A revised methodology for aortic-valvar complex calcium quantification for transcatheter aortic valve implantation

Hasan Jilaihawi 1*, Raj R. Makkar 1, Mohammad Kashif 1, Kazuaki Okuyama 1, Tarun Chakravarty 1, Takahiro Shiota 1, Gerald Friede 1, Mamoo Nakamura 1, Niraj Doctor 1, Asim Rafique 1, Kentaro Shibayama 1, Hirotsugu Mihara 1, Alfredo Trento 1, Wen Cheng 1, John Friedman 1, Daniel Berman 1, and Gregory P. Fontana 2

1 Advanced Health Sciences Pavilion, Cedars-Sinai Heart Institute, 127 S. San Vicente Blvd, Third Floor, Suite A3600, Los Angeles, CA 90048, USA; and 2 Lenox Hill Heart and Vascular Institute of New York, New York, NY, USA

Received 28 February 2014; accepted after revision 20 July 2014; online publish-ahead-of-print 3 September 2014

Aims

We sought to optimize a method for quantification of the calcium in the aortic-valvar complex for the prediction of significant paravalvular leak (PVL) after transcatheter aortic valve implantation (TAVI).

Methods and results

All patients had severe symptomatic aortic stenosis and were treated with balloon-expandable TAVI (Sapien/Sapien-XT, Edwards Lifesciences LLC, Irvine, CA, USA). In order to correct for precise annular sizing, only patients with available contrast computed tomography (CT) data for measurements were included (n = 198). Paravalvular leak was quantified using peri-procedural transoesophageal echocardiography by Valve Academic Research Consortium-2 (VARC-2) criteria (grade ≥ moderate was considered significant). A detailed region-of-interest methodology separated quantification of calcium in each of the aortic leaflets to that in the left ventricular outflow tract (LVOT) and was used to predict PVL in receiver operator characteristic curve analyses. For non-contrast scans, the greatest discriminatory value for PVL was seen at the 450 Hounsfield Unit (HU) threshold for detection (volume ≥ 626 mm^3), whereas for contrast scans it was at 850 HU (≥ 235 mm^3). Left ventricular outflow tract calcium predicted PVL but only as a binary variable with no incremental value of quantification. In a multivariable binary logistic regression model, annulus area ≥ prosthesis area (OR 3.5, 95% CI 1.5–8.2, P = 0.005), contrast leaflet calcium volume (850-HU threshold) ≥ 235 mm^3 (OR 2.8, 95% CI 1.2–6.7, P = 0.023), and presence of LVOT calcium (OR 2.8, 95% CI 1.2–7.0, P = 0.022) were independent predictors for PVL ≥ moderate.

Conclusion

Both leaflet and LVOT calcium are significant predictors of PVL and exert an important synergistic influence on this complication, even in appropriately sized valves. With careful attention to thresholds for detection, clinically relevant leaflet calcium volumes can be identified with either non-contrast or contrast CT scans.

Keywords

TAVR • TAVI • Transcatheter aortic valve • Calcium score • Calcification

Introduction

Early attempts to standardize calcium quantification for heart disease were designed for coronary artery assessment and have changed little since the original description of coronary artery calcium quantification using ultrafast computed tomography (CT) by Agatston et al. and later applied to the aortic valve. Calcium in the aortic-valvar complex (AVC) is known to be predictive of the important and life-threatening complication of paravalvarular leak (PVL) after transcatheter aortic valve implantation (TAVI). These data have lacked standardization or have been reported in studies insufficiently powered to evaluate clinically significant PVL (Supplementary data online, * Corresponding author. Tel: +1 310 423 3977; Fax: +1 310 423 0106. E-mail: hasanjilaihawi@gmail.com

Published on behalf of the European Society of Cardiology. All rights reserved. © The Author 2014. For permissions please email: journals.permissions@oup.com.
Appendix Table S1). This heterogeneity has led to a limited understanding of relevant volumes of calcium that can be incorporated into practice. Moreover, although it has been increasingly appreciated that cross-sectional measurements of the aortic annulus using contrast CT offer the most accurate dimensions for TAVI sizing,\(^6,9\) the interaction of AVC calcium burden, and distribution with precisely measured annular dimensions remains poorly understood. Using both contrast and non-contrast CT data, we sought to revise methodologies for AVC quantification for the prediction of PVL in the context of cross-sectional aortic annular dimensions that—in line with the ethos of the Valve Academic Research Consortium (VARC)\(^10\)—might lead to a standardization of reporting and prediction of outcome.

