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Regression of Paravalvular Aortic Regurgitation and Remodeling of Self-Expanding Transcatheter Aortic Valve

An Observation From the CoreValve U.S. Pivotal Trial

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CME Objective for This Article: After reading this article the reader should be able to: 1) define hemodynamic improvement of the patients with severe aortic stenosis at extreme surgical risk after receiving TAVR with the CoreValve bioprosthesis; 2) describe the concept of remodeling of self-expanding transcatheter aortic CoreValve; and 3) formulate possible mechanisms of regression of paravalvular aortic regurgitation after TAVR with the CoreValve bioprosthesis.

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ABSTRACT

OBJECTIVES The aim of this study was to describe the natural history and clinical importance of paravalvular aortic regurgitation (PVAR) after CoreValve transcatheter aortic valve replacement (TAVR) and to relate these findings to the structural and hemodynamic changes documented by serial echocardiographic analysis.

BACKGROUND PVAR after TAVR with the self-expanding CoreValve bioprosthesis has been shown to regress over time, but the time course and the mechanism of PVAR regression has not been completely characterized.

METHODS Patients with severe aortic stenosis who underwent CoreValve TAVR and followed up to 1 year in the multicenter CoreValve U.S. Pivotal Trial (Safety and Efficacy Study of the Medtronic CoreValve System in the Treatment of Symptomatic Severe Aortic Stenosis in High Risk and Very High Risk Subjects Who Need Aortic Valve Replacement) were studied. Serial echocardiography studies were analyzed by an echocardiographic core laboratory. Annular sizing ratio was calculated from computed tomography measurements. Paired, as well as total, data were compared.

RESULTS The CoreValve was implanted in 634 patients with a mean age of 82.7 $\pm$ 8.4 years. After a marked improvement noted at discharge, aortic valve velocity, mean gradient, and effective orifice area further improved significantly at 1 month (2.08 $\pm$ 0.45 m/s vs. 1.99 $\pm$ 0.46 m/s, $p < 0.0001$, 9.7 $\pm$ 4.4 mm Hg vs. 8.9 $\pm$ 4.6 mm Hg, $p < 0.0001$, and 1.78 $\pm$ 0.51 cm^2 vs. 1.85 $\pm$ 0.58 cm^2, $p = 0.03$, respectively). The improvement was sustained through 1 year. PVAR was moderate or severe in 9.9%, and of 36 patients with moderate PVAR at discharge and paired data, 30 (83%) improved at least 1 grade of regurgitation at 1 year. Annular sizing ratio was significantly associated with the degree of PVAR.

CONCLUSIONS There was further improvement in aortic prosthetic valve hemodynamics and regression of PVAR up to 1 year compared with discharge after TAVR with CoreValve. These changes are possibly due to remodeling and outward expansion of the self-expandable CoreValve with nitinol frame. (Safety and Efficacy Study of the Medtronic CoreValve System in the Treatment of Symptomatic Severe Aortic Stenosis in High Risk and Very High Risk Subjects Who Need Aortic Valve Replacement [Medtronic CoreValve U.S. Pivotal Trial]; NCT01240902) (J Am Coll Cardiol Img 2015;8:1364–75) © 2015 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

AR = aortic regurgitation

AS = aortic stenosis

AV = aortic valve

EF = ejection fraction

EOA = effective orifice area

IQR = interquartile range

LV = left ventricle/ventricular

LVEF = left ventricular ejection fraction

LVOT = left ventricular outflow tract

PVAR = paravalvular aortic regurgitation

SV = stroke volume

TAVR = transcatheter aortic valve replacement

VARC = Valve Academic Research Consortium

VTI = velocity time integral

Patients with severe aortic stenosis (AS) at extreme risk for surgical aortic valve (AV) replacement have substantially improved outcomes with transcatheter aortic valve replacement (TAVR) (1–3). However, paravalvular aortic regurgitation (PVAR) remains a major complication of TAVR, and its clinical impact varies depending on the patient population and type of valve. In the PARTNER (Placement of Aortic Transcatheter Valves) trial with inoperable patients, moderate-to-severe PVAR, which occurred in 10% of patients after TAVR, had a trend toward higher all-cause mortality at 1 year (2). In high-risk patients, even mild PVAR was associated with poor survival (4,5). In the CoreValve U.S. Pivotal Trial (Safety and Efficacy Study of the Medtronic CoreValve System in the Treatment of Symptomatic Severe Aortic Stenosis in High Risk and Very High Risk Subjects Who Need Aortic Valve Replacement), there was a gradual lessening of the severity of PVAR after TAVR with the CoreValve bioprosthesis (Medtronic, Minneapolis, Minnesota), and only severe PVAR was associated with increased 1-year mortality (3).

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One possible contributor to the limited association between PAVR and mortality in the CoreValve trial is that continuous aortic root remodeling by the self-expanding CoreValve bioprosthesis occurs after implantation. To validate the remodeling hypothesis, serial echocardiography studies obtained at multiple scheduled follow-up periods were analyzed, including the forward-flow hemodynamic performance of the bioprosthesis over time, the prevalence and longitudinal follow-up of PVAR, and the anatomic changes observed as a result of TAVR with a self-expanding valve with a nitinol frame.

METHODS

PATIENT POPULATION. We evaluated all patients at extreme surgical risk in the CoreValve U.S. Pivotal Trial undergoing TAVR. Inclusion and exclusion criteria and study details have been previously described (3). The study protocol was approved by the institutional review board of all participating clinical sites, and all patients provided written, signed consent.

ECHOCARDIOGRAPHY. Echocardiography was performed at baseline, post-procedure, hospital discharge, and 1, 6, and 12 months. All echocardiography studies were centrally analyzed using Digisonics workstation (Digisonics, Houston, Texas) by the echocardiography core laboratory at the Mayo Clinic (Rochester, Minnesota). A level 3-trained physician echocardiographer approved all measurements that were performed by sonographers, and determined valvular regurgitation severity, including PVAR, in all studies. Measurements were made from an average of 3 cardiac cycles in sinus rhythm and 3 to 5 cycles in atrial fibrillation. Assessment of the native AV and the bioprosthesis were made according to the original Valve Academic Research Consortium (VARC-1), American Society of Echocardiography, and European Association of Echocardiography (6–9). Measurements for left ventricular (LV) volumes, ejection fraction (EF), stroke volume (SV), and mass were performed according to published guidelines (10–12).

