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Transcatheter Aortic Valve Replacement in Pure Native Aortic Valve Regurgitation

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ABSTRACT

BACKGROUND Limited data exist about safety and efficacy of transcatheter aortic valve replacement (TAVR) in patients with pure native aortic regurgitation (AR).

OBJECTIVES This study sought to compare the outcomes of TAVR with early- and new-generation devices in symptomatic patients with pure native AR.

METHODS From the pure native AR TAVR multicenter registry, procedural and clinical outcomes were assessed according to VARC-2 criteria and compared between early- and new-generation devices.

RESULTS A total of 331 patients with a mean STS score of 6.7 ± 6.7 underwent TAVR. The early- and new-generation devices were used in 119 patients (36.0%) and 212 patients (64.0%), respectively. STS score tended to be lower in the new-generation device group (6.2 ± 6.7 vs. 7.6 ± 6.7; $p = 0.08$), but transfemoral access was more frequently used in the early-generation device group (87.4% vs. 60.8%; $p < 0.001$). Compared with the early-generation devices, the new-generation devices were associated with a significantly higher device success rate (81.1% vs. 61.3%; $p < 0.001$) due to lower rates of second valve implantation (12.7% vs. 24.4%; $p = 0.007$) and post-procedural AR ≥ moderate (4.2% vs. 18.8%; $p < 0.001$). There were no significant differences in major 30-day endpoints between the 2 groups. The cumulative rates of all-cause and cardiovascular death at 1-year follow-up were 24.1% and 15.6%, respectively. The 1-year all-cause mortality rate was significantly higher in the patients with post-procedural AR ≥ moderate compared with those with post-procedural AR ≤ mild (46.1% vs. 21.8%; log-rank $p = 0.001$). On multivariable analysis, post-procedural AR ≥ moderate was independently associated with 1-year all-cause mortality (hazard ratio: 2.85; 95% confidence interval: 1.52 to 5.35; $p = 0.001$).

CONCLUSIONS Compared with the early-generation devices, TAVR using the new-generation devices was associated with improved procedural outcomes in treating patients with pure native AR. In patients with pure native AR, significant post-procedural AR was independently associated with increased mortality. (J Am Coll Cardiol 2017;70:2752-63)

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The prevalence of aortic regurgitation (AR) increases with age, occurring in up to 2% of individuals over 70 years of age (1). Symptomatic patients with chronic severe AR have a poor prognosis and therefore should undergo surgery. However, in the aging population, an increasing number of patients with symptomatic severe AR have excessive comorbidities or a clinical condition that contraindicates open heart surgery, and most of them are deemed a high surgical risk and often treated conservatively.

Since the first report of successful transcatheter aortic valve replacement (TAVR), the growing experience, accumulated

ABBREVIATIONS AND ACRONYMS

AR = aortic regurgitation

CI = confidence interval

HR = hazard ratio

TAVR = transcatheter aortic valve replacement

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knowledge, and technological development lead to an expanded use of TAVR in a lower surgical risk population, as well as use in other valvular positions or pathologies such as pure native AR (2–8). However, pure native AR has been considered a contraindication for TAVR due to absent aortic valve calcification and the subsequent difficulty in anchoring the transcatheter valves. The initial report of TAVR using the early-generation self-expanding prostheses for pure native AR showed high rates of procedural complications (9). However, the new-generation devices with retrievability and repositioning capacity, external sealing cuff, or unique anchoring mechanisms could potentially overcome the procedural challenges in treating pure native AR. Therefore, we aimed to create an international multicenter registry of TAVR in pure native AR and evaluate the procedural and clinical outcomes of TAVR in patients with pure native AR, taking into consideration the technological developments of transcatheter valves.

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METHODS

STUDY DESIGN AND PATIENT POPULATION. The pure native AR TAVR registry is an international, multicenter, observational study that enrolled all consecutive patients with symptomatic severe AR undergoing TAVR. The registry was initiated in August 2016, and a total of 40 centers from Europe, North America, and Asia-Pacific participated in the registry. Patients were considered candidates for the procedure if they had severe AR with comorbid conditions that would preclude surgical valve replacement. Patients with aortic stenosis defined as a peak aortic jet velocity on continuous-wave Doppler of >2.5 m/s were excluded from this study. We collected data retrospectively for cases performed before study initiation and prospectively thereafter. This study was approved by the institutional review board of each institution, and all patients provided written informed consent for TAVR and the use of anonymous clinical, procedural, and follow-up data for research. For retrospective analysis of clinically acquired and anonymized data, the institutional review board of some institutions waived the need for written patient informed consent.

STUDY DEVICES AND TAVR PROCEDURE. Patients were selected for TAVR at the institutional level after discussions by the multidisciplinary heart team. Device size was selected based on 3-dimensional computed tomographic and transesophageal echocardiographic measurements. The access site and type of device were determined by the multidisciplinary heart team. All TAVR procedures were conducted in accordance with local guidelines using standard techniques via transfemoral or nontransfemoral access, and the self-expanding transcatheter valves (the CoreValve/Evolut R [Medtronic, Minneapolis, Minnesota], Portico [St. Jude Medical, Minneapolis, Minnesota], and Acurate [Symetis SA, Ecublens, Switzerland]), the balloon-expandable transcatheter valves (the Sapien XT/Sapien 3 [Edwards Lifesciences, Irvine, California]), and other transcatheter valves (JenaValve [JenaValve Technology, Munich, Germany], Lotus [Boston Scientific, Natick, Massachusetts], Direct Flow [Direct Flow Medical, Santa Rosa, California], and J-Valve [JieCheng Medical Technology CO., Suzhou, China]) were implanted (10–20).

DATA COLLECTION. Data collection included baseline clinical, laboratory, echocardiographic, and computed tomographic data, as well as procedural data and clinical follow-up data at pre-specified time points (1, 6, and 12 months and yearly thereafter). Follow-up was obtained by clinical visits and/or through telephone contacts, and information about cause of death and rehospitalization was collected. Referring cardiologists, general practitioners, and patients were contacted whenever necessary for further information. All data provided by each institution were anonymized and centrally collected, and all inconsistencies were resolved directly with local investigators and onsite data monitoring.

