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FOCUS ON AORTIC REGURGITATION AND TRANSCATHETER AORTIC VALVE REPLACEMENT

NEW RESEARCH PAPERS: STRUCTURAL

Transcatheter Treatment of Native Aortic Valve Regurgitation

The North American Experience With a Novel Device

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ABSTRACT

BACKGROUND Transcatheter treatment of patients with native aortic valve regurgitation (AR) has been limited by anatomical factors. No transcatheter device has received U.S. regulatory approval for the treatment of patients with AR.

OBJECTIVES The aim of this study was to describe the compassionate-use experience in North America with a dedicated transcatheter device (J-Valve).

METHODS A multicenter, observational registry was assembled of compassionate-use cases of J-Valve implantation for the treatment of patients with severe symptomatic AR and elevated surgical risk in North America. The J-Valve consists of a self-expanding Nitinol frame, bovine pericardial leaflets, and a valve-locating feature. The available size matrix (5 sizes) can treat a wide range of anatomies (minimum and maximum annular perimeters 57-104 mm).

RESULTS A total of 27 patients (median age 81 years [IQR: 72-85 years], 81% at high surgical risk, 96% in NYHA functional class III or IV) with native valve AR were treated with the J-Valve during the study period (2018-2022). Procedural success (J-Valve delivered to the intended location without the need for surgical conversion or a second transcatheter heart valve) was 81% (22 of 27 cases) in the overall experience and 100% in the last 15 cases. Two cases required conversion to surgery in the early experience, leading to changes in valve design. At 30 days, there was 1 death, 1 stroke, and 3 new pacemakers (13%), and 88% of patients were in NYHA functional class I or II. No patient had residual AR of moderate or greater degree at 30 days.

CONCLUSIONS The J-Valve appears to provide a safe and effective alternative to surgery in patients with pure AR and elevated or prohibitive surgical risk. (J Am Coll Cardiol Intv 2023;16:1953–1960) © 2023 by the American College of Cardiology Foundation.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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ABBREVIATIONS AND ACRONYMS

AR = aortic regurgitation

AS = aortic stenosis

LV = left ventricle/ventricular

SAVR = surgical aortic valve replacement

TA = transapical

TAVR = transcatheter aortic valve replacement

THV = transcatheter heart valve

Chronic aortic regurgitation (AR) invariably leads to left ventricular (LV) volume overload, chamber dilatation, and LV dysfunction. Surgical aortic valve replacement (SAVR) is recommended for patients with severe AR who exhibit heart failure symptoms or develop LV dysfunction or chamber enlargement, with specific thresholds for intervention defined by echocardiography and, more recently, cardiac magnetic resonance imaging.[1-6] Severe AR may account for 20% to 30% of isolated SAVR and may present concurrently in 20% to 30% of patients with aortic valve stenosis (AS).[7]

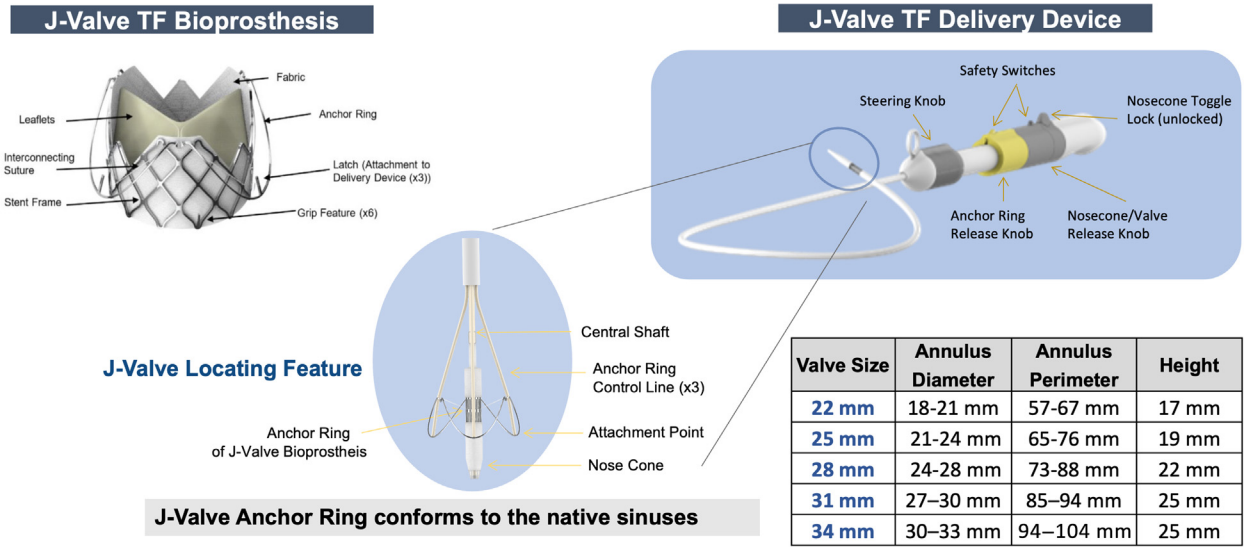
Transcatheter treatment of patients with AR has been limited by anatomical factors, including dilatation of the aortic root and annulus, large annular dimensions, and lack of sufficient leaflet calcification to securely anchor currently available transcatheter heart valves (THVs). Indeed, the experience with second-generation, commercially available THV devices designed for the treatment of AS has been characterized by high rates of complications and suboptimal results despite careful patient selection.[8] The fact that no current THV has received U.S. regulatory approval for the treatment of patients with AR has prompted the development of novel THV devices, currently under clinical trial investigation, that are designed to address the anatomical challenges of AR.[9,10] Importantly, enrollment into investigational device exemption trials may be limited by exclusionary comorbid or anatomical considerations which can make extrapolation of trial results to a broader, more inclusive population challenging.

