Prediction of Paravalvular Regurgitation After Transcatheter Aortic Valve Implantation by Computed Tomography: Value of Aortic Valve and Annular Calcification

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Background. The purpose of this study was to quantify and characterize aortic valve leaflet and aortic annular calcification with computed tomography angiography (CTA) and to define whether they predict paravalvular regurgitation (PAR) after transcatheter aortic valve implantation.

Methods. In all, 94 patients (aged 83.6 years) with severe aortic stenosis underwent CTA. Annular calcification was measured in two planes and defined as “protruding” (depth greater than length), “round,” or “adherent” (length less than depth) for the right, left, and non-c oral annulus. Leaflet calcification severity and asymmetry were scored. Transthoracic echocardiography grading of PAR severity was performed after the procedure (0.5 scale).

Results. Thirty-two percent of patients had no or trivial PAR (grade less than 1) and 68% had mild to severe PAR (‡1 [mild 45.7%, moderate 20.2%, moderate to severe 2.1%]). The size of annular calcium was higher in patients with moderate to severe PAR greater than 1 (p = 0.015, p = 0.007, and p = 0.004) and predictive (c = 0.67, 0.71, and 0.711) for noncoronary, left, and total annular calcium size, respectively. Increasing PAR severity was correlated with increasing total calcium size (r = 0.422, p < 0.001). Protruding annular calcification greater than 4 mm (p = 0.02) was more frequently found in moderate to severe PAR greater than 1, and predictive (c = 0.7). Adherent calcium greater than 4 mm did not predict PAR greater than 1 and PAR of 1 or less. There was no association of leaflet calcium severity and asymmetry with PAR severity.

Conclusions. Protruding annular calcium greater than 4 mm predicts moderate to severe PAR after transcatheter aortic valve implantation. Increasing annular calcium size is another predictor, whereas adherent calcium has a “sealing” effect.

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Transcatheter aortic valve implantation (TAVI) has shown excellent outcome recently, as in the Placement of Aortic Transcatheter Valves–Europe (PARTNER-EU) trial, for both the transfemoral and transapical access routes with 95% and 96% success rates, respectively [1–4]. Similar results were reported for 1,038 patients enrolled at 32 centers (SAPIEN Aortic Bioprosthesis European Outcome [SOURCE] registry) with 76% survival after 1 year after TAVI [2]. Improved quality of life of inoperable patients with severe aortic stenosis accounts for another major benefit of TAVI [5]. Moderate to severe paravalvular aortic regurgitation (PAR) is a serious complication with a prevalence of 12.2% after 30 days (PARTNER-US), as high as 42% (PARTNER-EU) [1, 4], and with even 5% severe PAR [1]. Most recent data released from the PARTNER studies indicate that even mild PAR is related to increased late mortality.

The nature of PAR development is not fully understood. Although PAR may decrease in severity after TAVI over time ("healing in"), with a decline from 25% to 6.6% after 1 year, PAR may persist or increase over time [1, 4]. In addition to device malpositioning or prosthesis undersizing, aortic valve leaflet and annular calcification have been suggested as risk factors for PAR.

Computed tomography angiography (CTA) is performed before TAVI for aortoiliac vessel and aortic root evaluation [6, 7]; CTA allows for quantitative and

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qualitative analysis of valvular and annulus calcification [8]. Therefore, the purpose of our study was to characterize and quantify aortic valve leaflet and annular calcification, and to assess whether quantitative and qualitative CTA variables predict moderate to severe PAR.

Material and Methods

Patients with severe aortic stenosis meeting current recommendations for TAVI were scheduled for CTA and enrolled into an Institutional Review Board–approved prospective study from January 2008 until November 2012. Written informed consent was obtained. Patient data were collected prospectively. For this study, data were analysis retrospectively, for which additional Institutional Review Board approval (amendment) was obtained, and further patient consent waived.

Inclusion criteria were high risk, namely, logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE) of 20% or more, or other contraindications for open chest surgery, such as expected high perioperative risk due to comorbidities. Exclusion criteria for TAVI were active endocarditis, myocardial infarction within 14 days, cardiogenic shock, and life expectancy of less than 1 year. The decision for TAVI was made by an interdisciplinary team (cardiologists, cardiothoracic surgeons, anesthesiologist, and radiologist). Transthoracic echocardiography (TTE) was performed immediately after the procedure, before hospital discharge, at 30 days, at 3 to 6 months, at 1 year, and at 2-year follow-up examinations. The last available echocardiography result was used for data analysis.