LV volume and EF were measured primarily from the biplane Simpson method, whenever possible. When LV volume measurement was not possible, left ventricular ejection fraction (LVEF) was measured using LV dimensions and also visually estimated by a physician echocardiographer. LV mass was derived from the established formula (6,10). Diastolic function was assessed mainly by mitral inflow velocities because LV relaxation or mitral annulus early diastolic velocity is expected to be reduced in elderly patients with severe AS, as recommended jointly by the American Society of Echocardiography and European Association of Echocardiography (13).

Aortic pressure gradient was calculated as: $(4 \times [\text{peak aortic valve velocity}^2 - \text{LVOT velocity}^2])$. When there was a dynamic left ventricular outflow tract (LVOT) gradient, aortic and LVOT velocities were not used. When there was accelerated flow velocity due to the position of the sample volume too close to the native AV or to the skirt of the CoreValve, LVOT velocity was not used.

The LVOT diameter of the native AV was measured within 5 mm of the aortic annulus, and after TAVR, was measured from the outer to the outer aspect of the bioprosthesis from the parasternal long-axis view (8). The AV effective orifice area (EOA) was calculated according to the continuity equation as: $(\text{LVOT diameter})^2 \times 0.785 \times (\text{LVOT VTI/AV VTI})$, where VTI is the velocity time integral, which is equal to SV/AV VTI (11,12). The severity of aortic regurgitation (AR) was graded based on multiple parameters including regurgitation color jet density and width, circumferential extent of turbulent regurgitation color jet around the aortic annulus for PVAR, and diastolic flow reversal in the descending aorta. It was classified as paravalvular or

transvalvular based on the origin of regurgitation. When the color flow aliasing velocity was low (<50 cm/s), the severity of valvular regurgitation was not assessed. For PVAR, the circumferential extent from multiple parasternal short axis views was one criterion in determining severity as recommended by VARC-1 (7): 1) trivial: a trace of short-lasting (less than the entire diastole) with usually laminar flow with or without a trace of regurgitation jet around the aortic annulus; 2) mild: the circumferential extent <10% (<36° in clock face), with turbulent AR jet; 3) moderate: the circumferential of 10% to 20% (36° to 72°); and 4) severe: the circumferential extent >20% (>72°). When there was more than 1 jet, the values of all regurgitation jets of at least mild degree were added. Because the circumferential extent could not be seen in some patients, all available parameters were used to determine the final severity grading. Pressure-half-time of aortic regurgitant jet alone was not used to determine severity because it is neither sensitive nor specific.

Interobserver and intraobserver variability of measuring these echocardiography variables was assessed in a selected cohort of the patients using the interclass correlation coefficients. For PVAR, the same number of patients in each severity category was randomly chosen for variability assessment.

DETERMINATION OF ANNULAR SIZING RATIO. All patients underwent multidetector computed tomography that was analyzed by a central laboratory. Perimeters of the CoreValve and the aortic annulus were measured using 3Mensio software, version 5.1 (Pie Medical, Maastricht, the Netherlands). The annular sizing ratio, which reflects incremental bioprosthesis diameter as a percentage of the aortic annulus perimeter, was calculated by the following formula:

$$\text{Annular sizing ratio} = [(\text{valve perimeter} - \text{annulus perimeter}) / \text{annular perimeter}] \times 100$$

STATISTICAL ANALYSIS. Patients who received successful TAVR by either iliofemoral or non-iliofemoral approach are included in these analyses. Categorical variables were compared using the Fisher exact test or the chi-square test, as appropriate. Continuous variables were presented as mean ± SD and compared using the Student *t* test or the analysis of variance, as appropriate. Paired data were compared using paired-sample *t* test for continuous variables and Wilcoxon signed rank sum test for ordinal variables. Survival curves were constructed using the Kaplan-Meier method, and compared between groups by grade of PVAR using the log-rank test. All testing used a 2-sided alpha level of 0.05. No adjustments were made for pairwise comparisons among multiple time points. Statistical analyses were performed using SAS software, version 9.2 (SAS Institute, Cary, North Carolina).

RESULTS

PATIENTS. The CoreValve bioprosthesis was implanted in 634 patients; 486 patients using the iliofemoral and 148 patients using a non-iliofemoral approach. Mean age was 82.7 ± 8.4 years, and 52.7% were women. Mean Society of Thoracic Surgeons (STS) mortality score was 10.4 ± 5.6%, and 91.8% had New York Heart Association functional class III to IV symptoms (Online Table 1).

ECHOCARDIOGRAPHY DATA. Because there were no substantial differences in any of echocardiography parameters between iliofemoral and non-iliofemoral groups, the data for the combined group are discussed. A summary of the echocardiography findings at baseline, hospital discharge, 1 month, 6 months, and 1 year following TAVR for the entire patient population is shown in **Table 1**. To assess the serial changes more accurately, echocardiography data paired for baseline and discharge, discharge and 1 month, and discharge and 1 year follow-up were compared (**Table 1**, Online Table 2). We also analyzed serial AV hemodynamic data in 272 patients who had data at all visits (Online Table 3). Interobserver and intraobserver variability for hemodynamic parameters and AR are in Online Table 4.

