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JACC: CARDIOVASCULAR INTERVENTIONS

VOL. 8, NO. 3, 2015

© 2015 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION

ISSN 1936-8798/$36.00

PUBLISHED BY ELSEVIER INC.

http://dx.doi.org/10.1016/j.jcin.2014.10.014

Incidence and Severity of Paravalvular Aortic Regurgitation With Multidetector Computed Tomography Nominal Area Oversizing or Undersizing After Transcatheter Heart Valve Replacement With the Sapien 3

A Comparison With the Sapien XT

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ABSTRACT

OBJECTIVES This study sought to compare the influence of the extent of multidetector computed tomography (MDCT) area oversizing on the incidence of paravalvular aortic regurgitation (PAR) between the Sapien 3 and the Sapien XT transcatheter heart valve (THV) to define a new MDCT sizing guideline suitable for the Sapien 3 platform.

BACKGROUND The inverse relationship of PAR occurrence and oversizing has been demonstrated for the Sapien XT but the incidence of PAR with comparable oversizing with the Sapien 3 is not known.

METHODS Sixty-one prospectively enrolled patients who underwent transcatheter aortic valve replacement with the Sapien 3 THV were compared with 92 patients who underwent transcatheter aortic valve replacement with the Sapien XT THV. Patients were categorized depending on the degree of MDCT area oversizing percentage: undersizing (below 0%), 0% to 5%, 5% to 10%, and above 10%. The primary endpoint was mild or greater PAR on transthoracic echocardiography.

RESULTS Mild or greater PAR was present in 19.7% of patients (12 of 61) in the Sapien 3 group and in 54.3% of patients (50 of 92) in the Sapien XT group ($p < 0.01$). The Sapien 3 group, compared with the Sapien XT group, consistently demonstrated significantly lower rates of mild or greater PAR except for oversizing >10% (p for interaction = 0.54). Moderate or severe PAR rates were also lower in the Sapien 3 group than in the Sapien XT group (3.3% vs. 13.0%, $p = 0.04$). In the Sapien 3 group, a MDCT area oversizing percentage value of ≤4.17% was identified as the optimal cutoff value to discriminate patients with or without mild or greater PAR.

CONCLUSIONS Our retrospective analysis suggests that the Sapien 3 THV displays significantly lower rates of PAR than does the Sapien XT THV. A lesser degree of MDCT area oversizing may be employed for this new balloon-expandable THV. (J Am Coll Cardiol Intv 2015;8:462–71) © 2015 by the American College of Cardiology Foundation.

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Transcatheter aortic valve replacement (TAVR) has become an effective treatment of severe aortic stenosis in patients considered to be of high perioperative mortality risk (1) and those deemed to be high risk for surgery (2,3). Despite continuous procedural refinements, paravalvular aortic regurgitation (PAR) and aortic root injury remain important limitations in the widening of its application to lower-risk patients (4,5). Appropriate sizing of the transcatheter heart valve (THV) is critically important to minimize the incidence of PAR. Moderate to severe PAR has been shown to be an independent predictor of mortality (3,5). Multidetector computed tomography (MDCT) has recently been shown to be predictive of PAR owing to its 3-dimensional capabilities and better appreciation of the noncircular annular geometry (6,7). Importantly, integration of a MDCT annulus area sizing algorithm reduced PAR in patients receiving Sapien XT THV in a prospective multicenter approach (8). However, it is well accepted that a single sizing algorithm for all valve platforms is not acceptable and that sizing needs to be refined depending on valve design.

The Sapien 3 THV has been recently introduced with an external sealing cuff and improved delivery catheter with the goal of reducing PAR by means of its enhanced paravalvular sealing and more accurate positioning. In the first case series, an MDCT sizing algorithm designed for a previous valve generation was used (9); however, it is unclear whether this is appropriate. We herein sought to compare the incidences of PAR with comparable MDCT area oversizing between the Sapien 3 and the Sapien XT THV and to serve as an exploratory analysis to help define a new MDCT sizing guideline for the Sapien 3 platform.

METHODS

STUDY POPULATION. Patients enrolled in the prospective safety and performance study of the Edwards Sapien 3 THV were considered for this analysis. The SAPIEN 3 THV study was a nonrandomized, prospective multicenter study that consisted of 150 patients with severe symptomatic calcific aortic valve stenosis (intermediate or high operative risk) at 15 participating centers across Canada, France, Germany, Italy, and the United Kingdom. Patients in whom the THV was implanted too high or low were excluded from the current study (6,7). Patients who did not undergo pre-TAVR MDCT or post-TAVR echocardiography, patients with nondiagnostic image quality on pre-TAVR MDCT, and patients without systolic image data on pre-TAVR MDCT were also excluded. At the time of this analysis, 135 of the anticipated 150 patients had been enrolled into the SAPIEN 3 THV study of whom 61 patients met the inclusion criteria for this analysis from January 1, 2013 to September 30, 2013 (**Figure 1**). For comparison, an historical cohort of 92 patients who underwent TAVR with the Sapien XT THV between January 1, 2011 and June 30, 2012 was investigated. These 92 patients were derived from our previous study to analyze MDCT annular dimension for the prediction of PAR (6). An experienced interventional cardiologist (J.W.) who was unaware of the grade of PAR, THV size, and MDCT annular dimension reviewed the THV position on pre- and post-implant aortic root angiography. Written consent was obtained from all patients.