ENDPOINTS AND DEFINITIONS. The primary endpoints of the present study were all-cause and cardiovascular mortality rates at 1 year. Secondary endpoints were rehospitalization, device success, and other 30-day major clinical endpoints defined according to the VARC (Valve Academic Research Consortium-2) criteria (21). Other endpoints included procedure- and device-related complications, and echocardiographic assessment of the valve and cardiac function at post-procedure. No echocardiographic core laboratory was used, and all echocardiographic data were site reported. The severity of post-procedural AR was qualitatively assessed and graded using transthoracic echocardiography at each institution according to established guidelines and VARC-2 criteria (21). The perimeter and area oversizing indexes were defined as: [(device nominal perimeter or area)/(annulus perimeter or area measured by computed tomography) − 1] × 100, respectively.

STATISTICAL ANALYSIS. Patients were stratified according to whether they received the early-generation devices (the CoreValve and Sapien XT) or the new-generation devices (the Evolut R, Sapien 3,

JenaValve, Lotus, Direct Flow, Acurate, Portico, and J-Valve). Continuous variables are presented as mean ± SD and compared using the Student's *t*-test or Mann-Whitney *U* test. Categorical variables are presented as counts or percentages, and compared using the chi-square or Fisher exact test. Receiver-operating characteristic curve analysis was performed, and areas under the curve were calculated to assess the discriminative powers of device sizing parameters for post-procedural AR ≥ moderate. Cumulative rates of death or rehospitalization were calculated using the Kaplan-Meier survival analysis, and the log-rank test was used for comparisons across the groups. For rehospitalization, data were censored at the time of death or the end of the observation period. Univariable Cox regression models were used to evaluate potential predictors of all-cause mortality or rehospitalization at 1-year follow-up. Statistically significant variables with a p value of <0.10 by univariable analysis were included in the multivariable model. The final model was determined by backward elimination procedures with a threshold of $p < 0.10$. The proportional hazards assumption was confirmed by examination of log (−log [survival]) curves and by testing of partial (Shoenfeld) residuals, and no relevant violations were found. The estimated hazard ratio (HR) with 95% confidence interval (CI) was provided by the Cox model. All statistical analyses were performed using SPSS software version 24.0 (SPSS, Chicago, Illinois) or MedCalc (MedCalc Software, Mariakerke, Belgium). A 2-sided p value of <0.05 was considered to be of statistical significance.

TABLE 1 Baseline Characteristics

	Overall (N = 331)	Early-Generation Devices (n = 119)	New-Generation Devices (n = 212)	p Value
Age, yrs	74.4 ± 12.2	74.2 ± 13.1	74.5 ± 11.6	0.81
Female	159 (48.0)	51 (42.9)	108 (50.9)	0.16
NYHA functional class III or IV	293 (88.5)	107 (89.9)	186 (87.7)	0.55
STS score	6.7 ± 6.7	7.6 ± 6.7	6.2 ± 6.7	0.08
Euro SCORE II	9.8 ± 10.7	11.7 ± 12.9	8.9 ± 9.4	0.03
Creatinine, mg/dl	1.4 ± 1.0	1.5 ± 1.1	1.4 ± 1.0	0.48
Hypertension	255 (77.0)	88 (73.9)	167 (78.8)	0.32
Diabetes mellitus	43 (13.0)	22 (17.6)	22 (10.4)	0.06
Chronic pulmonary disease	98 (29.6)	28 (23.5)	70 (33.0)	0.07
Peripheral vascular disease	65 (19.6)	20 (16.8)	45 (21.2)	0.33
Prior cerebrovascular accident	33 (10.0)	8 (6.7)	25 (11.8)	0.14
Coronary artery disease	156 (47.1)	52 (43.7)	104 (49.1)	0.35
Prior myocardial infarction	72 (21.8)	23 (19.3)	49 (23.1)	0.42
Prior PCI	90 (27.2)	29 (24.4)	61 (28.8)	0.39
Prior CABG	49 (14.8)	20 (16.8)	29 (13.7)	0.44
Prior mitral valve surgery	29 (8.8)	7 (5.9)	22 (10.4)	0.17
Prior permanent pacemaker	51 (15.4)	22 (18.5)	29 (13.7)	0.25
Atrial fibrillation	115 (34.7)	36 (30.3)	79 (37.3)	0.20
Echocardiographic findings				
LVEF, %	45.7 ± 14.6	44.5 ± 14.3	46.3 ± 14.8	0.28
Ascending aorta diameter, mm	36.0 ± 7.6	36.7 ± 8.3	35.5 ± 7.0	0.35
Mitral regurgitation ≥ moderate	113 (35.4)	40 (35.1)	73 (35.6)	0.93
Pulmonary hypertension	88 (26.6)	38 (31.9)	50 (23.6)	0.10

Values are mean ± SD or n (%).

CABG = coronary artery bypass graft surgery; EuroSCORE = European System for Cardiac Operative Risk Evaluation; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; STS = Society of Thoracic Surgeons.

RESULTS

BASELINE CHARACTERISTICS. A total of 331 patients with symptomatic, severe pure native AR were treated with TAVR across 40 participating centers between September 2007 and February 2017. The baseline characteristics of the study population are shown in Table 1. Of the study population, 119 patients (36.0%) had TAVR with the early-generation devices and 212 patients (64.0%) received the new-generation devices. In the overall cohort, approximately one-half of patients were male with a mean age of 74.4 years, and had increased surgical risk scores with a mean STS (Society of Thoracic Surgeons) score of 6.7 ± 6.7%, and EuroSCORE II (European System for Cardiac Operative Risk Evaluation II) of 9.8 ± 10.7%. All patients were discussed by the multidisciplinary heart team, taking into account increased surgical risk scores (STS score ≥8%: 28.0%), as well as other factors, including frailty (48.9%), porcelain aorta/previous radiation therapy/hostile chest (8.9%), severe pulmonary disease prohibiting intubation (6.4%), neurological disorders (4.2%), previous cardiac surgery for heart transplantation/congenital heart disease/aortic dissection (3.9%), critical pre-procedural state such as left ventricular assist device (3.5%), cancer (3.5%), end-stage liver failure (1.9%), and/or combination of other comorbidities such as poor left ventricular ejection fraction, severe pulmonary hypertension, or mitral regurgitation (8.1%). Surgical risk scores tended to be lower in the new-generation device group compared with the early-generation device group (STS score 6.2 ± 6.7% vs. 7.6 ± 6.7%; p = 0.08; EuroSCORE II 8.9 ± 9.4% vs. 11.7 ± 12.9%; p = 0.03). There were no significant differences between the 2 groups in terms of age, baseline New York Heart Association functional class, and other comorbidities except trends of more frequent chronic pulmonary disease (33.0% vs. 23.5%; p = 0.07) and less frequent diabetes mellitus (10.4% vs. 17.6%; p = 0.06) in the new-generation device group. There were no significant differences in echocardiographic findings between the 2 groups. The data regarding the etiology of AR were available

