TAVR as an alternative to SAVR for pure native aortic regurgitation

Short title: TAVR for pure native aortic regurgitation

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Key words: transcatheter aortic valve replacement (TAVR), pure native aortic regurgitation, transcatheter heart valve, valve embolization, paravalvular leak
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 will 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 due to excessive volume overload. It is often combined with a dilated aortic annulus and ascending aorta. Surgical aortic valve replacement remains the gold 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 no anchoring points nor fluoroscopic landmarks, the difficulty of valve sizing, and the increased stroke volume secondary to the aortic regurgitation making valve deployment more unstable than in the setting of aortic stenosis. The first-generation transcatheter valves were associated with a higher mortality rate and lower procedural success in relation to increased risk of paravalvular leak, 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.
Transcatheter aortic valve replacement (TAVR) has revolutionized the treatment of aortic valve stenosis with one randomized trial after the other showing its safety and efficacy in high, intermediate, and low surgical-risk patients for the care of severe degenerative aortic stenosis. 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, as well as the development of a multitude of different transcatheter heart valve (THV) designs have contributed to this expansion and 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 bio-prosthesis and severe pure aortic valve regurgitation (AR). In this review article, we will 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 between 2003 and 2010, the incidence of AR was in men and women respectively 19.7 and 10.8 per 100,000 person-years, while the incidence of aortic stenosis was 37.8 and 24.2 per 100,000 person-years, corresponding to about 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 the severe VHD whereas severe aortic stenosis was more than 7 times more common at 41.2%[5].

AR is in most cases a degenerative disease and, therefore frequently diagnosed in elderly patients with comorbidities. Symptoms tend to appear late in the course of the disease, coinciding with the onset of left ventricular 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 gold standard treatment for patients with pure severe native AR[1, 2]. Among 141905 patients in the USA who underwent first-time isolated SAVR between 2002 and 2010, 13.1% of SAVR 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) (≤ 50%) or left ventricular (LV) enlargement (LV end-systolic diameter (LVESD) > 50 mm or LVESD > 25mm/m²). The main indications for surgery are summarized 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 between 30 and 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 using different devices in an “off-label” setting to improve the outcome and the quality of life with varying levels of success. Recently, among the 11027 Medicare AR patients who underwent aortic valve replacement for pure AR in the USA between 2016 and 2019, 1147 (10.4%) had TAVR and 9880 (89.6%) SAVR[8]. Similarly, using the DRG (Diagnosis Related Groups) from all German hospitals between 2018 and 2020, 4861 procedures for pure AR were identified, with 4025 (82.8%) SAVR and 836 (17.2%) TAVR[9]. Finally, in the PANTHEON (Performance of Currently Available Transcatheter Aortic Valve Platforms in Inoperable Patients With Pure Aortic Regurgitation of a Native Valve) multi-centric international registry which collected data on second-generation THV between 2014 and 2022 in 16 centers, only 1.4% of the 15000 TAVR procedures were performed for AR [10].
As the prevalence of AR increases with age, we can anticipate a growing number 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 centers for selected patients with AR and ineligible for SAVR” [1]. Interestingly in the Medicare analysis, 40% of the TAVR in AR were performed in only 5% of the centers, highlighting the need for experienced operators and the concept of volume outcome relationship [8, 11].

**Specificity of TAVR in aortic regurgitation**

The THV were designed for calcified aortic stenosis and have demonstrated excellent outcomes compared to 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 either for balloon-expandable (BE) or self-expanding (SE) THV. The calcium is also a visual fluoroscopic landmark to help to position the valve during deployment. The absence of calcium along with an increased stroke volume and aortic root dilatation increase the risk of THV malposition, migration or embolization 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 embolization 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 embolization or migration was still 12.5% with no differences between SE and BE valves. [10]. In multivariate analysis, post-dilatation 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 embolization or migration was associated with a worse one-year composite endpoint (all-cause
death, heart failure rehospitalization) and all-cause mortality. BE valves move more frequently to the ventricular side (85.3%), while the SE valves move more to 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 mid-term as demonstrated in one of the first multi-centric series reporting 75% of mortality at 6 months in the presence of an ascending aorta aneurysm [13].