THV SIZE SELECTION. At each participating center, the THV size selection was at the discretion of the operators who were aware of the MDCT size

ABBREVIATIONS AND ACRONYMS

AUC = area under the curve
CI = confidence interval
MDCT = multidetector computed tomography
OR = odds ratio
PAR = paravalvular aortic regurgitation
TAVR = transcatheter aortic valve replacement
THV = transcatheter heart valve(s)

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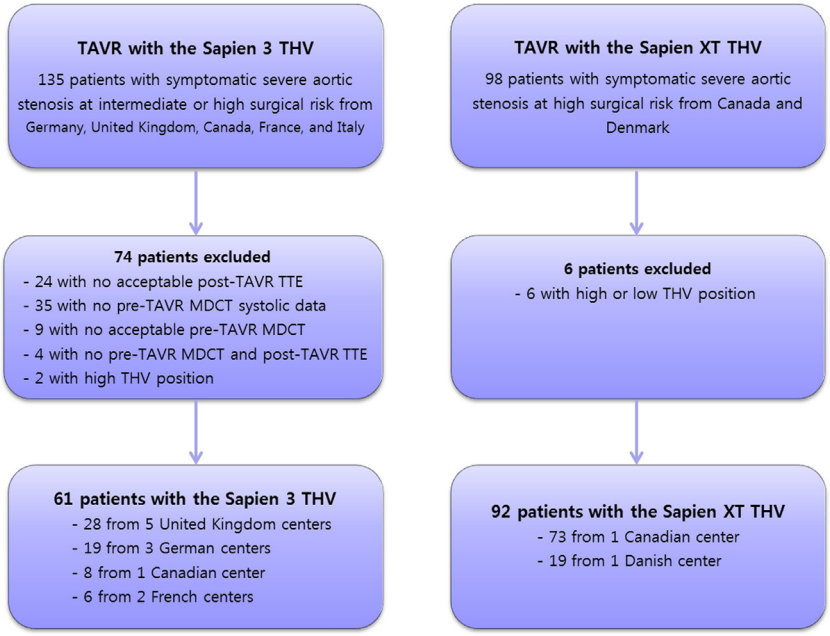
Manuscript received July 21, 2014; revised manuscript received September 10, 2014, accepted October 8, 2014.

FIGURE 1 Study Flowchart



The flowchart provides information about the included and excluded patients in the Sapien 3 and Sapien XT THV groups. MDCT = multidetector computed tomography; TAVR = transcatheter aortic valve replacement; THV = transcatheter heart valve; TTE = transthoracic echocardiography.

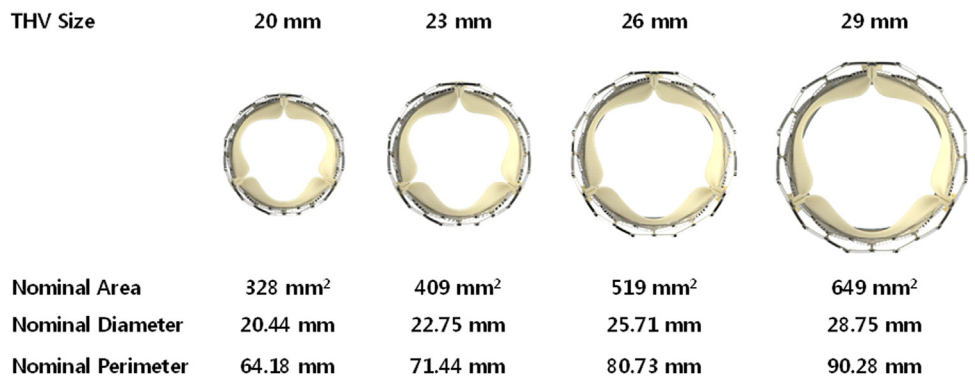
recommendation provided by the core laboratory (J.L.), transesophageal echocardiography annular measurements, and vendor specifications.

MDCT IMAGE ACQUISITION. MDCT protocols were applied according to each center's standard practice. Scans were performed with electrocardiography-synchronized data acquisition with a requirement for systolic phase imaging.

MDCT IMAGE ANALYSIS. All MDCT examinations were reviewed by 2 experienced cardiac CT readers (J.L. and T.H.Y.) at the MDCT core lab of the SAPIEN 3 THV study (St. Paul Hospital, Vancouver, British Columbia, Canada). A double-oblique transverse view at transecting through the basal hinge points of 3 aortic cusps was obtained, defining the aortic annulus plane (10). Planimetry of the annulus contours yielded area, long diameter, short diameter, and circumference. Annulus area was measured by manually tracking the luminal contours on double-oblique transverse plane. Annular measurements were performed in systole at 25% or 35% of the RR interval. When systolic imaging data was not available, systolic annulus dimensions were modeled based on the findings of a previous study (11). Aortic annular eccentricity was calculated as: 1 - short diameter/long diameter. The annulus was separately analyzed for calcification. 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 nodule of calcium extending <5 mm in any direction and covering <10% of the perimeter of the annulus; moderate, 2 nodules of calcification or 1 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 (12). All image data were analyzed offline on a 3-dimensional workstation (AW 4.4, GE Healthcare, Waukesha, Wisconsin, or Intuition, Terarecon, Foster City, California). By convention, all measurements were repeated 2 times by 2 cardiac CT readers with the final measurements representing the mean of both measurements.

