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Transcatheter Aortic Valve Replacement for Aortic Regurgitation --A Review

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ABBREVIATIONS AND ACRONYMS

TAVR = transcatheter aortic valve replacement
AR= aortic regurgitation
PNAR= pure native aortic regurgitation
LV= left ventricular
LVEF= left ventricular ejection fractions
LVD=left ventricle dysfunction
SAVR= surgical aortic valve replacement
AS= aortic stenosis
PVL= paravalvular leak
NGDs= new-generation devices
EGDs= early-generation devices
THV= transcatheter heart valve
PPA = post-procedural AR
STS= Society of Thoracic Surgeons Score
ESC= European Society of Cardiology
AKI= acute kidney injury
DM= diabetes mellitus
MDCT= multidetector computed tomography
NYHA = New York Heart Association
COPD = chronic obstructive pulmonary diseasePAD = peripheral arterial disease
PPI = permanent pacemakers implantation
MR = mitral regurgitation
CTA = computed tomography angiography
STS PROM = Society of Thoracic Surgeons predictive risk of mortality
SOV = the sinus of valsalva
STJ = sinotubular junction
FDA = Food and Drug Administration

Abstract

Transcatheter aortic valve replacement (TAVR) is now a widely adopted option for patients with severe symptomatic aortic stenosis from high to low surgical risk. However, aortic regurgitation (AR) is still an "off-label" indication for TAVR, especially for patients with mild or absent leaflet calcification or aortic annulus dimensions beyond the size of bioprosthesis, which causes increased risk of dislocation. With the advance of transcatheter heart valve device, the safety and efficacy of TAVR in treating patients with severe pure native AR has gained acceptance. This review examines the current evidence and clinical practice and presents the technological advancements in the device for AR.

Key words: transcatheter aortic valve implantation; transcatheter aortic valve replacement; aortic regurgitation; new generation devices

Introduction

Aortic regurgitation (AR) affects approximately 13% patients with sole native heart valvular disease and occurs in up to 2% of those over 70 years of age[1]. Severe pure native aortic regurgitation (PNAR) is distinguished by the eccentric myocardial hypertrophy and volume overloading associated with structural modifications of the left ventricular (LV) cavity and progressive LV dysfunction. The LV remodeling occurs because of cardiomyocyte enlargement stimulated by growth factors related to the Frank–Starling mechanism. When the compensatory ability is no longer present, the function of the left ventricle becomes permanently impaired and cannot be restored. [2 3]. Surgical aortic valve replacement (SAVR) is now recommended for those with chronic severe AR. However, a considerable proportion of the patients with symptom onset tend to seek treatment are always very late in the progression of the disease, and the operative risk is prohibitive. Research has demonstrated that a mere 20% of patients diagnosed with severe AR and left ventricular ejection fractions (LVEF) between 30% and 50% opted for SAVR, while a mere 5% of those with LVEF levels below 30% received valve replacement[1 4]. Patients who choosed conservative treatment are faced with a high risk of mortality, with a 20% annual mortality rate. As such, there is a pressing need to explore less invasive treatment options for these patients.

Since the first case of transcatheter aortic valve replacement (TAVR) was successfully performed in 2002 in patients with severe aortic stenosis (AS), the procedure has been performed over 800,000 in more than 65 countries until 2021, and covered the entire spectrum of surgical risk population in this decade[5-11]. Based on the efficacy and safety of TAVR, researchers started to pay attention on treating patients with PNAR percutaneously. The data on early-generation devices (EGDs) of TAVR for PNAR patients have been published in this decade. However, due to absence of valve calcification and the succeeding challenge in anchoring the bioprosthesis, the risks of valve embolization, malposition and paravalvular regurgitation were exacerbated post percutaneous intervention. Technological change has reinforced the performance of devices with retrievability, repositioning, and anchoring mechanisms. New-generation devices and dedicated device for AR are constantly emerging, and have been endorsed by Food and Drug Administration

(FDA) or clinical trials. This article reviews the current evidence of TAVR for PNAR and discusses the present technological development and future directions.

