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EDITORIAL COMMENT

Progressing Forward in Transcatheter Aortic Valve Replacement for Pure Aortic Regurgitation*

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Severe aortic regurgitation (AR) is associated with a significantly increased risk for morbidity, mortality, and heart failure.[1] Despite these risks, studies have shown that severe AR is frequently underdiagnosed and, especially in elderly populations, often goes untreated.[2] Surgical aortic valve replacement is gold standard for the treatment of severe symptomatic AR and asymptomatic severe AR associated with left ventricular systolic dysfunction in operable patients, with Class I indications in both European and American guidelines.[3,4] Despite this, older patients are often challenging to treat because of their higher surgical risk and operative mortality, and with an increasingly aging population, the prevalence of chronic AR is expected to increase significantly.[5] Although transcatheter aortic valve replacement (TAVR) is now the dominant treatment modality for patients undergoing aortic valve replacement for aortic stenosis (AS),[6] TAVR for isolated severe AR using valves designed primarily to treat AS has been challenging because of pathologic anatomical differences between the two disease processes (AS and AR).

Chronic severe AR anatomy has several unfavorable anatomical characteristics for traditional catheter-based treatment. First, there is often no significant aortic valve calcification for the anchoring of the transcatheter heart valve (THV). Second, chronic severe AR often occurs in the setting of bicuspid valve anatomy and is associated with aortopathy, which further adds to the procedural complexity. Last, a "suction effect" from regurgitation can result in increased instability during TAVR deployment and can lead to valve migration or embolization during deployment or postdilation. As such, prior reports from registry data on the outcomes of TAVR in patients with severe isolated AR have demonstrated poor outcomes compared with patients undergoing TAVR for AS.[7]

These challenges are highlighted in a study in this issue of *JACC: Cardiovascular Interventions* by Poletti et al,[8] which evaluates outcomes using current-generation THVs (indicated for the treatment of patients with calcific AS) in 201 patients from the PANTHEON (Performance of Currently Available Transcatheter Aortic Valve Platforms in Inoperable Patients With Pure Aortic Regurgitation of a Native Valve) registry, an international multicenter collaborative retrospective registry of patients undergoing transcatheter treatment of native severe AR (**Table 1**). Two-thirds of patients were treated with self-expanding prostheses (Medtronic CoreValve Evolut R or Evolut PRO in 58%, ACURATE neo or neo2 in 19%, JenaValve in 16%, and Abbott Portico or Navitor in 8%), and the remainder were treated with balloon-expandable prostheses (MyVal in 58% and Edwards Lifesciences SAPIEN S3 or SAPEIN Ultra in 42%). Technical (83.6%) and device (76.1%) success rates as defined by the Valve Academic Research Consortium 3 were suboptimal, with about 10% of patients ending up with at least moderate residual AR. Technical success was defined as a safe exit from the procedure room with correct positioning of a single prosthetic heart valve into the proper anatomical location by

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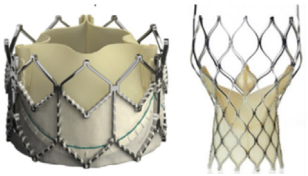
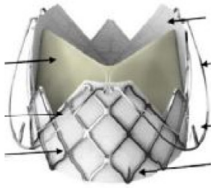
TABLE 1 Comparison of Key Outcomes of Various THVs for Severe Pure Native AR

	New-Generation THVs: PANTHEON Registry[8] (n = 201)	J-Valve: North American Compassionate-Use Experience[13] (n = 27)	JenaValve Trilogy: First Commercial Experience[10] (n = 58)
			
Mean age, y	79.0	81.0	76.5
Mean STS Predicted Risk of Mortality	5.1	4.3	4.2
Participating centers	16 international sites	5 major centers in the United States and Canada	6 tertiary care centers in Germany
Type of valve implanted	132 SE THVs and 69 BE THVs	SE J-Valve THV system	SE JenaValve Trilogy HV system
Technical success	83.6%	81%	100%
Device success	76.1%	81%	98%
Residual AR of more than moderate severity	9.5%	0%	0%
Transcatheter migration or embolization (%)	12.4%	14.8%	0%
Need for second valve	10.5%	11.1%	0%
Conversion to surgery	2.0%	7.4%	0%
Postprocedural mean gradient, mm Hg	6.7	7.0	4.3
New pacemaker implantation	22.3%	13.0%	19.6%
Stroke/transient ischemic attack	1.5%	4.0%	0%
Major vascular complication	7.5%	–	0%
Major bleeding	10.6%	–	0%
In-hospital all-cause death	5.0%	4.0%	0%

AR = aortic regurgitation; BE = balloon-expandable; PANTHEON = Performance of Currently Available Transcatheter Aortic Valve Platforms in Inoperable Patients With Pure Aortic Regurgitation of a Native Valve; SE = self-expandable; STS = Society of Thoracic Surgeons; THV = transcatheter heart valve.

successful access, delivery of the device, and retrieval of the delivery system without any procedural complications.[9] Device success was defined as optimal performance of the valve as intended, with mean gradient <20 mm Hg, peak velocity <3 m/s, Doppler velocity index ≥0.25, and less than moderate AR at 30 days after technical success.[9] Additionally, about 15% of cases were complicated by transcatheter valve embolization or migration, which in turn led to significantly higher risk for mortality and/or heart failure at 1 year. Among the patients who had valve embolization or migration, one-half were rescued with a second THV implantation after snaring of the embolized THV in 28% of cases, and 4 patients required surgical intervention. In-hospital mortality was 5.0% overall, and a substantial proportion of patients (22.2%) required pacemaker implantation.