AORTIC REGURGITATION AFTER COREVALVE IMPLANTATION. Of 634 implanted patients, 52 patients did not have echocardiography data at discharge due to missing site echocardiogram (n = 27), poor quality (n = 13), and death (n = 12). Of 582 patients in whom AR could be assessed at discharge, total AR was absent or trivial in 284 (48.8%); mild in 226 (38.8%), moderate in 64 (11.0%), and severe in 8 (1.4%). Most of the total AR was PVAR, which was none or trivial, mild, moderate, and severe in 52.1%, 38.0%, 8.6%, and 1.2%, respectively (**Table 1**). PVAR was assessed separately in 383 patients who had paired studies at discharge and 1 year after the index TAVR procedure. In this matched dataset at discharge, PVAR was mild, moderate, and severe in 137 patients (35.8%), 36 (9.4%), and 1 (0.3%), respectively; which changed to 102 (26.6%), 14 (3.7%), and 1 (0.3%) at 1 year ($p < 0.0001$) (**Figure 1A**). Between discharge and 1 year, 170 of

TABLE 1 Echocardiographic Parameters Over Time

	Baseline	Discharge	1 Month	6 Months	1 Year	p Value From Paired Data: Baseline vs. Discharge	Discharge vs. 1 Month	Discharge vs. 1 Year
Heart rate, beats/min	70.10 ± 13.03 (632)	74.21 ± 12.37 (593)	70.97 ± 12.81 (559)	68.38 ± 11.66 (470)	67.63 ± 11.31 (419)	<0.0001	<0.0001	<0.0001
LV end-systolic diameter, cm	3.33 ± 0.85 (482)	3.24 ± 0.81 (414)	3.27 ± 0.82 (415)	3.27 ± 0.83 (349)	3.33 ± 0.87 (299)	<0.0001	0.0024	0.4198
LV end-diastolic diameter, cm	4.94 ± 0.68 (548)	4.93 ± 0.72 (476)	4.92 ± 0.71 (463)	5.00 ± 0.73 (389)	4.97 ± 0.74 (340)	0.4424	0.2498	0.1492
LV end-diastolic volume, ml	113.0 (90.0–144.0) (325)	113.5 (85.0–148.0) (258)	121.0 (93.0–154.0) (261)	111.0 (85.0–151.0) (233)	125.0 (97.0–163.0) (177)	0.5465	0.5797	0.0896
LV end-systolic volume, ml	49.0 (32.0–79.0) (325)	49.0 (32.0–77.0) (257)	52.0 (37.0–79.0) (258)	47.0 (31.0–73.0) (232)	55.0 (40.0–80.0) (176)	0.3651	0.0279	0.0531
2DE SV–calculated, ml	60.28 ± 19.72 (325)	63.11 ± 24.94 (257)	65.36 ± 20.60 (258)	65.18 ± 23.14 (232)	70.03 ± 24.60 (176)	0.0224	0.8214	0.2294
LV ejection fraction–calculated, %	54.18 ± 14.24 (482)	56.80 ± 12.69 (414)	55.60 ± 12.99 (415)	57.32 ± 12.28 (349)	55.67 ± 12.81 (299)	<0.0001	0.0005	0.2818
LV ejection fraction–visual estimate, %	54.58 ± 14.33 (632)	58.09 ± 12.20 (589)	57.05 ± 12.47 (552)	57.93 ± 10.95 (469)	57.36 ± 11.73 (419)	<0.0001	0.0002	0.0786
Ventricular septal thickness, mm	12.56 ± 2.31 (538)	12.06 ± 2.18 (470)	11.68 ± 2.14 (456)	11.25 ± 1.91 (383)	10.97 ± 1.81 (331)	0.0004	<0.0001	<0.0001
Posterior wall thickness, mm	11.92 ± 1.95 (540)	11.42 ± 1.87 (469)	11.16 ± 1.81 (452)	10.85 ± 1.67 (382)	10.58 ± 1.79 (328)	<0.0001	0.0005	<0.0001
Relative wall thickness	0.49 ± 0.11 (533)	0.47 ± 0.11 (464)	0.46 ± 0.10 (449)	0.44 ± 0.09 (382)	0.43 ± 0.09 (328)	0.0093	0.0012	<0.0001
LV mass index, g/m^2	132.32 ± 36.19 (523)	124.32 ± 33.66 (460)	119.84 ± 32.90 (441)	115.61 ± 30.74 (377)	112.17 ± 30.71 (325)	<0.0001	0.0003	<0.0001
CoreValve LVOT diameter, outer to outer, cm	–	2.03 ± 0.24 (558)	2.05 ± 0.27 (532)	2.08 ± 0.23 (438)	2.09 ± 0.23 (401)	0.8055	0.0287	<0.0001
LVOT peak velocity, m/s	0.92 ± 0.21 (573)	1.07 ± 0.22 (552)	1.02 ± 0.21 (532)	1.04 ± 0.21 (442)	1.01 ± 0.20 (397)	<0.0001	<0.0001	<0.0001
LVOT velocity time integral	21.66 ± 5.58 (572)	20.86 ± 4.96 (552)	21.06 ± 5.24 (532)	22.12 ± 5.49 (442)	22.04 ± 5.48 (397)	0.0261	0.7965	<0.0001
AV peak velocity, m/s	4.33 ± 0.67 (624)	2.08 ± 0.45 (578)	1.99 ± 0.46 (543)	2.01 ± 0.44 (457)	2.01 ± 0.44 (413)	<0.0001	<0.0001	<0.0001
AV velocity time integral, cm	104.45 ± 22.27 (624)	39.06 ± 9.86 (577)	39.37 ± 11.27 (544)	41.66 ± 11.20 (457)	41.80 ± 11.01 (413)	<0.0001	0.9365	<0.0001
AV peak gradient, mm Hg	76.69 ± 23.60 (624)	18.17 ± 8.22 (578)	16.72 ± 8.26 (543)	17.00 ± 7.69 (457)	16.88 ± 8.05 (413)	<0.0001	<0.0001	<0.0001
AV mean gradient, mm Hg	47.81 ± 15.20 (624)	9.67 ± 4.44 (577)	8.93 ± 4.62 (544)	9.16 ± 4.29 (457)	8.98 ± 4.45 (413)	<0.0001	<0.0001	<0.0001
Doppler velocity index	0.211 ± 0.052 (570)	0.550 ± 0.133 (545)	0.557 ± 0.138 (524)	0.547 ± 0.134 (437)	0.546 ± 0.133 (395)	<0.0001	0.3597	0.6346
Doppler SV, ml	74.12 ± 23.32 (520)	67.45 ± 20.21 (516)	70.00 ± 22.06 (508)	76.20 ± 23.70 (414)	75.90 ± 23.14 (383)	<0.0001	0.0490	<0.0001
Effective orifice area, cm^2	0.73 ± 0.24 (518)	1.78 ± 0.51 (509)	1.85 ± 0.58 (500)	1.88 ± 0.54 (409)	1.87 ± 0.54 (381)	<0.0001	0.0345	0.0030
Effective orifice area index, cm^2/m^2	0.40 ± 0.12 (518)	0.99 ± 0.29 (509)	1.03 ± 0.33 (500)	1.04 ± 0.31 (409)	1.03 ± 0.30 (381)	<0.0001	0.0362	0.0038
≥Moderate total AR, %	9.3 (58/624)	12.4 (72/582)	14.6 (79/540)	8.9 (41/463)	5.8 (24/411)	0.0458	0.1608	0.0005
≥Moderate MR, %	17.2 (106/616)	11.7 (68/580)	13.9 (76/548)	9.9 (46/464)	7.7 (32/415)	0.0011	0.2601	0.0420
Total AR						0.4247	0.0147	<0.0001
None/trivial	46.5 (290/624)	48.8 (284/582)	44.3 (239/540)	54.9 (254/463)	64.7 (266/411)			
Mild	44.2 (276/624)	38.8 (226/582)	41.1 (222/540)	36.3 (168/463)	29.4 (121/411)			
Moderate	9.1 (57/624)	11.0 (64/582)	13.3 (72/540)	8.6 (40/463)	5.6 (23/411)			
Severe	0.2 (1/624)	1.4 (8/582)	1.3 (7/540)	0.2 (1/463)	0.2 (1/411)			
Paravalvular AR						N/A	0.2622	<0.0001
None/trivial	–	52.1 (296/568)	49.5 (263/531)	60.0 (276/460)	69.7 (285/409)			
Mild	–	38.0 (216/568)	39.0 (207/531)	32.6 (150/460)	26.4 (108/409)			
Moderate	–	8.6 (49/568)	11.1 (59/531)	7.4 (34/460)	3.7 (15/409)			
Severe	–	1.2 (7/568)	0.4 (2/531)	0.0 (0/460)	0.2 (1/409)			
Transvalvular AR						N/A	0.0260	0.4011
None/trivial	–	94.0 (530/564)	90.8 (481/530)	93.4 (427/457)	93.1 (378/406)			
Mild	–	4.8 (27/564)	7.9 (42/530)	5.9 (27/457)	6.9 (28/406)			
Moderate	–	1.1 (6/564)	1.1 (6/530)	0.7 (3/457)	0.0 (0/406)			
Severe	–	0.2 (1/564)	0.2 (1/530)	0.0 (0/457)	0.0 (0/406)			