Device and Clinical Evidence of TAVR for PNAR

The first-in-human reports on the feasibility and safety of transcatheter heart valve (THV) in treating AR were related to the non-dedicated device "SAPIEN valve". This device was used in 2012 by D'Antoni G et al. to treat a case of PNAR with left ventricle assistant device implanted for a long-term [19]. Subsequently, Roy et al. retrospectively analyzed a case series of 43 patients with PNAR at high surgical risk (mean age 75.3 ± 8.8 years, mean Society of Thoracic Surgeons Score (STS) 10.2 ± 5.3%) who received the first-generation valve "CoreValve." The success rate was 97.7%, and 18.6% of the patients required a second valve owing to residual AR during the procedure. At 30-day, the rate of all-cause mortality was 9.3%, stroke was 4.7%, and the mortality at 1-year was 21.4%[12]. The summarized studies of TAVR for AR are presented in Table 1.

With the development of the valve device, several studies on patients with PNAR received TAVR have been reported since 2017. Yoon et al. reported a cohort study of 331 patientwith severe AR, in which 36% received EGDs and 64% received NGDs. The age of included patients was 74.4 ± 12.2 years and the STS score was 6.7 ± 6.7%. Compared with EGDs, NGDs showed significant higher rate of device success (24.4% vs 12.7%), lower rate of second THV (12.7% vs 24.4%) and lower rate of moderate to severe PPA (4.2% vs 18.8%)

Comorbidities of the procedure were significantly lower with NGDs, but no significant difference in 1-year all-cause mortality was noted between the two devices (28.8% vs. 20.6%; p = 0.13). Of note, NGDs were related to significant lower 1-year cardiovascular mortality of 9.6% compared with 23.6% of EGDs [17].

Yousef et al. systematically reviewed the results of 175 patients with PNAR who underwent TAVR. THVs included Direct Flow, Acurate TA, CoreValve, SAPIEN, JenaValve, J-Valve, and Lotus. Device success was achieved in 86.3% of the patients defined by the criteria of VARC-2 (Valve Academic Research Consortium-2)[20], with no procedural deaths, annular ruptures, or myocardial infarction. In 30-day follow-up, the rate of mortality, second THV implantation, permanent pacemaker implantation (PPI), and moderate and severe paravalvular leak (PVL) was 9.6%,11.3%,10.7%, and 17.7%, respectively. In patients who received NGDs, the outcomes were significantly improved compared with those who received EGDs in the rate of device success: (96.2% vs.78.4%), residual AR (0.0% vs. 8.3%), and second THV implantation THV (1.7% vs.23.4%)[18].

De Backer et al. conducted a study on 254 patients with PNAR who underwent TAVR at high surgical risk in 46 different sites. The mean age of the patients was 74 ± 12 years, and the mean STS score was 6.6 ± 6.2%. The patients underwent THV with either EGDs (43%) or NGDs (57%). The study utilized VARC-2 criteria to assess outcomes. The study found that NGDs had a significantly higher device success rate than EGDs (82% vs. 47%). Additionally, NGDs had significant lowerrates of device misplacement (9% vs. 33%) and PPA (≥moderate) (4% vs. 31%) than EGDs. Furthermore, NGDs showed significant higher clinical effectiveness at 30 days (72% vs. 56%). Both device undersizing and oversizing were found to be correlated with a significantly higher risk of device malpositioning.[21].

Anwaruddin et al. recruited 230 patients with primary severe native AR at high surgical risk who received CoreValve (81) and Evolut R (149). The rate of device success was 81.7% of total patients. Of note, Evolute R showed a significant higher rate of device success (86.9%) than CoreValve (72.2%). At 30 days, the rate of all-cause mortality was 13.3%, moderate AR was 9.1%, and severe AR was 1.4%. Residual moderate/severe AR was significantly reduced in Evolut R compared (19.1%) with that in CoreValve (6.3%). Multi-variable analysis showed several risk factors including the amount of implanted valve, albumin < 3.3 mg/dL), and LVEF, were correlated with mortality at 30 days[22].