TABLE 2 Procedural Data

	Overall (N = 331)	Early-Generation Devices (n = 119)	New-Generation Devices (n = 212)	p Value
General anesthesia	192 (58.0)	58 (48.7)	134 (63.2)	0.01
Local anesthesia	139 (42.0)	58 (51.3)	78 (36.8)	0.01
Access site				
Transfemoral access	233 (70.4)	104 (87.4)	129 (60.8)	<0.001
Non-transfemoral access	98 (29.6)	15 (12.6)	83 (39.2)	<0.001
Transapical access	80 (24.2)	4 (3.4)	76 (35.8)	<0.001
Trans-subclavian access	10 (3.0)	4 (3.4)	6 (2.8)	0.79
Transaortic access	6 (1.8)	5 (4.2)	1 (0.5)	0.02
Transcarotid access	2 (0.6)	0 (0.0)	2 (1.7)	0.13
Device type				
Sapien XT	9 (2.7)	9 (7.6)	–	
Sapien 3	41 (12.4)	–	41 (19.3)	
CoreValve	110 (33.2)	110 (92.4)	–	
Evolut R	50 (15.1)	–	50 (23.6)	
JenaValve	64 (19.3)	–	64 (30.2)	
Direct Flow	35 (10.6)	–	35 (16.5)	
J-Valve	1 (0.3)	–	1 (0.5)	
Engager	7 (2.1)	–	7 (3.3)	
Portico	3 (0.9)	–	3 (1.4)	
Acurate	5 (1.5)	–	5 (2.4)	
Lotus	6 (1.8)	–	6 (2.8)	
Procedure time, min	102.1 ± 65.6	89.8 ± 50.2	109.1 ± 72.1	0.047
Fluoroscopy time, min	22.2 ± 17.8	29.1 ± 23.2	18.4 ± 12.5	<0.001
Contrast agent, ml	162.2 ± 88.7	180.1 ± 95.2	150.9 ± 82.7	0.01
Balloon pre-dilation	26 (7.9)	7 (5.9)	19 (9.0)	0.32
Balloon post-dilation	47 (14.2)	23 (19.3)	24 (11.3)	0.045

Values are n (%) or mean ± SD.

in 251 patients (76.8%): the majority of patients exhibited severe AR due to degenerative changes of the aortic cusps (56.6%), annular dilation (23.1%), and other etiologies (Online Figure 1).

PROCEDURAL DATA. Procedural and computed tomography findings are summarized in **Table 2 and** Online Table 1, respectively. Pre-procedural computed tomography assessment was performed in the majority of patients (84.9%), with a higher rate in the new-generation device group (90.6% vs. 74.8%; $p < 0.001$). The mean aortic annulus diameter, area, and perimeter were 25.2 mm, 488.0 mm^2, and 79.3 mm, respectively, without significant differences between the 2 groups. Aortic valve calcification was absent or mild in the majority of patients (85.9%), without significant difference between the 2 groups. The ascending aorta was assessed in 252 patients (81.0%), with a mean diameter of 36.5 mm, and 68 patients (27.0%) had a dilated ascending aorta with a diameter of more than 40 mm.

In terms of procedural data, patients in the new-generation device group had more frequent general anesthesia (63.2% vs. 48.7%; $p = 0.01$) and nontransfemoral approach (39.2% vs. 12.6%; $p < 0.001$) compared with those in the early-generation device group. The most frequently used prosthesis was the CoreValve (33.2%), followed by the JenaValve (19.3%), Evolut R (15.1%), Sapien 3 (12.4%), Direct Flow (10.6%), and other devices. Compared with the patients in the early-generation device group, the patients in the new-generation device group had a longer procedure time (109.1 ± 72.1 min vs. 89.8 ± 50.2 min; $p = 0.047$) but had a shorter fluoroscopy time (18.4 ± 12.5 min vs. 29.1 ± 23.2 min; $p < 0.001$) and a smaller contrast agent volume (150.9 ± 82.7 ml vs. 180.1 ± 95.2 ml; $p = 0.01$). Balloon pre-dilation was performed in 7.9% of patients due to absence of pre-procedural computed tomography (1.5%), any aortic valve calcification (6.6%), and/or initial experience (2.1%). Balloon post-dilation was less frequently performed in the new-generation device group compared with the early-generation device group (11.3% vs. 19.3%; $p = 0.045$).

PROCEDURAL AND CLINICAL OUTCOMES. The procedural and clinical outcomes of the study population are summarized in **Table 3**. In the overall cohort, procedure-related death, conversion to conventional surgery, coronary obstruction, aortic root injury, and re-intervention were observed in 10 (3.0%), 12 (3.6%), 4 (1.2%), 5 (1.5%), and 14 patients (4.2%), respectively. There was no significant difference in new permanent pacemaker insertion rates between the 2 groups, but the new-generation devices were associated with a lower incidence of second valve implantation (12.7% vs. 24.4%; $p = 0.007$). With respect to echocardiographic findings, post-procedural left ventricular ejection fraction was similar between the 2 groups (43.5 ± 14.2% vs. 44.3 ± 14.5%; $p = 0.68$), whereas the new-generation devices were associated with a lower incidence of post-procedural AR ≥ moderate (4.2% vs. 18.8%; $p < 0.001$), which resulted in significantly higher device success rate with the new-generation devices (81.1% vs. 61.3%; $p < 0.001$) (**Central Illustration**).

