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Cross-Sectional Computed Tomographic Assessment Improves Accuracy of Aortic Annular Sizing for Transcatheter Aortic Valve Replacement and Reduces the Incidence of Paravalvular Aortic Regurgitation

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Objectives In an effort to define the gold standard for annular sizing for transcatheter aortic valve replacement (TAVR), we sought to critically analyze and compare the predictive value of multiple measures of the aortic annulus for post-TAVR paravalvular (PV) regurgitation and then assess the impact of a novel cross-sectional computed tomographic (CT) approach to annular sizing.

Background Recent studies have shown clear discrepancies between conventional 2-dimensional (2D) echocardiographic and CT measurements. In terms of aortic annular measurement for TAVR, such findings have lacked the outcome analysis required to inform clinical practice.

Methods The discriminatory value of multiple CT annular measures for post-TAVR PV aortic regurgitation was compared with 2D echocardiographic measures. TAVR outcomes with device selection according to aortic annular sizing using a traditional 2D transesophageal echocardiography–guided or a novel CT-guided approach were also studied.

Results In receiver-operating characteristic models, cross-sectional CT parameters had the highest discriminatory value for post-TAVR PV regurgitation: This was with the area under the curve for [maximal cross-sectional diameter minus prosthesis size] of 0.82 (95% confidence interval: 0.69 to 0.94; $p < 0.001$) and that for [circumference-derived cross-sectional diameter minus prosthesis size] of 0.81 (95% confidence interval: 0.7 to 0.94; $p < 0.001$). In contrast, traditional echocardiographic measures were nondiscriminatory in relation to post-TAVR PV aortic regurgitation. The prospective application of a CT-guided annular sizing approach resulted in less PV aortic regurgitation of grade worse than mild after TAVR (7.5% vs. 21.9%; $p = 0.045$).

Conclusions Our data lend strong support to 3-dimensional cross-sectional measures, using CT as the new gold standard for aortic annular evaluation for TAVR with the Edwards SAPIEN device. (J Am Coll Cardiol 2012;59:1275–86)

Transcatheter aortic valve replacement (TAVR) with the Edwards SAPIEN device (Edwards Lifesciences, Irvine, California) has been shown to improve survival in nonoperative candidates (1) and to have equivalent survival outcomes to surgery in high-risk patients (2). Recent evidence suggests that the presence of significant paravalvular (PV) aortic regurgitation (AR) is an independent risk factor for mortality at short- and mid-term follow-up (3,4). Moderate or severe PV AR is not uncommon and was seen in 12.2% of TAVR patients in the PARTNER (Placement of Aortic Transcatheter Valves)

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Abbreviations and Acronyms

AR = aortic regurgitation

CI = confidence interval

CMPR = curved multiplanar reconstruction

CT = computed tomography

ECG = electrocardiogram

LVEF = left ventricular ejection fraction

LVOT = left ventricular outflow tract

NYHA = New York Heart Association

PV = paravalvular

ROC = receiver-operating characteristic

TAVR = transcatheter aortic valve replacement

TEE = transesophageal echocardiography

TTE = transthoracic echocardiography

trial, a significantly higher figure than for the surgical group (0.9%) (2). Inappropriate sizing is likely to be a major mechanism of PV AR.

There is a growing appreciation that 2-dimensional (2D) echocardiography fails to appreciate the noncircular geometry of the aortic annulus (Fig. 1) and that computed tomography (CT), as a 3-dimensional assessment, appears superior in this respect (5). There are discrepancies between conventional 2D echocardiographic and CT measurements (6,7). In an effort to determine whether CT should be the gold standard for aortic annular assessment, the objectives of the current study were 2-fold: 1) to retrospectively analyze CT dimensions in patients who had undergone transesophageal echocardiography (TEE)–guided TAVR and to compare the predictive value of multiple measures of the aortic annulus for post-TAVR PV regurgitation; and 2) to assess the impact on post-TAVR PV AR of a prospective application of CT annular measurements to choice of bioprosthesis size.

Methods

Patient population and study design. All patients were enrolled by a single center to the U.S. PARTNER trial. Patients with electrocardiogram (ECG)-gated contrast CT data, studied retrospectively, had a traditional TEE approach to aortic annular sizing. There was a later expansion of the study, after application of a CT annular sizing model derived from the retrospective analysis. A multivariable analysis for the predictors of PV regurgitation in those with available contrast CT studies was applied to the entire study population. These constituted consecutive patients with available systolic-phase contrast CT studies.

Patient assessment and procedure. Although a baseline thoracic CT study was performed at the outset, this was primarily to evaluate root geometry, aortic disease, and calcification and was not used for annular sizing before this analysis. The CT specialist only performed the protocol ECG-gated cardiac contrast study if the renal function was considered satisfactory, as is routine clinical practice; only these patients were included in this study. The procedure was performed under general anesthesia with combined TEE and fluoroscopic guidance (1).

Multi-slice CT image acquisition and preliminary image analysis. An ECG-gated, multi-slice CT angiography study was performed pre-procedure with a Siemens Somatom Cardiac 64 scanner (Siemens Medical Solutions USA, Inc., Malvern, Pennsylvania), using collimation of 0.6 mm at a fixed pitch of 0.2 with an injection of 110 ml of Isovue 370 (Bracco Diagnostics Inc., Princeton, New Jersey). A dedicated protocol was formulated, with 120 kV and tube current modified according to patient size. A standard convolution kernel of B35f was applied with a gantry rotation time of 330 ms. The ECG at the time of acquisition was reviewed before reconstruction to select out ectopy.

Three-dimensional images were reconstructed using INSIGHT software (Neoimagery Co., City of Industry, California). For reconstruction of mid-systolic data, the cine/movie feature of this software was used to determine the point in the cardiac cycle where the aortic valve was maximally open. This technique involved starting from 0% and going through to 100%, initially moving at 5%, then, within the 5% selected, at 1% increments across the cardiac cycle. Diastolic images were also reconstructed in mid-diastole. The cine/movie mode is standard and potentially available from several commercially available CT systems.

Conventional coronal and oblique sagittal (double oblique) measurements were made in mid-systole. Data were also used for curved multiplanar reconstructions (CMPRs) by tracing a line through the center point of the proximal ascending aorta, aortic valve, annulus, and left ventricular outflow tract (LVOT). The basal plane was defined as a plane perpendicular to the CMPR line at the ventricular aspect to where all 3 leaflets could be seen to disappear. This approximated to the nadir of the 3 leaflets and generated an image defined as the annular (or "basal") plane (also termed "ring") (Fig. 1, denoted by ellipsoid joining 3 stars).

Multi-slice CT image analysis. Calibrated images from basal ring CMPRs generated using INSIGHT were exported to Osirix (Geneva, Switzerland). A polygonal line circumscribing this basal ring was traced to determine its area and perimeter. Nonorthogonal true maximal (D_{max}) and true minimal (D_{min}) dimensions through the center point were determined electronically using this software. The D_{mean} was determined as the average of these 2 values. Given the placement of a bioprosthesis with an expected circular cross-section, D_{circ} was calculated as: [(perimeter of the traced polygon)/π] and D_{area} as: [$2 \times \sqrt{(\text{area of traced polygon in mm}^2/\pi)}$], as has been previously proposed (8) (Figs. 1 and 2).

