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Mid-Term Outcomes of Transcatheter Aortic Valve Replacement in Extremely Large Annuli With Edwards SAPIEN 3 Valve

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ABSTRACT

OBJECTIVES The aim of this study was to report the 1-year results of transcatheter aortic valve replacement (TAVR) with the Edwards SAPIEN 3 (S3) valve in extremely large annuli.

BACKGROUND Favorable 30-day outcomes of S3 TAVR in annuli >683 mm^2 have previously been reported. Pacemaker implantation rates were acceptable, and a larger left ventricular outflow tract and more eccentric annular anatomy were associated with increasing paravalvular leak.

METHODS From December 2013 to December 2018, 105 patients across 15 centers with mean area 721.3 ± 36.1 mm^2 (range: 683.5 to 852.0 mm^2) underwent TAVR using an S3 device. Clinical, anatomic, and procedural characteristics were analyzed. One-year survival and echocardiographic follow-up were reached in 94.3% and 82.1% of patients, respectively. Valve Academic Research Consortium-2 30-day and 1-year outcomes were reported.

RESULTS The mean age was 76.9 ± 10.4 years, and Society of Thoracic Surgeons predicted risk score averaged 5.2 ± 3.4%. One-year overall mortality and stroke rates were 18.2% and 2.4%, respectively. Quality-of-life index improved from baseline to 30 days and at 1 year ($p < 0.001$ for both). Mild paravalvular aortic regurgitation occurred in 21.7% of patients, while moderate or greater paravalvular aortic regurgitation occurred in 4.3%. Mild and moderate or severe transvalvular aortic regurgitation occurred in 11.6% and 0%, respectively. Valve gradients remained stable at 1 year.

CONCLUSIONS S3 TAVR in annular areas >683 mm^2 is feasible, with favorable mid-term outcomes. (J Am Coll Cardiol Intv 2019;■:■-■) © 2019 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

AR = aortic regurgitation

LVOT = left ventricular outflow tract

PPM = permanent pacemaker

PVL = paravalvular leak

S3 = SAPIEN 3

TAVR = transcatheter aortic valve replacement

TTE = transthoracic echocardiographic

Patients with symptomatic severe aortic stenosis who are at intermediate or greater risk for surgery have benefited from transcatheter aortic valve replacement (TAVR) over the past 2 decades (1–5). Recent studies have also shown that TAVR is a viable alternative to surgery in low-risk patients (6,7). The manufacturer-recommended maximum annular area for the 29-mm Edwards SAPIEN 3 (S3; Edwards Lifesciences, Irvine, California) valve is 683 mm^2. We have previously reported favorable 30-day outcomes, with acceptable paravalvular leak (PVL) and pacemaker rates, of S3 TAVR in extremely large annuli beyond the recommended range (>683 mm^2) (8). We sought to determine the 1-year outcomes of TAVR with the 29-mm S3 valve in such patients.

TABLE 1 Patient Characteristics (N = 105)

Age, yrs	76.9 ± 10.4
Female	5 (4.8)
STS risk score, %	5.15 ± 3.36
Coronary artery disease	53 (50.5)
Diabetes	36 (34.3)
TIA or stroke	19 (18.1)
Peripheral vascular disease	30 (28.6)
Moderate or severe COPD	24 (22.9)
Atrial fibrillation	51 (48.6)
Chronic kidney disease	32 (30.5)
Pulmonary hypertension, PASP >60 mm Hg	11 (10.5)
Prior permanent pacemaker	19 (18.1)
Prior cardiac surgery	29 (27.6)
Prior PCI	40 (38.1)
Bicuspid aortic valve	20 (19.0)
LVEF <35%	29 (27.6)

Values are mean ± SD or n (%).

COPD = chronic obstructive pulmonary disease; LVEF = left ventricular ejection fraction; PASP = pulmonary arterial systolic pressure; PCI = percutaneous coronary intervention; PVL = paravalvular leak; STS = Society of Thoracic Surgeons; TIA = transient ischemic attack.

