Chapter

Transcatheter Therapies for Aortic Regurgitation: Where Are We in 2023?

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Abstract

Aortic regurgitation (AR) is retrograde flow across the aortic valve in diastole and is classified from stage A to D based on severity and symptoms. Severe symptomatic AR (stage D) is a class I indication for surgical aortic valve replacement per the 2020 American College of Cardiology/American Heart Association guidelines. Though off-label, patients with prohibitive surgical risk may benefit from transcatheter aortic valve replacement (TAVR) in appropriately selected patients. However, TAVR is challenging in AR due to a lack of leaflet and annular calcification and dilation of the perivalvular apparatus, compromising the optimal anchorage of the bioprosthesis with a risk of prosthetic valve leak and embolization. Valve oversizing by 10–15% is frequently required, with caution not to oversize beyond 20%. Multimodality imaging, including echocardiography, magnetic resonance imaging, and computerized tomography, is essential for procedural planning. Registry data shows acceptable results for off-label TAVR with newer generation valves such as Medtronic Evolut and Edwards Sapien 3 for native AR. The JenaValve designed especially for TAVR for native AR is currently undergoing clinical trial. Until the results of randomized clinical trials are available, careful selection of native AR patients for TAVR is paramount to procedural and clinical success.

Keywords: aortic regurgitation, aortic insufficiency, aortic valve replacement, TAVR, transcatheter therapy, bioprosthetic valve, valvular heart disease, valvular leak, paravalvular leak, valve-in-valve

1. Introduction

Aortic regurgitation (AR) is defined as retrograde blood flow across the aortic valve (AV) during diastole. A normal AV is tricuspid, whereas a bicuspid aortic valve could accelerate the degenerative process leading to aortic stenosis (AS) or AR. According to Framingham Heart study, AR was observed in 13% of men (n = 1326) and 8.5% of women (n = 1539) using echocardiography data [1].

AR may be acute or chronic. While acute severe AR (e.g., with type A aortic dissection) is a surgical emergency, chronic AR progresses gradually, requiring serial imaging and appropriate therapy when it becomes severe. There are several etiologies of AR. Diseases of aortic valve leaflets, aortic root, annulus, or ascending aorta may result in AR. AR is subdivided into four clinical stages (A to D) elaborated in **Table 1** [2–4]. Stage D signifies severe symptomatic AR, and surgical aortic valve replacement (SAVR) is a class I indication per 2020 American College of Cardiology (ACC)/American Heart Association (AHA) [3]. Asymptomatic patients

Aortic regurgitation stage	Clinical Description	Echocardiography criteria	NYHA class
Stage A	**Patients at risk:** bicuspid AV, aortic root or ascending aorta dilation, aortic valve sclerosis, history of rheumatic valve disease	None to trace AR	I
Stage B	**Progressive AR:** Mild to moderate AR due to any cause	Mild AR: Central Jet with width < 25% of LVOT, VCW <0.3 cm, RVol <30 mL/beat; RF < 30%, PHT > 500 ms, soft or incomplete jet by CW, EROA <0.10 cm^2, LV size normal (AR grade I) Moderate AR: Central Jet width 25–64% of LVOT, VCW 0.3–0.6 cm, RVol 30–59 mL/beat, RF 30–49%, PHT 500-200 ms, dense CW jet, EROA 0.10–0.29 cm^2, normal or dilated LV (AR grade II-III)	I
Stage C1	Severe asymptomatic AR	Severe AR: Central Jet width ≥ 65% of LVOT, VCW >0.6 cm, large flow convergence, prominent holo-diastolic flow reversal in descending aorta, RVol ≥60 mL/beat, RF ≥ 50%, PHT < 200 ms, dense CW jet, EROA ≥0.3 cm^2, LVEF ≥55% and mild-to-moderate LV dilation (LVESD ≤50 mm) (AR grade Grade III-IV)	I
Stage C2	Severe asymptomatic AR	Same as stage C1 except with LVEF <55% or severe LV dilation (LVESD >50 mm or LVESD index >25 mm/m^2 (Grade III-IV) Exercise testing is reasonable to confirm symptoms.	I
Stage D	Severe symptomatic AR	Same as stage C1–2 with normal or abnormal LV size and LVEF	II-IV

AR = aortic regurgitation, AV = aortic valve, CW = continuous wave, EROA = effective regurgitant orifice area, LV = left ventricle, LVEF = left ventricle ejection fraction, LVOT = left ventricle outflow tract, PHT = pressure half time, RF = regurgitant fraction, RVol = regurgitant volume, VCW = vena contracta width.

