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Review

# TAVR as an Alternative to SAVR for Pure Native Aortic Regurgitation

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## ABSTRACT

Although transcatheter aortic valve replacement was originally fulfilling an unmet clinical need in the elderly population suffering from tricuspid aortic valve stenosis, its use has been progressively expanded to other groups of patients. In this review, we focus on pure native aortic valve regurgitation, which is in most cases a degenerative disease and therefore frequently diagnosed in elderly patients with comorbidities. Symptoms tend to appear late in the disease, when left ventricular dilation and systolic dysfunction are associated owing to excessive volume overload. It is often combined with a dilated aortic annulus and ascending aorta. Surgical aortic valve replacement remains the criterion standard treatment for severe aortic regurgitation. However, for patients at prohibitive surgical risk, transcatheter aortic valve replacement represents an attractive alternative. Various technical challenges are the absence of calcium at the level of the annulus, which means there are no anchoring points or fluoroscopic landmarks, the difficulty of valve sizing, and the increased stroke volume secondary to the aortic regurgitation, making valve deployment more

## RÉSUMÉ

Bien que le remplacement valvulaire aortique par cathéter ait initialement répondu à un besoin clinique non satisfait chez les personnes âgées souffrant de sténose de la valve aortique tricuspide, son usage a progressivement été étendu à d'autres groupes de patients. Dans cette revue de littérature, nous nous intéresserons à la régurgitation valvulaire aortique native pure, qui est dans la plupart des cas une maladie dégénérative, et donc fréquemment diagnostiquée chez les patients âgés présentant des comorbidités. Les symptômes ont tendance à apparaître tardivement pour cette maladie, lorsque la dilatation ventriculaire gauche et la dysfonction systolique sont associées en raison d'une surcharge volumique excessive. Elle est souvent combinée à une dilatation de l'anneau aortique et de l'aorte ascendante. La chirurgie de remplacement valvulaire aortique reste le traitement de référence pour une régurgitation aortique sévère. Cependant, pour les patients présentant un risque chirurgical prohibitif, le remplacement valvulaire aortique par cathéter représente une alternative intéressante.

Transcatheter aortic valve replacement (TAVR) has revolutionised the treatment of aortic valve stenosis with one randomised trial after another showing its safety and efficacy for the care of severe degenerative aortic stenosis in patients at high, intermediate, and low surgical risk. As a result, the European and American guidelines have expanded the indication for TAVR, and the number of procedures per year has increased exponentially worldwide.[1-3] Operator experience, better periprocedural management and patient selection, and the development of a multitude of different transcatheter heart valve (THV) designs have contributed to this expansion and the steadily improving outcomes.

Although TAVR was originally fulfilling an unmet clinical need in the elderly population suffering from tricuspid degenerative aortic valve stenosis, its use has been progressively expanded to other groups of patients, such as those with bicuspid aortic valve stenosis, degenerated bioprosthesis, and severe pure aortic valve regurgitation (AR). In this review article, we focus on patients suffering from pure native AR.

## Aortic Regurgitation

Pure native AR is the third most common left valvular heart disease (VHD) after aortic stenosis and mitral regurgitation. In the entire Swedish population from 2003 to 2010, the incidence of AR was 19.7 and 10.8 per 100,000 person-years in men and women, respectively, whereas the incidence of aortic stenosis was 37.8 and 24.2 per 100,000 person-years, respectively, corresponding to about one-half as much AR as aortic stenosis.[4] In the EURObservational Research Programme Valvular Heart Disease II Survey in 2017, severe pure native AR represented 5.3% of severe VHDs whereas severe aortic stenosis was more than 7 times more common, at 41.2%.[5]

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**unstable than in the setting of aortic stenosis. The first-generation transcatheter valves were associated with a higher mortality rate and lower procedural success related to increased risk of paravalvular leak and valve migration requiring a second valve or annular rupture than the more recent off-label or on-label transcatheter valves. Early studies with the dedicated on-label devices showed safety and promising results and will undoubtedly serve in the future a growing number of patients with native aortic regurgitation at prohibitive risk for surgery.**

**Parmi les défis techniques figurent l'absence de calcification au niveau de l'anneau, ce qui signifie qu'il n'y a pas de points d'ancrage ni de repères fluoroscopiques, la difficulté de dimensionnement de la valve et l'augmentation du volume d'éjection secondaire à la régurgitation aortique, rendant le déploiement de la valve plus instable que dans le cas de la sténose aortique. Les valves transcathéter de première génération ont été associées à un taux de mortalité plus élevé et à un succès procédural plus faible, en raison d'un risque accru de fuite paravalvulaire, de migration de la valve nécessitant une seconde valve ou de rupture annulaire, par rapport aux valves transcathéter plus récentes, hors indication ou sur indication. Les premières études avec les dispositifs dédiés, sur indication, ont montré un degré de sécurité et des résultats prometteurs et serviront sans aucun doute à l'avenir un nombre croissant de patients atteints de régurgitation aortique native à risque chirurgical prohibitif.**

Symptoms tend to appear late in the course of the disease, coinciding with the onset of left ventricular (LV) dilation and systolic dysfunction secondary to excessive volume overload. Pulmonary hypertension is also frequent. It is often combined with dilated aortic annulus and ascending aorta.

According to the European and American guidelines, surgical aortic valve replacement (SAVR) is the criterion standard treatment for patients with pure severe native AR.[1,2] Among 141,905 patients in the United States who underwent first-time isolated SAVR from 2002 to 2010, 13.1% of the SAVRs were performed for pure native AR.[6] In patients with severe native AR, SAVR is indicated when patients have symptoms, reduced left ventricular ejection fraction (LVEF) ($\leq$ 50%) or LV enlargement (LV end-systolic diameter $>$ 50 mm or $>$ 25 mm/m$^2$). The main indications for surgery are summarised in Table 1.