**Methods**

**Patient population, assessment, and procedure**

All patients had severe symptomatic aortic stenosis and were treated in a single centre with balloon-expandable TAVR ( Edwards Sapien/Sapien XT, Edwards Lifesciences LLC, Irvine, CA, USA), performed under predominantly fluoroscopic guidance, as has been previously described.\(^11\) In order to correct reliably for precise annular sizing, only patients with available contrast CT data for annular dimension assessment were included in this study. Patients also had peri-procedural TOE imaging for procedural guidance and post TAVR evaluation of valvular function. TOE was performed primarily using the iE33 xmatrix echocardiography system (Philips Ultrasound, Philips Medical Systems, Bothell, WA, USA). Within the confines of available contrast cross-sectional CT data, patients were consecutive.

Sizing for TAVR was made at the operator’s discretion, using data from all available imaging modalities at the time of the procedure, with a reliance on traditional cut-offs for annular size by 2D-TOE measurement (D\(_{2D,TOE}\)) early in the series, and a later emphasis on cross-sectional measurements by CT or three-dimensional echocardiography,\(^8\) within the confines of only two available valve sizes during the study period. The study complies with the Declaration of Helsinki: a locally appointed Ethics Committee approved the research protocol and informed consent was obtained from all subjects.

**MSCT image acquisition and preliminary image analysis**

The CT specialist only performed the protocol electrocardiogram (ECG)-gated cardiac contrast study if the renal function was considered satisfactory, as is routine clinical practice. A multi-slice CT angiography ECG-gated study was performed pre-procedure with a Siemen’s Somatom Cardiac 64 scanner using collimation of 0.6 mm at a fixed pitch of 0.2 with an injection of 110 cc of iopromide 370. A dedicated protocol was formulated, with 120 kV and tube current modified according to the patient size. Adjusting for body habitus, a standard convolution kernel of B35f was applied. The gantry rotation time was 330 ms. Image acquisition was performed throughout the cardiac cycle. The ECG at the time of acquisition was reviewed before reconstruction to select out ectopy. Images were reconstructed with slice thickness of 0.7 mm at 0.4 mm intervals through the heart and aortic arch. Electrocardiogram adaptive scanning was employed with a higher dose in systole but a low overall radiation dose, achieving high-quality systolic scans in all patients.

Computed tomography DICOM data were analysed retrospectively for the patients treated before May 2011 and were performed prior to the TAVR procedure for patients treated in May 2011 onwards. Three-dimensional images were reconstructed using Insight software (Neoimagery Co., City of Industry, CA, USA). 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.\(^9\) This yielded a systolic phase at 16.9 ± 7.0%.

**Calcium quantification**

Leaflet calcium was quantified by a standard Agatston methodology for all available non-contrast scans, with a threshold for calcium detection set at 130 Hounsfield Units (HU). Leaflet calcium was also quantified using 3mensio Valves software for all available contrast and non-contrast scans. A region of interest for calcium quantification was made from the basal annular plane to the leaflet tips. This excluded both LVOT calcium (measured separately) and coronary calcium which was carefully excluded from the region of interest. Thresholds for leaflet calcium detection were set at multiple levels: for contrast scans, this was at 450, 650, 850, 1050, and 1250 HU and for non-contrast scans this was at 50, 130, 300, and 450 HU. The correlation coefficients between calcium volumetric data from contrast and non-contrast scans obtained at these thresholds were studied. We also used receiver operator characteristic (ROC) curves to study the predictive value for each of these thresholds for: \(>\text{mild (moderate) PV AR.}\)

The presence of LVOT calcium was further defined as any calcium more than trivial, contiguous with the basal annular plane and in contact with the luminal surface. There were further attempts to quantify LVOT calcium (Supplementary data online, Appendix data).