Table 1.
Clinical stages of chronic aortic regurgitation.

with severe AR and left ventricular ejection function (LVEF) < 55% (stage C2) also qualify for SAVR if no other cause of left ventricle (LV) dysfunction is identified [3]. Symptomatic patients with severe AR have 10–20% annual mortality if left untreated. A study by Dujardin et al. demonstrated a mortality rate of 34 ± 5% at ten years in patients (n = 246) with moderate to severe AR [5]. They also had higher morbidity at ten years follow-up (47 ± 6% heart failure and 62 ± 4% AV surgery). A prospective study of valvular heart disease in Europe demonstrated that 7.8% of patients with severe AR qualifying for aortic valve replacement (AVR) had no intervention due to high peri-operative risk [6, 7]. Such patients may benefit from transcatheter aortic valve replacement (TAVR) after carefully assessing procedural safety and feasibility. In contrast to AS, TAVR is challenging in AR due to the dilation of the perivalvular apparatus and lack of annular/leaflet calcification, compromising the optimal anchorage of the bioprosthesis. The potential complications include improper valve seal, paravalvular leak (PVL), valve embolization, and malalignment or malposition of the bioprosthetic valve [8, 9]. This chapter discusses transcatheter therapies for chronic native valvular AR.

2. Imaging for aortic regurgitation

The incompetence of aortic valve leaflets during diastole results in the backflow of blood into the left ventricle. The regurgitation leads to increased blood volume at the end of diastole and elevated stress on the ventricular walls, eventually causing compensatory eccentric hypertrophy due to excessive volume.

Transthoracic echocardiography (TTE) is the primary tool to assess the mechanism, severity, secondary impact on LV remodeling, and hemodynamic consequences of AR. Moreover, TTE and computerized tomography (CT) are valuable in assessing aortic root size. Wenzel et al. demonstrated a proportional relationship between the degree of aortic root dilation and AR severity [10]. Even with nondilated aortic roots, pure AR is associated with degeneration of aortic walls as evidenced by histological and immunohistochemical analyses by Balint et al [11]. According to the 2020 ACC/AHA valvular heart disease guidelines [3], severe AR is defined by specific criteria: Doppler jet width of ≥65% of the left ventricular outflow tract (LVOT), vena contracta width >0.6 cm, regurgitant volume of ≥60 mL/beat, regurgitant fraction of ≥50%, and effective orifice area of ≥0.3 cm. However, identifying subtle LV dysfunction in the early stages of the disease is desirable, as severe dilation and reduced LVEF indicate a late stage of the disease.

2.1 Speckle tracking echocardiography in aortic regurgitation

With chronic AR, speckle tracking echocardiography reveals that the eccentric changes in the LV predominantly affect the circumferentially arranged fibers, leading to more severe impairment in global circumferential strain (GCS) compared to global longitudinal strain (GLS). Therefore, circumferential strain is a more sensitive marker for AR and volume overload compared to longitudinal strain for AS and pressure overload [12]. A retrospective study of 314 patients with chronic moderate to severe AR demonstrated that reduced GLS independently predicted mortality, with a threshold of −12.5% [13]. Patients with progressive AR and symptoms had significantly lower longitudinal strain compared to those with stable disease, despite similar LVEF.

In a longitudinal study of 64 patients, reduced GLS, strain rate, and early diastolic strain were associated with progressive disease and worse outcomes following surgery [14]. Impaired LV radial systolic strain rate was predictive of LVEF post-surgery, and decreased baseline GLS or GCS predicted the need for surgery in asymptomatic patients [15].