However, the first Euro Heart Survey on VHD in 2003 showed that the annual mortality rate of patients with AR and severe LV dysfunction (LVEF $<$ 30%) reached up to 20%.[7] Moreover, only 21.8% of patients with LVEF 30%-50% and 2.7% of those with LVEF $<$ 30% underwent SAVR, confirming the need for an alternative approach.

As an alternative, TAVR has been performed with the use of different devices in an "off-label" setting to improve the outcome and the quality of life with varying levels of success. Recently, among the 11,027 Medicare AR patients who underwent aortic valve replacement for pure AR in the United States from 2016 to 2019, 1147 (10.4%) had TAVR and 9880 (89.6%) SAVR.[8] Similarly, using the Diagnosis Related Groups (DRG) from all German hospitals from 2018 to 2020, 4861 procedures for pure AR were identified: 4025 (82.8%) SAVR and 836 (17.2%) TAVR.[9] Finally, in the PANTHEON (**P**erformance of Currently **A**vailable Tra**n**s-ca**the**ter Aortic Valve Platforms in Inoperable Patients With Pure Aortic Regurgitati**on** of a Native Valve) multicentre international registry, which collected data on second-generation THVs from 2014 to 2022 in 16 centres, only 1.4% of the 15,000 TAVR procedures were performed for AR.[10]

As the prevalence of AR increases with age, we can anticipate a growing frequency of severe AR in the elderly population who are often at high risk for surgery. The latest European guidelines state that "TAVR may be considered in experienced centres for selected patients with AR who are ineligible for SAVR."[1] Interestingly, in the Medicare analysis, 40% of the TAVRs in AR were performed in only 5% of the centres, highlighting the need for experienced operators and the concept of volume-outcome relationship.[8,11]

## Specificity of TAVR in Aortic Regurgitation

THVs were designed for calcified aortic stenosis and have demonstrated excellent outcomes compared with SAVR in such anatomies. However, these results cannot be directly translated to pure native AR without calcium.

The calcified annulus and leaflets provide anchoring points for either balloon-expandable (BE) or self-expanding (SE) THVs. The calcium is also a visual fluoroscopic landmark to help in positioning the valve during deployment. The absence of calcium, along with an increased stroke volume and aortic root dilation, increases the risk of THV malposition, migration, or embolisation, with, as a consequence, a risk of conversion to surgery, perivalvular leak (PVL), permanent pacemaker implantation, interference with the mitral valve, or procedural death. The incidence of THV migration or embolisation has been reported in close to 20% of AR cases in early series, clearly exceeding the 0.1% rate reported in the aortic stenosis setting.[12,13] In the PANTHEON registry, the rate of valve embolisation or migration was still 12.5% with no differences between SE and BE valves.[10] In multivariate analysis, postdilatation was a predicting factor and therefore the authors recommended avoiding it. More than 80% of the SE valves were deployed under rapid pacing. After propensity score adjustment, valve embolisation or migration was associated with a worse 1-year composite end point (all-cause death, heart failure rehospitalisation) and all-cause mortality. BE valves move more frequently toward the ventricular side (85.3%), whereas SE valves move more frequently toward the aortic root (56%).[10]

Frequently, patients with AR present with an elliptical annulus, dilated aortic root, and dilated ascending aorta. The aneurysmal ascending aorta also increases the risk of death at midterm, as demonstrated in one of the first multicentre series reporting 75% mortality at 6 months in the presence of an ascending aorta aneurysm.[13]

From the screening of ALIGN-AR [The ALIGN-AR EFS Trial: JenaValve Pericardial TAVR Aortic Regurgitation

**Table 1.** Indications for intervention in cases of aortic valve regurgitation

| Indication for intervention | ESC/EACTS 2021 | Class/level | ACC/AHA 2020 | Class/level |
|---|---|---|---|---|
| Symptomatic regardless of LVEF | | I B | | I B |
| Asymptomatic with LV dysfunction | LVEF $\leq$ 50% | I B | LVEF $\leq$ 55% | I B |
| Asymptomatic with severe LV dilation | LVESD $>$ 50 mm or LVESD $>$ 25 mm/m$^2$ BSA | I B | LVESD $>$ 50 mm or LVESD $>$ 2 5 mm/m$^2$ BSA | IIa B |
| Asymptomatic if surgery is at low risk and: | LVEF $\leq$ 55% | IIb C | Decrease in LVEF to $<$ 55%-60% on at least 3 serial studies | IIb B |
| Asymptomatic patients if surgery is at low risk | LVESD $>$ 20 mm/m$^2$ BSA | IIb C | Increase in LVEDD to $>$ 65mm on at least 3 serial studies | IIb B |
| Symptomatic or asymptomatic with severe aortic valve regurgitation undergoing CABG or surgery of the ascending aorta or of another valve | | I C | | I C |

ACC, American College of Cardiology; AHA, American Heart Association; BSA, body surface area; CABG, coronary artery bypass grafting; ESC, European Society of Cardiology; EACTS, European Association for Cardio-Thoracic Surgery; LV, left ventricular; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter.