Data from 20 randomly selected patients from the retrospective (n = 81) cohort were compared with CMPR analyses using software specifically customized to valve analysis (3mensio Valves, version 4.1, 3mensio Medical Imaging BV, Bilthoven, the Netherlands). This cohort was analyzed in both mid-systolic and diastolic phases.

Calcium severity index and calcium asymmetry index. INSIGHT was used for analysis of leaflet and LVOT calcium. Using maximal intensity projection, a slab perpendicular to the plane of the LVOT was generated with thickness from nadir to tips of the leaflets in mid-systole. Each leaflet was scored individually from 0 to 3, with 0 representing no calcium, 1 mildly calcified, 2 moderately

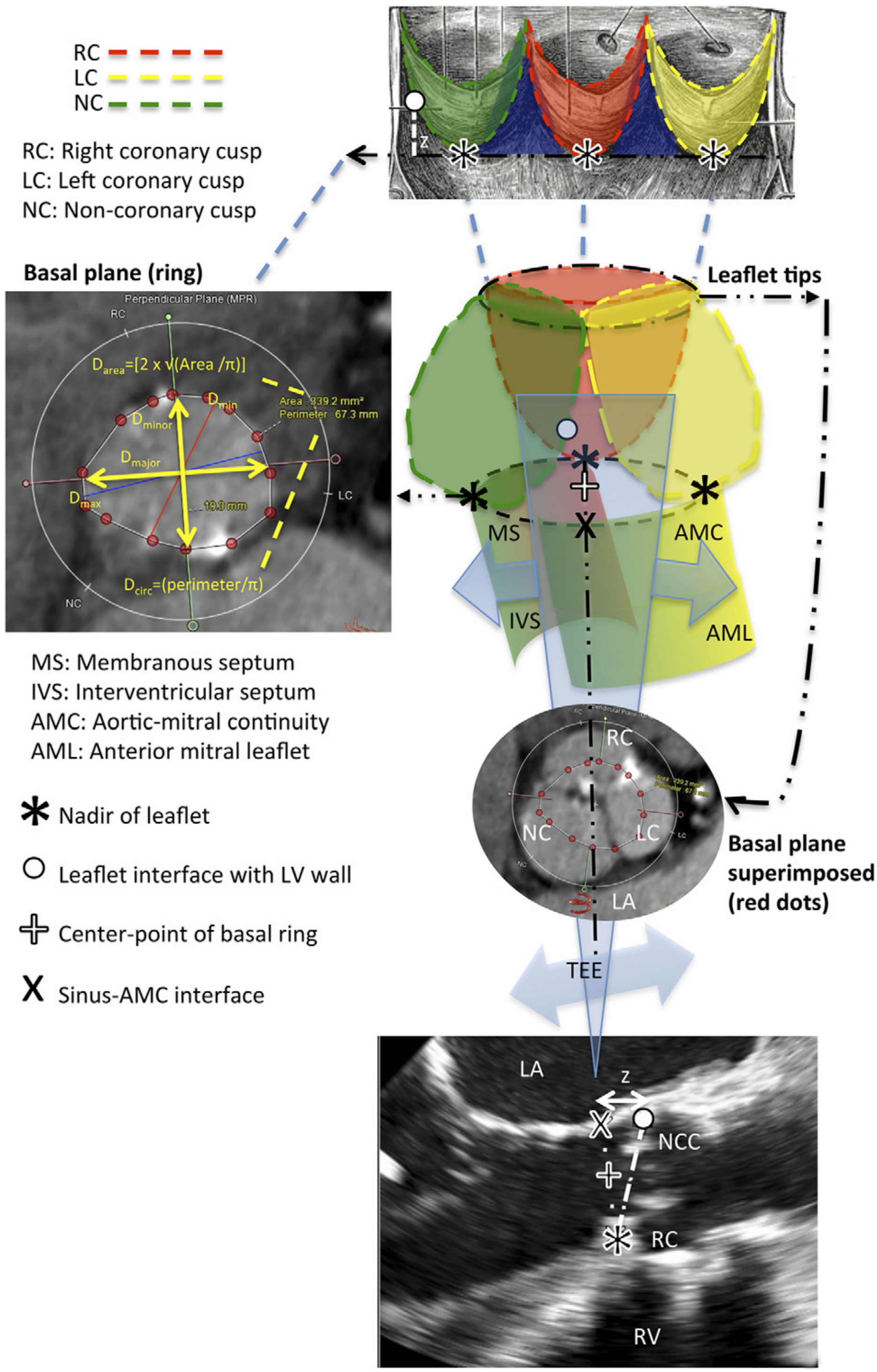

Figure 1 **Anatomic, Computed Tomography, and Echocardiographic Correlations of the Aortic Root**

In the trifoliate aortic valve, the aortic root and its 3 leaflets form a complex 3-dimensional structure (**top panel**, adapted from H. Gray. Anatomy of the Human Body. Philadelphia, PA: Lea & Febiger, 1918), which is incompletely appreciated by conventional 2-dimensional echocardiographic imaging (**bottom panel**, intra-procedural transesophageal echocardiography [TEE]). Leaflet hinge points seen on 2-dimensional images **(bottom panel)** represent the interface of the leaflet and the left ventricular wall at either the nadir of the leaflet **(asterisks)** or at a point **(white circle)** that is a highly variable distance (z) above the basal plane **(top, middle, and bottom panels)**. The TEE beam **(blue triangle)** represents a linear beam that images the aortic annulus posteriorly from the perspective of the left atrium. Often this cuts the basal plane obliquely, but even when through the center of the basal ring, it is impossible to determine the relationship of this cut to the true major and minor axis of the aortic basal ring **(center panel)**.

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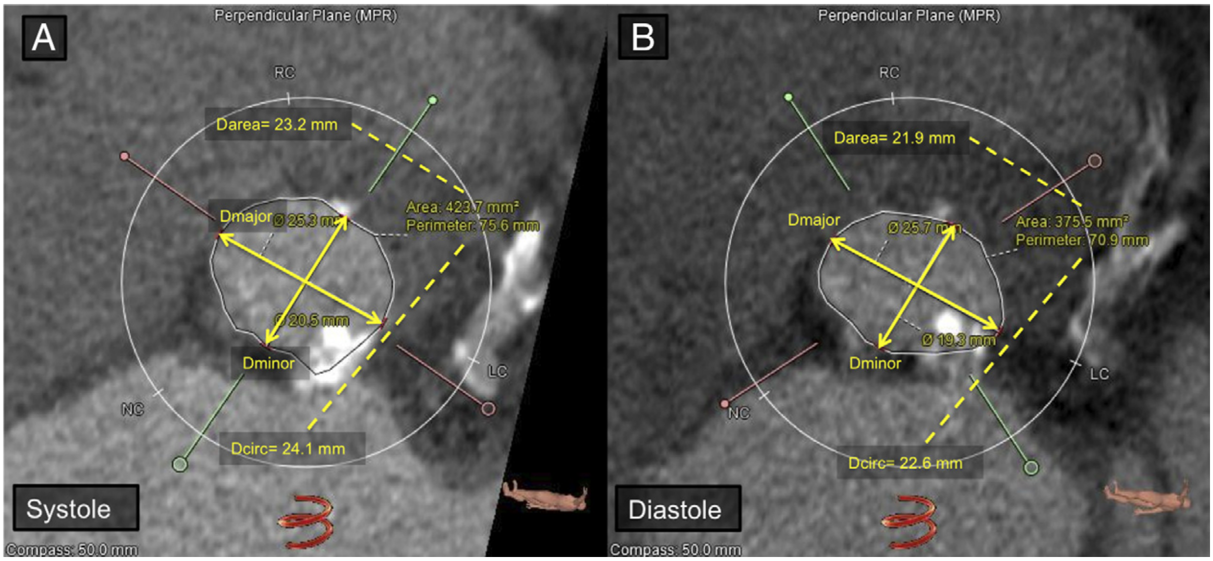