2.2 3-dimensional echocardiography

3-Dimensional (3D) echocardiography is crucial in assessing AR severity. While numerous 2-Dimensional (2D) echocardiography parameters can be used to quantify AR, it remains challenging due to variations in the scan plane and irregularities in the shape of the vena contracta jet. 3D echocardiography, specifically measuring the vena contracta area (3D-VCA), provides a direct and accurate evaluation. Studies have shown that severe AR can be detected with a sensitivity of 89% and specificity of 98% using a 3D-VCA cutoff of 32 mm^2 [16]. 2D-derived parameters such as proximal iso-velocity surface area (PISA) and regurgitant volume (RVol) affected by geometric assumptions, angle correction limitations, and difficulty assessing multiple jets. Full-volume color Doppler echocardiography in 3D has been reported to be more accurate than 2D-PISA, especially for eccentric or multiple jets [17]. Moreover, 3D color Doppler echocardiography has demonstrated high accuracy and reproducibility for AR evaluation, exhibiting a strong correlation with cardiac magnetic resonance (CMR) imaging, considered the gold standard [18].

2.3 Cardiac magnetic resonance imaging

CMR has emerged as a valuable tool for assessing AR patients. It is the current reference standard for evaluating cardiac volumes, mass, and systolic function. Furthermore, CMR provides insights into myocardial tissue characterization, offering additional prognostic information. It enables both anatomical and functional assessment of the aortic valve and the entire thoracic aorta.

2.4 Computed tomography

In preprocedural evaluations of patients with AR, ECG-gated CT is indispensable because it provides precise information about the aortic size and valve morphology, among other vital details, for optimal procedural planning. Additionally, CT can help exclude the presence of associated coronary artery disease. It is worth noting that the asymmetrical nature of the aortic root, especially in cases of a bicuspid aortic valve, can lead to underestimation of the actual size of the aortic valve when measured using single-plane echocardiography.

3. Transcatheter aortic valve replacement (TAVR) for native aortic regurgitation

TAVR has evolved as a treatment for AS in the United States (U.S.) across all risk categories [19, 20]. More recently, TAVR has been increasingly used for off-label

indications such as bicuspid AV stenosis, subaortic stenosis, and severe AR [21]. Off-label TAVR has shown similar 1-year mortality (25.6%) compared to on-label TAVR in a study using STS/TVT data [21].

According to 2020 ACC/AHA valvular heart disease guidelines, SAVR is a class I indication for pure native AR stage C2-D [3]. However, TAVR has been performed as an off-label treatment for AR in patients with prohibitive surgical risk [22]. TAVR poses unique technical challenges in pure AR due to lack of annular/leaflet calcification and, in some cases, aortic root dilation. Current data suggests oversizing the prosthetic valve by 10–15% with caution and not exceeding 20% due to the risk of annular rupture and conduction abnormalities [23–25]. Severe aortic root dilation with large annuli may exceed the size of commercially approved bioprosthetic valves and make the TAVR riskier and unsuccessful due to the risk of valve embolization. Additionally, it may cause more than mild residual PVL due to a lack of proper seal. The maximum size of the commercially available self-expanding valve is 34 mm (Evolut FX by Medtronic), providing a maximal annular area of 940 mm^2 [26]. It is larger than the area of the largest commercially available balloon-expandable valve, e.g., 29 mm Edwards SAPIEN 3 Ultra or RESILIA valve provides an annular area of 683 mm^2 [27].

Alharbi et al. compared TAVR (n = 912) vs. SAVR (n = 13,808) for pure native AR using the US national inpatient sample database from 2016 to 2017 and found no difference in in-hospital mortality between both groups. Although the need for a permanent pacemaker (PPM) was higher in the TAVR group, these patients had lower acute renal injury, cardiogenic shock, respiratory complications, and length of hospital stay despite having worse baseline characteristics compared to the SAVR group [28]. Another large-scale study by Arora et al [29] demonstrated 3.3% 30-day all-cause mortality with TAVR for AR compared with 3.4% in the PARTNER trial for AS in high-risk population [30]. Newer-generation devices depicted lower mortality with higher procedural success of TAVR in pure AR when compared with first-generation devices across observational studies [31–33].

