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Computed Tomography–Based Oversizing Degrees and Incidence of Paravalvular Regurgitation of a New Generation Transcatheter Heart Valve

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ABSTRACT

OBJECTIVES The aim of the study was to investigate the influence of the extent of computed tomography (CT)-based area and perimeter oversizing on the incidence and severity of paravalvular aortic regurgitation (PAR) for the Edwards SAPIEN 3 (Edwards Lifesciences, Irvine, California) device, using CT data and echocardiographic outcome data of the PARTNER II (Placement of AoRTic TraNscathetER Valves Trial II) SAPIEN 3 intermediate-risk cohort.

BACKGROUND Transcatheter heart valve (THV) sizing algorithms are device specific, requiring refinements for new valve designs.

METHODS A total of 835 intermediate-risk patients with severe, symptomatic aortic stenosis enrolled in a multicenter, nonrandomized registry at 57 sites in the United States and Canada with available systolic CT data and echocardiographic follow-up were included in this analysis. THV size selection was primarily CT guided based on annular area. Area-based and perimeter-based oversizing was calculated using systolic annular CT dimensions and nominal dimensions of the implanted THV size. PAR was assessed at 30 days according to a 5-class scheme.

RESULTS Mean oversizing by area was 7.7 ± 9.4% and mean oversizing by perimeter was 1.7 ± 4.4%. An inverse proportional relationship between degree of oversizing and frequency and severity of PAR was observed for both area and perimeter oversizing. Perimeter and area oversizing confer similar predictive capacity in regard to the occurrence of PAR after THV implantation (area under the curve: 0.78 [95% confidence interval: 0.70 to 0.85] vs. area under the curve: 0.78 [95% confidence interval: 0.72 to 0.85]; $p < 0.0001$). No aortic root ruptures were observed.

CONCLUSIONS For the SAPIEN 3 THV, the frequency and extent of PAR is inversely related to the degree of oversizing with acceptable rates of PAR being achieved at lower degrees of oversizing. Perimeter and area oversizing confer similar predictive capacity in regard to the occurrence of PAR after implantation of the SAPIEN 3 THV. Therefore, the SAPIEN 3 THV may offer the opportunity to reduce the risk of annular rupture associated with more significant degrees of oversizing in borderline annular anatomy. (The PARTNER II Trial: Placement of AoRTic TraNscathetER Valves [PARTNER II]; NCT01314313) (J Am Coll Cardiol Intv 2017;10:810–20) © 2017 by the American College of Cardiology Foundation.

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Transcatheter aortic valve replacement (TAVR) has become the therapy of choice for patients with severe aortic stenosis who are clinically deemed to be at high or prohibitive risk for surgical aortic valve replacement (1-3). Recently, the safety and efficacy of balloon-expandable TAVR has also been demonstrated for intermediate-risk patients using a new transcatheter heart valve (THV) design aimed at reducing rates of paravalvular aortic regurgitation (PAR) while maintaining hemodynamic THV performance (4).

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Integration of computed tomography (CT) for aortic annular assessment and THV sizing reduces the frequency of PAR, leading to its acceptance as essential component of TAVR planning (5). However, sizing algorithms are device specific, requiring refinements for new valve designs; fundamentally, all recommend the use of a THV with nominal perimeter or area larger than that of the native annulus, termed oversizing. Although an inverse relationship between PAR and oversizing is well established (6), a recent analysis of the initial European experience with the SAPIEN 3 THV (Edwards Lifesciences, Irvine, California) suggested a lesser degree of annular oversizing was required than with preceding valve generations, thus reducing the risk of annular injury due to oversizing while still allowing for the ability to control PAR (7,8).

The aim of this study was to investigate the influence of the extent of CT-based area and perimeter oversizing on the incidence and severity of PAR for the Edwards SAPIEN 3 device as a foundation for a device-specific CT sizing algorithm for the Edwards SAPIEN 3 platform, using CT data and echocardiographic outcome data of the PARTNER (Placement of AoRTic TraNscathetER Valves Trial II) SAPIEN 3 intermediate-risk cohort.

ABBREVIATIONS AND ACRONYMS

CT = computed tomography

PAR = paravalvular regurgitation

ROC = receiver-operating characteristic

TAVR = transcatheter aortic valve replacement

THV = transcatheter heart valve

METHODS

The PARTNER II SAPIEN 3 intermediate-risk trial was a prospective, single-arm nonrandomized registry designed to evaluate the third-generation SAPIEN 3 THV (4). Inclusion criteria included symptomatic (New York Heart Association functional class II or greater) severe aortic stenosis as determined by echocardiography (valve area <0.8 cm^2 or indexed valve area <0.5 cm^2/m^2 and mean gradient >40 mm Hg or peak velocity >4 m/s) and an intermediate-risk profile, as determined by Society of Thoracic Surgeons score (between 4 and 8) or a defensible intermediate-risk profile as per heart team determination (comprising experienced cardiac surgeons, interventional cardiologists, and others). Complete details on inclusion and exclusion criteria have been reported previously (4). In total, 1,078 patients were enrolled at 51 hospitals in the United States, of whom 1,069 received a SAPIEN 3 valve implantation. The study was approved by the institutional review board at each study site, and all patients provided written informed consent.

STUDY POPULATION. The analysis presented herein was restricted to patients undergoing successful implantation of the SAPIEN 3 THV who also had available systolic aortic annular dimensions as obtained by the CT core laboratory as well as post-implant PAR grading from the echocardiography core laboratory.

