Self-Expanding Valve System for Treatment of Native Aortic Regurgitation by Transcatheter Aortic Valve Implantation (from the STS/ACC TVT Registry)

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Transcatheter aortic valve implantation (TAVI) is approved for treatment of symptomatic aortic stenosis in patients at increased risk for surgical valve replacement, but outcomes data in patients with severe native aortic regurgitation (AR) treated with TAVI remain limited. The objective of this analysis was to evaluate outcomes among patients identified in the Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapies Registry who underwent TAVI for native AR with a commercially available self-expanding valve system. From January 2014 to December 2017, 230 patients in the TVT Registry underwent TAVI for primary severe native AR using a commercially available self-expanding valve (n = 81, CoreValve; n = 149, Evolut R). For inclusion, AR was either pure or mixed with predominantly moderate/severe AR and mean aortic valve gradient ≤20 mm Hg. Thirty-day outcomes were evaluated using time-to-event methods. Device success was reported in 81.7% of patients (CoreValve, 72.2%; Evolut R, 86.9%; p = 0.0.01). Thirty-day all-cause mortality was 13.3%. All patients presented with moderate/severe AR at baseline; at 30 days, 9.1% of implanted patients with data continued to have moderate and 1.4% severe AR. There was a significant reduction in residual moderate/severe AR from the CoreValve to Evolut R device (19.1% vs 6.3%, p = 0.02). Multivariable analysis revealed factors associated with 30-day all-cause mortality include number of valves used (hazard ratio [HR] 2.361, 1.643 to 3.391, p <0.001), albumin < 3.3 mg/dL (HR 3.358, 1.551 to 7.273, p=0.002), and left ventricular ejection fraction (HR 0.978, 0.957 to 1.000, p = 0.047). Despite higher 30-day all-cause mortality, self-expanding TAVI may be an option in selected patients with AR who have no surgical options. **(Am J Cardiol 2019;124:781−788)**

Transcatheter aortic valve implantation (TAVI) has become an established therapy for severe symptomatic aortic stenosis (AS) in patients considered high or intermediate risk for conventional surgical aortic valve replacement (SAVR) in the United States.[1−4] There is now emerging expansion to additional cohorts, including treatment of native aortic regurgitation (AR).[5] Although SAVR remains the standard in patients with AR, TAVI has been used to treat patients who are not good candidates for open-heart surgery. Still, nearly 1/4 of patients with severe AR have been referred for surgery.[6] Technical factors related to a transcatheter solution remain an important consideration. With AR, lack of extensive valvular or annular calcification presents challenges for accurate valve deployment with appropriate oversizing for valve stability. Reports on TAVI in AR have described significant limitations.[7−10] We utilized data from the Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapies (STS/ACC TVT) Registry to identify and characterize patients who underwent TAVI for native AR with a commercially available self-expanding valve system and evaluated outcomes.

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Methods

We identified patients in the STS/ACC TVT Registry[11,12] who underwent TAVI with a commercially available self-expanding valve whose primary indication was moderate/severe AR from January 2014 to December 2017. AR was pure or mixed, with predominantly moderate or severe AR. For subjects with mixed etiology with predominant AR, a mean aortic valve gradient ≤20 mm Hg was also required for inclusion in the present analysis. If no AS was reported for a patient, then mean gradient and aortic valve area were not collected. Patients with failed previous prosthetic valves were excluded. All in-hospital and 30-day safety events and echocardiographic data are site-reported. Valve utilization reported in the registry does not specify how many valves were actually implanted in the patient, and thus should only be interpreted as an approximation (and by definition an overestimation) of multiple valve implantation.

The primary outcome was 30-day all-cause mortality as reported in the STS/ACC TVT Registry. Secondary end points include in-hospital clinical outcomes, rates of AR postprocedure, device success, and 1-year all-cause mortality. Quality of life was assessed through Kansas City Cardiomyopathy Questionnaire overall summary score data. The TVT Registry defines device success based on the Valve Academic Research Consortium composite end point definition.[13] Although events including device success were site-reported, sites were encouraged to adhere to aforementioned definitions. The lead author had full access to all the data in the study and takes responsibility for its integrity and data analysis.