ECHOCARDIOGRAPHIC ASSESSMENT. Pre-TAVR transesophageal echocardiography and post-TAVR transthoracic echocardiography were performed by highly experienced echocardiographers at each participating center. Post-TAVR echocardiography was performed at 30 days after TAVR in the Sapien 3 group and at

FIGURE 2 Sapien 3 THV



The nominal external valve area, diameter, and perimeter are shown for the Sapien 3 transcatheter heart valve (THV).

discharge in the Sapien XT group. Echocardiographies performed within a range of post-TAVR 21 to 100 days in the Sapien XT group were also analyzed. Post-TAVR studies were interpreted by core labs blinded to the pre-TAVR annulus dimensions and implanted THV size (for the Sapien 3 THV, C5 Cleveland Clinic, Cleveland, Ohio; for the Sapien XT group, St. Paul Hospital). PAR was graded in the same fashion as none, mild, moderate, and severe according to the Valve Academic Research Consortium 2 criteria (13).

DEGREE OF AREA OVERSIZING OR UNDERSIZING. The nominal external valve area of an expanded Sapien 3 THV is 328 mm^2 (20-mm device), 409 mm^2 (23-mm), 519 mm^2 (26-mm), 649 mm^2 (29-mm) according to the manufacturer (Figure 2) as compared to the Sapien XT THV with expanded areas of 314 mm^2, 415 mm^2, 531 mm^2, and 661 mm^2, respectively. A THV was considered oversized when the THV nominal area was greater than the systolic MDCT annular area was. The percentage of oversizing (positive percentage) or undersizing (negative percentage) was calculated using the following formula: % oversizing = (THV nominal area/MDCT annular area - 1) × 100.

STUDY ENDPOINTS. The primary endpoint was the presence of mild or greater PAR. The secondary endpoint was the presence of moderate or severe PAR.

STATISTICAL ANALYSIS. The Student *t* test and the Mann-Whitney *U* test were used for comparison of continuous variables with normal or skewed distribution, when appropriate. The Fisher exact test was used to test for significant differences between categorical variables. A priori, we categorized patients depending on the degree of MDCT area oversizing percentage in the following cohorts: undersizing (below 0%); 0% to 5%; 5% to 10%; and above 10%. The interactions among THV type implanted, MDCT area oversizing category, and rates of mild or greater PAR were analyzed using the multivariable model with addition of an interaction term of THV type × MDCT area oversizing variables. A receiver-operating characteristics curve analysis was performed to evaluate the discriminative abilities of MDCT annular measurements in predicting mild or greater PAR and to identify the cutoff level for MDCT area oversizing percentage in predicting mild or greater PAR. The relationship of PAR, annulus calcification, or area oversizing percentage was investigated by univariate or multivariate logistic regression analysis. A p value ≤0.05 was considered statistically significant. All statistical analyses were performed by using SPSS (version 18.0, SPSS Inc., Chicago, Illinois) software.

RESULTS

PATIENT POPULATION. Baseline clinical characteristics are shown in Table 1. Except for patient age, there was no significant difference in regard to clinical or demographic baseline characteristics.

ANNULAR ASSESSMENT AND PROCEDURE. Annular dimensions and procedural characteristics are presented in Table 2. Average oversizing was 6.5 ± 11.0% in the Sapien 3 group (range -15.2 to 32.7%) and 4.7 ± 17.2% in the Sapien XT group (range -21.7 to 59.6%) with no significant different between groups (p = 0.42). Undersizing was present in 18 patients (29.5%) in the Sapien 3 group and in 41 patients (44.6%) in the Sapien XT group (p = 0.07). MDCT area

TABLE 1 Baseline Clinical Characteristics

	Sapien 3 Group (n = 61)	Sapien XT Group (n = 92)	p Value
Age, yrs	84.6 ± 5.2	81.1 ± 8.5	<0.01
Male	25 (41.0)	48 (52.2)	0.19
Height, cm	164.4 ± 10.1	164.9 ± 25.0	0.89
Weight, kg	74.9 ± 17.7	77.4 ± 21.9	0.50
Body mass index, kg/m^2	27.7 ± 6.3	26.9 ± 6.1	0.46
Diabetes	19 (31.1)	25 (27.2)	0.72
Hypertension	53 (86.9)	71 (77.2)	0.15
COPD	16 (26.2)	20 (21.7)	0.56
Atrial fibrillation	27 (44.3)	34 (37.0)	0.40
Peripheral vascular disease	11 (18.0)	17 (18.5)	1.00
Smoking history	24 (39.3)	31 (33.7)	0.50
Previous cerebrovascular accident	12 (19.7)	12 (13.0)	0.36
Previous myocardial infarction	7 (11.5)	15 (16.3)	0.49
Previous open heart surgery	12 (19.7)	26 (28.3)	0.26
Previous permanent pacemaker	10 (16.4)	8 (8.7)	0.20
GFR, ml/min	58.1 ± 26.7	57.4 ± 20.6	0.87
STS PROM, %	7.2 ± 4.1	6.2 ± 2.9	0.10

Values are mean ± SD or n (%).