Figure 2 **Dynamic Changes in the Aortic Annulus Cross-Sectional Morphology**

(A) Systole and **(B)** diastole. The aortic annulus is less elliptical in systole, and its maximal/major dimensions are relatively consistent throughout the cardiac cycle, whereas its minimal/minor dimensions show more variation.

calcified, and 3 severely calcified. Overall valvular calcium severity index was graded between 0 and 9 on the basis of the sum of the individual leaflet scores. A calcium asymmetry index was graded on the basis of the difference between adjacent leaflet calcium scores and the sum of the 3 differences. LVOT calcium was graded separately from 0 to 3.

Echocardiography. For the purposes of the procedure, annular size was confirmed using intra-procedural TEE measurements with a zoomed long-axis mid-systolic frame hinge point to hinge point measurement. Specifically, the protocol required annuli of 18 to 25 mm. Traditional cutoffs for annular size by TEE mandate that patients with annuli of 18 to 21 mm are prescribed a 23-mm prosthesis, and those with annuli of 22 to 25 mm are prescribed a 26-mm prosthesis. Patients with annuli of 21 to 22 mm receive either prosthesis, at the discretion of the treating physician. Pre-procedural transthoracic echocardiography (TTE) annular dimensions were those measured prospectively. Intraprocedural TEE annular dimensions included in the analysis were both a long-axis measurement used for the choice of prosthesis size by an expert clinician echocardiographer (D_{TEE}), as well as the largest peri-procedurally recorded long-axis TEE measurement ($D_{TEE(MAX)}$).

Post-TAVR bioprosthetic dysfunction was assessed in line with guidelines suggested by the Valve Academic Research Consortium (9). For the assessment of bioprosthetic regurgitation and device positioning, peri-procedural TEE examinations were reviewed retrospectively. This was performed by 1 of 2 physician readers with more than 4 years of experience in the assessment of TAVR echocardiograms who were not involved with the procedure and were blinded to the peri-procedural TEE report, CT images, and clinical and angiographic data. In view of a tendency to underestimate PV regurgitation, any regurgitation more than mild was regarded as significant. Doppler assessment of stenotic physiology was performed using pre-discharge TTE.

We accounted for malpositioning through an analysis of final device position by TEE using the long-axis view. This was device depth below the annulus, as measured by the distance of the lowest part of the stent frame below the interface of the noncoronary sinus and aortic-mitral conti-

Table 1 **CT-Determined Cross-Sectional Aortic Annular Dimensions Compared in Systole and Diastole in 20 Randomly Selected Cases From the Original 2D TEE-Guided Cohort**

	Systole (n = 20) (Mean Phase 15.9 ± 7.0%)	Diastole (n = 20) (Mean Phase 64.2 ± 4.3%)	p Value
D_{circ}, mm	24.7 ± 2.5	23.8 ± 2.4	<0.001
D_{area}	24.0 ± 2.5	22.9 ± 2.4	<0.001
D_{max}	27.1 ± 2.9	26.8 ± 2.8	0.43
D_{min}	21.3 ± 2.7	19.7 ± 2.3	<0.001
D_{major}	26.9 ± 2.7	26.8 ± 2.8	0.66
D_{minor}	21.5 ± 2.7	19.9 ± 2.2	<0.001
D_{mean}	24.2 ± 2.6	23.3 ± 2.3	<0.001
D_{max}/D_{min}	1.27 ± 1.0	1.37 ± 0.12	0.005
D_{major}/D_{minor}	1.26 ± 0.11	1.35 ± 0.12	<0.001

Values are mean ± SD.

CT = computed tomography; D_{area} = annular diameter derived from cross-sectional area; D_{circ} = annular diameter derived from cross-sectional circumference; D_{major} = annular diameter derived from orthogonal major axis cross-sectional diameter; D_{max} = annular diameter derived from maximal cross-sectional diameter; D_{min} = annular diameter derived from minimal cross-sectional diameter; D_{minor} = annular diameter derived from orthogonal minor axis diameter; TEE = transesophageal echocardiography.

Table 2 Receiver-Operating Characteristic Curve Analysis for Multiple Baseline Measures of the Aortic Annulus With Post-TAVR Paravalvular Regurgitation > Mild as the Outcome Measure

Variable	Area Under the Curve	SE	p Value	95% CI
CT parameters				
$\Delta D_{circ} = (D_{circ}$ – TAVR size)	0.81	0.063	<0.001	0.69–0.94
$\Delta D_{area} = (D_{area}$–TAVR size)	0.78	0.072	<0.001	0.64–0.92
$\Delta D_{max} = (D_{max}$–TAVR size)	0.82	0.062	<0.001	0.70–0.94
$\Delta D_{min} = (D_{min}$–TAVR size)	0.67	0.079	0.029	0.52–0.83
$\Delta D_{mean} = (D_{mean}$–TAVR size)	0.78	0.066	<0.001	0.65–0.91
$\Delta D_{coronal} = (D_{coronal}$–TAVR size)	0.65	0.083	0.061	0.49–0.81
$\Delta D_{OS} = (D_{OS}$–TAVR size)	0.64	0.083	0.088	0.47–0.80
Echocardiographic parameters				
$\Delta D_{TTE} = (D_{TTE}$–TAVR size)	0.49	0.086	0.94	0.33–0.66
$\Delta D_{TEE} = (D_{TEE}$–TAVR size)	0.53	0.08	0.67	0.37–0.70
$\Delta D_{TEE(MAX)} = (D_{TEE(MAX)}$–TAVR size)	0.64	0.09	0.087	0.46–0.81

Δ = delta; CI = confidence interval; $D_{coronal}$ = annular diameter derived from coronal diameter; D_{OS} = annular diameter derived from oblique saggital diameter; D_{TTE} = annular diameter derived from transthoracic echocardiography; D_{TEE} = annular diameter derived from transesophageal echocardiography; TAVR = transcatheter aortic valve replacement. Other abbreviations as in Table 1.

nuity. A final device depth of ≥60% of the stent frame length (corresponding to the covered skirt) below the annulus was regarded as low malpositioning, with high malpositioning defined as the lowest part of the stent frame above the aortic annulus.

Clinical endpoints. Clinical endpoints related to device sizing included need for emergent valve-in-valve, annular rupture, evidence of prosthesis instability, and periprocedural mortality.