In terms of 30-day clinical outcomes, all-cause and cardiovascular death were observed in 36 patients (10.9%) and 32 patients (9.7%), respectively. Compared with the early-generation devices, the new-generation devices tended to be associated with a higher rate of stroke (5.7% vs. 1.7%; $p = 0.08$) but a lower rate of stage 2 or 3 acute kidney injury (6.1% vs. 11.8%; $p = 0.07$). There were no significant differences in other major 30-day endpoints between the 2 groups. Given that the median number of TAVR procedures at each institution was 7, patients were

divided into the early experience group (the first 7 cases) and the late experience group (the eighth case and thereafter). There were no significant differences in procedural and clinical outcomes between the 2 groups, except that the late experience was associated with a reduction in major vascular complication (1.8% vs. 6.8%; p = 0.02) (Online Figure 2).

OUTCOMES ACCORDING TO DEVICE TYPE. With stratification according to the device type, including the CoreValve, Evolut R, Sapien 3, JenaValve, and Direct Flow devices, procedural outcomes are shown in **Figure 1**. Compared with the CoreValve, the JenaValve was associated with a significantly lower incidence of second valve implantation (9.4% vs. 26.4%; p = 0.007). Similarly, compared with the CoreValve, the new-generation devices (with the exception of the Direct Flow) were associated with a lower incidence of post-procedural AR ≥ moderate (Evolut R 4.0% vs. 18.2%; p = 0.016; Sapien 3 0.0% vs. 18.2%; p = 0.003; JenaValve 1.6% vs. 18.2%; p = 0.001). Accordingly, the new-generation devices were associated with higher device success rates compared with the CoreValve. There were no significant differences in new permanent pacemaker insertion rates between the devices. In terms of 30-day clinical outcomes, the JenaValve and Direct Flow were associated with higher rates of stroke (overall p = 0.001; JenaValve 7.8%; Direct Flow 17.1%; CoreValve 0.9%; Evolut R 2.0%; Sapien 3 0.0%), whereas there were no significant differences in other major 30-day endpoints between devices (Online Figure 3).

IMPACT OF AORTIC VALVE CALCIFICATION, ANNULUS SIZE, AND DILATED AORTA. The procedural and clinical outcomes were analyzed according to the degree of aortic valve calcification (none or mild vs. moderate) (Online Table 2). None or mild aortic valve calcification was associated with less frequent device success (70.6% vs. 87.2%; p = 0.03), which was consistently observed when using the early-generation devices (53.4% vs. 83.3%; p = 0.02). However, there were no significant associations between the aortic valve calcification and procedural outcomes when using the new-generation devices (Online Figure 4). Similarly, the procedural outcomes were analyzed according to the mean annulus diameter (mean diameter <25.2 mm vs. ≥25.2 mm) and diameter of ascending aorta (<40 mm vs. ≥40 mm). In the overall cohort, larger annulus was associated with less frequent device success (70.2% vs. 86.0%; p = 0.005), due to higher rates of second valve implantation (21.2 vs. 8.4%; p = 0.009) and post-procedural AR ≥ moderate (8.7% vs. 2.8%; p = 0.07) (Online Figure 5). When using the early-generation devices, dilated aorta was associated with more frequent post-procedural AR ≥ moderate (35.7% vs. 9.2%; p = 0.002) and less frequent device success (35.7% vs. 69.2%; p = 0.003) (Online Figure 6). However, there were no significant associations between procedural outcomes and dilated aorta when using the new-generation devices.

TABLE 3 Procedural and Clinical Outcomes

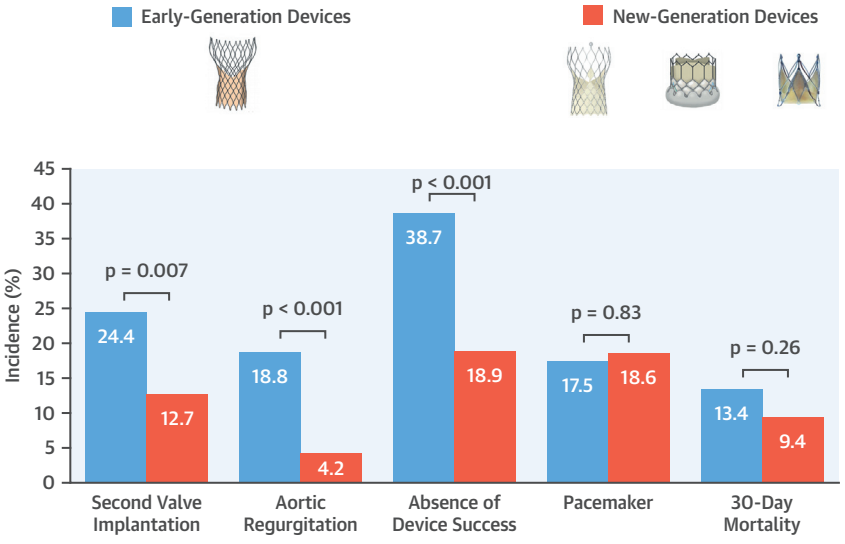
	Overall (N = 331)	Early-Generation Devices (n = 119)	New-Generation Devices (n = 212)	p Value
Procedural outcomes				
Procedure-related death	10 (3.0)	5 (4.2)	5 (2.4)	0.35
Conversion to conventional surgery	12 (3.6)	4 (3.4)	8 (3.8)	0.85
Coronary obstruction	4 (1.2)	0 (0.0)	4 (1.9)	0.30
Aortic root injury	5 (1.5)	2 (1.7)	3 (1.4)	>0.99
Need for second valve implantation	55 (16.6)	29 (24.4)	27 (12.7)	0.007
New permanent pacemaker*	51 (18.2)	17 (17.5)	34 (18.6)	0.83
Re-intervention	14 (4.2)	6 (5.0)	8 (3.8)	0.58
Echocardiographic findings at discharge				
Mean gradient, mm Hg	9.3 ± 4.8	7.7 ± 4.9	10.2 ± 4.5	<0.001
LVEF, %	44.0 ± 14.3	43.5 ± 14.2	44.3 ± 14.5	0.68
Aortic regurgitation ≥ moderate	29 (9.6)	21 (18.8)	8 (4.2)	<0.001
Device success	246 (74.3)	73 (61.3)	172 (81.1)	<0.001
Clinical outcomes at 30 days				
All-cause mortality	36 (10.9)	16 (13.4)	20 (9.4)	0.26
Cardiovascular mortality	32 (9.7)	14 (11.8)	16 (8.5)	0.33
Stroke	14 (4.2)	2 (1.7)	12 (5.7)	0.08
Bleeding	39 (11.8)	18 (15.1)	21 (9.9)	0.16
Major	25 (7.6)	12 (10.1)	13 (6.1)	0.19
Life-threatening	14 (4.2)	6 (5.0)	8 (3.8)	0.58
Major vascular complication	14 (4.2)	7 (5.9)	7 (3.3)	0.26
Acute kidney injury (stage 2 or 3)	27 (8.2)	14 (11.8)	13 (6.1)	0.07

