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NEW RESEARCH PAPER: STRUCTURAL

Transcatheter Aortic Valve Replacement for Pure Native Aortic Valve Regurgitation

The PANTHEON International Project

Enrico Poletti, MD,[a] Ole De Backer, MD, PhD,[b] Andrea Scotti, MD,[c] Giuliano Costa, MD,[d] Francesco Bruno, MD,[e] Claudia Fiorina, MD,[f] Nicola Buzzatti, MD,[g] Alessia Latini, MD,[h] Tanja K. Rudolph, MD,[i] Mark M.P. van den Dorpel, MD,[j] Christina Brinkmann, MD,[k] Kush P. Patel, MD,[l] Vasileios Panoulas, MD,[e] Joachim Schofer, MD, PhD,[k] Arturo Giordano, MD, PhD,[m,n] Marco Barbanti, MD,[o] Damiano Regazzoli, MD,[h] Maurizio Taramasso, MD,[p] Francesco Saia, MD, PhD,[q] Andreas Baumbach, MD, PhD,[l] Francesco Maisano, MD,[g] Nicolas M. Van Mieghem, MD, PhD,[j] Lars Søndergaard, MD, DMSc,[b] Azeem Latib, MD,[c] Ignacio J. Amat Santos, MD, PhD,[r] Francesco Bedogni, MD,[a] Luca Testa, MD, PhD[a]

ABSTRACT

BACKGROUND Transcatheter aortic valve replacement (TAVR) in patients with pure severe native aortic valve regurgitation (NAVR) has been associated with suboptimal results. The available evidence concerns mostly outdated transcatheter heart valves (THVs).

OBJECTIVES The aim of this study was to investigate the performance of new-generation THVs in patients treated for pure severe NAVR.

METHODS The PANTHEON (Performance of Currently Available Transcatheter Aortic Valve Platforms in Inoperable Patients With Pure Aortic Regurgitation of a Native Valve) study retrospectively included patients who underwent TAVR with currently available devices (both self-expanding [SE] and balloon expandable [BE]) for severe NAVR. Technical and device success rates as well as a composite of all-cause mortality and heart failure rehospitalization at 1 year were evaluated. The rate and clinical consequences of acute transcatheter valve embolization or migration (TVEM) were also considered.

RESULTS A total of 201 patients were included. Overall technical and device success rates were 83.6% and 76.1%, respectively, and did not differ between SE and BE devices. These figures were due mostly to TVEM occurrence (14.6% vs 16.1%; $P = 0.47$) and residual moderate or greater aortic regurgitation (9.2% vs 10.1%; $P = 0.87$). Patients who experienced TVEM compared with those without TVEM had a significantly higher incidence of the composite endpoint at 1 year (25.7% vs 15.8%; $P = 0.05$).

CONCLUSIONS Despite improved THV platforms and techniques, TAVR for pure severe NAVR remains a challenging procedure, with significant risk for TVEM. SE and BE platforms demonstrated comparable performance in this setting. (Performance of Currently Available Transcatheter Aortic Valve Platforms in Inoperable Patients With Pure Aortic Regurgitation of a Native Valve [PANTHEON]; NCT05319171) (J Am Coll Cardiol Intv 2023;16:1974–1985)

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Pure native aortic valve regurgitation (NAVR) is a multifactorial valvular disease, fairly diffuse worldwide,[1] with a prevalence of moderate or greater severity of NAVR ranging from 0.5% to 2.7%, depending on age, sex, and ethnicity.[2,3] Notably, severe NAVR is associated with a significant burden of mortality and morbidity.[4] Despite several small, randomized trials published so far, the efficacy of medical therapy in this setting is unclear.[5,6] The European[7] and American[8] guidelines recommend surgery for all operable patients with pure severe NAVR.[9,10]

In the field of aortic stenosis, transcatheter aortic valve replacement (TAVR) has achieved a primary role as a first-choice treatment for elderly patients regardless of surgical risk.[11,12] Beyond aortic stenosis, the role of TAVR has expanded also in patients with degenerated surgical or transcatheter bioprostheses.[13,14] Conversely, the role of TAVR in patients with pure severe NAVR is still debated. Anatomical and pathophysiological issues, as well as device-related features, challenge the technical feasibility and success of TAVR.[15] For instance, NAVR is frequently associated with aortic root and/or ascending aortic dilation and minimal calcification of the leaflets. Additionally, the increased tissue elasticity, combined with the elevated stroke volume and the "suction effect" resulting from regurgitation, collectively contribute to increase instability during transcatheter heart valve (THV) delivery. Consequently, the risk for moderate or greater aortic regurgitation (AR) and transcatheter valve embolization or migration (TVEM) are the main adverse events after TAVR.[16-18]

Finally, it should be noted that the available evidence regarding THVs pertains to earlier iterations that have been replaced by newer versions with improved performance in the treatment of calcific aortic stenosis. Whether this improved performance is also true for AR must be defined. Therefore, the purpose of this study was to assess the performance of new-generation THVs in patients with pure severe NAVR.

ABBREVIATIONS AND ACRONYMS

AR = aortic regurgitation

BE = balloon-expandable

NAVR = native aortic valve regurgitation

SE = self-expanding

TAVR = transcatheter aortic valve replacement

THV = transcatheter heart valve

TVEM = transcatheter valve embolization or migration

VARC-3 = Valve Academic Research Consortium 3

METHODS

REGISTRY DESIGN. The PANTHEON (Performance of Currently Available Transcatheter Aortic Valve Platforms in Inoperable Patients With Pure Aortic Regurgitation of a Native Valve; NCT05319171) is an international, investigator-initiated registry intended to collect data on patients with pure severe NAVR treated with new-generation THVs. Sixteen centers in Europe and United States contributed patient-level data using a predesigned form. Baseline clinical characteristics, preprocedural echocardiographic and computed tomographic measurements, TAVR procedural details, and follow-up data were collected at each institution. The study was conducted in accordance with the principles of the Declaration of Helsinki and good clinical practice.