From the screening of the ALIGN-AR (107 patients) and ALIGN-AS (92 patients), early feasibility trials using the dedicated JenaValve THV, Gogia et al reported data from 19 centers, which compared the range of annulus and aortic root sizes of the patients referred (i.e., rather than those 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 to patients with aortic stenosis. More patients with AR than with aortic stenosis were excluded based on the annulus perimeter (14% versus 2%, respectively). Conversely, more patients with aortic stenosis had a higher risk for coronary occlusion of the left main (21% versus 7%) or the right coronary artery (14% versus 3%). In the AR group, the annulus area and perimeter ranged from 283 to 884 mm² and 60 and 106 mm, respectively, compared to 299 to 647 mm² and 63 to 94 mm in the aortic stenosis group. No patients with aortic stenosis had an annulus larger than 660 mm² (the theoretical maximum nominal size for the Sapien 3 THV), while that was found in 7.5% of the AR group. Finally, only one 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 embolize 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, CA, US) 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 mm² with no calcium. They first implanted a 26mm Sapien S3 with 2 additional ml (29% of oversizing) which embolized. Subsequently, they successfully implanted a 29mm Sapien S3 at a nominal diameter which 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 to 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 to the BE group not only for perimeter (16.4±9.5% versus 8.5±7.0%, p<0.001), but also for the area (21.2±13.4% versus 9.9±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 analysis, AR patients who underwent TAVR were older with more comorbidities than the SAVR group[8]. In the Medicare cohort, TAVR patients experienced lower in-hospital and short-term mortality than SAVR for AR, but higher midterm risk of global mortality, heart failure, and need for re-intervention[8]. Table 2 summarizes the specific technical aspects to improve the procedural success of TAVR in AR and table 3 the different risk factors favoring migration/embolization of the THV.

**Literature review**
The experience in treating AR using TAVR is limited to observational studies enrolling carefully selected patients by the heart team of each center. In the earliest reports, 20 to 50% of the aortic valves had some degree of calcification [13, 17]. Currently, there is no randomized 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 multicentric 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 TAVR for AR were included with a total of 237 patients. More SE THV (79%) were used than BE THV (21%) [21]. They found a correlation between the absence of calcium and the need for a second valve.

In the early cohorts with the CoreValve (Medtronic Minneapolis, MN, US), 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 multicentric registry with 40 centers across Europe, Asia-Pacific, and North America enrolled 331 patients who underwent a TAVR for AR between 2007 and 2017 [20]. The early-generation devices (CoreValve n=110, Edwards 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 Inc, Irvine, CA, USA) (19.3%), Evolut R (15.1%), SAPIEN 3 (Edwards Lifesciences, Irvine CA, USA) (12.4%) and other devices. The mean aortic annulus diameter, area, and perimeter were 25.2mm, 488 mm², 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% versus 61.3% p<0.001) secondary to lower rates of second valve need (12.7% vs 24.4%, p=0.007) and post-procedural 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 both 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%) versus on-label devices (33%), namely the JenaValve and the J-Valve[22]. Compared to 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%) and 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 two devices were overcome by technical improvements (more sizes, addition of paravalvular skirts, recapturable and repositionable for the Evolut) in the 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 THV (66% of self-expanding) implanted in pure AR at 16 international centers 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 embolization being the most common cause of failure (12.4%) [10]. THV migration or embolization 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 self-expanding THV versus 21.8% for balloon-expandable THV) most probably due to a less precise valve positioning than in aortic stenosis.

**Different THV platforms used in TAVR for aortic regurgitation**

Different platforms used in TAVR for AR are described below and figure 1 summarizes 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.

**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 due to the possibility of oversizing with a low risk of annular rupture compared to the BE Edwards SAPIEN. The SE design of the CoreValve with its nitinol frame was considered to ensure stability during valve positioning and anchoring in the absence of calcium. However, the limitations of this device were the high rate 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 embolization in the aorta. PVL and permanent pacemaker implantation were also reduced with implantation at 3-5 mm[20].