Patients in the STS/ACC TVT Registry who underwent TAVI with a commercially available self-expanding valve whose predominant lesion was native severe AR from January 2014 to December 2017 were reported in the baseline, postprocedure and 30-day follow-up time periods. Continuous variables are reported as mean ± standard deviation and compared with the 2-sample *t* test. Paired sample *t* test was used to compare change from baseline in continuous outcomes. Categorical variables are reported as percentages and compared with the chi-square test. In-hospital events are reported as percentages. Thirty-day events are reported as Kaplan-Meier estimates and compared using the log-rank test. For predictors of 30-day mortality, methods are listed in the online supplement. For all other analyses, $p < 0.05$ was considered statistically significant. A 1-year

Table 1
Demographics and clinical characteristics

Characteristic	All patients (n = 230)	CoreValve (n = 81)	Evolut R (n = 149)	p value
Age (years)	68.7 ± 15.1	68.3 ± 15.1	668.9 ± 15.1	0.77
Men	134 (58.3%)	54 (67%)	80 (54%)	0.06
Body surface area (m^2)	1.9 ± 0.3	1.9 ± 0.3	1.8 ± 0.3	0.05
New York Heart Association Class				0.66
I	2/226 (0.9%)	1/79 (1%)	1/147 (1%)	
II	20/226 (8.8%)	7/79 (9%)	13/147 (9%)	
III	124/226 (54.9%)	41/79 (52%)	83/147 (57%)	
IV	80/226 (35.4%)	30/79 (38%)	50/147(34%)	
STS-PROM score (%)	8.6 ± 9.1 (213)	8.6 ± 7.3 (73)	8.6 ± 9.9 (140)	>0.99
Diabetes mellitus	47/229 (20.5%)	18/80 (23%)	29 (20%)	0.59
Chronic lung disease/COPD	105 (45.7%)	44 (54%)	61 (41%)	0.05
Prior cardiac surgery	118/226 (52.2%)	39/78 (50%)	79/148 (53%)	0.63
Creatinine level >2 mg/dl	33/229 (14.4%)	13/80 (16%)	20 (13%)	0.56
History of hypertension	181 (78.7%)	64 (79%)	117 (79%)	0.93
Peripheral vascular disease	62 (27.0%)	19 (24%)	43 (29%)	0.38
Prior stroke	32 (13.9%)	13 (16%)	19 (13%)	0.49
Coronary artery bypass surgery	55/229 (24.0%)	15 (19%)	40/148 (27%)	0.15
Balloon valvuloplasty	2 (0.9%)	0 (0%)	2 (1%)	0.54
Coronary artery disease	109 (47.4%)	36 (44%)	73 (49%)	0.51
Pre-existing pacemaker/ICD	87/229 (38.0%)	33 (41%)	54/148 (37%)	0.53
Cardiogenic shock*	11 (4.8%)	4 (5%)	7 (5%)	>0.99
Extreme risk†	96 (41.7%)	42 (52%)	54 (36%)	0.02
Annular calcium	118/227 (52.0%)	43/80 (54%)	75/147 (51%)	0.69
Porcelain aorta	17 (7.4%)	3 (4%)	14 (9%)	0.19
Hostile mediastinum/chest	53 (23.0%)	16 (20%)	37 (25%)	0.38
Albumin <3.3 g/dl	49/209 (23.4%)	22/75 (29%)	27/134 (20%)	0.13
5-meter gait speed (seconds)	9.3 ± 16.4(124)	13.0 ± 30.6 (34)	7.9 ± 3.9 (90)	0.34
Left ventricular ejection fraction (%)	42.0 ± 17.5 (226)	41.9 ± 17.3 (78)	42.0 ± 17.7 (148)	0.96

COPD = chronic obstructive pulmonary disease; ICD = implantable cardioverter defibrillator; STS-PROM = Society of Thoracic Surgeons Predicted Risk of Mortality.