Continued on the next page

TABLE 1 Continued

	Baseline	Discharge	1 Month	6 Months	1 Year	p Value From Paired Data		
						Baseline vs. Discharge	Discharge vs. 1 Month	Discharge vs. 1 Year
Mitral regurgitation						0.0003	0.2055	0.0011
None/trivial	37.3 (230/616)	42.2 (245/580)	41.8 (229/548)	48.9 (227/464)	51.6 (214/415)			
Mild	45.5 (280/616)	46.0 (267/580)	44.3 (243/548)	41.2 (191/464)	40.7 (169/415)			
Moderate	15.1 (93/616)	10.5 (61/580)	12.2 (67/548)	9.1 (42/464)	7.0 (29/415)			
Severe	2.1 (13/616)	1.2 (7/580)	1.6 (9/548)	0.9 (4/464)	0.7 (3/415)			
Mitral E/A ratio	1.00 (0.75–1.50) (443)	1.00 (0.80–1.40) (357)	0.93 (0.71–1.27) (362)	0.85 (0.70–1.14) (333)	0.87 (0.67–1.08) (288)	0.0012	<0.0001	<0.0001
Deceleration time of E, ms	189.0 (157.0–247.0) (471)	196.0 (166.0–236.0) (433)	204.0 (169.0–261.0) (419)	232.0 (179.0–291.0) (379)	241.0 (191.0–301.0) (327)	0.0064	0.2187	<0.0001

Values are mean ± SD (n), median (interquartile range) (n), or % (n/N).
2DE = 2-dimensional echocardiography; AR = aortic regurgitation; AV = aortic valve; LV = left ventricle/ventricular; LVOT = left ventricular outflow tract; MR = mitral regurgitation; SV = stroke volume.

383 (44%) patients showed improvement in PVAR by at least 1 grade, and 69 (18%) got worse, mostly to having mild PVAR. Of 137 patients with mild PVAR at discharge, 89 (65%) had none to trivial at 1 year. Of 36 patients with moderate PVAR at discharge, 30 (83%) improved by at least 1 grade at 1-year follow-up (**Figure 2**). The percentage of patients with none-to-trivial PVAR increased from 54.6% to 69.5% between discharge and 1-year follow-up.

Because the severity of PVAR may be associated with valve sizing, the mean annular sizing ratio was calculated for 3 patient groups: Group 1 were those with optimal results with respect to PVAR (i.e., none or trivial PVAR at both discharge and 1 year), Group 2 patients had mild or greater PVAR at discharge that improved to none or trivial by 1 year, and Group 3 patients had mild or greater PVAR at 1 year (**Figure 1B**). The mean annular sizing ratio was 17.5 ± 5.9% in Group 1, 15.6 ± 5.3% in Group 2, and 14.2 ± 5.7% in Group 3 ($p < 0.0001$).