Study; NCT02732704] (107 patients) and ALIGN-AS [JenaValve AS EFS Trial: Pericardial TAVR Aortic Stenosis Study; NCT02732691] (92 patients), early feasibility trials using the dedicated JenaValve THV, Gogia et al. reported data from 19 centres comparing the range of annulus and aortic root sizes of the referred patients (ie, rather than those already implanted) for TAVR in aortic stenosis and regurgitation.[14] Not only the annulus area, perimeter, and diameter, but also the sinus of Valsalva diameter and heights, were larger in AR patients compared with aortic stenosis patients. More patients with AR than with aortic stenosis were excluded based on the annulus perimeter (14% vs 2%, respectively). Conversely, more patients with aortic stenosis had a higher risk for coronary occlusion of the left main (21% vs 7%) or the right (14% vs 3%) coronary artery. In the AR group, the annulus area and perimeter ranged from 283 to 884 mm$^2$ and from 60 and 106 mm, respectively, compared with 299 to 647 mm$^2$ and 63 to 94 mm in the aortic stenosis group. No patients with aortic stenosis had an annulus larger than 660 mm$^2$ (the theoretical maximum nominal size for the Sapien 3 THV), whereas that was found in 7.5% of the AR group. Finally, only 1 patient in the AR group had an ascending aorta larger than 5.5 cm requiring surgery.[14]

Sizing the annulus and selecting the most appropriate THV are also significant challenges. A too-small THV might embolise, with all the associated complications. Conversely, an oversized THV increases the risk of annular rupture. In aortic stenosis, Barbanti et al. showed that the Edwards Sapien (Edwards Lifesciences, Irvine, CA) can be oversized by not more than 20% to reduce the risk of annular rupture.[15] Importantly, AR valves are commonly more elastic than calcified stenotic valves and can expand to a greater degree during deployment, especially in cases of BE valve implantation. Therefore, a standard sizing chart could select a significantly undersized THV. Le Ruz et al. reported an interesting case of pure native AR with an annulus area of 443 mm$^2$ and no calcium. They first implanted a 26 mm Sapien S3 with 2 additional mL (29% of oversizing), which embolised. Subsequently, they successfully implanted a 29 mm Sapien S3 at a nominal diameter that corresponded to 49% of oversizing.[16] This case shows how unpredictable annular distensibility can be and that you may require higher oversizing than what is recommended when using a BE THV in AR. However, the expert operators involved in the PANTHEON registry recommend an oversizing generally by 10%-20%, as well as the use of rapid pacing for the SE valve and avoiding post-dilatation.[10] In their experience, the rate of oversizing was significantly higher in the SE group compared with the BE group not only for perimeter (16.4 $\pm$ 9.5% vs 8.5 $\pm$ 7.0%—$P < 0.001$), but also for the area (21.2 $\pm$ 13.4% vs 9.9 $\pm$ 8.4%; $P < 0.001$).

Moreover, in addition to all the specificities of AR, the late clinical presentation and advanced disease stage with often irreversible LV dysfunction and severe pulmonary hypertension following a long silent clinical course expose patients with AR to greater vulnerability to complications than the aortic stenosis population. In the Medicare and German health care analyses, AR patients who underwent TAVR were older with more comorbidities than those undergoing SAVR.[8] In the Medicare cohort, patients undergoing TAVR for AR experienced lower in-hospital and short-term mortality than those undergoing SAVR, but higher midterm risk of global mortality, heart failure, and need for reintervention.[8] Table 2 summarises the specific technical aspects to improve the procedural success of TAVR in AR, and Table 3 lists the different risk factors favouring migration/embolisation of the THV.

## Literature Review

The experience in treating AR with the use of TAVR is limited to observational studies enrolling carefully selected patients by the heart team of each centre. In the earliest reports, 20% to 50% of the aortic valves had some degree of calcification.[13,17] Currently, there is no randomised data against SAVR. The latest analyses comparing SAVR and TAVR in AR are based on data from health care systems (Medicare and the German DRG).[8,9] Several reports using multicentre data demonstrated the feasibility of the TAVR approach in pure AR, with worse outcomes than in aortic stenosis.[12,13,18-20]

In a systematic review published in 2016, 13 reports of more than 5 TAVRs for AR were included for a total of 237 patients. More SE THVs (79%) were used than BE THVs (21%).[21] The authors found a correlation between the absence of calcium and the need for a second valve.

**Table 2.** Technical challenges of TAVR in aortic valve regurgitation

| Challenge | Objective | Solutions |
|---|---|---|
| Unstable deployment | Reduce stroke volume and limit THV motion | Rapid pacing:<br>• > 180 beats/min for BE valves<br>• 120 beats/min for SE valves |
| Absence of calcium to guide valve deployment | Annulus landmark providing a coplanar annular view | • 2 pigtails in different sinus of Valsalva<br>• CT-fluoroscopy fusion imaging |
| Absence of calcium to facilitate valve anchoring | Avoid valve migration or embolisation | Different anchoring design, such as clipping of the leaflets |
| Sizing of the THV | Avoid:<br>• valve migration/embolisation<br>• PVL<br>• annular rupture | Oversizing*:<br>• Medtronic SE: 15%<br>• Edwards Sapien: ≥ 15%<br>• Accurate Neo: 10%<br>• JenaValve: 10%-20% |

BE, balloon-expandable; CT, computed tomography; PVL, paravalvular leak; SE, self-expanding; TAVR, transcatheter aortic valve replacement; THV, transcatheter heart valve.

*Some authors described larger oversizing. The more oversizing, the higher the risk of annular rupture. Oversizing should be adapted to the computed tomographic assessment of the anatomy and the valve type used. Excessive oversizing can also be associated with valve migration, particularly for self-expanding valves.

