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Even aortic insufficiency can be treated percutaneously: right?

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Moderate or severe aortic insufficiency (AI) is a relatively rare condition but with significant clinical implications, especially in elderly patients at high surgical risk. Although surgical aortic valve replacement remains the gold standard for treatment, a significant proportion of patients are not eligible due to the high surgical risk. In recent years, transcatheter aortic valve implantation (TAVI) has revolutionized the treatment of aortic stenosis, but its application to AI has encountered significant challenges, mainly related to specific anatomical characteristics of this population. This review provides an overview of the evolution of the transcatheter treatment of AI, highlighting the critical issues of first-generation TAVI devices and the improvements achieved with new-generation and dedicated devices, such as JenaValve and J-Valve. Preliminary data demonstrate encouraging procedural results, including a reduction in residual insufficiency and improved safety in patients at high surgical risk. However, limitations remain, including the high incidence of pacemaker implantation and the lack of long-term randomized clinical trials. In light of technological advances, TAVI represents a promising therapeutic option for selected patients with AI, if performed in high-volume centres with extensive experience in the treatment of aortic disease.

Introduction

In patients aged >65 years, moderate aortic insufficiency (AI) has a prevalence of 1.6%.[1] In ∼2/3 of cases, AI is caused by primary degeneration of the aortic valve, associated or not with dilation of the aortic ring and aortic root.[2] Severe AI is a condition burdened by a significant risk of morbidity and mortality.[2] European guidelines recommend surgical aortic valve replacement (SAVR) as the gold standard for its treatment, in the presence of symptoms and/or dilation and systolic dysfunction of the left ventricle (LV).[3] However, recent studies demonstrate that this pathology is underdiagnosed and under-treated.[1] In recent years, the progressive improvement and large-scale diffusion of transcatheter aortic valve implantation (TAVI) have revolutionized the treatment of aortic stenosis (AS).[2] On the contrary, the role of TAVI in pure AI is still debated. The off-label use of first- and second-generation transcatheter valves (TAV) developed for the treatment of AS has demonstrated the limitations of these technologies in the anatomical and pathophysiological context of pure AI.[4] However, in recent years, the development of dedicated devices has opened new perspectives for TAVI in this clinical scenario.[4] This review aims to provide an overview of the transcatheter treatment of AI, trying to identify, based on the most current scientific evidence, which patients can benefit from it.

Transcatheter treatment of AI: challenges and evolution

SAVR has long been considered the gold standard for the treatment of severe AI.[3] However, 5% to 10% of patients

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with an indication for SAVR for AI receive no intervention, mainly due to advanced age or high surgical risk.[2] In the field of AS, TAVI has established itself as the first-line treatment for elderly patients, regardless of their surgical-risk profile.[5] Despite this, the use of TAVI for the treatment of AI has encountered considerable challenges. The salient aspects of the transcatheter treatment of AI are summarized in the central illustration.

The main challenges of TAVI in pure native AI arise from the following specific anatomical and pathophysiological factors:

(1) Dilation of the aortic annulus and root
(2) Lack of calcification of the valve leaflets
(3) Presence of a bicuspid aortic valve
(4) Dilation of the left ventricular outflow tract
(5) Increased stroke volume and the suction effect of AI

These elements limit the number of patients eligible for treatment, cause instability during deployment, and make anchoring of currently available TAV devices difficult, imposing significant oversizing compared with the native annulus, with consequent risk of valve migration or embolization, damage to the conduction system or aortic root and significant residual insufficiency. Despite these challenges, TAVR in pure native AI represents ~40% of cases treated off-label.[2] Furthermore, according to a report from the Society of Thoracic Surgeons/ACC Transcatheter Valve Therapy registry, in 2019, aortic regurgitation accounted for 0.7% of all TAVR indications in the United States. Among Medicare beneficiaries who received a valve replacement for AI between 2016 and 2019, ~11% were treated with TAVR, despite the lack of recommendations in the guidelines.[5]