In this context, we report the results from the North American compassionate-use study of the J-Valve THV (JC Medical), which is specifically designed for the treatment of patients with AR, in patients with symptomatic, severe native AR.

METHODS

STUDY DESIGN AND PATIENTS. The compassionate-use study is an investigator-initiated, multicenter, North American observational registry designed to capture the early clinical experience with J-Valve for the treatment of patients with symptomatic, severe, pure AR from May 2018 to October 2022. A total of 5 sites were included in the present analysis: 1) The Christ Hospital (Cincinnati, Ohio); 2) St. Paul's Hospital (Vancouver, British Columbia, Canada); 3) Houston Methodist (Houston, Texas); 4) Henry Ford Hospital (Detroit, Michigan); and 5) St. Michael's Hospital (Toronto, Ontario, Canada). The protocol was approved by each local Institutional Review

FIGURE 1 Overview of J-Valve TF System and Size Matrix



Valve Size	Annulus Diameter	Annulus Perimeter	Height
22 mm	18-21 mm	57-67 mm	17 mm
25 mm	21-24 mm	65-76 mm	19 mm
28 mm	24-28 mm	73-88 mm	22 mm
31 mm	27–30 mm	85–94 mm	25 mm
34 mm	30–33 mm	94–104 mm	25 mm

The transfemoral (TF) device used in the present series is a steerable, flexible 18-F catheter with a broader 5-size (22-34 mm) matrix that can be applied to aortic valve perimeters ranging from 94 to 104 mm.

Board or ethics committee, and all patients provided specific informed consent for treatment.

Patients were included if they had severe, symptomatic AR involving a native aortic valve, were deemed to be at high risk or inoperable for SAVR by the heart team, and received regulatory approval consistent with expanded access criteria.[11] Patients who were excluded from participating in the JenaValve ALIGN-AR Pivotal Trial (NCT04415047) who satisfied the aforementioned criteria were also offered compassionate-use study enrollment. Patients with bioprosthetic aortic valve dysfunction (valve-in-valve) were excluded. Patients with bicuspid aortic valves were not excluded. Standardized data collection forms, modeled after the Society of Thoracic Surgeons/American College of Cardiology TVT (Transcatheter Valve Therapy) Registry, and a secure web-based application (Research Electronic Data Capture) were used for data capture.

DEVICE DESCRIPTION. The J-Valve consists of: 1) a self-expanding, low-profile Nitinol frame and bovine pericardial leaflets; and 2) a valve-locating feature consisting of 3 Nitinol anchor rings designed to conform to the native aortic valve sinuses. The delivery system is steerable and flexible and was designed for transfemoral access. The available size matrix (5 sizes) can treat a wide range of anatomies (minimum and maximum annular diameters 18-33 mm, minimum and maximum annular perimeters 57-104 mm) (Figure 1).

STATISTICAL ANALYSIS. Discrete variables are expressed as count (percentage) and continuous variables as mean ± SD if distributed symmetrically or as median (IQR) if skewed. The data coordinating center at the Carl and Edyth Lindner Center for Research and Education at The Christ Hospital had full access to the dataset and performed the statistical analysis.