Values are n (%) or mean ± SD. *280 patients without prior pacemakers were analyzed.
LVEF = left ventricular ejection fraction; LVOT = left ventricular outflow tract.

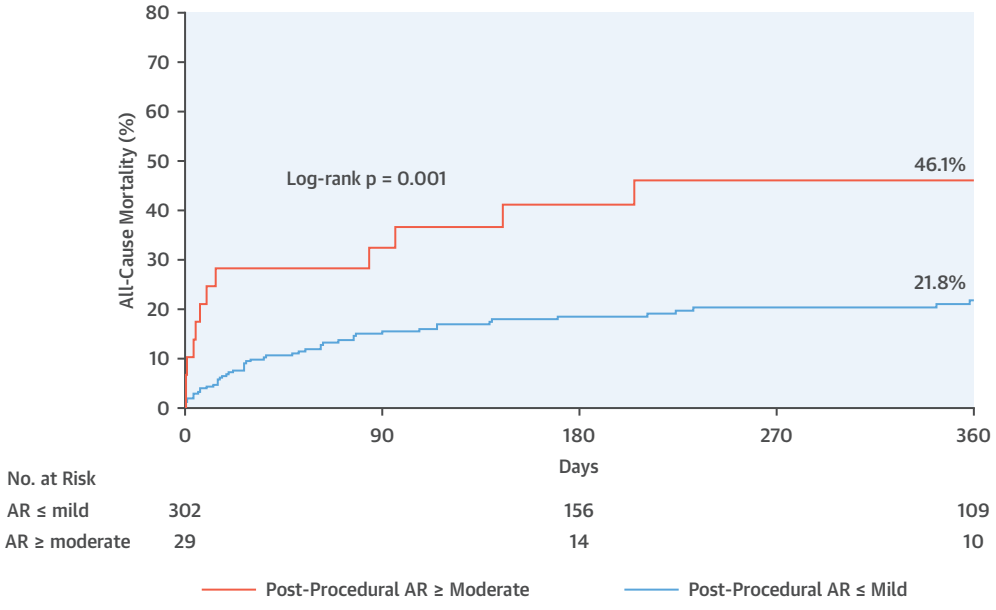
DEVICE SIZING AND POST-PROCEDURAL AORTIC REGURGITATION. The mean perimeter oversizing indexes were 14.8 ± 9.5% for the CoreValve and 19.9 ± 11.6% for the Evolut R. The mean area oversizing indexes were 13.6 ± 13.9% for the Sapien 3, 10.4 ± 8.7% for the JenaValve, and 24.9 ± 18.6% for the Direct Flow. Among patients with none or mild aortic valve calcification, 87 patients treated with the self-expanding valves had available computed tomography data. Receiver-operating characteristic curve analysis for predicting post-procedural AR ≥ moderate identified cutoff value of perimeter oversizing index as 15% (area under the curve 0.76; p < 0.001; sensitivity 81%; specificity 63%). When using the self-expanding valves, a higher degree of perimeter oversizing index (≥15%) was associated with less frequent post-procedural AR ≥ moderate (4.0% vs. 24.3%; p = 0.005).