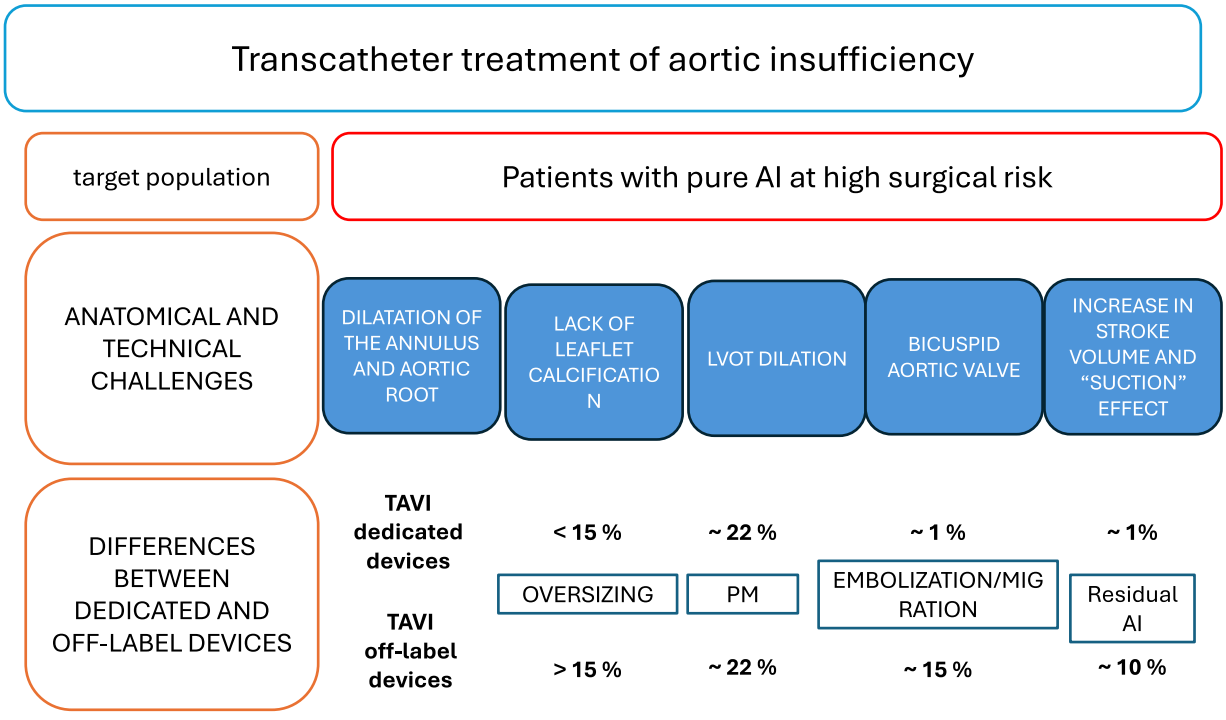
Off-label use of TAVI devices to treat AI

The off-label use of commercially available first- and second-generation TAVs is mainly burdened by the lack of a dedicated design and anchoring mechanism, which requires significant oversizing of the valve compared with the native annulus to allow its stabilization in the absence of calcifications. However, high oversizing leads to an increased risk of aortic root lesions and conduction system damage, which in the largest studies can reach 1.5%[6] and 22%[7], respectively.

Self-expanding valves (SEVs) were among the first devices used, as they were thought to allow less aggressive oversizing than balloon-expandable valves (BEVs) due to their lower radial force, with the advantage of being repositionable and recoverable. However, newer-generation BEV valves have demonstrated procedural success rates comparable to similar-generation SEV valves, with similar outcomes in terms of the need for a second valve, residual regurgitation, and pacemaker implantation.[6]

A 2013 multi-centre study of 43 patients treated with the CoreValve (Medtronic, Minneapolis, MN) showed a procedural success rate of 74.4% by VARC criteria with 18.6% need for a second valve during the index procedure, a rate of ≥moderate residual regurgitation of 20.9%, definitive PM implantation of 16.3%, and all-cause mortality of 9.3% at 30 days.[8] Similar results were observed in a subsequent 2014 study, which also reported higher mortality after TAVR for IA compared with AS (1-month mortality: 23% vs. 3.9%; 12-month mortality: 31% vs. 19%).[9]