Statistical analysis. Statistical analyses were made using SPSS software (PASW version 18, SPSS Inc., Chicago, Illinois) and SAS version 9.2 (SAS Institute, Cary, North Carolina). Normality of distributions for continuous variables was tested using the Shapiro-Wilks test, and data were analyzed appropriately thereafter. Paired data were assessed using a paired *t* test for normally distributed variables and a Wilcoxon signed rank test for non-normally distributed variables. A chi-square test was used for categorical variables compared across independent groups. For normally distributed continuous variables compared across independent groups, an independent samples *t* test was used. For non-normally distributed continuous variables compared across independent groups, a Mann-Whitney *U* test was used.

Receiver-operating characteristic (ROC) curves were generated using post-TAVR PV AR > mild as the event. Areas under the curve were compared for measures derived from traditional TEE sizing and novel CT measures using

Table 3 Clinical Data

	All Studied Patients (n = 136)	2D TEE-Guided Annular Sizing (n = 96)	Cross-Sectional CT-Guided Annular Sizing (n = 40)	p Value
Age, yrs	84.2 ± 8.2	84.9 ± 7.2	82.4 ± 10.2	0.17
Female	68 (50)	46 (47.9)	22 (55)	0.45
Diabetes	39 (29.1)	26 (27.7)	13 (32.5)	0.57
Hypertension	117 (87.3)	80 (85.1)	37 (92.5)	0.24
Prior PCI	48 (35.8)	36 (38.3)	12 (30.0)	0.36
Prior CABG	54 (39.7)	36 (37.5)	18 (45)	0.42
Prior BAV	25 (18.7)	17 (18.1)	8 (20)	0.80
Prior stroke	30 (22.4)	19 (20.2)	11 (27.5)	0.35
Baseline renal disease (creatinine >2 mg/dl)	9 (6.7)	7 (7.4)	2 (5)	0.61
Pulmonary disease	76 (56.7)	56 (59.6)	20 (50)	0.31
Porcelain aorta	4 (3)	2 (2.1)	2 (5)	0.37
STS-PROM score	10.3 ± 3.4	10.6 ± 2.9	9.8 ± 4.5	0.22
Logistic EuroSCORE	30.3 ± 15.7	31.2 ± 16.1	27.5 ± 14.5	0.24
Frailty	25 (18.5)	16 (16.8)	9 (22.5)	0.44
Height, cm	164 ± 11	164 ± 11	164 ± 11	0.72
Weight, kg	70.7 ± 16.8	69.1 ± 15.9	74.5 ± 18.4	0.11
BSA, cm^2/m^2	1.8 ± 0.2	1.7 ± 0.2	1.8 ± 0.2	0.28

Values are mean ± SD or n (%).

BAV = balloon aortic valvuloplasty; BSA = body surface area; CABG = coronary artery bypass grafting; CT = computed tomography; 2D = 2-dimensional; PCI = percutaneous coronary intervention; STS-PROM = Society of Thoracic Surgeons Predicted Risk of Mortality; TEE = transesophageal echocardiography.

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the method of DeLong et al. (10). Specific cutoffs were defined using these curves on the basis of the highest sum of the sensitivity and specificity for the prediction of PV AR > mild. Cross-sectional annular CT-derived cutoffs defined by this analysis were later applied to a prospectively treated population and outcomes compared with a traditional TEE-based annular sizing approach. For the entire population studied, candidate baseline and procedural factors related to post-TAVR PV AR were evaluated in a binary logistic regression model. Variables found to be significant to $p < 0.1$ were entered into an exploratory multivariable binary logistic regression model for AR > mild.

Results

Study population. From a series of 192 consecutive patients scheduled for TAVR between January 2008 and March 2011, ECG-gated contrast thoracic scans were available in 81 patients; a randomly selected 20-patient subset was compared in systole and diastole (Table 1). The 81-patient cohort was analyzed retrospectively for the predictive value of multimodality annular measures for post-TAVR PV leak (Table 2). Baseline clinical characteristics were analyzed with the subsequently expanded TEE-guided annular sizing cohort (Table 3).

Reliability assessment of native aortic annular dimensions and post-TAVR PV leak. CT measurements for the main study were made in systole, where maximal opening of the aortic valve was seen. In repeated reconstructions from raw Digital Imaging and Communications in Medicine (DICOM) data for the subset of 20 randomly selected patients previously described, intra observer variability was 0.53 ± 0.54 mm for D_{circ} measurements (paired sample correlation $r = 0.98$, $p < 0.001$) and 0.27 ± 0.89 mm (paired sample correlation $r = 0.95$, $p < 0.001$) for D_{max} measurements. Inter-observer variability was 0.07 ± 0.87 mm for D_{circ} measurements (paired sample correlation $r = 0.94$, $p < 0.001$) and 0.67 ± 1.19 mm for D_{max} measurements (paired sample correlation $r = 0.92$,