Holdings; and has provided computed tomography Core Lab services for Edwards Lifesciences, Medtronic, Neovasc, GDS, and Tendyne Holdings. Dr. Pibarot has Core Lab contracts with Edwards Lifesciences; and has served as a speaker for St. Jude Medical. Dr. Hahn has an institutional Core Lab contract with Edwards Lifesciences for which she receives no direct compensation and is a speaker for Philips Healthcare, St. Jude Medical, and Boston Scientific. Dr. Weissman has Core Lab contracts with Edwards Lifesciences, St. Jude Medical, Boston Scientific, Medtronic, Biostable, Sorin, Abbott Vascular, Direct Flow, and Mitralign; and has received research grant support from Boston Scientific, Edwards Lifesciences, Medtronic, St. Jude Medical, and Abbott Vascular. 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 Inc. Dr. Thourani has served as a consultant for Edwards Lifesciences and Abbott Medical; and has received research grant support from Edwards Lifesciences. Ms. Parvataneni is a consultant with Jazz Pharmaceuticals. Dr. Dvir has served as a consultant for Edwards Lifesciences. Dr. Nørgaard has received unrestricted institutional research grant support from Edwards Lifesciences and Siemens. Dr. Douglas has received research grant support from Edwards Lifesciences. Dr. Jaber has performed Echocore LAB work for the PARTNER trial. Dr. Khalique has served as on the Speakers Bureau for Edwards Lifesciences and Boston Scientific; and as a reader for a Core Lab that has contracts with Edwards Lifesciences. Dr. Jilaihawi has served as a consultant for Edwards Lifesciences and Venus Medtech. Dr. Webb has served as a consultant for Edwards Lifesciences. Dr. Leipsic has served as a consultant for Edwards Lifesciences and Circle CVI; and has provided computed tomography Core Lab services for Edwards Lifesciences, Medtronic, Neovasc, GDS, and Tendyne Holdings. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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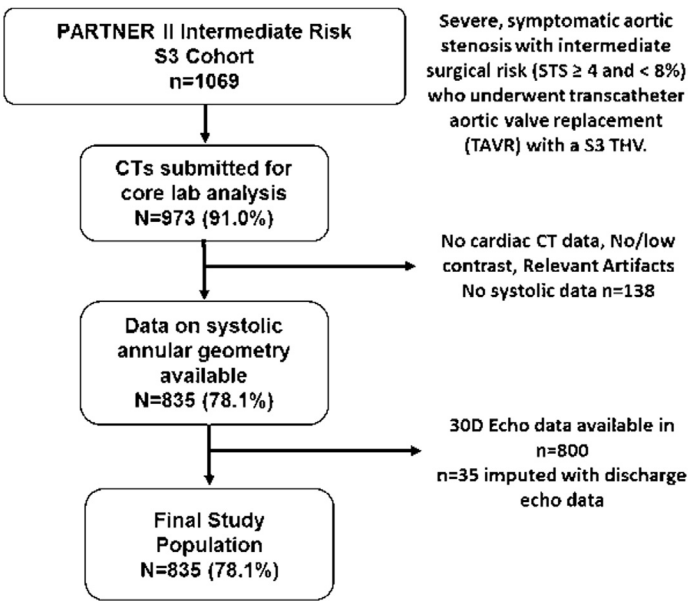
FIGURE 1 Derivation of Final Study Cohort



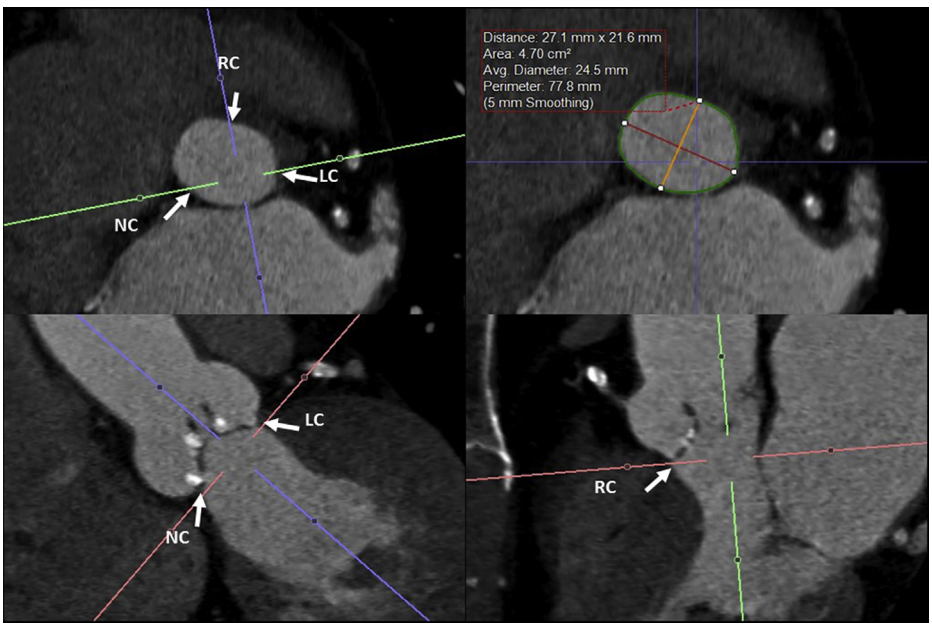
CT = computed tomography; Echo = echocardiography; PARTNER II = Placement of AoRTic TraNscathetER Valves Trial II; S3 = SAPIEN 3; STS = Society of Thoracic Surgeons; TAVR = transcatheter aortic valve replacement; 30D = 30 day.

Subjects without systolic anatomical data by CT were not included. Subjects with missing 30-day PAR data were imputed using discharge echocardiographic results. Derivation of the study cohort and reasons for exclusions are listed in Figure 1. The final study population of the subanalysis comprised 835 patients (78.1%).

PROCEDURE. The Edwards SAPIEN 3 balloon-expandable THV comprises a balloon-expandable cobalt-chromium alloy frame, a trileaflet bovine pericardial tissue valve, and a polyethylene terephthalate inner and outer skirt, which covers the lower portion of the frame and is specifically designed to reduce PAR. The THV system is delivered through expandable 14-F (20-, 23-, and 26-mm THV) or 16-F (29-mm THV) transfemoral delivery sheaths. The SAPIEN 3 THV can also be delivered via direct transaortic or transapical routes.