With increasing operator experience and technological evolution, the results of TAVI with off-label devices in native pure AI have improved.[6] Yoon *et al.* compared 119



Central illustration Transcatheter treatment of aortic insufficiency.

patients treated with first-generation devices and 212 patients with new-generation devices (of which 30.7% with dedicated AI devices) showed higher rates of procedural success (81.1% vs. 61.3%), a lower need for a second valve (12.7% vs. 24.4%) and a reduction in cases of moderate or severe residual insufficiency (4.2% vs. 18.8%) with new-generation devices.[6] Furthermore, the use of new-generation devices was associated with a reduction in cardiovascular mortality at 1 year (9.6% vs. 23.6%).[6] This study demonstrated that for SEV valves, oversizing <15% is associated with a higher risk of at least moderate residual AI, while oversizing ≥15% leads to a reduction in residual regurgitation.[6]

In addition, Poletti *et al*. reported the results of the latest-generation devices used off-label to treat pure AI, comparing the performance of SEV and BEV in 201 patients.[7] The overall technical success and device success rates were 83.6% and 76.1%, respectively, with no significant differences between SEV and BEV. These results were mainly influenced by the occurrence of valve embolization (14.6% vs. 16.1%; $P = 0.47$) and the presence of moderate or severe residual AI (9.2% vs. 10.1%; $P = 0.87$). The PM implantation rate was 22.6% and 21.8%, respectively.[7] Finally, compared with SAVR, the off-label use of TAVI devices showed lower rates of short-term complications and comparable short-term mortality, but with a higher risk of mortality and reintervention in the medium-term, even after adjustment for comorbidities.[10]

New dedicated devices: JenaValve and J-valve

The new dedicated devices for TAVI in IA exploit a different anchoring mechanism, mainly based on the clipping of the valve leaflets with a top-to-bottom release of the device that reduces the interaction with the conduction tissue during implantation.

The JenaValve Trilogy (JenaValve Technology, Irvine, CA) is a supra-annular SEV valve, made of porcine tissue and characterized by the presence of three 'locators'. In the initial phase of implantation, these hook the native leaflets between a positioning system and a sealing gasket, allowing the valve to anchor firmly even in the absence of calcifications and with a lower degree of oversizing required and favouring commissural alignment (*Figure 1A*). The device is available in three different sizes (23, 25, and 27 mm) to treat an annular perimeter range between 66 and 85 mm.

Initially, the JenaValve was implanted transapically. After receiving CE Mark in Europe, the JenaValve was evaluated in the JUPITER (JenaValve EvalUation of Long Term Performance and Safety in Patients with Severe Aortic Stenosis or AI) registry, which included 30 patients.[11] Compared with the first-generation CoreValve, the JenaValve had a lower incidence of residual IA greater than moderate (1.6% vs. 18.2%) and a reduction in the need for a second valve (9.4% vs. 26.4%).[11] However, stroke rates were higher (7.8% vs. 0.9%), likely due to the need for transapical access.[11] Currently, the JenaValve can be implanted via a transfemoral approach. In the United States, the ALIGN-AR EFS (Safety and Effectiveness/Performance of the Transfemoral JenaValve

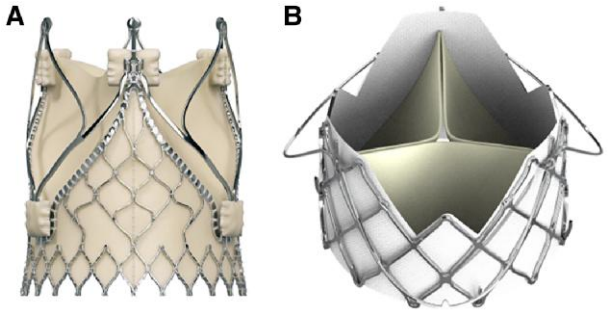


Figure 1 Dedicated devices for transcatheter treatment of AI. JenaValve Trilogy (JenaValve Technology, Irvine, CA) is currently the only CE-marked device available for the treatment of IA. Its design allows, thanks to the 'locators', to anchor the aortic valve leaflets and to obtain the alignment of the commissures (*A*). The J-Valve (JC Medical Inc., Burlingame, CA) ensures adhesion to the native leaflets thanks to the dedicated 'U's. The device is not yet available in Europe and the United States (*B*).