METHODS

PATIENT POPULATION. Between December 2013 and December 2018, 105 patients with symptomatic severe aortic stenosis and annular areas >683 mm^2 (mean area 721.3 ± 36.1 mm^2; range: 683.5 to 852.0 mm^2) underwent S3 TAVR in our study. All patients were at least intermediate risk for surgery at 15 centers in North America. Patient data were prospectively collected and retrospectively analyzed. This study was approved by the Institutional Review Board at each participating site, and the requirement to obtain patient consent was waived.

PRE-PROCEDURAL ASSESSMENT, IMPLANTATION TECHNIQUE, AND FOLLOW-UP. All patients underwent transthoracic echocardiographic (TTE) imaging, and aortic root dimensions were determined at end-systole using multidetector computed tomography (8). Evaluation of annular, left ventricular outflow tract (LVOT), and leaflet calcification, calculation of prosthesis sizing to the annulus and LVOT, calculations of annular and LVOT eccentricities, and implantation techniques have been previously described (8). Balloon volume for valve deployment was based on the degree of undersizing and the presence and severity of annular and LVOT calcification. The severity of intraprocedural PVL and transvalvular aortic regurgitation (AR) were determined by a combination of 1) hemodynamic assessment; 2)

and holds equity in Entourage Medical. Dr. Thourani is a member of the PARTNER Trial Steering Committee; and is a consultant for Edwards Lifesciences, Sorin Medical, St. Jude Medical, and Direct Flow Medical. Dr. Babaliaros has received grant and research support from Medtronic, Abbott Vascular, and Edwards Lifesciences; and is a consultant for Abbott Vascular and Edwards Lifesciences. Dr. Webb has served as a consultant for Edwards Lifesciences. Dr. Kaneko has served as a proctor and an educator for Edwards Lifesciences. Dr. Shah is a proctor and an educator for Edwards Lifesciences; and is an educator for St. Jude Medical. Dr. Szerlip has served as a speaker and proctor for Edwards Lifesciences; has served as a consultant and speaker for Medtronic; and has served as a speaker for Abbott Vascular. Dr. Mack is an uncompensated co-principal investigator of the COAPT trial (Abbott Vascular); and serves on the Apollo Trial Executive Committee (Medtronic). Dr. Don is an investigator for Edwards Lifesciences; and is a consultant for Medtronic. Dr. Gafoor is a consultant for Medtronic, Boston Scientific and Abbott Vascular. Dr. Zhang has served as proctor for Edwards Lifesciences; has served as a site principal investigator for the REPRISE trial (Boston Scientific); and has served as a site subinvestigator for the REFLECT trial (Keystone Heart) and the TAVR low risk trial (Medtronic). Dr. Kapadia is an unpaid coprincipal investigator of the SENTINEL trial, sponsored by Claret Medical. Dr. Salemi is a physician proctor for Edwards Lifesciences and Medtronic. Dr. Wong has served on the medical advisory board for Medtronic Vascular. Dr. Leon has served as a nonpaid member of the scientific advisory board of Edwards Lifesciences; and has served as a consultant for Abbott Vascular and Boston Scientific. Dr. Kodali is on the steering committee for Edwards Lifesciences; is a consultant for Medtronic and Claret Medical; and is on the scientific advisory board for Thubrikar Aortic Valve. Dr. George is a consultant for Edwards Lifesciences and Medtronic. Dr. Tang is a physician proctor for Edwards Lifesciences and Medtronic. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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TABLE 2 Anatomic Characteristics (N = 105)

Annulus	
Minimal diameter, mm	27.6 ± 1.8
Maximal diameter, mm	33.5 ± 1.6
Mean diameter, mm	30.6 ± 1.0
Area, mm^2	721.3 ± 36.1
Perimeter, mm	96.7 ± 2.7
% oversized (by area)	−9.8 ± 4.2
Eccentricity, %	17.5 ± 7.6
LVOT	
Minimal diameter, mm	27.8 ± 3.2
Maximal diameter, mm	34.4 ± 2.8
Mean diameter, mm	31.1 ± 2.6
Area, mm^2	735.8 ± 89.5
Perimeter, mm	97.5 ± 6.7
% oversized (by area)	−10.5 ± 10.6
Eccentricity, %	19.1 ± 8.2
Nontubularity index, %	2.7 ± 2.1

Values are mean ± SD.
LVOT = left ventricular outflow tract.