Examples of first-generation TAVR devices include Edwards Sapien XT and Medtronic CoreValve. Second-generation valves have an improved design to provide better anchoring mechanisms, optimal seal, and superior hemodynamic results. Examples of second-generation valves include Edwards Sapien 3, Medtronic Evolut R, Evolut PRO, Evolut FX, Acurate Neo, Acurate TA, Direct Flow Valve, J-valve, JenaValve, and Portico valves.

3.1 Edwards Sapien 3

The Edwards Sapien 3 valve by Edwards Lifesciences comprises bovine pericardial tissue with a balloon expandable cobalt-chromium frame and an inner and outer skirt. The outer skirt provides more durability and prevents PVL without excessive overexpanding [34]. The valve is designed to be delivered by transfemoral approach via 14 or 16 F sheath, depending on valve size, and is available in sizes 20 mm, 23 mm, 26 mm, and 29 mm. It is not approved for AR but has been used as an off-label indication in selected high-risk patients [35]. A recent observational study showed a 94.6% (n = 35) device success rate and 8.1% all-cause mortality at 30 days using Sapien 3 valve for pure AR with non-calcified leaflets. The valve migration occurred in 10.8% of cases (n = 4) (**Figures 1** and **2**) [36].

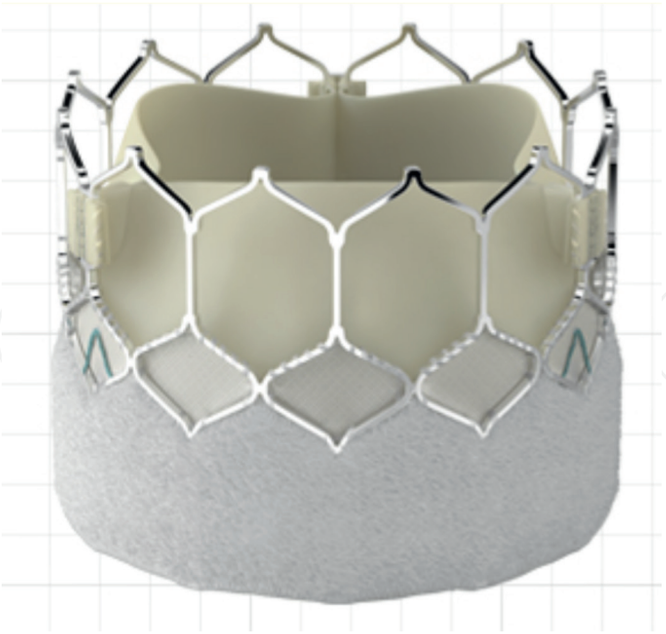

Figure 1.
Edwards Sapien 3 ultra valve comprises bovine pericardium tissue polyethylene terephthalate outer skirt (credit: Edwards Lifesciences).

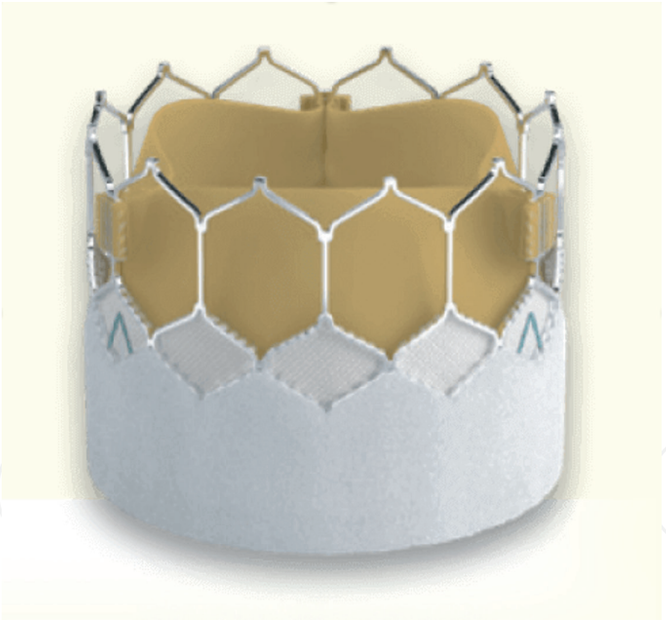

Figure 2.
Newer generation Edwards Sapien 3 RESILIA tissue valve with anti-calcification technology (credit: Edwards Lifesciences).