STUDY POPULATION. All patients with pure severe NAVR deemed to be at high or prohibitive surgical risk and treated using last-generation THVs after discussion by local heart teams were considered eligible.

Exclusion criteria were as follows: 1) the presence of a concomitant moderate to severe aortic valve stenosis; 2) TAVR procedures performed using THV

From the [a]Clinical and Interventional Cardiology Department, IRCCS Policlinico San Donato, Milan, Italy; [b]Department of Cardiology, The Heart Center, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark; [c]Montefiore-Einstein Center for Heart and Vascular Care, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, New York, USA; [d]Division of Cardiology, CAST, Azienda Ospedaliero - Universitaria Policlinico G. Rodolico - San Marco, University of Catania, Catania, Italy; [e]Department of Cardiology, Royal Brompton and Harefield Hospitals, Guy's and St. Thomas' NHS Foundation Trust, Harefield Hospital, Harefield, United Kingdom; [f]Spedali Civili Brescia, Brescia, Italy; [g]IRCCS, San Raffaele Scientific Institute, Milan, Italy; [h]Cardio Center, IRCCS Humanitas Research Hospital, Rozzano-Milan, Italy; [i]Department for General and Interventional Cardiology/Angiology, Heart and Diabetes Center North Rhine-Westphalia Bochum, University Hospital of the Ruhr University, Bad Oeynhausen, Germany; [j]Department of Interventional Cardiology, Erasmus University Medical Centre, Rotterdam, the Netherlands; [k]MVZ Department of Structural Heart Disease at St. Georg, Hamburg, Germany; [l]Department of Cardiology, Barts Heart Centre, Barts Health NHS Trust, London United Kingdom; [m]Cardiovascular Interventional Operative Unit, Presidio Ospedaliero Pineta Grande, Castel Volturno, Caserta, Italy; [n]Operative Unit of Hemodynamics, Casa di Salute Santa Lucia, Naples, Italy; [o]Università Degli Studi di Enna "Kore," Enna, Italy; [p]HerzZentrum Hirslanden Zurich Clinic of Cardiac Surgery, Zurich, Switzerland; [q]Cardiology Unit, Cardio-Thoracic-Vascular Department, IRCCS University Hospital of Bologna, Bologna, Italy; and the [r]Instituto de Ciencias del Corazón, Hospital Clínico Universitario de Valladolid, Valladolid, Spain.

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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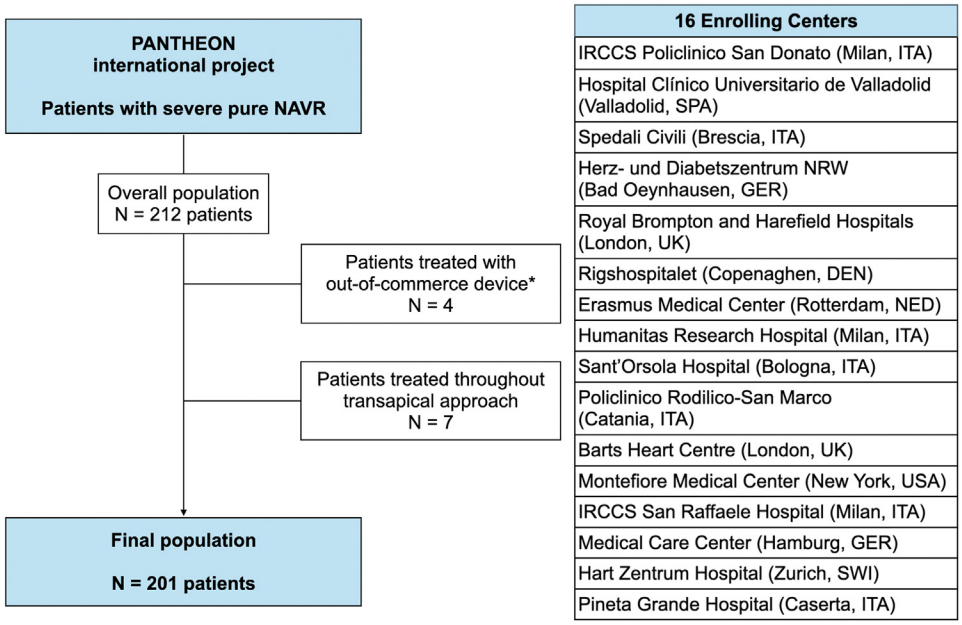
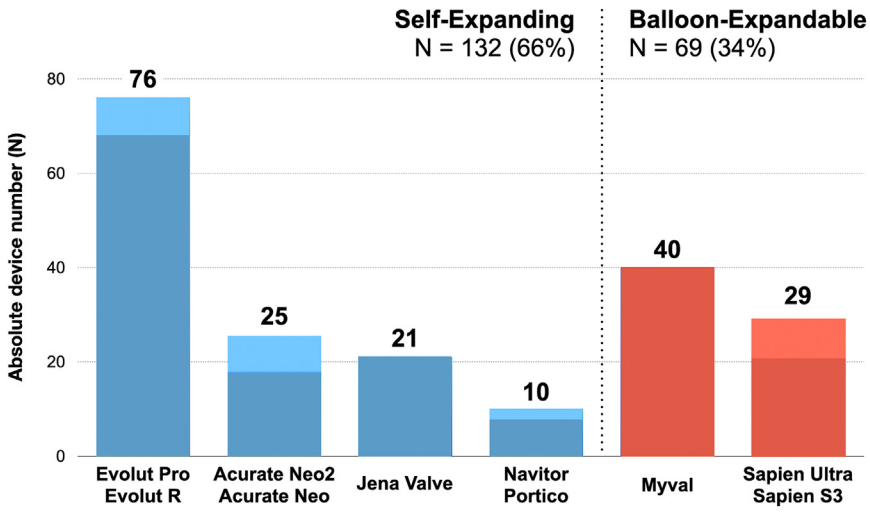
FIGURE 1 Study Population



Registry population among the 16 enrolling centers. *No longer commercially available devices include the following transcatheter heart valve (THV) devices: SAPIEN XT, CoreValve, Direct Flow, and Lotus THVs. NAVR = native aortic valve regurgitation; PANTHEON = Performance of Currently Available Transcatheter Aortic Valve Platforms in Inoperable Patients With Pure Aortic Regurgitation of a Native Valve.