COPD = chronic obstructive pulmonary disease; GFR = glomerular filtration rate; STS PROM = Society of Thoracic Surgeons predicted risk of mortality.

TABLE 2 Annular Assessment and Procedural Characteristics

	Sapien 3 Group (n = 61)	Sapien XT Group (n = 92)	p Value
Pre-TAVR aortic regurgitation			<0.01
None/trivial	35 (57.4)	79 (85.2)	
Mild	25 (41.0)	12 (13.0)	
Moderate	1 (1.6)	1 (1.1)	
Severe	0 (0.0)	0 (0.0)	
Left ventricular ejection fraction, %	52.3 ± 10.2	55.0 ± 12.9	0.33
Mean gradient, mm Hg	44.7 ± 14.3	43.9 ± 17.3	0.77
Aortic valve area, cm^2	0.64 ± 0.19	0.69 ± 0.17	0.18
MDCT short-axis diameter, mm	22.5 ± 2.4	21.0 ± 2.4	<0.01
MDCT long-axis diameter, mm	26.6 ± 2.2	26.8 ± 2.9	0.71
MDCT mean-diameter, mm	24.5 ± 2.1	23.9 ± 2.4	0.10
MDCT annular area, cm^2	485.8 ± 77.5	467.9 ± 90.6	0.21
MDCT annular circumference, mm	80.7 ± 6.3	78.5 ± 8.9	0.08
MDCT annular eccentricity	0.15 ± 0.07	0.21 ± 0.08	<0.01
Labeled prosthesis size			<0.01
20-mm	0 (0.0)	2 (2.2)	
23-mm	16 (26.2)	41 (44.6)	
26-mm	33 (54.1)	45 (48.9)	
29-mm	12 (19.7)	4 (4.3)	
MDCT nominal area oversizing, %	6.5 ± 11.0	4.7 ± 17.2	0.42
Post-dilation	2 (3.3)	9 (9.8)	0.20
Access type			0.10
Transfemoral	43 (70.5)	65 (70.7)	
Transapical	15 (24.6)	27 (29.3)	
Transthoracic	3 (4.9)	0 (0.0)	

Values are n (%) or mean ± SD.

MDCT = multidetector computed tomography; TAVR = transcatheter aortic valve replacement.

oversizing percentage of 0% to 5%, 5% to 10%, and above 10% was present in 10 patients (16.4%), 15 (24.6%), and 18 (29.5%) in the Sapien 3 cohort and in 10 (10.9%), 11 (12.0%), and 30 (32.6%) in the Sapien XT cohort.

PAR. Post-TAVR transthoracic echocardiography data is summarized in Table 3. Overall, mild, or greater PAR was present in 19.7% of patients (12 of 61) in the Sapien 3 group and in 54.3% of patients (50 of 92) in the Sapien XT group ($p < 0.01$). Figure 3 illustrates the rates of mild or greater PAR stratified by the extent of MDCT area oversizing percentage. The Sapien 3 group demonstrated significantly lower rates of mild or greater PAR compared with the Sapien XT group except for the subgroup with area oversizing above 10% (p for interaction = 0.54). In the Sapien 3 group, patients with 0% to 5% oversizing exhibited numerically higher rates of mild or greater PAR without statistical significance compared with patients with 5% to 10% oversizing (30.3% vs. 13.3%, $p = 0.36$). Similarly, patients with undersizing exhibited slightly higher rates of mild or greater PAR compared with patients with oversizing (27.8% vs. 16.3%, $p = 0.31$). We found a declining trend in the rates of mild or greater PAR in patients in the Sapien 3 group with increasing area oversizing, whereas the Sapien XT group provided little change (Figure 4). With regard to moderate or severe PAR, Sapien 3 patients demonstrated lower PAR rates than did Sapien XT patients throughout all subgroups: undersizing (0.0% vs. 19.5%, $p = 0.04$); area oversizing between 0% and 5% (10.0% vs. 20.0%, $p = 0.53$); and area oversizing between 5% and 10% (6.7% vs. 18.2%, $p = 0.36$). No patients with either Sapien 3 or Sapien XT exhibited moderate or severe PAR when MDCT area oversizing percentage exceeded 10%. A total of 96 Sapien 3 subjects, encompassing 61 patients with direct systolic measurements as well as 35 patients with modeled data, also manifested similar findings in the rates of mild or greater and moderate or greater PAR when compared with all Sapien XT subjects (20.8% vs. 54.3%, $p < 0.01$ and 3.1% vs. 13.0%, $p = 0.02$) (Figure 5). Likewise, the incidences of mild or greater and moderate or greater PAR were lower in the Sapien 3 patients ($n = 61$), which was consistent when compared with the Sapien XT patients with follow-up echocardiography conducted from 21 days to 100 days ($n = 61$) (19.7% vs. 47.7%, $p < 0.01$ and 3.3% vs. 12.3%, $p = 0.06$). Representative case examples are presented in Figure 6.