From repeated reconstructions for the subset of 10 randomly selected patients, intra-observer variability was 2.2 ± 6.9 mm\(^3\) for annulus area (paired sample correlation \(r = 0.99, P < 0.001\)), 17 ± 41 mm\(^3\) for leaflet calcium volume at the HU-450 threshold (paired sample correlation \(r > 0.99, P < 0.001\)), and 3 ± 10 mm\(^3\) for leaflet calcium volume at the HU-850 threshold (paired sample correlation \(r > 0.99, P < 0.001\)). \(6 ± 16 \text{ mm}^3\) for LVOT calcium volume at the HU-450 threshold (paired sample correlation \(r > 0.99, P < 0.001\)), and \(2 ± 3 \text{ mm}^3\) for LVOT calcium volume at the HU-850 threshold (paired sample correlation \(r > 0.99, P < 0.001\)).

Inter-observer variability was 14 ± 11 mm\(^3\) for annulus area (paired sample correlation \(r = 0.99, P < 0.001\)), 59 ± 119 mm\(^3\) for leaflet calcium volume at the HU-450 threshold (paired sample correlation \(r > 0.99, P < 0.001\)), and 3 ± 8 mm\(^3\) for leaflet calcium volume at the HU-850 threshold (paired sample correlation \(r > 0.99, P < 0.001\)), 14 ± 46 mm\(^3\) for LVOT calcium volume at the HU-450 threshold (paired sample correlation \(r > 0.99, P < 0.001\)), and 3 ± 8 mm\(^3\) for LVOT calcium volume at the HU-850 threshold (paired sample correlation \(r = 0.98, P < 0.001\)).

Calcium in left, right, and non-coronary cusps was quantified separately using the ‘Mercedes Benz’ tool (3mensio valves, Figure 1) for localization.
The threshold for this assessment was only at 450 HU for contrast and non-contrast scans, as this is the default threshold used by 3-menisio software.

**Post TAVR paravalvular leak**

Post TAVR PVL was assessed in line with VARC-2 criteria, with peri-procedural TOE examinations reviewed retrospectively. This was performed by one of the physician readers experienced in the assessment of TAVR echocardiograms, blinded to the peri-procedural TOE report, annular measurements, clinical, angiographic, and haemodynamic data. Reproducibility was excellent: for 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 ($P < 0.001$).

**Device positioning**

A three-chamber view on TEE was used to determine device positioning and, given that the anterior annulus often has echo drop-out and lacks clarity, positioning was defined according to the depth of the stent frame below the posterior annular margin, defined as the interface between sinus and aortic-mitral continuity.

**Statistical analysis**

Statistical analyses were made using SPSS software (PASW v18, SPSS Inc, Chicago, IL, USA) and MedCalc v12.7.0 (MedCalc, Ostend, Belgium). Normality of distributions for continuous variables was tested using the Shapiro–Wilks test and data analysed appropriately thereafter. The
Fisher exact test was used for categorical variables compared across independent groups. For normally distributed continuous variables compared across independent groups, an independent sampled t-test was employed. For non-normally distributed continuous variables compared across independent groups, a Mann–Whitney U-test was used. For paired continuous samples, a paired sampled t-test or Wilcoxon signed ranks test was used for normally and non-normally distributed data, respectively. To identify independent CT predictors of PVL ≥ moderate, a multivariable binary logistic model (using the ‘Enter’ method was employed); candidate predictors included parameters assessing annular sizing, leaflet, and LVOT calcium. Area under the receiver operator characteristic (AUC) curves were generated using post TAVR paravalvular AR ≥ moderate as the principal endpoint (state variable). Where there was a direct comparison of the discriminatory value of one measurement to another, we employed the method of DeLong et al. 12

Results

A total of 198 consecutive patients that had high quality contrast cardiac CT data (that enabled both calcium quantification and cross-sectional aortic annular measurements) were studied (Figure 2); 123 of these also had concurrent non-contrast cardiac CT scans (only contrast cardiac scans were performed in the centre’s early experience, with concurrent non-contrast scans systematically performed later in the series). Baseline and procedural characteristics are shown in Table 1. Mortality at 30 days was 5.1%.