FIGURE 2 Transcatheter Heart Valve Type Between the 2 Groups



The histogram shows the transcatheter heart valves deployed as upfront devices.

platforms no longer commercially available; and 3) the use of transapical access (whereas patients treated using percutaneous access methods other than transfemoral access were included in the final population).

DEFINITIONS. The severity of NAVR was graded using a combination of semiquantitative and quantitative assessments, as described by the European Association of Echocardiography and American Society of Echocardiography guidelines.[19] Preprocedural screening was performed using clinical, echocardiographic, and computed tomographic assessments. The degree of calcification in the native aortic valve and left ventricular outflow tract calcification were classified and graded using a semiquantitative scoring system, as previously described.[20] The prosthesis type and size were selected at the discretion of the treating physician at each institution.

All outcomes were defined according to the Valve Academic Research Consortium-3 (VARC-3) definitions.[21] Likewise, TVEM was defined in accordance with VARC-3 criteria as follows: 1) valve migration: after initial correct positioning, the valve prosthesis moves upward or downward, within the aortic annulus from its initial position, without valve embolization; 2) valve embolization: the valve prosthesis moves either upward or downward after final deployment such that it loses contact with the aortic annulus; and 3) ectopic valve deployment: irretrievable deployment of a valve prosthesis at a site other than the intended position because of valve embolization or inability to deliver the prosthesis to the desired location.[21] Additionally, detailed characteristics of TVEM causes and mechanisms were site reported, distinguishing among procedure related, anatomy related, due to excessive oversizing, or unknown causes. Finally, TVEM bailout technique and the final embolized THV position were recorded.

ENDPOINT DEFINITIONS. Technical and 30-day device success were considered the primary efficacy endpoints for comparing the performance of self-expanding (SE) vs balloon-expandable (BE) devices, whereas the incidence rates of TVEM and residual moderate or greater AR were the secondary endpoints.

A composite of all-cause mortality and heart failure rehospitalization was used as the co-primary endpoint for 1-year follow-up.

STATISTICAL ANALYSIS. Categorical variables are presented as frequencies and percentages, and statistical analysis was conducted using the chi-square test or Fisher exact test. Continuous variables are reported as mean ± SD or as median (IQR) and were compared using the Wilcoxon rank sum test or the Mann-Whitney *U* test as appropriate. Freedom from the composite endpoint rate was reported using the Kaplan-Meier method, and comparisons were performed using the log-rank test.

Two-step analysis was used to assess predictors of TVEM. First, univariate logistic regression was performed for each clinical, morphologic, and procedural variable. Any variable with a *P* value <0.10 entered the multiple logistic regression analysis. Results are reported as ORs with 95% CIs. To identify independent predictors of mortality and heart failure rehospitalization at 1 year, Cox regression models with HRs and 95% CIs were generated using a stepwise model with entry set at $P < 0.05$ and exit at $P < 0.10$.

Finally, to adjust for possible confounders, logistic and Cox regression multivariate analyses were performed, adjusting for multiple treatment propensity score, generated using a parsimonious logistic

TABLE 1 Baseline Clinical Characteristics

	Overall (N = 201)	Self-Expanding (n = 132, 66%)	Balloon Expandable (n = 69, 34%)	*P* Value
Age, y	79 (73-83)	79 (72-83)	79 (73-84)	0.773
Male	111 (55.2)	63 (47.7)	48 (69.6)	0.003
Body mass index, kg/m^2	25.1 (22.4-26.9)	24.6 (21.3-26.9)	25.4 (23.8-26.9)	0.038
Diabetes	37 (18)	26 (20)	14 (21)	0.42
Hypertension	152 (76)	100 (76)	52 (75)	0.951
Peripheral artery disease	31 (15.4)	23 (17.4)	8 (11.6)	0.277
Prior myocardial infarction	25 (12.4)	18 (13.6)	7 (10.1)	0.476
Prior percutaneous coronary intervention	34 (16.9)	28 (21.2)	12 (18)	0.25
Prior cardiac surgery	47 (23.4)	35 (26.5)	12 (17.4)	0.147
Prior pacemaker implantation	40 (19.9)	26 (19.7)	14 (20.3)	0.920
Atrial fibrillation history	87 (43.3)	57 (43.2)	30 (43.5)	0.968
Prior stroke	19 (9.5)	12 (9.1)	7 (10.1)	0.808
Chronic obstructive pulmonary disease	38 (18.9)	21 (15.9)	17 (24.6)	0.133
Severe chronic kidney disease[a]	49 (24.4)	33 (25.0)	16 (23.2)	0.776
NYHA functional class				
I	3 (1.6)	1 (0.8)	2 (3.2)	0.417
II	42 (22.2)	28 (22.2)	14 (22.2)	
III	118 (62.4)	77 (61.1)	41 (65.1)	
IV	26 (13.8)	20 (15.9)	6 (9.5)	
Society of Thoracic Surgery risk score	5.1 (4.1-6.1)	5.2 (4.3-6.2)	4.8 (2.8-6.9)	0.005
Left ventricular ejection fraction, %	45 ± 14	45 ± 13	45 ± 15	0.867
Left ventricle end-diastolic diameter, mm	59.9 ± 9.2	58.9 ± 9.3	61.5 ± 8.6	0.069

Values are median (IQR), n (%), or mean ± SD. [a]Defined as estimated glomerular filtration rate <30 mL/min/1.73 m^2.