In the early cohorts with the CoreValve (Medtronic, Minneapolis, MN), the incidence of valve in valve was close to 20%.[12,13] The outcome improved with the use of newer-generation devices and increasing operator experience.[20] Indeed, an international multicentre registry with 40 centres across Europe, Asia-Pacific, and North America enrolled 331 patients who underwent TAVR for AR from 2007 to 2017.[20] The early-generation devices (CoreValve: n = 110; Sapien XT: n = 9) were used in 119 patients (36%) and the new-generation devices in 212 patients (64%). The most used device was the CoreValve (33.2%), followed by the JenaValve (JenaValve Technology, Irvine, CA) (19.3%), Evolut R (15.1%), Sapien 3 (Edwards Lifesciences) (12.4%), and other devices. The mean aortic annulus diameter, area, and perimeter were 25.2 mm, 488 $mm^2$, and 79.3 mm, respectively, with no significant differences between the early and new device groups. The success rate was significantly higher in the new-generation device group (81.1% vs 61.3%; $P < 0.001$), secondary to lower rates of second valve need (12.7% vs 24.4%; $P = 0.007$) and postprocedural AR more than mild (4.2% vs 18.8%; $P < 0.001$). At 30 days, there were no significant differences in the main outcomes between the groups, but the 1-year global mortality was higher in the early-generation device group (24.1% vs 15.6%) and in the group of patients with more than mild residual AR.

In the German DRG analysis of TAVR for AR, when comparing transfemoral self-expanding TAVR (n = 457) with transfemoral BE TAVR (n = 329), the outcomes were better and in-hospital mortality lower (2.4% vs 5.2%; $P = 0.039$) in the SE group.[9]

In 2019, Wernly et al. reported an analysis of 12 studies with 640 patients in which they compared AR treatment using off-label devices (77%) vs on-label devices (33%), namely, the JenaValve and the J-Valve.[22] Compared with the second-generation off-label devices, the on-label devices had higher procedural success (on-label 93.0% vs off-label 83.6%) without worse global mortality (on-label 9.1% vs off-label 5.9%) or residual AR (on-label 2.8% vs off-label: 4.4%). Finally, the first-generation off-label group (223 CoreValve and 24 Sapien XT) had poor procedural success (68.4%), and more than trace AR occurred in 37.5%. The limitations of these first 2 devices were overcome by technical improvements (more sizes, addition of paravalvular skirts, and, for the Evolut, recapturable and repositionable) in second-generation devices. The on-label devices showed the highest procedural success and little residual AR, suggesting a potential benefit of these devices. In the next section, we present an overview of some devices used in TAVR for AR.

The result of 201 second-generation THVs (66% SE) implanted in pure AR at 16 international centres participating in the PANTHEON registry showed that technical and device success rates were 83.6% and 76.1%, respectively, without significant differences, between SE and BE valves, with THV migration or embolisation being the most common cause of failure (12.4%).[10] THV migration or embolisation was related to THV malposition in 32%, oversizing > 20% in 24%, failure to anchor the THV in 20%, and unknown cause in 12%. Of note, a high rate of permanent pacemaker implantation was reported in both types of THV (22.6% for SE vs 21.8% for BE) most probably owing to a less precise valve positioning than in aortic stenosis.

**Table 3.** Factors favouring transcatheter heart valve (THV) migration/embolisation

| |
|---|
| Absence of a circular rigid frame of calcium at the annulus level, which means absence of anchoring points and annulus fluoroscopic landmark |
| Increased stroke volume secondary to severe aortic valve regurgitation ("suction effect") |
| Low implantation height favoured by the absence of a fluoroscopic landmark |
| Oversizing < 10% or excessive oversizing (particularly for self-expanding valves) |
| Pacing failure for balloon-expandable THV and absence of pacing in self-expanding THV |
| Horizontal aorta |
| Postdilatation |

## Different THV Platforms Used in TAVR for Aortic Regurgitation

Different platforms used in TAVR for AR are described below, and Figure 1 summarises their sizes and the range of annulus sizes that each available valve could treat. Figure 2 is an algorithm to facilitate the selection of the THV in cases of AR.

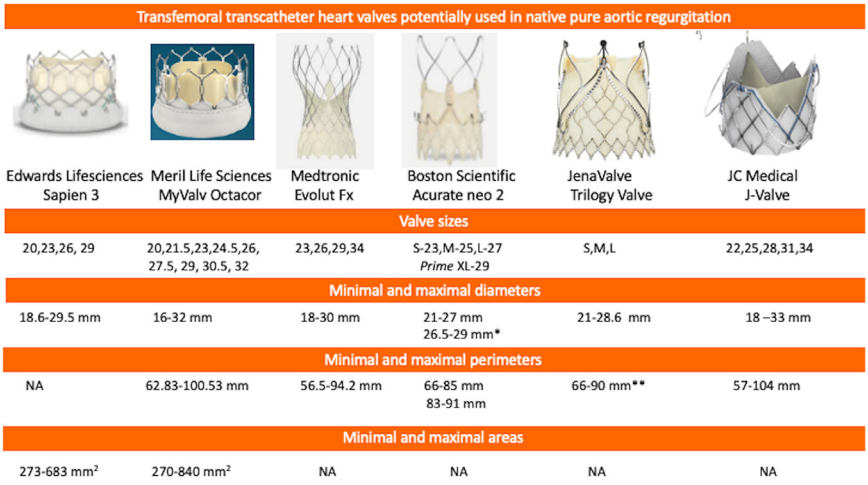


**Figure 1.** Sizes of available transcatheter heart valves (THVs) in Europe and the ranges of annulus size that each could treat. *Acurate Prime Aortic Valve System XL 29 mm: in the USA, restricted under federal law to investigational use only. The Acurate Prime XL is designed for an annulus perimeter of 83-91 mm. **The size of the perimeter compatible with the Trilogy JenaValve was recently upsized from 85 to 90 mm and therefore the diameter was upsized from 27 to 28.6 mm.[40]