Continuous data are reported as mean ± standard deviation (no. if different from column header). Categorical data are reported as no. (%). If denominators differ from column headers, they are presented.

* Within 24 hours before procedure.

† As reported by the site.

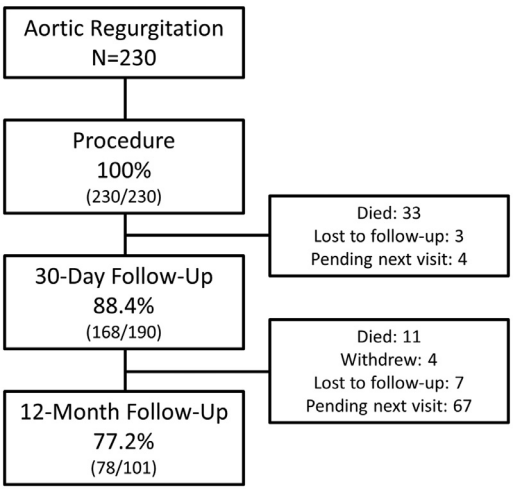

Figure 1. Patient disposition. In total, 230 patients with aortic regurgitation who underwent TAVI with the CoreValve or Evolut R devices were included.

Kaplan-Meier estimate of all-cause mortality was calculated for patients whose procedures were performed at least a year ago with 1-year follow-up data available, or who died, exited, or were otherwise lost to follow-up.

Results

From January 2014 until December 2017, 230 patients were identified who underwent TAVI with a self-expanding valve (Medtronic, Minneapolis, Minnesota) for AR in the STS/ACC TVT Registry (Figure 1). CoreValve was used to treat AR in 81 patients, whereas Evolut R was used to treat 149 patients. These 230 patients were treated at 103 sites, resulting in an average 2.2 cases per site. Baseline characteristics are listed in Table 1. Despite an average age of 68.7 ± 15.1 years of age, patients had a Society of Thoracic Surgeons Predicted Risk of Mortality score of 8.6 ± 9.1% and co-morbidities were common. Mean left ventricular ejection fraction (LVEF) at baseline was 42.0 ± 17.5%. Annular calcification was reported in 52.0% of patients.

In the overall cohort, 81.7% of patients were treated with 1 self-expanding TAVI valve and >75% of self-expanding TAVI valves used to treat AR patients were 29 mm or larger in size (Figure 2). All 31-mm valves used were CoreValve (21.4%), as Evolut R is not available in 31-mm size. Evolut R 34-mm self-expanding valves were used in 26.0% of patients. Of 118 patients who underwent TAVI for AR and had some degree of annular calcification reported, 15 (12.7%) used >1 valve. In the remaining 109 patients without report of annular calcification, >1 valve was used for the procedure in 27 (24.8%), p = 0.03 annular calcification versus none.

Device success was reported in 183/224 patients (81.7%) overall; this improved when comparing patients who underwent TAVI with older versus newer generation devices (CoreValve: 57 of 79, 72.2%; Evolut R: 126 of 145, 86.9%; p = 0.01). Despite all patients having moderate/severe AR at baseline, after TAVI, approximately 10% of patients had moderate/severe AR (Figure 3). Of the 6 patients with