RESULTS

The baseline characteristics of the study cohort are presented in Table 1. A total of 27 patients with native valve AR were treated with J-Valve during the study period. Consistent with the compassionate-use intent of the protocol, the study cohort was composed of elderly patients (median age 81 years; range: 72-85 years) at either high (81%) or extreme or prohibitive (8%) surgical risk (median Society of Thoracic Surgeons score 4.3; range: 2.6-5.3). Most patients exhibited advanced heart failure symptoms at presentation (96% in NYHA functional class III or IV).

TABLE 1 Baseline Demographic and Clinical Characteristics (N = 27)

Age, y	81 (72-85)
Male	16 (59)
Caucasian race	19 (86)
Atrial fibrillation	
Paroxysmal	3 (11)
Permanent	9 (33)
Carotid artery stenosis	4 (15)
Prior stroke	4 (15)
COPD	7 (26)
Diabetes	5 (19)
Prior endocarditis	3 (11)
Heart failure	
Within 2 wk of procedure	11 (41)
Within past year	15 (56)
NYHA functional class	
II	1 (4)
III or IV	26 (96)
Hypertension	24 (89)
Prior myocardial infarction	4 (15)
Prior PCI	13 (48)
Prior CABG	4 (15)
Peripheral artery disease	4 (15)
Porcelain aorta	0 (0)
Prior TIA	1 (4)
Immunocompromised	2 (7)
Tobacco use	
Current	2 (7)
Remote	12 (44)
Prior pacemaker	3 (11)
Number of previous open heart surgical procedures	
1	7 (27)
2	1 (4)
Previous AV repair	4 (15)
Mitral valve procedure	
Repair	3 (11)
Replacement	3 (11)

Values are median (IQR) or n (%).

AV = aortic valve; CABG = coronary artery bypass graft; COPD = chronic obstructive pulmonary disease; PCI = percutaneous coronary intervention; TIA = transient ischemic attack.

The majority of patients were on medical therapy for heart failure prior to the procedure, including 74% on angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or angiotensin receptor-neprilysin inhibitors; 69% on beta-blockers; 77% on loop diuretic agents; and 15% on aldosterone antagonists.

Baseline echocardiographic, computed tomographic angiographic, and hemodynamic data are presented in Table 2. The most common etiology of

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TABLE 2 Baseline Imaging and Hemodynamic Assessment

Computed tomographic angiography (n = 26)	
Average AV annular diameter, mm	25.6 ± 3.0
Minimum AV annular diameter, mm	22.2 ± 2.9
Maximum AV annular diameter, mm	28.5 ± 4.0
AV annular area, mm^2	501 ± 122
AV annular perimeter, mm	81 ± 10.5
Perimeter ≥ 85 mm	10 (38)
AV disease etiology	
Degenerative	21 (78)
Endocarditis	2 (7)
Congenital	1 (4)
Other	3 (11)
AV morphology	
Bicuspid	1 (4)
Tricuspid	24 (89)
Other	2 (8)
AV calcification severity	
None	14 (52)
Minimal	8 (30)
Moderate	3 (11)
Severe	2 (7)
Echocardiography (n = 27)	
LVEF, %	54 (37-60)
LVESD, cm	4.0 ± 1.0
LVEDD, cm	5.5 ± 0.9
LVESD/BSA, cm/m^2	2.19 ± 0.64
Aortic regurgitation severity	
Severe	22 (81)
Moderate to severe	5 (19)
Invasive hemodynamics (n = 12)	
Cardiac output, L/min	5.4 ± 1.6
Pulmonary capillary wedge pressure, mm Hg	16.3 ± 6.5
Mean pulmonary artery pressure, mm Hg	29.4 ± 9.9
Mean right atrial pressure, mm Hg	7.3 ± 3.7

Values are mean ± SD, n (%), or median (IQR).
AV = aortic valve; BSA = body surface area; LVEDD = left ventricular end-diastolic dimension; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic dimension.

