Wilson SR, Goncalves J, Levitt R, Hahn C, Parikh P, Bilfinger T, Butzel D, Buchanan S, Hanna N, Garrett R, Shults C, Garcia-Garcia HM, Kolm P, Satler LF, Buchbinder M, Ben-Dor I, Asch FM. Hemodynamics and Subclinical Leaflet Thrombosis in Low-Risk Patients Undergoing Transcatheter Aortic Valve Replacement. *Circ Cardiovasc Imaging*. 2019;12:e009608.

8. Yamamoto M, Yashima F, Shirai S, Tada N, Naganuma T, Yamawaki M, Yamanaka F, Mizutani K, Noguchi M, Ueno H, Takagi K, Ohno Y, Izumo M, Nishina H, Suzuyama H, Yamasaki K, Nishioka K, Hachinohe D, Fuku Y, Otsuka T, Asami M, Watanabe Y, Hayashida K, Ocean-Tavi Investigators OBOT. Performance and outcomes of the SAPIEN 3 Ultra RESILIA transcatheter heart valve in the OCEAN-TAVI registry. *EuroIntervention*. 2024;20:579-90.

9. Stinis CT, Abbas AE, Teirstein P, Makkar RR, Chung CJ, Iyer V, Généreux P, Kipperman RM, Harrison JK, Hughes GC, Lyons JM, Rahman A, Kakouros N, Walker J, Roberts DK, Huang PH, Kar B, Dhoble A, Logsdon DP, Khanna PK, Aragon J, McCabe JM. Real-World Outcomes for the Fifth-Generation Balloon Expandable Transcatheter Heart Valve in the United States. *JACC Cardiovasc Interv*. 2024;17:1032-44.

10. Izumi C, Eishi K, Ashihara K, Arita T, Otsuji Y, Kunihara T, Komiya T, Shibata T, Seo Y, Daimon M, Takanashi S, Tanaka H, Nakatani S, Ninami H, Nishi H, Hayashida K, Yaku H, Yamaguchi J, Yamamoto K, Watanabe H, Abe Y, Amaki M, Amano M, Obase K, Tabata M, Miura T, Miyake M, Murata M, Watanabe N, Akasaka T, Okita Y, Kimura T, Sawa Y, Yoshida K; Japanese Circulation Society Joint Working Group. JCS/JSCS/JATS/JSVS 2020 Guidelines on the Management of Valvular Heart Disease. *Circ J*. 2020;84:2037-119.

11. Blanke P, Weir-McCall JR, Achenbach S, Delgado V, Hausleiter J, Jilaihawi H, Marwan M, Norgaard BL, Piazza N, Schoenhagen P, Leipsic JA. Computed tomography imaging in the context of transcatheter aortic valve implantation (TAVI) / transcatheter aortic valve replacement (TAVR): An expert consensus document of the Society of Cardiovascular Computed Tomography. *J Cardiovasc Comput Tomogr*. 2019;13:1-20.

12. VARC-3 WRITING COMMITTEE; Généreux P, Piazza N, Alu MC, Nazif T, Hahn RT, Pibarot P, Bax JJ, Leipsic JA, Blanke P, Blackstone EH, Finn MT, Kapadia S, Linke A, Mack MJ, Makkar R, Mehran R, Popma JJ, Reardon M, Rodes-Cabau J, Van Mieghem NM, Webb JG, Cohen DJ, Leon MB. Valve Academic Research Consortium 3: Updated Endpoint Definitions for Aortic Valve Clinical Research. *J Am Coll Cardiol*. 2021;77:2717-46.

13. Ochiai T, Chakravarty T, Yoon SH, Kaewkes D, Flint N, Patel V, Mahani S, Tiwana R, Sekhon N, Nakamura M, Cheng W, Makkar R. Coronary Access After TAVR. *JACC Cardiovasc Interv*. 2020;13:693-705.

14. Ishizu K, Shirai S, Tashiro H, Kitano K, Tabata H, Morofuji T, Nakamura M, Murakami N, Morinaga T, Hayashi M, Isotani A, Arai Y, Ohno N, Kakumoto S, Ando K. Mid-term impact of underfilling and overfilling of the SAPIEN 3 balloon-expandable transcatheter aortic valve implantation on mortality and valve function. *Heart Vessels*. 2022;37:2067-82.

15. Fukui M, Olson MR, Bapat VN. Computed Tomography-Derived Nominal Dimensions of Transcatheter Heart Valves. *JACC Cardiovasc Interv*. 2025;18:129-33.

16. Tsunaki T, Yamamoto M, Shimura T, Kagase A, Naganuma T, Higashimori A, Araki M, Yamanaka F, Mizutani K, Watanabe Y, Otsuka T, Yanagisawa R, Hayashida K. Silent Valsalva thrombus between the native Valsalva and balloon-expandable transcatheter heart valve: multicentre Japanese registry analysis. *EuroIntervention*. 2019;15:892-9.

17. Redondo A, Baladrón Zorita C, Tchétché D, Santos-Martinez S, Delgado-Arana JR, Barrero A, Gutiérrez H, Serrador Frutos A, Ybarra Falcón C, Gómez MG, Carrasco Moraleja M, Sevilla T, Sanchez Lite I, Sanz E, San Román JA, Amat-Santos IJ. Commissural Versus Coronary Optimized Alignment During Transcatheter Aortic Valve Replacement. *JACC Cardiovasc Interv*. 2022;15:135-46.

18. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics*. 1988;44:837-45.

19. Sato Y, Torii S, Kawai K, Yahagi K, Kutyna M, Kawakami R, Konishi T, Vozenilek AE, Jinnouchi H, Sakamoto A, Mori H, Cornelissen A, Mori M, Tanaka T, Sekimoto T, Kutys R, Ghosh SKB, Forrest JK, Reardon MJ, Romero ME, Kolodgie FD, Virmani R, Finn AV. Pathology of Self-Expanding Transcatheter Aortic Bioprostheses and Hypoattenuated Leaflet Thickening. *Circ Cardiovasc Interv*. 2025;18:e014523.

20. Midha PA, Raghav V, Sharma R, Condado JF, Okafor IU, Rami T, Kumar G, Thourani VH, Jilaihawi H, Babaliaros V, Makkar RR, Yoganathan AP. The Fluid Mechanics of Transcatheter Heart Valve Leaflet Thrombosis in the Neosinus. *Circulation*. 2017;136:1598-609.

21. Tang L, Lesser JR, Schneider LM, Burns MR, Gössl M, Garberich R, Niikura H, Witt D, Sorajja P. Prospective Evaluation for Hypoattenuated Leaflet Thickening Following Transcatheter Aortic Valve Implantation. *Am J Cardiol*. 2019;123:658-66.

22. Gunning PS, Saikrishnan N, Yoganathan AP, McNamara LM. Total ellipse of the heart valve: the impact of eccentric stent distortion on the regional dynamic deformation of pericardial tissue leaflets of a transcatheter aortic valve replacement. *J R Soc Interface*. 2015;12:20150737.

23. Ishizu K, Kitano K, Yamamoto K, Hayashi M, Shirai S, Ohno N, Kakumoto S, Ando K, Yashima F, Nishina H, Izumo M, Asami M, Tada N, Yamawaki M, Naganuma T, Yamanaka F, Ohno Y, Ueno H, Noguchi M, Mizutani K, Takagi K, Watanabe Y, Yamamoto M, Hayashida K; OCEAN-TAVI Investigators. Update on Prosthesis-Patient Mismatch Following Transcatheter Aortic Valve Replacement in Asian Patients. *JACC Asia*. 2024;4:793-806.

24. Herrmann HC, Daneshvar SA, Fonarow GC, Stebbins A, Vemulapalli S, Desai ND, Malenka DJ, Thourani VH, Rymer J, Kosinski AS. Prosthesis-Patient Mismatch in Patients Undergoing Transcatheter Aortic Valve Replacement: From the STS/ACC TVT Registry. *J Am Coll Cardiol*. 2018;72:2701-11.

25. Blanke P, Leipsic JA, Popma JJ, Yakubov SJ, Deeb GM, Gada H, Mumtaz M, Ramlawi B, Kleiman NS, Sorajja P, Askew J, Meduri CU, Kauten J, Melnitchouk S, Inglessis I, Huang J, Boulware M, Reardon MJ; Evolut Low Risk LTI Substudy Investigators. Bioprosthetic Aortic Valve Leaflet Thickening in the Evolut Low Risk Sub-Study. *J Am Coll Cardiol*. 2020;75:2430-42.

26. Rashid HN, Michail M, Ramnarain J, Nasis A, Nicholls SJ, Cameron JD, Gooley RP. The impact of hypo-attenuated leaflet thickening on haemodynamic valve deterioration following transcatheter aortic valve replacement. *J Cardiovasc Comput Tomogr*. 2022;16:168-73.

27. Rashid HN, Rajani R, Leipsic J, Maurovitch-Horvat P, Patterson T, Redwood S, Lee J, Hurrell H, Nicholls SJ, Nasis A, Seneviratne S, Cameron JD, Prendergast B, Gooley RP. Computed tomography imaging for subclinical leaflet thrombosis following surgical and transcatheter aortic valve replacement. *J Cardiovasc Comput Tomogr*. 2023;17:2-10.

Supplementary data

Supplementary Appendix 1. Data collection.

Supplementary Appendix 2. CT image acquisition.

Supplementary Table 1. Severity of HALT and RLM according to leaflet-level analysis.

Supplementary Table 2. Univariate logistic regression analyses for HALT.

Supplementary Table 3. Linear regression analyses for prosthesis deformation index and asymmetric leaflet expansion.

Supplementary Figure 1. Assessment of HALT and RLM per THV leaflet.

Supplementary Figure 2. Assessment of implanted THV geometry.

Supplementary Figure 3. Area ratio of THV to SOV.

Supplementary Figure 4. Incidence of HALT according to antithrombotic regimens.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-25-00523

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ORIGINAL RESEARCH

Long-term outcomes and durability of balloon-expandable TAVI in small and large annuli

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ABSTRACT

BACKGROUND: Evidence regarding the long-term outcomes and durability of balloon-expandable transcatheter heart valves (BE-THVs) after transcatheter aortic valve implantation (TAVI) is still scarce.

AIMS: This study evaluates these outcomes and further examines their association with the annular size in patients.

METHODS: A total of 2,699 patients who had undergone TAVI with a BE-THV at least 5 years prior to our study were analysed. A small aortic annulus (SAA) was defined as an area ≤430 mm^2; any larger annuli were labelled large aortic annuli (LAA). The primary endpoints were the incidence of all-cause mortality and bioprosthetic valve failure (BVF) between the SAA and LAA groups. As a subanalysis, the primary endpoints were examined in relation to postprocedural mean pressure gradient (mPG) ≥20 mmHg, severe prosthesis-patient mismatch (PPM), and sex differences, comparing SAA and LAA each time.

RESULTS: Overall, 66.4% (n=1,793) of patients were categorised into the SAA group. At 7 years after TAVI, the cumulative all-cause mortality showed differences between the SAA and LAA groups (55.2% vs 58.6%), while BVF assessed by Gray's test was similar between the groups (3.3% vs 2.7%). The Cox multivariable analysis revealed no association between SAA and worse prognosis (hazard ratio 1.07, 95% confidence interval: 0.85-1.36; p=0.56). There were no significant differences in mortality or BVF regarding an mPG ≥20 mmHg, severe PPM, or sex between the SAA and LAA groups (all p>0.05).

CONCLUSIONS: Annular size differences were not found to influence long-term outcomes or valve durability following TAVI with a BE-THV, suggesting that other factors warrant further investigation.

KEYWORDS: balloon-expandable transcatheter heart valve; large aortic annulus; small aortic annulus; transcatheter aortic valve implantation

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The indications for transcatheter aortic valve implantation (TAVI) in aortic stenosis (AS) patients have been expanded with growing clinical evidence[1,2]. One of the key issues is the clinical demand for long-term durability data on transcatheter heart valves (THVs) to support TAVI expansion into a broader patient population. However, the data on this matter are limited and insufficient to draw definitive conclusions. Recent clinical concerns have also emerged regarding the impact of THV design on haemodynamic parameters assessed by postprocedural echocardiography and their association with long-term prognosis. Many studies indicate that balloon-expandable (BE)-THVs result in higher mean pressure gradients (mPG) and a greater incidence of prosthesis-patient mismatch (PPM) compared to self-expanding (SE)-THVs, especially in patients with a small aortic annulus (SAA)[3,4]. This trend has also been validated by previous reports in Asian patients with smaller body sizes[5,6]. Several of these parameters are featured in a recent pivotal randomised controlled trial (RCT) and the Valve Academic Research Consortium (VARC)-3 criteria as critical indicators for assessing valve function[3,7]. In contrast, another pivotal RCT using BE-THVs has demonstrated that long-term clinical outcomes do not differ significantly by annular size, suggesting that smaller annuli do not necessarily confer a worse prognosis[8]. Investigating the long-term outcomes and valve durability of patients with an SAA receiving a BE-THV is essential to explore the clinical significance and potential generalisability of the echocardiographic parameters observed in this subset of patients. Therefore, this study utilises a large cohort of 2,699 patients to examine whether long-term outcomes up to 7 years after TAVI differ based on variations in the baseline aortic annular size. Furthermore, the bioprosthetic valve failure (BVF) criteria defined by VARC-3 were adopted to accurately assess the relationship between annular size differences and THV durability.

Impact on daily practice

The long-term prognosis of elderly patients treated with a balloon-expandable transcatheter heart valve via transcatheter aortic valve implantation (TAVI) was worse than expected, though the frequency of bioprosthetic valve failure (BVF) was low and within acceptable limits. It was found that factors such as annular size and postoperative haemodynamic parameters, defined by echocardiography, had minimal impact on long-term prognosis and BVF. Moving forward, further research is needed to validate these findings. The focus should be on developing more comprehensive lifetime management strategies for elderly patients with aortic stenosis undergoing TAVI, as well as exploring new indicators that may more accurately predict long-term outcomes and BVF in these patients.

Methods

STUDY POPULATION

The data used in this study were extracted from the pooled Optimized transCathEter vAlvular interventioN-Transcatheter Aortic Valve Implantation (OCEAN-TAVI) registry database[9,10]. This study was registered with the University Hospital Medical Information Network Clinical Trials Registry (UMIN000020423) and received approval from the International Committee of Medical Journal Editors. The study protocol was created in alignment with the Declaration of Helsinki and approved by the ethics committees of all participating hospitals. Informed consent was obtained from all patients before their enrolment in the study. The study was conducted with a cohort of 2,756 patients who were scheduled to undergo treatment with a BE-THV of the SAPIEN 3 series (Edwards Lifesciences) between May 2016 and September 2019, with the expectation of a minimum follow-up of 5 years. Consistent with previous investigations[3,4], the definition of an SAA was a cutoff annulus size equal to or less than 430 mm^2 assessed by preprocedural multidetector computed tomography (CT). The exclusion criteria of this study were the following: (1) patients without CT examinations or missing information from CT findings were initially excluded (n=42), (2) THV delivery failure during TAVI (n=2), (3) patients who were discharged alive but required a surgical valve replacement due to procedural complications (n=5), and (4) patients who were discharged alive but had a second THV implantation during an index TAVI procedure (n=8). The remaining 2,699 patients constituted the study population, which was then divided into the SAA (≤430 mm^2) and large annulus area (LAA; >430 mm^2) groups according to the annular size. The study flowchart is shown in **Supplementary Figure 1**.

DEVICE DESCRIPTION

The valve sizes of the BE-THVs were 20, 23, 26, and 29 mm. Device size was determined at each institution using standard sizing charts, with a general recommendation to avoid oversizing by more than 20%. Predilatation, post-dilatation, and the approach route were determined by each institution's Heart Team, with approaches limited to transfemoral, transapical, or direct aortic access during this period, as subclavian access was not approved.

DATA DEFINITION AND STUDY ENDPOINTS

The OCEAN-TAVI database includes baseline patient characteristics, laboratory data, transthoracic echocardiography (TTE) findings, and CT parameters. The severity of aortic stenosis was determined by the aortic valve area (AVA), indexed AVA, peak aortic valve velocity,

Abbreviations

BE-THV	balloon-expandable transcatheter heart valve	**LAA**	large aortic annulus	**PVL**	paravalvular leakage
BVF	bioprosthetic valve failure	**mPG**	mean pressure gradient	**SAA**	small aortic annulus
EOA	effective orifice area	**PPM**	prosthesis-patient mismatch	**TAVI**	transcatheter aortic valve implantation

or mPG. All procedural complications, including vascular complications, bleeding, stroke, acute kidney injury, and newly required pacemaker implantation (PMI) were evaluated. The postprocedural TTE was performed during the index hospital stay before discharge. All procedure-related variables, complications, echocardiographic findings – including paravalvular leakage (PVL) and PPM – and BVF were defined using VARC-3 criteria[7]. The postprocedural degree of PVL was classified as none-trace, mild, moderate, or severe. The existence of severe PPM was classified as an indexed effective orifice area (EOA) ≤0.65 cm² in patients with a body mass index (BMI) <30 kg/m², whereas severe PPM was defined as an indexed EOA ≤0.55 cm² in patients with a BMI ≥30 kg/m². BVF is defined as the fulfilment of one of the following three criteria: Stage 1 involves any bioprosthetic valve dysfunction associated with clinically expressive criteria. This can include new-onset or worsening symptoms; left ventricular dilation, hypertrophy, or dysfunction; or the presence of pulmonary hypertension. Additionally, Stage 1 includes irreversible Stage 3 haemodynamic valve deterioration (HVD). Stage 3 HVD is characterised by a significant increase in the mean transvalvular gradient of 20 mmHg or more, resulting in a mean gradient of 30 mmHg or higher, accompanied by a reduction in EOA to 0.6 cm² or less, or a decrease of 50% or more. Alternatively, there may be a decrease in the Doppler velocity index of 0.2 or more, or a decrease of 40% or more, compared with an echocardiographic assessment conducted 1-3 months post-procedure. Another indicator of Stage 1 is the new occurrence or an increase of two or more grades of intraprosthetic aortic regurgitation (AR), resulting in severe AR. Stage 2 is defined by the need for an aortic valve intervention, typically indicating that surgical or other transcatheter aortic valve (TAV)-in-TAV interventions are necessary to address the valve dysfunction. Stage 3 is characterised by valve-related death, or death that is presumed to be directly related to bioprosthetic valve dysfunction, signifying the most severe form of failure. Patients who have died as a result of prosthetic valve endocarditis (PVE) are also classified under Stage 3 BVF. The primary endpoints were the incidence of all-cause mortality and BVF in the overall cohort and within the SAA or LAA groups. A subanalysis investigated the prognosis and frequency of BVF in patients with and without a postprocedural mPG ≥20 mmHg and severe PPM. Additionally, sex differences were analysed by comparing SAA and LAA outcomes between males and females. Heart failure (HF) rehospitalisation was also evaluated as a secondary outcome.

STATISTICAL ANALYSIS

Continuous variables are expressed as mean±standard deviation and median with interquartile range. Categorical data were compared between the groups using chi-square tests. Differences in non-categorical data were tested using the unpaired Student's t-test or Mann-Whitney U test, depending on the variable distribution. For the primary outcome, the Kaplan-Meier method was used to estimate the cumulative incidence of all-cause mortality. An exposure-adjusted event rate of BVF was estimated by dividing the number of events reported by the total follow-up time of the study population and reported using a patient-year unit (per 1,000 patient-years), based on the recommendation of the VARC-3 criteria[7]. The cumulative incidence function was used to estimate the incidence of BVF, accounting for competing risk, with death without BVF treated as a competing event. The Fine and Gray model was developed to analyse the association with the risk of BVF events while appropriately addressing competing risks. To detect the predictors of the primary endpoint of all-cause mortality, clinical variables in the univariable analysis (p<0.05) were included in a multivariable Cox regression analysis. A subsequent multivariable model that included all significant variables and hazard ratios (HRs) was constructed, and the 95% confidence intervals (CIs) were estimated. The interaction between annular size and the primary endpoint was evaluated using a forest plot. This analysis examined whether the incidence of the primary endpoint differed between the SAA and LAA groups depending on baseline characteristics such as patient demographics, postprocedural mPG, and the presence of severe PPM. All statistical analyses were performed using SPSS software, version 22 (IBM). Differences were considered statistically significant at a p-value<0.05, and 95% CIs are reported as appropriate.

Results

BASELINE CHARACTERISTICS

The baseline patient characteristics are presented in **Table 1**. In the overall cohort, the average age was 84.4 years old, and 33.4% were male. There were numerous differences in the clinical and echocardiographic variables between the groups. The proportion of males was lower in the SAA group, whereas it was higher in the LAA group (15.4% vs 68.9%; p<0.001). Patients in the SAA group had smaller body sizes, resulting in lower creatinine levels, although there was no significant difference in the estimated glomerular filtration rate. In the SAA group, increased peak flow velocity and mPG on echocardiography were observed, and stroke volume was lower. Procedurally, predilatation was more frequently performed in the LAA group.

POSTPROCEDURAL ECHOCARDIOGRAPHIC PARAMETERS AND PROCEDURAL OUTCOMES

Postprocedural echocardiographic parameters and procedural variables are presented in **Table 2**. Both EOA and indexed EOA were significantly smaller in the SAA group than in the LAA group. The postprocedural peak velocity and mPG were higher in the SAA group. The prevalence of an mPG ≥20 mmHg was significantly higher in the SAA group than in the LAA group (8.5% vs 1.8%; p<0.001). The rate of severe PPM was also higher in the SAA group than the LAA group (3.0% vs 1.0%). Except for the rate of PMI (6.9% vs 3.6%; p=0.001), the incidences of procedural complications were similar between the two groups. Important variables are summarised in **Supplementary Figure 2**.

LONG-TERM OUTCOMES

The median follow-up period was 4.8 years (interquartile range 2.4-5.7), with a maximum of 8.8 years after TAVI. At the 5-year mark, the follow-up rate reached 85.7%. A total of 1,139 deaths were observed, with a 7-year cumulative

Table 1. Baseline characteristics between the SAA and LAA groups.

	Overall (n=2,699)	SAA (n=1,793)	LAA (n=906)	*p*-value
Clinical variables				
Age, years	84.36±5.25	84.78±5.10	83.54±5.45	<0.001
Male	901 (33.4)	277 (15.4)	624 (68.9)	<0.001
Height, cm	151.05±9.31	147.92±7.81	157.24±8.95	<0.001
Body weight, kg	51.15±10.56	48.75±9.70	55.89±10.61	<0.001
BMI, kg/m^2	22.34±3.73	22.23±3.80	22.56±3.58	0.030
BSA, m^2	1.45±0.17	1.40±0.15	1.55±0.17	<0.001
Hypertension	2,278 (84.4)	1,537 (85.7)	741 (81.8)	0.009
Diabetes	806 (29.9)	507 (28.3)	299 (33.0)	0.013
Coronary artery disease	957 (35.5)	582 (32.5)	375 (41.4)	<0.001
Peripheral artery disease	277 (10.3)	186 (10.4)	91 (10.0)	0.846
Atrial fibrillation	622 (23.0)	362 (20.2)	260 (28.7)	<0.001
Previous stroke	313 (11.6)	202 (11.3)	111 (12.3)	0.492
NYHA III/IV	986 (36.5)	647 (36.1)	339 (37.4)	0.524
Chronic kidney disease	1,890 (70.0)	1,255 (70.0)	635 (70.1)	0.995
Haemodialysis	3 (0.1)	1 (0.1)	2 (0.2)	0.262
COPD	223 (8.3)	112 (6.2)	111 (12.3)	<0.001
Previous CABG	110 (4.1)	63 (3.5)	47 (5.2)	0.297
Blood examinations				
Creatinine, mg/dL	1.02±0.58	0.97±0.58	1.11±0.57	<0.001
eGFR, mL/min/1.73 m^2	51.53±18.34	51.33±18.23	51.94±18.56	0.417
Echocardiographic variables				
AVA, cm^2	0.64±0.18	0.62±0.17	0.68±0.19	<0.001
Indexed AVA, cm^2/m^2	0.44±0.12	0.45±0.12	0.44±0.12	0.410
Peak flow velocity, m/sec	4.44±0.78	4.50±0.76	4.32±0.78	<0.001
Peak PG, mmHg	81.28±28.00	83.45±28.18	77.00±27.14	<0.001
mPG, mmHg	47.30±17.42	48.52±17.63	44.89±16.77	<0.001
LVEF, %	60.15±12.31	62.16±11.43	56.17±12.99	<0.001
Stroke volume, mL	65.59±18.98	64.13±18.09	68.48±20.35	<0.001
CT variables				
Annulus size of area, mm^2	412.31±76.97	368.21±37.05	499.58±58.85	<0.001
Annulus size of perimeter, mm	72.84±7.30	69.13±4.62	80.11±6.02	<0.001
Procedural variables				
Transfemoral access	2,620 (97)	1,742 (97)	878 (97)	0.66
Transapical access	50 (2)	30 (2)	20 (2)	
Direct aortic access	20 (1)	14 (1)	6 (1)	
Predilatation	1,042 (38.6)	641 (35.8)	401 (44.3)	<0.001
Post-dilatation	575 (21.3)	376 (21.0)	199 (22.0)	0.590
THV size				<0.001
20 mm	175 (6)	175 (10)	0 (0)	
23 mm	1,528 (57)	1,440 (80)	88 (10)	
26 mm	829 (31)	178 (10)	651 (72)	
29 mm	167 (6)	0 (0)	167 (18)	

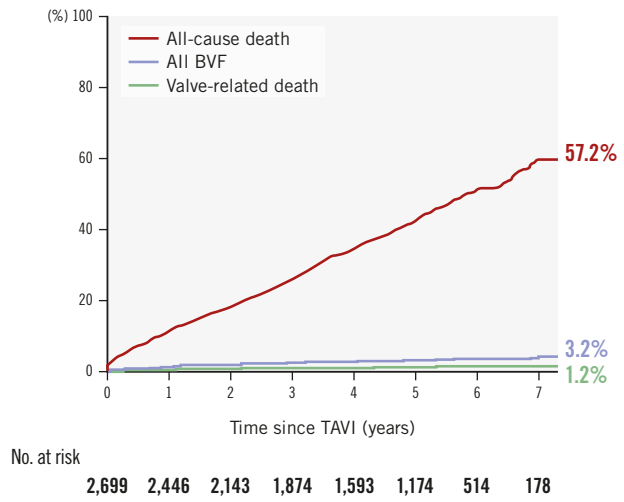
Values are numbers (%) or mean±SD. Standardised difference for categorical variables and standardised mean difference for continuous variables.
AVA: aortic valve area; BMI: body mass index; BSA: body surface area; CABG: coronary artery bypass grafting; COPD: chronic obstructive pulmonary disease; CT: computed tomography; eGFR: estimated glomerular filtration rate; LAA: large aortic annulus; LVEF: left ventricular ejection fraction; mPG: mean pressure gradient; NYHA: New York Heart Association; PG: pressure gradient; SAA: small aortic annulus; SD: standard deviation; THV: transcatheter heart valve

Table 2. Postprocedural echocardiographic parameters and procedural variables.