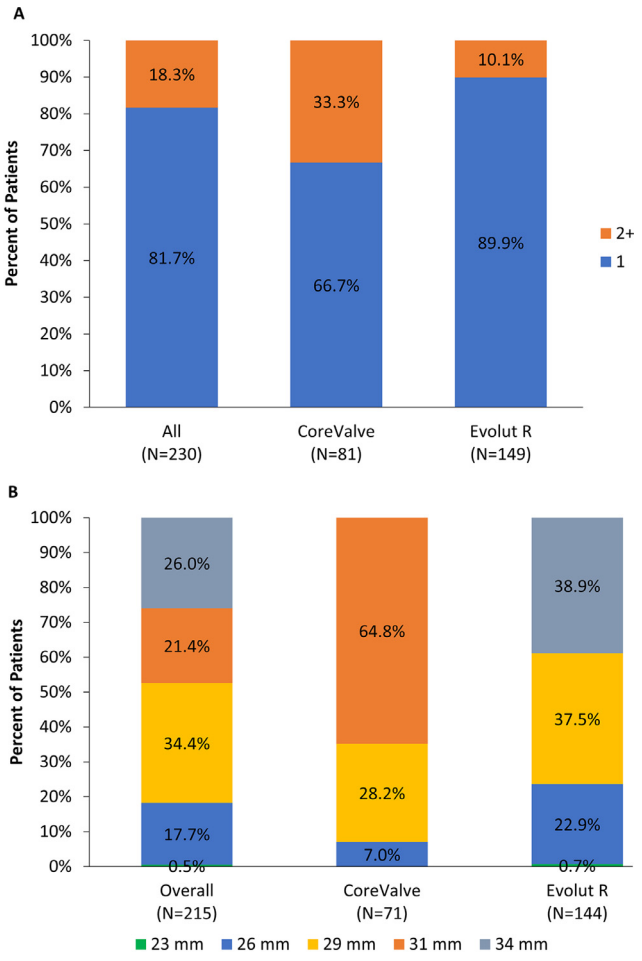

Figure 2. Valve utilization. *(A)* Number of valves used, either 1 or 2+. There was a significant reduction in multiple valves used between CoreValve and Evolut R (p <0.001). *(B)* Valve sizes implanted.

postprocedure severe total AR, 5 subsequently died (4 of which were in-hospital deaths; 3 were cardiac). The fifth death was a cardiac-related death that occurred approximately 1 month after procedure. Moderate/severe AR was significantly less with the Evolut R device compared with CoreValve (Figure 3).

Overall, in-hospital all-cause mortality occurred in 12.2% of patients (Evolut R 9% vs CoreValve 19%, p = 0.03). Device migration occurred in 5.7% of patients, whereas aortic valve reintervention, vascular complications, and neurological events occurred less frequently (Table 2). The overall median hospital length of stay was 5.5 days.

The 30-day all-cause mortality rate was 13.3% (Evolut R 10% vs CoreValve 19%, p = 0.08). The stroke rate was 3.7%, with no transient ischemic attacks or myocardial infarctions reported. New pacemakers were required in 19.4% of patients (Table 3).

At 30 days, for subjects with paired data (n = 140), LVEF decreased 0.5 ± 10.6% from baseline, p = 0.57. Overall mean gradient across the self-expanding TAVI valve was 6.8 ± 3.4 mm Hg. In a paired analysis (n = 114), the Kansas City Cardiomyopathy Questionnaire overall summary score significantly improved from pre-TAVI to 30 days (Δ = 24.3 ± 28.9, p <0.001).