CENTRAL ILLUSTRATION **TAVR for Pure Native Aortic Valve Regurgitation**

Outcomes According to Devices



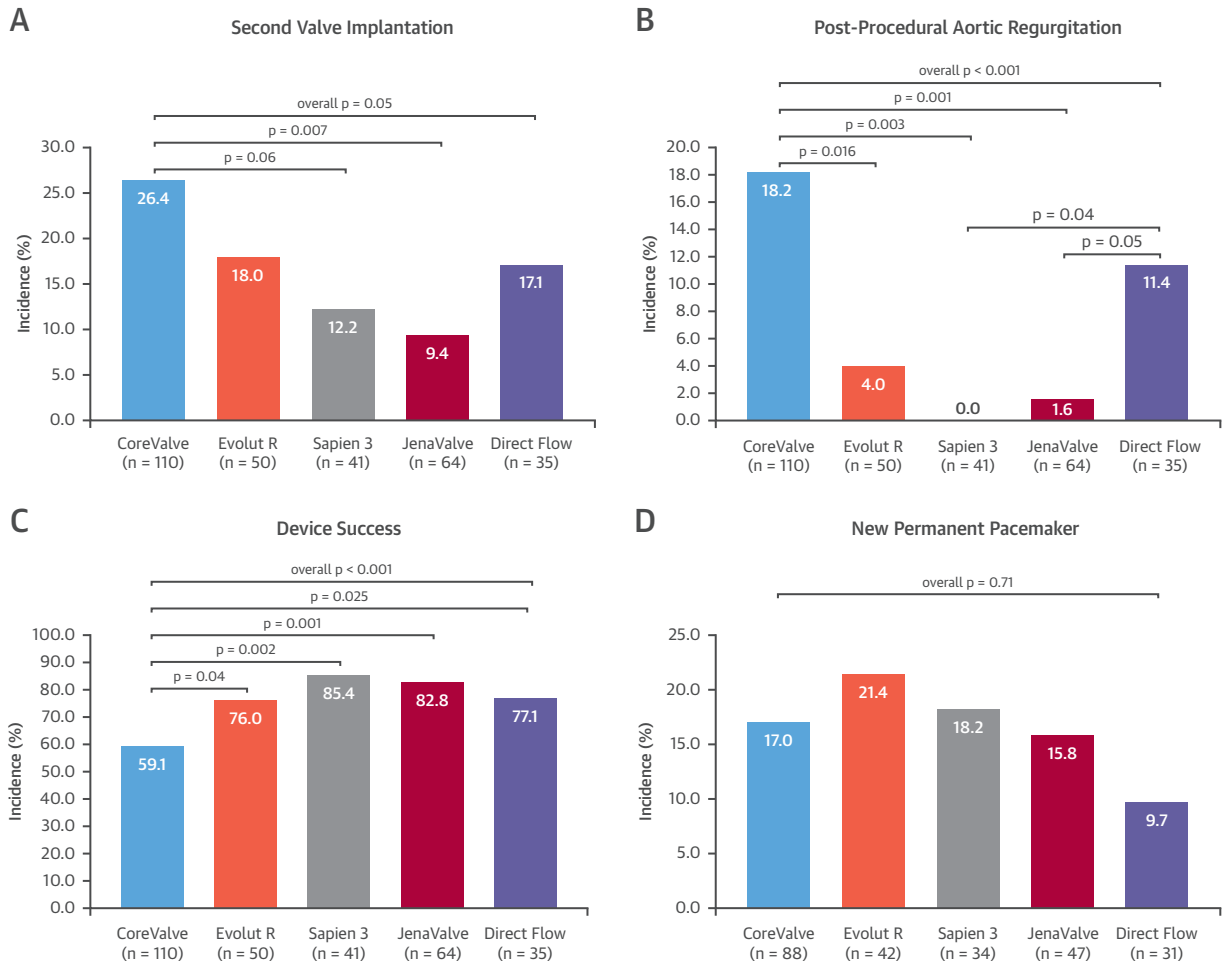
Mortality and Post-Procedural Aortic Regurgitation



Yoon, S.-H. et al. J Am Coll Cardiol. 2017;70(22):2752–63.

Incidences of second valve implantation, post-procedural aortic regurgitation (AR) ≥ moderate, device success, new permanent pacemaker insertion, and 30-day mortality following transcatheter aortic valve replacement (TAVR) for patients with pure native AR using the early- and new-generation devices are shown **(top)**. The cumulative 1-year all-cause mortality rates in patients with post-procedural AR ≥ moderate **(orange line)** and those with post-procedural AR ≤ mild **(blue line)** after TAVR in pure native AR are shown **(bottom)**.

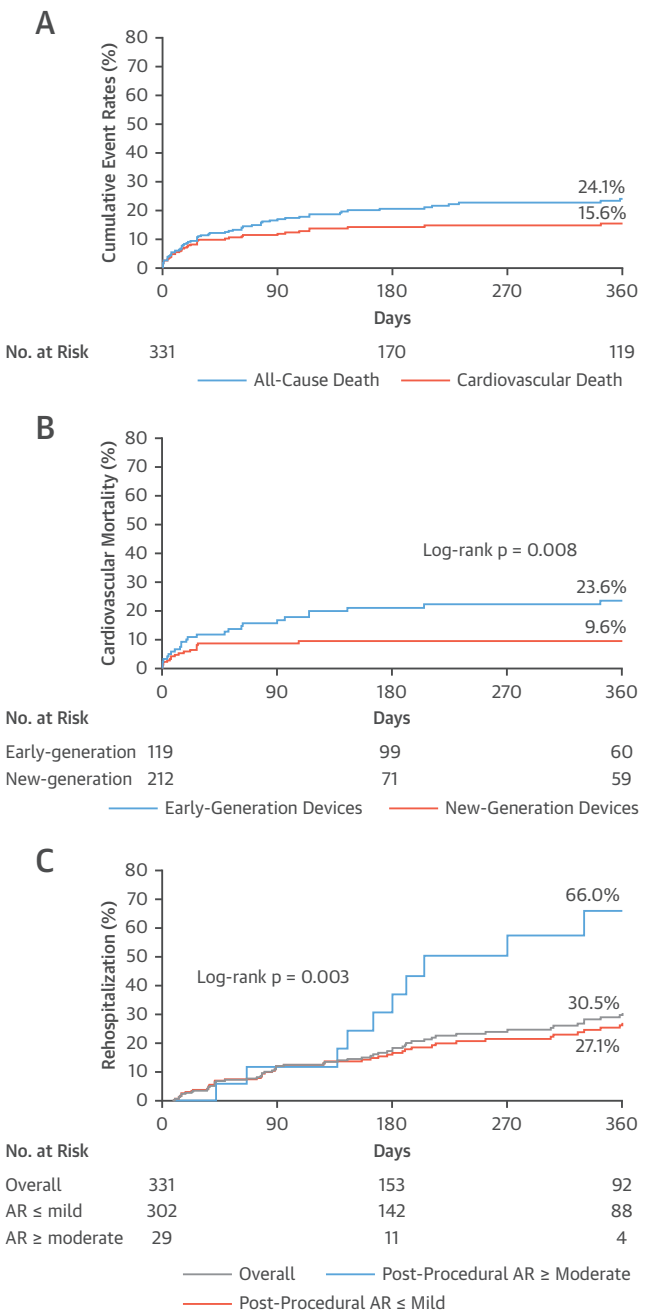
FIGURE 1 Procedural Outcomes According to Devices



Incidences of **(A)** second valve implantation, **(B)** post-procedural aortic regurgitation ≥ moderate, **(C)** device success, and **(D)** new permanent pacemaker insertion following transcatheter aortic valve replacement for patients with pure native aortic regurgitation using the CoreValve, Evolut R, Sapien 3, JenaValve, and Direct Flow devices are shown.