**Acurate neo and neo 2 THV**
The design of the SE Acurate neo 2 THV (Boston Scientific, MA, USA) (distal stabilization arches, upper/lower stent crowns, inner /outer pericardium skirts, X-shape, supra-annular leaflets) has the potential to adapt to non-calcified anatomy and avoid valve embolization and residual AR. The Acurate neo 2 compared to the earliest generation Acurate neo has a sealing
skirt that is 60% larger, and it is higher, reaching to the waist of the stent. The Acurate neo 2 also has a new 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 improve the procedural success in AR. Figure 3 shows a case of a LargeAcurate neo 2 THV in a case of pure native AR in a high-risk patient.

A multicentric series of 24 AR patients from 13 European countries between 2016 and 2018 reported 4.1% of 30-day all-cause mortality, 21.1% of new permanent pacemaker implantation, and 87.5% of device success with a need for a second device in 12.5%. Residual AR was more than mild in 2 patients with no case 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 between 2015 and 2017. Device success was achieved in 90% (18/20) with one patient requiring a second valve (Edwards SAPIEN 3) due to a low position of the Acurate neo resulting in severe AR, and one patient presenting a more than mild residual regurgitation. There was no death or stroke at 30 days, but 15% of new permanent pacemaker implantation [24]. The largest treated perimeter was 82 mm while the large Acurate neo 2 is indicated for perimeters between 79 and 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 millimeters higher than in aortic stenosis.

An Italian center reported its experience with the Acurate neo valve between 2017 and 2021 with 9 patients [25]. Device success was achieved in all patients and 30-day mortality was 0%. No new permanent pacemaker was implanted and residual AR was mild in 2 patients (22.2%). Their sizing algorithm was also in favor 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 (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 centers including patients with severe aortic stenosis [26]. The valve was successfully implanted in all thirteen enrolled patients with no 30-day mortality nor stroke reported. The mean gradient was < 20 mmHg 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.

The balloon-expandable valves

Edwards SAPIEN

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

In 2016 Urena et al reported the first experience using the SAPIEN 3 in 3 inoperable patients with pure AR[19]. They oversized their valve by 16%, 23%, and 27%. At one month, all patients were in New York Heart Association functional class I or II and the echocardiographic control
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 multicenter S3AR study was reported with the inclusion of 49 pure native AR with no calcium treated between 2015 and 2021[28]. Active endocarditis, aortic dissection, and annulo-ectasia were excluded. The largest annulus area was 605 mm² while the 29mm SAPIEN 3 valve can be implanted up to 683 mm² according to the Edwards sizing chart. They used a 29mm SAPIEN THV in 70% of the procedures. The procedural success was 94.6% with two valve embolizations. One was with a too-low implantation with embolization into the LV solved by conversion to surgery, but the patient died on day 3. The second one was related to an undersized valve (23 mm instead of 26 mm) and too slow rapid pacing. The embolized valve was implanted in the descending aorta and an Evolut R was subsequently deployed in the aortic annulus. Interestingly, two patients experienced a secondary embolization/migration. The first one had a suboptimal immediate result with a moderate PVL and surgery was performed at day 5 with a patient who died at day 4 post-surgery. The second one had an undersized valve (26 mm) and a TAVR-in TAVR was performed at day 1 using a 29mm SAPIEN with a patient alive at one year. All four patients with an embolization 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 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 annulus more than 605 mm², 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 mm² [29]. A follow-up CT scan showed a valve area of 806 mm². Of note, the largest ever reported annulus treated with a SAPIEN S3 was 1007 mm² in the setting of a calcified bicuspid aortic stenosis[30]
In the case of a very large annulus, a recent balloon expandable THV namely the Myval system (Meril Life Sciences, Gujarat, India) has become commercially available in Europe in June 2021. Recently, the second-generation named the Myval Octacor THV was introduced. The 32mm Myval THV covers annulus dimension to a perimeter up to 100.53 mm and may be interesting in cases of very large annulus. Recently a 32mm Myval THV was successfully implanted after 2 weeks of antibiotics in a patient suffering from an active endocarditis with perivascular abscess and severely symptomatic AR secondary to central leaflet perforation [31].