TABLE 2 Baseline Computed Tomographic and Procedural Characteristics

	Overall (N = 201)	Self-Expanding (n = 132, 66%)	Balloon Expandable (n = 69, 34%)	*P* Value
Aortic annular area, mm^2	502 (427-591)	472 (414-531)	602 (486-700)	<0.001
Annular perimeter, mm	81 (74-88)	78 (74-83)	88 (80-94)	<0.001
Sinus of Valsalva diameter, mm	34 (31-40)	33 (29-37)	39 (32-43)	<0.001
Left ventricular outflow tract mean diameter, mm	25 (23-27)	25 (23-26)	27 (23-29)	0.033
Ascending aortic dilation	63 (31.3)	23 (17.4)	40 (57.9)	<0.001
Horizontal aorta (>47°)	45 (27.3)	30 (28.3)	15 (25.4)	0.691
Bicuspid aortic valve	13 (6.9)	6 (5.0)	7 (10.3)	0.169
Leaflet calcifications				
None	112 (63.6)	69 (61.6)	43 (67.2)	0.312
Mild	51 (29.0)	32 (28.6)	19 (29.7)	
Moderate	13 (7.4)	11 (9.8)	2 (3.1)	
Severe	0 (0)	0 (0)	0 (0)	
Transfemoral main access	192 (95.5)	124 (93.4)	68 (98.6)	0.314
Perimeter oversizing, %[a]	13.6 ± 9.5	16.4 ± 9.5	8.5 ± 7.0	<0.001
Area oversizing, %[b]	17.0 ± 13.0	21.2 ± 13.4	9.9 ± 8.4	<0.001
General anesthesia	40 (19.9)	35 (26.5)	5 (7.3)	0.001
Intraprocedural transesophageal echocardiography	25 (12.8)	20 (15.8)	5 (7.4)	0.095
Rapid pacing during deployment	177 (88.1)	108 (81.8)	69 (100)	<0.001
Postdilation	17 (8.5)	12 (9.1)	5 (7.3)	0.655
Cerebral protection	4 (2.5)	3 (2.3)	1 (3.1)	0.795
Contrast used, mL	110 (90-150)	125 (93-168)	100 (79-119)	<0.001
Procedural time, min	74 (54-110)	92 (65-124)	60 (49-79)	<0.001

Values are median (IQR), n (%), or mean ± SD. [a]Perimeter oversizing defined as the ratio of aortic annular perimeter-derived diameter to transcatheter heart valve nominal diameter. [b]Area oversizing defined as the ratio of aortic annular area-derived diameter to transcatheter heart valve nominal diameter.

regression model.[22] The propensity score contained both clinical and anatomical variables, as specified in Supplemental Table 1.

All statistical analyses were performed using R version 4.2.2 (R Foundation for Statistical Computing).

RESULTS

POPULATION CHARACTERISTICS. Between May 2014 and September 2022, among about 15,000 patients who underwent TAVR in the participating centers, 212 (1.4%) were treated for pure severe NAVR. Four patients treated with THVs no longer commercially available (SAPIEN XT, CoreValve, Direct Flow, and Lotus valves) and 7 patients treated via transapical access were excluded. Ultimately, 201 patients were included in the present analysis (**Figure 1**).

SE valves were implanted in most patients (n = 132 [66%]). The types of valves implanted are shown in **Figure 2**. The transfemoral approach was used in most patients (n = 192 [95.5%]), whereas the transsubclavian approach was the most common alternative access route (n = 8 [4.0%]).

Overall, the median age was 79 years (IQR: 73-83 years), with a median Society of Thoracic Surgeons risk score of 5.1% (IQR: 4.1%-6.1%), which was significantly higher in the SE group ($P = 0.005$). The SE and BE groups differed with respect to sex (47.7% in the SE group vs 69.6% in the BE group were men; $P = 0.003$) and body mass index (24.6 kg/m^2 [IQR: 21.3-26.9 kg/m^2] vs 25.4 kg/m^2 [IQR: 23.8-26.9 kg/m^2]; $P = 0.038$), while the rate of NYHA functional class III or IV was 76.2%, with a consistent distribution across the groups. The prevalence of other cardiovascular comorbidities was high but well balanced between the groups, as presented in **Table 1**.

PREPROCEDURAL ASSESSMENT AND PROCEDURAL CHARACTERISTICS. Preprocedural computed tomography revealed a prevalence of enlarged annular anatomies, as indicated by the median annular area of 502 mm^2 and perimeter of 81 mm. Notably, dilation of the ascending aorta was observed in approximately one-third of the total population, particularly in patients treated with BE devices ($P < 0.001$). Likewise, patients treated with BE platforms exhibited greater diameter of the aortic valve annulus and left ventricular outflow tract, whereas the remaining morphologic characteristics were similar between the 2 groups, as reported in **Table 2**. Consistent with the tendency for large aortic annuli in this population, the selection of THVs tended to favor larger sizes, as shown in Supplemental Table 2.

The rate of oversizing (calculated as the ratio of both aortic annular perimeter-derived and area-derived diameters and THV nominal diameter) appeared to be significantly higher in the SE group (perimeter oversizing, 16.4% ± 9.5% vs 8.5% ± 7.0% [$P < 0.001$]; area oversizing, 21.2% ± 13.4% vs 9.9% ± 8.4% [$P < 0.001$]). Interestingly, rapid pacing was performed during THV deployment in more than 80% of SE patients. Finally, both procedural time and contrast medium used were lower in the BE group ($P < 0.001$).

PROCEDURAL OUTCOMES. The overall technical success rate according to the VARC-3 criteria was 83.6%, while the device success rate at 1 month was 76.1%, both because of TVEM (n = 25 [12.4%]) and/or residual moderate or greater AR (n = 19 [9.6%]),

without a significant difference between the 2 THV types. Within this subset, 7 patients (among the 19) were found to have significant residual AR that was secondary to TVEM. Of the remaining patients, 2 had oversizing of >20%, and 2 had oversizing between 10% and 20%. The remaining 8 patients exhibited oversizing of <10%.