MID-TERM MORTALITY AND REHOSPITALIZATION. Over a median follow-up period of 200 days (interquartile range: 40 to 500 days), 82 patients died in the overall cohort (42 patients in the early-generation device group and 40 patients in the new-generation device group). The cumulative event rates for all-cause and cardiovascular death at 1-year follow-up were 24.1% and 15.6%, respectively (**Figure 2A**). The cumulative event rates for all-cause death at 1-year follow-up were significantly higher in patients with post-procedural AR ≥ moderate compared with those with post-procedural AR ≤ mild (46.1% vs. 21.8%; log-rank p = 0.001) (**Central Illustration**). Although there were no significant differences in 1-year all-cause mortality between the early- and new-generation device groups (28.8% vs. 20.6%; log-rank p = 0.13) (Online Figure 7), the new-generation devices were associated with a lower 1-year cardiovascular mortality (9.6% vs. 23.6%; log-rank p = 0.008) (**Figure 2B**). Over the entire follow-up period, 72 patients experienced rehospitalization (39 patients in the early-generation device group and 33 patients in the new-generation device group). The overall cumulative event rate of rehospitalization at 1-year follow-up was 30.5% with significant higher rate of rehospitalization in the patients with post-procedural AR ≥ moderate compared with those with post-procedural AR ≤ mild (66.0% vs. 27.1%; log-rank p = 0.003) (**Figure 2C**).

FIGURE 2 Kaplan-Meier Curves



(A) The overall all-cause **(blue line)** and cardiovascular mortality rates **(orange line)** at 1-year follow-up in patients undergoing transcatheter aortic valve replacement (TAVR) for pure native aortic regurgitation (AR) are shown. **(B)** The cumulative 1-year cardiovascular mortality rates in patients with the early-generation devices **(blue line)** and those with the new-generation devices **(orange line)** after TAVR in pure native AR are shown. **(C)** The cumulative 1-year rehospitalization rates of the overall cohort **(gray line)**, patients with post-procedural AR ≥ moderate **(blue line)**, and those with post-procedural AR ≤ mild **(orange line)** after TAVR in pure native AR are shown. Event rates were compared using the log-rank test.

After adjustment with multivariable analysis, STS score (HR: 1.03; 95% CI: 1.00 to 1.06; p = 0.037), left ventricular ejection fraction ≤45% (HR: 1.78; 95% CI: 1.07 to 2.94; p = 0.026), baseline mitral regurgitation ≥ moderate (HR: 2.11; 95% CI: 1.29 to 3.45; p = 0.003), and post-procedural AR ≥ moderate (HR: 2.85; 95% CI: 1.52 to 5.35; p = 0.001) were all independently associated with 1-year all-cause mortality (**Table 4**). On multivariable analysis, independent predictors for rehospitalization at 1-year follow-up were baseline mitral regurgitation ≥ moderate (HR: 1.96; 95% CI: 1.17 to 3.28; p = 0.011) and post-procedural AR ≥ moderate (HR: 2.85; 95% CI: 1.44 to 5.64; p = 0.003) (Online Table 3).

DISCUSSION

The present study is the largest study to our knowledge that evaluated the safety, efficacy, and clinical outcomes of TAVR in patients with pure native AR. The major findings of the present study are as follows: 1) In the overall cohort, TAVR in pure native AR was associated with relatively high rates of procedural complications, particularly when using the early-generation devices; 2) However, the new-generation devices were associated with improved procedural outcomes with lower rates of second valve implantation and post-procedural AR ≥ moderate; and 3) Post-procedural AR ≥ moderate was associated with increased all-cause mortality and rehospitalization.

The previous major trials established TAVR as a standard treatment for inoperable or increased surgical risk patients with severe aortic stenosis (3–6). The majority of currently available transcatheter devices are designed for treating calcified aortic stenosis, relying on the fixation of the transcatheter valve within an extensively calcified annulus. In case of pure native AR, the large aortic annulus with minimal calcification challenges the anchoring of the prosthesis. Therefore, patients with predominant AR are not indicated for TAVR according to the current guidelines (22). However, accumulated experience and advancement of device technology lead to the increased off-label use of TAVR for untreated patients with significant valvular disease other than severe aortic stenosis (23). Given the increasing number of patients with valvular heart disease in the aging population, these unmet needs will keep increasing, and therefore, understanding the outcomes of TAVR in patients with pure native AR is essential.

With technological development of transcatheter valves designed for treating patients with aortic

"stenosis," the new-generation devices possess new specific features: namely, retrievability and repositioning capacity, an external sealing cuff, and a unique anchoring mechanism with clipping of the native aortic valve cusps. The initial report by Roy et al. (9) showed high rates of second valve implantation and post-procedural AR ≥ moderate after TAVR in pure native AR using the CoreValve system. However, the improved outcomes of TAVR with increased experience of the new-generation devices in "aortic stenosis" lead to applying these new technologies to treatment of pure native AR. Recently, several studies demonstrated the acceptable clinical outcomes of TAVR using the new-generation devices in patients with pure native AR (24–27). However, these studies were limited in sample size, type of device, and follow-up period. Furthermore, limited data exist about the impact of the absence of sufficient aortic valve calcification and dilation of ascending aorta on outcomes of TAVR in pure native AR.

In the present study, the overall cohort exhibited an intermediate to high surgical risk profile with mean STS score and EuroSCORE II of 6.7% and 9.8%, respectively. Although there was a trend of lower surgical risk scores in the new-generation device group compared with the early-generation device group, the indications of TAVR were thoroughly discussed by the multidisciplinary heart team and took into account, not only the STS score, but also other factors such as frailty, neurological disorders, liver failure, and porcelain aorta. The rate of non-transfemoral access was higher in the new-generation device group (39.2% vs. 12.6%; $p < 0.001$) because of the predominant use of transapical access for the JenaValve (98.4%). Relatively high rates of stroke with the JenaValve and Direct Flow were probably due to transapical access, complex procedures, and baseline comorbidities of patients.