Takagi et al. analyzed 911 patients undergoing TAVR for AR from 11 eligible studies in 2020. The study reported a total device success rate of 80.4%, with NGDs having a higher success rate of 90.2% compared to EGDs at 67.2%. The study also found that moderate to severe PVL was shown in 7.4% of patients, with NGDs having a lower rate of 3.4% compared to EGDs at 17.3%. Additionally, the study reported a 30-day all-cause mortality rate of 9.5%, with NGDs having a lower rate of 6.1% compared to EGDs at 14.7%. Mid-term (4 months-1 year) all-cause mortality was reported at 18.8%, with NGDs having a lower rate of 11.8% compared to EGDs at 32.2%. Furthermore, the study found that life-threatening or major bleeding complications occurred in 5.7% of patients, with NGDs having a lower rate of 3.5% compared to EGDs at 12.4%. Major vascular complications were reported at 3.9%, with NGDs having a lower rate of 3.0% compared to EGDs at 6.2%. All results indicated significant better outcomes for NGDs compared to EGDs. Multivariable analysis identified >8% STS, major vascular complications, and moderate or higher PPA as independent risk factors associated with a higher rate of 30-day mortality. Additionally, moderate or higher baseline MR, LVEF less than 45%, STS over 8%, stage 2 or over AKI, and moderate PPA were identified as independent risk factors for mortality at 1 year.[14].

In 2022, Yin et al. studied 25 consecutive patients with PNAR who received new-generation THVs compared with early-generation self-expanding CoreValve. The authors observed significant higher success rate for NGDs compared with EGDs (100% vs. 33%) and lower rate of second valve implantation (0% vs. 53%). Patients who received NGDs had better event-free survival during a median follow-up of 14 months than those receiving EGD, although the differences were not statistically significant (log-rank test, $p = 0.137$)[16]. Most recently, Schneeberger et al. reported the cases of nine patients with PNAR treated with self-expandable Acurate Neo and Neo2. The device success rate was 100%, and early safety was 77.7% owing to two cases of acute kidney injury (22.2%). At 30 days, mortality was 0%. PVL was traced in 77.7% patients (), and mild in 22.2%. No PPI was required[23]. Thus, the new device offers advantages in TAVR for PNAR.

In 2023, Koch et al. enrolled 125 patients, of which 91 received SAVR and 34 received TAVR. Patients received TAVR had a significant higher STS PROM score than SAVR group (3.96% vs 1.25%). However, the in-hospital mortality and 30-day outcomes (including mortality, stroke, myocardial infarction, residual AR, or repeat valve intervention) did not show the differences between the two groups. Meanwhile, the results demonstrated a significant higher rate of complete heart block requiring PPI in TAVR group (20.9 % vs. 0 %)[24].

The risk factors related to clinical outcomes

Takagi et al[14] reported several factors including age, COPD, PAD, LVEF, sex, hypertension, atrial fibrillation, previous stroke, and pulmonary hypertension, negatively related to mortality at 30 days for AR. Diabetes mellitus (DM) and concomitant moderate or higher MR was correlated with poor results in AR patients treated with TAVR.

Besides, several studies demonstrated that the number of valves implanted, albumin < 3.3 mg/dL, longer intensive care unit stays, <20 kg/m^2 body mass index, >8% STS-PROM, major vascular complication, and moderate or higher PPA, low LVEF at baseline were related to higher mortality at 30 days, and that moderate or higher baseline MR, LVEF less than 45%, STS-PROM over 8%, stage 2 or over AKI, and moderate or severe PPA were related to an increased1-year mortality[16 17 21 22 25]. Moreover, new left bundle branch block and moderate to severe AR at discharge were positively associated with NYHA functional class III or IV[25]. Larger annulus, and dilated aorta were associated with less frequent device success[17].

Device embolization/migration are the main caveats to off-label use of TAVR devices designed for AR patients. De Backer et al[21] showed that relative device undersizing and oversizing was significantly related to device embolization/migration and worse clinical outcomes as compared to TAVR with neutral THV sizing.

Guidelines and Clinical Management

Based on these trials, 2021 ESC guideline suggested that TAVR may be considered in experienced centers for selected patients with AR who are ineligible for SAVR. In clinical practice, the cardiac team needs to carefully choose patients with valvular calcification and annular size appropriate for a transcatheter approach (Figure 1). However, according to the current Guidelines, SAVR remains the primary treatment option for symptomatic patients with significant AR who have reduced left ventricular systolic function or severe LV dilatation[26 27].