During the hospital stay, comparable rates of all-cause death (5.3% vs 4.4%; $P = 0.767$), cardiovascular death (3.8% vs 4.4%; $P = 0.847$), disabling stroke (2.3% vs 0%; $P = 0.553$), and major vascular complications (8.1% vs 6.5%; $P = 0.532$) were recorded. On the contrary, looking at the postprocedural echocardiographic assessment, the final transvalvular gradient was significantly higher in the BE group (6.3 ± 2.7 mm Hg for the SE group vs 7.5 ± 5.3 mm Hg for the BE group; $P = 0.049$). Finally, a high incidence of new permanent pacemaker implantation was observed in both at-risk populations (22.6% vs 21.8%; $P = 0.918$) (**Table 3**).

TABLE 3 Procedural Outcomes and in-Hospital Events

	Overall (N = 201)	Self-Expanding (n = 132, 66%)	Balloon Expandable (n = 69, 34%)	*P* Value
All-cause death	10 (5.0)	7 (5.3)	3 (4.4)	0.767
Cardiovascular death	8 (4.0)	5 (3.8)	3 (4.4)	0.847
Stroke/transient ischemic attack	3 (1.5)	3 (2.3)	0 (0.0)	0.553
New permanent pacemaker implantation	36 (22.3)	24 (22.6)	12 (21.8)	0.918
Major vascular complication	13 (7.5)	9 (8.1)	4 (6.5)	0.532
Major bleeding	20 (10.6)	16 (12.6)	4 (6.5)	0.197
Myocardial infarction	0 (0.0)	0 (0.0)	0 (0.0)	…
Conversion to surgery	4 (2.0)	2 (1.5)	2 (2.9)	0.612
Acute kidney injury[a]	18 (10.5)	12 (10.9)	6 (9.8)	0.827
TVEM	25 (12.4)	18 (13.6)	7 (10.1)	0.476
Second valve needed	21 (10.5)	15 (11.4)	6 (8.7)	0.557
Residual moderate or greater AR	19 (9.5)	12 (9.2)	7 (10.1)	0.835
Postprocedural mean gradient, mm Hg	6.7 ± 3.9	6.3 ± 2.7	7.5 ± 5.3	0.049
Technical success	168 (83.6)	106 (80.3)	62 (89.9)	0.108
Device success	153 (76.1)	100 (75.8)	53 (76.8)	0.868

Values are n (%) or mean ± SD. [a]Acute kidney injury was defined as Acute Kidney Injury Network classification ≥2.
AR = aortic regurgitation; TVEM = transcatheter valve embolization or migration.

As depicted in Supplemental Table 3, after adjusting for propensity score, there was no association between the use of an SE or a BE device and an increased risk for technical failure (adjusted OR: 0.48; 95% CI: 0.18-1.18; $P = 0.127$), device failure (adjusted OR: 1.04; 95% CI: 0.49-2.13; $P = 0.923$), the occurrence of TVEM (adjusted OR: 0.71; 95% CI: 0.25-1.81; $P = 0.486$), or the rate of residual moderate or greater AR (adjusted OR: 1.07; 95% CI: 0.36-2.98; $P = 0.894$).

TVEM OCCURRENCE: FROM CAUSES TO BAILOUT STRATEGY. Supplemental Table 4 shows that among 201 TAVR procedures for pure severe NAVR, there were 25 cases (12.4%) of TVEM, with no significant difference between the SE and BE groups (14.6% vs 16.1%; $P = 0.835$). In sensitivity analyses excluding patients treated with Conformité Européenne mark-approved THVs, results did not significantly change (Supplemental Tables 5 and 6). Similar findings were recorded in terms of the second valve implantation, as 21 patients (10.4%) required additional THVs, without any difference between the 2 groups (11.4% vs 8.7%; $P = 0.557$).

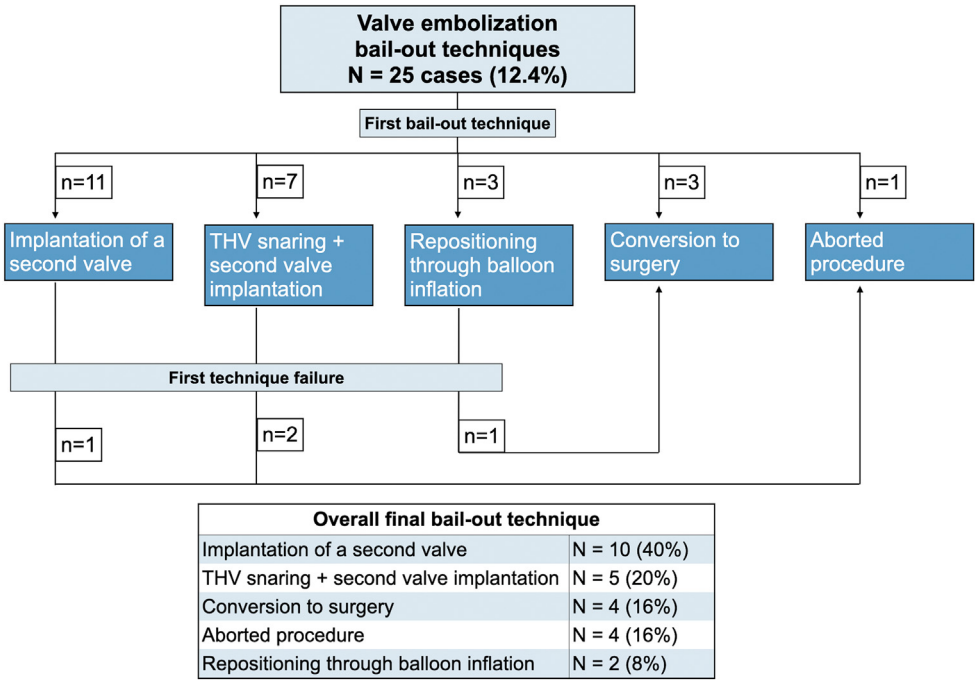
All but 1 case of TVEM occurred during the index procedure. Delayed embolization was observed in 1 case of BE device implantation, in which ventricular migration of the THV was detected on echocardiographic assessment with moderate residual AR. The patient underwent a second valve implantation 6 months after the index procedure.