## Self-expandable off-label devices

**CoreValve and Evolut.** As mentioned earlier, the Medtronic SE CoreValve was the most preferentially used THV in the early reports of TAVR in AR owing to the possibility of oversizing with a low risk of annular rupture compared with the BE Edwards Sapien. The SE design of the CoreValve with its nitinol frame were thought to ensure stability during valve positioning and anchoring in the absence of calcium. However, the limitations of this device were the high rates of valve-in-valve implantation and more than mild residual AR. The development of the Evolut THV, which was recapturable, repositionable, and retrievable, allowed higher implantation with less fear of embolisation in the aorta. PVL and permanent pacemaker implantation were also reduced with implantation at 3-5 mm.[20]

**Acurate Neo and Neo 2.** The design of the SE Acurate Neo 2 THV (Boston Scientific, Marlborough, MA) (distal stabilisation arches, upper/lower stent crowns, inner/outer pericardium skirts, X-shape, supra-annular leaflets) has the potential to adapt to noncalcified anatomy and avoid valve embolisation and residual AR. The Acurate Neo 2, compared with the earliest generation Acurate Neo, has a sealing skirt that is 60% larger and higher, reaching to the waist of the stent. The Acurate Neo 2 also has a radiopaque positioning marker to facilitate the accuracy of the positioning.[23] In addition, the delivery catheter was improved with a new atraumatic tip design. These iterations may contribute to improved procedural success in AR. Figure 3 shows a case of a large Acurate Neo 2 THV in a case of pure native AR in a high-risk patient.

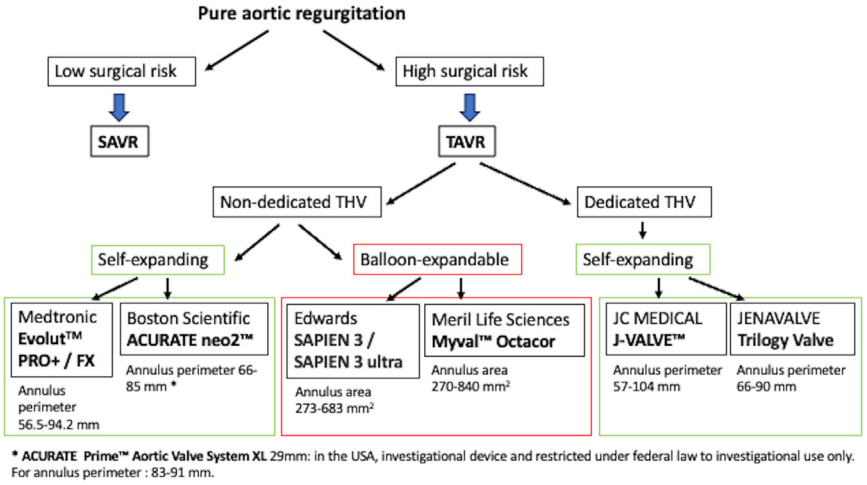


**Figure 2.** Algorithm to facilitate the selection of the transcatheter heart valve (THV) in cases of aortic valve regurgitation. SAVR, surgical atrial valve replacement; TAVR, transcatheter atrial valve replacement.