Pericardial TAVR system in the treatment of patients with symptomatic severe aortic regurgitation) trial demonstrated the safety and efficacy of the pure IA JenaValve in patients at high surgical risk.[12] The procedural success rate was 100%. In-hospital and 1-year mortality and adverse events were non-inferior to those expected for TAVI in high-risk patients with AS. The presence of at least a moderate peri-valvular leak was observed in only one patient. Of 180 patients, 24% underwent PM implantation following the procedure.[12] The retrospective multi-centre PURPOSE study analysed a cohort of 256 patients with pure IA who underwent TAVI.[4] 168 patients were treated with off-label devices, while 88 with JenaValve. The latter has shown better outcomes in terms of procedural technical success, embolization, and the need for second valve implantation and residual IA. The reported PM implantation rate is 24%.[4]

The J-Valve (JC Medical Inc., Burlingame, CA) is another porcine tissue SEV mounted on a nitinol stent. It features three 'U'-shaped rings that facilitate the attachment of native leaflets, allowing for secure anchoring and effective commissural alignment (*Figure 1B*). The device is available in five different sizes (22, 25, 28, 31, and 34 mm) to treat an annular perimeter range of 57 to 107 mm. The transapical version of the J-Valve has been studied primarily in China. A study of 134 patients with pure AI reported a 96.3% success rate with only 0.7% of patients developing residual insufficiency greater than moderate and a 3.7% mortality rate at six months.[13] The first North American experience with the transfemoral device in 27 patients at high surgical risk reported a procedural success rate of 81%.[14] Following design modifications, success was achieved in 100% of cases (15/15). At 30 days, residual AI greater than moderate was not observed in any of the patients. Three of 27 patients required a new PM implant following the procedure.[14]

Our centre was the first in Italy to implant JenaValve for the treatment of AI. Patients are carefully selected based on: annulus perimeter (<90 mm), absence of aortic bicuspid, aortic length (>7.5 mm), and adequate diameter of peripheral accesses. Baseline characteristics and intraoperative results of the first 10 patients, we treated between July 2022 and July 2023 are reported in

Table 1 Baseline characteristics

	Clinical characteristics N = 10[a]
Female sex	5 (50%)
Age in years	81 (74, 84)
BMI	25.7 (24.5, 30.3)
Atrial fibrillation	4 (40%)
Stroke	1 (10%)
eGFR, mL/min	53 (40, 63)
STS score mort, %	2.24 (1.69, 3.24)
ESII score mort, %	2.74 (2.02, 3.44)
NYHA ≥ 3	6 (60%)

STS, society of thoracic surgeons; ESII, euroscore II; NYHA, New York Health Association.
[a]N (%); Median (IQR).

Table 2 Pre-procedural echocardiographic data

Echo features	N = 10[a]
LV EF, %	53 (49, 55)
LV DTD, mm	55 (50, 59)
AI	
3+	3 (30%)
4+	7 (70%)
SA 4+	3 (30%)
IM ≥ 3+	5 (50%)
IT ≥ 3+	3 (30%)

LV, left ventricle; EF, ejection fraction; DTD, end-diastolic diameter; AI, aortic regurgitation; AS, aortic stenosis; MR, mitral regurgitation; TR, tricuspid regurgitation.
[a]N (%); Median (IQR).

Table 3 Pre-procedural CT analysis

CT analysis	N = 10[a]
VBR diameter min, mm	22 (21, 24)
VBR diameter max, mm	28 (25, 29)
VBR mean diameter, mm	26 (24, 29)
VBR area, mm^2	497 (399, 528)
Perimeter, mm	81 (74, 85)

VBR, virtual basal ring.
[a]N (%); Median (IQR).