CTA Examination

A 64-slice (until December 2009) or 128-slice dual source CT (after December 2009) was used (detector collimation 64 × 0.6 mm and 2 × 24 × 0.6 mm, gantry rotation 0.33 s and 0.28 s, respectively). Retrospective electrocardiography gating was applied for 64-slice CT and high-pitch prospective electrocardiography-gated dual source CTA (pitch 3.2) for 128-slice dual source CT [9]. An iodine contrast agent (370 mg/dL) was injected (80 to 110 cc) with flow rate 5 cc/s, triggered into arterial phase. Thin axial slices were reconstructed (0.75 mm slice width, overlap 70%).

CTA Image Analysis

The aortic root was reformatted using multiplanar reformations. Multiple cross-sectional planes (1 mm slice width) of the aortic root from sinus of Valsalva downward to the annulus were reconstructed perpendicular along to the aortic root centerline placed into left coronal and left sagittal oblique views of the aortic root. Best phase, mostly end-diastolic data sets (between 65% and 80% of RR interval) were selected. An experienced radiologist (7 years cardiac CT experience) performed image analysis, as follows.

ANNULAR CALCIUM. The cross-sectional axial annulus plane was used for the following analysis: annular calcification was measured in two planes, depth (D) and width (W), and evaluated for shape (1 = protruding [D > W], 2 = round [D = W], and 3 = adherent [W > D]) for each side (noncoronary, right coronary, and left coronary annulus side). A total size (D + W) score was calculated for all sides together and for each side separately.

LEAFLET CALCIUM SEVERITY AND ASYMMETRY. The cross-sectional axial aortic root planes distally to the annulus were reviewed for the following: calcifications were evaluated regarding severity (score 0 to 4: 4 = excessive, 3 = severe, 2 = moderate, 1 = mild, 0 = no calcium), modified according to Rosenhek and coworkers [10] for each leaflet (right, left, and noncoronary) separately. An asymmetry score based on left/right/noncoronary calcium distribution was given for each score deviation among two sides (eg, +1 score point if left coronary was 3 and right coronary was 4).

ANNULUS DIMENSIONS. Two diameters, the anteroposterior (AP) short axis and the mediolateral (ML) long axis were measured, and the mean ([ML plus AP] divided by 2) was calculated. The annulus eccentricity index was defined as ratio of AP/ML diameter.

“Undersizing” of the prosthesis was quantified as a negative deviation of finally implanted prosthesis size (selected based on transesophageal echocardiographic annulus diameter) in relation to the mean annulus diameter (prosthetic valve size minus mean diameter by CTA). Relevant undersizing or oversizing was defined if deviation of 1 mm or greater was found, namely, more than +1 for oversizing and more than −1 for undersizing.

TAVI Procedure

The valve implantation procedure was performed in hybrid operating rooms equipped with an angiography suite by an interdisciplinary team of cardiac surgeons, interventional cardiologists, echocardiographer, and anesthesiologist. Transfemoral, transapical, or subclavian access routes were used, or transaortal bailout. The prosthetic valve size was selected based on the echocardiographic measurements of the annular dimensions [11]. The TAVI was performed during general anesthesia under transesophageal, intracardiac echocardiography, and fluoroscopy guidance [12, 13].

Two different devices were implanted. The Edwards SAPIEN transcatheter valve (Edwards Lifesciences, Irvine, CA) is a second-generation bovine pericardial balloon-expandable prosthesis with 23-mm and 26-mm sizes for native aortic annulus diameters between 18 mm and 25 mm. The transfemoral delivery system was used for iliofemoral vessels with a diameter 7 mm or greater for the 22F and 8 mm or greater for the 24F sheath. For the transapical approach, 23-mm or 26-mm Edwards SAPIEN valves were used. The CoreValve (Medtronic, Minneapolis, MN), a self-expanding porcine-pericardial tissue valve with a nitinol frame (26 mm or 29 mm), was implanted through the transfemoral or transsubclavian access route.
Balloon valvuloplasty was performed before implantation. If PAR was noticed during the procedure, dilation after with a balloon was performed with a model provided by the company of the balloon-expandable valve. For self-expandable valves, a nuCLEUS-X (Hopkinton, NY) percutaneous balloon valvuloplasty catheter in the appropriate size was applied. Balloon dilation was performed under rapid pacing with as much as 2 cc saline volume above the initial calculated volume for more than 5 s after positioning of the balloon catheter at the designated site to cover all the parts of the implanted valve. The device was evaluated for malpositioning (too low or too high; relevant or minor) after the implantation. A 3/2 ratio (above/below annulus plane) was defined as correct position for the balloon-expandable device, and a contour fit for the self-expandable device.