	Overall (n=2,699)	SAA (n=1,794)	LAA (n=905)	*p*-value
Postprocedural echocardiographic variables				
EOA, cm^2	1.63±0.44	1.51±0.38	1.86±0.46	<0.001
Indexed EOA, cm^2/m^2	1.13±0.29	1.09±0.27	1.21±0.31	<0.001
Peak flow velocity, m/sec	2.38±0.45	2.46±0.46	2.21±0.39	<0.001
Peak PG, mmHg	23.46±10.41	25.11±11.25	20.19±7.47	<0.001
mPG, mmHg	12.22±4.87	13.13±4.92	10.41±4.23	<0.001
mPG ≥20 mmHg	168 (6.2)	152 (8.5)	16 (1.8)	<0.001
PVL ≥mild	654 (24)	430 (24)	224 (25)	0.76
PVL				0.88
None-trivial	2,028 (75)	1,355 (76)	673 (75)	
Mild	625 (23)	411 (23)	214 (24)	
≥Moderate	29 (1)	19 (1)	10 (1)	
PPM				<0.001
None	2,230 (84)	1,432 (81)	798 (90)	
Moderate	377 (14)	295 (16)	82 (9)	
Severe	52 (2)	45 (3)	7 (1)	
Procedural complications (in-hospital)				
In-hospital death	27 (1.0)	16 (0.9)	11 (1.2)	0.554
Conversion to open-heart surgery	13 (0.5)	11 (0.6)	2 (0.2)	0.241
Major stroke	13 (0.5)	11 (0.6)	2 (0.2)	0.127
≥Major bleeding	126 (4.7)	92 (5.1)	34 (3.8)	0.133
Major vascular complication	96 (3.6)	65 (3.6)	31 (3.4)	0.877
Cardiac tamponade	22 (0.9)	15 (1.0)	6 (0.7)	0.530
New pacemaker implantation	157 (5.8)	124 (6.9)	33 (3.6)	0.001

Values are numbers (%) or mean±SD. Standardised difference for categorical variables and standardised mean difference for continuous variables.
EOA: effective orifice area; LAA: large aortic annulus; mPG: mean pressure gradient; PG: pressure gradient; PPM: prosthesis-patient mismatch; PVL: paravalvular leakage; SAA: small aortic annulus; SD: standard deviation

mortality rate of 57.2%, while BVF occurred in 3.2% and BVF-related mortality was 1.2% **(Figure 1A)**. The cumulative all-cause mortality rate at 7 years after TAVI was lower in the SAA group than in the LAA group (55.2% vs 58.6%; p<0.001, log-rank test) **(Central illustration)**. The Cox regression multivariable analysis identified multiple clinical variables associated with an increased risk of late all-cause mortality after TAVI, whereas an SAA was not related to late mortality (HR 1.07, 95% CI: 0.85-1.36; p=0.56) **(Table 3)**. In addition to the analysis comparing small versus large annulus groups, a multivariable analysis was also performed for the CT-derived annulus area (per 1 mm^2 increase) and annulus perimeter (per 1 mm increase). However, neither an increase in area (per 1 mm^2) nor in perimeter (per 1 mm) was associated with long-term mortality risk (HR 1.00, 95% CI: 0.99-1.00; p=0.22; HR 1.00, 95% CI: 0.99-1.02; p=0.69, respectively). An interaction was observed between annulus size and sex (p for interaction=0.03) **(Figure 2A)**. However, when stratified by sex, there was no consistent trend favouring worse outcomes in the SAA group in either the male or female subgroup **(Figure 2B-Figure 2C)**. In both sexes, hazard ratios varied among subpopulations, and no subgroup demonstrated a uniformly poorer prognosis associated with smaller annulus area. The comparison of prognosis between SAA and LAA by sex showed that, in males, those with an SAA tended to have a lower mortality rate (61.8% vs 64.9%; p=0.053), while in females, no significant difference was observed between the groups (44.6% vs 54.0%; p=0.27) **(Figure 3A-Figure 3B)**. Subgroup analysis for mPG ≥20 mmHg and severe PPM showed no significant difference in long-term outcomes between the SAA and LAA groups **(Supplementary Figure 3A-Supplementary Figure 3B)**. Focusing on the SAA group, the incidence of mPG ≥20 mmHg and severe PPM did not reveal any significant difference in terms of mortality **(Supplementary Figure 4A-Supplementary Figure 4B)**. In the Cox univariable analysis, an mPG >20 mmHg was not significant, whereas an increase of 1 mmHg in the mPG suggested a potential reduction in mortality risk. Based on this finding, mPG (per 1 mmHg increase) was included in the multivariable analysis, but it did not reach statistical significance. Severe PPM tended to be associated with increased mortality in the univariable analysis; however, this association was attenuated in the multivariable analysis. Regarding HF risk, Fine-Gray analysis showed a trend towards a higher risk in the SAA group in univariable analysis, but this was not significant in multivariable analysis, where other clinical factors were identified as independent predictors **(Supplementary Table 1)**.



B

Overall population (N=2,699; 11,088 patient-years)	
Bioprosthetic valve failure (n=63)	
5.7 events/1,000 patient-years	
Stage 1 (n=25)	**2.3 events/1,000 patient-years**
10 cases	HVD Stage 3 (mPG↑+EOA↓)
1 case	HVD Stage 3 (new-onset severe AR)
3 cases	CHF due to mPG↑ by thrombosis
1 case	CHF due to mPG↑ by SVD
9 cases	CHF due to PVL ≥moderate
1 case	CHF due to PVE
Stage 2 (n=10)	**0.9 events/1,000 patient-years**
2 cases	Explant and SAVR for PVE
2 cases	Explant and SAVR for failed THV
6 cases	TAV-in-TAV for failed THV
Stage 3 (n=28)	**2.5 events/ 1,000 patient-years**
22 cases	PVE-related death
4 cases	Death by HF in PVL ≥moderate
2 cases	SCD after detection of BVD

Figure 1. *Cumulative incidence of all-cause death, all BVF, and valve-related death in the overall cohort up to 7 years after TAVI. The all-cause mortality rate was 57.2%, all BVF rate was 3.2%, and valve-related death rate was 1.2% (A). The overall BVF events rate was 5.7 events per 1,000 patient-years, with stage-specific rates as follows: Stage 1: 2.3 events, Stage 2: 0.9 events, and Stage 3: 2.5 events per 1,000 patient-years (B). AR: aortic regurgitation; BVD: bioprosthetic valve deterioration; BVF: bioprosthetic valve failure; CHF: congestive heart failure; EOA: effective orifice area; HF: heart failure; HVD: haemodynamic valve deterioration; mPG: mean pressure gradient; PVE: prosthetic valve endocarditis; PVL: paravalvular leakage; SAVR: surgical aortic valve replacement; SCD: sudden cardiac death; SVD: structural valve deterioration; TAV: transcatheter aortic valve; TAVI: transcatheter aortic valve implantation; THV: transcatheter heart valve*

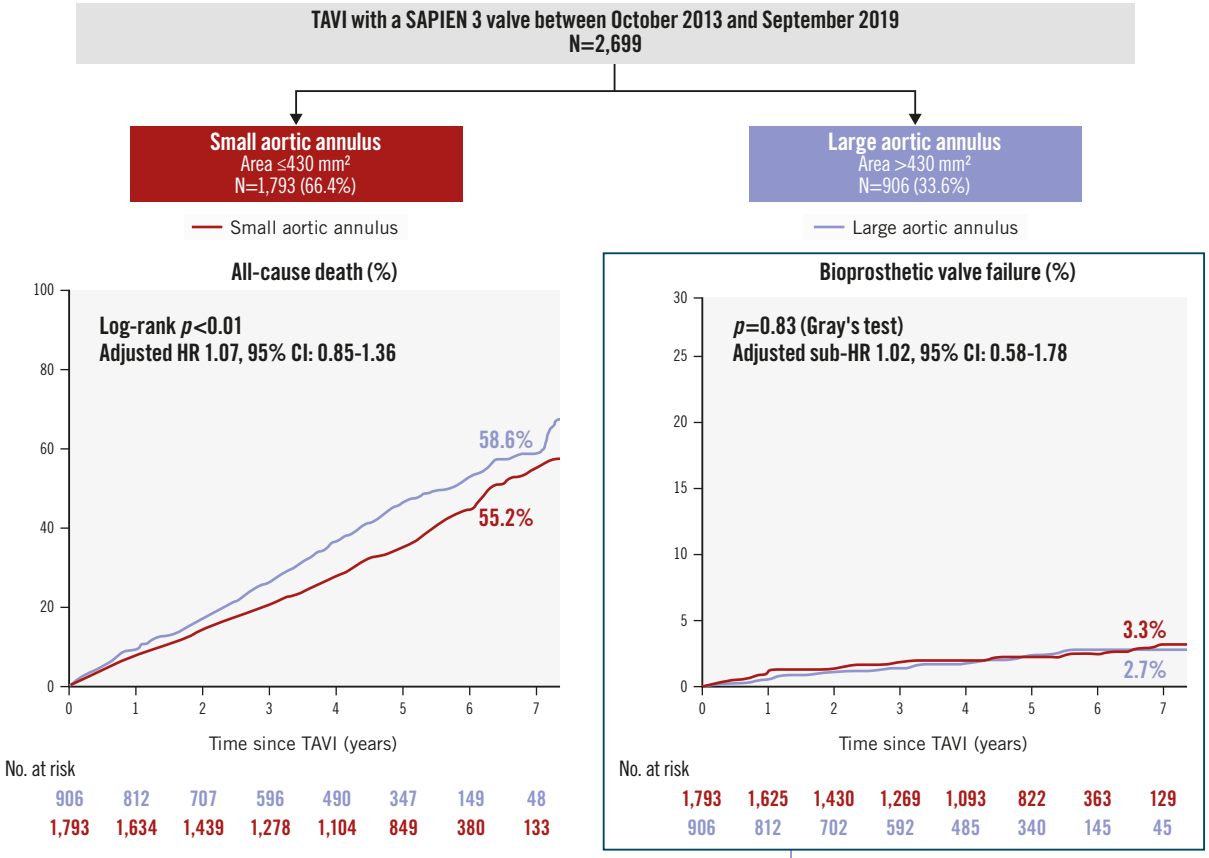
THE INCIDENCE OF BVF

The results of the Fine-Gray competing risk regression analysis to predict the association between patient characteristics and BVF are presented in **Table 4**. The presence of SAA, CT-derived annulus area (per 1 mm² increase), and annulus perimeter (per 1 mm increase) were not associated with increased risk of BVF after TAVI. In addition, the presence of an mPG ≥20 mmHg and severe PPM were not found to be risk factors of BVF. According to the VARC-3 criteria, the overall incidence rate of BVF was 5.7 events per 1,000 patient-years (n=63) during a total follow-up period of 11,088 patient-years **(Figure 1B)**. Among the 63 BVF cases, Stage 1 BVF occurred at 2.3 events per 1,000 patient-years (n=25), Stage 2 BVF at 0.9 events per 1,000 patient-years (n=10), and Stage 3 BVF at 2.5 events per 1,000 patient-years (n=28). Regarding the relationship between annular size and BVF, patients with SAA and LAA had nearly identical incidence rates of BVF (5.6 vs 5.9 events per 1,000 patient-years; p=0.80), and Gray's test also showed no significant difference in the cumulative incidence of BVF between the groups (3.3% vs 2.7%; p=0.83) **(Central illustration)**. The frequency of BVF between SAA and LAA was examined by sex. In males, there was no significant difference (2.6% vs 3.6%; p=0.37), and in females, no significant difference was found either (4.1% vs 1.6%; p=0.14) **(Figure 3C-Figure 3D)**. Subgroup analysis of mPG ≥20 mmHg and severe PPM demonstrated no significant differences in the incidences of BVF between groups, irrespective of their presence **(Supplementary Figure 3C-Supplementary Figure 3D)**. Similarly, within the SAA group, neither mPG ≥20 mmHg nor severe PPM was associated with a significant difference in BVF incidences **(Supplementary Figure 4C-Supplementary Figure 4D)**.

Discussion

The main findings of this study are summarised as follows: (1) after TAVI with a BE-THV, the 7-year mortality rate was 57.2%, the incidence of BVF was 3.2%, and BVF-related death was observed in 1.2%. In addition to the appearance of structural valve deterioration (SVD), and the new onset of AR, the involvement of PVE was confirmed in one-third of the BVF cases. 2) In TAVI using a BE-THV, multivariable analysis showed no significant differences between the SAA and LAA groups in terms of HF events or all-cause mortality. Additionally, the incidence of BVF did not differ between the groups based on the person-year method (5.6 events/1,000 patient-years vs 5.9 events/1,000 patient-years; p=0.80) or Gray's test (3.3% vs 2.7%; p=0.83). 3) The SAA group had a higher incidence of severe PPM and mPG ≥20 mmHg after TAVI compared to the LAA group. However, these factors were not identified as predictive factors of late

Long-term outcomes and durability of a balloon-expandable transcatheter heart valve in small and large annuli.



Small aortic annulus (n=1,793; 7,560 patient-years)	VARC-3 BVF	Large aortic annulus (n=906; 3,528 patient-years)
5.6 events/1,000 patient-years	p=0.80*	5.9 events/1,000 patient-years

*p-value comparing SAA vs LAA from a Poisson regression model using the number of BVF as the dependent variable and log (follow-up duration) as an offset.

Exposure-adjusted events rate	Stage	Exposure-adjusted events rate
2.3 events/1,000 patient-years (n=18)	Stage 1	1.9 events/1,000 patient-years (n=7)
0.7 events/1,000 patient-years (n=6)	Stage 2	1.1 events/1,000 patient-years (n=4)
2.3 events/1,000 patient-years (n=18)	Stage 3	2.8 events/1,000 patient-years (n=10)

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Among 2,699 patients who underwent TAVI with a BE-THV, patients with an SAA (n=1,793) had a lower 7-year mortality rate compared to patients with an LAA (n=906). Whilst the mortality rate among patients with an SAA was lower than that of those with an LAA, the adjusted hazard ratio was 1.07 with a 95% confidence interval of 0.85 to 1.36, indicating no statistically significant difference. Gray's test also showed no difference in BVF between the SAA and LAA groups. Similarly, the incidence of BVF assessed by the person-year method did not differ significantly between the two groups. BE-THV: balloon-expandable transcatheter heart valve; BVF: bioprosthetic valve failure; CI: confidence interval; HR: hazard ratio; LAA: large aortic annulus; SAA: small aortic annulus; TAVI: transcatheter aortic valve implantation; VARC: Valve Academic Research Consortium

Table 3. The Cox regression multivariable analysis for the association of all-cause mortality and clinical findings.

Clinical variables	Univariable analysis			Multivariable analysis Model 1			Multivariable analysis Model 2			Multivariable analysis Model 3		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value	HR	95% CI	*p*-value	HR	95% CI	*p*-value
CT-measured aortic annulus size												
SAA (compared to LAA)	0.77	0.68-0.87	<0.001	1.07	0.85-1.36	0.561						
Aortic annulus area (per 1.0 mm^2 increase)	1.00	1.00-1.00	<0.001				1.00	0.99-1.003	0.223			
Aortic annulus perimeter (per 1.0 mm increase)	1.02	1.01-1.03	<0.001							1.00	0.99-1.02	0.693
Patient background												
Age (per 1 year increase)	1.04	1.03-1.05	<0.001	1.02	1.00-1.04	0.023	1.02	1.00-1.04	0.016	1.02	1.00-1.04	0.018
Male (compared to female)	1.54	1.37-1.73	<0.001	1.82	1.49-2.24	<0.001	1.72	1.40-2.12	<0.001	1.76	1.43-2.17	<0.001
BSA* (per 1.0 m^2 increase)	0.54	0.38-0.77	0.001									
BMI (per 1.0 kg/m^2 increase)	0.92	0.91-0.94	<0.001	0.94	0.92-0.96	<0.001	0.94	0.92-0.96	<0.001	0.94	0.92-0.97	<0.001
Hypertension	0.90	0.77-1.05	0.189									
Diabetes mellitus	1.11	0.98-1.25	0.115									
Chronic kidney disease*	1.15	1.01-1.31	0.04									
Atrial fibrillation/flutter	1.37	1.20-1.57	<0.001	1.01	0.85-1.21	0.877	1.02	0.85-1.21	0.865	1.03	0.86-1.23	0.787
Coronary artery disease	1.20	1.06-1.35	0.003	0.95	0.79-1.13	0.557	0.95	0.80-1.13	0.570	0.96	0.80-1.14	0.615
Previous CABG	0.72	0.44-1.18	0.195									
Previous cardiac surgery	1.30	1.02-1.64	0.031	1.15	0.87-1.52	0.317	1.16	0.88-1.53	0.288	1.10	0.82-1.46	0.538
Peripheral artery disease	1.51	1.27-1.80	<0.001	1.06	0.84-1.21	0.645	1.06	0.84-1.34	0.608	1.08	0.86-1.37	0.503
Previous stroke	1.34	1.13-1.60	0.001	1.17	0.94-1.46	0.161	1.18	0.95-1.47	0.139	1.17	0.94-1.47	0.163
Pulmonary disease	1.68	1.46-1.94	<0.001	1.69	1.37-2.08	<0.001	1.71	1.39-2.10	<0.001	1.72	1.40-2.13	<0.001
NYHA Class III/IV (compared to Class II)	1.74	1.55-1.95	<0.001	1.25	1.06-1.48	0.01	1.25	1.05-1.48	0.010	1.22	1.02-1.45	0.026
Clinical Frailty Scale (per 1 scale increase)	1.27	1.22-1.33	<0.001	1.17	1.09-1.24	<0.001	1.16	1.09-1.24	<0.001	1.16	1.08-1.24	<0.001
Laboratory data												
Albumin (per 1.0 g/dL increase)	0.41	0.37-0.46	<0.001	0.67	0.56-0.79	<0.001	0.67	0.56-0.80	<0.001	0.66	0.56-0.79	<0.001
eGFR (per 1.0 mL/dL/1.73 m^2 increase)	0.99	0.99-0.99	<0.001	0.99	0.99-1.00	0.001	0.99	0.99-1.00	0.001	0.99	0.99-1.00	0.002
Haemoglobin (per 1.0 g/dL increase)	0.84	0.81-0.87	<0.001	0.91	0.86-0.96	0.001	0.91	0.86-0.97	0.001	0.91	0.86-0.96	0.001
Echocardiographic findings												
LVEF (per 1.0% increase)	0.98	0.98-0.99	<0.001	1.00	0.99-1.01	0.975	1.00	0.99-1.01	0.806	1.00	0.99-1.01	0.985
Preprocedural mPG* (per 1.0 mmHg increase)	0.99	0.99-1.00	<0.001									
Preprocedural mPG <40 mmHg	1.28	1.14-1.45	<0.001	1.24	1.05-1.46	0.011	1.26	1.07-1.49	0.007	1.26	1.06-1.49	0.009
Preprocedural AR ≥moderate	1.05	0.87-1.26	0.645									
Preprocedural MR ≥moderate	1.36	1.16-1.60	<0.001	1.07	0.86-1.33	0.554	1.06	0.86-1.32	0.584	1.09	0.87-1.35	0.468
Preprocedural TR ≥moderate	1.64	1.37-1.96	<0.001	1.06	0.83-1.35	0.635	1.07	0.84-1.36	0.590	1.02	0.79-1.31	0.884
Postprocedural EOA (per 1.0 cm^2 increase)	1.02	0.89-1.17	0.741									
Postprocedural indexed EOA* (per 1.0 cm^2/m^2 increase)	1.21	0.99-1.47	0.06									
Postprocedural mPG (per 1.0 mmHg increase)	0.97	0.96-0.98	<0.001	0.99	0.97-1.01	0.146	0.99	0.97-1.01	0.153	0.98	0.96-1.00	0.093
Postprocedural mPG ≥20 mmHg	0.84	0.66-1.08	0.186									
Severe PPM	1.39	0.96-2.01	0.078	1.12	0.64-1.95	0.688	1.11	0.64-1.93	0.720	0.96	0.49-1.90	0.907
PVL ≥mild	1.09	0.96-1.24	0.167									
TAVI procedural variables												
Transfemoral (compared to non-transfemoral)	0.59	0.43-0.81	0.001	0.81	0.51-1.29	0.38	0.81	0.51-1.28	0.369	0.81	0.50-1.29	0.367
20 mm size THV (compared to non-20 mm size THV)	1.02	0.81-1.28	0.887									
THV size (per 1 size increase)	1.18	1.08-1.28	<0.001	1.08	0.91-1.28	0.408	0.96	0.78-1.17	0.663	1.01	0.84-1.22	0.902

*Variables were not entered in the multivariable model. AR: aortic regurgitation; BMI: body mass index; BSA: body surface area; CABG: coronary artery bypass grafting; CI: confidence interval; CT: computed tomography; eGFR: estimated glomerular filtration rate; EOA: effective orifice area; HR: hazard ratio; LAA: large aortic annulus; LVEF: left ventricular ejection fraction; mPG: mean pressure gradient; MR: mitral regurgitation; NYHA: New York Heart Association; PPM: prosthesis-patient mismatch; PVL: paravalvular leakage; SAA: small aortic annulus; TAVI: transcatheter aortic valve implantation; THV: transcatheter heart valve; TR: tricuspid regurgitation

prognosis or BVF in the entire cohort. Even when focusing on the data separately by sex, a lack of association was consistently observed between the sex difference and long-term outcomes, HF hospitalisation, and BVF.

As TAVI indications continue to expand, one of the key remaining challenges is clarifying long-term durability of THVs, including SVD. The absence of sufficient durability data has led to different age-based guidelines worldwide. In Europe, the cutoff age for TAVI and surgical aortic valve replacement (SAVR) candidates is clearly set at 75 years, while in Japan, the 75-80 age range is considered a grey zone[11,12]. The United States has adopted a broader approach, defining the entire 65-80 age range as a grey zone for considering both TAVI and SAVR indications[13]. In the context of lifetime management for AS patients, it is crucial to consider differences in life expectancy across racial groups. Japanese individuals, who are known for their longevity, have notably higher life expectancies. According to Japan's national census, an 85-year-old male typically has around 6 more years to live, while a female of the same age has about 8 years. In this study cohort, males with an average age of 83.8 years had a 7-year cumulative mortality rate of 64.2%, while females with an average age of 84.7 years had a rate of 52.7%. Although these patients received TAVI, their survival was markedly worse than that of the general population. These results highlight that even in Japan, where life expectancy is among the longest in the world, the poor long-term outcomes support the appropriateness of the current age thresholds for TAVI set by different countries. Although THV durability remains a key issue, the fact that BVF-related mortality is approximately 1% suggests that a broader perspective is needed to identify more effective strategies for improving long-term outcomes in elderly AS patients.

Recent discussions have increasingly focused on the variation in THV postoperative haemodynamics, as evaluated by echocardiography, based on a patient's aortic annulus size. In patients following SAVR, previous studies have reported that an SAA is associated with inferior outcomes, haemodynamic limitations, and an elevated risk of PPM[14,15]. In fact, in this study, an increase in mPG, an mPG ≥20 mmHg, and severe PPM were all more prevalent in the SAA group compared to the LAA group. It is evident that a larger annulus size facilitates the implantation of a bigger THV, which results in favourable postoperative haemodynamic outcomes. Numerous studies, transcending racial differences in body sizes, have shown that patients with SAA tend to have an elevated mPG and a higher frequency of PPM after TAVI using BE-THVs compared to those using SE-THVs[3-6]. However, the prognostic implications of these findings regarding annulus size differences, as well as mPG elevation and PPM, are still controversial and remain under debate[16-20]. In this study, the proportion of females in the SAA group was 84.6%, while the proportion of females in the LAA group decreased to 31.1%. A key aspect in the discussion of annular size is the consideration of the patient's body size, and therefore, an additional analysis was conducted to investigate sex differences separately. Indeed, there was a significant interaction between sex and SAA-LAA status in relation to long-term prognosis. Nevertheless, differences in annulus size did not show any impact on long-term prognosis or BVF in both the male and female groups.