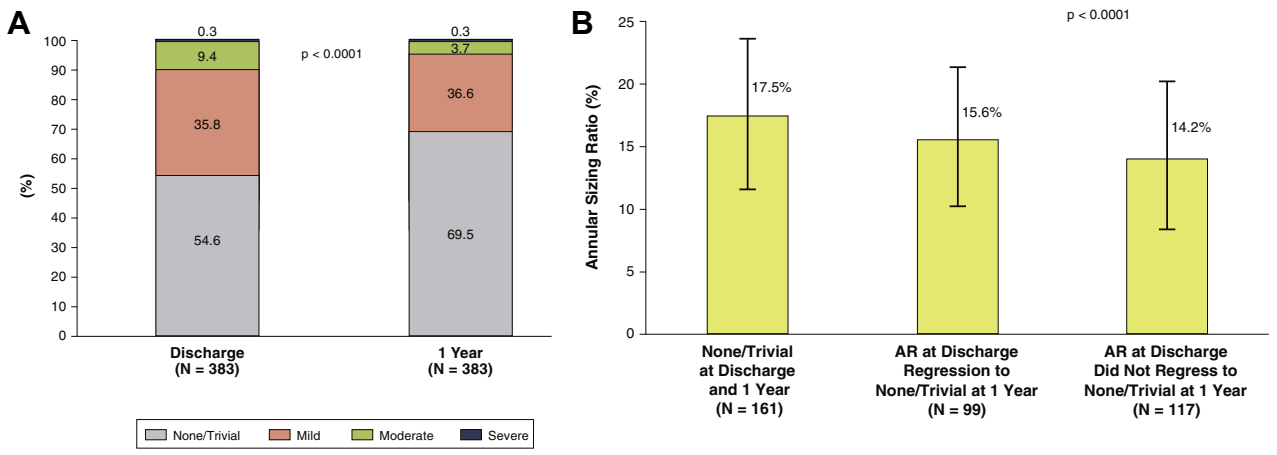
Severe PVAR at discharge predicted overall mortality, most of which occurred by 1-month follow-up, but there were no significant differences in mortality among patients with moderate or less PVAR (3). Because there was a reduction in PVAR severity over time, overall mortality was reassessed for patients with adjusted PVAR severity at 1 and 6 months (**Figure 3**). There was no significant difference in overall mortality after 6 months among the different severities of AR.

IMPACT OF COREVALVE IMPLANTATION ON AV HEMODYNAMICS. AV velocity and mean gradients improved acutely from 4.33 ± 0.67 m/s at baseline to 2.08 ± 0.45 m/s at discharge ($p < 0.0001$), and from 47.8 ± 15.2 mm Hg to 9.7 ± 4.4 mm Hg ($p < 0.0001$), respectively. EOA increased from 0.73 ± 0.24 cm^2 to 1.78 ± 0.51 cm^2 ($p < 0.0001$).

SV calculated by Doppler increased significantly from discharge to 1 year (67.5 ± 20.2 ml vs. 75.9 ± 23.1 ml, $p < 0.0001$), whereas heart rate decreased (74 ± 12 beats/min vs. 68 ± 11 beats/min, $p < 0.0001$). Both LVOT VTI and the dimension from the outer-to-outer edges of the ventricular end of the CoreValve bioprosthesis increased from discharge to 1 year (from 20.9 ± 5.0 cm to 22.0 ± 5.5 cm, and from 2.03 ± 0.24 cm to 2.09 ± 0.23 cm, respectively, $p < 0.0001$ for both).

SV derived from LV volume measurements was slightly smaller than Doppler-measured SV, but increased similarly (**Table 1**, Online Figure 1); SV increase from discharge to 1-year follow-up was 8.4 ml by Doppler, and was 6.9 ml by 2-dimensional

FIGURE 1 PVAR at Discharge and 1 Year



(A) The proportion of patients with varying degrees of paravalvular aortic regurgitation (PVAR) in 383 patients with paired echocardiography studies available. **(B)** Mean annular sizing ratio (100 × [valve perimeter − aortic annulus perimeter] / aortic annulus perimeter) for patients without PVAR, with PVAR that regressed by 1 year, and with residual PVAR that remained at 1 year. Error bars represent standard deviation. AR = aortic regurgitation.

volumetric methods. Despite the increase in SV, there were statistically significant reductions in AV velocity and mean gradient from discharge to 1-month follow-up, from 2.08 ± 0.45 m/s to 1.99 ± 0.46 m/s, and from 9.7 ± 4.4 mm Hg to 8.9 ± 4.6 mm Hg, respectively, $p < 0.0001$ for both (Table 1). Both variables increased slightly with further increase in SV at 1 year to 2.01 ± 0.44 m/s and 9.0 ± 4.5 mm Hg, respectively. EOA increased from 1.78 ± 0.51 cm^2 to 1.87 ± 0.54 cm^2 ($p = 0.003$ for the overall 5% increase). The longitudinal changes in AV mean gradient and Doppler SV are shown in Figure 3. Because the change in SV could have been due to improved LVEF, we also analyzed the data in patients with an LVEF ≥50%, and the results were the same (Online Table 5).

The further hemodynamic improvement with CoreValve after discharge was similar for all valve sizes (Table 2).