Outcome Analysis
Transthoracic echocardiography was performed after the procedure and at 1, 12, and 24 months after the implantation [11]. The PAR was located by TTE, and the paravalvular regurgitation graded as 0.5 (minimal), 1 (mild), 1.5 (mild to moderate), 2 (moderate), 2.5 (moderate to severe), and 3 (severe) according to standardized criteria (Table 2). Transvalvular regurgitation was distinguished from paravalvular.

Data and Statistical Analysis
A commercial software package (SSPS version 15; SSPS, Chicago, IL) was used for statistical analysis. The differences in the prevalence of PAC greater than 4 mm and adherent calcium greater than 4 mm was tested with Fisher’s exact or $c^2$ test. The variation in the severity and asymmetry scores among the PAR severity groups was evaluated using the nonparametric Mann-Whitney U test. Differences for parametric data (calcium size, depth and width, the calcium size score, and so forth) were assessed with the independent t test. The correlation between leafllet calcium severity and asymmetry by CTA and PAR severity by TTE was determined with Spearman rank correlation coefficient. Receiver-operating characteristics curve analysis (ROC) with area under the curve (AUC) (c-statistic) was performed to estimate prediction of PAR greater than 1 and PAR 1 or greater by annular or leafllet calcium parameters. For PAC and adherent calcium size analysis, a stepwise increasing approach (increments of 1 mm calcium size score) was conducted to identify a significant threshold in millimeters.

Results
Ninety-four patients were enrolled; population characteristics are shown in Table 1. One patient underwent a valve-in-valve procedure and was excluded. Table 2 shows PAR severity by TTE after a follow-up period of mean 14 months (range, 1 to 24) after TAVI. Overall, 31.9% patients had no or trivial PAR (grade less than 1) and 67.1% had mild to severe PAR (grade 1 or greater). The PAR remained stable in the majority of patients ($n = 88, 93.6\%$). The PAR increased in severity by 0.5 in 4 patients and declined in 2 during the follow-up time (from PAR 1 to 0). No patient had a relevant prosthesis malposition. One patient (2%) had a minor “too low” positioned prosthesis, who had minimal PAR (grade 0.5) and was included.
Annular Calcium Quantification

The mean size of calcium was significantly higher in moderate to severe PAR greater than 1 as compared with the other groups ($p = 0.015$, $p = 0.007$, and $p = 0.004$, respectively). Increasing total, left coronary, and non-coronary size annulus calcium was correlated with increasing PAR severity (Fig 1), and a weak to moderate but significant correlation was observed, being strongest for total size ($r = 0.422$, $p < 0.001$), as compared with left and noncoronary, with $r = 0.331$ ($p < 0.001$) and $r = 0.303$ ($p = 0.003$). Increasing total annular calcium size score and left calcium size were the strongest predictors for moderate to severe PAR greater than 1 (AUC 0.711, $p < 0.001$, and AUC 0.710, respectively). For mild to severe PAR 1 or greater, c-statistic values were lower (AUC 0.58, 0.64, and 0.67 for noncoronary, left coronary, and total size, respectively).

CHARACTERIZATION. The majority of patients had left coronary (protruding 32.6%, adherent 8.7%, round 28.3%; and 30.4% no calcium) and noncoronary annulus calcium (protruding 34.8%, adherent 6.5%, round 19.6%; and 39.1% had no calcium) whereas right coronary calcium was absent in 70% (protruding 8.7%, adherent 3.3%, and round 17.4%).

PROTRUDING ANNULAR CALCIFICATION. The criterion “protruding annular calcification” (PAC) greater than 4 mm size was more often found in patients with moderate to severe PAR greater than 1 (66.6%) than in patients with PAR of 1 or less (38.3%; $p = 0.02$; Table 3). PAC greater than 4 mm at the left and noncoronary annulus was more often found with PAR of greater than 1, but not right coronary. Right coronary prevalence was low in both groups PAR of greater than 1 (4.7%) and PAR of less than 1 (8.2%). Adherent annular calcium greater than 4 mm size prevalence was similar in both groups (19% versus 23%, $p = 0.9$); with a trend to more patients among those with no or mild PAR. Similar trends were noted (Table 4) for patients with mild to severe PAR of greater than 1: there were more PAC greater than 4 mm, both per-patient based ($p = 0.002$) and for the left annulus ($p = 0.05$). There was no difference in adherent calcium greater than 4 mm prevalence in both groups.