Particularly in patients receiving a BE-THV, the mPG elevation showed no correlation with prognosis[21]. Moreover, the prognosis for those implanted with the exceptionally small 20 mm bioprosthetic valve was similar to that for other larger valve sizes, as reported in both Japan and Western countries[22,23]. The finding of prior evidence, including the recent subanalysis of the RCTs, demonstrated comparable 5-year clinical outcomes between patients with SAA and LAA treated with BE-THVs[8]. Together, these results suggest that with appropriate valve sizing and implantation strategies, a smaller annulus size does not inherently confer worse long-term outcomes. In line with this, our study also found no significant association between annular size and the risk of subsequent HF. The current study further supports this notion in a real-world cohort with contemporary devices and diverse patient backgrounds. On the contrary, the findings of this study show that severe PPM tends to worsen prognosis. Additionally, the large-scale OCEAN-TAVI study, which included over 7,000 patients and examined all THV types, reported that severe PPM may be associated with poor prognosis[24]. Given the smaller sample size in our cohort compared to previous OCEAN-TAVI data, it is possible that the current study is underpowered to detect the prognostic significance of severe PPM. Therefore, the influence of severe PPM on long-term outcomes remains an important issue that warrants further investigation in larger cohorts.

In this study, BVF was strictly evaluated according to the VARC-3 definition. However, the Fine-Gray competing risk regression analysis did not identify significant risk factors of BVF. This may be due to an insufficient number of BVF events in our cohort. Recent national registry data have reported that factors such as age, mPG >20 mmHg, and postprocedural AR ≥grade 2, etc., were associated with an increased risk of reintervention after TAVI[25]. Given this context, the number of cases with severe PPM or an mPG ≥20 mmHg in our study was relatively low, making it difficult to determine whether these factors are truly unrelated to BVF. Therefore, a larger cohort is needed to further evaluate these associations. However, a unique feature of the OCEAN-TAVI registry is that patients treated at a given institution tend to receive follow-up care and consultations there as well. Since 2023, TAV-in-TAV for BVF has been approved in Japan, and nearly all patients have undergone TAV-in-TAV procedures at the same institution where they were initially treated. The 0.9 events/1,000 patient-years for THV explants and TAV-in-TAV reinterventions performed up to the 7-year mark can be considered a favourable outcome. Another important point to note is the fact that more than one-third of BVF cases were associated with PVE (n=24) as the underlying cause. Among these, 22 patients died as a result of PVE-related complications. Moreover, 13 cases of PVE were found that did not lead to BVF and were treated successfully with antibiotics (data not shown). The high in-hospital mortality rate following THV explant due to PVE emphasises the necessity of early diagnosis and appropriate preventive approaches[26]. As TAVI patients are

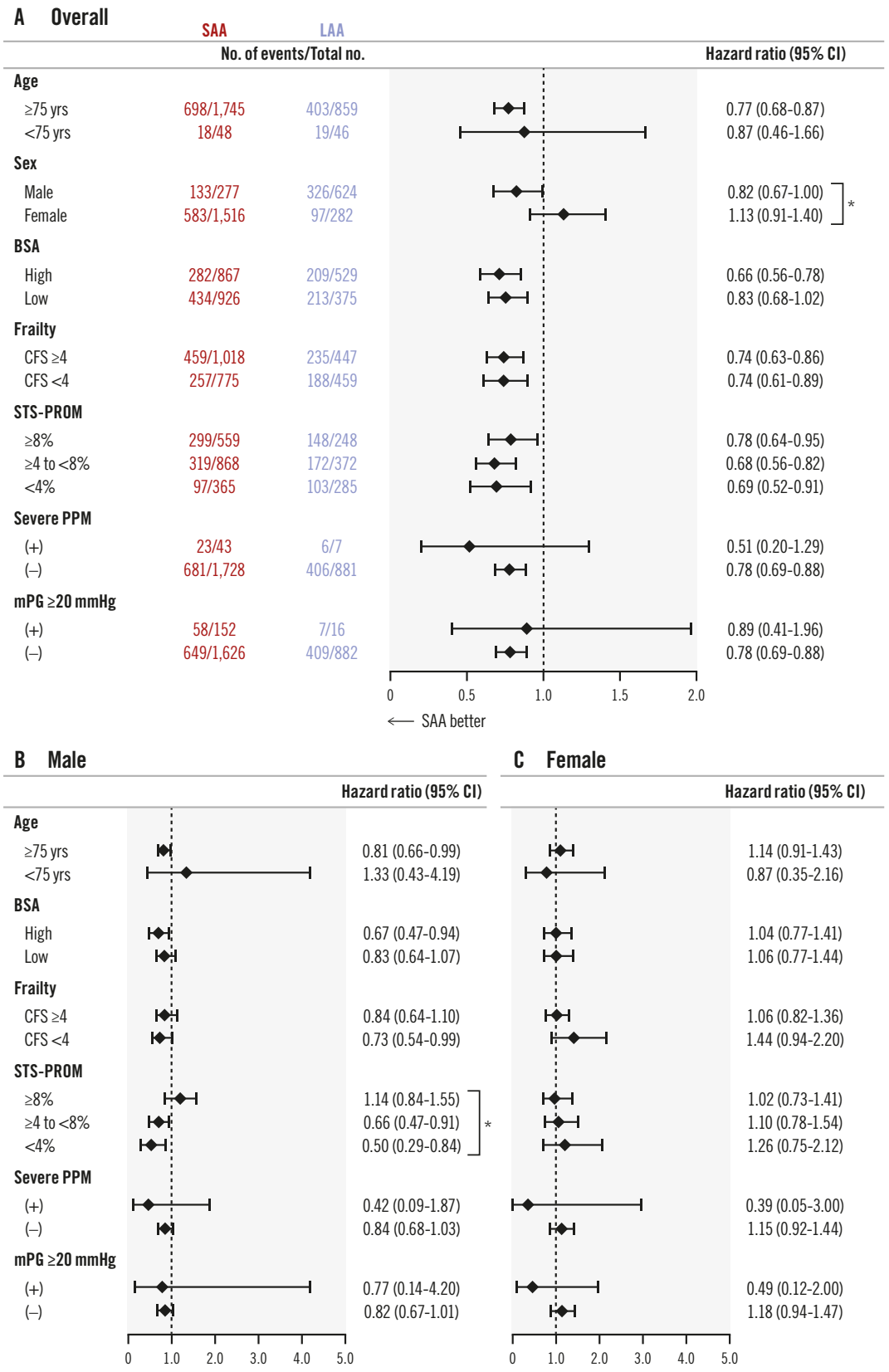

Figure 2. *Subgroup analysis of the association between annular size and all-cause mortality. Overall cohort (A), male patients (B), female patients (C). BSA: body surface area; CFS: Clinical Frailty Scale; CI: confidence interval; LAA: large aortic annulus; mPG: mean pressure gradient; PPM: prosthesis-patient mismatch; SAA: small aortic annulus; STS-PROM: Society of Thoracic Surgeons Predicted Risk of Mortality*

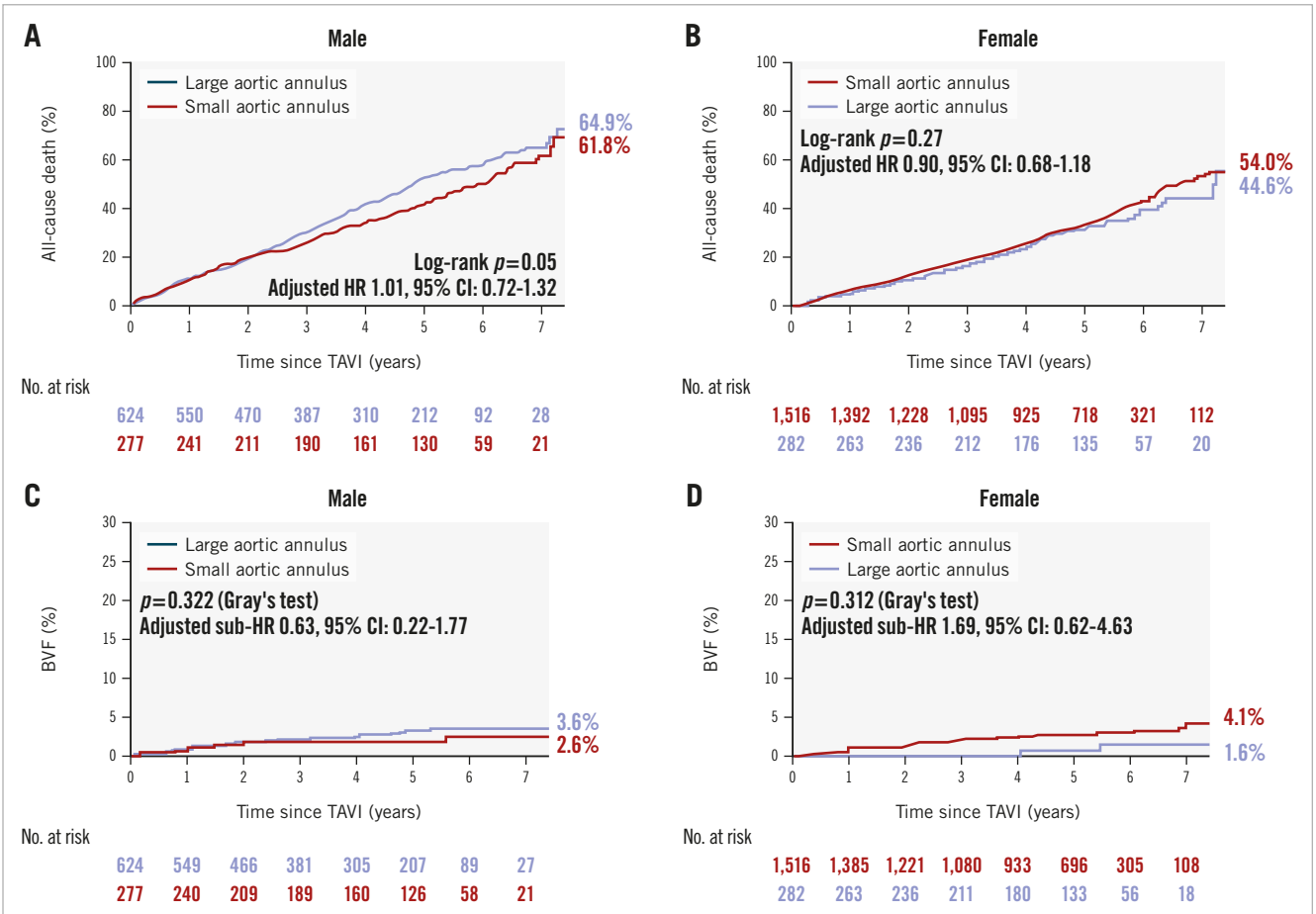

Figure 3. *The rates of all-cause mortality and BVF between SAA and LAA, focused on differences between sexes. The Kaplan-Meier curve showed no statistically significant differences in the rate of all-cause death between SAA and LAA in either males or females (A, B). Adjusted hazard ratios were derived from a Cox regression model adjusted for SAA, age, body mass index, frailty, New York Heart Association Class III/IV, albumin, haemoglobin, baseline mPG, left ventricular ejection fraction, transfemoral approach, valve size, and postprocedural mPG ≥20 mmHg. Similarly, Gray's test indicated that an SAA had no significant impact on BVF compared to an LAA in males or females (C, D). BVF: bioprosthetic valve failure; CI: confidence interval; HR: hazard ratio; LAA: large aortic annulus; mPG: mean pressure gradient; SAA: small aortic annulus*

mostly elderly, it is essential to emphasise the importance of infection prevention, including oral care, through patient education and information exchange among healthcare providers.

Limitations

This study is based on registry data and has a retrospective design, which inherently introduces selection bias. Additionally, events were self-reported by each institution, leading to the possibility of underreporting. Regarding follow-up data, survival follow-up beyond 5 years was achieved in over 85% of patients; however, echocardiographic data were available for only approximately 70% of these cases. This is a limitation of registry-based studies, and the presence of missing data may affect the stability of the results. The slightly higher use of 26 mm valves in the SAA group likely reflects real-world practice, where operators have some discretion in borderline annulus cases. Unlike strictly controlled RCTs, such variation is common in daily clinical settings and had a minimal impact on our overall findings. This study does not address early-stage valve deterioration, due to inconsistent echocardiographic follow-up and variability in measurements, which limited reliable classification. As a result, we restricted our analysis to more robust clinical endpoints such as BVF. Long-term prognostic risk factors were properly identified, while the study could not determine specific predictive factors for BVF. BVF can result from various causes, including structural valve deterioration, AR, and PVE, making its precise prediction challenging. Although the frequency of TAV-in-TAV, THV explant, and BVF in this study was comparable to previous reports, the data were derived from a single-race Asian (Japanese) population. Therefore, the applicability of these findings to Western populations requires further validation. Body size differences between the Japanese and Western populations significantly affect the frequency of severe PPM, which differs considerably in Japanese and Western cohorts. It is also necessary to assess the impact of this difference on long-term prognosis and BVF.

Table 4. The Fine-Gray competing risk regression analysis for predicting BVF.

Clinical variables	Univariable analysis		
	HR	95% CI	*p*-value
CT-measured aortic annulus size			
SAA (compared to LAA)	0.96	0.57-1.60	0.86
Aortic annulus area (per 1.0 mm^2 increase)	0.99	0.99-1.00	0.72
Aortic annulus perimeter (per 1.0 mm increase)	0.99	0.99-1.00	0.98
Patient background			
Age (per 1 year increase)	0.97	0.92-1.01	0.14
Male (compared to female)	1.12	0.67-1.86	0.67
BSA (per 1.0 m^2 increase)	2.87	0.70-11.8	0.14
BMI (per 1.0 kg/m^2 increase)	1.01	0.94-1.08	0.76
Hypertension	0.90	0.77-1.05	0.19
Diabetes mellitus	1.05	0.80-1.38	0.71
Chronic kidney disease	1.18	0.68-2.05	0.56
Atrial fibrillation	1.65	0.98-2.77	0.058
Coronary artery disease	0.83	0.49-1.42	0.50
Previous CABG	0.12	0.01-1.14	0.065
Laboratory data			
Albumin (per 1.0 g/dL increase)	1.11	0.69-1.77	0.68
eGFR (per 1.0 mL/dL/1.73 m^2 increase)	0.99	0.98-1.01	0.51
Haemoglobin (per 1.0 g/dL increase)	1.01	0.86-1.18	0.93
Echocardiographic findings			
LVEF (per 1.0% increase)	1.02	0.99-1.04	0.10
Postprocedural mPG ≥20 mmHg	1.56	0.67-3.64	0.30
Severe PPM	1.60	0.39-6.49	0.51
PVL ≥mild	1.33	0.78-2.27	0.29
TAVI procedural variables			
Transfemoral (compared to non-transfemoral)	1.76	0.24-12.72	0.57
20 mm size THV (compared to non-20 mm size THV)	1.48	0.64-3.43	0.36
THV size (per 1 size increase)	0.93	0.74-1.16	0.53

BMI: body mass index; BSA: body surface area; BVF: bioprosthetic valve failure; CABG: coronary artery bypass grafting; CI: confidence interval; CT: computed tomography; eGFR: estimated glomerular filtration rate; HR: hazard ratio; LAA: large aortic annulus; LVEF: left ventricular ejection fraction; mPG: mean pressure gradient; PPM: prosthesis-patient mismatch; PVL: paravalvular leakage; SAA: small aortic annulus; TAVI: transcatheter aortic valve implantation

Conclusions

In elderly AS patients, longer survival after TAVI remained poor, while BVF occurred at a low frequency, with only a small proportion of deaths linked to BVF. Although further research is necessary to confirm our findings, neither annular size (regardless of sex) nor echocardiographic parameters of BE-THV haemodynamics were associated with long-term prognosis. Furthermore, these factors showed no significant association with BVF. To improve long-term outcomes following TAVI, a more comprehensive approach to lifetime management for AS patients may be required.

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Conflict of interest statement

M. Yamamoto, S. Shirai, Y. Watanabe, G. Nakazawa, M. Asami, Y. Fuku, and K. Hayashida served as clinical proctors for Edwards Lifesciences, Abbott, and Medtronic. K. Ishizu is a proctor of intracardiac echocardiography for Johnson & Johnson. M. Izumo is a screening proctor for Edwards Lifesciences. F. Yashima and H. Nishina are clinical proctors for Medtronic. T. Naganuma is a clinical proctor for Edwards Lifesciences and Medtronic. Y. Ohno is a clinical proctor for Medtronic and Abbott. T. Shimura is a clinical proctor for Medtronic and Abbott. The other authors have no conflicts of interest relevant to the content of this manuscript to declare.

References

1. Mack MJ, Leon MB, Thourani VH, Makkar R, Kodali SK, Russo M, Kapadia SR, Malaisrie SC, Cohen DJ, Pibarot P, Leipsic J, Hahn RT, Blanke P, Williams MR, McCabe JM, Brown DL, Babaliaros V, Goldman S, Szeto WY, Genereux P, Pershad A, Pocock SJ, Alu MC, Webb JG, Smith CR; PARTNER 3 Investigators. Transcatheter Aortic-Valve Replacement with a Balloon-Expandable Valve in Low-Risk Patients. *N Engl J Med*. 2019;380:1695-705.

2. Popma JJ, Deeb GM, Yakubov SJ, Mumtaz M, Gada H, O'Hair D, Bajwa T, Heiser JC, Merhi W, Kleiman NS, Askew J, Sorajja P, Rovin J, Chetcuti SJ, Adams DH, Teirstein PS, Zorn GL 3rd, Forrest JK, Tchétché D, Resar J, Walton A, Piazza N, Ramlawi B, Robinson N, Petrossian G, Gleason TG, Oh JK, Boulware MJ, Qiao H, Mugglin AS, Reardon MJ; Evolut Low Risk Trial Investigators. Transcatheter Aortic-Valve Replacement with a Self-Expanding Valve in Low-Risk Patients. *N Engl J Med*. 2019;380:1706-15.

3. Herrmann HC, Mehran R, Blackman DJ, Bailey S, Möllmann H, Abdel-Wahab M, Ben Ali W, Mahoney PD, Ruge H, Wood DA, Bleiziffer S, Ramlawi B, Gada H, Petronio AS, Resor CD, Merhi W, Garcia Del Blanco B, Attizzani GF, Batchelor WB, Gillam LD, Guerrero M, Rogers T, Rovin JD, Szerlip M, Whisenant B, Deeb GM, Grubb KJ, Padang R, Fan MT, Althouse AD, Tchétché D; SMART Trial Investigators. Self-Expanding or Balloon-Expandable TAVR in Patients with a Small Aortic Annulus. *N Engl J Med*. 2024;390:1959-71.

4. Scotti A, Sturla M, Costa G, Saia F, Pilgrim T, Abdel-Wahab M, Garot P, Gandolfo C, Branca L, Santos IA, Mylotte D, Bedogni F, De Backer O, Nombela Franco L, Webb J, Ribichini FL, Mainardi A, Andreaggi S, Mazzapicchi A, Tomii D, Laforgia P, Cannata S, Fiorina C, Fezzi S, Criscione E, Lunardi M, Poletti E, Mazzucca M, Quagliana A, Montarello N, Hennessey B, Mon-Noboa M, Akodad M, Meier D, De Marco F, Adamo M, Sgroi C, Reddavid CM, Valvo R, Strazzieri O, Motta SC, Frittitta V, Dipietro E, Comis A, Melfa C, Calì M, Sammartino S, Laterra G, Thiele H, Sondergaard L, Tamburino C, Barbanti M, Latib A. Evolut PRO and SAPIEN ULTRA Performance in Small Aortic Annuli: The OPERA-TAVI Registry. *JACC Cardiovasc Interv*. 2024;17:681-92.

5. Hase H, Yoshijima N, Yanagisawa R, Tanaka M, Tsuruta H, Shimizu H, Fukuda K, Naganuma T, Mizutani K, Yamawaki M, Tada N, Yamanaka F, Shirai S, Tabata M, Ueno H, Takagi K, Watanabe Y, Yamamoto M, Hayashida K; OCEAN-TAVI Investigators. Transcatheter aortic valve replacement with Evolut R versus Sapien 3 in Japanese patients with a small aortic annulus: The OCEAN-TAVI registry. *Catheter Cardiovasc Interv*. 2021;97:E875-86.

6. Hioki H, Yamamoto M, Shirai S, Ohno Y, Yashima F, Naganuma T, Yamawaki M, Watanabe Y, Yamanaka F, Mizutani K, Ryuzaki T, Noguchi M, Izumo M, Takagi K, Asami M, Ueno H, Nishina H, Otsuka T, Suzuyama H, Yamasaki K, Nishioka K, Hachinohe D, Fuku Y, Hayashida K; OCEAN-TAVI Investigators. Valve Performance Between Latest-Generation Balloon-Expandable and Self-Expandable Transcatheter Heart Valves in a Small Aortic Annulus. *JACC Cardiovasc Interv*. 2024;17:2612-22.

7. VARC-3 WRITING COMMITTEE; Généreux P, Piazza N, Alu MC, Nazif T, Hahn RT, Pibarot P, Bax JJ, Leipsic JA, Blanke P, Blackstone EH, Finn MT, Kapadia S, Linke A, Mack MJ, Makkar R, Mehran R, Popma JJ, Reardon M, Rodes-Cabau J, Van Mieghem NM, Webb JG, Cohen DJ, Leon MB. Valve Academic Research Consortium 3: Updated Endpoint Definitions for Aortic Valve Clinical Research. *J Am Coll Cardiol*. 2021;77:2717-46.

8. Hahn RT, Pibarot P, Abbas A, Makkar R, Thourani VH, Généreux P, Kodali S, Kapadia S, Babaliaros V, Ternacle J, Theron A, Cristell N, Clarke S, Zhao Y, Alu M, Madhavan MV, Cohen DJ, Leipsic J, Webb J, Mack MJ, Leon MB. Late Clinical Outcomes of Balloon-Expandable Valves in Small Annuli: Results From the PARTNER Trials. *JACC Cardiovasc Interv*. 2025;18:506-17.

9. Shimura T, Yamamoto M, Kano S, Kagase A, Kodama A, Koyama Y, Tsuchikane E, Suzuki T, Otsuka T, Kohsaka S, Tada N, Yamanaka F, Naganuma T, Araki M, Shirai S, Watanabe Y, Hayashida K; OCEAN-TAVI Investigators. Impact of the Clinical Frailty Scale on Outcomes After Transcatheter Aortic Valve Replacement. *Circulation*. 2017;135:2013-24.

10. Yamamoto M, Yashima F, Shirai S, Tada N, Naganuma T, Yamawaki M, Yamanaka F, Mizutani K, Noguchi M, Ueno H, Takagi K, Ohno Y, Izumo M, Nishina H, Suzuyama H, Yamasaki K, Nishioka K, Hachinohe D, Fuku Y, Otsuka T, Asami M, Watanabe Y, Hayashida K, Ocean-Tavi Investigators OBOT. Performance and outcomes of the SAPIEN 3 Ultra RESILIA transcatheter heart valve in the OCEAN-TAVI registry. *EuroIntervention*. 2024;20:579-90.

11. Vahanian A, Beyersdorf F, Praz F, Milojevic M, Baldus S, Bauersachs J, Capodanno D, Conradi L, De Bonis M, De Paulis R, Delgado V, Freemantle N, Haugaa KH, Jeppsson A, Jüni P, Pierard L, Prendergast BD, Sádaba JR, Tribouilloy C, Wojakowski W. 2021 ESC/EACTS Guidelines for the management of valvular heart disease. *EuroIntervention*. 2022;17:e1126-96.

12. Izumi C, Eishi K, Ashihara K, Arita T, Otsuji Y, Kunihara T, Komiya T, Shibata T, Seo Y, Daimon M, Takanashi S, Tanaka H, Nakatani S, Ninami H, Nishi H, Hayashida K, Yaku H, Yamaguchi J, Yamamoto K, Watanabe H, Abe Y, Amaki M, Amano M, Obase K, Tabata M, Miura T, Miyake M, Murata M, Watanabe N, Akasaka T, Okita Y, Kimura T, Sawa Y, Yoshida K; Japanese Circulation Society Joint Working Group. JCS/JSCS/JATS/JSVS 2020 Guidelines on the Management of Valvular Heart Disease. *Circ J*. 2020;84:2037-119.

13. Otto CM, Nishimura RA, Bonow RO, Carabello BA, Erwin JP 3rd, Gentile F, Jneid H, Krieger EV, Mack M, McLeod C, O'Gara PT, Rigolin VH, Sundt TM 3rd, Thompson A, Toly C. 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: Executive Summary: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2021;143:e35-71.

14. Freitas-Ferraz AB, Tirado-Conte G, Dagenais F, Ruel M, Al-Atassi T, Dumont E, Mohammadi S, Bernier M, Pibarot P, Rodés-Cabau J. Aortic Stenosis and Small Aortic Annulus. *Circulation*. 2019;139:2685-702.

15. Vaidya YP, Cavanaugh SM, Sandhu AA. Surgical aortic valve replacement in small aortic annulus. *J Card Surg*. 2021;36:2502-9.

16. Abdel-Wahab M, Landt M, Neumann FJ, Massberg S, Frerker C, Kurz T, Kaur J, Toelg R, Sachse S, Jochheim D, Schäfer U, El-Mawardy M, Robinson DR, Richardt G; CHOICE Investigators. 5-Year Outcomes After TAVR With Balloon-Expandable Versus Self-Expanding Valves: Results From the CHOICE Randomized Clinical Trial. *JACC Cardiovasc Interv*. 2020;13:1071-82.

17. Okuno T, Tomii D, Lanz J, Heg D, Praz F, Stortecky S, Reineke D, Windecker S, Pilgrim T. 5-Year Outcomes With Self-Expanding vs Balloon-Expandable Transcatheter Aortic Valve Replacement in Patients With Small Annuli. *JACC Cardiovasc Interv.* 2023;16:429-40.

18. Pibarot P, Weissman NJ, Stewart WJ, Hahn RT, Lindman BR, McAndrew T, Kodali SK, Mack MJ, Thourani VH, Miller DC, Svensson LG, Herrmann HC, Smith CR, Rodés-Cabau J, Webb J, Lim S, Xu K, Hueter I, Douglas PS, Leon MB. Incidence and sequelae of prosthesis-patient mismatch in transcatheter versus surgical valve replacement in high-risk patients with severe aortic stenosis: a PARTNER trial cohort--a analysis. *J Am Coll Cardiol*. 2014;64:1323-34.