The dedicated on-label devices

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

The JenaValve Trilogy THV

The JenaValve Pericardial TAVR system was the first self-expanding dedicated THV for severe native AR. It was CE (Conformité Européenne) mark approved for the TA approach in aortic stenosis in 2011 and in AR in 2013. However, with the decline of TA approach, the company removed it from the market in 2016. They came back with the transfemoral device the Everdur TM Plus prosthesis. The first experience raised concerns about the safety of the delivery system which was modified. Today the Coronatix transfemoral delivery catheter is used through an 18 Fr sheath[32]. Shortly before commercialization, the company changed the name to Trilogy THV system.
The JenaValve consists of a low-profile self-expanding nitinol frame with integrated locators (formerly named feelers) and a supra-annular porcine pericardial tri-leaflet valve. The THV anchors to the leaflets using 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 transfemoral procedure is a second generation. It has a very low sealing height (~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 the CE mark approval in aortic stenosis and AR in May 2021. However, despite the CE Mark, its availability is currently limited to already trained centers.

An initial multicenter registry reported the outcomes of 31 TA implantations for AR in 9 German centers [35]. Device implantation was successful in 30/31 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. Post-procedural AR was none/trace in 28/31 patients and mild in the remaining 3 patients.

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

In 2023, M Adam et al published the results of an observational registry reporting the transfemoral experience of 6 German centers between September 2021 and July 2022 with 58 patients presenting with a 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 whom 70% had pre-existing 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 endpoint to a performance goal derived from contemporary high-risk aortic stenosis TAVR trials (REPRISE III, PORTICO IDE; SOLVE TAVR) and for the primary efficacy endpoint to a performance goal derived from a weighted average of one-year mortality with conservative treatment. The Trilogy valve 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 of more than 85 mm, but it was subsequently upsized for 90 mm [40]. Post-dilatation was performed in only 3.9%. Technical success was achieved in 95%, device success in 96.7%, and procedure success in 92.8% with no in-procedural death, annular rupture, or coronary obstruction. Valve embolization (n=4) was seen in 2.2%. At 30 days, all-cause mortality and cardiovascular mortality rates were both at 2.2%, as well as the stroke rate. New pacemaker implantation was required in 24% of the cases with a decrease to 14% for the last 60 cases due to changes in the insertion technique (locators were finally placed above the nadir of the native valve cups), a reduction in oversizing as well as 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 left ventricle remodeling at one year. The functional class improved with more than 90% of the patients in NYHA class I or II and the quality of life significantly improved from 55.8 to 77.6 points in the KCCQ score at one year. The primary safety endpoint at 30 days as well as the primary efficacy endpoint at one 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 two 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, self-expanding 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 bio-prosthesis 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 grasper minimizes the risk of native leaflet perforation.

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

This THV is not recapturable and deployed in a two-step process: the anchor rings are first opened above the native valve and are advanced into the valve (when transfemoral, retracted if TA) allowing anatomic alignment in the sinus of Valsalva and clasping of the valve leaflets[43].

There is a wide range of sizes with currently five different frame dimensions allowing the treatment of annulus diameters from 18 to 33 mm and annulus perimeters from 57 to 104 mm [6].

Liu H et al reported in 2018 the one-year result of the multicentric Chinese study including 3 centers and 43 patients. Successful TA implantation was achieved in 97.7% of the cases (42/43). The one-year rate of all-cause mortality was 4.7%, disabling stroke 2.3%, new permanent pacemaker implantation 4.7%, and valve-related re-intervention 7%.
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 centers between 2018 and 2022[44]. The procedural success (no conversion to surgery and no need for a second valve) was obtained in 81% of the patients (n=22) and 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 residual mild 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.

**Conclusions**

The growing experience of the operators and the development by the engineers of new THV platforms during the last 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 dilatation of the aortic root or ascending aorta showed mixed results in TAVR for AR. The first-generation THV were associated with a higher mortality rate and lower procedural success due to an increased risk of more than mild paravalvular leak, valve migration requiring a second THV, or annular rupture, than the more recent off-label or on-label THV. Early studies with dedicated on-label devices showed safety and promising results and will undoubtedly serve in the future a growing number of patients with severe native AR at prohibitive risk for surgery.
Figure legends

Figure 1: summarizes the sizes and the range of annulus sizes that each available THV in Europe could treat.