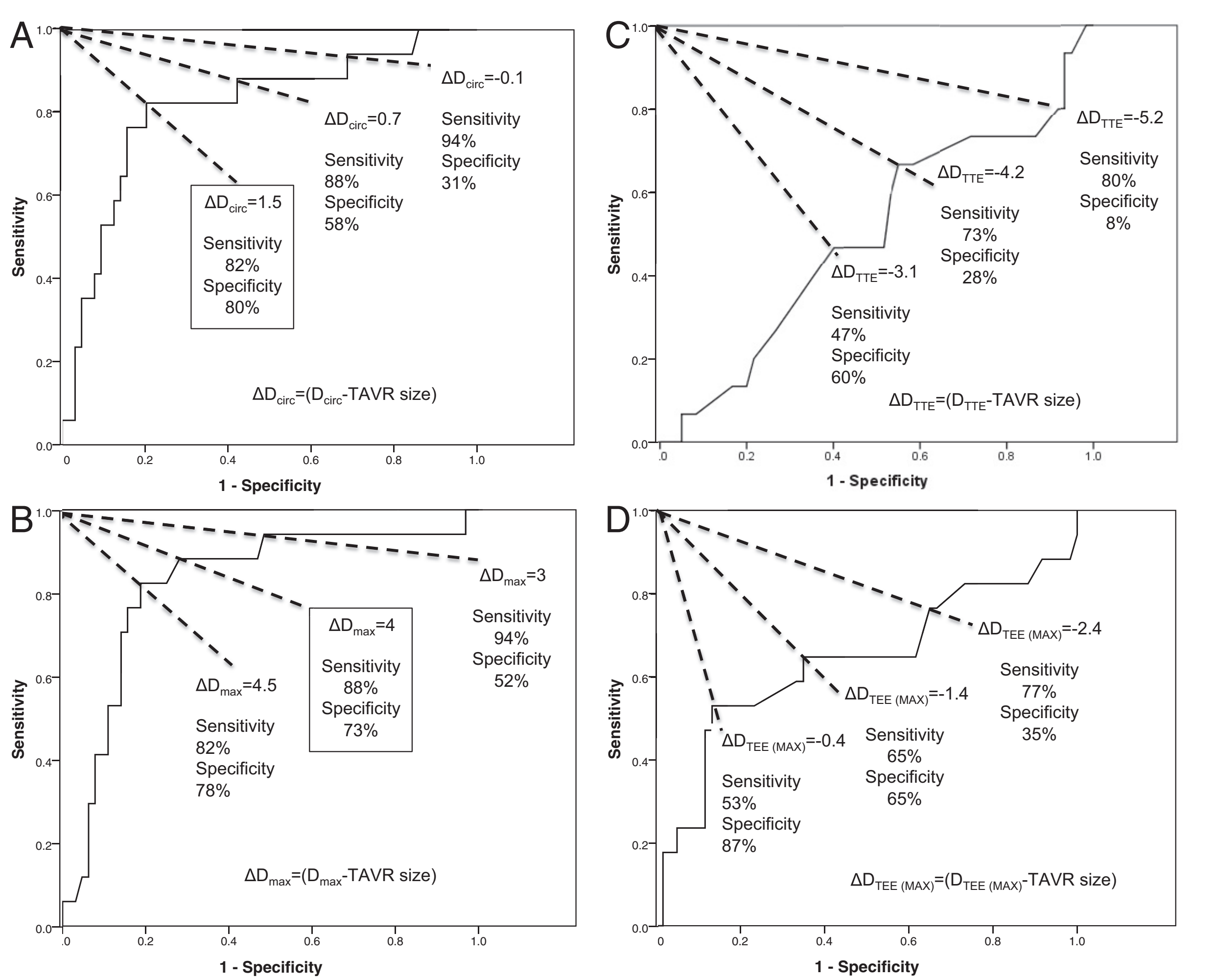

Figure 3 **ROC Curves Evaluating Predictive Value of Cross-Sectional CT and Standard Echocardiographic Measurements for Post-TAVR Paravalvular Regurgitation (> Mild)**

(A) ΔD_{circ}. **(B)** ΔD_{max}. **(C)** ΔD_{TTE}. **(D)** ΔD_{TEE}. CT = computed tomography; ROC = receiver-operating characteristic; TAVR = transcatheter aortic valve replacement.

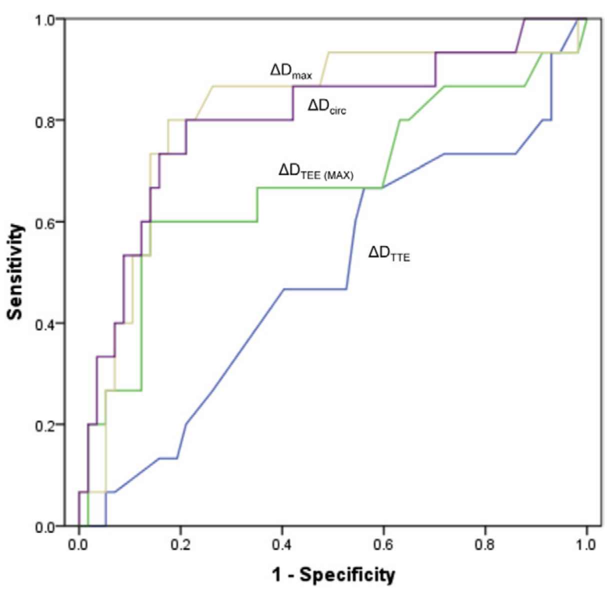

Figure 4 **Superimposed ROC Curves Evaluating Predictive Value of Cross-Sectional CT and Standard Echocardiographic Measurements for Post-TAVR Paravalvular Regurgitation (> Mild)**

The cross-sectional CT-derived parameters (ΔD_{circ} and ΔD_{max}) had a considerably greater discriminatory value (with larger areas under the curve) for significant paravalvular regurgitation (>mild) than 2-dimensional echocardiography-derived measurements ($\Delta D_{TEE\ (MAX)}$ and ΔD_{TTE}). See Table 2 and text for further details. Abbreviations as in Figure 3.

$p < 0.001$). With regard to intra-observer agreement for the assessment of significant PV regurgitation, the kappa statistic was 0.77 ($p < 0.001$), and for inter-observer agreement, the kappa was also 0.77 ($p < 0.001$).

There was a significant variation throughout the cardiac cycle for all CT-derived measurements, which were generally larger in systole (Table 1). The lower ratios of D_{max}/D_{min} and D_{major}/D_{minor} in systole were consistent, with a less elliptical and more circular morphology of the aortic annulus in systole than in diastole.

ROC curve analyses and the prediction of PV regurgitation. Multiple CT and echocardiographic annular measurement parameters were evaluated for their predictive value for PV regurgitation > mild in the original retrospective 81-patient cohort (Table 2). ΔD_{max} (D_{max} minus TAVR size) and ΔD_{circ} (D_{circ} minus TAVR size) were of greatest discriminatory value (Table 2, Figs. 3 and 4). Echocardiographic and CT coronal and oblique sagittal measurements were nondiscriminatory. Comparing ΔD_{TEE}, derived from the traditional TEE measurement (used for the decision for prosthesis size for the retrospective cohort), with ΔD_{max} and ΔD_{circ}, measurements derived from the novel CT methodology of sizing yielded significant differences, with $p = 0.004$ for ΔD_{max} versus ΔD_{TEE} and $p = 0.003$ for D_{circ} versus ΔD_{TEE}. The discriminatory value of CT parameters held if PV AR ≥ moderate was used as the dichotomous endpoint (for ΔD_{max}: area under the curve 0.82, 95% confidence interval [CI]: 0.66 to 0.97, $p = 0.001$; for ΔD_{circ}: area under the curve 0.80, 95% CI: 0.66 to 0.95, $p = 0.001$). Using the coordinates of each curve, ΔD_{max} of 4 mm or a ΔD_{circ} of 1.5 mm had the highest sum of sensitivity and specificity (Fig. 3).

Prospective cross-sectional CT-guided annular sizing approach. An additional 15 patients were treated by a TEE-based annular sizing approach before the CT-guided approach was implemented in May 2011. With the 81 patients analyzed for the initial retrospective ROC curve analysis, this comprised the 96-patient TEE-guided annular sizing cohort (Table 3). Subsequently, 40 patients were treated using a cross-sectional CT method of annular sizing. This incorporated an annular sizing approach based on the ROC curve analysis prosthesis observing cutoffs of a ΔD_{max} of ≤4 mm and a ΔD_{circ} of ≤1.5 mm. The overall 136-patient cohort with systolic contrast CT scans was derived from a total of 270 consecutive patients scheduled for TAVR with the Edwards SAPIEN device until September 2011. There were no differences in clinical, echocardiographic, and procedural characteristics in the patients treated according to either annular sizing approach (Tables 3 and 4).

Central aortic regurgitation of grade ≥ moderate was observed in only 1 patient (0.73%). Excellent hemodynamic outcomes (Table 5) were achieved with the cross-sectional CT approach to annular sizing with a significant reduction in the incidence of PV AR. Only 2 cases of moderate PV AR (5%) occurred after observing the annular sizing protocol dictated by cross-sectional CT. In one of these cases, there was extremely bulky native leaflet calcification, and in the other, extensive LVOT calcification.

For the 96-patient TEE-guided sizing cohort, 60 patients received a 23-mm Edwards SAPIEN device, and 36 received a 26-mm Edwards SAPIEN device. If our cross-sectional CT criteria were applied, 26 of 60 patients would have received a 26-mm rather than a 23-mm device, and 17 of 36 would have had annuli deemed too large for a 26-mm bioprosthesis. Of these 17, 12 could have had a 29-mm device (commercially available in Europe and Canada) if it were available, but 5 of 17 had annuli that would have been considered too large even for that device. Overall, treatment reassignment would have existed in 43 of 96 patients (44.8%).