As provided by the manufacturer, the 20-, 23-, 26-, and 29-mm SAPIEN 3 THVs have nominal areas of 309.2, 407.2, 519.2, and 649.2 mm^2 and perimeters of 62.3, 71.5, 80.8, and 90.3 mm, respectively. Patients were required to have an aortic annular area between 273 and 680 mm^2, appropriate for treatment with a 20-, 23-, 26-, or 29-mm SAPIEN 3 THV. For

FIGURE 2 Planimetric Assessment of Systolic Annular Dimensions



Multiplanar reformatted images of a contrast-enhanced computed tomography scan for the purposes of transcatheter aortic valve replacement planning. Identification of all 3 aortic cusp (LC, NC, and RC) insertion allows for the definition of the aortic annulus for measurement. In this example, the annulus measures an area of 4.70 cm^2 suggesting the implantation of a 26-mm SAPIEN 3 device (Edwards Lifesciences, Irvine, California). LC = left cusp; NC = noncoronary cusp; RC = right cusp.

pre-procedural sizing, operators were provided with annular and aortic root dimensions as assessed by the CT core lab. Oversizing was calculated as: (THV nominal area / 3-dimensional annular area − 1) • 100. THV size selection aimed achieving effective area oversizing of approximately -5% (undersizing) to 20% oversizing by area. Anatomical dimensions and sizing were also discussed on regular case selection committee calls. The final decision on THV size was at the discretion of the operator.

CT DATA ACQUISITION. CT examinations were performed according to site-specific institutional CT protocols, comprising electrocardiography synchronized, multiphasic, contrast-enhanced cardiac CT using 64-detector or greater CT systems. Anonymized CT datasets, including thin-sliced axial reconstructions throughout multiple time points in the cardiac cycle, were provided to the CT core laboratory at St. Paul's Hospital, Vancouver, Canada. For this analysis all datasets were transferred to a dedicated post-processing platform (Aquarius iNtuition, Version 4.4.2, TeraRecon, Foster City, California).

ANNULAR QUANTIFICATION. The aortic annular plane was defined by the basal attachment points of the 3 aortic valve cusps. CT datasets were reformatted into multiplanar reconstructions of the aortic root. Multiplanar reconstructions were manually oriented to display the aortic annulus at the level of the basal attachment points. For multiphasic datasets, the annular plane was readjusted for every reconstruction phase to compensate for displacement during the cardiac cycle, aiming at identifying the reconstruction frame with the largest anatomical dimensions during systole. For planimetric assessment the aortic annular contours were manually segmented. Planimetry yielded maximum and minimum diameters (short and long axis), cross-sectional area, and perimeter (**Figure 2**). Importantly, post-processing software allowed for automated smoothing of the segmentation contour to avoid artificial distortion of the annular perimeter due to contour irregularities and spikes that have been shown to increase the perimeter measures (9).

The annular and subannular landing zone was assessed for the presence of calcifications. If present, the distribution of calcification and extension into the left ventricular outflow tract were also assessed in a semiquantitative fashion as follows: mild, 1 or more nonprotruding nodules of calcium extending <5 mm in any direction and covering <10% of the annular perimeter; moderate, 1 or more nodules protruding or extending >5 mm in any direction or covering >10% of the perimeter of the annulus; severe, multiple nodules of calcification of single focus extending >1 cm in length or covering >20% of the perimeter of the annulus.

TABLE 1 Demographic and Clinical Baseline Characteristics

Age, yrs	82.09 ± 6.46
Male	61.4 (512)
Body surface area, m^2	1.92 ± 0.23
STS score	5.27 ± 1.28
Race	
White	92.1 (769)
Hispanic or Latino	1.7 (14)
American Indian or Alaska Native	0.0 (0)
Black or African American	3.4 (28)
Asian	0.5 (4)
Unknown of not reported	1.9 (16)
Logistic EuroSCORE II	5.27 ± 4.34
NYHA functional class	
II	28.7 (240)
III or IV	71.3 (595)
Coronary artery disease	67.7 (565)
Previous myocardial infarction	15.0 (125)
Previous cardiac intervention	
CABG	27.4 (229)
PCI	31.7 (265)
Balloon aortic valvuloplasty	5.3 (44)
Previous stroke	8.4 (70)
Peripheral vascular disease	28.0 (234)
Diabetes	34.1 (285)
Creatinine >2 mg/dl (177 μmol/l)	6.5 (54)
Atrial fibrillation	36.3 (303)
Permanent pacemaker	12.8 (107)

Values are mean ± SD or % (n).

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

COMPREHENSIVE TRANSTHORACIC ECHOCARDIOGRAM 30 DAYS AFTER INDEX PROCEDURE. Transthoracic echocardiography was performed by the sites at the 30-day follow-up visit following the study protocol or American Society of Echocardiography guidelines. Anonymized datasets were provided to and evaluated by a dedicated core laboratory. PAR was graded using a 5-class grading scheme (0 = none or trace, 1 = mild, 2 = mild to moderate, 3 = moderate, 4 = moderate to severe, and 5 = severe) as recently described in Pibarot et al. (10) and Hahn et al. (11) (Online Table 1). Mean gradient and aortic valve effective orifice area indexed to body surface area were calculated.

OVERSIGHT AND DATA MANAGEMENT. The trial was designed collaboratively by the sponsor (Edward Lifesciences) and members of the executive steering committee. The sponsor funded the study,

TABLE 2 Systolic Annular Dimensions, Degree of Oversizing, and PAR Stratified by THV Size