The causes of TVEM were malpositioning (32%), oversizing >20% (24%), device failure to anchor the virtual basal ring (20%), manipulation (8%), and unknown causes (12%). Supplemental Figure 1 shows that SE devices embolized slightly more frequently on the aortic side (56%) than BE devices (14.3%), which moved more frequently to the left ventricular outflow tract.

Figure 3 illustrates that most cases of TVEM were treated with upfront second THV implantation (44%), but 1 case (among 11 cases) was unsuccessful because of ventricularization of the second THV. Snaring of the embolized THV was performed in 28% of the cases before releasing a second valve in the proper position, but THV snaring was unsuccessful in 2 of 7 cases. Three cases of THV repositioning with intraprosthetic balloon inflation was reported, but 1 patient required urgent surgical intervention. Overall, 4 patients (16%) underwent surgical conversion after TVEM, while in 4 other patients (16%), the procedure was aborted (Supplemental Table 4).

Finally, in almost every case in which a second valve was implanted, there was concordance between the embolized valve and the implanted second THV. However, in 3 of 15 cases (20%), BE prostheses were implanted into SE THVs, while embolized BE valves were always treated with second BE devices (see Supplemental Figure 2).

FIGURE 3 TVEM Bailout Strategies



Overall final bail-out technique	
Implantation of a second valve	N = 10 (40%)
THV snaring + second valve implantation	N = 5 (20%)
Conversion to surgery	N = 4 (16%)
Aborted procedure	N = 4 (16%)
Repositioning through balloon inflation	N = 2 (8%)

The flowchart shows transcatheter valve embolization and migration (TVEM) bailout strategies: different bailout techniques were used to manage TVEM, with different success rates as shown in this chart. THV = transcatheter heart valve.

TVEM PREDICTORS. The main predictors of TVEM are shown in Table 4. Although an impaired left ventricular ejection fraction ($P = 0.004$), postdilation ($P = 0.035$), left ventricular end-diastolic diameter ($P = 0.049$), and horizontal aorta ($P = 0.042$) were found to be significantly associated with the occurrence of TVEM in the univariate analysis, only postdilation (OR: 4.0; 95% CI: 0.91-15.4; $P = 0.049$) was recognized as an independent predictor of TVEM in the multivariate analysis.

1-YEAR CLINICAL OUTCOMES. Median follow-up duration was 377 days (IQR: 138-915 days). One-year follow-up was available for 181 patients (90.0%). At survival analysis (Supplemental Figure 3), the cumulative incidence of the composite endpoint at 1 year was 17.1% (95% CI: 10.4%-23.4%), specifically 18.1% (95% CI: 9.1%-26.2%) for the SE group and 15.1% (95% CI: 4.7%-24.4%) for the BE group (log-rank $P = 0.52$); whereas it was 25.7% (95% CI: 5.6%-41.5%) in patients who had TVEM vs 15.8%

TABLE 4 Predictors of Transcatheter Valve Embolization or Migration

	Univariate Analysis			Multivariate Analysis		
	OR	95% CI	*P* Value	OR	95% CI	*P* Value
Left ventricular ejection fraction	0.96	0.93-0.99	0.004	0.97	0.93-1.00	0.054
Postdilation	3.42	1.01-10.30	0.035	4.00	0.91-15.40	0.049
Horizontal aorta (>47°)	2.75	1.02-7.36	0.042	2.59	0.92-7.19	0.066
Left ventricular end-diastolic diameter	1.05	1.00-1.10	0.049	–	–	–
Female	0.44	0.16-1.06	0.077	–	–	–

TABLE 5 Propensity-Adjusted Estimates of 1-Year Risk for the Composite Endpoint and All-Cause Death, by Transcatheter Valve Choice and TVEM Occurrence

	Composite Endpoint			All-Cause Death		
	Adjusted HR	95% CI	*P* Value	Adjusted HR	95% CI	*P* Value
BE device	0.72	0.30-1.74	0.461	0.45	0.14-1.45	0.182
TVEM occurrence	2.45	1.00-6.18	0.049	4.06	1.50-11.00	0.006

BE = balloon-expandable; TVEM = transcatheter valve embolization or migration.

(95% CI: 8.5%-22.5%) in the non-TVEM group (log-rank $P = 0.05$).

After propensity score adjustment, TVEM was associated with both a higher 1-year incidence of the composite endpoint (adjusted HR: 2.45; 95% CI: 1.00-6.18; $P = 0.05$) and all-cause mortality (adjusted HR: 4.06; 95% CI: 1.50-11.0; $P = 0.006$), while THV choice (SE vs BE) was not (see **Table 5**).

DISCUSSION

The aim of the PANTHEON international registry was to describe the efficacy and safety of SE and BE devices in patients with pure severe NAVR treated using TAVR (**Central Illustration**). Although previous studies compared earlier generation THVs,[17,23,24] this study features the results of the largest real-world, off-label use of currently available THVs in this particular population.

The main findings of this study can be summarized as follows: 1) TAVR in patients with NAVR is still burdened by a significant risk for TVEM, with technical and device success rates of 83.6% and 76.1%, respectively; 2) SE and BE devices demonstrated comparable safety and efficacy; 3) TVEM remains the main complication, occurring in 12.4% of the overall population; 4) postdilation was identified as an independent predictor of TVEM in the NAVR setting; and 5) TVEM has an ominous impact on short-term and 1-year follow-up.