AREA UNDER THE CURVE. Sapien 3 THV nominal area and MDCT annular area provided weak prediction of mild or greater PAR (area under the curve

[AUC]: 0.67, 95% confidence interval [CI]: 0.54 to 0.78, p = 0.04). The difference between the Sapien 3 THV nominal diameter and MDCT annular mean diameter (AUC: 0.54, 95% CI: 0.40 to 0.67, p = 0.68), the Sapien 3 THV nominal circumference and MDCT annular circumference (AUC: 0.58, 98% CI: 0.44 to 0.71, p = 0.44) did not show significant predictive value. In contrast, the relationship between the Sapien XT THV size and MDCT annular size ([area: AUC: 0.73, 95% CI: 0.63 to 0.82, p < 0.01], [mean diameter: AUC: 0.74, 95% CI: 0.64 to 0.83, p < 0.01], circumference: AUC: 0.73, 95% CI: 0.63 to 0.81, p < 0.01]) had moderate predictive value.

THE RELATIONSHIP BETWEEN PAR AND ANNULUS CALCIFICATION. Mild or greater PAR occurred more frequently in patients with moderate or severe annulus calcification than in patients without moderate or severe annulus calcification in the Sapien 3 group (odds ratio [OR]: 7.80, 95% CI: 1.95 to 31.22, p < 0.01), whereas this difference could not be found in the Sapien XT group (Table 4). Similarly, moderate or severe PAR was more common in patients having moderate or severe annulus calcification (11.1% vs. 0.0%, p = 0.08) in the Sapien 3 group. In the multivariate logistic regression analysis, moderate or severe annulus calcification (OR: 10.0, 95% CI: 1.22 to 81.48, p = 0.03) was found to be significant and independent predictors of mild or greater PAR after adjusting for age, sex, annulus eccentricity, and MDCT area oversizing percentage in the Sapien 3 patients.

THE IMPACT OF MINIMAL AREA OVERSIZING ON PAR. In the Sapien 3 group, an MDCT area oversizing percentage value of ≤4.17% was identified as the optimal cutoff value to discriminate patients with or without mild or greater PAR that provided a sensitivity of 66.7%, a specificity of 65.3%, a positive predictive value of 32.0%, and a negative predictive value of 88.9%. We then dichotomized the area oversizing value at a practical value of 5.0%. For patients with area oversizing below 5.0%, the rate of mild or greater PAR was 25.0% (7 of 28) versus 9.1% (3 of 33) (OR: 2.90, 95% CI: 0.77 to 10.95, p = 0.11) when the area oversizing was above 5.0%. In the Sapien XT group, an optimal MDCT area oversizing cutoff value to predict mild or greater PAR was 7.27% (sensitivity: 84.0%, specificity: 61.9%, positive predictive value: 72.4%, negative predictive value: 76.5%). In the Sapien 3 subgroup (n = 33) whose area oversizing was above 5%, if 2 patients with moderate or severe annulus calcification and mild or greater PAR were excluded from total 4 patients who had mild or greater PAR, only 2 patients (of 31 patients, 6.5%) would have had mild or greater PAR.

TABLE 3 Post-TAVR Outcomes

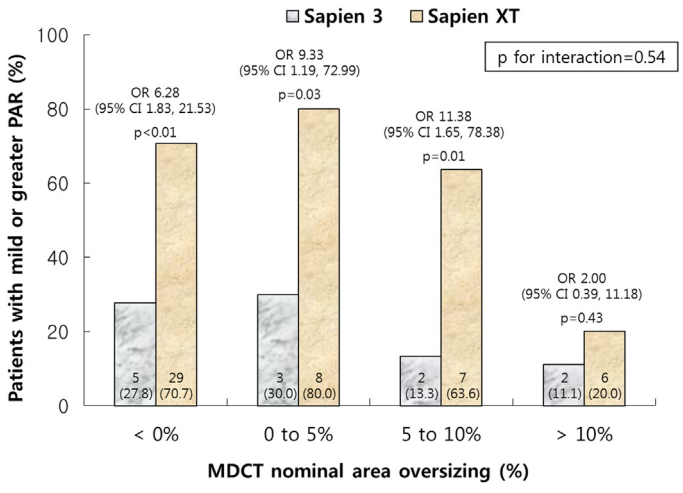
	Sapien 3 Group (n = 61)	Sapien XT Group (n = 92)	p Value
Post-TAVR PAR			
None/trivial	49 (80.3)	42 (45.7)	<0.01
Mild	10 (16.4)	38 (41.3)	<0.01
Moderate	2 (3.3)	12 (13.0)	0.04
Severe	0 (0.0)	0 (0.0)	1.00
Mild or greater	12 (19.7)	50 (54.3)	<0.01
Mean gradient, mm Hg	10.9 ± 5.5	11.0 ± 4.4	0.88
Aortic valve area, cm^2	1.6 ± 0.5	1.5 ±0.3	0.31
Procedural mortality	0 (0.0)	0 (0.0)	1.00
30-day mortality	0 (0.0)	2 (2.2)	0.24
Annular rupture	0 (0.0)	0 (0.0)	1.00
Device embolization	0 (0.0)	0 (0.0)	1.00
Procedural myocardial infarction	0 (0.0)	1 (1.1)	0.49

Values are n (%) or mean ± SD.
PAR = paravalvular aortic regurgitation; TAVR = transcatheter aortic valve replacement.