	20 mm (n = 37)	23 mm (n = 261)	26 mm (n = 378)	29 mm (n = 159)	Entire cohort (N = 836)	p Value (Overall)
Nominal THV area, mm^2	309	409	519	649	N/A	N/A
Nominal THV perimeter, mm	62.3	71.5	80.8	90.3	N/A	N/A
Systolic annular dimensions						
Mean annular area, mm^2	313.7 ± 26.1	386.9 ± 32.3	485.6.1 ± 38.4	578.9 ± 46.6	465.1 ± 83.8	N/A
Mean annular perimeter, mm^2	63.9 ± 2.7	71.0 ± 3.0	79.6 ± 3.2	86.9 ± 3.5	77.6 ± 7.1	N/A
Degree of oversizing						
Mean area oversizing, %	-0.7 ± 8.6	6.5 ± 9.1	7.5 ± 8.6	12.9 ± 9.4	7.7 ± 9.4	<0.0001
Mean perimeter oversizing, %	-2.4 ± 4.2	0.9 ± 4.3	1.7 ± 4.1	4.1 ± 4.3	1.7 ± 4.4	<0.0001
Frequency of PAR						
None	13.6 (5/37)	19.2 (50/261)	25.4 (96/378)	39.0 (62/159)	25.5 (213/835)	<0.0001
Trace	10.8 (4/37)	23.8 (62/261)	29.4 (111/378)	22.0 (35/159)	25.4 (212/835)	0.0345
Mild	48.7 (18/37)	39.5 (103/261)	35.7 (135/378)	34.0 (54/159)	37.1 (310/835)	0.3031
Mild-moderate	16.2 (6/37)	11.1 (29/261)	7.4 (28/378)	4.4 (7/159)	8.4 (70/835)	0.0224
Moderate	8.1 (3/37)	5.4 (14/261)	1.9 (7/378)	0.6 (1/159)	3.0 (25/835)	0.0035
Moderate-severe	2.7 (1/37)	1.2 (3/261)	0.3 (1/378)	0.0 (0/159)	0.6 (5/835)	0.1003
Severe	0.0 (0/37)	0.0 (0/261)	0.0 (0/378)	0.0 (0/159)	0.0 (0/835)	N/A

Values are mean ± SD or % (n/N), unless otherwise indicated.
N/A = not applicable; PAR = paravalvular aortic regurgitation; THV = transcatheter heart valve.

participated in the selection and management of sites and monitored the data. P.B. and the coprincipal investigators had unrestricted access to the data after the database was locked, prepared all drafts of the manuscript, and made the final decision to submit the manuscript. Data analysis was performed by independent statisticians at the Cardiovascular Research Foundation. The sponsor had no role in data analysis, drafting the manuscript, or the decision to publish.

STATISTICAL ANALYSIS. Categorical variables were summarized as percentages whereas continuous variables were reported as mean ± SD or median (first and third quartile). Chi-square test or Fisher exact test, as appropriate, was used to test for differences among categorical variables. Kruskal-Wallis test was used to test for differences among continuous variables. Relative percent area and perimeter oversizing was calculated as follows, using the nominal THV values provided by the manufacturer: (SAPIEN 3 nominal measurement / annular measurement − 1) • 100. Patients were a priori categorized depending on the degree of relative oversizing: 1) for area: undersizing (below 0%), 0% to 5%, 5% to 10%, and above 10%; and 2) for perimeter: undersizing (below 0%), 0% to 2.5%, 2.5% to 5%, and above 5%. The eccentricity index was calculated as follows: 1 – (minimal diameter/maximum diameter). PAR was modeled in 3 ways (greater than or equal to mild, greater than or equal to mild to moderate, and greater than or equal to moderate). The receiver-operating characteristic (ROC) modeled varying categories of PAR based on relative area and perimeter oversizing. Cutoff values were selected based on the point nearest to (0,1) on the ROC curve. Univariable Poisson regression model the association between subannular calcification and PAR in the overall sample as well by each oversizing category. A p value of ≤0.05 was considered statistically significant. Analyses were performed using R version 3.2.1 (R Development Core Team, Vienna, Austria).

RESULTS

STUDY POPULATION. The mean age of the study cohort was 82.1 ± 6.5 years, 61.4% were men, and the mean Society of Thoracic Surgeons score was 5.3 ± 1.3%. Baseline demographics and procedural characteristics are reported in Table 1. Transfemoral access was used in 88.5% (739 of 835) of patients, transapical and transaortic access in 7.3% (61 of 835) of patients, and 4.2% (35 of 835) of patients. Post-dilation was performed in 11.1% (93 of 835) of patients. Three patients (0.4%) received more than 1 THV during the index procedure. No aortic root or annulus rupture was observed in this study population.

THV SELECTION AND ANNULAR OVERSIZING ACROSS THE STUDY POPULATION. Annular dimensions and oversizing stratified by valve size is listed in Table 2. A 20-mm THV was implanted in 4.4% (37 of 835) of patients, 31.3% (261 of 835) received a 23-mm THV, 45.3% (378 of 835) received a 26-mm THV, and 19.0% (159 of 835) received a 29-mm THV. This resulted in mean

TABLE 3 Frequency and Extent of PAR Stratified by Degree of Area Undersizing/Oversizing

	Undersizing/Oversizing by Systolic Area					
	Below -5% (n = 53)	**-5% to 0% (n = 140)**	**0% to 5% (n = 145)**	**5% to 10% (n = 167)**	**Above 10% (n = 330)**	**Combined (n = 835)**
PAR at 30 days						
None	7.5 (4/53)	15.0 (21/140)	19.3 (28/145)	20.4 (34/167)	38.2 (126/330)	25.5 (213/835)
Trace	11.3 (6/53)	17.9 (25/140)	24.1 (35/145)	29.3 (49/167)	29.4 (97/330)	25.4 (212/835)
Mild	47.2 (25/53)	44.3 (62/140)	44.8 (65/145)	38.3 (64/167)	28.5 (94/330)	37.1 (310/835)
Mild-Moderate	20.8 (11/53)	15.0 (21/140)	9.0 (13/145)	7.8 (13/167)	3.6 (12/330)	8.4 (70/835)
Moderate	7.5 (4/53)	7.1 (10/140)	2.1 (3/145)	4.2 (7/167)	0.3 (1/330)	3.0 (25/835)
Moderate-Severe	5.7 (3/53)	0.7 (1/140)	0.7 (1/145)	0.0 (0/167)	0.0 (0/330)	0.6 (5/835)
Severe	0.0 (0/53)	0.0 (0/140)	0.0 (0/145)	0.0 (0/167)	0.0 (0/330)	0.0 (0/835)
Nominal THV size, mm						
20 mm	24.5 (13/53)	6.4 (9/140)	5.5 (8/145)	1.2 (2/167)	1.5 (5/330)	4.4 (37/835)
23 mm	39.6 (21/53)	37.1 (52/140)	34.5 (50/145)	32.9 (55/167)	25.2 (83/330)	31.3 (261/835)
26 mm	35.8 (19/53)	47.1 (66/140)	46.2 (67/145)	48.5 (81/167)	43.9 (145/330)	45.3 (378/835)
29 mm	0.0 (0/53)	9.3 (13/140)	13.8 (20/145)	17.4 (29/167)	29.4 (97/330)	19.0 (159/835)