TABLE 3 Procedural Characteristics

Procedure status	
Elective	26 (96)
Urgent	1 (4)
Procedure location	
Hybrid OR	12 (44)
Hybrid catheterization laboratory	13 (48)
Catheterization laboratory	2 (7)
Anesthesia type	
Moderate sedation	4 (15)
General anesthesia	23 (85)
Procedural success	22 (81)
Case successfully treated with 1 or more THVs without need to convert to surgery	25 (93)
Converted to open heart surgery	2 (7)
Access site	
TF	21 (78)
Carotid	1 (4)
Subclavian	4 (15)
Transcaval	1 (4)
Sheath size, F	
16	3 (13)
18	9 (38)
20	9 (38)
22	3 (13)
Fluoroscopy time, min	28.8 (21.7-42.6)
Contrast volume, mL	92.0 ± 36.0

Values are n (%), median (IQR), or mean ± SD.
OR = operating room; TF = transfemoral; THV = transcatheter heart valve.

AR was degenerative (78%), and the most common valve morphology was tricuspid (89%). The median LV ejection fraction was 54% (range: 37%-60%), with average LV end-systolic and end-diastolic dimensions of 4 ± 1 and 5 ± 1 cm, respectively. Preprocedural computed tomographic angiographic evaluation revealed an average annular area of 501 ± 122 mm^2 and perimeter of 81 ± 10 mm, with 10 patients (38%) having perimeters >85 mm. Most patients had no or mild annular calcification.

Procedural characteristics are presented in Table 3. Most procedures were elective (96%), performed under general anesthesia (85%) and via transfemoral access (75%). Representative fluoroscopic and echocardiographic intraprocedural images are presented in Videos 1 to 3.

Procedural success (J-Valve delivered to the intended location without the need for surgical conversion or a second THV) was 81% (22 of 27 cases). Two cases required conversion to surgery in the early experience (2018-2019). In 1 case, the nose cone of the first-generation J-Valve separated from the device during retrieval, which led to a redesign of the attachment points and bonding methods. In the second case, the J-Valve embolized to the ventricle shortly after deployment. During surgery, 2 of the 3 native aortic valve leaflets were found to be prolapsing into the LV, which resulted in inadequate anchoring of the device. This case led to exclusion of subsequent valves with prolapsing leaflets from enrollment. In 3 additional cases, a second THV was needed to stabilize the J-Valve because of premature deployment in the sinuses above the annular plane. Two of these 3 cases were treated with balloon-expandable valves and the third with an additional J-Valve after trapping the first valve in the descending aorta with a Palmaz stent. The last 15 consecutive cases in this compassionate-use experience were successful without surgical conversion or need for a second THV device.

IN-HOSPITAL OUTCOMES. There was 1 in-hospital death related to multiorgan failure and sepsis after a complicated transcatheter aortic valve replacement (TAVR) procedure (device embolization), 1 stroke (nondisabling) in a patient undergoing transcarotid access, and 5 access-site complications. Among surviving patients (26 of 27), the median length of stay was 3 days (range: 2-5 days), with 100% of patients discharged home. Prior to discharge, residual AR was graded as none in 12 (46%), trace in 8 (31%), mild in 5 (19%), and moderate in 1 (4%).

30-DAY OUTCOMES (N = 24). Short- and mid-term outcomes are presented in Table 4. There were no additional deaths, strokes, or rehospitalizations at 30 days. New pacemakers were required in 3 patients (13%) at 30 days. Most patients (88%) were in NYHA functional class I or II at 30 days. On echocardiography, the mean effective orifice area was 2.1 ± 0.6 cm^2, with a median gradient of 7 mm Hg (range: 5-10 mm Hg). Residual AR was graded as none (52%), trace (14%), and mild (33%), with no patient having moderate or greater residual AR.

1-YEAR OUTCOMES (N = 17). Of the 24 patients successfully treated with the J-Valve and discharged from the hospital, complete 1-year follow-up was available in 17 (2 deaths [12%] occurred between day 30 and 1 year, and 5 patients were treated in the second half of 2022) (Figure 2). One of the deaths was related to liver cancer, and the other was presumed to be cardiac (sudden death at home) 8 months after the procedure. The second patient who died had normal J-Valve and LV function with no residual AR on echocardiography performed 3 months prior to death. There were no strokes or aortic valve reinterventions at 1 year. On echocardiography (n = 14), the mean effective orifice area was 2.3 ± 0.8 cm^2, with a median gradient of 7 mm Hg (range: 5-10 mm Hg). Residual AR was graded as none in 6 (43%), trace in 3 (21%), mild in 4 (29%), and moderate in 1 (7%) patient. All patients were in NYHA functional class I or II.