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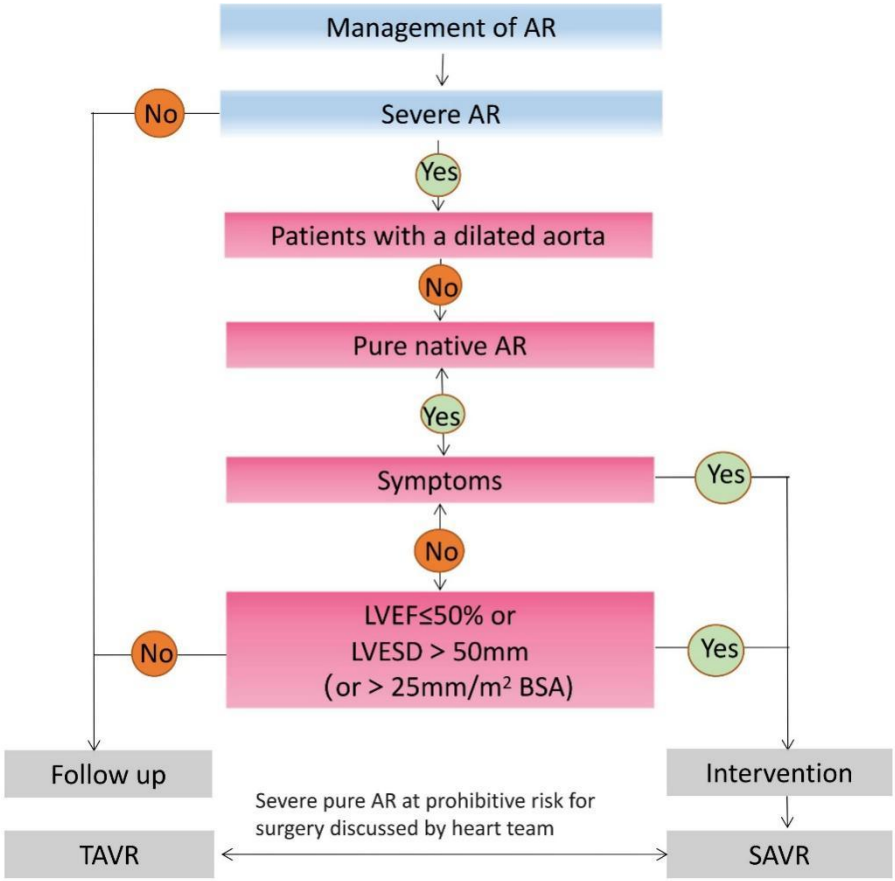

Figure 1. Treatment of aortic regurgitation. BSA = body surface area; LVESD = left ventricle end-systolic diameter;

Tips and tricks to perform TAVR in PNAR

The key points of tips and tricks to perform TAVR in PNAR as follows:

(1) Careful pre-procedure MDCT assessment to choose THV type, radiography position, and approach vessels, etc.

(2) It is essential to ensure that the position of THV is located at the right depth to avoid THV malposition when the THV is released until it can start working. If the position of THV does not fit properly, it could be modulated through the recycling delivery system.

(3) The THV release should follow the principle of "first slow and then fast": before the THV is not properly anchored, it's crucial to carefully control the speed of THV releasing and the frequency of ventricular pacing; From working position to complete decoupling of THV, it should be given appropriate assistance of ventricular pacing, and controlling of blood pressure, to help stabilize the THV implantation. After the THV is fully released and the THV adaptive position adjustment is manually controlled, the TIP part can be carefully exited.

(4) Several limiting factors need to be considered before the procedure: First, about half of AR is due to aortic disease rather than valvular dysfunction according to the etiology. Patients with diameters of annulus greater than 30mm are unsuitable for the implantation of THV because of the coexistence of severe AR with pathological dilatation of the aortic root and ascending aorta. In addition, adequate and timely salvage strategies should be available for complications such as THV displacement or annulus rupture.

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Clinical Case

A 74-year-old male with previous coronary artery disease and chronic obstructive pulmonary disease was admitted to our hospital due to dyspnea and syncope, classified him as NYHA functional class III. Transthoracic echocardiograms revealed a PNAR with an central regurgitant jet, regurgitant volume of 55 mL/beat, regurgitation fraction of 50%, end-diastolic velocity of 20 cm/s, and diastolic flow reversal in the descending aorta. Additionally, he had LVD with a LVEF of 45%.

CTA showed a dilated aortic annulus (aortic annulus area of 613.2 mm^2 and aortic annulus perimeter of 89.6 mm) with no calcification of the annulus or leaflets (Figure 2). The ascending aorta diameter was measured at 34.2 mm. The anatomy of the Sinus of Valsalva (SOV), Sinotubular Junction (STJ), coronary arteries, and iliofemoral system were all deemed suitable for TAVR.