*ACURATE Prime™ Aortic Valve System XL 29mm: in the USA, investigational device and restricted under federal law to investigational use only. The Acurate Prime XL is designed for an annulus perimeter between 83 and 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].

Figure 2: algorithm to facilitate the selection of the THV in cases of AR.

Figure 3: example of Acurate neo 2 size L in a case of pure AR

73-year-old lady who was turned down by the surgeons (chronic pulmonary disease, invasive ductal carcinoma treated by mastectomy and adjuvant therapy). The CT scan showed measurements as follows (Panel A-B-C): aortic annulus perimeter: 75.5mm, sinus of Valsalva width: 26x28x29 mm, height of the sinus of Valsalva: 22.9 mm, 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 bpm. Panel D shows the severe aortic regurgitation, Panel E and F shows the top-down 2-step deployment with first the opening of the stabilization arches and the upper crown followed by the full release of the valve. Panel G shows the final result post deployment. Panel H shows the trace of PVL on transthoracic echocardiography at one month. The mean gradient was 6 mmHg. A permanent pacemaker was implanted post-procedure, the THV being implanted rather low. We started lower than in aortic stenosis to prevent aortic embolization. However, the valve stayed in the starting position. According to Toggweiler et al [24], in AR the deployment...
starting point should be 2 mm higher than in aortic stenosis. The oversizing was 12% based on the perimeter-derived annular diameter since the derived perimeter was 24 mm and the Acurate neo 2 L is 27 mm.

Table 1: Indications for intervention in cases of aortic regurgitation

<table>
<thead>
<tr>
<th>Indications for intervention</th>
<th>ESC/EACTS 2021</th>
<th>Class/Level</th>
<th>ACC/AHA 2020</th>
<th>Class/Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic patients regardless of LVEF</td>
<td></td>
<td>I B</td>
<td></td>
<td>I B</td>
</tr>
<tr>
<td>Asymptomatic patients with LV dysfunction</td>
<td>LVEF ≤50%</td>
<td>I B</td>
<td>LVEF ≤55%</td>
<td>I B</td>
</tr>
<tr>
<td>Asymptomatic patients with severe LV dilatation</td>
<td>LVESD &gt;50mm or LVESD &gt;25mm/m² BSA</td>
<td>I B</td>
<td>LVESD &gt;50mm or LVESD &gt;25mm/m² BSA</td>
<td>IIa B</td>
</tr>
<tr>
<td>Asymptomatic patients if surgery is at low risk and:</td>
<td>LVEF ≤55%</td>
<td>IIb C</td>
<td>Decrease in LVEF to &lt;55-60% on at least 3 serial studies</td>
<td>IIb B</td>
</tr>
<tr>
<td>Asymptomatic patients if surgery is at low risk and:</td>
<td>LVESD &gt;20 mm/m² BSA</td>
<td>IIb C</td>
<td>Increase in LVEDD to &gt;65mm on at least 3 serial studies</td>
<td>IIb B</td>
</tr>
<tr>
<td>Symptomatic and asymptomatic patients with severe aortic regurgitation undergoing CABG or surgery of the ascending aorta or of another valve</td>
<td></td>
<td>I C</td>
<td></td>
<td>I C</td>
</tr>
</tbody>
</table>

Table 2: Technical challenges of TAVR in aortic regurgitation

<table>
<thead>
<tr>
<th>Challenges</th>
<th>Objectives</th>
<th>Solutions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Instable deployment</td>
<td>Reduce stroke volume and limit THV motion</td>
<td>Rapid pacing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; 180 bpm for BE valves</td>
</tr>
<tr>
<td></td>
<td></td>
<td>120 bpm for SE valves</td>
</tr>
<tr>
<td>Absence of calcium to guide valve deployment</td>
<td>Annulus landmark providing a coplanar annular view</td>
<td>-2 pigtails in different sinus of Valsalva</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-CT fusion</td>
</tr>
</tbody>
</table>
**Absence of calcium to facilitate valve anchoring**
Avoid valve migration or embolization
Different anchoring design such as clipping of the leaflets

**Sizing of the THV**
Avoid valve migration/embolization
-PVL
-annular rupture
Oversizing*
-Medtronic SE: 15%
-Edwards SAPIEN: at least 15%
-Accurate Neo: 10%
-JenaValve: 10-20%

*some authors described larger oversizing. The more oversizing the higher the risk of annular rupture. Oversizing should be adapted to the CT scan assessment of the anatomy and the valve type used. Excessive oversizing can also be associated with valve migration particularly for SE valves.