In the overall cohort, relatively high rates of procedural complications were observed. Given that the outcomes in patients with moderate aortic valve calcification were comparable to those in the population with severe "aortic stenosis," procedural challenges of TAVR in pure AR may be attributed to the lack of sufficient calcification and subsequent difficulties in anchoring the devices. Due to poor visibility of the aortic annulus on fluoroscopy and regurgitation of contrast into the ventricle, there is a need for increased contrast volume for opacification, and placing an additional pigtail catheter may help the optimal positioning. In addition to the absence of aortic valve calcification, dilation of the ascending aorta may contribute to the increased rate of valve embolization. Therefore, the possibility of valve dislocation and subsequent need for second valve implantation should be considered during the planning process. Given the relatively high rates of complications, general anesthesia and intraprocedural echocardiography assessment of post-procedural AR would help to optimize the procedural results. In terms of device sizing, a relatively higher degree of device oversizing was associated with a reduction in post-procedural AR rates when using the self-expanding valves, which confirms the importance of pre-procedural computed tomography assessment in this population as well. Further studies are required to evaluate the optimal sizing for other valves in treating pure native AR.

The association between new-generation devices and improved procedural outcomes was affected by multiple factors. Even in patients without sufficient aortic valve calcification or those with a dilated aorta, more accurate positioning and lower rates of post-procedural AR and second valve implantation were achieved with the device enhancements: longer stent frame, new delivery system, and sealing skirt in the Sapien 3; recapturability/repositionability, reduced overall height, and redesigned stent frame with

TABLE 4 Predictors of All-Cause Mortality

	Univariable Model		Multivariable Model	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Age, yrs	1.00 (0.98–1.02)	0.98		
Female	1.05 (0.65–1.72)	0.84		
NYHA functional class IV at baseline	1.33 (0.79–2.26)	0.29		
STS score	1.03 (1.01–1.06)	0.019	1.03 (1.00–1.06)	0.037
Creatinine, mg/dl	1.00 (0.80–1.25)	0.99		
Peripheral vascular disease	1.42 (0.81–2.50)	0.23		
Chronic pulmonary disease	1.34 (0.80–2.25)	0.26		
Prior cerebrovascular accident	0.78 (0.31–1.94)	0.59		
Prior coronary artery bypass graft surgery	1.41 (0.84–2.37)	0.19		
LVEF ≤45%	1.89 (1.15–3.10)	0.012	1.78 (1.07–2.94)	0.026
Mitral regurgitation ≥ moderate at baseline	1.99 (1.22–3.25)	0.006	2.11 (1.29–3.45)	0.003
Pulmonary hypertension	1.41 (0.83–2.40)	0.20		
Transfemoral access	0.81 (0.48–1.34)	0.41		
New-generation devices	0.69 (0.42–1.12)	0.13		
Need for second valve implantation	1.69 (0.93–2.96)	0.087		
Post-procedural aortic regurgitation ≥ moderate	2.72 (1.45–5.10)	0.002	2.85 (1.52–5.35)	0.001
Late experience	0.83 (0.50–1.36)	0.46		

CI = confidence interval; HR = hazard ratio; other abbreviations as in Table 1.

optimized radial force in the Evolut R; and new anchoring mechanism with clipping of the native aortic valve cusps in the JenaValve. In addition, several factors would contribute to the improved outcomes: 1) more frequent use of pre-procedural computed tomography assessment; 2) more frequent general anesthesia with intraprocedural transesophageal guidance; 3) more frequent transapical access; and 4) improved patient selection and accumulated procedure experience. Although the new-generation devices were associated with relatively high rates of second valve implantation in patients with a larger annulus, it should be noted that the second valve implantation was not associated with increased 1-year all-cause mortality. More importantly, the technological advancement of transcatheter valves succeeded in eliminating or reducing post-procedural AR in the pure native AR population. Given the significant impact of post-procedural AR on long-term mortality, this advantage of the new-generation devices should be highlighted.

The mid- and long-term mortality may be affected by procedural complications, as well as baseline comorbidities. The present study showed the higher mid-term mortality in patients with post-procedural AR $\geq$ moderate compared with those with post-procedural AR $\leq$ mild. The impact of post-procedural AR on increased mortality, which is well recognized in the aortic stenosis population (28), was consistently observed in the present pure native AR population. Furthermore, our cohort showed the increased rehospitalization rates in patients with significant post-procedural AR. The advantage of new-generation devices over the early-generation devices was observed in 1-year cardiovascular mortality, which may be due to decreased post-procedural AR as well as fewer baseline comorbidities in the new-generation device group.

The present study showed that the patient characteristics in pure native AR were not identical to those in severe aortic stenosis. The majority of patients had reduced left ventricular ejection fraction, and one-third of patients had significant mitral regurgitation and/or pulmonary hypertension, which may render patients with pure native AR more vulnerable and contribute to the relatively higher short- and mid-term mortality than is observed in aortic stenosis patients. Furthermore, due to lack of randomized studies in pure native AR, the findings in the present study need cautious interpretation. TAVR in pure native AR should be considered for patients deemed high surgical risk after consultation with the multidisciplinary heart team, and the generalization of this procedure should be recommended only after further investigation. Further device development dedicated for treating pure native AR, establishment of device sizing guideline in this population, and accumulation of procedural experience and scientific knowledge are awaited to provide improved procedural and clinical outcomes in the future.

STUDY LIMITATIONS. First, evaluating the impact of a specific treatment using an observational study could lead to weaker conclusions than using a randomized trial because of confounding factors. Also, this study had the inherent limitations due to lack of center-independent adjunction of adverse events and an independent core laboratory to assess aortic regurgitation severity. The outcomes in this study could differ from those in "real-world" practice due to potential selection biases. Finally, device selection was not randomized, but rather at the operator's discretion, and patient selection, as well as operator experience, may have affected the observed outcomes.

CONCLUSIONS

Compared with the early-generation devices, TAVR using the new-generation devices was associated with improved procedural outcomes in treating patients with pure native AR. In patients with pure native AR, significant post-procedural AR was independently associated with increased mortality.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Compared with earlier-generation devices, newer-generation TAVR devices are associated with better procedural outcomes in patients with pure native AR. In these cases, significant post-procedural AR was associated with mortality.

TRANSLATIONAL OUTLOOK: Additional studies are needed to evaluate long-term outcomes and optimal selection of patients and device types for TAVR in pure native AR.

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KEY WORDS aortic regurgitation, transcatheter valve implantation

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