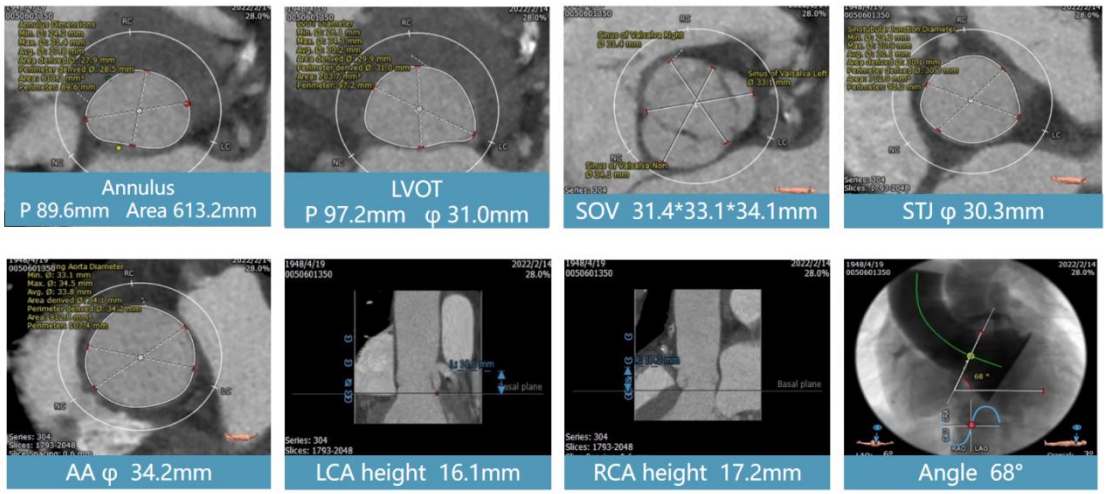

Figure 2. A preoperative CT evaluation showed the dilated annulus (area 613.2 mm2, perimeter 89.6mm) and normal ascending aorta dimensions.

Following a thorough discussion among the heart team and taking into account the patient's high risk for cardiac surgery (EuroSCORE II 21.15%, STS score 10.56%), we opted to proceed with a TAVR procedure using the self-expanding bioprosthesis (Vita Flow 30mm) that was accessible at our center.

The procedure was performed under general anesthesia. A 5F pigtail catheters were used to perform aortogram (a). The THV was carefully proceeded until the aortic annulus, another aortogram was performed to ensure THV position(b). With the help of pigtail guidance, the deployment was carried out under rapid ventricular pacing (180 beats/min) and in an extremely slow and careful technic, without recapture, in a single attempt when the THV was released to 2/3, aortogram was performed to ensure position(c). Then the THV was final released, and final contrast injection indicated proper prosthesis expansion, 3–5 mm depth of implantation, no central or paravalvular leak, and coronary arteries with satisfactory flow (d). No rhythm disturbances presented. (Figure 3)

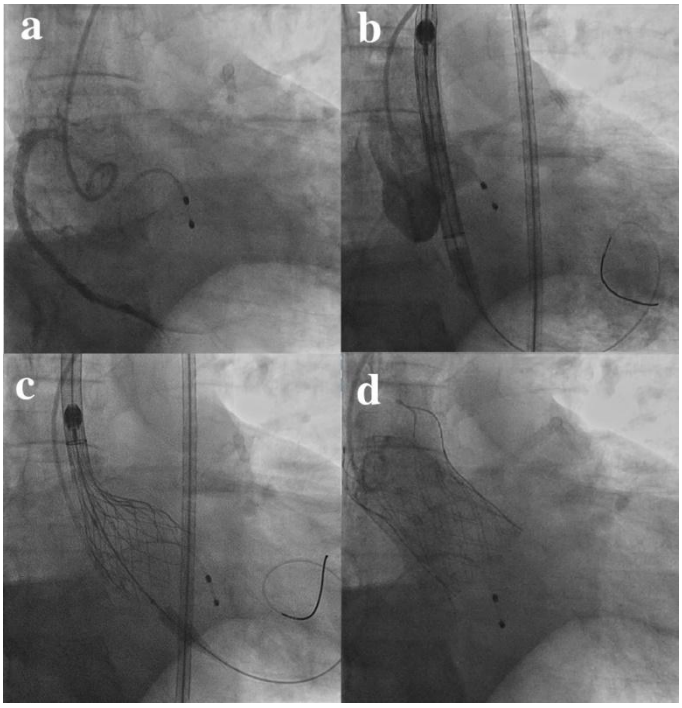

Figure 3. procedural steps of TAVR: Firstly, pigtail catheter is positioned in the aortic Sinuses of Valsalva (a); Then, the transcatheter heart valve is initially deployed in position (b); Next, TAVR is slowly deployed under rapid ventricular pacing (c); Finally, the nose cone is removed with care, and the final deployment position is achieved(d).