IMPACT OF COREVALVE IMPLANTATION ON LV FUNCTION, MASS, AND MITRAL REGURGITATION. For 203 patients who had an LVEF <50% at baseline,

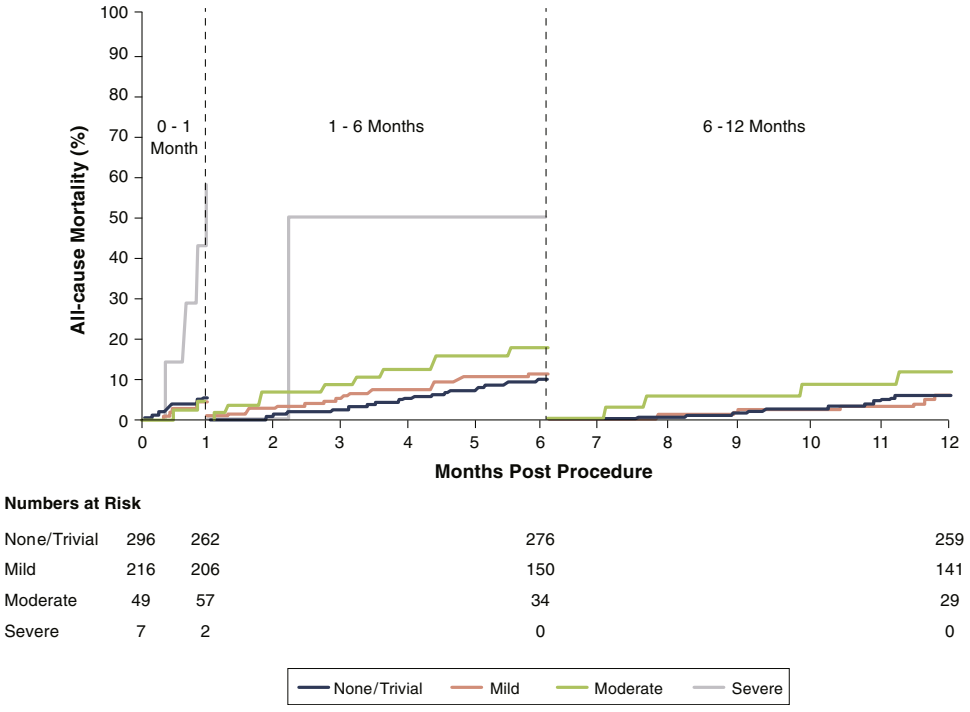
FIGURE 2 Paired PVAR Data at Discharge and 1 Year

	One Year				
Discharge	**None (N =123)**	**Trivial (N =143)**	**Mild (N =102)**	**Moderate (N =14)**	**Severe (N =1)**
None	49	18	7	1	0
Trivial	50	48	34	2	0
Mild	23	66	42	6	0
Moderate	1	11	18	5	1
Severe	0	0	1	0	0

Improvement in PVAR by at least 1 grade
Worsening in PVAR by at least 1 grade

Of 173 patients with mild (n = 137) or moderate (n = 36) paravalvular aortic regurgitation (PVAR) at discharge, 119 (69%) improved by at least 1 grade at 1-year follow-up. **Green** = improvement in PVAR by at least 1 grade; **pink** = worsening in PVAR by at least 1 grade.

FIGURE 3 All-Cause Mortality According to PVAR Severity



Because there was a reduction in PVAR severity over time, all-cause mortality was reassessed for patients with adjusted PVAR severity at 1 and 6 months. There was no significant difference in overall mortality among the different severities of PVAR except for severe AR. Abbreviations as in Figure 2.

we observed significant improvement from 37.2 ± 10.0% to 47.4 ± 12.9% at discharge ($p < 0.0001$) to 49.1 ± 12.1% at 1 year. LV mass index gradually decreased up to 1 year (132 g/m^2 at baseline to 112 g/m^2 at 1 year, $p < 0.0001$) (Table 1). LV diastolic function and filling pressure improved gradually, with reduction of median E/A ratio (from 1.00 [interquartile range (IQR): 0.75 to 1.50] at baseline to 0.87 [IQR: 0.67 to 1.08] at 1 year, $p = 0.0004$) and prolongation of median mitral inflow deceleration time (from 189 ms [IQR: 157 to 247 ms] to 241 ms [IQR: 191 to 301 ms], $p < 0.0001$). The number of patients with moderate or greater mitral regurgitation decreased from 17.2% at baseline to 11.7% at discharge ($p = 0.001$), and to 7.7% at 1 year.

DISCUSSION

Core laboratory analysis of serial echocardiography examinations in extreme risk patients with severe AS who underwent TAVR using a self-expandable CoreValve bioprosthesis demonstrated the following results: 1) PVAR of moderate or greater severity occurred in 9.9% after TAVR, but 83% of patients with moderate PVAR decreased in severity at 1-year follow-up, and only severe PVAR was associated with decreased survival; 2) in addition to acute improvement in AV velocity, mean gradient, and EOA noted at discharge, these parameters significantly improved further at 1 month and were sustained to 1 year, whereas SV increased; and 3) the annular sizing ratio was significantly associated with the degree of PVAR.

CONTINUOUS IMPROVEMENT OF COREVALVE HEMODYNAMICS. Although small, there was statistically significant improvement of CoreValve hemodynamics with lower bioprosthesis velocity, lower gradient, and higher EOA at 1 month compared with at discharge. This improvement occurred while LV SV increased, with slower heart rate and less mitral regurgitation. The majority of the SV increase took place between the 1- and 6-month follow-ups (Figure 4). After a significant reduction at 1 month, peak AV velocity and mean gradient increased slightly during that period, but remained significantly lower than discharge values. Because higher AV velocity and gradient are expected with a higher SV if the EOA