Table 3: Factors favoring THV migration/embolization

<table>
<thead>
<tr>
<th>Description</th>
<th>THV Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absence of a circular, rigid frame of calcium at the annulus level which means absence of anchoring points and annulus fluoroscopic landmark</td>
<td></td>
</tr>
<tr>
<td>Increased stroke volume secondary to severe AR (“suction effect”)</td>
<td></td>
</tr>
<tr>
<td>Low implantation height favored by the absence of fluoroscopic landmark</td>
<td></td>
</tr>
<tr>
<td>Oversizing &lt; 10% or excessive oversizing (particularly for self-expanding valves)</td>
<td></td>
</tr>
<tr>
<td>Pacing failure for balloon-expandable THV and absence of pacing in self-expanding THV</td>
<td></td>
</tr>
<tr>
<td>Horizontal aorta</td>
<td></td>
</tr>
<tr>
<td>Post-dilatation</td>
<td></td>
</tr>
</tbody>
</table>
References:


Transfemoral transcatheter heart valves potentially used in native pure aortic regurgitation

<table>
<thead>
<tr>
<th>Valve Manufacturer</th>
<th>Valve Sizes</th>
<th>Minimal and Maximal Diameters</th>
<th>Minimal and Maximal Perimeters</th>
<th>Minimal and Maximal Areas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edwards Lifesciences Sapien 3</td>
<td>20,23,26, 29</td>
<td>18.6-29.5 mm</td>
<td>NA</td>
<td>273-683 mm²</td>
</tr>
<tr>
<td>Meril Life Sciences MyVal Octacor</td>
<td>20,21.5,23,24.5,26, 27.5,29,30.5, 32</td>
<td>16-32 mm</td>
<td>62.83-100.53 mm</td>
<td>270-840 mm²</td>
</tr>
<tr>
<td>Medtronic Evolut Fx</td>
<td>23,26,29,34</td>
<td>18-30 mm</td>
<td>56.5-94.2 mm</td>
<td>NA</td>
</tr>
<tr>
<td>Boston Scientific Acurate neo 2</td>
<td>S-23,M-25,L-27 Prime XL-29</td>
<td>21-27 mm</td>
<td>66-85 mm</td>
<td>NA</td>
</tr>
<tr>
<td>JenaValve Trilogy Valve</td>
<td>S,M,L</td>
<td>21-28.6 mm</td>
<td>83-91 mm</td>
<td>NA</td>
</tr>
<tr>
<td>JC Medical J-Valve</td>
<td>22,25,28,31,34</td>
<td>18 –33 mm</td>
<td>66-90 mm**</td>
<td>NA</td>
</tr>
</tbody>
</table>
Pure aortic regurgitation

Low surgical risk
SAVR

High surgical risk
TAVR

Non-dedicated THV
Self-expanding
Medtronic Evolut™ PRO+ / FX
Annulus perimeter 56.5-94.2 mm
Boston Scientific ACURATE neo²™
Annulus perimeter 66-85 mm *
Annulus area 273-683 mm²
Edwards SAPIEN 3 / SAPIEN 3 ultra
Annulus area 270-840 mm²
Meril Life Sciences Myval™ Octacor
JenaValve J-VALVE™
Annulus perimeter 57.104 mm
Annulus perimeter 66-90 mm

Dedicated THV
Balloon-expandable
JenaValve Trilogy Valve

* ACURATE Prime™ Aortic Valve System XI. 29mm: in the USA, investigational device and restricted under federal law to investigational use only. For annulus perimeter : 83-91 mm.