TABLE 4 Short- and Mid-Term Outcomes After J-Valve Implantation

	30 Days (n = 24)	30 Days to 1 Year (n = 17)
Death	1 (4)	2 (12)
Stroke	1 (4)	0
New pacemaker	3 (13)	1 (6)
NYHA functional class I or II	88	100
AR moderate or greater	0	1 (7)
Mean gradient, mm Hg	7 ± 4	8 ± 4
EOA, cm^2	2.1 ± 0.6	2.3 ± 0.8

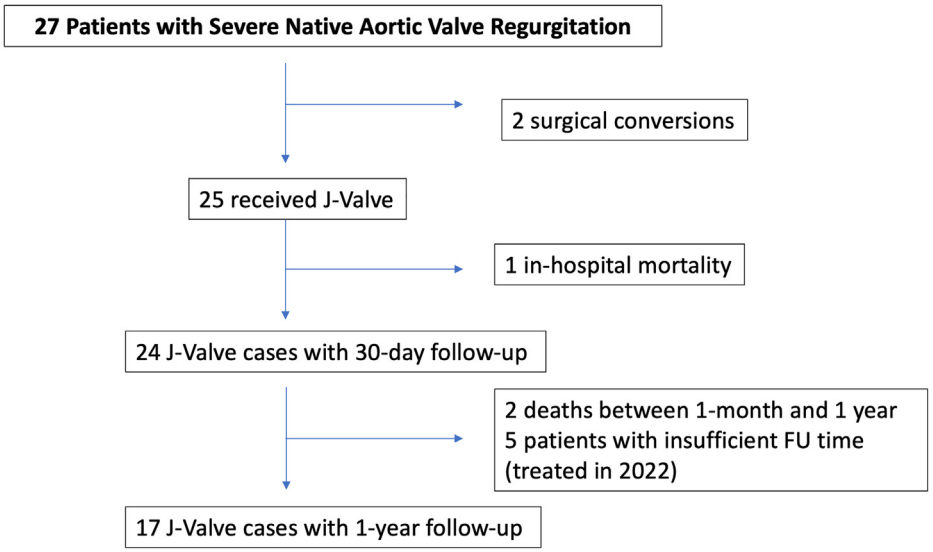
Values are n (%), %, or mean ± SD.
AR = aortic regurgitation; EOA = effective orifice area.

DISCUSSION

This 5-year (2018-2022) compassionate-use experience with a dedicated THV designed to treat severe native AR in patients at high or prohibitive surgical risk provides several important observations (Central Illustration). First, overall procedural success was 81%, with all complications requiring surgery or urgent placement of a second valve occurring during the first 2 years of the experience with the first generation of the device. Root-cause analyses of these cases led to modifications in J-Valve design and/or change in anatomical eligibility criteria for enrollment. These modifications in valve and protocol resulted in the successful performance of the last 15 consecutive cases. Second, despite the elevated surgical risk of the population treated, J-Valve implantation was associated with a relatively low rate of serious complications (1 death, 1 stroke) and 3 (13%) pacemakers at 30 days. Third, successful J-Valve implantation was associated with satisfactory acute, mid-term, and late (1-year) hemodynamic performance, with no patient having moderate or greater residual AR, an average mean gradient of ≤10 mm Hg, and effective orifice area >2 cm^2. Fourth, 10 patients (38%) treated effectively with the J-Valve had aortic valve perimeters exceeding 85 mm, which was an exclusion criterion for participation in the ALIGN-AR trial of the JenaValve for severe AR and consistent with regulatory criteria for Conformité Européenne mark approval.[12,13] This observation provides valuable insights into J-Valve performance in a broader, expanded population with severe AR. Taken together, our collective experience with the J-Valve suggests that it may provide a reasonably safe and effective alternative to surgery in patients with pure AR and elevated or prohibitive surgical risk.