Within the constraints of only two available prosthesis sizes during the treatment period (23 and 26 mm), prosthesis sizing was heavily influenced by cross-sectional CT measurements after May 2011 (‘CT-sizing era’: n = 119) and prior to this time it was exclusively by 2D TOE measurements, as was then conventional practice (‘pre-CT sizing era’: n = 79).

By VASC-2 criteria, a total of 31 patients (15.7%) had PVL of grade moderate or greater. This frequency was 20.2% in the pre-CT sizing era and 12.6% in the CT sizing era (P = 0.17). The frequency of patients with (aortic annular area > transcatheter heart valve, THV, area) was also studied and was 44.3% in the pre-CT sizing era and 35.3% in the CT sizing era (non-significant trend, P = 0.24).

Overall, 77/198 (38.9%) were undersized by CT (aortic annular area > THV area) and in those undersized by CT, PVL ≥ moderate occurred in 27.3 vs. 8.3% in those not undersized (aortic annular area ≤ THV area), P = 0.001. A number of CT sizing variables were related to PVL (Supplementary data online, Appendix Table S2), as has been previously demonstrated. 6 The annulus eccentricity index (major/minor dimension) was unrelated to PVL (P = 0.51). The annulus area/THV area was employed as the principal sizing parameter in the study as it is most widely used for balloon-expandable TAVR. 9

Device positioning and post-dilatation

There was no correlation between depth of implantation as a continuous variable and PV AR ≥ moderate (r = −0.096, P = 0.19). However, there was a trend to higher PVL ≥ moderate with high implants (depth of stent frame by above definition negative); 5/21 (23.8%) vs. 25/166 (15.1%), P = 0.34. Post-dilatation was performed infrequently, in 10/198 (5.1%) of patients overall and in 5/31 (16.1%) of those who ended the procedure with PVL ≥ moderate.

Calcium scoring

Traditional calcium scoring of the aortic valve leaflets, using a non-contrast CT with a 130-HU threshold for calcium detection (Agatston scoring using Insight software, Neoimagery Co., City of Industry, CA, USA), was possible in 123/198 cases (62.1%), who had non-contrast as well as contrast scans. In these non-contrast scans, 3-mensio was also used to quantify leaflet calcium at multiple thresholds for detection. Receiver operator characteristic curve analyses for PVL ≥ moderate were performed. Using 3-mensio, the greatest discriminatory value for PVL was numerically highest at the 450-HU threshold (AUC 0.84, 95% CI 0.73 − 0.94, P < 0.001; Supplementary data online, Appendix Table S3).

For leaflet calcium scoring using contrast CT scans, ROC curve analyses for PVL ≥ moderate were also performed at multiple thresholds for detection. The greatest discriminatory value for PVL...
Table 1  Baseline and procedural characteristics

<table>
<thead>
<tr>
<th>Clinical variables</th>
<th>(n = 198)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (IQR)</td>
<td>86 (81–90)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>99 (50.0)</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>66 (33.5)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>177 (89.8)</td>
</tr>
<tr>
<td>Prior PCI, n (%)</td>
<td>68 (34.5)</td>
</tr>
<tr>
<td>Prior CABG, n (%)</td>
<td>74 (37.4)</td>
</tr>
<tr>
<td>Prior BAV, n (%)</td>
<td>34 (17.3)</td>
</tr>
<tr>
<td>Prior stroke, n (%)</td>
<td>45 (22.8)</td>
</tr>
<tr>
<td>Baseline creatinine over 2 mg/dL (177 μmol/L), n (%)</td>
<td>14 (7.1)</td>
</tr>
<tr>
<td>Pulmonary disease, n (%)</td>
<td>105 (53.3)</td>
</tr>
<tr>
<td>Porcelain aorta, n (%)</td>
<td>8 (4.1)</td>
</tr>
<tr>
<td>Frailty, n (%)</td>
<td>47 (23.7)</td>
</tr>
<tr>
<td>STS score, median (IQR)</td>
<td>10.2 (8.3–12.1)</td>
</tr>
<tr>
<td>Log EuroSCORE, median (IQR)</td>
<td>25.6 (17.3–35.9)</td>
</tr>
</tbody>
</table>