Table 4 Procedural results

Procedural data	N = 10[a]
Valve dimension, mm	25 (24, 27)
Surgival approach	5 (50%)
Percutaneous approach	5 (50%)

[a]N (%); Median (IQR).

Table 5 In-hospital results

Results at discharge	N = 10[a]
LV EF, %	55 (50, 60)
AI ≤ 1	10 (100%)
Mild LPV	2 (20%)
Mean gradient, mmHg	6 (4, 8)
Length of stay, days	4 (4,6)

LV, left ventricle; EF, ejection fraction; AI, aortic insufficiency; LPV, peri-valvular leak.
[a]N (%); Median (IQR).

Tables 1-5, respectively. The enrolled population has a median age of 81 years [74–84 years, IQR] and moderate surgical risk (median STS score 2.24% [1.69–3.24, IQR]). Concomitant presence of significant AS is present in three patients. The median perimeter is 81 mm [74–85 mm, IQR]. Procedural success was observed in all patients. Residual AI was less than or equal to mild in the entire cohort. The post-operative course was uneventful in terms of vascular access complications, major intraprocedural adverse events, and stroke. Only one patient required PM implantation at the end of the procedure for third-degree atrioventricular block (AVB), starting at baseline with unfavourable factors (first-degree AVB, right bundle branch block). In our experience, JenaValve has proven to be easily implantable, after adequate training, ensuring excellent procedural results. The dedicated anchoring system allows to mitigate the need for oversizing, without risk of embolization. Of note, among the first 10 cases, is the implantation of this device in a patient with a permanent left ventricular assist device (LVAD). In this particular population, in which the incidence of IA is frequent and weighs heavily on mortality and hospitalizations for heart failure, the use of dedicated devices for the percutaneous treatment of aortic pathology could lead to a significant turning point (*Figure 2*).

Discussion

The incidence of pure native AI is relatively low compared with other valvular diseases.[2] Compared with AS, AI develops at an earlier age and is often associated with the presence of a bicuspid aortic valve and dilated ascending aorta. SAVR is the treatment of choice for severe AI with proven survival benefits compared with medical therapy. However, this disease is underdiagnosed and under-treated and the treatment of patients with pure native AI considered inoperable or at high surgical risk is a current and much debated topic.[1] The use of TAVI in this setting is burdened by the specific anatomical characteristics of this disease that impose significant technical challenges.

Over the past 10 years, technological evolution has led to a significant improvement in the results of TAVI for the treatment of pure native AI. Compared with first- and second-generation devices developed for the treatment of AS and used off-label in this setting, the advent of dedicated devices has resulted in better procedural results and improved 30-day clinical