Receiver-operating characteristic curve analysis showed $c = 0.709$ for PAC greater than 4 mm for prediction of moderate to severe PAR of greater than 1. For mild to severe PAR of 1 or greater, c-statistic values were lower ($c = 0.681$). Figure 2 shows a patient with PAC causing moderate PAR. Figure 3 shows adherent annular calcification.

Aortic Valve Leaflet Calcification Severity and Asymmetry

Leaflet calcification severity and asymmetry scores were not different in patients without or patients with mild and moderate to severe PAR of 1.5 or greater (8.01 versus 8.09, $p = 0.08$, and 1.47 versus 1.68, $p = 0.56$). Similar values were found if cutoff was PAR of 1 or greater. Receiver-operating characteristic curve analysis showed, with $c = 0.45$ to 54, no predictive value for either cutoff, PAR of 1.5 or greater and PAR of 1 or greater. Severity score by CTA and increasing PAR severity showed no correlation ($r = 0.07$).

Fig 1. Total annulus calcium size scores were correlated with increasing paravalvular aortic regurgitation (PAR) severity by transthoracic echocardiography (grade 0 to 2.5, y-axis; $r = 0.397$, $p < 0.001$).
Our study reveals novel insights into the pathogenesis of PAR after TAVI, supporting the hypothesis that specific quantitative CTA parameters are risk factors for moderate to severe PAR. Protruding annulus calcification greater than 4 mm, particularly at the left and non-coronary side, predicted relevant leaks. A similar trend was seen for PAR of 1 or greater, while being less significant. Even mild PAR has recently been shown to be associated with adverse outcome in terms of increased late mortality 2 years after TAVI with an increased hazard risk of 2.11 [20]. Interestingly, although adherent calcium was less common than protruding and round, there was a trend toward more adherent calcium if leak severity was less, suggesting that adherent calcium may have “sealing” effect between the aortic annulus and the metallic stent struts.

Further, increasing size of the annular calcium had a strong correlation and was predictive for PAR of greater than 1. Our results are supported by another investigation by Ewe and colleagues [14], suggesting that calcifications located at the aortic wall annulus, rather than commissural and leaflet calcium, are associated with PAR—of any severity—after TAVI for the balloon-expandable percutaneous heart valve device, in 63 patients who had PAR equal to or greater than 1 [14].

Furthermore, annular calcium had a markedly higher prevalence in left coronary and noncoronary rather than right coronary aortic wall and leaflet in our study. Possibly as a direct—or indirect—consequence, the left, noncoronary, and total annulus calcium size, but not the right, were predictors for PAR. One reason for less calcium on the right coronary annulus might be the strictly anterior and prone orientation of the right coronary annulus. Given the left posterior angulation of the ascending aorta, the right coronary side is less exposed to retrograde turbulences from aortic valve jet than the more posterior (left, or opposite) side of the annulus, as indicated by finite element models of pulsatile ascending aortic flow profiles [15]. Indeed, the highest mechanical stress of the aortic valve is measured in the flexion area of the leaflet, near the attachment of the aortic root. Also, sheer stress across the endothelium is higher at the left coronary side, due to turbulences from the left coronary ostium [16].

John and colleagues [17] reported a positive, but weak, correlation between total calcium leaflet severity at the device landing zone and the grade of PAR after deployment ( \( r = 0.33, p = 0.001 \)). They suggested that the calcium lesion location might be of greater importance [17]. Similarly, we noted a positive correlation of increasing annular calcium and PAR severity. On the contrary, leaflet calcium severity and asymmetry were neither correlated with nor predictive for PAR. This finding is explained by the mechanical effect of the valve deployment, during which the marginal leaflet calcium is pushed laterally toward the aortic wall during stent expansion. That results in a distal adhesion without affecting the PAR development, which occurs at the annulus level. Based on our results, we prove that annular calcification is more important for incomplete stent

### Table 3. Annular Calcium Differences Between Moderate to Severe Paravalvular Aortic Regurgitation and No or Mild Paravalvular Aortic Regurgitation