19. Herrmann HC, Daneshvar SA, Fonarow GC, Stebbins A, Vemulapalli S, Desai ND, Malenka DJ, Thourani VH, Rymer J, Kosinski AS. Prosthesis-Patient Mismatch in Patients Undergoing Transcatheter Aortic Valve Replacement: From the STS/ACC TVT Registry. *J Am Coll Cardiol.* 2018;72:2701-11.

20. Ternacle J, Pibarot P, Herrmann HC, Kodali S, Leipsic J, Blanke P, Jaber W, Mack MJ, Clavel MA, Salaun E, Guzzetti E, Annabi MS, Bernier M, Beaudoin J, Khalique OK, Weissman NJ, Douglas P, Bax J, Dahou A, Xu K, Alu M, Rogers E, Leon M, Thourani VH, Abbas AE, Hahn RT. Prosthesis-Patient Mismatch After Aortic Valve Replacement in the PARTNER 2 Trial and Registry. *JACC Cardiovasc Interv.* 2021;14:1466-77.

21. Khalili H, Pibarot P, Hahn RT, Elmariah S, Pilgrim T, Bavry AA, Maini B, Okuno T, Al-Azizi K, Waggoner TE, Mack M, Rodès-Cabau J, Abbas AE. Transvalvular Pressure Gradients and All-Cause Mortality Following TAVR: A Multicenter Echocardiographic and Invasive Registry. *JACC Cardiovasc Interv.* 2022;15:1837-48.

22. Eng MH, Abbas AE, Hahn RT, Lee J, Wang DD, Eleid MF, O'Neill WW. Real world outcomes using 20 mm balloon expandable SAPIEN 3/ultra valves compared to larger valves (23, 26, and 29 mm)-a propensity matched analysis. *Catheter Cardiovasc Interv.* 2021;98:1185-92.

23. Okuno T, Izumo M, Takahiko K, Kuwata S, Koga M, Akashi YJ, Shirai S, Watanabe Y, Naganuma T, Tada N, Yamanaka F, Noguchi M, Ueno H, Ohno Y, Nishina H, Takagi K, Asami M, Mizutani K, Yashima F, Otsuka T, Yamamoto M, Hayashida K. Extremely Small 20-mm Versus Standard-Size Balloon-Expandable Transcatheter Heart Valves: Propensity-Matched Analysis From the OCEAN-TAVI Registry. *JACC Asia*. 2025;5:245-54.

24. Ishizu K, Kitano K, Yamamoto K, Hayashi M, Shirai S, Ohno N, Kakumoto S, Ando K, Yashima F, Nishina H, Izumo M, Asami M, Tada N, Yamawaki M, Naganuma T, Yamanaka F, Ohno Y, Ueno H, Noguchi M, Mizutani K, Takagi K, Watanabe Y, Yamamoto M, Hayashida K; OCEAN-TAVI Investigators. Update on Prosthesis-Patient Mismatch Following Transcatheter Aortic Valve Replacement in Asian Patients. *JACC Asia*. 2024;4:793-806.

25. Durand E, Eltchaninoff H, Tchetche D, Levesque T, Garmendia C, Iung B, Benamer H, Cayla G, Van Belle E, Commeau P, Le Breton H, Cuisset T, Akodad M, Verhoye JP, Beurtheret S, du Chayla F, Leclere M, Gilard M; STOP-AS and France TAVI Investigators; Dumonteil N. Predictors of Outcomes of Reintervention After Transcatheter Aortic Valve Replacement: FRANCE 2 and FRANCE TAVI Registries. *J Am Coll Cardiol*. 2025;85:896-907.

26. Regueiro A, Linke A, Latib A, Ihlemann N, Urena M, Walther T, Husser O, Herrmann C, Nombela-Franco L, Cheema A, Le Breton H, Stortecky S, Kapadia S, Bartorelli L, Sinning JM, Amat-Santos I, Munoz-Garcia J, Lerakis S, Gutíerrez-Ibanes E, Abdel-Wahab M, Tchetche D, Testa L, Eltchaninoff H, Livi U, Castillo JC, Jilaihawi H, Webb G, Barbanti M, Kodali S, de Brito Jr S, Ribeiro B, Miceli A, Fiorina C, Actis Dato GM, Rosato F, Serra V, Masson JB, Wijeysundera C, Mangione A, Ferreira MC, Lima C, Carvalho A, Abizaid A, Marino A, Esteves V, Andrea C.M., Messika-Zeitoun D, Himbert D, Kim WK, Pellegrini C, Auffret V, Nietlispach F, Pilgrim T, Durand E, Lisko J, Makkar R, Lemos P, Leon B, Puri R, San Roman A, Vahanian A, Søndergaard L, Mangner N, Rodés-Cabau J. Infective Endocarditis Following Transcatheter Aortic Valve Replacement: Comparison of Balloon- Versus Self-Expandable Valves. *Circ Cardiovasc Interv.* 2019;12:e007938.

Supplementary data

Supplementary Table 1. The Fine-Gray competing risk regression analysis for predicting HF hospitalisation.

Supplementary Figure 1. Patient selection and study flow.

Supplementary Figure 2. The incidence of severe PPM, mPG ≥20 mmHg, and moderate AR across SAA and LAA patients.

Supplementary Figure 3. The clinical impact of severe or non-severe PPM and mPG ≥20 mmHg or <20 mmHg regarding all-cause mortality and BVF.

Supplementary Figure 4. The incidence of all-cause mortality and BVF for the presence or absence of severe PPM and mPG ≥20 mmHg in patients with an SAA.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-25-00682

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ORIGINAL RESEARCH

Assessment of coronary cannulation after TAVI with the Evolut FX valve: the CANNULATE TAVR EXPANDED study

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ABSTRACT

BACKGROUND: The new-generation supra-annular, self-expanding Evolut FX system has the potential to facilitate commissural alignment.

AIMS: We sought to assess the feasibility of coronary cannulation (CC) and the impact of commissural and coronary alignment on CC execution, as confirmed by post-transcatheter aortic valve implantation (TAVI) computed tomography (CT).

METHODS: The CANNULATE TAVR EXPANDED study is a multicentre, prospective study which included consecutive patients who underwent transfemoral TAVI with the Evolut FX, CC, and angiography after valve deployment. Post-TAVI CT was performed to assess commissural and coronary alignment. Moderate-to-severe commissural and coronary misalignments based on the ALIGN-TAVR Consortium definition were categorised as the misalignment group. The primary endpoint was the rate of successful CC after Evolut FX implantation.

RESULTS: A total of 126 patients were included. CC was successful in 100% of cases for the left coronary artery (LCA) and 96.7% for the right coronary artery (RCA). Moderate-to-severe commissural misalignment was observed in 13.5%, and moderate-to-severe coronary misalignment was observed in 20.6% (LCA) and 22.2% (RCA). Misaligned LCA and RCA required significantly longer CC times. In multivariable analysis, factors associated with suboptimal LCA cannulation were coronary height (odds ratio [OR] 0.73, 95% confidence interval [CI]: 0.57-0.90; p=0.006) and coronary misalignment (OR 4.58, 95% CI: 1.45-14.47; p=0.009), whereas right coronary cusp width (OR 0.63, 95% CI: 0.44-0.90; p=0.007) and coronary misalignment (OR 4.64, 95% CI: 1.29-16.74; p=0.019) were identified for the RCA.

CONCLUSIONS: High rates of CC, and commissural and coronary alignment post-TAVI with the Evolut FX were observed in this prospective, multicentre study. Coronary misalignment was identified as the strongest predictor of suboptimal CC for both the LCA and the RCA.

KEYWORDS: aortic stenosis; commissural alignment; coronary alignment; coronary cannulation; Evolut FX; transcatheter aortic valve implantation

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As transcatheter aortic valve implantation (TAVI) expands to younger, lower-risk patients with longer life expectancies, lifetime management including the need for future coronary cannulation (CC) becomes crucial. While challenges in CC after TAVI with tall-frame, supra-annular as compared to short-frame, intra-annular transcatheter heart valves (THVs) have been reported, those studies were hindered by the absence of commissural alignment enforcement during the procedure[1] and by the absence of post-TAVI computed tomography (CT) to better determine both commissural and coronary alignment[1,2]. In order to optimise commissural alignment following TAVI, device-specific methods have been proposed and have proven to be helpful[3]. The new iteration of the supra-annular, self-expanding Evolut FX system (Medtronic), whose 3 markers are designed to align with the valve commissures, has the potential to facilitate commissural alignment[4]. We therefore aimed to prospectively assess the impact of commissural and coronary alignment, as determined by postprocedural CT, on the feasibility and timing of CC after TAVI with the Evolut FX in consecutive patients.

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Impact on daily practice

Coronary cannulation after transcatheter aortic valve implantation (TAVI) with tall-frame, supra-annular transcatheter heart valves (THVs) has been reported to be challenging. In this study, we demonstrated that coronary cannulation after TAVI with the new-generation Evolut FX – implanted using best contemporary practice – was highly feasible due to a high achievement rate of commissural and coronary alignment. We furthermore identified coronary misalignment as a strong predictor for suboptimal coronary cannulation of both the left coronary artery and the right coronary artery. Larger multicentre studies are required to confirm whether a newer-generation THV platform can further improve coronary access.

Methods

STUDY POPULATION AND DESIGN

CANNULATE TAVR EXPANDED is an investigator-driven, prospective, multicentre study enrolling consecutive patients undergoing TAVI for severe symptomatic aortic stenosis (AS) using the Evolut FX and subsequent CC and angiography immediately after valve implantation from March 2023 to February 2024. Patients undergoing a valve-in-valve procedure, those undergoing non-transfemoral access, those having an Evolut FX that was not implanted into the proper anatomical position, and those with unstable haemodynamics were excluded. All patients underwent multidetector CT before and after TAVI. The study protocol was developed in accordance with the Declaration of Helsinki and was approved by the ethics committee of each participating hospital. All patients provided informed consent prior to participating in this prospective registry.

PERIPROCEDURAL CT IMAGING

PRE-TAVI ANALYSIS

Aortic root complex measurement was performed as previously described[5]. Coronary heights were measured from the annular plane to the inferior border of each coronary ostium in a stretched multiplanar image. Sinus of Valsalva (SoV) diameters were tracked from the commissure to the opposite side of each coronary sinus. The sinotubular junction (STJ) width was measured as an average of the shortest and longest diameters at the level of the STJ. The angles between the commissure and each coronary ostium were measured. The percentage of annular oversizing was calculated as (THV perimeter/annular perimeter – 1) × 100. The THV-SoV relation percentage was calculated as (THV diameter/SoV mean diameter – 1) × 100[1].

POST-TAVI ANALYSIS

Using the 3 orthogonal multiplanar reconstruction planes, a centreline perpendicular to the THV was generated, and the outflow and inflow levels of each THV were identified. The angle between the native commissure and the THV commissure was assessed using end-diastolic phase data. At the cross-sectional level of the THV leaflet coaptation, the positions of the THV commissures were identified and marked. Then, the native commissures were identified in a cross-section perpendicular to the axis of the aorta, and the angle relative to the centre of the THV frame was measured. Likewise, the ostium of each coronary was identified in a similar fashion, and 2 angles were measured: from the left coronary artery (LCA) ostium to its nearest THV commissure marker, and from the right coronary artery (RCA) ostium to its nearest THV commissure marker[6]. The horizontal distance between the THV and STJ was measured.

The definitions for the degrees of commissural and coronary misalignments were based on the Alignment of Transcatheter Aortic-Valve Neo-Commissures (ALIGN-TAVR) Consortium[7]. Moderate-to-severe commissural and coronary misalignment were categorised as the misaligned group, and two groups (aligned vs misaligned) were compared for further analysis. CT analysis post-TAVI was performed by experienced analysts with documented high reproducibility[6].

PROCEDURE DETAILS

All enrolled patients underwent transfemoral TAVI using the Medtronic Evolut FX system. Prosthesis size and access site were decided by the local Heart Team based on the findings of preprocedural echocardiography and multidetector CT images. Detailed TAVI procedures have been previously described[8]. All the procedures followed the current best practice **(Figure 1)**: an Evolut FX was inserted with the flush port of the delivery catheter positioned at 3 o'clock, and the position of the hat marker was assessed at the descending aorta. If the hat marker was not located at the outer curve

Abbreviations

CC	coronary cannulation	**LCA**	left coronary artery	**TAVI**	transcatheter aortic valve implantation
CT	computed tomography	**RCA**	right coronary artery	**THV**	transcatheter heart valve

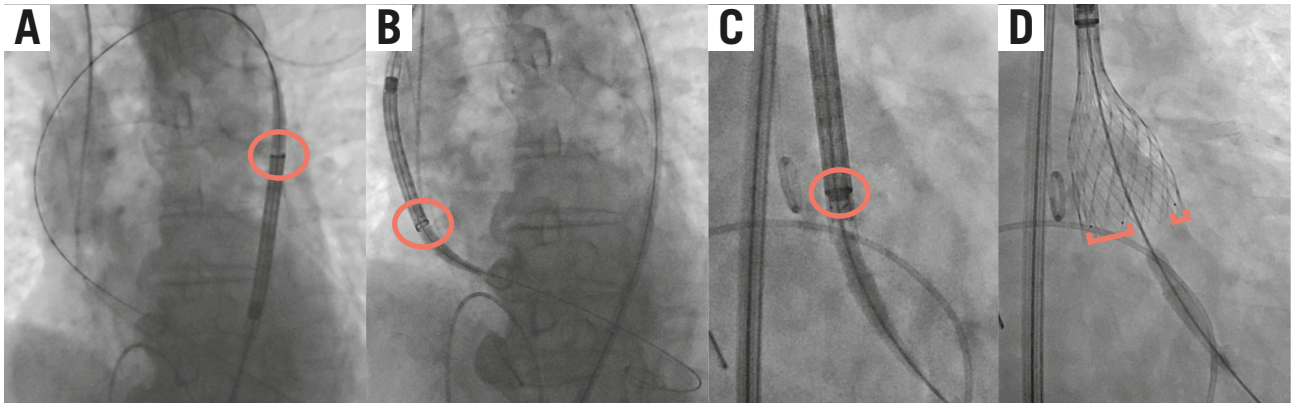


Figure 1. *Steps of transfemoral TAVI using the Evolut FX. This figure shows the key steps of transfemoral TAVI using the cusp-overlap technique. The red circles show the hat marker; the red brackets show the golden markers. A) The hat marker faces the outer curve of the descending aorta in the LAO projection. B) The hat marker faces the outer curve of the ascending aorta in the LAO projection. C) The hat marker faces "centre front" in the cusp-overlap view. D) One marker is at the left-right commissure (right side) and two markers are towards the non-coronary cusp (left side) of the annulus in the cusp-overlap view. LAO: left anterior oblique; TAVI: transcatheter aortic valve implantation*

of the descending aorta in the left anterior oblique (LAO) projection, the delivery system was rotated counterclockwise to achieve the optimal orientation **(Figure 1A)**. The position of the hat marker was again assessed at the ascending aorta, to determine whether it remained at the outer curve **(Figure 1B)**. Finally, valve orientation was confirmed in the cusp-overlap view and implanted in the same projection **(Figure 1C)**. Commissural alignment on fluoroscopy was defined as 1 marker at the left-right commissure (right side) and 2 markers towards the non-coronary cusp (left side) of the annulus in the cusp-overlap view **(Figure 1D)**.

Immediately after valve implantation, CC of both the LCA and RCA was attempted via either a femoral or radial approach. Judkins left (JL) 3.5 and Judkins right 4 diagnostic catheters were used as default catheters to engage the LCA and RCA, but different types of diagnostic catheters were chosen per the operators' discretion if the initial catheters were deemed inadequate[9]. Coronary guidewires or guide extension catheters were not allowed to be used for coronary cannulation.

ENDPOINTS AND DEFINITIONS

The primary endpoint was the rate of successful CC after Evolut FX implantation. Secondary endpoints were the identification of factors associated with the failed or delayed CC. Consistently with prior studies, CC was defined as "selective" when the catheter completely engaged the coronary ostium; "non-selective" when the catheter tip was near the coronary ostium without complete engagement, but resulting in adequate opacification of the coronary; or "failed" when it was deemed impossible to obtain selective or non-selective coronary engagement, thus precluding proper opacification of the coronary artery with contrast media injection[1,2]. CC was deemed "successful" when the demonstration of opacification of the coronary artery with the proximity of the catheter tip to the coronary ostium, including non-selective injections, was possible within 10 minutes. We defined suboptimal CC as cases of "failed" or longer cannulation time (longer than the third quartile of cannulation time) with non-selective cannulation. All clinical and echocardiographic outcomes were defined according to the Valve Academic Research Consortium-3 criteria[10].

STATISTICAL ANALYSIS

Continuous variables are expressed as mean±standard deviation or median (interquartile range [IQR]), as appropriate. Categorical variables are described as frequency and percentage. Continuous variables were compared using the Student's t-test or the Mann-Whitney U test depending on the variable's distribution, whereas an analysis of variance (ANOVA) test or the Kruskal-Wallis test were used for comparing more than 2 groups for normally distributed and skewed variables, respectively. Categorical variables were compared by the chi-square or Fisher's exact test. Factors associated with failed/delayed CC were assessed using logistic regression analyses. All variables that were significantly associated with the outcome of interest at univariate analysis ($p<0.10$) and those considered clinically relevant were then included in the multivariable analysis. Results are reported as odds ratios (ORs) with 95% confidence intervals (CIs). All p-values reported are 2-sided, and p values<0.05 were considered significant. All analyses were performed with JMP, version 15 (SAS Institute).

Results

BASELINE AND PROCEDURAL CHARACTERISTICS

A total of 126 patients (45% female) with a median age of 81 years were enrolled in the CANNULATE TAVR EXPANDED study. Baseline demographic, clinical, and CT characteristics according to commissural alignment are summarised in **Table 1**. Baseline CT data including annular size (perimeter and area), coronary heights, sinus of Valsalva width, STJ width, angles between the commissure and each coronary, and aortic root angles were comparable between

Table 1. Baseline patient characteristics.

Baseline characteristics	Commissural alignment				
	N	Overall	Aligned	Misaligned	*p*-value
N	126	126	109	17	
Age, yrs	126	81 [75-86]	81 [75-86]	81 [76-86]	0.75
Female	126	57 (45)	48 (44)	9 (53)	0.49
Past medical history					
Hypertension	126	111 (88)	94 (86)	17 (100)	0.10
Dyslipidaemia	126	101 (80)	88 (80)	13 (76)	0.68
Diabetes	126	45 (36)	39 (36)	6 (35)	0.97
Coronary artery disease	126	45 (36)	42 (39)	3 (18)	0.09
CABG	126	12 (10)	12 (11)	0 (0)	0.15
Baseline CT data					
Annular perimeter, mm	126	76.3 [71.2-82.1]	76.7 [71.3-82.4]	74.8 [67.1-81.2]	0.25
Annular area, mm^2	126	432 [384-502]	436 [387-504]	419 [349-497]	0.29
LCA height, mm	126	14 [12-16]	14 [12-16]	13 [12-16]	0.48
RCA height, mm	126	16 [14-19]	16 [14-19]	15 [11-18]	0.10
LCC width, mm	126	31 [29-34]	31 [29-35]	31 [28-33]	0.17
RCC width, mm	126	30 [28-33]	31 [28-33]	29 [27-31]	0.09
STJ width, mm	126	28 [25-31]	28 [25-31]	27 [23-31]	0.29
LCA-comm angle, degrees	126	64 [55-71]	64 [55-71]	67 [56-76]	0.44
RCA-comm angle, degrees	126	77 [69-86]	77 [68-84]	85 [76-90]	0.05
Aortic root angle, degrees	126	50.0±9.4	49.7±9.1	51.8±11.0	0.38
Bicuspid aortic valve	126	6 (4.8)	4 (3.7)	2 (12)	0.19

Values are n (%), mean±standard deviation, or median [interquartile range]. CABG: coronary artery bypass graft; comm: commissure; CT: computed tomography; LCA: left coronary artery; LCC: left coronary cusp; RCA: right coronary artery; RCC: right coronary cusp; STJ: sinotubular junction

the 2 groups. All the TAVI procedures followed the current best practice, and no cases required a delivery catheter being retrieved from the ascending aorta to the descending aorta after crossing the aortic arch. The sizes of Evolut FX used in this study were also similar between the groups. The median implantation depth was 3 (IQR 3-3) mm at the non-coronary cusp (NCC) and 4 (IQR 3-6) mm at the left coronary cusp (LCC) **(Table 2)**.

COMMISSURAL AND CORONARY ALIGNMENT

Post-TAVI CT was performed in all patients (126/126). Among them, moderate or severe commissural misalignment was observed in 13.5% (17/126) patients, and moderate or severe coronary misalignment was observed in 20.6% (26/126) and 22.2% (28/126) patients for the LCA and RCA, respectively **(Central illustration)**. There was no significant difference regarding valve performance, i.e., mean pressure gradient and effective orifice area, between patients with commissural alignment and misalignment (mean pressure gradient 7.9 [IQR 5.8-10.5] mmHg vs 10.5 [IQR 7.4-13.7] mmHg; p=0.06, effective orifice area 1.7 [IQR 1.6-1.9] cm^2 vs 1.7 [IQR 1.6-1.8] cm^2; p=0.73, for commissural alignment vs misalignment, respectively). No patient with transvalvular aortic regurgitation was identified. Among the 17 patients with commissural misalignment, coronary misalignment was observed in 10 (58.8%) for the LCA and 13 (76.5%) for the RCA. Among the 109 patients with commissural alignment, coronary alignment was achieved in 93 (85.3%) for the LCA and 94 (86.2%) for the RCA.

CORONARY CANNULATION OUTCOMES

Coronary artery cannulation was performed via the femoral artery in 75.4% of cases (95/126), while in 24.6% (31/126), it was performed via the radial artery. Coronary cannulation was successful in 100% (126/126) for the LCA and 96.7% (118/122) for the RCA. Selective cannulation was carried out in 73.8% (93/126) for the LCA and in 63.1% (77/122) for the RCA. The median times required for LCA and RCA cannulation were 99 [IQR 48-175] sec and 140 [IQR 70-290] sec, respectively. Four cases required switching the catheter from JL3.5 to JL4; among them, 2 cases were cannulated selectively, 2 cases non-selectively. No cases required an access site change for coronary cannulation.

As for the approach site (femoral vs radial) of CC, when we combine the results of the left radial and femoral approaches due to the similarity of catheter trajectory, LCA cannulation time was comparable between the two approaches (p=0.56), whereas RCA cannulation time via the left radial/femoral artery was significantly shorter compared with the time via the right radial approach (p=0.006) **(Supplementary Table 1, Figure 2A)**. The incidence of selective/non-selective cannulation for the LCA was comparable between the right radial versus the left radial approach. However, as for RCA cannulation, right radial approach cases had less frequent selective cannulation compared with the left radial approach,

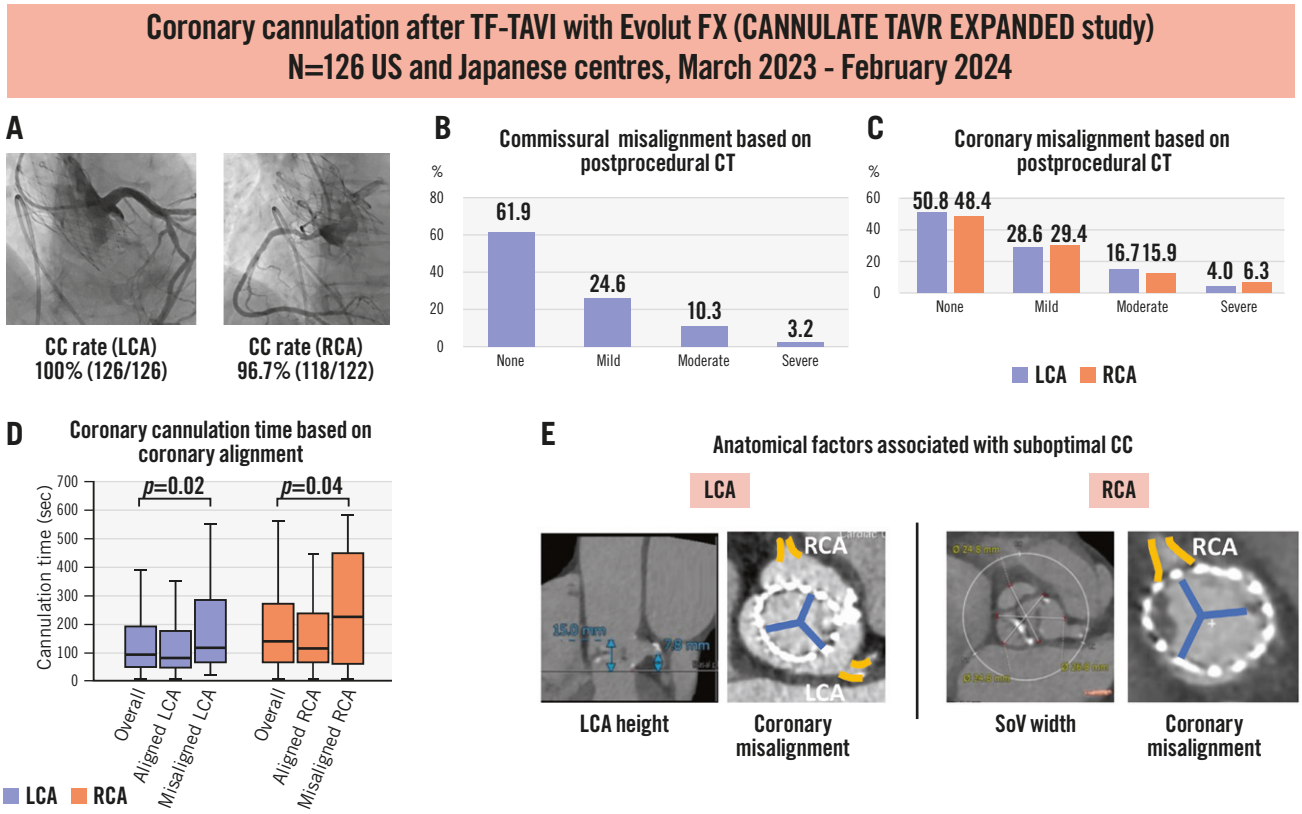
Table 2. Procedural characteristics based on commissural alignment.