DISCUSSION

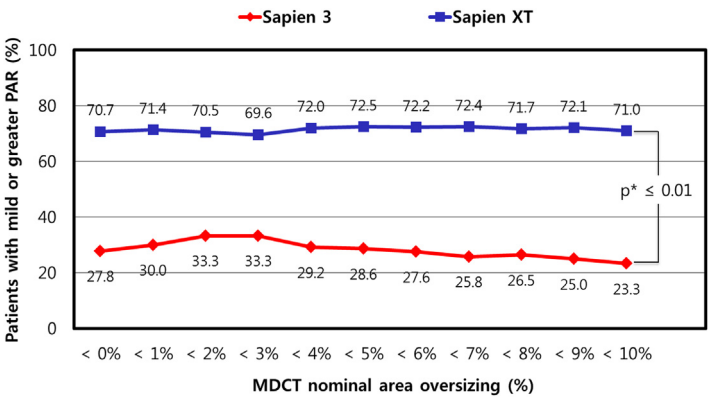
In our comparison of the incidence and severity of PAR with MDCT nominal area oversizing or undersizing after TAVR with the Sapien 3 or Sapien XT THV, the Sapien 3 THV appears to tolerate a lesser degree of area oversizing. Our current results demonstrate the following. 1) The Sapien 3 THV, compared with the

FIGURE 3 Rates of Mild or Greater PAR According to MDCT Nominal Area Oversizing Group in All Study Populations



The numbers in the columns denote the absolute numbers and rates of mild or greater paravalvular aortic regurgitation (PAR). CI = confidence interval; MDCT = multidetector computed tomography; OR = odds ratio.

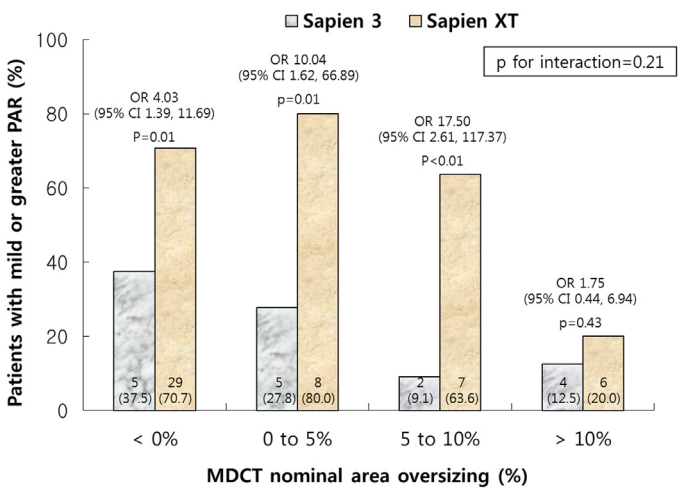
FIGURE 4 Rates of Mild or Greater PAR Stratified by Extent of MDCT Nominal Area Oversizing in All Study Populations



Each subgroup on the x-axis indicates all patients with area oversizing below each criterion and inclusive of undersizing. *All p values between the Sapien 3 group and Sapien XT group were <0.02 at all area oversizing criteria. Abbreviations as in Figures 1 and 3.

Sapien XT, appears to exhibit significantly lower rates of mild or greater PAR when all minimal area oversizing criteria are applied. 2) MDCT annular size measurements provide weaker prediction of mild or greater PAR after the Sapien 3 THV implantation than the Sapien XT THV implantation. 3) Annulus calcium plays a role in the occurrence of mild or greater PAR after the Sapien 3 THV implantation. 4) A lesser degree of MDCT area oversizing might be employed for this new balloon-expandable THV than the currently recommended value for the Sapien XT THV.

FIGURE 5 Rates of Mild or Greater PAR According to MDCT Nominal Area Oversizing Group in Patients With Systolic MDCT Measurements



The numbers in the columns denote the absolute numbers and rates of mild or greater PAR. Abbreviations as in Figures 1 and 3.