Echocardiographic variables

| Peak AV velocity (m/s), median (IQR) | 4.3 (4–4.8) |
| Mean AV gradient (mmHg), median (IQR) | 45 (41–55) |
| EF, median (IQR)                     | 63.5 (54–70) |
| MR grade ≥ moderate, n (%)          | 30 (16.0)   |
| AR grade ≥ moderate, n (%)          | 23 (11.6)   |

CT variables

| Calcium volume from contrast scan (HU-850 threshold, mm³), median (IQR) | 146 (58–268) |
| Calcium quantification from non-contrast scan (Agatston methodology, AU), median (IQR) | 3559 (2465–4953) |

Procedural variables

| Transfemoral approach, n (%) | 173 (87.4) |
| Transapical approach, n (%)  | 25 (12.6)  |
| Valve size: 23 mm, n (%)     | 117 (59.1) |
| Valve size: 26 mm, n (%)     | 81 (40.9)  |
| Edwards Sapien, n (%)        | 164 (82.8) |
| Sapien XT, n (%)             | 34 (17.2)  |

Table 2  Calcium leaflet quantification cut-offs for PVL ≥ moderate depending on methodology and threshold for calcium detection

<table>
<thead>
<tr>
<th>Methodology</th>
<th>Cut-off</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume: 3-mensio contrast (850-HU)</td>
<td>≥235 mm³</td>
</tr>
<tr>
<td>Volume: 3-mensio non-contrast (130-HU)</td>
<td>≥2506 mm³</td>
</tr>
<tr>
<td>Volume: 3-mensio non-contrast (450-HU)</td>
<td>≥626 mm³</td>
</tr>
<tr>
<td>Agatston score (non-contrast 130-HU)</td>
<td>≥4528 AU</td>
</tr>
</tbody>
</table>

The numerical cut-off for calcium quantification with the highest sum of sensitivity and specificity for PVL for contrast scan leaflet calcium volume with the 850-HU threshold was ≥235 (sensitivity 61%, specificity 75%) and for non-contrast scan leaflet volume with the 130-HU threshold, it was ≥2506 (sensitivity 71%, specificity 86%). For non-contrast scans with a 450-HU threshold, the cut-off was ≥626 with a sensitivity of 81% and a specificity of 77%. The traditional Agatston score had a predictive value for PVL with AUC 0.74, 95% CI 0.63–0.86, P = 0.001. For the traditional Agatston score, the cut-off with the highest sum of sensitivity and specificity for PVL prediction was ≥4528 Agatston units with a sensitivity of 68% and a specificity of 73%. These cut-offs are summarized in Table 2. Contrast scan 850-HU threshold calcium volumes correlated better with non-contrast 450-HU threshold data (r = 0.87, P < 0.001) than non-contrast 130-HU data (r = 0.78, P < 0.001) and traditional Agatston (HU-130 threshold) scores (r = 0.70, P < 0.001). Differences in individual leaflet calcium burden were observed but asymmetry of distribution was associated with higher overall volumes and not independently predictive of PVL (Supplementary data online, Appendix data).

To assess the relative contribution of sizing and leaflet calcium burden before and after the inception of CT-guided annular sizing, ROC curves for annulus/THV area and contrast scan leaflet volume appeared to peak at the 850-HU threshold (AUC 0.84, 95% CI 0.70–0.94, P < 0.001; Supplementary data online, Appendix Table S3). A head-to-head comparison of PVL prediction using conventional Agatston scoring, the 450-HU threshold for non-contrast data using 3-mensio and the 850-HU threshold for contrast data using 3-mensio in patients with both contrast and non-contrast scans showed no statistical difference in the predictive value for PVL (Figure 3).