The early transapical (TA) experience with the J-Valve for the treatment of patients with AR has been previously described.[14] In a case series of 6 patients at prohibitive or high surgical risk, TA implantation was feasible, with no major complications or mortality at follow-up (mean follow-up 110 days). All cases were performed without rapid pacing or balloon postdilatation. The early TA system was 27-F in size, with limited valve sizes (21-27 mm). The transfemoral device used in the present series is a steerable, flexible

FIGURE 2 Flowchart of Patients Included in the Study



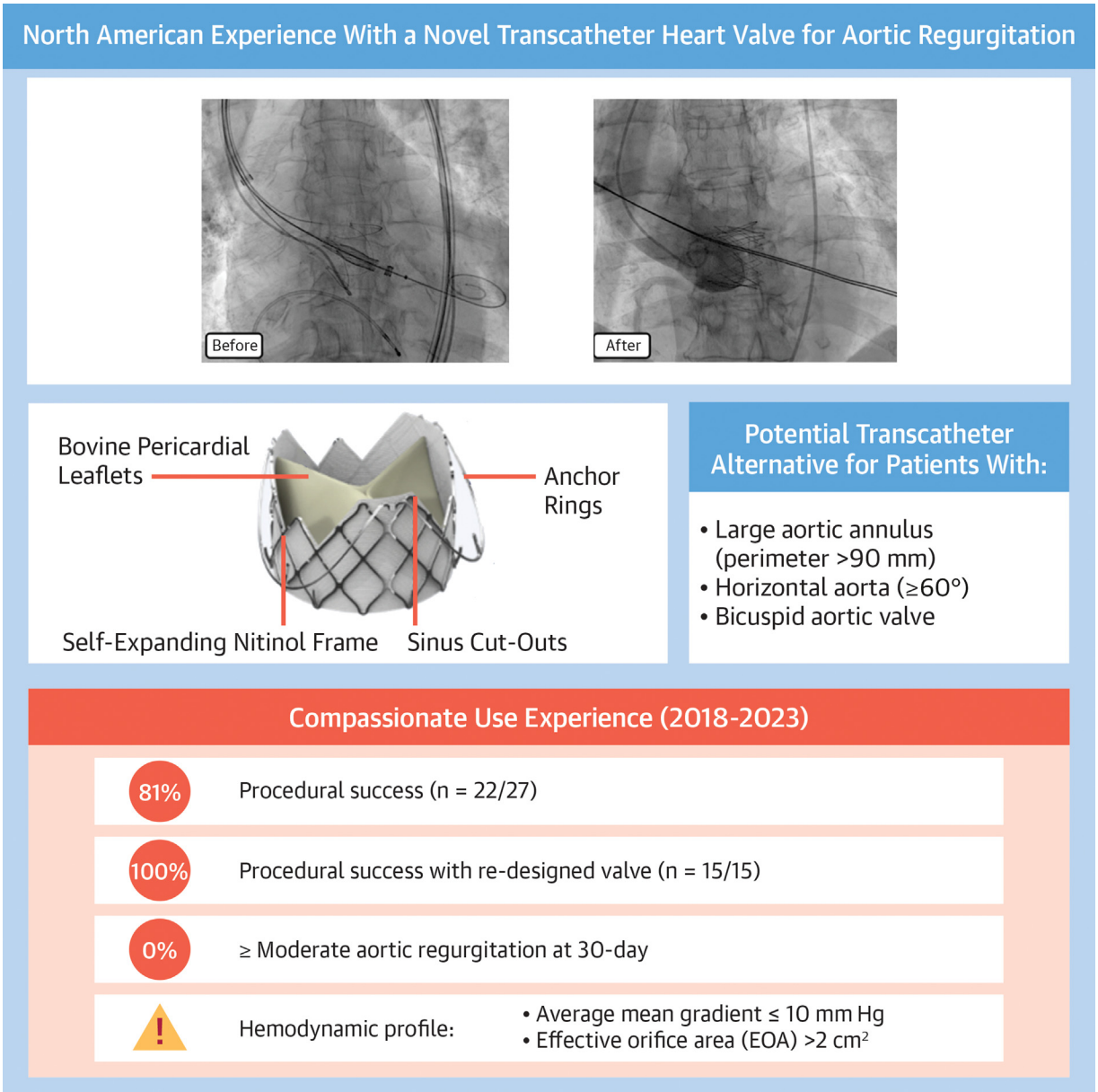
A total of 27 patients with native valve aortic regurgitation and elevated or prohibitive surgical risk were treated with the J-Valve during the study period. FU = follow-up.

18-F catheter with a broader, 5-size (22-34 mm) matrix that can be applied to aortic valve perimeters ranging from 57 to 104 mm. These device enhancements have also facilitated alternative vascular access (axillary, carotid, and transcaval) when required, as well as more horizontal aortas and larger aortic annulus.