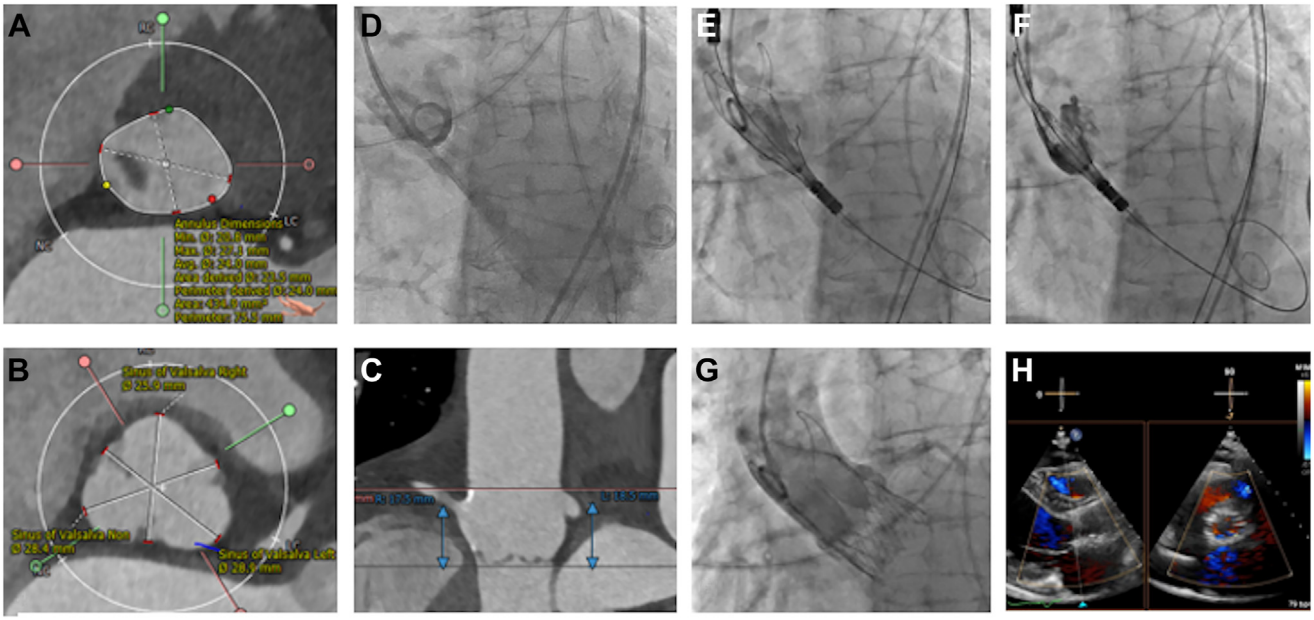


**Figure 3.** Example of Acurate Neo 2 size L in a case of pure aortic valve regurgitation. The 73-year-old woman was refused for surgery (chronic pulmonary disease, invasive ductal carcinoma treated by mastectomy and adjuvant therapy). Computed tomography showed measurements as follows: (**A**) aortic annulus perimeter 75.5mm, (**B**) sinus of Valsalva width 26 × 28 × 29 mm, height of sinus of Valsalva 22.9 mm, (**C**) height of the left main ostium 18.5 mm, height of the right coronary artery ostium 17.5 mm. Calcium score 1.3 HU. She was treated with the implantation of an Acurate Neo 2 L with rapid pacing at 120 beats/min. (**D**) The severe aortic valve regurgitation. (**E, F**) Top-down 2-step deployment with first the opening of the stabilisation arches and the upper crown, followed by full release of the valve. (**G**) The final result after deployment. (**H**) Ttransthoracic echocardiography at 1 month, showing trace paravalvular leak. The mean gradient was 6 mm Hg. A permanent pacemaker was implanted after the procedure, the valve having been implanted rather low. We started lower than in aortic stenosis to prevent aortic embolisation. However, the valve stayed in the starting position. According to Toggweiler et al.,[24] in aortic valve regurgitation the deployment starting point should be 2 mm higher than in aortic stenosis. The oversizing was 12% based on the perimeter-derived annular diameter, as the derived perimeter was 24 mm and the Acurate Neo 2 L is 27 mm.

A multicentre series of 24 AR patients from 2016 to 2018 in 13 European countries reported 4.1% 30-day all-cause mortality, 21.1% new permanent pacemaker implantation, and 87.5% device success, with a need for a second device in 12.5%. Residual AR was more than mild in 2 patients, and there were no cases of severe PVL.[17] More than mild residual AR and the need for a second device were seen only in patients with less than 10% oversizing. Indeed, all patients with a perimeter-based oversizing of more than 10% achieved device success, but at the cost of more permanent pacemaker implantation.

Another international registry from 9 countries in Europe and Israel reported 20 cases of pure AR treated with the Acurate Neo valve from 2015 to 2017. Device success was achieved in 90% (18/20), with 1 patient requiring a second valve (Edwards Sapien 3) owing to a low position of the Acurate Neo resulting in severe AR, and 1 patient presenting more than mild residual regurgitation. There was no death or stroke at 30 days, but new permanent pacemaker implantation in 15%.[24] The largest treated perimeter was 82 mm, and the large Acurate Neo 2 is indicated for perimeters from 79 to 84 mm. In borderline measurement, they selected the larger valve, and the degree of oversizing was on average 9 ± 4% (approximately 2 mm). They suggested implanting the valve 2 mm higher than in aortic stenosis.

An Italian centre reported its experience with the Acurate Neo valve from 2017 to 2021 with 9 patients.[25] Device success was achieved in all patients, and 30-day mortality was 0%. No new permanent pacemakers were implanted, and 2 patients had mild residual AR (22.2%). Their sizing algorithm also was in favour of an oversizing of more than 10%. They attributed their excellent results in this small cohort to their extensive experience with the device in aortic stenosis, their sizing algorithm, and the positioning 1 mm higher than in aortic stenosis. However, one of the current limitations of the Acurate Neo 2 valve is its maximum size. The THV is available in 3 sizes for annulus perimeters from 66 mm to 85 mm in aortic stenosis (size S, M, L). Recently, the Acurate Prime XL, an iteration of the Acurate Neo 2 with improved radial force with an additional frame connector and larger design adapted for annulus perimeter and diameter up to 91 mm and 29 mm, respectively, still compatible with the 14 iSleeve introducer, has been tested in a first-in-human study at 3 Australian centres including patients with severe aortic stenosis.[26] The valve was successfully implanted in all 13 enrolled patients with no 30-day mortality or stroke reported. The mean gradient was < 20 mm Hg in all patients. No patients had more than mild PVL, and the permanent pacemaker implantation rate was 7.7%. The Acurate Prime XL will undoubtedly be of interest in the setting of AR.

## Balloon-expandable valves

**Edwards Sapien.** The first Edwards Sapien THV implanted in the setting of AR was in a patient with a left ventricular

assist device (LVAD) and a noncalcified aortic valve in 2012.[27] Indeed, up to 30% of LVAD patients can develop severe AR within the first year. The recurrence of symptoms is a real challenge, and surgical risk usually prohibits SAVR. An oversized Edwards Sapien XT, namely, a 29 mm THV when 23 mm would have been recommended in the setting of a calcified valve, was successfully implanted within a 21 mm annulus.

In 2016, Urena et al. reported the first experience using the Sapien 3 in 3 inoperable patients with pure AR.[19] They oversized the valves by 16%, 23%, and 27%. At 1 month, all patients were in New York Heart Association (NYHA) functional class I or II, and echocardiography showed no residual AR nor valve displacement. They recommended oversizing by at least 15% with some additional contrast volume in the inflation pump.