Values are % (n/N).
Abbreviations as in Table 2.

oversizing by area of 7.7 ± 9.4% and mean oversizing by perimeter of 1.7 ± 4.4%. Of all 835 patients, nominal THV dimensions were larger than the native systolic annular area (positive area oversizing) in 76.9% (642 of 835) and larger than the systolic annular perimeter (positive perimeter oversizing) in 63.2% (528 of 835).

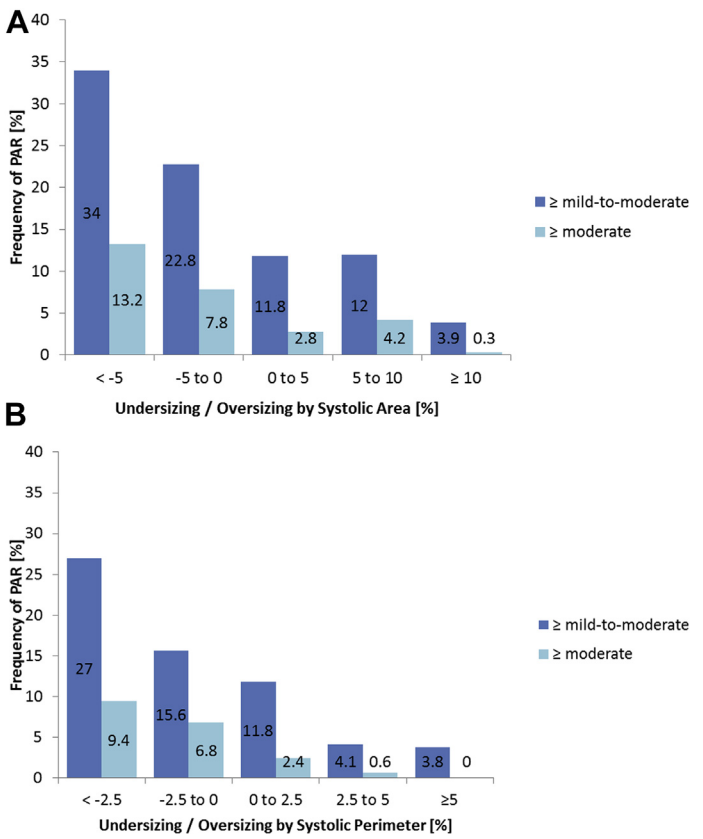
PAR INCIDENCE AND SEVERITY STRATIFIED BY PERCENTAGE AREA AND PERIMETER OVERSIZING. Frequency and severity of PAR stratified by extent of oversizing is listed in Tables 3 and 4 and illustrated in Figures 3 and 4. No patient experienced severe PAR. Moderate and moderate-to-severe PAR was observed in 3.0% (25 of 835) and 0.6% (5 of 835) of patients, respectively. Mild and mild-to-moderate PAR was found in 37.1% (310 of 835) and 8.4% (70 of 835) of patients, respectively, whereas no PAR or trace PAR was found in 50.9% (425 of 835) of patients. Overall, the frequency and extent of PAR decreased with greater degree of oversizing, which is consistent with an inversely proportional relationship of oversizing and PAR extent. In patients with area oversizing ≥10%, moderate or greater PAR was observed infrequently (0.3%). For lesser degrees of oversizing, the rate of greater than or equal to moderate PAR increased to 4.2% and 2.8% for oversizing

TABLE 4 Frequency and Extent of PAR Stratified by Degree of Perimeter Undersizing/Oversizing

	Undersizing/Oversizing by Systolic Perimeter					
	Below -2.5% (n = 159)	**-2.5% to 0% (n = 148)**	**0% to 2.5% (n = 170)**	**2.5% to 5% (n = 172)**	**Above 5% (n = 186)**	**Combined (N = 835)**
PAR at 30 days						
None	12.6 (20/159)	16.9 (25/148)	21.2 (36/170)	34.3 (59/172)	39.2 (73/186)	25.5 (213/835)
Trace	13.8 (22/159)	24.3 (36/148)	30.0 (51/170)	28.5 (49/172)	29.0 (54/186)	25.4 (212/835)
Mild	46.5 (74/159)	43.2 (64/148)	37.1 (63/170)	33.1 (57/172)	28.0 (52/186)	37.1 (310/835)
Mild-Moderate	17.6 (28/159)	8.8 (13/148)	9.4 (16/170)	3.5 (6/172)	3.8 (7/186)	8.4 (70/835)
Moderate	6.9 (11/159)	6.1 (9/148)	2.4 (4/170)	0.6 (1/172)	0.0 (0/186)	3.0 (25/835)
Moderate-Severe	2.5 (4/159)	0.7 (1/148)	0.0 (0/170)	0.0 (0/172)	0.0 (0/186)	0.6 (5/835)
Severe	0.0 (0/159)	0.0 (0/148)	0.0 (0/170)	0.0 (0/172)	0.0 (0/186)	0.0 (0/835)
Functioning THV size						
20 mm	13.2 (21/159)	4.1 (6/148)	2.9 (5/171)	2.3 (4/172)	0.5 (1/186)	4.4 (37/836)
23 mm	37.7 (60/159)	3.9 (57/148)	31.6 (54/171)	25.0 (43/172)	25.3 (47/186)	31.2 (261/836)
26 mm	43.4 (69/159)	45.3 (67/148)	46.5 (79/170)	47.7 (82/172)	43.5 (81/186)	43.4 (69/159)
29 mm	5.7 (9/159)	12.2 (18/148)	18.7 (32/171)	25.0 (43/172)	30.6 (57/186)	19.0 (159/836)

Values are % (n/N).
Abbreviations as in Table 2.