The experience with off-label use of commercially available TAVR devices for the treatment of severe AR has been limited and variable.[8] In the pure native AR TAVR registry, 119 (36%) and 212 (64%) patients received a first- or second-generation commercial TAVR devices. Device success was 61% and 81% for first- and second-generation devices, respectively, mainly because of a lower rate of second valve implantation (12% vs 24%; $P = 0.007$) and post-procedural AR moderate or greater (4% vs 18%; $P < 0.001$) with second-generation devices. All-cause mortality and new pacemaker rates were 10% and 17% at 30 days, respectively. Residual AR moderate or greater was identified as a strong predictor of 1-year mortality. In contrast, our overall device success rate with the J-Valve was relatively high (81%) despite early design iterations and, importantly, reached 100% in the last consecutive 15 cases performed after device modifications and refinement in eligibility criteria. Importantly, no patient had residual AR mild or greater, and the hemodynamic performance of the device was maintained at 1 year among those patients eligible for evaluation. Mortality and new pacemaker requirement at 30 days were 4% and 13%, respectively, which compare favorably with previous experience. The Trilogy Heart Valve System (JenaValve Technology) received Conformité Européenne mark approval for the treatment of patients with AS and those with AR in Europe in 2021. Tamm[12] presented the early commercial experience in 58 patients with AR treated with JenaValve Trilogy TAVR system at 6 German centers via transfemoral access. Technical success was 100%, and 30-day mortality and new pacemaker requirement were 1.7% and 18%, respectively. Residual AR was none to trace in 96% of patients. Importantly, 66% received the largest size device (27 mm), 28% received the 25-mm device, and 9% received the 23-mm valve. The Jena Valve ALIGN-AR Pivotal Trial (NCT04415047) has completed enrollment in the United States.

Although dedicated devices for AR are still under investigation or in the early phase of clinical experience, it would appear that they offer significant advantages to commercial TAVR devices in terms of both procedural efficacy and safety. Certain AR subsets continue to pose treatment challenges, including horizontal aortas, bicuspid valves with or without aortopathy, large aortic annulus, and the presence of AR in the setting of a LV assist device.

CENTRAL ILLUSTRATION **Compassionate-Use Experience With the J-Valve**



Garcia S, et al. J Am Coll Cardiol Intv. 2023;16(16):1953–1960.

The J-Valve may provide a safe and effective alternative to surgery in patients with pure aortic regurgitation and elevated or prohibitive surgical risk.

STUDY LIMITATIONS. Our study of 27 patients with native AR treated under the compassionate-use program with J-Valve over 5 years in North America is the largest experience to date with this device. Several limitations should be acknowledged. First, echocardiographic and angiographic data were site reported. We lacked an independent angiographic or echocardiographic core laboratory to adjudicate AR severity preprocedure or postprocedure. Second, over the course of the study, several changes occurred in

the design of the device and enrollment criteria, which is expected at this early stage of development. Finally, our follow-up time is limited (>1 year or less), an important consideration in the lifetime management of patients with valvular heart disease.

CONCLUSIONS

The early North American compassionate-use experience with the J-Valve for the treatment of patients with native AR is characterized by increasingly higher procedural success, few complications, marked reductions in heart failure symptoms, and improvements in valve hemodynamic status. Transcatheter treatment of patients with AR is rapidly evolving, and device enhancements will likely result in expansion of this therapy in the near future.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

This study was supported by a JC Medical grant to the data coordinating center at the Lindner Center for Research and Education. Dr Garcia has received institutional grant support from Edwards Lifesciences, Medtronic, Boston Scientific, and Abbott Vascular; serves as a proctor and steering committee member for Edwards Lifesciences; and serves on advisory boards for Boston Scientific and Medtronic. Dr Kereiakes is a consultant for JC Medical and JenaValve; and is a member of the ALIGN-AR trial steering committee. Dr Ye is a consultant for Edwards Lifesciences and JC Medical. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

WHAT IS KNOWN? Transcatheter treatment of patients with AR with current technology is limited by anatomical factors.

WHAT IS NEW? Compassionate use of a novel transcatheter valve (J-Valve) designed for the treatment of patients with AR was associated with encouraging procedural outcomes and excellent hemodynamic status to 1-year postimplantation.

WHAT IS NEXT? The safety and effectiveness of the J-Valve will be evaluated in early feasibility and pivotal trials soon to be initiated in the United States.

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KEY WORDS aortic regurgitation, compassionate use, transcatheter aortic valve replacement

APPENDIX For supplemental videos, please see the online version of this paper.