Although new-generation THVs have demonstrated favorable results in treating severe aortic stenosis,[25] a device designed for percutaneous management of pure NAVR with robust clinical data is still missing. Developing a device for this purpose is a technical challenge because of the peculiar anatomical and hemodynamic characteristics of patients with pure NAVR (**Figure 4**). The PANTHEON registry has shown that nonspecific devices for NAVR provide acceptable performance in term of VARC-3 efficacy outcomes, in particular compared with previous original studies.[17,23,24] Nevertheless, new-generation nondedicated devices have only slightly improved outcomes compared with their predecessors.[17,18]

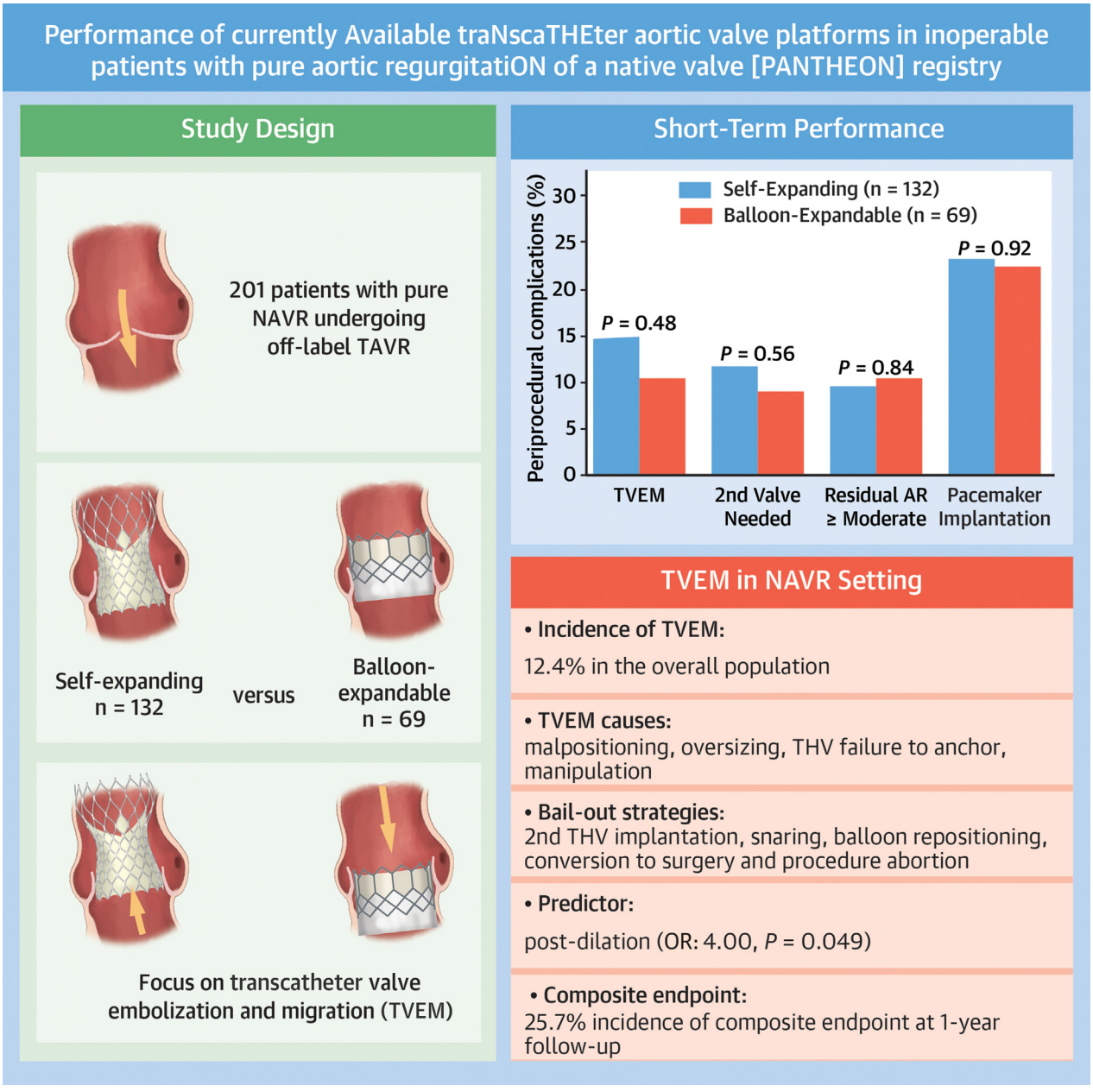
The SE and BE THVs showed comparable outcomes (**Central Illustration**). It is not surprising that BE devices were associated with a slightly higher post-procedural mean gradient ($P = 0.049$), although this is not a significant concern in this particular setting.

Of note, in our series, only 3 patients (1.5%) had mean transvalvular gradients >20 mm Hg, which is much lower than what is typically observed in aortic stenosis.[26] Apparently, the event of coronary obstruction is quite unlikely: according to the previous literature,[18,27] no cases of coronary obstruction were reported in our registry. The absence of leaflet calcification and the high prevalence of large sinuses and ascending aorta may reasonably explain this reassuring finding. However, it is important to note that because of the low incidence of this complication and the relatively small sample size of our registry, these findings should be interpreted with caution and regarded as hypothesis generating.

As previously shown,[16] the occurrence of cerebrovascular events after TAVR in NAVR does not appear to be a significant concern compared with stroke rates in TAVR for aortic stenosis.[28] This could be due to the limited amount of calcium on the aortic leaflets, as 92.6% of the overall population has no or only a mild degree of leaflet calcification. Conversely, the lack of calcium on the aortic leaflets may contribute to the need for permanent pacemaker implantation, as it could render the atrioventricular conduction system more susceptible to mechanical damage. Furthermore, the tendency of the valve to migrate and the potential for less precise device positioning in patients with pure NAVR may also play a role in the higher pacemaker implantation rates observed. Consequently, more than 20% of patients in both groups underwent pacemaker device implantation following TAVR.