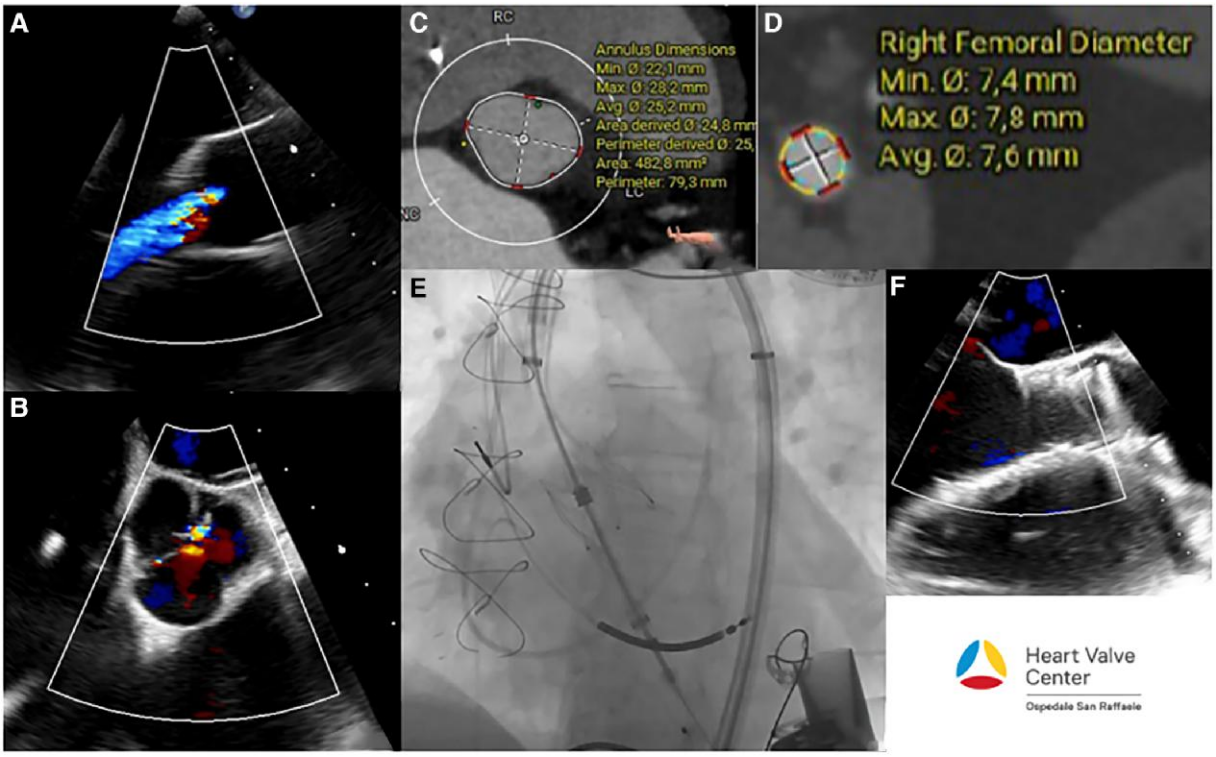


Figure 2 Percutaneous treatment of IA in a patient with an LVAD. We report the case of a patient treated with JenaValve with an LVAD. The patient (a 63-year-old man) visited our acute heart failure unit 4 years after LVAD implantation. Transthoracic echocardiogram (*A*, *B*) revealed severe IA. Given the prohibitive surgical risk, a transcatheter strategy was chosen. CT analysis showed a VBR perimeter of 79 mm and no evident valvular calcifications (*C*). Vascular access was adequate (>7.5 mm) (*D*). A JenaValve size L (27) was successfully implanted. (*E*) The post-operative course was free of adverse events and the patient was discharged home after 1 week in cardiocirculatory compensation. Pre-discharge echocardiogram showed minimal anterior peri-valvular leak (*F*).

outcomes. Devices such as JenaValve and J-VALVE can be effectively used transfemorally to treat patients with a wide range of annular dimensions with encouraging results in terms of device stability, hemodynamic performance, and reduction of residual AI. However, the rate of definitive PM implantation remains high, likely due to the combination of anatomical characteristics of greater laxity and fragility of the tissues in this population and the oversizing required to ensure effective anchoring in addition to clipping of native leaflets. Finally, 1-year follow-up data show equivalence between dedicated devices and off-label devices in terms of cardiovascular mortality and rehospitalization for heart failure.[4] Prospective clinical data and more extensive follow-up are expected to clarify the long-term benefits and durability of these devices. To date, a major gap in the field is the lack of randomized clinical trials (RCTs) directly comparing TAVI and SAVR in patients with IA, stratified by surgical risk. The available evidence comes mainly from observational registries, which suggest similar short-term outcomes, but with higher reintervention and mortality rates in the medium-term for TAVI. RCT data are essential to understand whether the extension of TAVI indications in pure native IA is justified outside the context of inoperable or high surgical-risk patients.[10] However, it is reasonable to think that further technological innovations aimed at improving the performance of TAV devices are necessary before proceeding with a randomized comparison with SAVR. Looking ahead, one of the most intriguing challenges of the coming years is the development of innovative transcatheter solutions such as endo-Bentall to treat patients with IA and ectasia of the aortic root and ascending aorta.[15]

Conclusion

Currently, the use of TAVI for the treatment of pure native AI allows to offer a cure to patients considered inoperable or at prohibitive surgical risk. The development of dedicated devices has demonstrated better procedural results compared with off-label devices. However, while waiting for long-term data on clinical outcomes and durability, the anatomical challenges for transcatheter devices remain important. To ensure the best possible outcome, a multi-disciplinary discussion in high-volume centres dedicated to the surgical and transcatheter treatment of valvular diseases (Heart Valve Centres), able to offer customized solutions for the individual patient, is essential.