Procedural characteristics	Commissural alignment				
	N	Overall	Aligned	Misaligned	*p*-value
N	126	126	109	17	
Evolut FX size		126			0.30
23 mm		15	11 (10)	4 (24)	
26 mm		31	27 (25)	4 (24)	
29 mm		49	42 (39)	7 (41)	
34 mm		31	29 (27)	2 (12)	
NCC depth, mm	126	3 [3-3]	3 [3-3]	3 [3-5]	0.33
LCC depth, mm	126	4 [3-6]	4 [3-6]	4 [4-6]	0.85
Valve angle, degrees	126	42.6±8.8	42.3±8.9	44.6±8.4	0.33
THV/annular oversizing by perimeter, %	126	17.2 [13.1-21.4]	17.3 [13.4-21.4]	14.3 [12.1-20.6]	0.26
THV/SoV relation*, %	126	–7.5 [–13.4 to –3.2]	–7.2 [–13.4 to –3.0]	–8 [–14.8 to –3.3]	0.74
THV/SoV relation**, %	126	–26.5 [–31.3 to –23.0]	–26.7 [–31.4 to –23.3]	–24.5 [–28.7 to –22.0]	0.23
LCA cannulation	126	126	109	17	0.36
Selective		93	82 (75)	11 (65)	
Non-selective		33	27 (25)	6 (35)	
Failure		0	0	0	
LCA cannulation time, sec	126	99 [48-175]	86 [47-165]	188 [112-302]	0.002
RCA cannulation	122	122	106	16	0.003
Selective		77	71 (67)	6 (38)	
Non-selective		41	34 (32)	7 (44)	
Failure		4	1 (1)	3 (19)	
RCA cannulation time, sec	122	140 [70-290]	140 [72-271]	176 [60-592]	0.34
Coronary cannulation access	126	126	109	17	0.24
Via femoral		95	80	15	
Via radial		31	29	2	
Neo-comm-comm angle, degrees	126	13 [6-22]	10 [5-17]	41 [39-45]	<0.001
Commissural misalignment	126	126	109	17	<0.001
None		78	78 (72)	0	
Mild		31	31 (28)	0	
Moderate		13	0	13 (76)	
Severe		4	0	4 (24)	
Neo-comm-LCA angle, degrees	126	46 [34-53]	49 [36-54]	24 [15-37]	<0.001
Coronary misalignment (LCA)	126	126	109	17	<0.001
None		64	62 (57)	2 (12)	
Mild		36	31 (28)	5 (29)	
Moderate		21	15 (14)	6 (35)	
Severe		5	1 (1)	4 (24)	
Neo-comm-RCA angle, degrees	126	44 [34-52]	46 [36-53]	25 [7-32]	<0.001
Coronary misalignment (RCA)	126	126	109	17	<0.001
None		61	58 (53)	3 (18)	
Mild		37	36 (33)	1 (6)	
Moderate		20	12 (11)	8 (47)	
Severe		8	3 (3)	5 (29)	
STJ-THV distance, mm	126	2.5 [1.9-3.6]	2.5 [2-3.7]	2.7 [1.7-3.7]	0.83

Values are n, n (%), mean±standard deviation, or median [interquartile range]. *Calculated using the label size diameter provided by the THV manufacturer. **Calculated using the waist diameter provided by the THV manufacturer. comm: commissure; LCA: left coronary artery; LCC: left coronary cusp; NCC: non-coronary cusp; RCA: right coronary artery; SoV: sinus of Valsalva; STJ: sinotubular junction; THV: transcatheter heart valve

EuroIntervention — Central Illustration

Highlights of the CANNULATE TAVR EXPANDED study.



Yohei Ohno *et al*. • *EuroIntervention* 2025;21:1364-1376 • DOI: 10.4244/EIJ-D-24-01050

This figure shows the highlights of the CANNULATE TAVR EXPANDED study. Coronary cannulation after TAVI with the Evolut FX was highly feasible due to high achievement rates of commissural and coronary alignment (A-C). Significantly longer cannulation times were required both for misaligned left and right coronary arteries (D). Coronary misalignment was strongly associated with suboptimal CC for both the LCA and the RCA (E). CC: coronary cannulation; CT: computed tomography; LCA: left coronary artery; RCA: right coronary artery; SoV: sinus of Valsalva; TAVI: transcatheter aortic valve implantation; TF: transfemoral

although it was not statistically significant between the two groups.

COMMISSURAL ALIGNMENT

Procedural characteristics based on commissural alignment are depicted in **Table 2**. Although the selective/non-selective rate for LCA cannulation was comparable in the aligned versus misaligned groups, the former required a significantly shorter cannulation time compared to the latter (p=0.002). As for RCA cannulation, a significant number of patients had less selective and more frequent failed cannulation in the misaligned group (p=0.003); however, the cannulation time did not differ between the groups **(Figure 2B)**.

CORONARY ALIGNMENT

Procedural characteristics based on coronary alignment are reported in **Table 3**. Patients who achieved coronary alignment showed significantly shorter cannulation times compared to the misaligned group for both the LCA (p=0.02) and the RCA (p=0.04) **(Central illustration)**. The selective/non-selective rate for LCA cannulation was comparable in the aligned and misaligned coronary groups, whereas a significant number of patients had less selective and more frequent failed cannulation in the misaligned group (p=0.0007) for RCA cannulation.

PREDICTORS OF SUBOPTIMAL CC AFTER TAVI WITH EVOLUT FX

The main predictors of failed/delayed coronary cannulation after TAVI with Evolut FX are shown in **Table 4** and the **Central illustration**. On multivariable analysis, LCA height (adjusted OR 0.73, 95% CI: 0.57-0.90; p=0.006) and coronary misalignment (adjusted OR 4.58, 95% CI: 1.45-14.47; p=0.009) were associated with failed/delayed LCA cannulation. Predictors of suboptimal CC for the RCA were sinus of Valsalva width (adjusted OR 0.63, 95% CI:

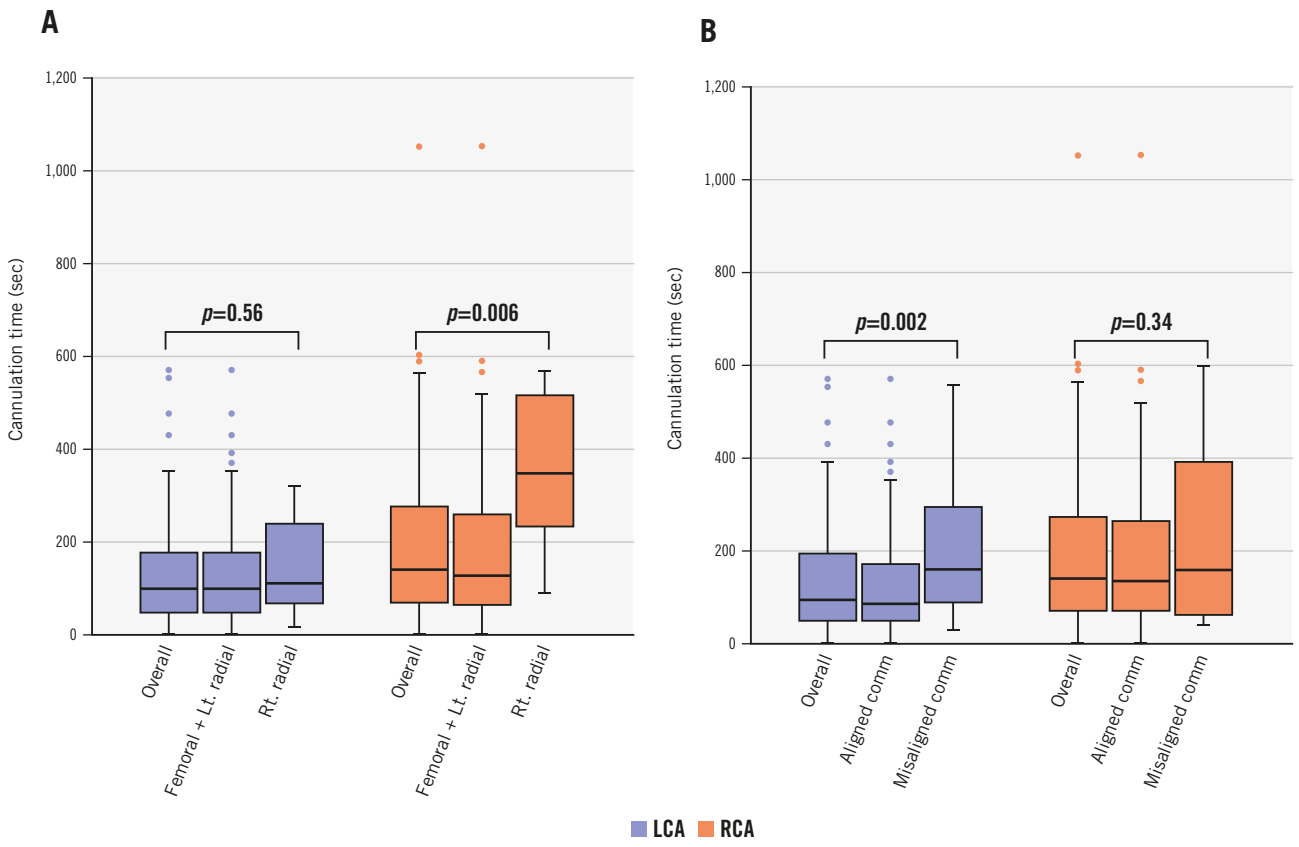


Figure 2. *Coronary cannulation time based on access site and commissural alignment. The median times of left and right coronary cannulation are shown, based on (A) access site and (B) commissural alignment. Upper whisker: maximum value to quartile 3; lower whisker: quartile 1 to minimum value; box: interquartile range; central line: median. Comm: commissure; LCA: left coronary artery; Lt.: left; RCA: right coronary artery; Rt.: right*

0.44-0.90; p=0.007) and coronary misalignment (adjusted OR 4.64, 95% CI: 1.29-16.74; p=0.019). Representative cases of favourable and unfavourable RCA cannulation with post-TAVI CT are shown in **Figure 3**.

Discussion

This study represents the first multicentre dataset to demonstrate the impact of both commissural and coronary alignment on CC, as confirmed by post-TAVI CT, after Evolut FX implantation. Our main findings are as follows: (1) CC after TAVI with the Evolut FX was successfully achieved in the majority of our patients; (2) most individuals who underwent TAVI with the Evolut FX achieved commissural and coronary alignment; (3) significantly longer cannulation times were required in misaligned left and right coronary arteries, compared to those that were aligned; (4) the type of coronary access site (femoral/left radial vs right radial) did not impact successful cannulation rates, but RCA cannulation via right radial access required a longer cannulation time than via femoral/left radial access; and (5) predictors associated with suboptimal LCA cannulation were LCA height and misaligned LCA, whereas factors associated with suboptimal RCA cannulation were RCC width and misaligned RCA.

The recommended age for indication of TAVI varies among guidelines[11-13], but a recent study showed that a significant number of cases have been performed in younger patients, even below the age of 65 in the United States[14]. These patients have longer life expectancy; therefore, future coronary events and a need for CC could be anticipated. Previous studies have reported challenges with coronary access in patients with supra-annular THVs[1,2]. The ALIGN-ACCESS study was the first to demonstrate the association of commissural misalignment and impaired coronary access in patients who received supra-annular self-expanding THVs[2]. However, only fluoroscopic assessment was utilised in that study, and no information was obtained regarding coronary alignment, since post-TAVI CT was not performed. Moreover, only prior iterations, the Evolut R and PRO, were included for the CoreValve platform (all Medtronic).

Our CANNULATE TAVR EXPANDED study is the first multicentre evaluation to show the association of both commissural and coronary alignment with the feasibility of CC using the Evolut FX. Thus, we were able to provide new insights from this study. First, we only included cases with the new generation of the supra-annular, self-expanding Evolut FX which has 3 markers located 3 mm from the distal edge of the stent frame, designed to align with the valve commissures. This new feature could facilitate achieving "angiography-guided" commissural alignment, which ultimately helps to make CC easier[6,9]. Indeed, we were able to demonstrate a high

Table 3. Procedural characteristics based on coronary alignment.

Procedural characteristics	LCA coronary alignment					RCA coronary alignment				
	N	Overall	Aligned	Misaligned	p-value	N	Overall	Aligned	Misaligned	p-value
N	126	126	100	26		126	126	98	28	
Evolut FX size		126			0.0002		126			0.49
23 mm		15	6 (6)	9 (35)			15	12 (12)	3 (11)	
26 mm		31	26 (26)	5 (19)			31	21 (21)	10 (36)	
29 mm		49	38 (38)	11 (42)			49	40 (41)	9 (32)	
34 mm		31	30 (30)	1 (4)			31	25 (26)	6 (21)	
NCC depth, mm	126	3 [3-3]	3 [3-3]	3 [3-5]	0.02	126	3 [3-3]	3 [3-3]	3 [2-4]	0.62
LCC depth, mm	126	4 [3-6]	4 [3-6]	4 [4-7]	0.71	126	4 [3-6]	4 [3-6]	4 [4-6]	0.48
THV/annular oversizing by perimeter, %	126	17.2 [13.1-21.4]	18.1 [13.3-22.7]	15.0 [12.7-18.9]	0.05	126	17.2 [13.1-21.4]	17 [13.4-21.4]	18.2 12.2-21.4]	0.86
THV/SoV relation*, %	126	–7.5 [–13.4 to –3.2]	–6.8 [–13.3 to –2.8]	–10.2 [–14.3 to –4.9]	0.186	126	–7.5 [–13.4 to –3.2]	–8 [–13.4 to –3.3]	–6.1 [–10.7 to –2.8]	0.21
THV/SoV relation**, %	126	–26.5 [–31.3 to –23.0]	–26.9 [–31.5 to –23.3]	–24.6 [–27.8 to –22.0]	0.0497	126	–26.5 [–31.3 to –23.0]	–26.9 [–31.6 to –23.3]	–24.8 [–27.3 to –22.0]	0.049
Coronary cannulation†	126	126	100	26	0.92	122	122	96	26	0.0007
Selective		93	74 (74)	19 (73)			77	66 (68)	11 (42)	
Non-selective		33	26 (26)	7 (27)			41	31 (32)	11 (42)	
Failure		0	0	0			4	0	4 (16)	
Coronary cannulation time†, sec	126	99 [48-175]	83 [48-165]	152 [65-304]	0.02	122	140 [70-290]	129 [72-255]	243 [85-508]	0.04
Coronary cannulation access†	126	126	100	26	0.76	126	126	98	28	0.63
Via femoral		95	76	19			95	77	18	
Via radial		31	24	7			31	21	10	
Neo-comm-comm angle, degrees	126	13 [6-22]	10 [5-17]	30 [17-41]	<0.001	126	13 [6-22]	11 [5-18]	30 [10-41]	<0.001
Commissural misalignment	126	126	100	26	<0.001	126	126	98	28	<0.001
None		77	72 (72)	5 (19)			77	66 (67)	11 (39)	
Mild		32	21 (21)	11 (42)			32	28 (29)	4 (14)	
Moderate		14	7 (7)	7 (27)			14	4 (4)	10 (36)	
Severe		3	0	3 (12)			3	0	3 (11)	
Neo-comm-CA angle†, degrees	126	46 [34-53]	50 [42-55]	20 [16-25]	<0.001	126	44 [34-52]	48 [40-54]	20 [14-28]	<0.001
Coronary misalignment††	126	126	100	26	<0.001	126	126	98	28	<0.001
None		64	64 (57)	0			61	61 (62)	0	
Mild		36	36 (28)	0			37	37 (38)	0	
Moderate		21	0	21 (81)			20	0	20 (71)	
Severe		5	0	5 (19)			8	0	8 (29)	
STJ-THV distance, mm	126	2.5 [1.9-3.6]	2.8 [2-3.9]	2.2 [1.7-3]	0.048	126	2.5 [1.9-3.6]	2.5 [2-3.8]	2.6 [1.6-3.5]	0.45

Values are n, n (%), or median [interquartile range]. *Calculated using the label size diameter provided by the THV manufacturer. **Calculated using the waist diameter provided by the THV manufacturer. †Corresponds to LCA cannulation for LCA coronary alignment and RCA cannulation for RCA coronary alignment. ††Corresponds to LCA misalignment for LCA coronary alignment and RCA misalignment for RCA coronary alignment. CA: coronary artery; comm: commissure; LCA: left coronary artery; LCC: left coronary cusp; NCC: non-coronary cusp; RCA: right coronary artery; SoV: sinus of Valsalva; STJ: sinotubular junction; THV: transcatheter heart valve

Table 4. Univariate and multivariable logistic regression analyses of factors associated with suboptimal coronary cannulation.

	Univariate			Multivariable		
	Crude OR	95% CI	*p*-value	Adjusted OR	95% CI	*p*-value
LCA						
LCA height, mm	0.75	0.62-0.88	0.001	0.73	0.57-0.90	0.006
LCC width, mm	0.87	0.77-0.97	0.015	1.12	0.81-1.54	0.489
Commissural misalignment	6.34	2.18-20.19	0.001	3.77	0.99-14.24	0.051
LCA coronary misalignment	6.65	2.66-17.50	<0.001	4.58	1.45-14.47	0.009
Radial approach	0.76	0.27-1.29	0.572	0.52	0.15-1.82	0.305
Valve depth <3 mm (LCC)	2.07	0.81-6.03	0.135	1.35	0.42-4.35	0.614
STJ-THV distance, mm	0.81	0.58-1.11	0.193	0.87	0.49-1.48	0.620
THV/annular oversizing, %	0.97	0.90-1.03	0.280	0.99	0.91-1.08	0.855
THV/SoV relation*, %	1.09	1.02-1.18	0.015	1.07	0.91-1.27	0.402
RCA						
RCA height, mm	0.88	0.77-0.99	0.030	0.96	0.83-1.12	0.644
RCC width, mm	0.77	0.66-0.89	<0.001	0.63	0.44-0.90	0.007
Commissural misalignment	4.19	1.45-12.43	0.008	1.70	0.37-7.81	0.498
RCA coronary misalignment	4.28	1.70-10.94	0.002	4.64	1.29-16.74	0.019
Radial approach	1.90	0.74-4.71	0.173	1.67	0.48-5.78	0.421
Valve depth <3 mm (NCC)	1.45	0.55-4.30	0.460	2.79	0.80-9.78	0.109
STJ-THV distance, mm	0.65	0.42-0.93	0.019	0.98	0.55-1.74	0.947
THV/annular oversizing, %	0.96	0.89-1.03	0.234	1.02	0.93-1.11	0.705
THV/SoV relation*, %	1.09	1.01-1.18	0.021	0.86	0.72-1.02	0.074

*Calculated using the waist diameter provided by the THV manufacturer. CI: confidence interval; LCA: left coronary artery; LCC: left coronary cusp; NCC: non-coronary cusp; OR: odds ratio; RCA: right coronary artery; RCC: right coronary cusp; SoV: sinus of Valsalva; STJ: sinotubular junction; THV: transcatheter heart valve

commissural alignment rate, which potentially led to the high successful CC rate for both the LCA (100%) and the RCA (96.7%). Although we did not retrieve the delivery catheter from the ascending aorta to the descending aorta in order to adjust the alignment of the valve, a 3-marker-based further adjustment could potentially decrease the rate of commissural and coronary misalignment. Future investigation using CT simulation might guide us to close the current gap.

The RE-ACCESS 2 study, a similar post-TAVI CC study but using older-generation THVs (Evolut R/PRO/PRO+ [Medtronic]) showed a higher rate of unsuccessful cannulation, compared to our study, for both the LCA (2.5%) and the RCA (6.3%)[15]. Several factors are considered to be associated with the CC rate after TAVI, e.g., the type of THV, operator skill and experience, the study period, etc.; however, we assume that the above difference was mainly due to the difference between the Evolut FX and older-generation Evolut platforms. We experienced 4 cases of failed cannulation for the RCA (3.3%). Among them, coronary misalignment was observed in all cases, commissural misalignment in 75% (3/4), and a bicuspid aortic valve in 50% (2/4). Cusp asymmetry and coronary ostia eccentricity are frequently observed in patients with a bicuspid aortic valve[16], so it may have impacted CC in our study; however, only 6 patients (4.8%) with a bicuspid aortic valve were included in this study, so further prospective study is warranted in this specific population. Second, differently from the previous studies, we performed post-TAVI CT assessment in all patients, which provided additional insights. The majority of patients who underwent TAVI with the Evolut FX in our series achieved commissural and coronary alignment, which was in line with our initial reports[6,9]. Additionally, with detailed analysis of coronary alignment using post-TAVI CT, we were able to demonstrate for the first time that coronary misalignment was strongly associated with suboptimal CC for both the LCA (OR 4.58) and the RCA (OR 4.64). Coronary misalignment remained significant even after adjusting for other considerable factors such as coronary height, the size of the sinus of Valsalva, STJ-THV distance, commissural alignment, access site, implanted THV depth, THV/annular oversizing, and THV/SoV relation. In our study, THV depth was not associated with suboptimal cannulation, in line with the RE-ACCESS 2 study[15]. The reasons to explain this are as follows: (1) the optimal implantation depth is achieved (LCC depth 4 [IQR 3-6] mm, NCC depth 3 [IQR 3-3] mm) in the majority of the cases, guided by 3 markers located 3 mm from the distal stent frame, and the operators potentially adjust the depth based on patients' anatomy (e.g., implanting slightly deeper in patients with relatively low coronary takeoff); and (2) the impact of coronary alignment is much higher than that of the implantation depth, since the non-accessible stent frame can be as high as 26 mm (from the distal stent frame, in case of a severe coronary misalignment case) to as low as 13 mm (from the distal stent frame, in case of optimal coronary alignment).

As for the access site, previous studies have all assessed CC feasibility only from the femoral artery[1,2,15]. Although a limited number of patients (N=31) received CC from

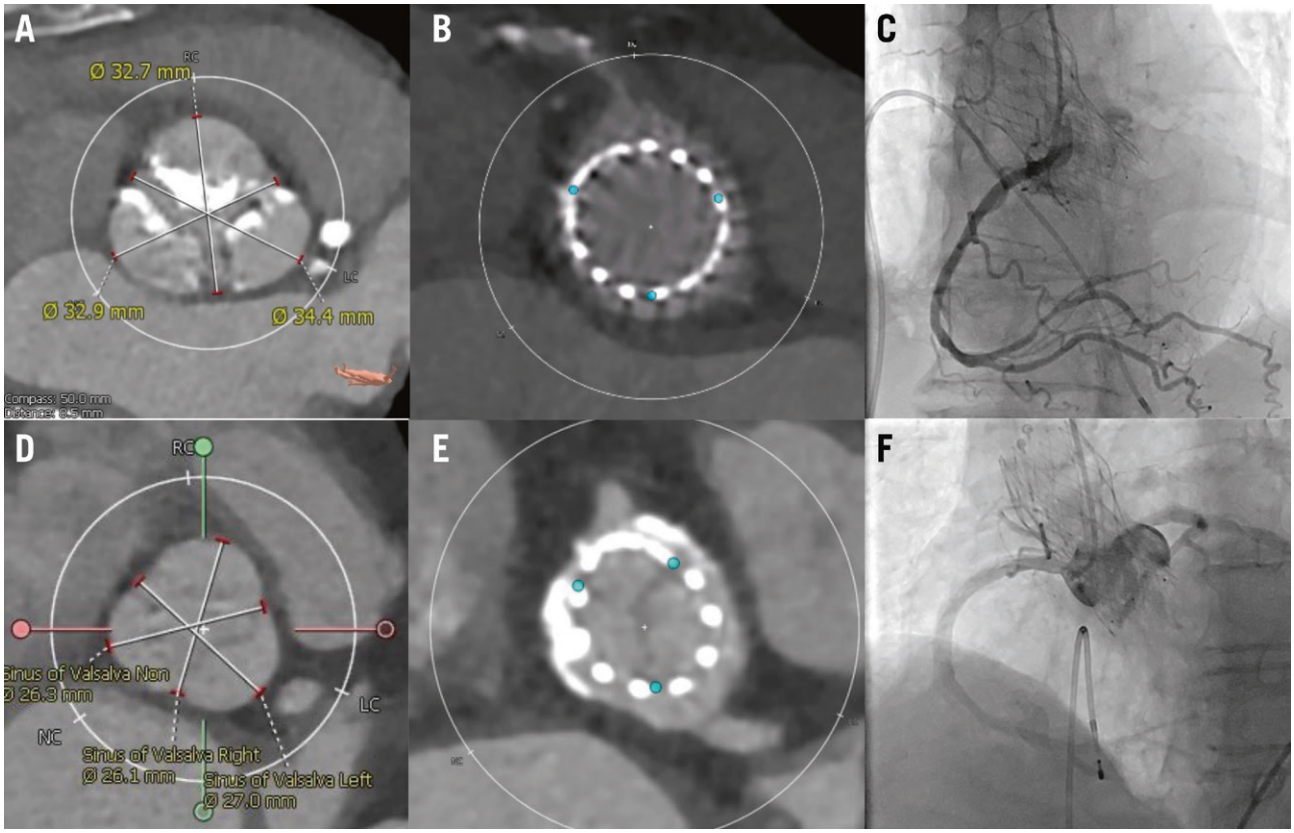


Figure 3. *Post-TAVI CT showing favourable and unfavourable RCA cannulation. This figure shows post-TAVI CT which shows favourable (A-C) and unfavourable (D-F) anatomy for RCA cannulation. A) Wide sinus of Valsalva, (B) space between the Evolut FX 29 mm and the coronary ostium, (C) selective coronary cannulation achieved. D) Narrow sinus of Valsalva, (E) limited space between the Evolut FX 26 mm and the coronary ostium, (F) non-selective coronary cannulation. CT: computed tomography; RCA: right coronary artery; TAVI: transcatheter aortic valve implantation*

the radial artery in our study, we were able to capture some important findings. We combined the results of the left radial and femoral approaches due to the similarity of their catheter trajectories. The success rate for LCA cannulation and cannulation time via the right radial artery were comparable to those via the femoral/left radial artery approach, whereas for RCA cannulation, the success rate was comparable between the two groups. However, cannulation time via the right radial artery was significantly longer than the time via the femoral/left radial artery approach. The presence of a tortuous brachiocephalic artery can limit the subtle manipulation of the catheter which is required to engage the RCA, and it can be more prominent in case of a horizontal aorta. Whether this finding is also relevant in patients undergoing percutaneous coronary intervention (PCI) warrants further investigation.