TABLE 2 Echocardiographic Parameters Over Time by Implanted Valve Size

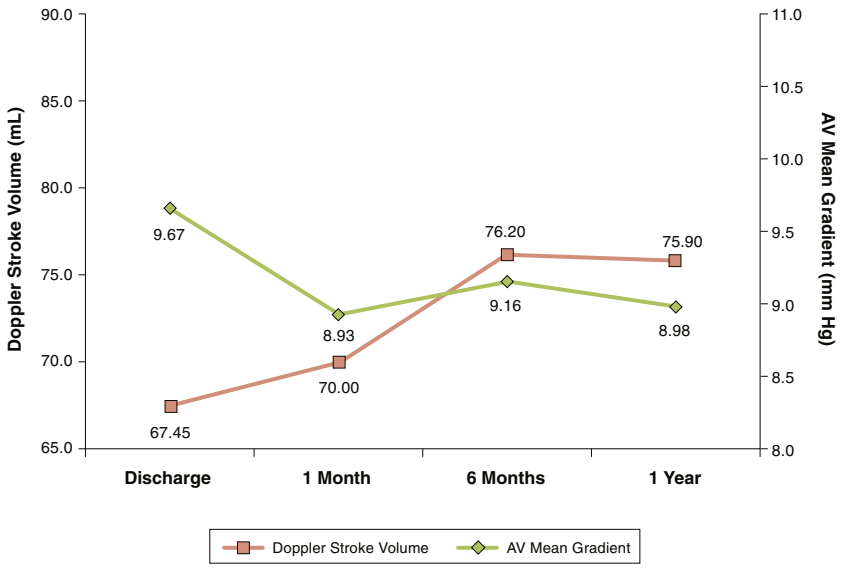
	23 mm (n = 21)	26 mm (n = 231)	29 mm (n = 357)	31 mm (n = 25)	All Sizes (N = 634)
LVOT diameter outer to outer, cm					
Discharge	1.74 ± 0.15 (17)	1.90 ± 0.20 (204)	2.11 ± 0.22 (315)	2.30 ± 0.23 (22)	2.03 ± 0.24 (558)
1 yr	1.87 ± 0.09 (13)	1.96 ± 0.20 (147)	2.18 ± 0.20 (229)	2.34 ± 0.19 (12)	2.09 ± 0.23 (401)
LVOT velocity time integral, cm^2					
Discharge	23.36 ± 5.32 (17)	22.21 ± 4.87 (203)	20.04 ± 4.80 (309)	18.03 ± 4.06 (23)	20.86 ± 4.96 (552)
1 yr	24.03 ± 5.86 (14)	23.39 ± 5.09 (147)	21.18 ± 5.47 (223)	19.28 ± 5.82 (13)	22.04 ± 5.48 (397)
AV peak velocity, m/s					
Discharge	2.61 ± 0.44 (18)	2.04 ± 0.42 (209)	2.07 ± 0.45 (328)	2.23 ± 0.40 (23)	2.08 ± 0.45 (578)
1 yr	2.33 ± 0.57 (13)	2.01 ± 0.43 (153)	1.98 ± 0.42 (234)	2.10 ± 0.59 (13)	2.01 ± 0.44 (413)
AV velocity time integral, cm					
Discharge	50.66 ± 11.46 (18)	38.87 ± 9.23 (208)	38.51 ± 10.00 (328)	39.57 ± 6.31 (23)	39.06 ± 9.86 (577)
1 yr	51.82 ± 12.42 (13)	43.05 ± 10.59 (153)	40.47 ± 10.67 (234)	40.95 ± 14.60 (13)	41.80 ± 11.01 (413)
AV mean gradient, mm Hg					
Discharge	15.74 ± 5.49 (18)	9.10 ± 3.77 (208)	9.66 ± 4.60 (328)	10.29 ± 3.43 (23)	9.67 ± 4.44 (577)
1 yr	11.20 ± 4.91 (13)	9.05 ± 4.60 (153)	8.76 ± 4.22 (234)	9.92 ± 5.75 (13)	8.98 ± 4.45 (413)
AV effective orifice area, cm^2					
Discharge	1.11 ± 0.24 (15)	1.67 ± 0.47 (191)	1.87 ± 0.52 (281)	1.91 ± 0.41 (22)	1.78 ± 0.51 (509)
1 yr	1.36 ± 0.45 (12)	1.70 ± 0.46 (141)	2.01 ± 0.54 (216)	1.98 ± 0.39 (12)	1.87 ± 0.54 (381)

Values are mean ± SD (n).
Abbreviations as in Table 1.

remains unchanged, the finding of reduced AV velocity and gradient with a higher SV suggests that EOA increased further after discharge. A continuous improvement in AV bioprosthesis hemodynamics after implantation has not been documented previously in other studies of TAVR. In fact, EOA did not change significantly and the mean gradient increased slightly over the 1- to 3-year follow-up in the PARTNER trial (1,14). There are 3 possible explanations for our findings: 1) the findings are related to a variability in echocardiography measurement; 2) the hemodynamic improvement is caused by increased SV that made the EOA larger; or 3) gradual remodeling due to self-expansion of the CoreValve is responsible for the increase in EOA, reduced AV velocity, and reduced mean gradient. Our interobserver and intraobserver variability in measuring flow velocities, gradients, and dimensions was good, and all the measurements changed in the same direction. It would be very difficult to create such a consistent hemodynamic improvement by technical measurement errors in a large number of studies. It is possible that increased SV enlarged the EOA, but that does not explain reduced AV velocity, and the degree of SV change was relatively small during the first month after discharge when most of those improvements occurred. The increase in SV calculation was partly related to a gradual increase in LVOT diameter (outer-to-outer aspects of CoreValve at the ventricular end), but LVOT VTI also increased. When SV was calculated by the modified Simpson volumetric method, it also increased over 1 year after implantation, although the increase was not statistically significant due to a smaller increase in fewer patients (Online Figure 1). However, the amount of SV increase from discharge to 1-year follow-up was similar between Doppler and 2-dimensional volumetric methods (8.4 ml vs. 6.9 ml, respectively).

Therefore, we propose that the additional improvement in AV hemodynamics over time is most likely related to gradual self-expansion of the CoreValve after implantation. The proposed mechanism of continuous self-expansion of the bioprosthesis could be further investigated in a prospective study performing serial measures of EOA or bioprosthesis perimeter by computed tomography or 3-dimensional echocardiography. Much of our findings depend on reliable measurements of SV, which was calculated from LVOT diameter and VTI. LVOT diameter after CoreValve implantation was obtained from the outer-to-outer edge of the ventricular end of the bioprosthesis, as recommended by the American Society of Echocardiography guideline for prosthetic valves. Jilaihawi et al. (15) measured the inner-to-inner diameter at the level of the leaflets in 50 CoreValve patients in their study of patient-prosthesis mismatch. But their method of measuring SV was not compared with another method, and it is often difficult to visualize the valve leaflets. More comparative studies are needed to determine the best way to calculate SV in patients with CoreValve bioprosthesis.