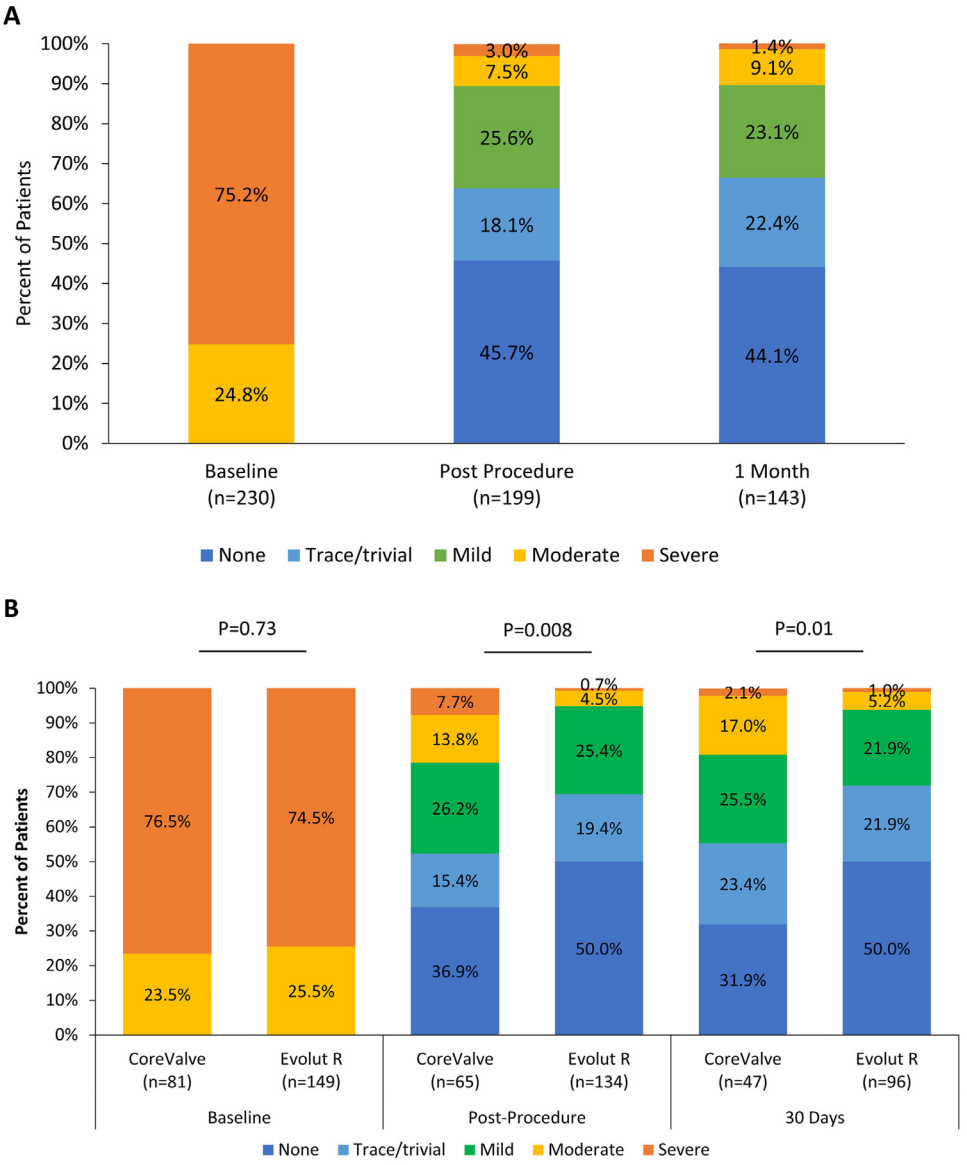

Figure 3. Total aortic regurgitation (AR) over time. *(A)* Total AR in all patients and *(B)* separated by those implanted with CoreValve versus Evolut R. In both *(A)* and *(B)*, baseline values reported on all attempted patients. Postprocedure and 1-month values reported on implanted patients. In (B), % moderate/severe AR, CoreValve versus Evolut R = 21.5% versus 5.2%, p<0.001 (post-procedure) and 19.1% versus 6.3%, p=0.02 (30 days).

The number of TAVI valves used (hazard ratio [HR] 2.361, 95% CI 1.643 to 3.391, p <0.001), albumin <3.3 mg/dl (HR 3.358, 95% CI 1.551 to 7.273, p = 0.002), and LVEF (HR 0.978 per 1% increase, 95% CI 0.957 to 1.000, p = 0.047) were all independently associated with 30-day all-cause mortality in patients treated for AR (Supplementary Table 1). Procedures were performed at least a year ago on a total of 145 patients. In these patients, 1-year all-cause mortality was 22.8% (Figure 4). Landmark analysis demonstrated that the majority of mortality occurred within the first 30 days of the procedure (Figure 4).