Cannulation of the RCA is usually considered to be more difficult than that of the LCA. In our study, the size of the SoV and RCA misalignment were identified as predictors of suboptimal cannulation. If the patient has a wider SoV, there is less chance of suboptimal cannulation (OR 0.63). This is in line with previous studies showing a high THV/SoV relation is associated with impaired coronary access[1,2]. In case of a small SoV relative to THV size, the free space between the THV frame and the coronary ostia is limited; therefore, it makes it difficult for operators to freely manipulate the catheters, which negatively impacts CC.

The newest-iteration – Evolut FX+ (Medtronic) – was designed to improve coronary access. Its frame features 3 large windows which are the size of 4 normal frame cells and positioned 120 degrees apart between the commissures without affecting the radial strength or valve performance. It is considered to facilitate rapid coronary access; however, its advantage may be attenuated if the valve is implanted with coronary misalignment. Whether implantation of this latest platform improves the coronary cannulation success rate and shortens cannulation time warrants further evaluation.

A previous study has shown the impact of commissural alignment on valve performance[17]. In that study, haemodynamic performance indices such as mean pressure gradient and effective orifice index were not significantly different between patients with commissural alignment and misalignment. No transvalvular aortic regurgitation was identified in that series. However, the relatively small sample size precludes definitive conclusions, and a larger-scale study is warranted to investigate the impact of commissural alignment on valve performance.

Limitations

Although this study was conducted as a multicentre study, the operators were highly skilled and experienced in both structural and coronary interventions; therefore, these findings might not be reproducible in every centre. The relatively small sample size of this study might have affected the results, especially the comparison between CC via the femoral versus the radial artery; however, this was the first study to assess CC feasibility from the radial artery post-TAVI. While larger, multicentre studies are required to confirm our results, it is important to emphasise that the prospective nature associated with the inclusion of consecutive patients and consistent performance of CT post-TAVI allowed for interesting insights on this important topic. Although all the CT analyses performed in this study were evaluated by experienced interventional imagers in each large-scale hospital, it should be acknowledged that the CT analyses in this study were not reviewed by an independent core laboratory. The success rate of CC could be higher in the setting of PCI which allows the utilisation of a coronary guidewire, balloon, and guide extension catheter, which can facilitate coronary access.

Conclusions

Coronary cannulation after TAVI with the new-generation Evolut FX was highly feasible when implanted using best contemporary practice due to a high rate of commissural and coronary alignment. Significantly longer cannulation times were required for both misaligned left and right coronary arteries. Coronary misalignment was associated with suboptimal CC for both the LCA and the RCA.

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Conflict of interest statement

Y. Ohno is a clinical proctor for Medtronic and Abbott. N. Kamioka is a clinical proctor for Edwards Lifesciences. G.F. Attizzani is a consultant, serves on the advisory board, and has research grants with Medtronic, Boston Scientific, and Dasi Simulations. A. Ukaigwe is a consultant for Medtronic. S. Filby is a consultant for Boston Scientific. The other authors have no conflicts of interest relevant to the contents of this paper to declare.

References

1. Barbanti M, Costa G, Picci A, Criscione E, Reddavid C, Valvo R, Todaro D, Deste W, Condorelli A, Scalia M, Licciardello A, Politi G, De Luca G, Strazzieri O, Motta S, Garretto V, Veroux P, Giaquinta A, Giuffrida A, Sgroi C, Leon MB, Webb JG, Tamburino C. Coronary Cannulation After Transcatheter Aortic Valve Replacement: The RE-ACCESS Study. *JACC Cardiovasc Interv.* 2020;13:2542-55.

2. Tarantini G, Nai Fovino L, Scotti A, Massussi M, Cardaioli F, Rodinò G, Benedetti A, Boiago M, Matsuda Y, Continisio S, Montonati C, Cacciavillani L, Pavei A, Masiero G, Napodano M, Fraccaro C, Fabris T, Iliceto S. Coronary Access After Transcatheter Aortic Valve Replacement With Commissural Alignment: The ALIGN-ACCESS Study. *Circ Cardiovasc Interv.* 2022;15:e011045.

3. Bieliauskas G, Wong I, Bajoras V, Wang X, Kofoed KF, De Backer O, Søndergaard L. Patient-Specific Implantation Technique to Obtain Neo-Commissural Alignment With Self-Expanding Transcatheter Aortic Valves. *JACC Cardiovasc Interv.* 2021;14:2097-108.

4. Khera S, Krishnamoorthy P, Sharma SK, Kini AS, Dangas GD, Goel S, Lerakis S, Anastasius M, Moreno P, Tang GHL. Improved Commissural Alignment in TAVR With the Newest Evolut FX Self-Expanding Supra-Annular Valve: First-in-Human Experience. *JACC Cardiovasc Interv.* 2023;16:498-500.

5. Blanke P, Weir-McCall JR, Achenbach S, Delgado V, Hausleiter J, Jilaihawi H, Marwan M, Nørgaard BL, Piazza N, Schoenhagen P, Leipsic JA. Computed Tomography Imaging in the Context of Transcatheter Aortic Valve Implantation (TAVI)/Transcatheter Aortic Valve Replacement (TAVR): An Expert Consensus Document of the Society of Cardiovascular Computed Tomography. *JACC Cardiovasc Imaging.* 2019;12:1-24.

6. Yoon SH, Gabasha S, Dallan LAP, Ukaigwe A, Tang GHL, Rushing G, Pelletier M, Filby S, Baeza C, Attizzani GF. Commissural and Coronary Alignment After Transcatheter Aortic Valve Replacement Using the New Supra-Annular, Self-Expanding Evolut FX System. *Circ Cardiovasc Interv.* 2023;16:e012657.

7. Tang GHL, Amat-Santos IJ, De Backer O, Avvedimento M, Redondo A, Barbanti M, Costa G, Tchétché D, Eltchaninoff H, Kim WK, Zaid S, Tarantini G, Søndergaard L. Rationale, Definitions, Techniques, and Outcomes of Commissural Alignment in TAVR: From the ALIGN-TAVR Consortium. *JACC Cardiovasc Interv.* 2022;15:1497-518.

8. Miyamoto J, Ohno Y, Kamioka N, Ikari Y, Otsuka T, Tada N, Naganuma T, Yamawaki M, Yamanaka F, Shirai S, Mizutani K, Tabata M, Ueno H, Takagi K, Watanabe Y, Yamamoto M, Hayashida K; OCEAN-TAVI Investigators. Impact of Periprocedural Pulmonary Hypertension on Outcomes After Transcatheter Aortic Valve Replacement. *J Am Coll Cardiol.* 2022;80:1601-13.

9. Attizzani GF, Gabasha S, Ukaigwe A, Elgudin Y, Rushing G, Pelletier M, Filby S, Baeza C, Yoon SH. Coronary Cannulation, Commissure, and Coronary Alignment Post-TAVR With Evolut FX System: CANNULATE TAVR Study. *JACC Cardiovasc Interv.* 2024;17:825-7.

10. VARC-3 WRITING COMMITTEE; Généreux P, Piazza N, Alu MC, Nazif T, Hahn RT, Pibarot P, Bax JJ, Leipsic JA, Blanke P, Blackstone EH, Finn MT, Kapadia S, Linke A, Mack MJ, Makkar R, Mehran R, Popma JJ, Reardon M, Rodes-Cabau J, Van Mieghem NM, Webb JG, Cohen DJ, Leon MB. Valve Academic Research Consortium 3: Updated Endpoint Definitions for Aortic Valve Clinical Research. *J Am Coll Cardiol.* 2021;77:2717-46.

11. Otto CM, Nishimura RA, Bonow RO, Carabello BA, Erwin JP 3rd, Gentile F, Jneid H, Krieger EV, Mack M, McLeod C, O'Gara PT, Rigolin VH, Sundt TM 3rd, Thompson A, Toly C. 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: Executive Summary: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation.* 2021;143:e35-71.

12. Vahanian A, Beyersdorf F, Praz F, Milojevic M, Baldus S, Bauersachs J, Capodanno D, Conradi L, De Bonis M, De Paulis R, Delgado V, Freemantle N, Haugaa KH, Jeppsson A, Jüni P, Pierard L, Prendergast BD, Sádaba JR, Tribouilloy C, Wojakowski W. 2021 ESC/EACTS Guidelines for the management of valvular heart disease. *EuroIntervention.* 2022;17:e1126-96.

13. Izumi C, Eishi K, Ashihara K, Arita T, Otsuji Y, Kunihara T, Komiya T, Shibata T, Seo Y, Daimon M, Takanashi S, Tanaka H, Nakatani S, Ninami H, Nishi H, Hayashida K, Yaku H, Yamaguchi J, Yamamoto K, Watanabe H, Abe Y, Amaki M, Amano M, Obase K, Tabata M, Miura T, Miyake M, Murata M, Watanabe N, Akasaka T, Okita Y, Kimura T, Sawa Y, Yoshida K; Japanese Circulation Society Joint Working Group. JCS/JSCS/JATS/JSVS 2020 Guidelines on the Management of Valvular Heart Disease. *Circ J.* 2020;84:2037-119.

14. Sharma T, Krishnan AM, Lahoud R, Polomsky M, Dauerman HL. National Trends in TAVR and SAVR for Patients With Severe Isolated Aortic Stenosis. *J Am Coll Cardiol.* 2022;80:2054-6.

15. Costa G, Sammartino S, Strazzieri O, Motta S, Frittitta V, Dipietro E, Comis A, Calì M, Garretto V, Inserra C, Cannizzaro MT, Sgroi C, Tamburino C, Barbanti M. Coronary Cannulation Following TAVR Using Self-Expanding Devices With Commissural Alignment: The RE-ACCESS 2 Study. *JACC Cardiovasc Interv.* 2024;17:727-37.

16. Wang X, De Backer O, Bieliauskas G, Wong I, Bajoras V, Xiong TY, Zhang Y, Kofoed KF, Chen M, Sondergaard L. Cusp Symmetry and Coronary Ostial Eccentricity and its Impact on Coronary Access Following TAVR. *JACC Cardiovasc Interv.* 2022;15:123-34.

17. Amat-Santos IJ, Gómez-Herrero J, Pinon P, Nombela-Franco L, Moreno R, Munoz-García AJ, Redondo A, Gómez-Menchero A, Gómez-Salvador I, San Román JA. Impact of commissural alignment on the hemodynamic performance of supra-annular self-expandable transcatheter aortic valves. *Catheter Cardiovasc Interv.* 2024;104:1060-70.

Supplementary data

Supplementary Table 1. Procedural characteristics based on coronary access site (right radial vs left radial/femoral).

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-24-01050

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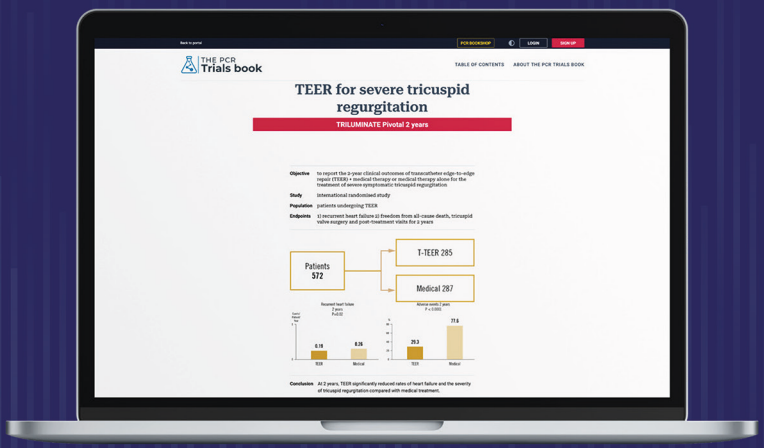

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ORIGINAL RESEARCH

TRICURE: first-in-human study of the Topaz transcatheter tricuspid heart valve system

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ABSTRACT

BACKGROUND: Given the poor prognosis of tricuspid regurgitation (TR) patients, there is growing interest in addressing TR, particularly since the emergence of novel transcatheter tricuspid valve interventions for patients at high risk for surgery.

AIMS: The TRICURE first-in-human (FIH) study evaluates the initial feasibility and clinical safety of the Topaz transcatheter tricuspid valve replacement (TTVR) system in treating TR. Featuring a novel dual-stent design, the system is specifically engineered for the unique anatomy of the tricuspid valve. It has a flexible outer stent with low radial force designed to accommodate annular dynamics and conform to the non-circular, variable shapes of the tricuspid valve, coupled to a rigid inner stent aiming to maintain valve function integrity.

METHODS: TRICURE FIH is a prospective, multicentre, first-in-human study with follow-up extending to 5 years. The primary safety endpoint is a composite measure including all-cause mortality, heart failure rehospitalisation, and reintervention for failed tricuspid therapy at 30 days. The primary performance endpoint is device success, defined as a TR reduction ≥1 grade with no more than moderate TR post-procedure.

RESULTS: A total of 20 patients were enrolled. The procedure time (from delivery system insertion to removal) was 35±16 minutes. At 30 days, the primary safety endpoint, a composite of major adverse events, was observed in 35%, and the primary performance endpoint was successfully achieved in all patients (100%), with all patients having a TR reduction of at least 3 grades, and none of the patients having more than mild TR post-procedure. No device-related pacemaker implant was reported. An exemplary case report demonstrates complete elimination of TR and a reverse remodelling of the right ventricle of 19% at 6 months.

CONCLUSIONS: The TRICURE FIH study provides evidence of the feasibility and safety of a novel TTVR system. Outcomes need to be confirmed in a larger series. (ClinicalTrials.gov: NCT05126030)

KEYWORDS: femoral; tricuspid disease; TTVR

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Once considered the "forgotten valve", the tricuspid valve has gained increasing attention due to advances in novel treatment strategies for tricuspid regurgitation (TR) and a growing recognition of its prevalence, adverse prognostic impact, and substantial symptom burden associated with progressive right heart failure[1]. Current guidelines acknowledge the rising interest, supported by encouraging preliminary experience with transcatheter tricuspid valve interventions[2,3].

However, the tricuspid valve presents unique anatomical and physiological challenges compared to other heart valves. For example, its large orifice area is highly dynamic, influenced by volume status, while the fragile, three-dimensional D-shaped annulus undergoes substantial changes throughout the cardiac cycle[1,4-7]. These complexities make the development and implantation of novel transcatheter therapies particularly challenging.

Evidence has been published in support of transcatheter tricuspid valve repair; however, certain patient anatomies – such as large annuli, large coaptation gaps, severe tethering, or right ventricular dysfunction – may be better suited for transcatheter tricuspid valve replacement (TTVR). Furthermore, TTVR offers potential advantages such as shorter procedure times, more effective TR reduction, greater procedural reproducibility, and the option for future valve-in-valve procedures[7,8]. To date, the EVOQUE valve (Edwards Lifesciences) is the only TTVR system to have received both European Conformity (CE) certification and U.S Food and Drug Administration (FDA) approval, underscoring the need for other TTVR systems.

The Topaz TTVR system (TRiCares) has been specifically designed to address the challenges of tricuspid valve replacement. Its innovative dual-stent design consists of a flexible outer stent and a more rigid inner stent. The outer stent features extremely low radial force, designed to minimise the risk of conduction disturbances while seamlessly adapting to the various native annulus morphologies. The inner stent, which houses the trileaflet valve and serves as the "replacement valve", is designed to maintain a circular shape, thereby ensuring long-term valve integrity and reliable haemodynamic performance. Additionally, atraumatic anchors aim to provide secure and stable fixation below the annulus within the native leaflets **(Central illustration, Moving image 1)**.

The TRICURE first-in-human (FIH) study intends to evaluate the feasibility and initial safety of the Topaz TTVR system. This report presents the study's primary endpoints along with an exemplary case report with 6-month follow-up.

Impact on daily practice

The TRICURE first-in-human study demonstrated the feasibility of the Topaz transcatheter tricuspid valve replacement (TTVR) system, featuring an innovative double-stent design. Although initial procedural challenges led to refinements in screening and implant technique, the consistently short procedure times, absence of device-related pacemaker implantation, and successful elimination of tricuspid regurgitation in nearly all patients support the device design and position the valve as a promising alternative to existing technologies. These encouraging results have led to the launch of two studies aiming to further evaluate the Topaz TTVR system in a broader patient population.

Methods

STUDY DESIGN

The TRICURE FIH study is a prospective, multicentre, single-arm study conducted at 8 centres in Europe. Clinical follow-up is scheduled at 30 days, 3 and 6 months, and annually at 1, 2, 3, 4, and 5 years. Follow-up assessments include a physical examination, electrocardiography, laboratory tests, echocardiography, a 6-minute walk test, and quality-of-life evaluation using the Kansas City Cardiomyopathy Questionnaire. A computed tomography (CT) assessment will be performed at the 6-month follow-up.

Approval was obtained from the competent authorities and all site ethics committees, and all patients provided written informed consent. Study oversight was ensured through an independent clinical events committee that adjudicated all adverse events (including all safety endpoints), an independent data monitoring committee, a screening committee, and independent core laboratories (MedStar Health Research Institute and Georgetown University, Washington, USA, for echocardiography and St. Paul's Cardiac CT Core Laboratory, Vancouver, Canada, for CT imaging). The trial is registered at ClinicalTrials.gov: NCT05126030.

PATIENT POPULATION

Key inclusion criteria were age above 18 years; TR grade ≥3 (on a 0 to 5 scale)[9], as assessed by an independent core laboratory, and/or symptoms requiring diuretic therapy; New York Heart Association (NYHA) Class ≥II; and patients not eligible for tricuspid valve surgery due to high operative risk, as determined by the site Heart Team. Major exclusion criteria included a need for emergent or urgent intervention or any planned cardiac intervention within 12 months; cardiac interventions within 30 days prior to the index procedure; concomitant clinically relevant mitral, aortic, or pulmonary regurgitation or stenosis; prior tricuspid valve replacement or repair with a device *in situ*; and severe pulmonary hypertension **(Supplementary Table 1)**.

STUDY DEVICE AND PROCEDURES

The TRiCares Topaz TTVR system comprises four components: (1) the heart valve prothesis; (2) the introducer

Abbreviations

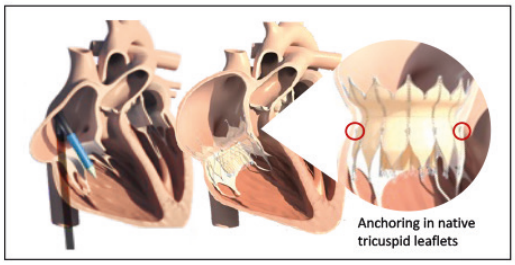
CT	computed tomography	**NYHA**	New York Heart Association	**TR**	tricuspid regurgitation
FIH	first-in-human	**TAPSE**	tricuspid annular plane systolic excursion	**TTVR**	transcatheter tricuspid valve replacement
MAE	major adverse events				

EuroIntervention — Central **Illustration**

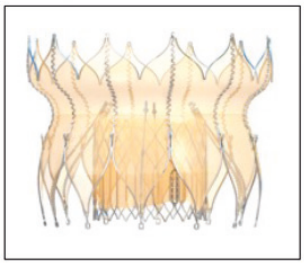
TRICURE first-in-human study assessing the TRiCares Topaz transcatheter tricuspid heart valve system.

TRICURE first-in-human study

Purpose	To assess the feasibility and safety of the **TRiCares Topaz transcatheter heart valve system** in patients with tricuspid regurgitation not eligible for open heart surgery
Design	Prospective, multicentre, international, single-arm first-in-human study enrolling 20 patients



Key design features of the Topaz TTVR system
- Softer outer stent with low radial force
- Rigid inner stent
- Atraumatic anchors



Primary safety endpoint - 30-day hierarchical composite incl.
- All-cause mortality (n=3)
- Elective reintervention (n=2)
- Non-elective reintervention (n=1)
- Rehospitalisation for heart failure (n=1)

Endpoint observed in 7 patients

Primary performance endpoint
- TR reduction by at least one grade
- TR reduction by 3 or more grades in 100%
- TR reduced to none/mild in 100%

Endpoint met in 100%

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Data were adjudicated by a clinical events committee and assessed by a core laboratory. TR: tricuspid regurgitation; TTVR: transcatheter tricuspid valve replacement

system; (3) the delivery system for transcatheter access, which together with the introducer system constitutes the implantation system; and (4) the loading system.

The Topaz heart valve prosthesis is a self-expanding biological artificial heart valve with a double-stent design consisting of an outer stent and an inner stent, both made of nitinol. The outer stent safely anchors the prosthesis in an orthotopic position by means of an hourglass shape (v-groove) and 12 atraumatic anchors. The inner stent serves as the skeleton for the trileaflet heart valve, which is made of porcine pericardium. The seal, also made of porcine pericardium, is designed to prevent intraprosthetic as well as paravalvular leakage. The available valve size was suitable for native annulus sizes of up to approximately 45 mm.

The introducer system consists of a steerable sheath (29 Fr) and a dilator compatible with a 0.035 inch guidewire. The delivery system is designed as a pullback system and has a soft, radiopaque tip aiming to prevent damage to the ventricle, as well as a stent holder designed to securely attach the Topaz prosthesis. The outer shaft maintains the crimped state of the prosthesis until a controlled release is intentionally initiated with the deployment wheel on the delivery system handle. The radiopaque marker band of the outer shaft allows for visual position control under fluoroscopy during deployment. An animation of TTVR with the Topaz system is provided as **Moving image 1**.

Baseline assessments included transthoracic and transoesophageal echocardiography, CT, and right heart catheterisation. Anticoagulation therapy was to be prescribed according to hospital standard of care for heart valve replacement and/or following the European Society of Cardiology/European Association for Cardio-Thoracic Surgery (ESC/EACTS) Guidelines for the management of valvular heart disease[2].

ENDPOINTS AND DEFINITIONS

The primary safety endpoint is a composite endpoint measure that includes all-cause mortality, rehospitalisation for heart failure, and reintervention for failed tricuspid intervention at 30 days. In cases where the patient was still in hospital on day 30 post-intervention, this was considered a rehospitalisation. The primary performance endpoint is device success, defined as a reduction of tricuspid regurgitation by at least 1 grade between the baseline and post-intervention evaluation (as assessed by the echo core laboratory), and no more than moderate tricuspid regurgitation. Secondary clinical endpoints are listed in the results section[10]. Functional and quality-of-life endpoints, along with comprehensive imaging

analysis covering all follow-up timepoints, will be reported in a separate publication.

STATISTICS

A sample size of 20 patients was deemed to be adequate to get first data on feasibility, safety, and performance of the TRiCares Topaz TTVR system.

Safety outcomes are reported for the intention-to-treat population. Procedure time was calculated based on the patients in whom the delivery system was introduced. Performance analyses were done for all patients with the investigational device *in situ*. Patients who did not receive a study valve or had a study valve explanted were followed for 30 days for safety assessment. Continuous data are summarised as mean±standard deviation (minimum and maximum). Categorical variables are summarised as frequency counts and percentages. The statistical analysis was performed using SAS, version 9.4 (SAS Institute).

Results

Patients who were deemed ineligible for open heart surgery were enrolled; none of the 8 sites enrolled more than 20% of patients (maximum of 4 patients per site).

BASELINE CHARACTERISTICS

Twenty patients were enrolled, with a mean age of 77.0±6.6 years, and 18 patients (90%) were female. Baseline characteristics are presented in **Table 1**.

PROCEDURAL OUTCOME

The Topaz valve was implanted in 18 patients. The mean procedure time was 35±16 min (range 17 to 65 min), and the mean right atrial pressure decreased from 21±13 mmHg preimplant to 12±5 mmHg post-implant.

Two patients did not receive the device due to access-related challenges. In one patient, venous access was not achievable because of a thrombotic vessel, which was a result of long-term dialysis. The other patient had a rupture of the access vessel that was due to the vessel's frailty after radiation therapy. Both patients were alive at 30 days post-procedure. Since then, the screening committee has also begun assessing the access vessels with particular care, recognising that even though the venous system may appear more forgiving, it still warrants a thorough evaluation to ensure that transcatheter access can be achieved.

One patient experienced procedural mortality due to a ventricular perforation. It cannot be ruled out that the stiff guidewire may have contributed to the ventricular perforation, particularly given the known fragility of the right ventricular wall in transcatheter interventions. The patient underwent emergency surgery, but died the same day. In another patient, the stiff guidewire inadvertently became wrapped underneath the moderator band. This detail went unnoticed, leading to deployment of the Topaz valve above the moderator band, which resulted in a suboptimal position that ultimately required surgical reintervention.