3.2 Medtronic Evolut

Medtronic Evolut valve consists of a porcine tissue pericardial valve with a self-expanding nitinol frame. The latest iteration is the Evolut FX system. It is delivered transfemorally via 14 F or 16 F inline sheath, and available sizes are 23 mm, 26 mm, 29 mm, and 34 mm. The delivery system is designed to fully retrieve the valve for

Figure 3.
Evolut FX 34 mm self-expanding nitinol frame with bovine tissue (credit: Medtronic).

repositioning. Federal Drug Administration (FDA) has not yet approved it for AR. However, it has been used off-label in patients with AR who are not eligible for surgery with acceptable results (**Figure 3**) [32, 37].

3.3 ACURATE valve Neo2

The ACURATE Neo2 valve by Boston Scientific is a porcine tissue pericardial valve with a self-expanding nitinol frame. It is available in 23 mm, 25 mm, and 27 mm sizes and is inserted transfemorally. In a multicenter European study, [38] the ACURATE Neo valve demonstrated good feasibility and early safety in 24 patients with native AR. The device success rate was 87.5%, with 4.1% all-cause mortality at 30 days. Two patients had moderate PVL and three required implantation of a second device for severe PVL and device displacement. The need for new PPM was 21.1% which is higher than the other commercially available TAVR valves. Acurate Neo2 is an investigational device restricted to experimental use in the United States (**Figure 4**) [39].

3.4 ACURATE TA

The ACCURATE TA device by Symetis, Switzerland, is composed of a self-expanding nitinol frame and is delivered trans-apically (**Figure 5**). It was explored as a treatment for severe native AR in patients with high surgical risk. A small single-center German case center series demonstrates the feasibility of transapical TAVR with the self-expandable ACURATE TA device in high-risk patients with 100%

Figure 4.
ACURATE Neo2 valve with self-expanding nitinol frame (credit: Boston Scientific).

procedural success and 0% all-cause mortality at 30 days. However, in the current era of transfemoral TAVR, the transapical approach may be considered too invasive [40].

3.5 Portico valve system

The Portico valve by Abbot comprises bovine pericardial tissue with a self-expandable nitinol frame. It comes in 23 mm, 25 mm, 27 mm, and 29 mm sizes (**Figure 6**). It provides a fully retrievable system.

3.6 J-valve Ausper system

J-valve Ausper system by Jiecheng Medical Technology has been certified by China FDA for AR. It consists of bovine pericardial leaflets with nitinol stent frame within three U-shaped anchor rings (**Figure 7**). The earlier device was designed to be delivered via transapical access. A large-scale single-center Chinese study for severe AS and severe AR showed acceptable safety with 3% and 3.7% mortality at 30 days and 6 months, respectively [41]. The newer device can be delivered by a transfemoral approach using an 18 F sheath. Available sizes are 21 mm, 23 mm, 25 mm, 27 mm, and 29 mm.

3.7 JenaValve system

The JenaValve system by JenaValve technology is designed for patients with severe AS, AR, and both [42]. The valve comprises porcine leaflets with a self-expanding framework for transfemoral delivery. Sizes in development include 65–92 mm (**Figure 8**). It provides the advantage of calcium-independent anchorage by grasping

Figure 5.
ACURATE TA valve with self-expanding nitinol frame (credit: Symetis).

Figure 6.
Portico valve with self-expandable nitinol frame (credit: Abbot).