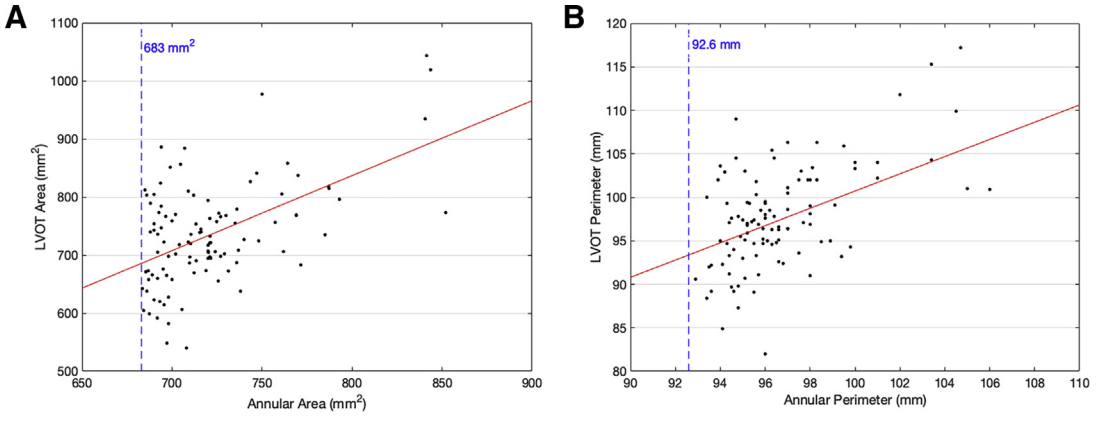
aortography; and 3) echocardiography using the Valve Academic Research Consortium-2 criteria (9). Balloon post-dilatation was performed at the operator's discretion. Procedural success was defined as device success, along with no aortic root or coronary complications, valve migration or embolization, severe PVL or transvalvular AR, and need for a second prosthesis (9). All patients underwent pre-discharge TTE imaging. Follow-up for survival was 98% complete at 30 days and 94.3% complete (99 patients) at 1 year; 3 patients have yet to reach the 1-year mark, and 3 were lost to follow-up. The median duration of follow-up for survival was 12.3 months (interquartile range: 3.4 to 16.0 months). TTE data were complete for 82.1% (69 of 84 patients who were alive) at 1 year. Outcomes were reported using the Valve Academic Research Consortium-2 and American College of Cardiology/Society of Thoracic Surgeons TVT (Transcatheter Valve Therapy) Registry definitions.

STATISTICAL ANALYSIS. Clinical and echocardiographic characteristics of patients at 30 days were compared with those at 1 year. In particular, a paired analysis was performed using the chi-square test for equality of proportions to assess the progression of paravalvular and transvalvular AR from 30 days to 1 year. Continuous variables are reported as mean ± SD, and categorical variables are reported as proportions. The independent Student's *t*-test was used for normally distributed continuous variables, the Wilcoxon rank sum test for nonparametric variables, and the chi-square or Fisher exact test for categorical variables. Statistical significance was indicated with p values <0.05 for comparisons of 30-day and 1-year outcomes. Statistical analyses were performed using SPSS version 23 (IBM, Armonk, New York).

RESULTS

Baseline patient characteristics are shown in Table 1. The mean age was 76.9 ± 10.4 years, and 4.8% were women. Society of Thoracic Surgeons Predicted Risk of Mortality averaged 5.2 ± 3.4%. Twenty patients (19.0%) had bicuspid aortic valves, and 29 (27.6%) had left ventricular ejection fractions <35%.

FIGURE 1 Distribution of Area and Perimeter by Annulus and Left Ventricular Outflow Tract



Blue dotted line indicates the manufacturer-recommended limit for sizing of the 29-mm SAPIEN 3 valve. **Red line** separates patients with annular area **(A)** and perimeter **(B)** greater than (below) or less than (above) the corresponding left ventricular outflow tract (LVOT) area.