Thirty-day data are available for all patients. The primary safety endpoint, a composite of major adverse events (MAE), was observed in 7 patients (35%) **(Table 2)**.

Table 1. Baseline characteristics.

	N=20
Age, years	77.0±6.6 (61-81)
Sex	
Male	2 (10)
Female	18 (90)
NYHA Class	
II	6 (30)
III	13 (65)
IV	1 (5)
EuroSCORE II, %	4.2±2.3 (1.3-10.2)
STS-PROM score, %	9.7±5.4 (4.6-22.1)
TRI-SCORE	4.6±2.5 (2-11)
TRI-SCORE predicted in-hospital mortality, %	17.6±20.1 (3-65)
Concomitant mitral valve disease	10 (50)
Concomitant aortic valve disease	3 (15)
Coronary artery disease	4 (20)
Cardiac rhythm	
Bundle branch block	4 (20)
Atrial flutter/fibrillation	17 (85)
History of previous CIED implantation	0 (0)
Previous stroke	5 (25)
Peripheral vascular disease	3 (15)
Chronic obstructive pulmonary disease	2 (10)
Renal insufficiency*	19 (95)
eGFR, mL/min/1.73 m^2	40±19
Pulmonary hypertension	9 (45)
Pulmonary artery systolic pressure, mmHg	39.8±13.1
Cancer	6 (30)
Diabetes	5 (25)
Arterial hypertension	15 (75)
Hyperlipidaemia	13 (65)
Smoker	6 (30)

Data are presented as mean±SD (min-max), mean±SD, or n (%). *eGFR of ≤89 mL/min/1.73 m^2. CIED: cardiac implantable electronic device; eGFR: estimated glomerular filtration rate; EuroSCORE: European System for Cardiac Operative Risk Evaluation; NYHA: New York Heart Association; SD: standard deviation; STS-PROM: Society of Thoracic Surgeons Predicted Risk of Mortality

In two patients, perpendicular alignment of the delivery system could not be achieved, resulting in the prothesis being deployed slightly higher than intended. In one of these cases, the nose cone of the delivery system (catheter tip) became entrapped in the prothesis during retrieval, causing valve displacement. As the valve was not securely anchored, the implantation team reached a consensus to proceed with an elective reintervention on the same day, during which the Topaz prosthesis was successfully secured with a few sutures. The patient showed initial improvement but subsequently developed cardiogenic shock and right ventricular failure,

Table 2. Clinical outcomes at 30-day follow-up.

	N=20
Hierarchical composite MAE endpoint*	**7 (35)**
All-cause mortality	3 (15)
Cardiovascular mortality	2 (10)
Non-cardiovascular mortality	1 (5)
Reintervention#	3 (15)
Elective (Topaz remained *in situ*)	2 (10)
Non-elective	1 (5)
Hospitalisation for heart failure	1 (5)
Additional safety endpoints	
Myocardial infarction	0 (0)
Stroke	0 (0)
Renal complications	0 (0)
Vascular bleeding	0 (0)
Device-related pulmonary embolism	0 (0)
Topaz-related pacemaker implantation†	0 (0)
Thrombotic event	0 (0)

Data are presented as n (%). *Includes all-cause mortality, rehospitalisation for heart failure, and reintervention for failed tricuspid intervention. #N=1 explanted; N=2 Topaz prosthesis remained *in situ*. †None of the enrolled patients had a prior pacemaker implant. MAE: major adverse events

passing away on day 5. In the other patient, perpendicular deployment proved difficult because of a small, short right ventricle. Although the Topaz valve initially appeared well-seated, postprocedural migration – likely caused by upward pressure from subvalvular structures, including a dominant papillary muscle and trabeculations – was detected on day 2, prompting elective replacement with a conventional valve. The Topaz valve was explanted at the surgeon's discretion rather than secured with sutures. The patient was alive at 30 days. In a third patient, the procedure was uneventful, with initially correct valve placement. Shortly after, the valve migrated slightly posteriorly but remained stable. Echocardiography showed mild to moderate paravalvular regurgitation. Root cause analysis revealed an underappreciated posterior shelf that impaired complete anchoring, with a subannular diameter of 58 mm likely exceeding the valve's anchoring capacity. In an elective reintervention on postinterventional day 1, the valve was successfully secured with a few sutures. As a result, screening was refined to include more detailed assessment of annular and right ventricular dimensions.

In addition to the two patients described above, one patient – an 80-year-old with multiple comorbidities and a recent history of catheter-related sepsis – died of septic shock and mesenteric ischaemia 19 days post-procedure. The patient had received levosimendan both pre- and post-intervention and was on haemodialysis. The infection was likely linked to a previously infected access site; endocarditis was ruled out.

No Topaz-related pacemaker implantation was reported.

The primary performance endpoint was achieved in all patients (100%) with a device *in situ*. In fact, TR was reduced by at least 3 grades in all patients (100%). At 30 days, tricuspid regurgitation was absent in all but two patients, both of whom presented with mild TR **(Figure 1)**.

Independent core lab analysis of paired transthoracic echocardiograms showed that, from baseline to 30 days, right atrial volume decreased from 75.8±22.1 mL to 62.3±13.3 mL, inferior vena cava (IVC) diameter decreased from 19.1±4.5 mm to 17.4±2.4 mm, tricuspid annular plane systolic excursion (TAPSE) decreased from 18.6±6.1 mm to 16.3±5.0 mm, and right ventricular fractional area change decreased from 36.0±8.7% to 29.4±9.6%.

EXEMPLARY CASE REPORT

We report the case of a frail 78-year-old female with New York Heart Association (NYHA) Class III symptoms and massive TR grade 4/5 due to annular dilatation in the setting of permanent atrial fibrillation, a retracted septal leaflet, and clefts in both the posterior and anterior leaflets **(Moving image 2-Moving image 4)**. The core laboratory measured the tricuspid annulus as 41 mm on echocardiography, while CT assessment in end-systole showed dimensions of 42 mm × 45 mm in orthogonal planes. The TAPSE was 15 mm.

The patient experienced fatigue and exertional chest pain; she had a TRI-SCORE of 4 out of 12, resembling a predicted in-hospital mortality of 8%, and a Society of Thoracic Surgeons (STS) score of 9.7%. Further details are provided in **Figure 2**. Her multiple comorbidities included aortic insufficiency, mild mitral insufficiency, arterial hypertension, permanent atrial fibrillation, left bundle branch block, moderate pulmonary hypertension, a history of decompensated heart failure (baseline N-terminal pro-brain natriuretic peptide [NT-proBNP] of 2,372 pg/mL and cardiac output of 3.0 L/min), renal insufficiency (baseline estimated glomerular filtration rate of 44 mL/min/1.73 m²), and previous left mastectomy and radiotherapy.

Right heart catheterisation revealed a pulmonary artery pressure of 40/20/26 mmHg, a pulmonary capillary wedge pressure of 16/20 mmHg, and a right atrial pressure of 15/19 mmHg.

The procedure was performed under general anaesthesia. Access was gained through the left femoral vein. The CT scan was used to define the implant angulation and the spatial relationship between the right coronary artery and the tricuspid annulus. Via the steerable sheath, the valve was advanced towards the right ventricle. After achieving perpendicular alignment of the delivery system with the tricuspid annulus and confirming the correct height at the annular level, a bottom-to-top release was performed under fast pacing **(Moving image 5-Moving image 8)**. The procedure time (from delivery system insertion to removal) was 28 min, and TR was successfully and completely eliminated (grade 0/5) **(Moving image 9-Moving image 11)**. Two adverse events were observed. Following successful valve implantation, the patient developed a complete heart block requiring temporary pacing, and the temporary pacemaker was safely removed on postoperative day 2. Notably, the patient had a pre-existing left bundle branch block. Additionally, the patient experienced a transient post-anaesthesia delirium, with a normal neurological examination and a negative brain CT. The condition resolved fully by postoperative day 2, without any residual confusion or disorientation. The patient was discharged in a stable condition on postoperative day 10.

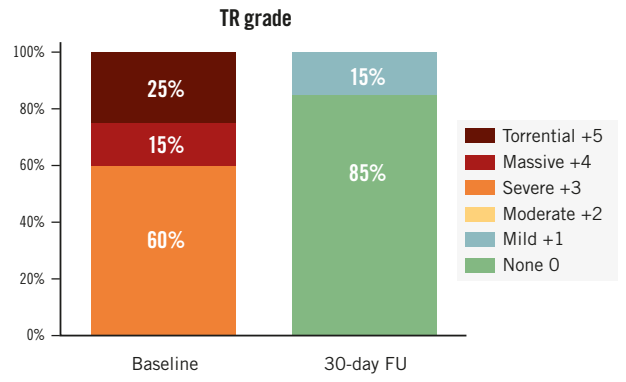

Figure 1. *Tricuspid regurgitation at baseline and 30-day follow-up. Data were assessed by a core laboratory and were available for 20 patients at baseline and 13 patients at 30-day follow-up. Each patient improved by at least 3 grades at 30 days. FU: follow-up; TR: tricuspid regurgitation*

At 30 days, and again at 3 and 6 months, the patient showed a sustained and remarkable improvement to NYHA Class I, with no recurrence of TR and a restored TAPSE of 19 mm. By 3 months post-procedure, diuretics were no longer needed. At 6 months, the CT scan revealed a 19% reduction in right ventricular end-diastolic volume, evidence of reverse remodelling, and ongoing cardiac recovery.

Discussion

The main findings of this FIH series are as follows: (1) acceptable safety, with an MAE composite rate of 35%, (2) low technical and procedural complexity, as reflected by a mean procedure time of 35±16 minutes; (3) a substantial and sustained reduction in TR at 30 days in all patients, accompanied by early signs of reverse right heart remodelling, illustrated by the exemplary case; and (4) a procedural learning curve, which initially led to some elective reinterventions and ultimately drove refinement of screening criteria and optimisation of the implantation technique, including the adoption of additional access routes.

FEASIBILITY AND DESIGN OBJECTIVE

The Topaz TTVR system is uniquely designed for the tricuspid space, featuring a double-stent system. The TRICURE first-in-human study confirms that the design objectives were met.

First, ease of use is supported by the design features of the Topaz valve, such as the hourglass shape and v-groove, which promote intuitive positioning and partial self-alignment. Importantly, the system does not require leaflet grasping or capture prior to deployment, as is necessary with some other transcatheter tricuspid valve systems[11-13]. Valve deployment is guided by transoesophageal echocardiography, although in select cases transthoracic echocardiography may be sufficient, making the imaging requirements less demanding than for some other devices[11-13]. In the TRICURE FIH study, ease of use was reflected by the very short mean procedure time of 35±16 min (from delivery system insertion to removal), despite all centres being first-time users and only enrolling a maximum of four patients each. For comparison, the EVOQUE valve, the first valve that gained CE certification and FDA approval, demonstrated procedural times of 71.6±31.4 min in TRISCEND and 56.5 min (interquartile range 41-75 min) in TRISCEND II[14,15].

Second, the conformity of the outer stent and its sealing are intended to prevent paravalvular leakage and rhythm disturbances that may result in permanent pacemaker implantation. This has been confirmed by the successful reduction of TR at 30 days and the fact that there were no Topaz-dependent permanent pacemaker implants at 30 days, compared to 13.3% in TRISCEND and 24.7% in TRISCEND II[14,15]. As shown in the exemplary case, the conformity of the outer stent also prevents imposing a round valve shape on the annulus and permits the outer stent to flex and adapt during the cardiac cycle, which may prevent thrombotic events and has the potential to lower the need for anticoagulation therapy.

Third, the rigid inner stent helps maintain the valve's integrity. While 30-day outcomes are too early to draw any conclusions about long-term efficacy, the fact that all patients experienced no or mild TR, along with the round shape of the inner stent, the absence of TR in the exemplary case at 6 months, and evidence of reverse remodelling, all provide initial support for the device concept's potential for success.

Fourth, the atraumatic anchoring is designed to prevent annular injury. No such injury was observed in the TRICURE FIH study. However, these complications are rare, and the sample size may be too small to draw a valid conclusion on this aspect.

INSIGHTS

This first-in-human study included first-time users, with each centre enrolling a maximum of 20% of the total patients (n=4). Thus, the learning curve includes both individual practitioner experience and the development of effective screening and implantation strategies. While the number of reinterventions, including both elective and non-elective procedures, was notable, this early experience provided valuable insights into patient screening, including vascular access, device sizing, subvalvular structures, and IVC--to-annulus offset (IVC offset), all of which contributed to the challenging tricuspid valve morphology.

As expected in FIH studies, suboptimal outcomes were not tolerated and required reintervention. All reinterventions, except two in which the investigator preferred to use a conventional heart valve, were successfully managed by repositioning and securing the Topaz prosthesis with a few sutures. In these cases, the minimally invasive procedure was faster and less invasive compared to conventional open heart surgery.

Root cause analyses identified various contributing factors, with sizing and IVC offset emerging as key issues. Subsequently, the implantation guidelines were updated, particularly regarding valve sizing and inclusion of left femoral vein access to address the IVC-to-annulus angle (offset), which allows for a more central position of the delivery system. The development

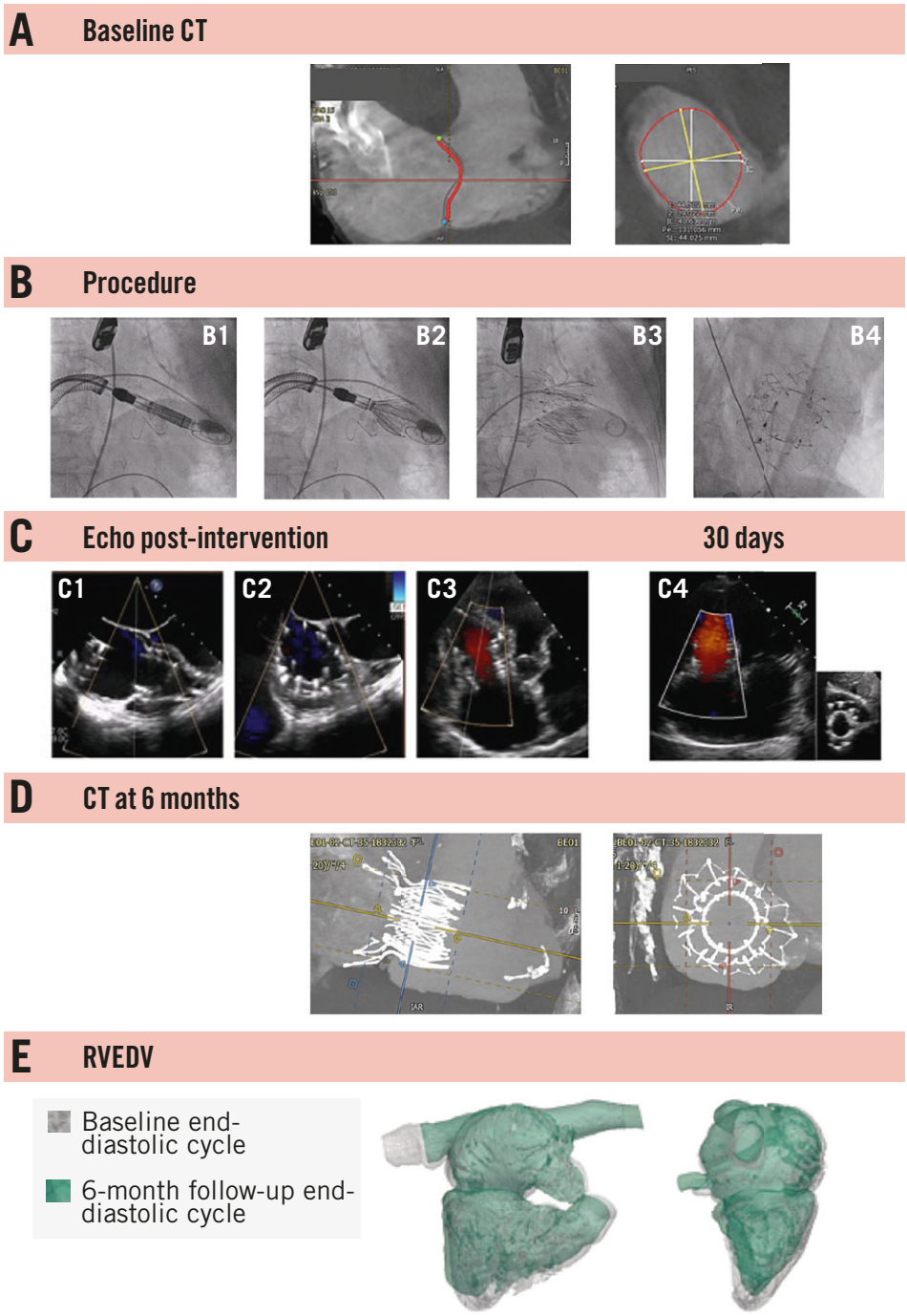

Figure 2. *Exemplary case report with echocardiographic and computed tomography assessments. Exemplary case report of a 78-year-old female. A) Baseline computed tomography (CT) revealed an oval-shaped annulus in systole, delineated by a red line, with a minimum diameter of 42 mm and a maximum diameter of 45 mm. B1) Using a steerable sheath, the valve was advanced towards the right ventricle. The wire in the right coronary artery served as a landmark for the tricuspid annulus during positioning. B2) The delivery sheath was partially retracted, allowing for the assessment of valve height and perpendicular alignment with the annulus using multiplanar transoesophageal imaging. B3) After confirming the valve position, the valve was deployed from bottom to top under fast pacing. B4) Final angiography demonstrated excellent results: no residual leakage, a circular inner ring/stent, and an outer ring well-conformed and adapted to the anatomical annular shape in the en face view. C1-C3) Postprocedural results by transoesophageal echocardiography and (C4) transthoracic echocardiography on day 30 post-procedure. D) CT imaging at the 6-month follow-up confirmed the persistent round shape of the inner ring and continued conformity of the outer ring to the annulus. E) The right ventricular end-diastolic volume (RVEDV) decreased by 19%, from 175 mL at baseline to 142 mL at 6 months, as assessed by the core laboratory.*

of a larger valve size – already successfully tested in humans – enables the inclusion of more patients with larger annulus dimensions. Another key lesson learned is the importance of screening access vessels, even when venous access is planned. In retrospect, the two patients with failed access should have been excluded during screening.

OUTLINE

There is still much to learn, and these findings, particularly the updated implant and sizing recommendations, will need validation in larger patient populations with long-term follow-up. The follow-up of the current study is scheduled for up to 5 years, and as of manuscript preparation, two clinical trials are ongoing: a European pivotal study (TRICURE EU Pivotal Study [ClinicalTrials.gov: NCT06581471]) and an early feasibility study (EFS) in the USA and Canada (TRICURE EFS [ClinicalTrials.gov: NCT06506942]).

The outcomes of these studies may help to define the role of this novel system within the current landscape of tricuspid regurgitation therapies. Provided that the number of reinterventions will be reduced with updated screening guidelines, high-risk patients with multiple comorbidities, patients with renal impairment, and patients with end-stage heart failure might benefit from the shorter procedure times, which may also improve cost-effectiveness. Additionally, patients with pre-existing conduction disturbances who do not yet require a pacemaker may benefit from this device. The findings of this FIH study indicate that Topaz might be a viable treatment option for a vast majority of patients, given its design, which is specifically tailored for the tricuspid valve.

Limitations

The TRICURE FIH study has several inherent limitations typical of FIH trials. These include a learning curve, with each site enrolling a maximum of 4 patients; amended implantation and screening guidelines; and a non-randomised design along with a small sample size, limiting the ability to draw meaningful comparisons with other devices; and lastly, only one prosthesis size was available for the study, though a second size is currently being tested. A positive aspect is the rigorous study conduct, with no patient lost to follow-up.

Conclusions

The Topaz TTVR system is an innovative technology that shows considerable potential in achieving its intended design objectives. If the updated screening and implantation guidelines effectively reduce the number of reinterventions observed in this early experience, the Topaz TTVR system has the potential to offer a user-friendly solution with short procedure times, low complication rates, particularly pacemaker implantations, and effective elimination of tricuspid regurgitation. However, long-term follow-up and data from a larger patient population are essential to validate these results and confirm the safety and efficacy of the revised implantation strategy.

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Conflict of interest statement

L. Rosseel reports institutional research grants from Medtronic; consulting fees from GE HealthCare; proctor fees from TRiCares; and speaker fees from Medtronic and Boston Scientific. S. Verheye reports consulting fees from Shockwave Medical; and honoraria from Elixir Medical. J.-F. Obadia reports participation in DSMB/advisory board meetings of Trinity (Jenscare). F.M. Asch directs an Academic Echocardiography Core Laboratory with institutional research grants/contracts from TRiCares, Abbott, Edwards Lifesciences, Boston Scientific, Medtronic, VDyne, CroiValve, InnovHeart, Polares Medical, Ancora Heart, Xeltis, Neovasc, Foldax, CorFlow, Laminar, Aria CV, Us2.ai, Ultromics, GE HealthCare, Philips/Tomtec, egnite, and MyCardium; and is a board/committee member of the American Society of Echocardiography and the American Heart Association. P. Blanke is a consultant for TRiCares, Laralab, and Edwards Lifesciences; and reports stocks/stock options from Laralab and TRiCares. J. Dreyfus reports consulting and/or proctoring fees from Abbott, Edwards Lifesciences, and TRiCares. The other authors have no conflicts of interest to declare.

References

1. Agarwal V, Hahn R. Tricuspid Regurgitation and Right Heart Failure: The Role of Imaging in Defining Pathophysiology, Presentation, and Novel Management Strategies. *Interv Cardiol Clin*. 2024;13:81-99.

2. Vahanian A, Beyersdorf F, Praz F, Milojevic M, Baldus S, Bauersachs J, Capodanno D, Conradi L, De Bonis M, De Paulis R, Delgado V, Freemantle N, Haugaa KH, Jeppsson A, Jüni P, Pierard L, Prendergast BD, Sádaba JR, Tribouilloy C, Wojakowski W. 2021 ESC/EACTS Guidelines for the management of valvular heart disease. *EuroIntervention*. 2022;17:e1126-96.

3. Writing Committee Members; Otto CM, Nishimura RA, Bonow RO, Carabello BA, Erwin JP 3rd, Gentile F, Jneid H, Krieger EV, Mack M, McLeod C, O'Gara PT, Rigolin VH, Sundt TM 3rd, Thompson A, Toly C. 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/

American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2021;77:e25-197.

4. Ben Ali W, Ruf T, Perrin N, Bouhout I, Fam N, Kresoja KP, Lurz P, von Bardeleben RS, Modine T, Ibrahim R. Indications, Limitations, and Development of Tricuspid Valve Interventions in Adults. *Can J Cardiol*. 2022;38:S66-78.

5. Cammalleri V, Carpenito M, Bono MC, Mega S, Ussia GP, Grigioni F. Transcatheter Tricuspid Valve Therapy: From Anatomy to Intervention. *Front Cardiovasc Med*. 2021;8:778445.

6. Alperi A, Almendárez M, Álvarez R, Moris C, Leon V, Silva I, Hernández-Vaquero D, Pascual I, Avanzas P. Transcatheter tricuspid valve interventions: Current status and future perspectives. *Front Cardiovasc Med*. 2022;9:994502.

7. Hagemeyer D, Ong G, Peterson MD, Fam NP. Transcatheter tricuspid valve intervention: to repair or to replace? *Curr Opin Cardiol*. 2022;37:495-501.

8. Chang CC, Veen KM, Hahn RT, Bogers AJJC, Latib A, Oei FBS, Abdelghani M, Modolo R, Ho SY, Abdel-Wahab M, Fattouch K, Bosmans J, Caliskan K, Taramasso M, Serruys PW, Bax JJ, van Mieghem NMDA, Takkenberg JJM, Lurz P, Modine T, Soliman O. Uncertainties and challenges in surgical and transcatheter tricuspid valve therapy: a state-of-the-art expert review. *Eur Heart J*. 2020;41:1932-40.

9. Hahn RT, Lawlor MK, Davidson CJ, Badhwar V, Sannino A, Spitzer E, Lurz P, Lindman BR, Topilsky Y, Baron SJ, Chadderdon S, Khalique OK, Tang GHL, Taramasso M, Grayburn PA, Badano L, Leipsic J, Lindenfeld J, Windecker S, Vemulapalli S, Redfors B, Alu MC, Cohen DJ, Rodés-Cabau J, Ailawadi G, Mack M, Ben-Yehuda O, Leon MB, Hausleiter J. Tricuspid Valve Academic Research Consortium Definitions for Tricuspid Regurgitation and Trial Endpoints. *Eur Heart J*. 2023;44:4508-32.

10. Stone GW, Adams DH, Abraham WT, Kappetein AP, Généreux P, Vranckx P, Mehran R, Kuck KH, Leon MB, Piazza N, Head SJ, Filippatos G, Vahanian AS; Mitral Valve Academic Research Consortium (MVARC). Clinical Trial Design Principles and Endpoint Definitions for Transcatheter Mitral Valve Repair and Replacement: Part 2: Endpoint Definitions: A Consensus Document From the Mitral Valve Academic Research Consortium. *J Am Coll Cardiol*. 2015;66:308-21.

11. Hahn RT, Makkar R, Makar M, Davidson C, Puthamana J, Zahr F, Chadderdon S, Fam N, Ong G, Yadav PK, Thourani VH, Vannan MA, Tchétché D, Dumonteil N, Bonfils L, Lepage L, Smith R, Grayburn PA, Webb JG, Moss R, Windecker S, Brugger N, Nabauer M, Hausleiter J, Kodali S. EVOQUE Tricuspid Valve Replacement System: State-of-the-Art Screening and Intraprocedural Guidance. *JACC Cardiovasc Interv*. 2024;17:2093-112.