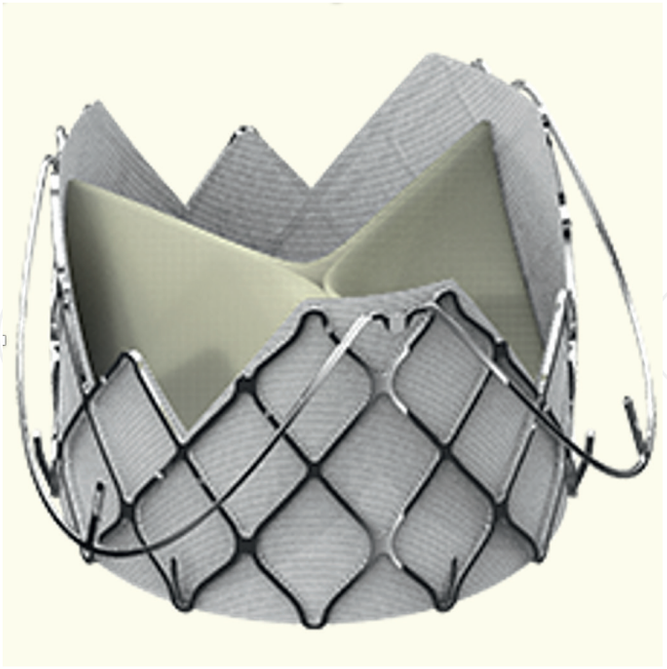

Figure 7.
J-valve Ausper with nitinol stent frame (credit: Jiecheng medical technology).

Figure 8.
Jena valve with self-expanding calcium-independent anchorage frame.

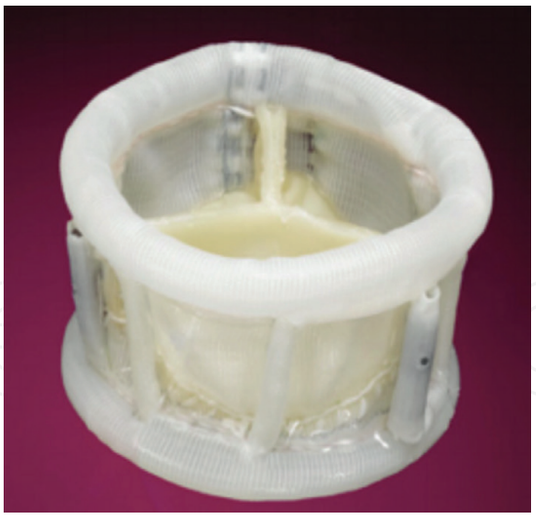

Figure 9.
Direct flow medical valve with two rings and polyester fabric skirt (credit: Direct flow medical).

the native leaflets and moving them towards the periphery, forming a natural seal (paper clip-like anchorage) [43]. The prosthetic leaflets are supra-annular. Large cells provide easy access for coronary engagement post-procedure. JenaValve is currently explored in ALIGN-AR pivotal, multicenter trial (NCT04415047) for severe AR in the USA. Key inclusion criteria include severe AR, high surgical risk, and NYHA class ≥ II. Exclusion factors are previous prosthetic valves, hemodynamic instability, endocarditis, unicuspid or bicuspid valve, and severe mitral regurgitation.

3.8 Direct flow medical

Direct Flow Medical (DFM) valve by Direct Flow Medical, California, comprises three bovine pericardial leaflets attached to a frame covered with polyester fabric (**Figure 9**). The frame comprises aortic (upper) and ventricular (lower) rings [44]. The size chart includes 25 mm, 27 mm, and 29 mm valves. It is delivered via an 18 F transfemoral approach and is commercially available in Europe. A small multicenter retrospective European study of 11 patients showed the feasibility of DFM valve for severe non-calcific native AR [45]. The device success rate was 100%, with one patient requiring SAVR after the downward dislocation of the prosthesis by TAVR. All patients had a reduction in NYHA class, and 30-day all-cause mortality was 9% (n = 1 due to pneumonia).

4. Procedural technique

Appropriate valve sizing is crucial in TAVR for pure AR to allow optimal valve anchorage and prevent complications such as annular rupture from oversizing or prosthetic valve embolization from under-sizing. Pre-procedural multimodality imaging (i.e., TTE, transesophageal echocardiogram (TEE), CT, and CMR) can help understand the size of the aortic annulus and aortic root [46, 47]. Fluoroscopy and TEE are important intra-operative tools for deploying the prosthetic valve at the appropriate position. Valve oversizing is frequently required for optimal apposition of the valve to dilated annulus and prevent PVL. Oversizing by 10–15% is recommended