TABLE 3 Procedural Characteristics (N = 105)

Transfemoral approach	99 (94.3)
Conscious sedation	54 (51.4)
Post-dilatation (n = 86)	30 (34.9)
Bottom of balloon center marker position (n = 74)	
Above annulus	21 (28.4)
At annulus	35 (47.3)
Below annulus	18 (24.3)
Final balloon filling (n = 86)	
Nominal	21 (24.4)
Underfill	0 (0)
Overfill	65 (75.6)
Contrast (ml)	110 ± 59
Valve implantation depth	
% ventricular, NCC	24.0 ± 12.4
% ventricular, LCC	20.8 ± 10.8
% ventricular, mean	22.8 ± 11.1

Values are n (%) or mean ± SD.
LCC = left coronary cusp; NCC = noncoronary cusp.

ANATOMIC CHARACTERISTICS. Anatomic characteristics, as determined by computed tomography, are shown in Table 2. The largest annular and LVOT areas in our cohort were 852 and 1,043.5 mm^2, with corresponding perimeters of 105 and 115 mm, respectively. Figure 1 shows the distribution of annular and LVOT areas and perimeters.

PROCEDURAL CHARACTERISTICS. Procedural success was obtained in all patients, and there was no annular rupture, embolization, or coronary obstruction. A transfemoral approach was used in 94.3% of patients, and 51.4% of patients were under conscious sedation. In 58 patients (69.9%), the 29-mm S3 valve was overexpanded by adding 1 to 5 ml extra volume on initial deployment; nominal filling was performed in the remaining 30.1%. Post-dilatation occurred in 34.9% of patients, resulting in a total of 75.6% of patients having balloon overfilling (1 to 5 ml extra). Implantation depth averaged 24.0 ± 2.4% (range: 5.0% to 60.7%) at the noncoronary cusp and 20.8 ± 10.8% (range: 3.1% to 50.0%) at the left coronary cusp (Table 3).

CLINICAL AND ECHOCARDIOGRAPHIC OUTCOMES. In-hospital, 30-day, and 1-year outcomes are listed in Table 4. Overall survival was 81.8% among 99 patients, and there were no delayed strokes seen up to 1 year (median duration of follow-up 12.3 months; interquartile range: 3.4 to 16.0 months). New persistent left bundle branch block occurred in 12 of 89 patients (13.5%) without prior pacemakers. New permanent pacemakers (PPMs) were required in 7.5% of patients (n = 94) at 30 days and 16.2% (n = 68) at 1 year (p = 0.08). One-year echocardiography showed that 51 patients (73.9%) had no or trace PVL, 15 patients (21.7%) had mild PVL, and 3 patients (4.3%) had moderate or severe PVL. Rates of transvalvular AR at 1 year were as follows: 88.4% none or trace, 11.6% mild, and no moderate or severe. Paired analyses of 69 patients revealed no differences in moderate or greater PVL and transvalvular AR at 30 days versus 1 year (Central Illustration). Note that the Central Illustration shows data from the 69 patients for whom 1-year echocardiographic data were available, while Table 4 displays data from all patients with TTE data at each follow-up period (i.e., in-hospital, 30 days, and 1 year). Quality-of-life index, as measured using the Kansas City Cardiomyopathy Questionnaire, improved from baseline to both 30 days and 1 year (p < 0.001) (Figure 2).

TABLE 4 In-Hospital, 30-Day, and 1-Year Outcomes (N = 105)