Although there was no difference in TTE and TEE measures of the aortic annulus between TEE-guided and CT-guided sizing approaches, there were significant differences in many CT parameters, including D_{max}, D_{mean}, D_{circ}, and D_{area} (Table 4).

Prospective CT assessment and exclusion of patients for TAVR. After the change in our practice of aortic annular assessment, 3 patients during the time period studied were accepted by the PARTNER committee (with aortic annular dimensions based on TTE), but were subsequently rejected internally for TAVR. Two additional patients were internally declined for TAVR before presentation to the PARTNER committee. These decisions were based on an analysis of their

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Table 4 Baseline Echocardiographic, CT, and Procedural Variables

	All Studied Patients (n = 136)	2D TEE-Guided Annular Sizing (n = 96)	Cross-Sectional CT-Guided Annular Sizing (n = 40)	p Value
Echocardiographic variables				
Peak velocity, m/s	4.2 ± 0.9	4.2 ± 0.8	4.2 ± 1.2	0.92
Mean aortic gradient, mm Hg	44 (41–53)	43 (40–55)	44.5 (42.0–51.5)	0.47
Concomitant MR ≥3+	15 (12.5)	12 (14.5)	3 (8.1)	0.33
LVEF, %	59.7 ± 13.9	58.9 ± 14.7	61.5 ± 11.8	0.30
Baseline AR ≥ 3+	11 (8.5)	10 (10.9)	1 (2.6)	0.13
Annular dimensions				
TTE, mm	20.4 ± 1.1	20.5 ± 1.1	20.2 ± 1.0	0.06
TEE, mm	21.7 ± 2.0	21.7 ± 1.9	21.5 ± 2.1	0.66
TEE (MAX), mm	22.5 ± 2.1	22.6 ± 2.2	22.4 ± 2.0	0.59
$\Delta D_{TTE} = (D_{TTE}$–TAVR size)	−3.7 ± 1.2	−3.6 ± 1.2	−4.0 ± 1.2	0.07
$\Delta D_{TEE} = (D_{TEE}$–TAVR size)	−2.4 ± 1.3	−2.4 ± 1.2	−2.6 ± 1.3	0.44
$\Delta D_{TEE\ (MAX)} = (D_{TEE\ (MAX)}$–TAVR size)	−1.6 ± 1.6	−1.5 ± 1.7	−1.8 ± 1.5	0.30
Computed tomography variables				
Annular dimensions, mm				
$D_{coronal}$	24.4 ± 2.4	24.3 ± 2.5	24.7 ± 2.0	0.33
D_{OS}	21.7 ± 2.3	22.0 ± 2.4	21.3 ± 2.5	0.079
D_{max}	27.2 ± 2.9	27.8 ± 3.0	25.6 ± 2.2	<0.001
D_{min}	21.3 ± 2.6	21.5 ± 2.7	20.8 ± 2.2	0.15
D_{mean}	24.2 ± 2.6	24.7 ± 2.7	23.2 ± 2.1	0.001
D_{circ}	24.7 ± 2.4	25.2 ± 2.5	23.6 ± 1.9	<0.001
D_{area}	24.0 ± 2.5	24.4 ± 2.5	23.0 ± 1.9	0.001
$\Delta D_{max}=(D_{max}$–TAVR size)	3.0 ± 2.4	3.7 ± 2.4	1.3 ± 1.6	<0.001
$\Delta D_{circ}=(D_{circ}$–TAVR size)	0.5 ± 1.9	1.0 ± 1.9	0.7 ± 1.3	<0.001
Valve calcium severity index	7.75 (6–9)	8 (6–9)	7.5 (6–8.75)	0.46
Valve calcium asymmetry index	2 (0–3)	2 (0.5–3.0)	1 (0–3)	0.13
LVOT calcium score	0.5 (0–2)	0.75 (0–1.75)	0.5 (0–2.0)	0.97
Any LVOT calcium	82 (60.3)	59 (61.5)	23 (57.5)	0.67
Procedural variables				
Approach				0.45
Transfemoral	114 (83.8)	79 (82.3)	35 (87.5)	
Transapical	22 (16.2)	17 (17.7)	5 (12.5)	
Bioprosthesis diameter (mm)				0.59
23	83 (61)	60 (62.5)	23 (57.5)	
26	53 (39)	36 (37.5)	17 (42.5)	
Malpositioned bioprosthesis	3 (2.3)	3 (3.3)	0	0.26

Values are mean ± SD, n (%), or median (25th to 75th interquartile range).
AR = aortic regurgitation; CT = computed tomography; 2D = 2-dimensional; LVEF = left ventricular ejection fraction; LVOT = left ventricular outflow tract; TEE = transesophageal echocardiography; TTE = transthoracic echocardiography. Other abbreviations as in Table 2.

pre-procedural CT cross-sectional dimensions (all with a D_{max} >30 mm and a D_{circ} >27.5 mm). By our present CT criteria, 4 of 5 of these patients would have been suitable for a 29-mm Edwards SAPIEN bioprosthesis, which is currently unavailable to PARTNER trial investigators.

Exploratory multivariable analysis. Candidate clinical, echocardiographic, CT, and procedural variables were evaluated for their predictive value for significant PV AR (> mild) in univariate binary logistic regression analysis (Table 6). In the exploratory stepwise multivariable model for post-TAVR PV AR > mild, only ΔD_{max} by CT and presence of LVOT calcium remained predictive. ΔD_{max} and ΔD_{circ} were highly correlated (Pearson r = 0.91, p < 0.001). Given this collinearity, the multivariable model was also run for ΔD_{circ} without ΔD_{max}, which yielded only presence of LVOT calcium (multivariable odds ratio = 19.4, 95% CI: 1.7 to 226, p = 0.018) and ΔD_{circ} (multivariable odds ratio per mm ΔD_{circ} = 1.71, 95% CI: 1.2 to 2.4, p = 0.003) as independently predictive of significant PV AR.

Other clinical outcomes. This study was underpowered for prediction of clinical outcomes. Importantly, annular rupture resulting in peri-procedural death was seen in 1 patient (Fig. 5). One 26-mm SAPIEN device was seen to rock on TEE, producing variable significant AR (Fig. 6, Online Video 1); this patient died from congestive heart failure on the ninth post-procedural day. The ΔD_{max} for this case was almost 10 mm, but TEE had yielded highly heterogeneous measures ranging from 21 to 28 mm (Fig. 6).

Table 5 Comparison of Outcomes Related to Prosthesis Sizing With TEE- and CT-Guided Approaches

Outcomes	All Studied Patients (n = 136)	2D TEE-Guided Annular Sizing (n = 96)	Cross-Sectional CT-Guided Annular Sizing (n = 40)	p Value
PV AR				0.001
None	41 (30.1)	23 (24)	18 (45)	
Trivial or mild	71 (52.2)	52 (54.1)	19 (47.5)	
Mild-moderate	9 (6.6)	8 (8.3)	1 (2.5)	
Moderate	12 (8.8)	10 (10.4)	2 (5)	
Moderate-severe	3 (2.2)	3 (3.1)	0	
Severe		0	0	
PV AR > mild	24 (17.6)	21 (21.9)	3 (7.5)	0.045
Need for bail-out valve-in-valve	1 (0.7)	1 (1)	0	0.52
Annular rupture	1 (0.7)	1 (1)	0	0.52
Prosthesis instability (rocking)	1 (0.7)	1 (1)	0	0.52
Peri-procedural mortality	4 (3)	3 (3.2)	1 (2.5)	0.82

Values are n (%).
AR = aortic regurgitation; CT = computed tomography; 2D = 2-dimensional; PV = paravalvular; TEE = transesophageal echocardiography.