After the surgery, the patient's recovery was smooth and without complications. They were discharged home with no symptoms (NYHA functional class II). At the 30-day follow-up, an echocardiogram showed a well-functioning bioprosthesis with a mean aortic valve gradient of 9 mmHg and no residual aortic regurgitation.

Dedicated Device for AR

TAVR can be challenging due to aortic annulus and root dilation, as well as the absence of leaflet calcification, which can make device positioning and deployment difficult. Valve migration to the aorta or deep into the LV after implantation is associated with poor outcomes. Therefore, to reduce the risk of valve migration, valve oversizing has been proposed. Published studies recommend an oversizing of 15%–20% when selecting the THV size but not beyond 20% to avoid the risk of annular rupture and conduction system abnormalities[25,26].

Self-expandable THVs, such as the widely used CoreValve, have been the preferred non-specific devices for TAVR in cases of PNAR. These THVs can be retrieved and relocated, which can increase predictability during the procedure. [28 29]. Till now, several devices have been advanced for pure AR, including JenaValve, J-valve, Acurate neo-2, Edwards HELIO, and Medtronic Engager.

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The JenaValve™ was the first self-expanding device to receive the CE mark for NPAR, as shown in Figure 4. This valve is transapical and features three integrated locators, which enables precise placement in the native cusps and secure attachment of the THV onto the native leaflets.[30] [31]. In 2017, a new generation transfemoral system was successfully used to treat PANR in a first case report in human.[32]. The JUPITER registry, which evaluated the long-term outcomes of JenaValve, reported a procedural success rate of 96.7%, with no incidence of valve malpositioning and moderate to severe PPA. In a single-center experience with transfemoral access reported in 2020, 11 patients underwent TAVR with the JenaValve, and the device was implanted successfully in all cases[28]. In the 30-day follow-up, there were no instances of mortality or stroke, and all patients showed improvement in heart failure symptoms. The rate of PPI is 36.4%. In the 6-month follow-up, mild PVL was present in only one case, and trace or no PVL was observed in the remaining patients.

The Trilogy Heart Valve System will be evaluated for safety and efficacy in high-risk patients diagnosed with severe AR through the ALIGN-AR trial, which is a single-arm, prospective study. The study's objective is to generate data that will support a future Premarket Approval (PMA) submission to the U.S. FDA. In patients with symptomatic AR at high surgical risk, transfemoral JenaValve implantation demonstrated a 95.7% success rate (68 out of 71 patients) with mortality and stroke rates of 2.8% (2 out of 71 patients) and 4.2% (3 out of 71 patients), respectively, in the 30-day follow-up[29]. The rate of PPI was 21.1% (15 out of 71 patients), and the PVL rates were none/trace in 82% (58 out of 71 patients), mild in 14% (10 out of 71 patients), and mild-moderate in 4% (3 out of 71 patients) of patients.