Recently, the French multicentre Transcatheter Aortic Valve Implantation Using the **S**APIEN **3** Valve to Treat **A**ortic **R**egurgitation (S3AR) study, including of 49 pure native AR with no calcium treated from 2015 to 2021, was reported.[28] Active endocarditis, aortic dissection, and annuloectasia were excluded. The largest annulus area was 605 $mm^2$, although the 29 mm Sapien 3 valve can be implanted up to 683 $mm^2$ according to the Edwards sizing chart. They used a 29 mm Sapien THV in 70% of the procedures. The procedural success was 94.6%, with 2 valve embolisations, one with a too-low implantation with embolisation into the LV solved by conversion to surgery, although the patient died on day 3, and the other related to an undersized valve (23 mm instead of 26 mm) and too-slow rapid pacing. The embolised valve was implanted in the descending aorta, and an Evolut R was subsequently deployed in the aortic annulus. Interestingly, 2 patients experienced a secondary embolisation/migration. One had a suboptimal immediate result with moderate PVL, and surgery was performed at day 5; the patient died at day 4 after surgery. The other had an undersized valve (26 mm), and TAVR-in TAVR was performed at day 1 with the use of a 29 mm Sapien; the patient was alive at 1 year. All 4 patients with an embolisation had a THV oversizing of less than 15% (2.2%, 9.2%, 12.8%, and 0%). The authors recommended an oversizing of at least 15% and positioning of the valve lower than in aortic stenosis to obtain better anchoring in the LV outflow tract, which, in addition to oversizing, can contribute to explaining the 35% permanent pacemaker implantation rate. They did not treat any annulus larger than 605 $mm^2$, which is a common finding in pure native AR.

An Italian team reported the successful implantation of a 29 mm Sapien 3 for pure native AR with a minimally calcified annulus measured at 716 $mm^2$.[29] Follow-up computed tomography showed a valve area of 806 $mm^2$. Of note, the largest ever reported annulus treated with a Sapien S3 was 1007 $mm^2$ in the setting of a calcified bicuspid aortic stenosis.[30]

In the case of a very large annulus, a recent BE THV, the Myval system (Meril Life Sciences, Gujarat, India), became commercially available in Europe in June 2021. Recently, the second-generation Myval Octacor THV was introduced. The 32 mm Myval THV covers annulus dimensions to a perimeter up to 100.53 mm and may be interesting in cases of a very large annulus. Recently a 32 mm Myval THV was successfully implanted after 2 weeks of antibiotics in a patient suffering from active endocarditis with perivascular abscess and severely symptomatic AR secondary to central leaflet perforation.[31]

## Dedicated on-label devices

There are 2 dedicated devices, the JenaValve (JenaValve Technology, Irvine, CA) and the J-Valve (JC Medical, Burlingame, CA, and Suzhou, China). They have similar features designed for the anatomic characteristics of pure AR in the absence of calcium. Initially, they were deployed by means of a transapical approach, but recently both devices became available for transfemoral access with successful outcomes and lower rates of vascular complications.

**JenaValve Trilogy.** The JenaValve Pericardial TAVR system was the first SE dedicated THV for severe native AR. It was CE (Conformité Européenne) approved for the transapical approach in aortic stenosis in 2011 and in AR in 2013. However, with the decline of the transapical approach the company removed it from the market in 2016. They came back with the transfemoral device the Everdur Plus prosthesis. The first experience raised concerns about the safety of the delivery system, which was then modified. Today, the Coronatix transfemoral delivery catheter is used through an 18 F sheath.[32] Shortly before commercialization, the company changed the name to Trilogy THV system.

The JenaValve consists of a low-profile SE nitinol frame with integrated locators (formerly named feelers) and a supra-annular porcine pericardial trileaflet valve. The THV anchors to the leaflets by means of a paper clip—like mechanism that does not rely on calcium but simply on the leaflets. The locators align the device with the native leaflets and act as a strut onto which the nitinol frame is deployed, causing the native leaflets to be clipped in between the locators and the frame.

The Trilogy THV system, which was introduced to allow a transfemoral procedure, is second generation. It has a very low sealing height ($\sim$ 5 mm) to avoid coronary obstruction in the presence of low coronary ostia.[33] The first transfemoral case was published in 2017.[34] It received CE approval in aortic stenosis and AR in May 2021. However, despite the CE mark, its availability is currently limited to already trained centres.

An initial multicentre registry reported the outcomes of 31 transapical implantations for AR in 9 German centres.[35] Device implantation was successful in 30 of the 31 patients (97%). One patient required a valve-in-valve procedure after dislodgement of the first THV. The rate of all-cause mortality was 13% at 30 days and 19% at 6 months. Postprocedural AR was none/trace in 28 patients and mild in 3.

There are 3 other transapical series with the JenaValve THV in AR, a total of 104 patients.[20,36,37] The 30-day all-cause mortality rate was 12.5% to 30% (the latter in a series of 10 patients[36]), and the rate of more than mild PVL was 0% in 2 series and 1.6% in 1.

In 2023, Adam et al. published the results of an observational registry reporting the transfemoral experience of 6 German centres from September 2021 to July 2022 with 58 patients presenting with pure native AR on a tricuspid valve.[38] Technical success was achieved in all cases. Device success at 30 days was 98%. There was no PVL more than mild. Permanent pacemaker implantation was indicated in 19.6% of

the cases, of which 70% had preexisting conduction abnormalities. These results were promising.