FIGURE 3 Frequency of Paravalvular Regurgitation Stratified by CT Annular Area Sizing



(A) Extent and frequency of paravalvular aortic regurgitation (PAR) stratified by degree area undersizing of oversizing. **(B)** Extent and frequency of PAR stratified by degree perimeter undersizing of oversizing.

by area of ≥5% to 10% and ≥0% to 5%, respectively. In patients with undersizing by area (i.e., patients with a native annular area exceeding the nominal area of the selected THV), the rate of greater than or equal to moderate PAR increased to 7.8% for -5% to 0%, but then further increased to 13.2% when undersizing was >-5.0%. A similar inverse proportional relationship was exhibited between oversizing by perimeter and the frequency and extent of PAR, with a rate of 2.4% for 0% to 2.5% perimeter oversizing and 0.6% for both ≥2.5% to 5% oversizing and ≥5% oversizing. With perimeter undersizing up to 2.5%, the rate of greater than or equal to moderate PAR increased to 6.8% and then further increased to 9.4% for more pronounced undersizing of >2.5%. Interestingly, in patients with ≥0% oversizing for both area and perimeter, greater than or equal to moderate PAR was observed in 0.9% (5 of 528) of patients. The frequency of greater than or equal to moderate PAR increased to 6.1% (7 of 114) for patients with ≥0% oversizing by area, but <0% oversizing by perimeter, and further to 9.3% (18 of 193) in patients with <0% oversizing by area and perimeter.

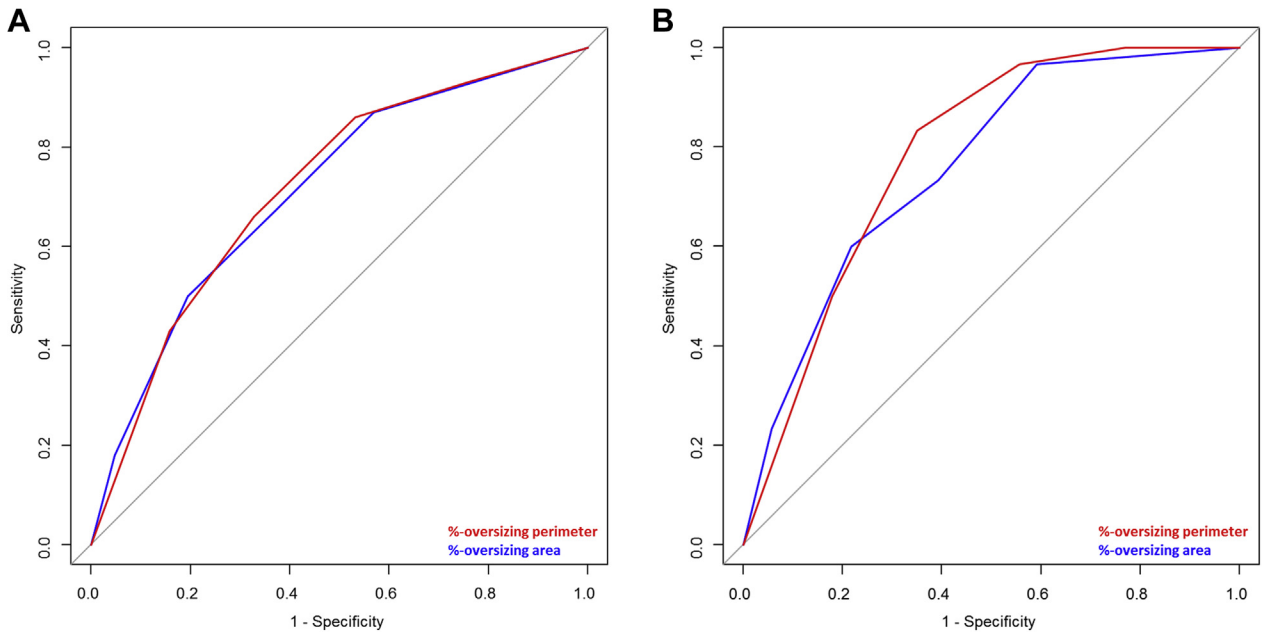
ROC ANALYSES FOR PREDICTION OF PAR. For the entire cohort, ROC analysis of the prediction of greater than or equal to mild-to-moderate and greater than or equal to moderate PAR demonstrated similar area under the curve values for oversizing by perimeter compared to oversizing by area (Table 5, Figures 3 and 4). The optimal cutoff for predicting greater than or equal to moderate PAR was 0.05% for oversizing by area and -1.24% for perimeter oversizing by perimeter.

IMPACT OF ANNULAR CALCIFICATION OF FREQUENCY OF PAR. Results of the regression analysis to investigate the impact of landing zone calcium on the frequency of PAR are listed in Table 6. There were no significant associations between any severity of landing zone calcium and greater than or equal to moderate PAR. However, the presence of any degree of landing zone calcium carried a relative risk of 1.23 (95% confidence interval: 1.01 to 1.49; $p = 0.0365$) for greater than or equal to mild PAR. The presence of moderate or severe landing zone calcification carried a relative risk of 1.36 (95% confidence interval: 1.09 to 1.69; $p = 0.0056$) for greater than or equal to mild PAR compared to patients with none or mild landing zone calcifications.

DISCUSSION

The growing evidence for the negative effect of greater than or equal to moderate PAR on patient outcomes after balloon-expandable TAVR (12) emphasizes the need for optimization of anatomical sizing and device selection to reduce severity and frequency of PAR. In light of this, major findings of this investigation were as follows: 1) validation of a clear, inverse proportional relationship of oversizing and frequency and extent of PAR, as previously reported for preceding generations of balloon-expandable THVs; 2) demonstration that acceptable rates of PAR can be achieved at historically low degrees of oversizing; 3) evidence that the SAPIEN 3 THV tolerates well-defined modest undersizing by area, while still allowing for a predictable result with regard to PAR; and 4) establishing that perimeter and area oversizing confer similar predictive capacity in regard to the occurrence of PAR after implantation of the SAPIEN 3 THV.