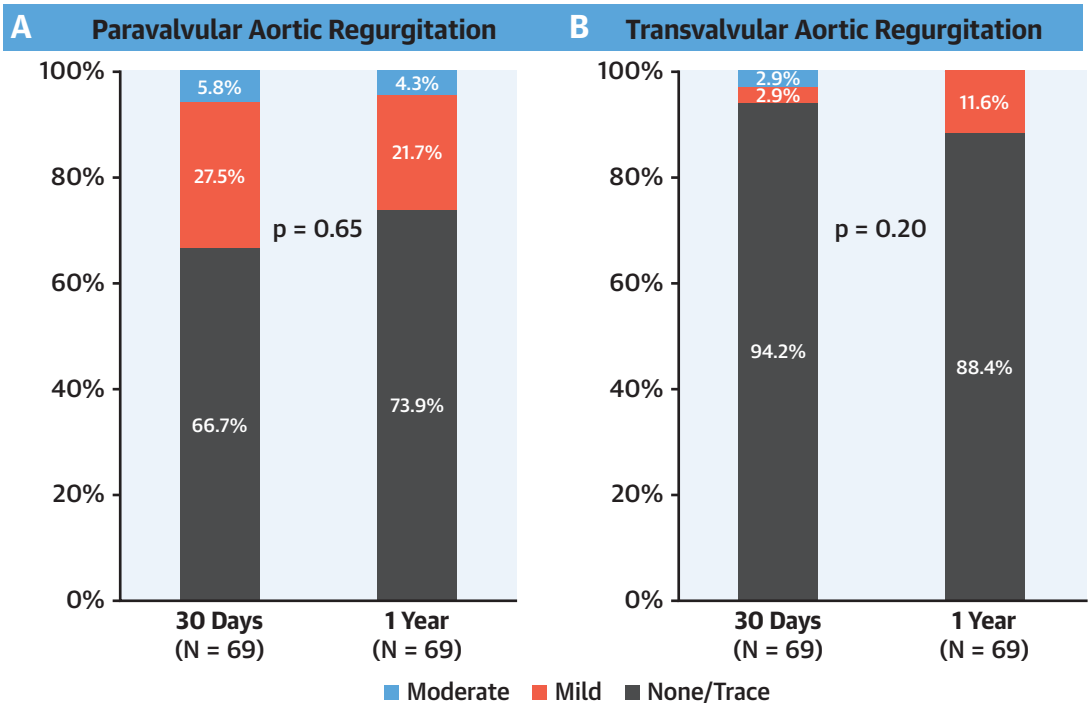
	In-Hospital	30 Days	1 Year
Death	1 (1.0)	2 (1.9)	18/99 (18.2)
Stroke	1 (1.0)	2 (1.9)	2/83 (2.4)
Major vascular complication	3 (2.9)	3 (2.9)	3 (2.9)
New persistent LBBB*		12/89 (13.5)	
New PPM†	7/94 (7.5)	7/94 (7.5)	11/68 (16.2)
ICU stay, h	19.7 (0-24)		
Hospital stay, days	2 (1-5)		
Paravalvular aortic regurgitation	(n = 98)	(n = 101)	(n = 69)
None	39 (39.8)	37 (36.6)	36 (52.2)
Trace	30 (30.6)	30 (29.7)	15 (21.7)
Mild	28 (28.6)	32 (31.7)	15 (21.7)
Moderate	1 (1.0)	2 (2.0)	3 (4.3)
Severe	0 (0)	0 (0)	0 (0)
Transvalvular aortic regurgitation	(n = 98)	(n = 101)	(n = 69)
None	85 (86.7)	89 (88.1)	50 (72.5)
Trace	7 (7.1)	6 (5.9)	11 (15.9)
Mild	6 (6.1)	4 (4.0)	8 (11.6)
Moderate	0 (0)	2 (2.0)	0 (0)
Severe	0 (0)	0 (0)	0 (0)
SAPIEN 3 valve hemodynamics			
Mean gradient, mm Hg		9.3 ± 3.8	10.0 ± 3.9
Peak gradient, mm Hg		17.1 ± 6.9	18.0 ± 8.1
Valve area, cm^2		1.94 ± 0.55	2.03 ± 0.62

Values are n (%), median (interquartile range), or mean ± SD. Note that the rates of paravalvular and transvalvular aortic regurgitation reflected here are different from those in the Central Illustration, as the latter includes only the 69 patients who had echocardiographic follow-up at 1 year (paired analysis). *Sixteen patients with prior PPMs and/or LBBB were excluded. †Eleven patients with prior PPMs were excluded.
ICU = intensive care unit; LBBB = left bundle branch block; PPM = permanent pacemaker.

DISCUSSION

In this study, we demonstrated the continued successful performance of S3 TAVR with the 29-mm valve and excellent clinical outcomes in patients with extremely large annuli. This was supported by several notable findings.