Clinical trial	Valve	Trial description and location	Outcomes of interest	Inclusion criteria	Exclusion criteria
ALIGN-AR (NCT02732704)	JenaValve by JenaValve technology	Safety and effectiveness of TAVR by JenaValve for symptomatic severe AR (single arm) **Location**: USA, Germany, Netherlands	**Primary**: All-Cause Mortality at 30 days **Secondary**: Peri-Procedural AMI within 72 hr., stroke-free Survival at 30 days, bleeding & vascular complications	Severe AR, NYHA≥II, high surgical risk	History of AVR, hemodynamic instability, endocarditis, unicuspid or bicuspid valve, and severe MR.
SENSE-AR (NCT05737264)	Unspecified	Safety and effectiveness of TAVR for severe native AR with self-expandable valve implantation (single arm) **Location**: China	**Primary**: 12-month all-cause mortality, 12-month disabling stroke, 12-month heart failure hospitalization **Secondary**: Device success, new PPM, new LBBB, valve dysfunction, periprocedural complications (life-threatening bleeding, AKI, vascular complications, repeat procedure for valve-related dysfunction), NYHA class III or IV	Age > 60, severe AR	History of AVR, mod-severe MR, acute endocarditis
SEASON-AR (NCT04864145)	Unspecified	Safety and effectiveness of TAVR for severe native AR with self-expandable valve implantation (compared with medical therapy) **Location**: China	**Primary**: 12-month composite of all-cause death, disabling stroke, or heart failure rehospitalization **Secondary**: (all within 12 months) procedural complications (aortic, coronary, or vascular complications, new ppm), 6-minute walk distance, NYHA class, stroke, mortality, bleeding complications, prosthetic valve dysfunction, rehospitalization for valve-related symptoms or worsening congestive heart failure.	Symptomatic severe AR, asymptomatic AR with LVEF<55%, LVEDD>65 mm or LVESD>50 mm, AV mean pressure gradient <20 mmHg; annular perimeter ≤85 mm, LVOT: AV annulus perimeter 0.95–1.05, STS score ≥ 8.	Age < 60, ascending aorta >45 mm, multivessel CAD, life expectancy <1 year, LVEF <30%, AMI within 30 days.

AMI = acute myocardial infarction, AKI = acute kidney injury, AR = aortic regurgitation, AV = aortic valve, AVR = aortic valve replacement, CAD = coronary artery disease, LBBB = left bundle branch block, LVEF = left ventricular ejection fraction, LVEDD = left ventricular end-diastolic dimension, LVESD = left ventricular end-systolic dimension, LVOT = left ventricular outflow tract, MR = mitral regurgitation, NYHA = New York Heart Association, STS = Society of Thoracic Surgeons, TAVR = transcatheter aortic valve replacement.

Table 2.
Comparison of ongoing TAVR clinical trials.

with caution not to oversize beyond 20% [23–25]. The newer generation valve, JenaValve, is designed for pure AR grasps onto native leaflets and can be beneficial in the absence of leaflet calcium [43].

5. Future directions

The newer generation valves are undergoing clinical trials for TAVR for treating pure AR. As with any procedure, patient selection is key to procedural and clinical success. Ongoing prospective trials are listed in **Table 2**.

6. Conclusion

Symptomatic AR carries a high mortality if left untreated. Patients at high or prohibitive surgical risk may be candidates for off-label TAVR on a case-by-case basis, as determined by the heart team. The off-label use of TAVR for AR has shown promising results from registry data. The challenges of TAVR for AR include improper valvular seal, PVL, valve embolization, and malalignment or malposition of the bioprosthetic valve due to lack of calcification and enlarged aortic annuli. Valve oversizing can help overcome technical issues but carries the risk of annular rupture. The newer generation transcatheter valves designed especially for the treatment of pure native AR are undergoing clinical trials. Until the results of randomized clinical trials are available, careful selection of patients is paramount to procedural and clinical success.

Conflict of interest

Poonam Velagapudi received speaking fees from Medtronic, Abiomed, Opsens, and Shockwave and participated in advisory boards for Abiomed and Sanofi.

Muhammad Asim Shabbir and Nidhish Tiwari have nothing to disclose.

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