FIGURE 4 Discrimination of Paravalvular Regurgitation by Area and Perimeter Annular Oversizing



(A) Greater than or equal to mild-to-moderate paravalvular aortic regurgitation for oversizing by systolic area and perimeter. **(B)** Greater than or equal to moderate paravalvular aortic regurgitation for oversizing by systolic area and perimeter.

FREQUENCY AND EXTENT OF PAR. As previously reported (4), the implantation of the balloon-expandable SAPIEN 3 THV allows for an overall low frequency and extent of PAR, with moderate or greater PAR encountered in only 3.6% of patients. These historically low rates of PAR for balloon-expandable TAVR are in part attributable to the following: 1) an improved device design with a sealing skirt aiming at mitigation of PAR; 2) facilitated accurate positioning; and 3) full integration of 3-dimensional imaging into the THV sizing process. In the vast majority of patients enrolled in the PARTNER II trial SAPIEN 3 intermediate-risk study, valve selection was based on annular area derived by CT, with a minority of patients (6%, excluded from the present study) sized by 3-dimensional transesophageal echocardiography if CT image quality was insufficient for reliable annular assessment. Because of aortic annular dimensions being larger in systole than in diastole (13) and to increase the reliability and applicability of our analysis, we purposefully only included patients with available CT systolic annular dimensions. We confirmed prior reports of a strong inverse proportional relationship between the degree of area or perimeter oversizing and the frequency and extent of PAR.

Reduction of PAR by integration of CT into preprocedural planning has been previously demonstrated for the SAPIEN XT THV (Edwards Lifesciences), with reported frequency of moderate or severe PAR of approximately 5.3% (6). However, to reliably prevent moderate or severe PAR when using the SAPIEN XT, relative oversizing by area has to exceed 10%. In contrast, this study demonstrates, that similar PAR rates for the SAPIEN 3 can be achieved at as little as ≥0% to 5% area oversizing. These findings are in line with a recent report by Yang et al. (7), demonstrating lesser extent of oversizing needed for SAPIEN 3 than SAPIEN XT by means of a retrospective comparison of both devices. The lesser degree of oversizing required improves the safety of the procedure by reducing the chance of annular injury or rupture.

Noteworthy for a more granular assessment of PAR, a 5-class grading scheme was used for core laboratory echocardiographic analysis as previously reported by Pibarot et al. (10), subdividing the former 3-class mild PAR into mild and mild-to-moderate PAR and former 3-class moderate PAR into moderate and moderate-severe PAR. The 5-class scheme provides more flexibility for the grading of PAR and with the potential to improve the overall accuracy and

TABLE 5 ROC Analysis for Prediction of PAR by Percent Area or Percent Perimeter Oversizing

% Oversizing by	PAR	Events	Cutoff	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)	AUC	95% Confidence Interval
Area	≥ mild to moderate	100	4.11	64.38	64.82	19.94	93.04	64.77	0.715	0.662-0.768
Perimeter	≥ mild to moderate	100	0.25	64.58	64.48	19.83	93.05	64.49	0.716	0.665-0.767
Area	≥ moderate	30	0.05	73.58	69.36	8.21	98.6	69.51	0.776	0.704-0.848
Perimeter	≥ moderate	30	-1.24	75.73	69.39	8.44	98.71	69.62	0.784	0.722-0.846

AUC = area under the curve; NPV = negative predictive value; PAR = paravalvular aortic regurgitation; PPV = positive predictive value; ROC = receiver-operating characteristic.

reproducibility of PVR grading by echocardiography, avoiding an intuitive trend to select the middle grade of a 3-class grading scheme when uncertain (10,11). Importantly to ensure that the results are translatable, the 5-class grading scheme can be collapsed to a 3-class grading scheme, allowing for direct comparison of data previously derived using the 3-class grading scheme.

IMPLICATION FOR DEVICE SIZING. Although the SAPIEN 3 THV allows for overall reduced rates of moderate or severe PAR, the most important finding in regard to device sizing is the ability to minimally oversize the native aortic annulus or modest undersizing while maintaining these low rates and more modest severity of PAR. This allows for a paradigm shift regarding device selection for balloon-expandable TAVR in borderline anatomy: cases that previously were approached by oversizing the device but implanting with balloon-underfilling (14) may now be treated by full expansion of a smaller device. Preventing aggressive oversizing by means of selecting a smaller device (i.e., undersizing) in borderline anatomy has the potential to significantly reduce the risk of rupture associated with significant oversizing with a balloon-expandable TAVR (15,16). Importantly, no annular rupture was observed in patients included into this analysis. This approach may not only be acceptable but actually preferable in patients with adverse root features, although the impact on hemodynamic performance is not yet known.

For this trial, the proceduralists were instructed to use the nominal balloon filling volume according to the instructions for use and filling volume was altered in only a minority if cases. However, recent reports suggest that increasing the filling volume can increase the THV expansion (17), potentially useful to reduce or avoid undersizing in borderline anatomy, thereby further mitigating PAR but warranting further investigation.

PREDICTION OF PAR BY AREA AND PERIMETER OVERSIZING. Instructions for use of commercially available balloon-expandable THV platforms rely on annular area for THV sizing, whereas self-expandable platforms mainly use perimeter-based sizing. The different measures for annular sizing have significant implications on THV selection (9).