The higher threshold non-contrast scan at detection threshold of 850-HU had numerically the highest predictive value for PVL, although its superiority was of borderline statistical significance compared with the traditional Agatston scoring.
calcium volume (HU-850) were compared. In the pre-CT sizing era, annulus/THV area had a numerically greater predictive value than calcium volume (AUC 0.81, 95% CI 0.71–0.89 vs. AUC 0.64, 95% CI 0.52–0.74, \(P\) for difference in curves = 0.07). In contrast, in the CT-guided sizing era, calcium volume had a numerically greater predictive value than the annulus/THV area (AUC 0.80, 95% CI 0.71–0.86 vs. AUC 0.58, 95% CI 0.49–0.67, \(P\) for difference in curves = 0.02).

**Left ventricular outflow tract calcium**

Left ventricular outflow tract calcium was present in over a third of patients (\(n = 79/198, 39.9\%\)). Its distribution was predominantly posterior (i.e. in the region of the aortic-mitral continuity). Presence of LVOT calcium was highly predictive of PVL (OR 5.23, 95% CI 1.53–17.9, \(P = 0.008\)). Multiple techniques to quantify LVOT calcium did not improve the discrimination of PVL beyond the binary presence/absence of calcium at the annular level (Supplementary data online, Appendix data).

There was a weak correlation between calcium volume and presence of LVOT calcium (\(r = 0.37, P < 0.001\)). However, they occurred independently; in those with ‘high’ leaflet calcium (volume \(\geq 235\) mm\(^3\) at the 850 HU threshold for a contrast scan), LVOT calcium was present in 63.9% and in those with leaflet calcium below the threshold the incidence was approximately halved at 29.2%. Overall, 97 patients (49.0%) had no LVOT calcium and low leaflet calcium, 22 (11.0%) high leaflet calcium and no LVOT calcium, 40 (20.2%) LVOT calcium, but low leaflet calcium, and 29 (14.3%) both high leaflet calcium and LVOT calcium.

**Multivariable model for the prediction of paravalvular leak**

Candidate CT predictors included in the multivariable model were (annulus area \(\geq\) THV area), contrast leaflet calcium volume (850-HU threshold) \(\geq 235\), and presence of LVOT calcium. All were found to be independently predictive of PVL (Table 3). A study of the interaction of sizing, leaflet, and LVOT calcium found the co-existence of severe leaflet calcification (contrast scan 850-HU threshold \(\geq 235\)) and any LVOT calcification to pose the greatest risk of PVL (Figure 4). This combination occurred in 19.7% of patients and overall PVL \(\geq\) moderate was seen in 35.9% of these. Even if TAVI sizing was appropriate by cross-sectional criteria (annulus area \(<\) THV area), the incidence of PVL \(\geq\) moderate remained high (23.5%) if both LVOT and severe leaflet calcification were present. In the absence of both prosthesis undersizing and the leaflet/LVOT combination of calcium, significant PVL was extremely low (3.1%) (Figure 4).

**The impact of calcium on appropriately sized and positioned TAVR**

Of those that had appropriately sized valves by present guidelines (prosthesis area > annulus area) and did not have high device implantations (total \(n = 97\)), the contrast HU-850 leaflet calcium volume threshold \(\geq 235\) mm\(^3\) clearly stratified PV AR (\(P = 0.008\)); those with a high leaflet calcium volume by this methodology of quantification had 47.6% with no/trivial PV AR, 38.1% with mild PVAR and 14.3% with moderate PV AR vs. 76.3% with no/trivial PV AR, 19.7% with mild PV AR and 3.9% with moderate PV AR in those with a low leaflet calcium volume.