CENTRAL ILLUSTRATION **Incidence of Paravalvular and Transvalvular Aortic Regurgitation in Paired Analyses**



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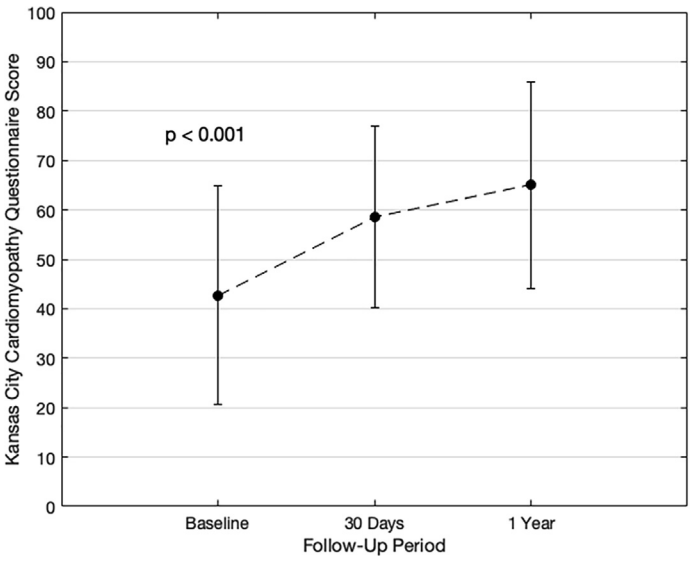
Rates of paravalvular leak **(A)** and transvalvular aortic regurgitation **(B)** at 30 days and 1 year are shown. Note that this analysis included only the 69 patients for whom 1-year echocardiography data were available.

First, the procedure was safe, with acceptable 1-year mortality. There were no new strokes or major vascular complications between the 30-day and 1-year follow-up periods.

Second, there were no differences in the incidence of moderate or severe PVL and transvalvular AR at 30 days compared with 1 year (although there was a trend toward less mild or greater PVL at 1 year), and our outcomes were similar to those reported in published research among patients with smaller annuli (10,11). In contrast, multiple studies have demonstrated the association between annular undersizing with the S3 valve and PVL. For instance, in their multicenter, nonrandomized registry involving 835 intermediate-risk patients, Blanke et al. (12) reported that those with <−5% oversizing by area had a 34% rate of at least mild PVL. This was corroborated by Yang et al. (13) and was also seen in the PARTNER (Placement of Aortic Transcatheter Valve) 2 S3 intermediate-risk registry, in which undersizing was associated with increasing PVL and balloon post-dilatation. These discrepancies with our results may be explained by the differing motives for undersizing. In our study, undersizing was secondary to the presence of very large annuli and the lack of transcatheter heart valves to treat these patients, whereas the decision to undersize in the aforementioned studies may have been motivated by the risk for annular rupture, injury to the LVOT, and need for a PPM. It should be emphasized that adding balloon volume before valve deployment, or by post-dilatation with additional volume, may foreshorten the inflow and improve sealing of the 29-mm S3 valve against native anatomy in extremely large annuli. This hypothesis would need validation by post-procedural multidetector computed tomographic analysis. These factors, in addition to greater procedural experience, more precise positioning with the S3 valve (mean implantation depth <25% ventricular), and more frequent balloon overfilling (75.6%) and

FIGURE 2 **Kansas City Cardiomyopathy Questionnaire Scores at Baseline, 30 Days, and 1 Year**



The **filled circles** correspond to the average Kansas City Cardiomyopathy Questionnaire scores at the specified time intervals, and the error bars represent the standard error of the mean.

post-dilatation (34.9%), might have accounted for the lower rates of PVL seen in the present study despite the larger annular sizes.