Discussion

TAVI has been performed for off-label indications with similar outcomes to on-label cases at 1 year as noted in this registry.[14] Our goal was to examine outcomes associated with self-expanding TAVI in patients with native AR. The main findings of this analysis are as follows: (1) despite having a Society of Thoracic Surgeons Predicted Risk of Mortality of 8% and significant co-morbidities, use of self-expanding TAVI appears to be effective in the short term in reducing AR and improving quality of life despite important procedural challenges; (2) treating AR was associated with high all-cause mortality at 1 year, although the highest risk was incurred early; (3) in AR patients treated with self-expanding TAVI, multiple valves used, presence of low albumin and low LVEF were all associated with higher mortality at 30 days; (4) use of the Evolut R device in patients treated for AR was associated with improved procedural and in-hospital outcomes.

The 30-day mortality rate of 13.3% is higher than that typically seen in AS patients after TAVI but similar to the 30-day rates (12.9% and 14%) in 2 other studies for AR patients using various transcatheter valves,[10,15] and lower

Table 2
In-hospital events

End points	All patients (n = 230)	CoreValve (n = 81)	Evolut R (n = 149)	p value
All-cause mortality	28 (12.2%)	15 (19%)	13 (9%)	0.03
Intraprocedural death	4 (1.7%)	2 (3%)	2 (1%)	0.61
Any stroke	6 (2.6%)	0 (0%)	6 (4%)	0.09
Ischemic stroke	5 (2.2%)	0 (0%)	5 (3%)	0.16
Device migration	13 (5.7%)	8 (10%)	5 (3%)	0.04
Device embolization, left ventricle	5 (2.2%)	2 (3%)	3 (2%)	>0.99
Device embolization, aorta	4 (1.7%)	1 (1%)	3 (2%)	>0.99
Aortic valve reintervention	9 (3.9%)	5 (6%)	4 (3%)	0.28
Any bleeding	23 (10.0%)	11 (14%)	12 (8%)	0.18
Vascular complication	8 (3.5%)	3 (4%)	5 (3%)	>0.99
Major vascular complication	3 (1.3%)	1 (1%)	2 (1%)	>0.99
New pacemaker implantation*	43 (18.7%)	14 (17%)	29 (20%)	0.69

Values are proportions reported as no. (%).
* Includes patients with baseline pacemaker.

Table 3
Clinical outcomes at 30 days

End points	All patients (n = 230)	CoreValve (n = 81)	Evolut R (n = 149)	p value
All-cause mortality	30 (13.3%)	15 (19%)	15 (10%)	0.08
Any stroke	8 (3.7%)	0 (0%)	8 (6%)	0.04
Ischemic stroke	6 (2.7%)	0 (0%)	6 (4%)	0.07
Transient ischemic attack	0 (0.0%)	0 (0%)	0 (0%)	NA
Myocardial infarction	0 (0.0%)	0 (0%)	0 (0%)	NA
Life-threatening/major bleed	23 (10.5%)	11 (14%)	12 (8%)	0.18
Vascular complication	8 (3.5%)	3 (4%)	5 (3%)	0.89
Major vascular complication	3 (1.3%)	1 (1%)	2 (1%)	0.95
New pacemaker implantation*	43 (19.4%)	14 (18%)	29 (20%)	0.75
Aortic valve re-intervention	11 (5.2%)	6 (8%)	5 (4%)	0.16
Unplanned other cardiac surgery or intervention	10 (4.6%)	1 (1%)	9 (6%)	0.09
Unplanned vascular surgery or intervention	11 (4.9%)	5 (6%)	6 (4%)	0.45
Valve-related readmission	5 (2.5%)	3 (4%)	2 (2%)	0.23
Non valve-related readmission	27 (13.6%)	9 (13%)	18 (14%)	>0.99

Values are Kaplan-Meier event rates, reported as no. (%).
* Includes patients with baseline pacemaker.

than the 23% rate in a series of 26 AR patients treated with the CoreValve device.[16] Yoon et al[8] reported a 30-day all-cause mortality rate of 10.9% in 331 patients with symptomatic severe native AR. The 30-day stroke rate (3.7%) was higher in patients treated with Evolut R than with CoreValve. However, without adjudication by an independent neurologist and considering small sample sizes, it is difficult to conclude if this is more than a spurious finding.