**Discussion**

The present study demonstrates that the ability of calcium quantification to predict PVL after balloon expandable TAVI is fundamentally determined by the thresholds set to detect calcium. For both contrast and non-contrast scans, these thresholds were high, suggesting that it is only the most dense (and therefore bright) calcium that appears to influence PVL, and also that the discriminatory value for PVAR can be enhanced by removing ‘noise’ arising at lower thresholds for detection. With these parameters clearly defined, contrast and non-contrast calcium quantification data are highly correlated, albeit with very different cut-offs for values of clinical relevance. Although non-contrast data with a HU-450 threshold are preferred, contrast data with an HU-850 threshold offer a similarly high predictive value for PVAR that was equivalent to, and possibly slightly better than the traditional Agatston score (130-HU threshold) from a non-contrast scan (Figure 3). The high contrast threshold of 850-HU is similar to the empiric threshold employed in a smaller study by Ewe et al.\(^a\) that also looked at PVL after balloon expandable TAVI (Supplementary data online, Appendix Table S1) and was higher than the 450-HU employed by Schultz et al.\(^5\).

**The interaction of device sizing, leaflet, and left ventricular outflow tract (or ‘annular’) calcification**

Leaflet calcium burden, presence of LVOT calcium, and degree of device oversizing relative to cross-sectional annular dimensions were seen to be independently predictive of PVL and demonstrated a synergistic interaction (Figure 4). However, even in the presence of device undersizing, over 90% of patients did not experience PVL if

---

**Table 3 Multivariable analysis of computed tomography candidate predictors of paravalvular leak.**

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Univariate OR (95% CI)</th>
<th>(P)-value</th>
<th>Multivariable OR (95% CI)</th>
<th>(P)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any LVOT calcium</td>
<td>3.9 (1.7–8.9)</td>
<td>0.001</td>
<td>2.8 (1.2–7.0)</td>
<td>0.022</td>
</tr>
<tr>
<td>Leaflet calcium volume (\geq 235) mm(^3)</td>
<td>4.7 (2.1–10.5)</td>
<td>&lt; 0.001</td>
<td>2.8 (1.2–6.7)</td>
<td>0.023</td>
</tr>
<tr>
<td>Annulus area (&gt;) THV area</td>
<td>4.2 (1.8–9.4)</td>
<td>0.001</td>
<td>3.5 (1.5–8.2)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

\(^a\)Contrast scan, HU-850 threshold for calcium detection.
neither LVOT calcium or high leaflet calcium burden were present (Figure 4), suggesting that either a leaflet-facilitated or a supra-annular seal (perhaps at the commissural level) can be achieved. In support of this, Figure 5 illustrates an example of a patient without excessive leaflet calcification in whom an undersized supra-valvular implant was associated with no PVL.

Cross-sectional imaging has become the gold standard in the assessment of aortic annular dimension for TAVR sizing. To date only Schultz et al. examined the interaction of device oversizing by cross-sectional CT and quantification of AVC calcium burden, in a study employing the Medtronic Corevalve device (MCV, Medtronic Inc., Minneapolis, MN, USA). The study demonstrated a much greater predictive value for leaflet calcium burden than device oversizing. Similarly, other studies have demonstrated a poor discriminatory value of cross-sectional sizing parameters for PVL with the MCV device in contradistinction, one of the latter studies concurrently showed a strong predictive value of cross-sectional CT sizing with the Sapien device.

Greater adherence to optimal sizing will inevitably diminish the contribution of sizing to PVL cases seen and perhaps explains the disparity observed between devices. In line with this, the present study, in the era of cross-sectional CT-guided sizing, with greater adherence to appropriate device sizing, showed a much greater predictive value of leaflet calcium burden for PVL than sizing, in contrast to the pre-CT sizing era, when sizing was much more predictive of PVL. Our findings suggest AVC calcification as a mechanism for PVL will be of ongoing critical importance for both balloon-expandable and self-expanding TAVR devices. Aortic-valvar complex calcification will demand evaluation of new device strategies such as the additional fabric cuff attached to the ventricular aspect of the Sapien-3 device. With the emergence of next-generation valves with several distinct capabilities including additional PVL seal, such as Sapien-3 and...
retrievability, such as the Portico and next generation Medtronic valves, extreme leaflet calcium may favour the former rather than the latter, but this will require prospective evaluation.