FIGURE 4 SV and AV Mean Gradient Change After TAVR



Although stroke volume (SV) increased after discharge to 1-year follow-up, the aortic valve (AV) mean gradient was significantly reduced ($p < 0.0001$) due to a further increase by CoreValve in the effective orifice area after discharge. TAVR = transcatheter aortic valve replacement.

PARAVALVULAR AORTIC REGURGITATION. The prevalence of AR after TAVR varies significantly depending on the type of prosthesis and the method of detection (5,16). In our study, moderate-to-severe PVAR was present in 9.9% at discharge, which is similar to previous reports in a self-expandable bioprosthesis (17,18). As originally reported by Popma et al. (3), severe PVAR was associated with worse survival in this trial with extreme-risk patients. However, in contrast to previous reports (4,5,19), patients with mild or moderate AR at discharge had similar survival as patients with none-to-trivial AR. One possible contributing factor to the limited association between residual mild or moderate AR and mortality observed in this study may be the regression of AR severity observed throughout follow-up. It is worth noting the prevalence of competing risks in our cohort also was likely to obscure the effects of regurgitation and diminish the strength of the association (1). The association between residual AR and mortality has been defined in different patient populations and the findings presented here are not necessarily generalizable to other risk groups for surgical AV replacement, nor should they be interpreted as minimizing the well-established physiological implications of residual AR.

Conflicting data exist about the natural history of PVAR from post-implantation to follow-up. The significant reduction in AR severity over 1-year follow-up found in our study has not been reported by others, although 31.9% improved in severity of PVAR over 2 years in the PARTNER trial (20,21). Possible explanations for this finding of regression of PVAR are tissue ingrowth covering the paravalvular spaces, the continuing expansion of the nitinol frame, or also possible aortic root remodeling. Rallidis et al. (22) followed 40 patients with mild/moderate PVAR who had surgical AVs at early follow-up and in 39 (97.5%) the severity of the leaks were unchanged at 5 years. Because tissue ingrowth with surgical valves is an early phenomenon, leaks that remain past this point are generally persistent. This study indicates that the mechanism of regression of PVAR we saw with CoreValve probably has additional contributing factors distinct from tissue ingrowth seen with surgical valves.

A plausible explanation is that the self-expanding nature of the CoreValve resulted in continuing outward expansion and remodeling of the aortic root as the additional contributing factor for reduced PVAR. The significantly increased EOA and decreased mean gradient as well as the gradual increase, albeit very small, in the outer-to-outer dimension of the bioprosthesis from discharge to 1-year follow-up are all consistent with continuous expansion of the nitinol frame. Additional support for this hypothesis of the continuous expansion is provided by the observation that patients whose PVAR regressed to none or trivial

at 1 year tended to have a larger annular sizing ratio than those who did not. When the native aortic annulus is stretched fully, additional small outward expansion of the CoreValve may reduce paravalvular gap sufficiently to allow more tissue growth to reduce PVAR. If the native aortic annulus is not stretched enough, PVAR or paravalvular gaps may not regress or close even with self-expansion of CoreValve.

PVAR remains a serious problem affecting clinical outcome of the patients who receive TAVR. We need to continue to improve technical expertise and valve design to minimize PVAR after TAVR. Our finding of regression of PVAR after CoreValve implantation requires further validation.

STUDY LIMITATIONS. First, a main limitation is the lack of validated quantitative criteria and volumetric data for assessing the severity of PVAR associated with TAVR. Although this problem is not unique to our study, a wrong conclusion can be reached if there is a significant variability among different readers. In our study, the fact that several physician echocardiographers assessed AR severity could have potentially introduced variability in AR assessment, especially mild and moderate severity, although our physician interobserver variability in AR assessment was good. Recently, a more granular grading scheme using multiparametric integrative approach has been proposed (23,24), and further studies will be required to establish a standardized method for assessment of PVAR after TAVR. Second, a potential bias could exist from the echocardiography core laboratory practice that the date of a particular study had to be known to sonographers for downloading and identifying correct images in the workstation. However, they were not aware of any other clinical data, and studies were analyzed as they were available. Third, echocardiography data were not available in all patients at all follow-ups. Therefore, we analyzed paired data, which showed similar results to the data analyzed for all patients. Lastly, when feasible, we defined severe PVAR as a >20% circumferential extent as recommended in the original VARC. If we were to use the VARC-2 recommendation, the percentage of the patients with severe AR decreases slightly, but the overall conclusions are unchanged.

CONCLUSIONS

After TAVR with the CoreValve bioprosthesis in extreme-risk patients with severe AS, there was a further AV hemodynamic improvement after discharge resulting in a significantly larger EOA and lower aortic valve gradient at 1-year follow-up compared with discharge. There was also a significant regression of PVAR over time up to 1 year. This is possibly related to continuous expansion of the CoreValve with nitinol frame resulting in the remodeling of aortic root.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: TAVR is an innovative therapy for patients with severe aortic stenosis deemed to be at high risk for surgical aortic valve replacement. More knowledge and understanding of natural history of TAVR are essential for appropriate use and further improvement of TAVR.

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: PVAR is a major problem after TAVR. Understanding of its mechanism and clinical impact is important in care of the patients who develop PVAR.

COMPETENCY IN INTERPERSONAL AND COMMUNICATION SKILLS: TAVR requires the strong team work of a heart team comprising a surgeon, interventionalist, imager, and clinicians involved in patient care. It is important for the team to communicate potential risks and benefits of this new therapeutic procedure.

TRANSLATIONAL OUTLOOK: In this study, we are reporting on patients with aortic stenosis at extreme surgical risk and 1-year follow-up. A longer follow-up in this patient population and studies in different populations will be necessary to obtain comprehensive knowledge about the hemodynamics and PVAR after TAVR.

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KEY WORDS CoreValve self-expansion, paravalvular aortic regurgitation regression

APPENDIX For a supplemental figure and tables, please see the online version of this article.

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