To date, standard of care for treatment of native AR in the United States remains SAVR. In Europe, the JenaValve (JenaValve Technology, Munich, Germany) is approved for treatment of pure AR.[15] Unlike AS, technical and procedural challenges associated with using TAVI to treat native AR are numerous,[9] highlighting the need for dedicated transcatheter technology to treat AR.

Per site case experience is extremely low in this series, limiting the ability to move beyond any learning curve.[17] Additionally, this cohort had high rates of New York Heart Association class IV symptoms, renal insufficiency, and a baseline LVEF lower than seen in native AS patients from this registry.[18]

Technical challenges posed by TAVI in AR are reflected in higher rates of both in-hospital and intraprocedural complications and of multiple valve use. The importance of improvements in device technology cannot be overstated. Yoon et al[8] recently demonstrated improved outcomes with newer generation devices. We show a reduction in use of multiple valves to treat AR patients with the newer generation Evolut system, as well as higher device success. The advantages with Evolut R over CoreValve are noted in more uniform radial force over its expansion range and ability to reposition and recapture.

The lack of 34-mm Evolut R valve during part of this study may have influenced the decision regarding valve size selection. It is not clear how many 29-mm Evolut valves were utilized instead of 31-mm CoreValve in annular sizes between 26 and 27 mm in diameter. Furthermore, with the currently available Evolut PRO with a pericardial wrap and a larger 34-mm Evolut R, it is possible that an expanded size range in newer generation valves may have led to different size selection, possibly influencing outcomes.