Importantly, a greater degree of device oversizing did not counteract the relevance of leaflet and LVOT calcium to PVL (Figure 4). Although the present study was insufficiently powered to assess annular rupture, a recent multi-centric registry demonstrated both >20% annular over-sizing by area and LVOT calcium to be independent predictors of this complication.17 Indeed, it is of concern that, although this 20% upper limit threshold oversizing by annular area is considered acceptable for balloon-expandable TAVI, we have observed root injury in the presence of extreme AVC calcification with much more conservative sizing with a balloon-expandable design (Supplementary data online, Appendix Figure S2).

Study limitations
A quantification of calcium according to anatomic distribution, particularly commissural calcium, was not studied; this has been shown to be important in some3,4 but not other7 studies. Only a balloon-expandable device was evaluated here and the clinically significant thresholds of calcium burden may well be different for self-expanding devices. The study was insufficiently powered to assess relevant complications other than PVL, including device embolization and annular rupture as well as the frequency of post-dilatation. The latter could have improved some cases of PVL, albeit with a potential increased risk of rupture.7 Given the moderate predictive value of AVC for PVL, it should be considered marker of occurrence of PVL but patients should not be excluded from TAVI based on these criteria alone.

The standardization of and objectivity in assessment of TAVR outcomes
A particular strength in the present study was the independent assessment of PVL by echocardiography specialists according to the VARC-2 criteria.10 This was performed in complete isolation to and in blinded fashion to the CT assessment and vice versa. This objective methodology has been reported in only one other calcium quantification study looking at TAVI outcomes and is important given subjectivity of PVL assessment.7 Quantification offers the ideal in terms of objective assessment and—although not yet reliable with the intra-procedural assessment of PVL—it is feasible for calcium quantification with a standardized methodology that the present study sought to establish. An illustration of the importance of these concepts of objectivity and standardization is that, in spite of the wealth of data supporting the importance of AVC calcium to PVL, the German registry recently showed no relationship of site-reported semi-quantitative (mild/moderate/severe) aortic leaflet calcium severity to site-reported PVL severity despite evaluating 1365 patients.18

Figure 5: Impact of leaflet calcium on PVL in (A) a grossly undersized TAVI with a 23 mm Sapien and (B) a reasonably sized TAVI with a 26 mm Sapien. (i) Cross-sectional CT dimensions of the aortic annulus are shown. (ii–iii) Immediate post-implantation TOE is shown. Despite gross undersizing and implantation above the aortic annulus, case A shows only trivial PVL. Despite more appropriate sizing and a well-positioned prosthesis, case B shows moderate PVL. A visual CT calcium assessment using (iv) maximal intensity projection (MIP) and (v) volume rendering (VR) shows moderate leaflet calcium with case A, and severe leaflet calcification with case B, with additional LVOT calcium below the LCC (B; iv). These cases support the hypothesis that a seal can also be achieved higher than the aortic annulus, at the commissural level, and that this may be further mitigated by the degree of leaflet calcification.
Conclusion

Both high leaflet calcium burden and LVOT calcium are significant independent predictors of PVL after balloon expandable TAVI and— with careful attention to thresholds for detection—clinically relevant leaflet calcium volumes can be precisely delineated with either noncontrast or contrast CT scans. Asymmetry of leaflet calcium distribution was predictive of PVL but only through its association with a high calcium leaflet burden. Patients exceeding the identified numerical cut-offs for leaflet calcium, particularly when seen in combination with LVOT calcium, present an important technical risk to TAVI that should be incorporated into the Heart Team evaluation and may benefit from innovative technologies to mitigate PVL.

Supplementary data

Supplementary data are available at European Heart Journal – Cardiovascular Imaging online.

Conflict of interest: None declared.

References