TABLE 6 Impact of Landing Zone Calcification on the Occurrence of PAR

Cohort	Dependent Variable	Independent Variable Landing Zone Calcification	Relative Risk	95% Confidence Interval	p Value	Events
Entire cohort	≥ mild	Mild/moderate/severe vs. none	1.23	1.01-1.49	**0.0365**	410
Oversizing by area 0% to 5%	≥ mild	Mild/moderate/severe vs. none	1.19	0.77-1.83	0.4334	82
Entire cohort	≥ mild to moderate	Mild/moderate/severe vs. none	1.07	0.72-1.59	0.7238	100
Oversizing by area 0% to 5%	≥ mild to moderate	Mild/moderate/severe vs. none	1.01	0.39-2.61	0.9893	17
Entire cohort	≥ mild	Moderate/severe vs. none/mild	1.36	1.09-1.69	**0.0056**	410
Oversizing by area 0% to 5%	≥ mild	Moderate/severe vs. none/mild	1.47	0.90-2.39	0.1244	82
Entire cohort	≥ mild to moderate	Moderate/severe vs. none/mild	1.5	0.97-2.31	0.0672	100
Oversizing by area 0% to 5%	≥ mild to moderate	Moderate/severe vs. none/mild	1.67	0.59-4.73	0.3372	17
Entire cohort	≥ mild	Severe vs. none/mild/moderate	1.33	0.91-1.92	0.1374	410
Oversizing by area 0% to 5%	≥ mild	Severe vs. none/mild/moderate	1.20	0.58-2.49	0.6271	90
Entire cohort	≥ mild to moderate	Severe vs. none/mild/moderate	1.46	0.71-3.00	0.3080	100
Oversizing by area 0% to 5%	≥ mild to moderate	Severe vs. none/mild/moderate	0.69	0.09-5.22	0.7217	17

P values in **bold** indicate the significant variables.
PAR = paravalvular aortic regurgitation.

For the common spectrum of annular anatomy, the numerical percentage value for oversizing by area is roughly 2 to 3 times that of perimeter for a given device size and annular dimensions. However, the exact relationship between the percentage values for area and perimeter oversizing varies according to patient-specific annular eccentricity (9). This geometrical reality limits the comparison of a priori defined, incremental cohorts of oversizing (e.g., 0% to 5% area oversizing), which were used for description of the relationship of oversizing and the extent of PAR. For that reason, we performed ROC analysis to assess the predictive capabilities of both approaches in regard to occurrence of PAR. Interestingly, ROC analysis demonstrated similar area under the curve values for oversizing by perimeter and by area in regard to the prediction of PAR, indicating similar ability to discriminate risk of moderate or greater PAR, with ideal cutoff points of 0.05% and -1.24% for area and perimeter oversizing, respectively. However, the use of perimeter for sizing is intriguing, as our data show that the frequency of moderate or greater PAR is higher in patients with area oversizing but perimeter undersizing compared to patients with both area and perimeter oversizing. Perimeter oversizing may thus serve as an additional criterion to guide THV selection in borderline anatomy as it eliminates the impact that annular eccentricity has on area sizing. We propose that when a proposed THV will result in only nominal area sizing that annular perimeter be considered to ensure there is no more than 1% to 2% perimeter undersizing to help reduce the incidence of moderate PAR.

IMPACT OF LANDING ZONE CALCIUM ON PAR. Presence of annular and subannular calcification was associated with mild or greater PAR. However, we did not find a clear association of the presence of annular and subannular calcifications and higher degrees of PAR alone. It has been previously demonstrated that annular calcification is a risk factor for PAR in addition to THV undersizing and malpositioning (15). The lack of a stronger signal for higher degrees of PAR alone despite the large study cohort is surprising, and may be accounted for by the mechanism of the sealing skirt but also by the small number of events in regard to the occurrence of greater than or equal to moderate PAR.

STUDY LIMITATIONS. Although this investigation is based on data of a prospective multicenter trial, using core lab-adjudicated echocardiographic data on PAR and core lab-derived anatomical data regarding anatomical baseline dimensions, it is not without limitations. The major limitation of this investigation is the lack of core lab-adjudicated data on the level of implantation of the SAPIEN 3 THV. The mechanism of the sealing skirt requires a rather high level of implantation to provide its full potential. Thus low implantation in the left ventricular outflow tract may influence the frequency and extent of PAR. However, as this limitation applies uniformly to the entire cohort studied, we do not expect that it biased the main findings of this study. In fact, PAR rates may continue to fall with greater operator experience and more precise positioning. As well, the reported nominal areas supplied by the early engineering tests are slightly different from the reported nominal areas for the 20-mm SAPIEN 3 valve used in clinical practice (18). Nonetheless the relationship between oversizing and PAR is consistent across all valve sizes with the 20-mm valve being used in a minority of subjects. We are also unable to comment on the potential relationship between oversizing and permanent pacemaker, as we lack post-implant imaging to assess the depth of implant, which is known to be the most significant procedural driver permanent pacemaker, and as a result we could not perform this analysis. We lack consistent information on balloon filling and therefore cannot comment on the potential impact of over or underfilling on PAR. Finally, it should be noted that bicuspid valve morphology was an exclusion criteria for the trial and as a result our sizing algorithm is meant for use in tricuspid valves only.

CONCLUSIONS

For the SAPIEN 3 THV, the frequency and extent of PAR is inversely related to the degree of oversizing with acceptable rates of PAR being achieved at lower degrees of oversizing. Perimeter and area oversizing confer similar predictive capacity in regard to the occurrence of PAR after implantation of the SAPIEN 3 THV. Therefore, the SAPIEN 3 THV may offer the opportunity to reduce the risk of annular rupture associated with more significant degrees of oversizing in borderline annular anatomy.

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PERSPECTIVES

WHAT IS KNOWN? CT plays an essential role in preprocedural planning for TAVR to help with device selection and sizing which is device specific.

WHAT IS NEW? Our study supports the role of CT sizing for the SAPIEN 3 device and highlights an inverse relationship between oversizing and paravalvular regurgitation. It is incremental to the current knowledge by helping define a SAPIEN 3-specific sizing approach supporting the use of lesser degrees of oversizing given the realized low rates of moderate PAR with only nominal oversizing.

WHAT IS NEXT? Further studies are needed to assess the impact of the proposed sizing thresholds on valve hemodynamics.

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KEY WORDS aortic stenosis, aortic regurgitation, computed tomography, oversizing, paravalvular regurgitation, transcatheter aortic valve replacement, transcatheter heart valve

APPENDIX For a supplemental table, please see the online version of this article.