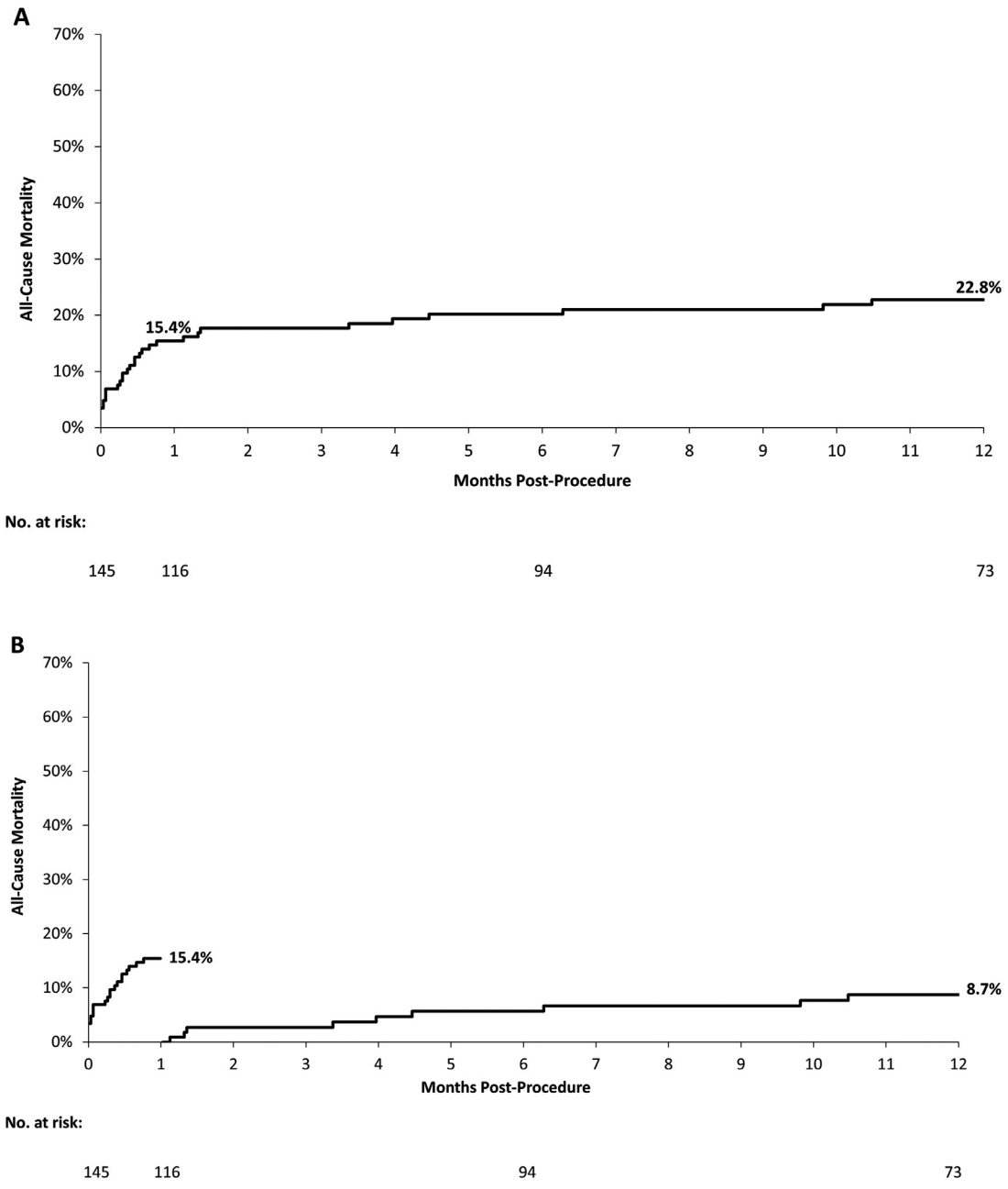

Figure 4. Cumulative incidence of all-cause mortality in all patients with 1-year data available (n = 145). *(A)* One-year all-cause mortality Kaplan-Meier curve and *(B)* landmark analysis for all-cause mortality.

Although technical factors are important considerations when considering overall outcomes, clinical factors and patient selection should not be overlooked. Although 30-day mortality remains sobering, likely with improved case selection, operator experience, and iterative device improvements, short-term outcomes can be improved. As the landmark analysis demonstrates, those successfully treated for AR who overcame the early hazard had more acceptable longer-term outcomes. Despite the ability of TAVI to treat AR in select populations, SAVR should remain standard of care in patients unless surgical risk is prohibitive.

Our study has important limitations. The inclusion criteria allowed for mixed aortic valve disease as long as the predominant lesion was moderate/severe or severe AR and a mean aortic valve gradient of ≤20 mm Hg, which may not reflect the typical surgical AR population. Further, approximately 27% of patients in this registry were lost to follow-up at 1 year, which limits the ability to fully evaluate longer-term outcomes. Although comparisons between CoreValve and Evolut R are informative, they are limited due to being nonrandomized data and confounded by the potential for selection bias or temporal changes in practice. Likewise, the sample size was small, with no statistical adjustment. We also could not account for potentially heterogeneous uptake of the newer generation device, by center volume or experience. Finally, the data were obtained from site-reported case forms, and echocardiographic and computed tomography data were not core-lab adjudicated. Despite the aforementioned limitations,

this study is one of a few series examining self-expanding TAVI in treating AR patients.

In conclusion, AR patients, although younger than average AS patients, were a very sick cohort with over 90% having New York Heart Association class III or IV symptoms, low LVEF, almost 15% with a creatinine >2 mg/dl and average STS risk score of >8.0%. Despite high 30-day all-cause mortality, self-expanding TAVI for treatment of native AR may be considered an option in extreme-risk patients otherwise not suitable for surgery. Self-expanding TAVI for the treatment of AR appears effective in the short term at reducing AR and improving quality of life. Improved outcomes with newer generation devices highlight the need for advancements in device technology and careful patient selection.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2019.05.045.

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