12. Sondergaard L, Møller JE, De Backer O, Møller-Sørensen PH, Cheng Y, Rossing K, Smerup M, Quadri A. First-in-Human Implantation of a New Transcatheter Tricuspid Valve Replacement System. *JACC Case Rep*. 2023;14:101841.

13. Wong LN, Kam KK, Lai LK, Chow SC, Lam YY, Wan S, Lee AP, So KC. Step-by-Step Transcatheter Tricuspid Valve Replacement Using the LuX-Valve Plus System. *JACC Case Rep*. 2024;29:102699.

14. Kodali S, Hahn RT, Makkar R, Makar M, Davidson CJ, Puthumana JJ, Zahr F, Chadderdon S, Fam N, Ong G, Yadav P, Thourani V, Vannan MA, O'Neill WW, Wang DD, Tchétché D, Dumonteil N, Bonfils L, Lepage L, Smith R, Grayburn PA, Sharma RP, Haeffele C, Babaliaros V, Gleason PT, Elmariah S, Inglessis-Azuaje I, Passeri J, Herrmann HC, Silvestry FE, Lim S, Fowler D, Webb JG, Moss R, Modine T, Lafitte S, Latib A, Ho E, Goldberg Y, Shah P, Nyman C, Rodés-Cabau J, Bédard E, Brugger N, Sannino A, Mack MJ, Leon MB, Windecker S; the TRISCEND study investigators. Transfemoral tricuspid valve replacement and one-year outcomes: the TRISCEND study. *Eur Heart J*. 2023;44:4862-73.

15. Hahn RT, Makkar R, Thourani VH, Makar M, Sharma RP, Haeffele C, Davidson CJ, Narang A, O'Neill B, Lee J, Yadav P, Zahr F, Chadderdon S, Eleid M, Pislaru S, Smith R, Szerlip M, Whisenant B, Sekaran NK, Garcia S, Stewart-Dehner T, Thiele H, Kipperman R, Koulogiannis K, Lim DS, Fowler D, Kapadia S, Harb SC, Grayburn PA, Sannino A, Mack MJ, Leon MB, Lurz P, Kodali SK; TRISCEND II Trial Investigators. Transcatheter Valve Replacement in Severe Tricuspid Regurgitation. *N Engl J Med*. 2025;392:115-26.

16. Faqih SA, Noto-Kadou-Kaza B, Abouamrane LM, Mtiou N, El Khayat S, Zamd M, Medkouri G, Benghanem MG, Ramdani B. Pulmonary hypertension: prevalence and risk factors. *Int J Cardiol Heart Vasc*. 2016;11:87-9.

17. Kovacs G, Zeder K, Rosenstock P, Avian A, Bachmaier G, Douschan P, Foris V, Sassmann T, Olschewsk H. Clinical Impact of the New Definition of Precapillary Pulmonary Hypertension. *Chest*. 2021;159:1995-7.

18. Opitz I, Ulrich S. Chronic thromboembolic pulmonary hypertension. *Swiss Med Wkly*. 2018;148:w14702.

19. Galiè N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, Simonneau G, Peacock A, Vonk Noordegraaf A, Beghetti M, Ghofrani A, Gomez Sanchez MA, Hansmann G, Klepetko W, Lancellotti P, Matucci M, McDonagh T, Pierard LA, Trindade PT, Zompatori M, Hoeper M. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Respir J*. 2015;46:903-75.

20. Gall H, Hoeper MM, Richter MJ, Cacheris W, Hinzmann B, Mayer E. An epidemiological analysis of the burden of chronic thromboembolic pulmonary hypertension in the USA, Europe and Japan. *Eur Respir Rev*. 2017;26:160121.

Supplementary data

Supplementary Table 1. Inclusion and exclusion criteria.

Moving image 1. Animated visualisation of transcatheter tricuspid valve replacement with the Topaz transcatheter heart valve system (video provided with permission of TRiCares, Germany).

Moving images 2, 3 and 4. Baseline transthoracic and transoesophageal echocardiography.

Moving images 5, 6, 7 and 8. Procedural steps under fluoroscopy.

Moving images 9. Immediate postprocedural results by transoesophageal echocardiography.

Moving image 10. Transthoracic echocardiography on day 3 post-procedure.

Moving image 11. Transthoracic echocardiography on day 6 post-procedure.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-25-00423

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Five-year follow-up of transcatheter tricuspid valve replacement with the EVOQUE valve

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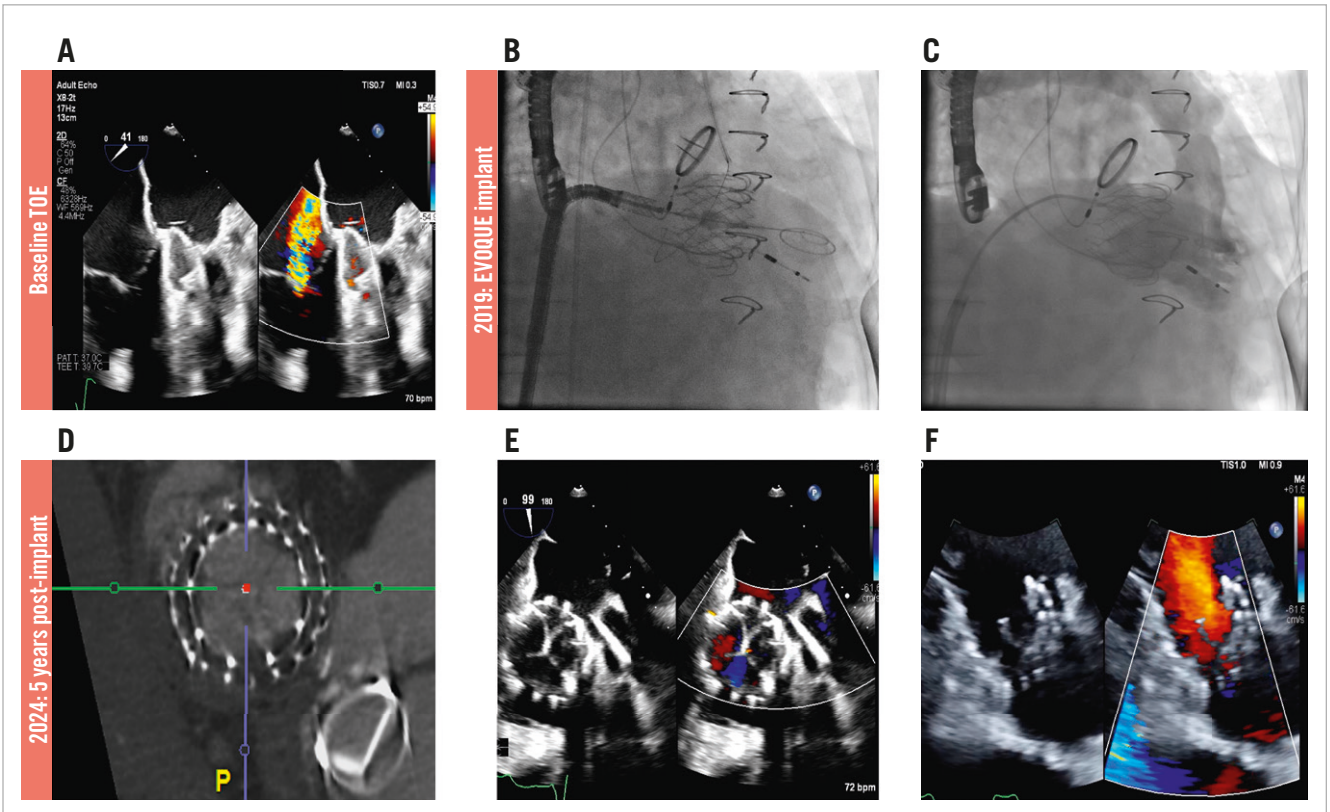

Figure 1. *Five-year follow-up of transcatheter tricuspid valve replacement with the EVOQUE valve A) Preprocedural transoesophageal echocardiogram shows severe tricuspid regurgitation. B) Fluoroscopy of the EVOQUE valve implant shows the deployed valve. C) Right ventricular angiogram via a pigtail catheter immediately post-implant shows minimal residual TR. D) CT 5 years post-implant shows no evidence of structural valve deterioration. E,F) Transoesophageal and transthoracic echocardiogram images 5 years post-TTVR shows minimal residual TR. CT: computed tomography; TR: tricuspid regurgitation; TTVR: transcatheter tricuspid valve replacement*

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Transcatheter tricuspid valve replacement (TTVR) is an alternative treatment modality for a subset of patients with severe tricuspid regurgitation who are unsuitable for traditional surgery or transcatheter edge-to-edge repair. One TTVR device, the EVOQUE valve (Edwards Lifesciences), has recently become the first TTVR device to receive U.S. Food and Drug Administration approval for the treatment of severe tricuspid regurgitation. Reported midterm outcomes of the EVOQUE valve have been favourable, demonstrating reductions in tricuspid regurgitation, symptom burden, and heart failure hospitalisation rates[1,2]. However, there remains a paucity of data on long-term outcomes following TTVR with the EVOQUE valve.

A 69-year-old female patient with a background history of rheumatic heart disease, mitral valve commissurotomy, and subsequent mechanical mitral valve replacement (St. Jude Medical 25 mm mechanical prosthesis) presented with New York Heart Association (NYHA) IV dyspnoea, refractory peripheral oedema, ascites, and multiple recent heart failure hospitalisations. Transthoracic echocardiography (TTE) revealed a left ventricular ejection fraction of 50%, a dilated right ventricle (RV; basal diameter of 46 mm) with mildly reduced function (tricuspid annular plane systolic excursion [TAPSE] of 9 mm), a well-functioning mitral prosthesis with trivial valvular mitral regurgitation, severe tricuspid regurgitation, and pulmonary hypertension, with an RV systolic pressure of 48 mmHg **(Moving image 1)**. She was pacing dependent, having had a dual-chamber permanent pacemaker implanted prior to undergoing atrioventricular node ablation. She was felt to have prohibitive surgical risk and therefore underwent TTVR with a 44 mm EVOQUE valve **(Moving image 2)**. Postprocedural transoesophageal echocardiography (TOE) showed trivial tricuspid regurgitation and a tricuspid valve mean gradient of 2 mmHg **(Figure 1)**. Her immediate postoperative course was uncomplicated, and at 30-day follow-up, the patient reported NYHA II dyspnoea. She was prescribed aspirin 81 mg once daily and warfarin for 12 months post-TTVR, followed by warfarin monotherapy for life.

At 5-year follow-up, the patient reported NYHA II dyspnoea. Her six-minute walk test distance had increased from 115 metres preprocedure to 450 metres. The patient had had only one hospitalisation in the 5 years following EVOQUE implantation; this was due to multifocal pneumonia and sepsis. The TOE performed during that admission revealed a well-seated 44 mm EVOQUE valve with a mean gradient of 4 mmHg, and trivial tricuspid regurgitation with no evidence of paravalvular regurgitation **(Moving image 3)**. Computed tomography (CT) showed no evidence of structural valve degeneration. TTE showed a normal RV size, with a basal RV diameter of 41 mm and mildly reduced RV function (TAPSE of 15 mm). Her baseline conduction remained unchanged, despite the RV lead having been jailed during the procedure. She remained pacing dependent and underwent a routine generator change 4 years after TTVR.

In this report of the 5-year follow-up TOE and CT imaging of a patient undergoing TTVR with the EVOQUE device, there was normal leaflet function, with no evidence of degeneration. Residual tricuspid regurgitation was trivial to mild. The patient had had no heart failure hospitalisations and had noted a significant improvement in symptom burden. Further studies are needed to evaluate the long-term efficacy and safety of TTVR with the EVOQUE valve.

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Conflict of interest statement

J.G. Webb is a consultant for Edwards Lifesciences; and receives research funding from Edwards Lifesciences, Medtronic, and Boston Scientific. The other authors have no relevant conflicts of interest to declare.

References

1. Arnold SV, Hahn RT, Thourani VH, Makkar R, Makar M, Sharma RP, Haeffele C, Davidson CJ, Narang A, O'Neill B, Lee J, Yadav P, Zahr F, Chadderdon S, Eleid M, Pislaru S, Smith R, Szerlip M, Whisenant B, Sekaran N, Garcia S, Stewart-Dehner T, Grayburn PA, Sannino A, Snyder C, Zhang Y, Mack MJ, Leon MB, Lurz P, Kodali S, Cohen DJ; TRISCEND II Pivotal Trial Investigators. Quality of Life After Transcatheter Tricuspid Valve Replacement: 1-Year Results From TRISCEND II Pivotal Trial. *J Am Coll Cardiol.* 2025;85:206-16.

2. Kodali S, Hahn RT, Makkar R, Makar M, Davidson CJ, Puthumana JJ, Zahr F, Chadderdon S, Fam N, Ong G, Yadav P, Thourani V, Vannan MA, O'Neill WW, Wang DD, Tchétché D, Dumonteil N, Bonfils L, Lepage L, Smith R, Grayburn PA, Sharma RP, Haeffele C, Babaliaros V, Gleason PT, Elmariah S, Inglessis-Azuaje I, Passeri J, Herrmann HC, Silvestry FE, Lim S, Fowler D, Webb JG, Moss R, Modine T, Lafitte S, Latib A, Ho E, Goldberg Y, Shah P, Nyman C, Rodés-Cabau J, Bédard E, Brugger N, Sannino A, Mack MJ, Leon MB, Windecker S; the TRISCEND study investigators. Transfemoral tricuspid valve replacement and one-year outcomes: the TRISCEND study. *Eur Heart J.* 2023;44:4862-73.

Supplementary data

Moving image 1. Preprocedural transthoracic echocardiogram showing severe tricuspid regurgitation.

Moving image 2. Fluoroscopic images from the implant procedure, showing the initial RV angiogram with severe tricuspid regurgitation, followed by deployment of the EVOQUE valve over a SAFARI² XS wire in the right ventricle. Initial deployment of the nine ventricular anchors followed by final deployment of the EVOQUE valve and the final RV angiogram following implant showing a well-placed EVOQUE valve with minimal residual tricuspid regurgitation.

Moving image 3. Transoesophageal echocardiogram at 5 years post-implant showing the well-seated EVOQUE valve with trivial tricuspid regurgitation and no paravalvular regurgitation.

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Letter: Transcatheter aortic valve implantation and covert brain injury: does silence equal reassurance?

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We read with great interest the study by Jimenez Diaz et al[1], evaluating antiplatelet and oral anticoagulation (OAC) strategies to prevent cerebral microembolism after transcatheter aortic valve implantation (TAVI). This study showed that the use of OAC instead of antiplatelets in patients without indication for anticoagulation did not have any benefit in cerebral microembolism at three-month follow-up. Along with these important findings, several clinical implications arise.

Despite all patients having elevated biomarkers of cerebral injury and the majority having new brain lesions on magnetic resonance imaging (MRI) following TAVI, the true mechanism and clinical significance of this silent injury is not clear. Recent analyses show an adverse effect of covert brain lesions in early neurocognitive outcomes that require longer term evaluation[2]. In this study[1], the authors reported neurocognitive decline in the total patient population during follow-up compared to baseline. In contrast, other investigations show that TAVI can enhance cognitive function, potentially due to improved cerebral blood flow as a result of the enhanced postprocedural cardiac haemodynamics[3]. As currently there are no established predictors of cognitive improvement or decline following TAVI, future evaluations should comprehensively assess neurological status through clinical examination and questionnaires and determine such characteristics. Focus should be also given on how medical treatment can prevent cognitive decline and particularly in the role of different antithrombotic strategies in cognitive function, considering the steeper neurocognitive decline observed with OAC in this investigation and the key role of increased platelet activation post-TAVI.

As noted by the authors, the interaction of the bioprosthetic valve with the native valve may initiate proinflammatory and prothrombotic pathways due to shear stress, which increases thrombotic risk independently of valve type[1]. Activation of such mechanisms may enhance thrombus formation in both native and bioprosthetic valve leaflets, which can be presented as hypoattenuated leaflet thickening and has been associated with stroke and new silent cerebral lesions after TAVI[4]. Given the association of inflammation with this process, the addition of anti-inflammatory to antithrombotic agents may prevent covert cerebral injury. Recently, Ryffel et al[5] reported that the administration of colchicine post-TAVI significantly reduces the risk for subclinical leaflet thrombosis (risk difference –27.1%; 95% confidence interval: –46.0% to –8.2%; p=0.007). In light of these findings, future studies evaluating the addition of novel pharmacotherapy to currently used regimens are needed to clarify whether such combinations lead to enhanced outcomes regarding both leaflet thrombosis and cerebral injury.

As further studies become available, it is important to identify patient and device characteristics associated with more extensive cerebral injury and further delineate the pathophysiology and clinical significance of such events. Thus, investigating differences between antithrombotic strategies and combinations of pharmacotherapy regimens could uncover substantial clinical benefit in select patients, potentially altering post-TAVI antithrombotic clinical practice.

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Conflict of interest statement

The authors have no conflicts of interest regarding the content herein to declare.

References

1. Jimenez Diaz VA, Juan-Salvadores P, Bellas Lamas P, Arias Gonzalez M, Santos Armentia E, Vila Nieto O, Gonzalez Mao C, Torrado Chedas T, Muñoz Garcia AJ, Blazquez IG, Bastos Fernandez G, De Miguel Castro A, Fernandez Barbeira S, Ortiz Saez A, Baz Alonso JA, Ocampo Miguez J, Rioboo Leston L, Pazos Lopez P, Calvo Iglesias F, Salgado Barreira A, Diaz Lopez CM, Figueiras A, Veiga Garcia C, Iñiguez Romo A. A comparison of antiplatelet and oral anticoagulation strategies to prevent cerebral microembolism after transcatheter aortic valve implantation: the AUREA trial. *EuroIntervention*. 2025;21:e737-48.

2. Woldendorp K, Indja B, Bannon PG, Fanning JP, Plunkett BT, Grieve SM. Silent brain infarcts and early cognitive outcomes after transcatheter aortic valve implantation: a systematic review and meta-analysis. *Eur Heart J*. 2021;42:1004-15.

3. Tsuchiya S, Matsumoto Y, Suzuki H, Takanami K, Kikuchi Y, Takahashi J, Miyata S, Tomita N, Kumagai K, Taki Y, Saiki Y, Arai H, Shimokawa H. Transcatheter aortic valve implantation and cognitive function in elderly patients with severe aortic stenosis. *EuroIntervention*. 2020;15:e1580-7.

4. Reddy P, Merdler I, Ben-Dor I, Satler LF, Rogers T, Waksman R. Cerebrovascular events after transcatheter aortic valve implantation. *EuroIntervention*. 2024;20:e793-805.

5. Ryffel C, Lanz J, Guntli N, Samim D, Fürholz M, Stortecky S, Tomii D, Heg D, Boscolo Berto M, Peters AA, Reineke D, Reichlin T, Gräni C, Windecker S, Pilgrim T. Colchicine in patients with aortic stenosis undergoing transcatheter aortic valve replacement: a double-blind randomized trial. *Nat Commun*. 2025;16:6501.

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Reply: Transcatheter aortic valve implantation and covert brain injury: does silence equal reassurance?

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We sincerely thank Dr Pyrpyris and colleagues for their thoughtful comments[1] regarding our recent publication, the AUREA trial[2].

We fully agree with their perspective on the complex and multifactorial nature of cerebral microembolism during transcatheter aortic valve implantation (TAVI) procedures. Despite significant procedural advances, the cerebral impact of microembolic events, often silent, remains a major concern, particularly in elderly patients already at risk of cognitive impairment.

In line with the authors' comments, we emphasise the critical need to identify novel and reliable biomarkers of cerebral microembolism after TAVI. Current approaches to detect brain injury, including magnetic resonance imaging (MRI), though highly sensitive, are not always practical in daily clinical settings due to availability, cost, and patient frailty. Developing blood biomarkers such as glial fibrillary acidic protein, neurofilament light chain, tau and its peptides, and β-synuclein[3] that are not only sensitive and specific but also easy to use and interpret could greatly enhance early detection, monitoring, and risk stratification of patients undergoing TAVI, as well as prediction of complications and clinical outcomes at follow-up.

In addition, artificial intelligence-enhanced imaging enables accurate quantification of vascular and valvular calcium burden[4]. Beyond improving procedural planning, it may allow identification of patients at highest embolic risk and support tailored neuroprotective strategies.

Equally important is the implementation of standardised neurocognitive assessments before and after the procedure. Cognitive outcomes after TAVI are variable and may depend on multiple factors, including baseline status, cerebral perfusion changes, embolic burden, and systemic inflammation. Objective neurological testing, both clinical and through validated cognitive questionnaires, should be routinely incorporated in TAVI trials and, when feasible, in clinical practice[5]. This would allow more accurate characterisation of cognitive trajectories and identification of patients at risk of deterioration or, conversely, those likely to experience neurocognitive improvement.

We also fully agree on the potential role of cerebral embolic protection devices (CEPDs). Although current evidence on clinical outcomes remains mixed, these devices consistently demonstrate their potential to reduce cerebral lesion volume and embolic burden[6]. The integration of CEPDs in TAVI, especially in selected high-risk patients or as part of comparative strategy trials (ClinicalTrials.gov: NCT05873816, NCT03130491), may prove beneficial in minimising microembolisation and its consequences[7]. Furthermore, combining CEPDs with refined antithrombotic approaches could offer synergistic protection and deserves exploration.

Finally, as the authors mention, the identification of pharmacological strategies targeting both thrombotic and inflammatory pathways post-TAVI is a promising avenue. The interplay between prosthetic material, residual native leaflets, and flow dynamics can trigger proinflammatory and prothrombotic cascades, potentially leading to leaflet thrombosis and cerebral embolisation. Recent results with colchicine are promising, although they should be interpreted with caution given the reported increased risk of stroke in treated patients[8]. Further studies evaluating

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combinations of antiplatelet agents (ClinicalTrials.gov: NCT05283356), anticoagulants, and anti-inflammatory therapies (NCT06076824) are warranted to define optimal post-TAVI regimens that balance ischaemic, embolic, bleeding, and cognitive risks.

In conclusion, the prevention and understanding of covert brain injury in the TAVI population must become a multidimensional effort: identifying feasible biomarkers, integrating neurocognitive assessment, evaluating device-based protection, and refining pharmacological strategies.

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Conflict of interest statement

The authors have no conflicts of interest to declare regarding this manuscript.

References

1. Pyrpyris N, Beneki E, Dimitriadis K, Tsioufis K. Letter: Transcatheter aortic valve implantation and covert brain injury: does silence equal reassurance? *EuroIntervention*. 2025;21:1388-9.

2. Jimenez Diaz VA, Juan-Salvadores P, Bellas Lamas P, Arias Gonzalez M, Santos Armentia E, Vila Nieto O, Gonzalez Mao C, Torrado Chedas T, Muñoz Garcia AJ, Blazquez IG, Bastos Fernandez G, De Miguel Castro A, Fernandez Barbeira S, Ortiz Saez A, Baz Alonso JA, Ocampo Miguez J, Rioboo Leston L, Pazos Lopez P, Calvo Iglesias F, Salgado Barreira A, Diaz Lopez CM, Figueiras A, Veiga Garcia C, Iñiguez Romo A. A comparison of antiplatelet and oral anticoagulation strategies to prevent cerebral microembolism after transcatheter aortic valve implantation: the AUREA trial. *EuroIntervention*. 2025;21:e737-48.

3. Barba L, D'Anna L, Abu-Rumeileh S, Foschi M, Montellano FA, Neugebauer H, Otto M. Implementing Blood Biomarkers in Stroke Research and Clinical Practice. *Stroke*. 2025;56:2380-4.

4. Veiga Garcia C, Campanioni S, Juan Salvadores P, Busto L, González-Nóvoa JA, Martínez C, Iñiguez Romo A, Jiménez Díaz VA. TCT-867 Vcal+CT: Detect, Evaluate and Prevent Complications by Accurately Assessing Vascular and Valvular Calcium. *J Am Coll Cardiol*. 2024;84:B356.

5. Khan MM, Lanctôt KL, Fremes SE, Wijeysundera HC, Radhakrishnan S, Gallagher D, Gandell D, Brenkel MC, Hazan EL, Docteur NG, Herrmann N. The value of screening for cognition, depression, and frailty in patients referred for TAVI. *Clin Interv Aging*. 2019;14:841-8.

6. Jimenez Diaz VA, Kapadia SR, Linke A, Mylotte D, Lansky AJ, Grube E, Settergren M, Puri R. Cerebral embolic protection during transcatheter heart interventions. *EuroIntervention*. 2023;19:549-70.

7. Ghezzi ES, Ross TJ, Davis D, Psaltis PJ, Loetscher T, Keage HAD. Meta-Analysis of Prevalence and Risk Factors for Cognitive Decline and Improvement After Transcatheter Aortic Valve Implantation. *Am J Cardiol*. 2020;127:105-12.

8. Ryffel C, Lanz J, Guntli N, Samim D, Fürholz M, Stortecky S, Tomii D, Heg D, Boscolo Berto M, Peters AA, Reineke D, Reichlin T, Gräni C, Windecker S, Pilgrim T. Colchicine in patients with aortic stenosis undergoing transcatheter aortic valve replacement: a double-blind randomized trial. *Nat Commun*. 2025;16:6501.

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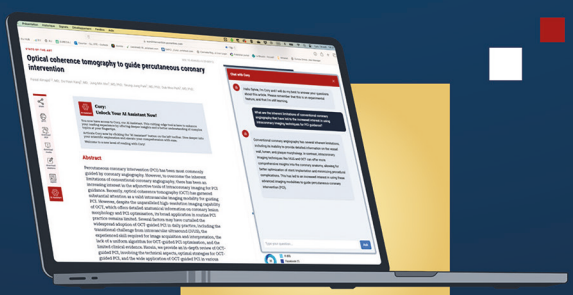

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