These results are largely consistent with (at best marginally improving upon) previous data from the AR TAVR registry comparing outcomes of TAVR with early- and new-generation THVs in patients with symptomatic severe AR.[7] To put these results in context, the 30-day rate of death of any cause in the PARTNER (Placement of Aortic Transcatheter Valve) B inoperable cohort using the original SAPIEN valve was 5.0% among treated patients, with higher rates of procedural success. This highlights the challenges of using traditional technology designed for treatment of calcific AS for patients with different anatomical challenges. Approximately 10% of patients in the PANTHEON registry underwent implantation with the JenaValve and 12% with ACURATE neo or neo2, which may have design elements better suited for the treatment of native AR. Excluding these patients from

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AUGUST 28, 2023:1986–1989

the analysis would suggest even worse outcomes among currently used THVs, again emphasizing the compelling need for dedicated THV platforms to treat this challenging condition.

Into this void come the initial results on the JenaValve Trilogy platform. Also in this issue, Adam et al[10] report the key findings of the first commercial experience of the Conformité Européenne-marked transfemoral JenaValve Trilogy THV in the treatment of 58 patients with symptomatic severe pure native AR in Germany. The Trilogy system is a supra-annular porcine pericardial bioprosthetic valve with 3 radial locators that allow commissural alignment but also anchor the valve in the native cusps; the device thus does not rely on the presence of calcification for anchoring. The valve is delivered using an 18-F, 85-cm-long sheath that extends all the way to the sinotubular junction. In striking contrast to the conventional THV experience as described in the PANTHEON registry, the JenaValve system had 100% technical success, without any reported incidents of valve embolization or migration or need for surgical intervention or second valve implantation. The device success rate was 98%, with no in-hospital death or major vascular or bleeding complications (**Table 1**).

It is important to note that the study comprised only 58 patients, all with tricuspid anatomy favorable for this device (currently available in 3 sizes and able to treat annuli 21.0-28.6 mm in size). Nevertheless, these outcomes appear even better than the contemporary outcomes with current-generation THVs for the treatment of AS.[11] It is difficult to compare mortality data in such a small population, but the contemporary benchmark for operative mortality following surgical aortic valve replacement for chronic severe AR (overall 1.1%) on the basis of Society of Thoracic Surgeons adult cardiac surgery database suggests that outcomes may be comparable.[12]

One major limitation is the high rate of new permanent pacemaker implantation (19.6%), although this is consistent with what was observed in the PANTHEON registry. Although the precise etiology of this remains unclear at this time, the higher rate may be due to anatomical predisposition with a lack of protective effect due to minimal annular calcification, a higher propensity for patients with AR to have underlying conduction disturbances,[10] device characteristics, or operator technique. In comparison, the need for permanent pacemaker implantation following surgical aortic valve replacement for severe AR is only 3%,[12] suggesting that device characteristics and/or operator technique may account for this high rate to some degree. Future iterations of the THVs and optimization of implantation technique should improve outcomes with reduced need for permanent pacemaker implantation.

The initial results for the JenaValve Trilogy platform described in this analysis are encouraging as we await the results from the ALIGN-AR Pivotal IDE Study (NCT04415047), a prospective, single-arm, multicenter study evaluating 180 patients with severe AR at high surgical risk. The primary outcome is all-cause mortality at 1 year. Of note, bicuspid anatomies are excluded from this study as well.

Additionally, other platforms currently in development may also allow the treatment of patients with broader pathologies. The J-Valve (JC Medical) is a self-expanding, low-profile bovine pericardial leaflet system on a Nitinol frame with 3 anchor rings designed to attach to the native aortic valve sinuses, facilitating anchoring. The delivery system is 18- to 21-F, and the platform is available in 5 valve sizes, allowing the treatment of annuli up to 104 mm in perimeter. As summarized in **Table 1**, a recent study reported the outcomes of compassionate-use experience of the J-Valve for the treatment of high surgical risk patients with severe native AR.[13] Early implantations were associated with technical failure due primarily to anatomical factors, and subsequent modifications in the THV and stricter anatomical eligibility criteria led to successful implantation in the last 15 consecutive cases. After successful implantation, the performance of J-Valve in terms of hemodynamic status and residual AR was comparable with that of JenaValve Trilogy system, with a slightly lower, but significant, rate of new pacemaker implantation (13%).

Given the suboptimal performance of currently available THVs for the treatment of patients with native severe AR demonstrated in the PANTHEON registry, there is a compelling clinical need for technological innovation in this space. The promising early results of the JenaValve Trilogy platform as described by Adam et al,[10] if corroborated in the larger ALIGN-AR Pivotal Trial, will pave the way for a safe, effective transcatheter option in the treatment of patients deemed to be at increased risk for surgery. Future development will likely mirror the past decade of innovation in the transcatheter treatment of patients with severe AS, as subsequent iterations of the platform (as well as competing transcatheter valves) will allow the treatment of broader annular anatomies and of patients across risk strata. Additionally, increasing operator experience may lead to better technical results with lower pacemaker implantation rates. These 2 studies set the benchmark for the

contemporary state of the field and allow us to simultaneously look backward to contemporary experience with current technologies and forward to the future possibilities with developing technologies.

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Dr Vora is a consultant for Medtronic. Dr Forrest is an advisory board member for Medtronic and Edwards Lifesciences; and is a consultant for Boston Scientific. Dr Sreenivasan has reported that he has no relationships relevant to the contents of this paper to disclose.

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