TVEM, often referred to as the Achilles' heel of TAVR in NAVR, remains a common complication (**Central Illustration**), regardless of the type of THV

CENTRAL ILLUSTRATION **Performance of Currently Available THVs in Pure NAVR**

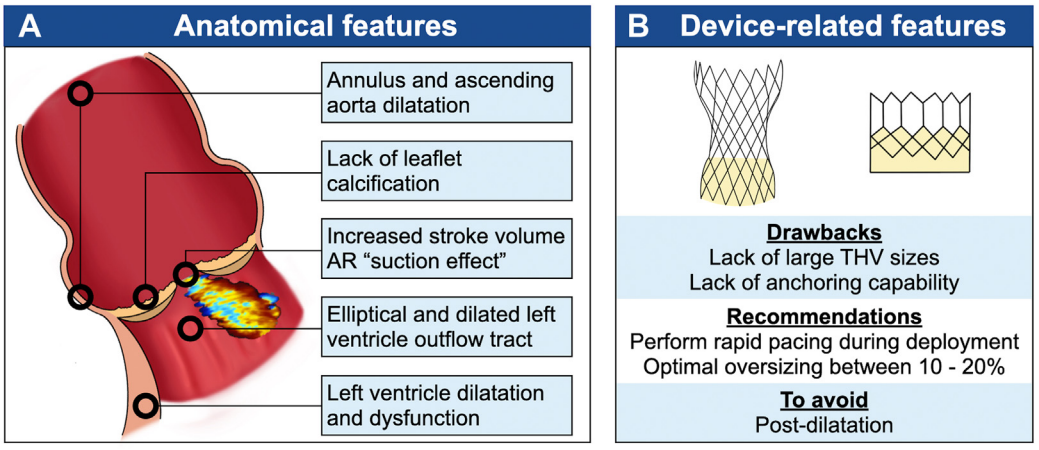


Poletti E, et al. J Am Coll Cardiol Intv. 2023;16(16):1974–1985.

A total of 201 patients with native aortic valve regurgitation (NAVR) underwent off-label transcatheter aortic valve replacement (TAVR) with currently available transcatheter heart valve (THV) devices. In comparing the performance and short-term results of self-expanding (SE) and balloon-expandable (BE) THVs, both appeared to be similar. Transcatheter valve embolization and migration (TVEM) remained the most frequent complication and had a significant impact on outcomes in both the short term and during the 1-year follow-up period. AR = aortic regurgitation.

used (Supplemental Tables 5 and 6). Compared with TVEM in aortic stenosis, embolization in NAVR is much more frequent and tends to involve the ventricular side more often. The latter has strong clinical implications, as ventricular TVEM has been linked to a higher incidence of surgical conversion and in-hospital death.[29] As inferred from multivariate analysis, postdilation is an independent predictor of

FIGURE 4 TAVR in the Setting of NAVR and Factors Associated With TVEM



C Performance of current generation THVs

	Aortic Stenosis	Aortic Regurgitation
TVEM	+	-
Need for second valve implantation	+	-
Residual AR/paravalvular leak	+	-
Pacemaker rate	+	-
Cerebrovascular events	-	+
High residual gradient	-	+
Risk of coronary obstruction	+	+

(A) Anatomical and **(B)** device-related features contributing to increased risk for TVEM. **(B)** Technical tips provided to mitigate this risk. **(C)** Performance of current THVs in pure NAVR compared with aortic stenosis. Plus symbol denotes "in favor of." AR = aortic regurgitation; other abbreviations as in Figures 1 and 3.

TVEM in patients undergoing TAVR for NAVR. During postdilation, the mechanical interaction between the dilated prosthesis and the native valve may not provide a secure anchor at the aortic ring because of the absence of leaflet calcifications. Typically, postdilation is performed when significant residual AR persists, which can arise from incorrect THV sizing or malpositioning during deployment. Therefore, the mechanical interaction among native valve, THV and balloon, along with an incorrect sizing or malpositioning of the device, may potentially increase the risk of TVEM during postdilation.

Additional factors that may contribute to TVEM occurrence in pure NAVR include the increased regurgitant volume that may act as a "suction force" for the THV toward the left ventricular cavity and an increased stroke volume that causes the THV to shift on the aortic side (Figure 4).[30] To mitigate the risk for TVEM for SE THVs, together with postdilation avoidance, rapid pacing should be considered during THV deployment. In our population, rapid pacing during THV deployment was performed in >88% of the procedures. Of note, it is widely accepted that ventricular pacing after deployment can improve hemodynamic status and platform stability. Therefore, rapid ventricular pacing during and after THV deployment should be advised regardless of the device used (SE or BE).

STUDY LIMITATIONS. First, the retrospective nature of the PANTHEON study and the lack of an echocardiography and angiography core laboratory may have resulted in residual unadjusted confounders that may have affected the results.

Second, the intermediate sample size limits the power of statistical analysis in the assessment of differences in procedural success rates. However, in contrast to previous studies, the present registry is

the first to represent a contemporary cohort of patients treated with currently available devices (both SE and BE).

Finally, the potential role of new dedicated devices for NAVR treatment was not considered, and it is of great interest to determine the results of the ongoing trial on the device that received Conformité Européenne mark approval in May 2021 for the percutaneous treatment of pure severe NAVR (JenaValve ALIGN-AR Pivotal Trial [NCT04415047]).

CONCLUSIONS

TAVR for pure severe NAVR remains a challenging procedure, burdened by a significant risk for TVEM. Nondedicated SE and BE platforms seem to have comparable performance in this setting. Dedicated TAVR devices are needed to provide a safe and effective alternative to surgery in high-risk patients.

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ADDRESS FOR CORRESPONDENCE: Dr Luca Testa, IRCCS Policlinico San Donato, "Vita e Salute" University, San Raffaele Hospital, Piazza E. Malan 1, 20149 Milan, Italy. E-mail: luctes@gmail.com.

PERSPECTIVES

WHAT IS KNOWN? In patients with severe pure NAVR unsuitable for cardiac surgery, TAVR is associated with suboptimal results. However, the available evidence concerns mostly outdated THVs.

WHAT IS NEW? In patients undergoing off-label TAVR for severe pure NAVR, SE and BE new-generation devices demonstrated comparable rates of technical success and device success. However, TVEM remains a common adverse event, contributing to significant complication rates and having an impact on short-term and 1-year outcomes.

WHAT IS NEXT? Additional studies are necessary to evaluate the long-term performance of TAVR in patients with pure NAVR. Furthermore, the potential role of new dedicated devices for the treatment of NAVR should be explored.

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KEY WORDS pure native aortic regurgitation, transcatheter aortic valve replacement, transcatheter valve embolization

APPENDIX For supplemental tables and figures, please see the online version of this paper.