Discussion

This study substantiates hypotheses suggested by several prior studies, highlighting the putative value of a 3-dimensional CT-based evaluation of the aortic annulus for TAVR (6,8). Its central finding is that 3-dimensionally derived cross-sectional measurements of the aortic annulus are superior to conventional 2D echocardiographic sizing in the discrimination of patients with PV regurgitation. Importantly, a CT cross-sectional assessment of the aortic annulus affects device sizing and patient selection and reduces post-TAVR PV AR. CT measurements were reproducible and precisely defined using ECG gating in a dynamic anatomical framework. Notably, they have provided a scientific basis for device sizing, which is lacking from previous research (8).

Delgado et al. (11) examined Edwards SAPIEN valve function in relation to CT dimensions, but did not use a cross-sectional evaluation. They found larger baseline annular coronal and oblique saggital dimensions in patients with significant PV leak, although the discriminatory value of CT relative to echocardiography was not assessed. Messika-Zeitoun et al. (6) went further to examine end-systolic/mid-diastolic cross-sectional dimensions of the aortic annulus in patients referred for TAVR and found clear differences to TEE dimensions but did not evaluate outcomes. Schultz et al. (8) evaluated end-systolic cross-sectional CT annular dimensions in patients undergoing TAVR with the CoreValve ReValving system. They compared operator choice of prosthesis size based on TEE to that based on various cross-sectional CT dimensions. D_{mean} and D_{CSA} (D_{area}) were found to correspond most closely to operator choice. However, it was assumed that the cutoffs for device appropriateness would be the same as for echocardiography.

This study demonstrates for the first time that CT cross-sectional annular assessment for TAVR sizing is superior to 2D TEE assessment in reducing PV AR. Maximal dimension (D_{max}) and measures of average dimension (D_{circ}, D_{mean}, and D_{area}) were significantly lower in the CT-guided group as compared with the TEE-guided group, suggesting more aggressive sizing in the CT-guided group (Table 4). Importantly, these differences were not apparent on echocardi-

Table 6 Multivariable Model Applied to the Overall Cohort (n = 136) for Post-TAVR Paravalvular Regurgitation > Mild

	Univariate OR	95% CI	p Value	Multivariable OR	95% CI	p Value
ΔD_{max} (per mm)	1.60	1.3–2.1	<0.001	1.6	1.3–2.0	<0.001
Any LVOT calcium present	5.90	1.7–20.7	0.006	9.1	1.6–50.3	0.021
ΔD_{circ} (per mm)	1.70	1.3–2.2	<0.001	Dropped	—	
Aortic valve CSI (per point)	1.50	1.1–2.1	0.018	Dropped	—	
Female sex	0.15	0.05–0.47	0.001	Dropped	—	—
BSA (per m^2)	8.60	1.3–58.8	0.029	Dropped	—	—
Malpositioning	9.90	0.9–101.0	0.066	Dropped		
Small prosthesis size	0.47	0.19–1.1	0.097	Dropped	—	—
ΔD_{TEE} (per mm)	1.10	0.7–1.5	0.73	Not entered		
$\Delta D_{TEE\ (MAX)}$ (per mm)	1.20	0.92–1.60	0.18	Not entered		
Baseline AR grade	0.88	0.52–1.47	0.62	Not entered		

All variables shown entered into stepwise forward:logistic regression multivariable model.
AR = aortic regurgitation; BSA = body surface area (Dubois calculation); CSI = calcium severity index; Dropped = dropped by multivariable model; LVOT = left ventricular outflow tract; Not entered = not entered into model as univariate p > 0.1; OR = odds ratio. Other abbreviations as in Table 2.

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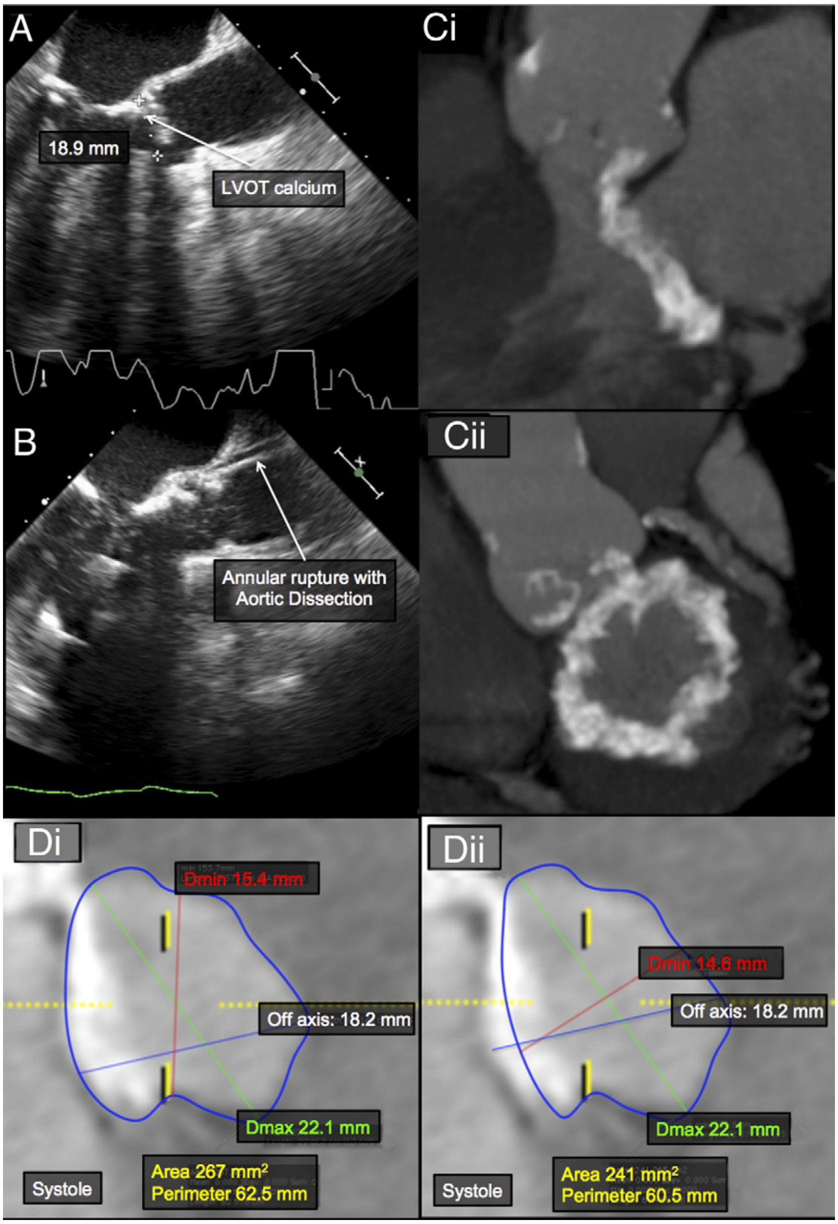