<table>
<thead>
<tr>
<th>Annular Calcification</th>
<th>Moderate/Severe (PAR &gt;1)</th>
<th>No/Mild (PAR &lt;1)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAC &gt;4 mm</td>
<td>14/21 (66.6%)</td>
<td>28/73 (38.3%)</td>
<td>0.02*</td>
</tr>
<tr>
<td></td>
<td>11/21</td>
<td>14/73</td>
<td>0.002*</td>
</tr>
<tr>
<td></td>
<td>10/21</td>
<td>14/73</td>
<td>0.018*</td>
</tr>
<tr>
<td></td>
<td>1/21</td>
<td>6/73</td>
<td>0.95</td>
</tr>
<tr>
<td>AAC &gt;4 mm</td>
<td>4/21 (19%)</td>
<td>17/73 (23%)</td>
<td>0.90</td>
</tr>
<tr>
<td></td>
<td>2/21</td>
<td>7/73</td>
<td>0.68</td>
</tr>
<tr>
<td></td>
<td>3/21</td>
<td>10/73</td>
<td>0.77</td>
</tr>
<tr>
<td></td>
<td>0/21</td>
<td>5/73</td>
<td>0.54</td>
</tr>
</tbody>
</table>

* Significant.

### Table 4. Annular Calcium Differences Between Mild to Severe Paravalvular Aortic Regurgitation and No or Trivial Paravalvular Aortic Regurgitation

<table>
<thead>
<tr>
<th>Annular Calcification</th>
<th>Mild to Severe (PAR ≥1)</th>
<th>No/Trivial (PAR &lt;1)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 64</td>
<td>n = 30</td>
<td></td>
</tr>
<tr>
<td>PAC &gt;4 mm</td>
<td>35/64 (54.7%)</td>
<td>6/30 (20%)</td>
<td>0.002*</td>
</tr>
<tr>
<td></td>
<td>21/64</td>
<td>2/30</td>
<td>0.05*</td>
</tr>
<tr>
<td></td>
<td>21/64</td>
<td>5/30</td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td>4/64</td>
<td>1/30</td>
<td>0.6</td>
</tr>
<tr>
<td>AAC &gt;4 mm</td>
<td>12/64 (18.8%)</td>
<td>6/30 (20%)</td>
<td>0.8</td>
</tr>
<tr>
<td></td>
<td>4/64</td>
<td>2/30</td>
<td>0.9</td>
</tr>
<tr>
<td></td>
<td>9/64</td>
<td>2/30</td>
<td>0.1</td>
</tr>
<tr>
<td></td>
<td>4/64</td>
<td>1/30</td>
<td>0.3</td>
</tr>
</tbody>
</table>

* Significant.
adaption and consequent development of PAR, but not leaflet calcium.

An advantage of our study is that, in contrast to previous studies [14, 17], we applied a more distinct echocardiographic (0.5 subscale) graduation of PAR severity. Beyond that, PAR severity was monitored over time at predefined follow-up intervals up to 2 years. Computed tomography also allows for accurate sizing of the aortic annulus from three-dimensional CTA datasets to select the most appropriate prosthesis size [18, 19].

Annulus eccentricity is supposed to contribute to PAR. However, this hypothesis is not supported by our results and goes in line with a previous study reporting annulus eccentricity as nonpredictive for moderate to severe leaks (c = 0.58) [19], whereas percutaneous heart valve undersizing was predictive. We observed a similar trend in our study, with higher absolute values of percutaneous heart valve undersizing in PAR of more than 1. Prosthetic valve malposition may also cause PAR. Therefore, relevant malpositioned valves were excluded.

Study Limitations
Both self-expanding devices (8.1%) and balloon-expandable percutaneous heart valve devices (91.1%) were included. Device-related postoperative complications for those devices may slightly vary [3]. Few patients showed PAR progression or regression whereas the vast majority remained stable, not permitting subanalysis. We did not adjust our results for percutaneous heart valve undersizing. We suppose that large annular calcium may be a contributing factor to relative undersizing of annulus measurement on TTE, in addition to technical differences (CT allows for a true three-dimensional measurement of the annulus, hence accounts for eccentricity). There was a tendency toward more undersizing in patients with PAR greater than 1.

In conclusion, protruding annulus calcification greater than 4 mm, particularly on the left coronary and non-coronary side, and an increasing calcium size, predicts moderate to severe PAR greater than 1. Adherent calcium has a protective, sealing effect between the annulus and the prosthetic valve. These measurements by CTA allow for estimation of a patient’s risk for PAR. In those patients, more intraprocedural postdilations with a balloon may be necessary [21]. These must be carefully balanced with risk of annulus rupture, particularly when applying “hard prep” (higher intraballoon pressure). A softer balloon (“soft prep” [low intraballoon pressure]) should be chosen in the presence of large calcifications to avoid annulus rupture. In case of borderline cases in terms of sizing, the larger balloon expandable valve size should be selected to prevent PAR, offering the advantage of soft preparation dilations.
References