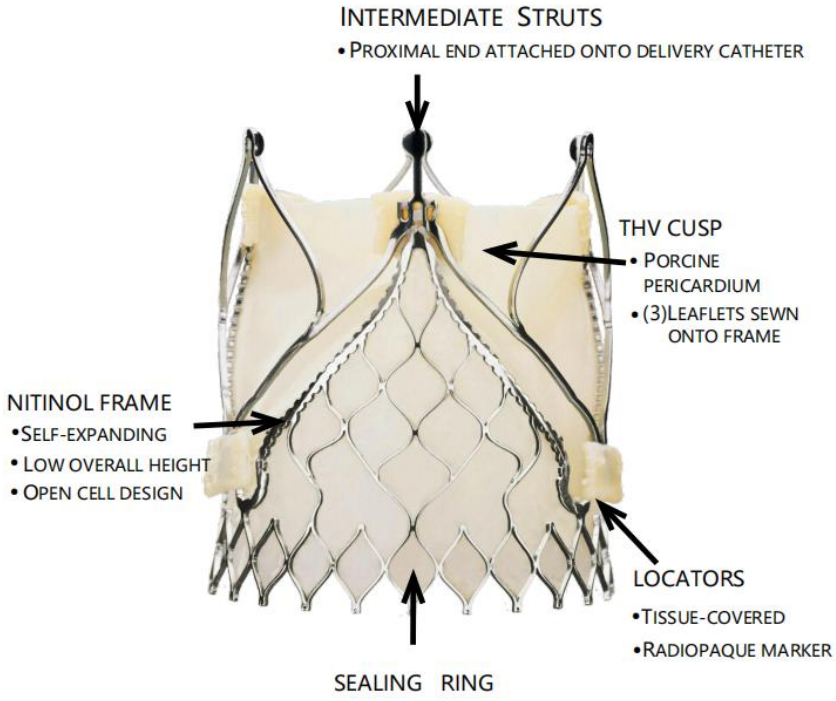

Figure 4. JenaValve™

The J-Valve™ is another PNAR-dedicated second-generation device that has a unique system composed of three U-shaped graspers. These facilitate intuitive self-positioning implantation and provide axial and radial fixation by embracing the native valve leaflets (Figure 5). A successful first-in-human implantation was reported in 2015. In a study by Liu H et al., [34] the J-Valve was implanted through transapical access in 43 patients with severe PNAR who were at high surgical risk. The implantation was successful in 97.7% of cases (42/43), and the 1-year clinical outcomes included mortality (4.7%), disabling stroke (2.3%), and PPI (4.7%). After a 1-year follow-up, the rate of none/trace postprocedural PVL was 76.9%, mild PVL was 20.5%, and the mean transvalvular gradient was 10.4 ± 4.5 mmHg. In a study by Li F et al., the 4-year outcomes of 4 patients with AR treated with the transapical J-valve were reported. The mean gradient remained <10 mmHg and did not increase significantly, and no residual valvular AR or PVL were detected. [35]. In 2019, the first-in-human implantation of the transfemoral device was successfully performed[36], growing evidence supported the safety and efficacy of dedicated AR devices through transfemoral access.

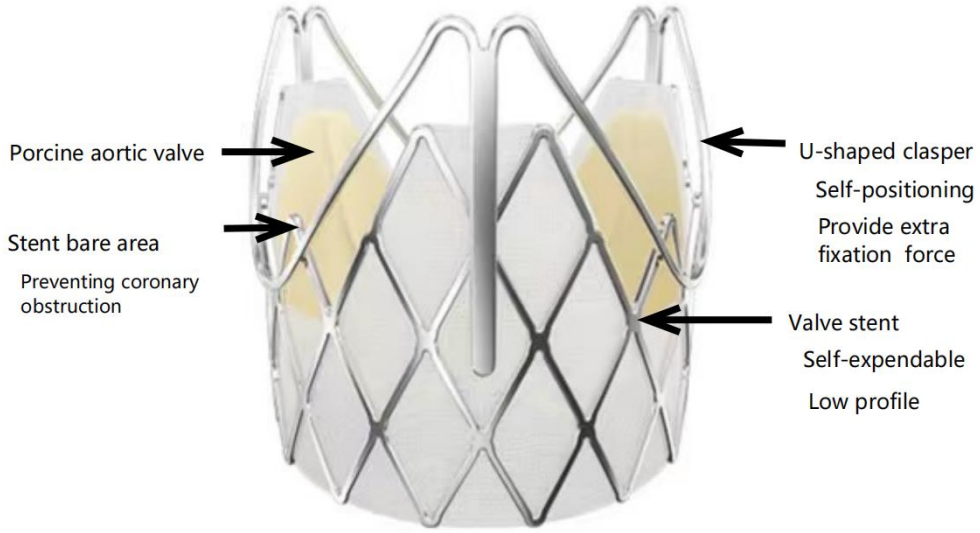

Figure 5. J-Valve™

Future Directions

Patients with AR tend to have poorer clinical conditions than those with AS owing to irreversible LV dilatation and dysfunction. Although SAVR remains the standard intervention, TAVR has emerged as an alternative option for patients at high or inoperable risk. Although anatomical and technical difficulties faced during the procedure make TAVR for NPAR an “off-label” treatment, experienced cardiac teams and dedicated devices have aided in overcoming these challenges. In recent clinical trials, the NGDs and dedicated devices have achieved better results than EGDs, with lower rates of valve malpositioning and second valve implantation and lower incidence of moderate to severe PPA.