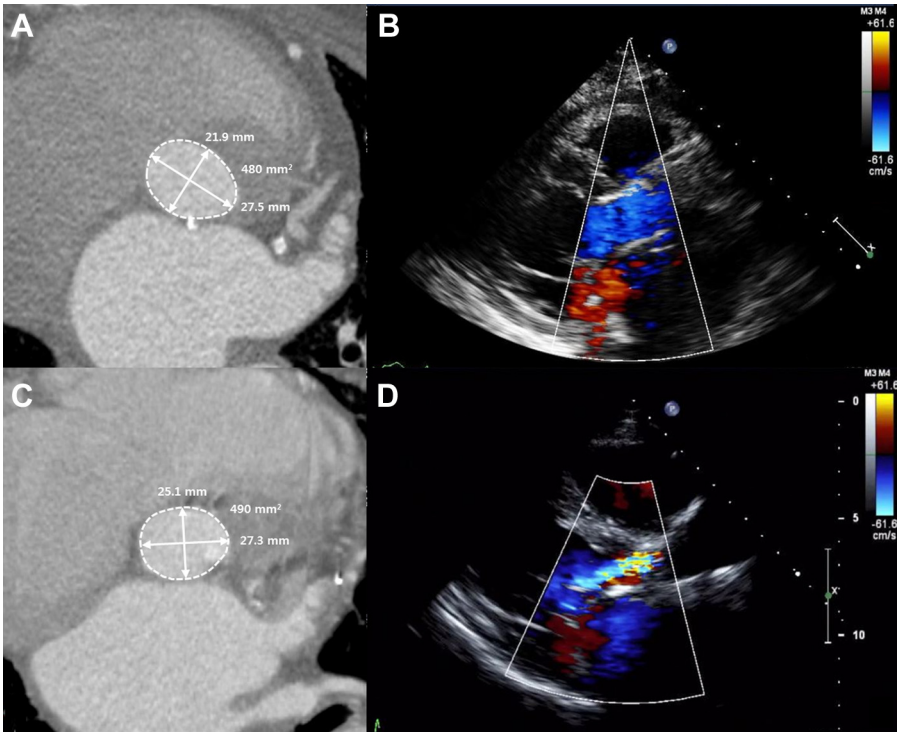
PAR continues to be an important complication after TAVR because the prognostic implications are not negligible (3,5). Even mild PAR has been associated with a worse prognosis (3). A meta-analysis of 45 studies also demonstrated that patients with mild PAR had a 1.8× higher risk of 1-year mortality than did those without this complication (14).

DECREASED PAR WITH THE SAPIEN 3 THV. Two main causes of PAR with balloon-expandable prostheses are felt to be implantation of a THV that is relatively smaller than aortic annulus (undersizing) or positioning the device too high or too low (14,15). In the present study, the rate of mild or greater PAR was significantly lower in the Sapien 3 group than in the Sapien XT group except for patients with area oversizing above 10% where both groups had a low incidence of PAR. Possible reasons for this lower PAR rate are the outer polyethylene terephthalate sealing cuff, which enhances paravalvular sealing and more accurate positioning. The enhanced paravalvular sealing with the Sapien 3 THV was especially useful in patients with area oversizing below 10%.

PREDICTION OF PAR. In the Sapien 3 group, AUC of MDCT annular measurements were not as high as those in the Sapien XT group. Two possible explanations for the discriminatory value of these MDCT measurements are as follow: 1) the differences between oversizing percentage in patients without PAR and undersizing percentage in patients with PAR in the Sapien 3 group have become smaller than those in the Sapien XT group, possibly due to increased awareness of appropriate annular oversizing and the integration of a MDCT-based THV sizing algorithm; and 2) the occurrence of mild or greater PAR in the Sapien 3 group can be affected by factors other than THV undersizing or inappropriate THV positioning (i.e., annulus calcification).

ANNULUS CALCIFICATION AS A POTENTIAL CAUSE OF PAR. Moderate or severe annulus calcification was associated with mild or greater PAR in the Sapien 3 group. This finding is in line with previous studies demonstrating that annulus calcification is a risk factor for PAR in addition to THV undersizing and malpositioning (16). Therefore, it is important to understand that appropriate annular oversizing, although crucial, is not the only factor that affects the development of PAR after TAVR even with the Sapien 3 THV. The presence of anatomical modifiers such as annulus calcification should be considered particularly when the degree of annulus area oversizing is

FIGURE 6 Pre- and Post-TAVR Imaging in A Patient in the Sapien 3 Group With No Significant PAR and in A Patient in the Sapien XT Group With Moderate PAR



(A) Double oblique transverse reformat of the annulus on MDCT with an area of 480 mm^2 in an 82-year-old female patient in the Sapien 3 group who had 8.1% area oversizing with the use of the 26-mm Sapien 3 THV. **(B)** The parasternal long-axis 2-dimensional echocardiography showing no significant PAR. **(C)** Double oblique transverse reformat of the annulus on MDCT with an area of 490 mm^2 in a 69-year-old male patient in the Sapien XT group who had 8.4% area oversizing with the use of 26-mm Sapien XT. **(D)** The parasternal long-axis 2-dimensional echocardiography showing moderate degree of PAR. Abbreviations as in Figures 1 and 3.

modest (below 10%). Interestingly, the impact of annular calcification appears to be greater for the Sapien 3 than for the Sapien XT. This most likely reflects that the Sapien XT is more profoundly affected by modest oversizing, thereby muting the potential impact of annular calcification.