At the TCT meeting in October 2023, the early feasibility study of the transfemoral Trilogy THV system in AR cases at high risk for open surgical replacement and without congenital bicuspid or unicuspid valve morphology, the ALIGN-AR EFS trial (NCT02732704), conducted in Germany, the Netherlands, and the USA, was presented as a late-breaking trial.[39] They reported the results of 180 AR patients compared for the primary safety end point vs a performance goal derived from contemporary high-risk aortic stenosis TAVR trials (Repositionable Percutaneous Replacement of Stenotic Aortic Valve Through Implantation of Lotus Valve System–Randomized Clinical Evaluation [REPRISE III], **Portico** Re-sheathable Transcatheter Aortic Valve System US **I**nvestigational **D**evice **E**xemption [PORTICO IDE], and **Sec**ond-Generation Se**l**f-Expandable vs Balloon-Expandable **V**alves and G**e**neral vs Local Anesthesia in **TAV**I [SOLVE-TAVI] [NCT02737150]) and for the primary efficacy end point vs a performance goal derived from a weighted average of 1-year mortality with conservative treatment. The Trilogy valves implanted were small, medium, and large in 22.8%, 20%, and 57.2%, respectively. Of note, the screening process initially excluded patients with an annulus perimeter $> 85$ mm, but it was subsequently upsized to 90 mm.[40] Post-dilatation was performed in only 3.9%. Technical success was achieved in 95%, device success in 96.7%, and procedural success in 92.8%, with no in-procedural death, annular rupture, or coronary obstruction. Valve embolisation ($n = 4$) was seen in 2.2%. At 30 days, all-cause mortality, cardiovascular mortality, and stroke rates were all 2.2%. New pacemaker implantation was required in 24% of the cases, with a decrease to 14% for the last 60 cases owing to changes in the insertion technique (locators were finally placed above the nadir of the native valve cups), a reduction in oversizing, and a change in the management of the conduction abnormalities. More than mild PVL was reported in 0.6% at 30 days, but there was none at 6 months and beyond. There was significant LV remodelling at 1 year. The functional class improved, with more than 90% of the patients in NYHA class I or II, and quality of life significantly improved from 55.8 to 77.6 points in the Kansas City Cardiomyopathy Questionnaire score at 1 year. The primary safety end point at 30 days and the primary efficacy end point at 1 year were met.

**J-Valve.** The J-Valve is approved by the National Medical Products Administration of China for aortic stenosis and AR and is available in the USA for compassionate use for AR. It consists of 2 components: first, the valve-locating feature composed of 3 U-shaped nitinol anchor rings designed to conform to the sinus of Valsalva, and second, a low-profile SE Nitinol frame with bovine pericardial leaflets and a polyester skirt covering the outer surface of the valve frame.

This valve was designed to treat pure native AR with the nitinol grasping elements to anchor the device in a non-calcified annulus. It may also be used to treat native aortic stenosis or degenerated bioprosthesis at high risk of coronary occlusion, considering that the anchor rings have the potential to retract the native or bioprosthetic valve leaflets and thus may avoid interference with the coronary ostia. The U-shape of the graspers minimises the risk of native leaflet perforation.

Initial implantations were performed with a transapical approach in 2015.[41,42] In 2019 the first transfemoral case was reported with the use of an 18 F flexible and steerable delivery system.[43]

This THV is not recapturable and is deployed in a 2-step process: The anchor rings are opened above the native valve and are advanced into the valve (when transfemoral, retracted if transapical) allowing anatomic alignment in the sinus of Valsalva and clasping of the valve leaflets.[43] There is a wide range of sizes with 5 different frame dimensions allowing the treatment of annulus diameters from 18 to 33 mm and annulus perimeters from 57 to 104 mm.[6]

Liu et al. reported in 2018 the 1-year result of a multicentre Chinese study including 3 centres and 43 patients. Successful TA implantation was achieved in 97.7% of the cases (42/43). The 1-year rate of all-cause mortality was 4.7%, disabling stroke 2.3%, new permanent pacemaker implantation 4.7%, and valve-related reintervention 7%.[44]

Recently in 2023, Garcia et al. reported the results of the North American compassionate use registry of the J-Valve including 27 patients from 3 US and 2 Canadian centres between 2018 and 2022.[45] Procedural success (no conversion to surgery and no need for a second valve) was attained in 81% of the patients (22/27) and in 100% of the last 15 patients after valve design modifications and exclusion of patients with leaflets prolapse. Procedures were transfemoral in 75% of the cases. No patient had more than mild residual AR. Of note, 38% of the cases had a perimeter $> 85$ mm, which was an exclusion criterion in the ALIGN-AR study with the JenaValve THV.

## Conclusion

The growing experience of operators and the development by engineers of new THV platforms during the past decade has helped push the boundaries of TAVR in pure native AR. Multiple series excluding patients with active endocarditis or unsuitable anatomies, such as significant dilation of the aortic root or ascending aorta, showed mixed results in TAVR for AR. The first-generation THVs were associated with a higher mortality rate and lower procedural success due to increased risks of more than mild PVL, valve migration requiring a second THV, and annular rupture compared with more recent off-label and on-label THVs. Early studies with dedicated on-label devices show promising results and will undoubtedly serve in the future a growing number of patients with severe native AR at prohibitive risk for surgery.

## Ethics Statement

This review article followed the relevant ethical guidelines.

## Patient Consent

The authors confirm that patient consent does not apply to this article, which is a review article with a retrospective case report using de-identified data in Figure 3. Therefore, the Institutional Review Board did not require consent from the patient who had already signed a consent to be included in the local and national TAVR registry.

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