Given the anatomy of aorta is also critical for TAVR procedure, AURORA study was designed to figure out the morphological characteristics of aortic root to enforce the anchoring strength of THV[37]. Meanwhile, multiple trails worldwide are going on to explore the safety and efficacy of device in TAVR procedure, like SEASON-AR (NCT 04864145) and SENSE-AR trial (NCT 05737264), RIVAL - AR EFS trial, and the PANTHEON trial (NCT 05319171). We look forward to more studies that will benefit for AR patients' long-term outcomes, to fill in the gaps in interventional treatment in this field.

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Table 1. TAVR for PNAR: Characteristics of the Included Studies

Author（year）	Country	Study design	No.of patients	Age (year)	Male	STS score	Logistic Euroscore	Reason Surgery declined	Valve
Roy et al (2013)[12]	Worldwide/ multicenter	Retrospective and prospective	42	75.3±8.8	20	10.2±5.3	NR	High risk	CoreV
Seiffert et la (2013)[38]	Germany	Retrospective	5	66.6±7	4	NR	NR	Inoperable	JenaV
Seiffert et al (2014)[30]	Germany/ multicenter	Retrospective	31	73.8±9.1	20	5.4±3.6	23.6±14.5	Inoperable	JenaV
Testa et al (2014)[31]	Italy/ multicenter	Prospective	26	73±10	16	13.1±2	24±8	Inoperable	CoreV
Wendt et al (2014)[32]	Germany	Retrospective	8	72.5±8.4	5	7.9±3.4	34.0±7.9	High risk	Acurat
Schofer et al (2015)[39]	Europe/ multicenter	Retrospective	11	74.7±12.9	4	8.84±8.90	19.9±7.1	High risk	Direct
Wei et al (2015)[32]	China	Prospective	5	74.8±8.9	3	NR	29.59	High risk	J-Va
Yoon et al (2017)[17]	USA/ Europe/Asia/ multicenter	Retrospective and prospective	331	74.4 ±12.2	159	6.7±6.7	NR	Inoperable	CoreValve R, Portico, Sapi XT/Sap

									JenaValve Direct J-Va
Sawaya et al (2017)[25]	Germany/ multicenter	Retrospectivel and prospective	78	74±10	46	6.7±4.8	20.4±11.8	Inoperable	CoreValve， R，SAPI /SAPIEN 3 Direct
De Backer, et al (2018)[21]	Europe/ multicenter	Retrospective	254	74 ± 12	134	6.6 ± 6.2	NR	High risk	JenaValve, CoreV Evolu Porti Acur Lotu Direct Sapien XT/
Liu et al (2018)[34]	China/ multicenter	Prospective	43	73.9±5.7	30	NR	25.5±5.3	High risk	J-Va
Anwaruddin et al (2019)[22]	USA/ multicenter	Retrospective	230	68.7± 15.1	134	8.6±9.1	NR	NR	CoreValve R
Li et al (2020)[35]	China/ Single center	Prospective	4	76.0± 6.9	3	NR	31.7±3.6	High risk	J-Va
Gogia et al (2020)[28]	USA/ Single center	Prospective	11	77.6	NR	NR	NR	High risk	Jena V
Vahl et al (2021)[29]	USA/ multicenter	Prospective	71	74	NR	NR	NR	High risk	Jena V
Yin et al	China/	Retrospective	25	72.0±17.2	18	8±4.5	NR	Intermediate	CoreValve

(2022)[16]	2 centers							to high risk	R, J-valve XT
Schneeberger et al (2022)[23]	Germany/ Single center	Retrospective	9	74.4±7.1	8	6.2 ± 3	NR	High risk	Acurate ne
Koch et al (2023)[24]	USA/ Single center	Retrospective	34	68.8± 12.2	25	3.96	NR	High risk	CoreValve R, Evol

Table 2: The risk factors related to clinical outcomes

Outcomes	Risk Factors
30-day mortality	the number of valves implanted, albumin < 3.3 mg/dL, longer intensive care unit stays Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM), major vascular post-procedural AR, low LVEF at baseline
1-year mortality	moderate or higher baseline MR, LVEF≤ 45%, STS-PROM>8%, stage 2 or higher acute post-procedural AR
NYHA functional class III or IV	left bundle branch block and moderate to severe AR at discharge
Device success	Larger annulus, and dilated aorta