Figure 5 **Gross Over-Sizing Based on Echocardiographic Measurements Resulting in Complicated Transcatheter Aortic Valve Replacement**

(A) Transesophageal echocardiography measurement appeared appropriate for a 23-mm Edwards SAPIEN valve. **(B)** Annular rupture with aortic dissection occurred after the procedure. **(Ci, Cii)** A retrospective evaluation of computed tomography (CT) data demonstrated extensive left ventricular outflow tract calcium extending to the mitral annulus. **(Di, Dii)** Whether or not the calcium was included in the measurement of annular dimension, CT cross-sectional annular assessment revealed well-aligned measurements as small as 14 to 15 mm.

ography, with no difference in TTE- or TEE-derived dimensions between sizing strategies, re-iterating the fact that significant differences are masked if one relies entirely on the 2D analysis of annular dimension. Because malpositioning can be another reason for PV AR, we also assessed the outcomes after excluding 3 patients who had high placement in the TEE-guided cohort. Even with exclusion of these 3 cases, the reduction of PV AR was significant on the adoption of the CT-guided approach relative to the TEE sizing cohort (PV AR: any, 75.3% to 55%; mild-moderate, 7.5% to 2.5%; moderate, 10.8% to 5%; and moderate-severe, 2.2% to 0%; $p = 0.001$).

Study limitations. This was a single-center retrospective study. The grading of PV regurgitation remains challenging. However, the predictive value of cross-sectional CT measures for PV regurgitation after TAVR remained robust, regardless of whether $>$ mild or $\geq$ moderate was regarded as the significant endpoint. Only the Edwards SAPIEN valve was

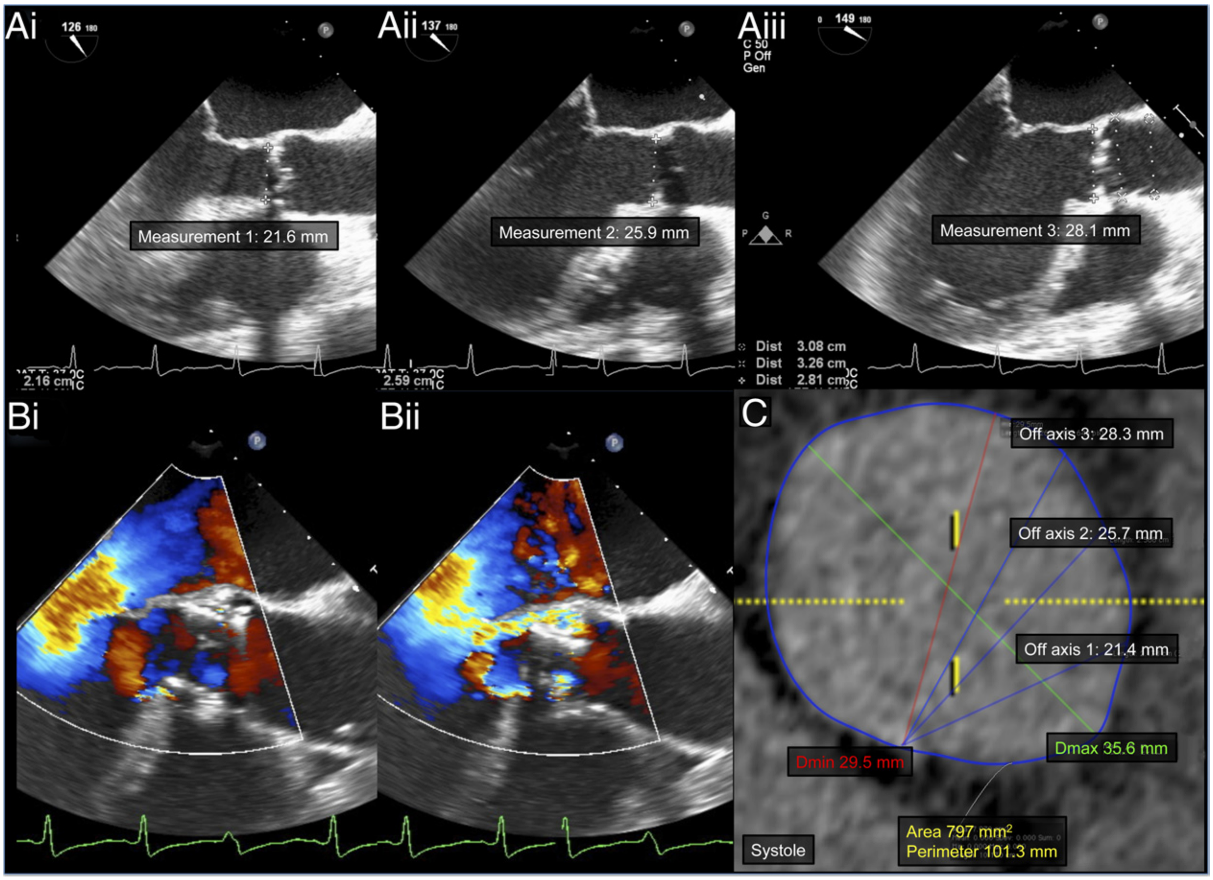

Figure 6 **Gross Under-Sizing Based on Echocardiographic Measurements Resulting in Complicated TAVR**

(Ai to Aiii) Heterogeneous measurements were observed on transesophageal echocardiography (TEE). Highly variable but significant paravalvular regurgitation **(Bi, Bii)** and a rocking valve were observed after transcatheter aortic valve replacement (TAVR) with a 26-mm Edwards SAPIEN bioprosthesis. **(C)** Erroneous off-axis TEE measurements are explained by computed tomography evaluation in the same patient.

studied, and hence application of these data to other valve types is at present unproven.

Moreover, the nature of contrast CT imaging with exposure to both contrast and radiation provides some limitations to patients with renal impairment and those of younger age. Such patients may benefit from alternative 3-dimensional imaging of the cross-section of the aortic annulus, such as magnetic resonance imaging (12) or 3-dimensional TEE (13). A publication by Otani et al. (14) compared 3-dimensional TEE with contrast CT in 71 patients with and 80 without aortic stenosis and found good correlation between the 2 techniques. Additionally, Ng et al. (5) found that 3-dimensional TEE correlated more strongly with CT than with 2D TEE. Indeed, it is likely that systematic 3-dimensional echocardiography could overcome some of the deficiencies in conventional 2D TEE.

Conclusions

The minimization of PV regurgitation is critical before TAVR can be applied to low surgical-risk populations. Our data lend strong support to 3-dimensional cross-sectional measures, using CT as the new gold standard for aortic annular evaluation for TAVR with the Edwards SAPIEN device. We found annular dimensions derived from this approach to be highly correlated to PV regurgitation, and a prospective application of this principle significantly reduced the incidence of PV AR. The routine application of such methods in this setting is likely to reduce complications, and clinical practice should be updated accordingly. The specific cutoffs used merit validation in larger series. Enhanced aortic annular sizing will, in turn, also demand more valve sizes to match native annular dimensions more precisely, which is likely to lead to a further optimization of outcomes.

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Key Words: aortic annulus ▪ aortic stenosis ▪ computed tomography ▪ paravalvular aortic regurgitation ▪ transcatheter aortic valve implantation ▪ transcatheter aortic valve replacement.

APPENDIX

For a supplementary video, please see the online version of this article.