Of particular concern in our study was a numeric increase in mild transvalvular AR from 2.9% at 30 days to 11.6% at 1 year in the paired echocardiographic analysis of 69 patients (**Central Illustration**). There were no univariate predictors (patient, anatomic, or procedural characteristics) of this increase. Although we did not find an association between mild transvalvular AR and mortality at 1 year (note that hospital readmission rates were not available in our study), the longer term impact of mild transvalvular AR on valve durability and outcomes remains to be seen. The obvious concern is the late result of excessive balloon overfilling to overexpand the S3 valve and minimize PVL in the extremely large annuli cohort, thus increasing the risk for leaflet malcoaptation over time. A recent ex vivo study of the S3 valve by Sathananthan et al. (14) showed that although possible, excessive overexpansion may be associated with impaired hydrodynamic function, increased leaflet tethering, acute leaflet failure, and reduced durability. Note that the investigators also found less leaflet restriction with the maximally overexpanded 29-mm S3 valve as opposed to both the 23-mm and 26-mm valves. Overexpansion may also lead to increased leaflet thrombosis, which then results in impaired leaflet motion. All the above, along with changes in hemodynamic performance of a thick left ventricle, may potentially compromise ventricular remodeling after TAVR (15,16). As mentioned previously, the durability of overexpanded valves in patients with extremely large annuli is unknown past the 1-year mark. This has special importance for younger patients in whom overexpansion may not be advisable. Thus, our observed increase in the incidence of mild transvalvular AR needs to be followed closely in this specific population.

Third, new left bundle branch block and PPM rates were acceptable and similar to those reported in other S3 studies (10). At 30 days, 7.5% of patients underwent PPM implantation. Subsequently, 4 additional patients developed late conduction issues requiring new PPMs at 1 year. Delayed PPM implantation after S3 TAVR is not common (17); it remains to be seen if the extremely large annulus population is more vulnerable to delayed PPM implantation. The degree of balloon post-dilatation used has been cited as a potential contributor to this phenomenon (18), but this association was not seen in our study. Longer term follow-up is warranted.

Finally, a significant improvement in quality of life, as measured by the Kansas City Cardiomyopathy Questionnaire, occurred not only from baseline to 30 days but persisting to the 1-year follow-up period. This is in line with the findings reported by Baron et al. (19), in which S3 TAVR was shown to be associated with substantial improvements in Kansas City Cardiomyopathy Questionnaire score from baseline to 30 days ($n = 1{,}009$; $p < 0.001$) and 1 year ($n = 907$; $p < 0.001$) (19).

STUDY LIMITATIONS. First, our sample size was small because of the very low incidence of extremely large annuli evaluated for TAVR. However, our multicenter study with 105 patients represents the largest series thus far that has implanted the 29-mm S3 valve in annuli >683 mm^2.

Second, annular dimensions were evaluated at each site instead of a core laboratory; thus, over- or underestimation was possible. Similarly, intraprocedural, in-hospital, 30-day, and 1-year echocardiographic outcomes were site-reported and not adjudicated at a core laboratory.

Post-dilatation was performed at the site operator's discretion and was thus subject to interinstitutional differences in practice. In general, this was done if the PVL was mild or greater in severity after assessment of the patient's anatomic risk for annular injury. Additionally, extra volume used in balloon

filling for inflation or post-dilatation was not uniformly recorded and thus was not included in the analysis.

Furthermore, cause of death was unknown for the vast majority of patients, and thus we do not know if any or all of these deaths were potentially related to valve failure.

Finally, our follow-up was not 100% complete, as 3 patients have yet to reach the 1-year mark. Similarly, our TTE data were available for only 82.1% of patients at 1 year because of incomplete follow-up and issues with patient compliance, thus raising the question of reporting error. Nevertheless, our 1-year follow-up rate was better than that in the TVT Registry (20).

CONCLUSIONS

S3 TAVR with the 29-mm valve in patients with extremely large annuli is safe, with acceptable mid-term outcomes. Longer term follow-up in a larger patient population is needed to determine the durability of S3 TAVR in patients with annuli >683 mm^2.

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PERSPECTIVES

WHAT IS KNOWN? TAVR with the 29-mm S3 in patients with extremely large annuli (>683 mm^2) is feasible, with favorable short-term outcomes and acceptable pacemaker implantation rates.

WHAT IS NEW? We demonstrated the continued utility of S3 TAVR in annuli >683 mm^2, with satisfactory mid-term clinical and echocardiographic outcomes.

WHAT IS NEXT? Longer follow-up will be needed to evaluate the durability of the 29-mm S3 valve in patients with extremely large annuli.

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