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Data availability

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Disclaimer

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References

1. 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**:3515–3522.
2. Iung B, Delgado V, Rosenhek R, Price S, Prendergast B, Wendler O *et al*. Contemporary presentation and management of valvular heart disease: the EURObservational research programme valvular heart disease II survey. *Circulation* 2019;**140**:1156–1169.
3. Vahanian A, Beyersdorf F, Praz F, Milojevic M, Baldus S, Bauersachs J *et al*. 2021 ESC/EACTS guidelines for the management of valvular heart disease. *Eur Heart J* 2022;**43**:561–632.
4. Poletti E, Adam M, Wienemann H, Sisinni A, Patel KP, Amat-Santos IJ *et al*. Performance of purpose-built vs off-label transcatheter devices for aortic regurgitation. *JACC Cardiovasc Interv* 2024;**17**:1597–1606.
5. Carroll JD, Mack MJ, Vemulapalli S, Herrmann HC, Gleason TG, Hanzel G *et al*. STS-ACC TVT registry of transcatheter aortic valve replacement. *J Am Coll Cardiol* 2020;**76**:2492–2516.
6. Yoon SH, Schmidt T, Bleiziffer S, Schofer N, Fiorina C, Munoz-Garcia AJ *et al*. Transcatheter aortic valve replacement in pure native aortic valve regurgitation. *J Am Coll Cardiol* 2017;**70**:2752–2763.
7. Poletti E, De Backer O, Scotti A, Costa G, Bruno F, Fiorina C *et al*. Transcatheter aortic valve replacement for pure native aortic valve regurgitation. *JACC Cardiovasc Interv* 2023;**16**:1974–1985.
8. Roy DA, Schaefer U, Guetta V, Hildick-Smith D, Möllmann H, Dumonteil N *et al*. Transcatheter aortic valve implantation for pure severe native aortic valve regurgitation. *J Am Coll Cardiol* 2013;**61**:1577–1584.
9. Testa L, Latib A, Rossi ML, De Marco F, De Carlo M, Fiorina C *et al*. CoreValve implantation for severe aortic regurgitation: a multicentre registry. *EuroIntervention* 2014;**10**:739–745.
10. Mentias A, Saad M, Menon V, Reed GW, Popovic Z, Johnston D *et al*. Transcatheter vs surgical aortic valve replacement in pure native aortic regurgitation. *Ann Thorac Surg* 2023;**115**:870–876.
11. Silaschi M, Conradi L, Wendler O, Schlingloff F, Kappert U, Rastan AJ *et al*. The JUPITER registry: one-year outcomes of transapical aortic valve implantation using a second generation transcatheter heart valve for aortic regurgitation. *Catheter Cardiovasc Interv* 2018;**91**:1345–1351.
12. Vahl TP, Thourani VH, Makkar RR, Hamid N, Khalique OK, Daniels D *et al*. Transcatheter aortic valve implantation in patients with high-risk symptomatic native aortic regurgitation (ALIGN-AR): a prospective, multicentre, single-arm study. *The Lancet* 2024;**403**:1451–1459.
13. Liu L, Chen S, Shi J, Qin C, Guo Y. Transcatheter aortic valve replacement in aortic regurgitation. *Ann Thorac Surg* 2020;**110**:1959–1965.
14. Garcia S, Ye J, Webb J, Reardon M, Kleiman N, Goel S *et al*. Transcatheter treatment of native aortic valve regurgitation. *JACC Cardiovasc Interv* 2023;**16**:1953–1960.
15. Grimm JC, Ibrahim M, Szeto WY. Endo-Bentall: is this feasible? *Ann Cardiothorac Surg* 2022;**11**:46–47.