THE OPTIMAL DEGREE OF AREA OVERSIZING IN THE SAPIEN 3 THV. It has been established that significant oversizing of a THV can minimize the risk of significant PAR; however, excessive oversizing comes at the expense of increasing the potential risk of aortic root rupture (12), coronary obstruction (17), periaortic hematoma, atrioventricular block, or ventricular septal rupture, whereas significant THV undersizing will increase the risk of significant PAR (6) and, less frequently, prosthesis embolization (18). Furthermore, treating significant PAR due to THV undersizing is challenging (19), so optimal sizing and appropriate selection of THV are crucial to reduce significant PAR and mechanical aortic root injuries. In our previous study, patients who underwent TAVR with the integration of MDCT-based area sizing algorithm had a significant reduction in greater than mild PAR (5.3%) as compared with those who underwent exclusively 2-dimensional echocardiography-based sizing (12.8%) (8). However, this positive finding was based on the annulus area sizing algorithm of the Sapien XT THV. Therefore, a new area sizing algorithm that is suitable for the Sapien 3 THV would be desirable.

In the current study, the optimal cutoff value of MDCT area oversizing for the prediction of mild or greater PAR was lower in the Sapien 3 group than in the Sapien XT group and the currently recommended area oversizing thresholds of 5% to 15%. In addition, patients with 0% to 5% oversizing had only numerically higher rates of mild or greater PAR without statistical significance when compared with patients with 5% to 10% oversizing. These findings

TABLE 4 Relationship Between Moderate or Severe Annulus Calcification and Mild or Greater PAR

	Present*	Absent*	p Value
Sapien 3			
All patients	8/18 (44.4)	4/43 (9.3)	<0.01
Oversizing <0%	3/8 (37.5)	2/10 (20.0)	0.61
Oversizing between 0% and 10%	5/8 (62.5)	0/17 (0.0)	<0.01
Oversizing >10%	0/2 (0.0)	2/16 (12.5)	1.00
Sapien XT			
All patients	5/7 (71.4)	45/85 (52.9)	0.45
Oversizing <0%	4/5 (80.0)	25/36 (69.4)	1.00
Oversizing between 0% and 10%	0/0	15/21 (71.4)	NA
Oversizing >10%	1/2 (50.0)	5/28 (17.9)	0.37

Values are n/N (%). *Moderate or severe annulus calcium present or absent.
PAR = paravalvular aortic regurgitation.

suggest that the optimal goal of annulus area oversizing with the Sapien 3 THV may be decreased down to between 1% and 5%. This minimal area oversizing may confer a great advantage of a lower risk of annulus injury without an increased risk of PAR. In addition, the more modest burden of PAR in the setting of mild undersizing of the annulus noted with the Sapien 3 THV may prove to be extremely helpful for borderline annular geometry where the operator has been historically faced with the difficult decision of undersizing or extreme annular oversizing with a larger THV leaving the patient at an elevated risk of moderate PAR or annular injury. We have previously described a strategy of balloon underfilling with the Sapien XT to help optimize the degree of annular oversizing and mitigate the risk of annular rupture (20). The role of underfilling with the Sapien 3 is not known, although there are concerns about employing this strategy owing to different design features that may result in earlier valve degeneration.

STUDY LIMITATIONS. The timing of post-TAVR echocardiography was somewhat different between the 2 groups. Although the prevalence and degree of PAR can diminish as time passes, it may be reasonable to assume that the time gap (20 days) was not great enough to result in substantive reduction or increase in PAR. In addition, we found similar findings in the rates of mild or greater and moderate or greater PAR between the Sapien 3 patients and the Sapien XT patients with echocardiographic assessment at a comparable time frame (post-TAVR 21 to 100 days).

Whereas all MDCT scans were read in a single core lab, post-TAVR echocardiography was read at 2 different core labs. Grading of PAR may be heterogeneous across sites. However, all sites' reads were performed by Level 3 echocardiographers with significant experience in TAVR and graded according to a standard definition.

The number of patients in both groups was small and thus the results, particularly the comparison between the 2 THV should be taken cautiously and as grounding for future investigation.

In addition, the baseline annulus dimensions were different and therefore larger THV were implanted in the Sapien 3 group. But the degree of MDCT nominal area oversizing was not different, so we do not think that such a baseline difference could have an effect on final results.

Finally, the Sapien XT group consisted of patients who underwent TAVR a year earlier than the Sapien 3 group. A learning effect, which may have led to improved outcomes in the Sapien 3 cohort, could be postulated. However, highly experienced operators in high-volume centers performed >200 TAVR procedures prior to implanting the Sapien XT.

CONCLUSIONS

In our exploratory comparative analysis, the Sapien 3 THV appears to display significantly lower rates of PAR than the Sapien XT THV does. A lesser degree of MDCT area oversizing appears appropriate for this new balloon-expandable THV, thereby potentially reducing the potential risk of annular rupture; however, further studies evaluating this new MDCT sizing guideline for the Sapien 3 THV are needed.

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KEY WORDS **annulus area, multidetector computed tomography, paravalvular aortic regurgitation, transcatheter aortic valve replacement**