Non-calcific aortic tissue quantified from computed tomography angiography improves diagnosis and prognostication of patients referred for transcatheter aortic valve implantation

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Aims

We aimed to investigate the role of aortic valve tissue composition from quantitative cardiac computed tomography angiography (CTA) in patients with severe aortic stenosis (AS) for the differentiation of disease subtypes and prognostication after transcatheter aortic valve implantation (TAVI).

Methods and results

Our study included 447 consecutive AS patients from six high-volume centres reporting to a prospective nationwide registry of TAVI procedures (POL-TAVI), who underwent cardiac CTA before TAVI, and 224 matched controls with normal aortic valves. Components of aortic valve tissue were identified using semi-automated software as calcific and non-calcific. Volumes of each tissue component and composition [(tissue component volume/total tissue volume) × 100%] were quantified. Relationship of aortic valve composition with clinical outcomes post-TAVI was evaluated using Valve Academic Research Consortium (VARC)-2 definitions.

High-gradient (HG) AS patients had significantly higher aortic tissue volume compared to low-flow low-gradient (LFLG)-AS (1672.7 vs. 1395.3 mm³, $P < 0.001$) as well as controls (509.9 mm³, $P < 0.001$), but increased non-calcific tissue was observed in LFLG compared to HG patients (1063.6 vs. 860.2 mm³, $P < 0.001$). Predictive value of aortic valve calcium score [area under the curve (AUC) 0.989, 95% confidence interval (CI): 0.981–0.996] for severe AS was improved after addition of non-calcific tissue volume (AUC 0.995, 95% CI: 0.991–0.999, $P = 0.011$). In the multivariable analysis of clinical and quantitative computed tomography parameters of aortic valve tissue, non-calcific tissue volume [odds ratio (OR) 5.2, 95% CI 1.8–15.4, $P = 0.003$] and history of stroke (OR 2.6, 95% CI 1.1–6.5, $P = 0.037$) were independent predictors of 30-day major adverse cardiovascular event (MACE).

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Conclusion Quantitative CTA assessment of aortic valve tissue volume and composition can improve detection of severe AS, differentiation between HG and LFLG-AS in patients referred for TAVI as well as prediction of 30-day MACEs post-TAVI, over the current clinical standard.

Keywords aortic stenosis • transcatheter aortic valve implantation • computed tomography angiography

Introduction

Calcific aortic stenosis (AS) with high transvalvular gradient results from the progression of aortic valve calcification, restrictive opening of thickened valve leaflets and eventual obstruction of flow across the aortic valve.¹ Among patients with low-flow low-gradient (LFLG)-AS, restricted leaflet opening is considered to result from reduced stroke volume due to increased left ventricular stiffness.² Animal and histopathological studies have shown the association of fibrotic changes and progression of restricted valve leaflet opening in calcific AS. Differences in patterns of fibrocalcific abnormalities based on sex and aortic valve morphology have also been reported.^{3–5} However, whether tissue composition of the aortic valve is abnormal in LFLG-AS, has not yet been investigated.

Recent studies have demonstrated the role of calcium in the overall prognosis of post-transcatheter aortic valve implantation (TAVI) patients. Increased aortic valve calcium has been associated with paravalvular regurgitation, higher frequency of post-dilatation, and adverse clinical events following TAVI.^{6–8} Yet, the impact of non-calcific leaflet thickening on post-TAVI outcomes has not been characterized.^{9–11} Electrocardiogram-gated non-contrast cardiac computed tomography (CT) has been used for quantification of aortic valve calcium and assessment of AS severity in individuals in whom echocardiography is inconclusive.^{6,12} However, CT angiography (CTA) performed for procedural planning of TAVI can be used for a more complete characterization of aortic valve tissue beyond calcium assessment. Semi-automated quantitative techniques are now often used for plaque characterization using CTA.^{13,14} We hypothesized that CTA-derived quantitative characterization of aortic valve tissue composition would further differentiate patients with high-gradient (HG)-AS from patients with LFLG-AS and may provide prognostic information with respect to post-TAVI outcomes.

The objective of this study, therefore, was to examine aortic valve tissue composition in HG-AS and LFLG-AS in patients undergoing routine planning cardiac CTA prior to TAVI and to evaluate the significance of CTA-based tissue characteristics on post-TAVI outcomes.

Methods

Study design

A total of 609 consecutive TAVI procedures were reported to the prospective nationwide POL-TAVI registry from January 2018 to December 2018 by six participating high-volume centres.¹⁵ Inclusion criteria for the study were: (i) performance of pre-procedural planning CTA at the participating centre; (ii) TAVI for severe calcific stenosis of the native aortic valve. After the exclusion of 26 patients without available pre-procedural CTA scans, 35 patients with CTA scans performed off-site and 18 patients with non-diagnostic CTA scans, there were 530 patients with

images of good quality and uniform contrast opacification in the aortic root. Subsequently, 19 patients treated for pure aortic regurgitation, 12 patients with rheumatic valve disease, 22 patients receiving valve-in-valve TAVI, as well as 6 dialysis patients were excluded. Among 471 eligible patients, 24 were excluded due to missing data and the final cohort included 447 patients (*Figure 1*). Patients were matched using gender, age, body mass index, and year of CT scan with 224 control patients, who underwent a CTA scan for assessment of chest pain at the Medical University of Warsaw.

Scan protocol and image reconstruction

Pre-interventional planning CTA scans were performed on a variety of different scanner platforms (*Supplementary data online, Table S1*) using tube voltage of 100–120 kV and tube current adjusted to patients' size. The bolus-tracking technique was used, and the acquisition was triggered when the attenuation of the region of interest placed in the ascending thoracic aorta reached the threshold of 180–200 HU. During the image acquisition, 80–100 mL of iodinated contrast was injected at a rate of 3.5–5 mL/s, followed by a 30–50 mL saline chaser. Image data were reconstructed in diastole (70–80% of the R–R interval) using a soft kernel, slice thickness of 0.6 mm and an increment of 0.4 mm. Three centres (Medical University of Gdansk, Gdansk; Medical University of Lodz, Lodz; and Medical University of Silesia, Katowice; all Poland) performed concurrent non-contrast CT scans gated from 70% to 80% of the R–R interval with a tube voltage of 120 kV for CT aortic valve calcium scoring. At the discretion of the attending clinician, β -blockade could be administered to achieve a resting heart rate of ≤ 65 beats per minute.

CT image analysis

Quantitative analysis of aortic valve composition was based on pre-interventional planning CTA images using semi-automated software (Autoplaque version 2.5, Cedars-Sinai Medical Center, Los Angeles, CA, USA) and a standard mediastinal window (width: 400 HU; level 40 HU). First, region of interest was defined between the lower coronary ostium and the virtual basal ring formed by the hinge points of each aortic valve cusp (*Figure 2A and B*) using multiplanar reconstructions. Then, serial multiplanar reformatted images orthogonal to the longitudinal axis of the ascending aorta were rendered to obtain cross-sectional images of the respective region with contouring—comprising of 15–20 adjustable points (*Figure 2C*).¹⁶ Finally, tissue components were identified using HU thresholds as calcific (>650 HU) and non-calcific (-30 to 350 HU) tissues and adjusted when needed at the discretion of an expert reader (*Figure 2D–F*).¹⁷ Volumes of respective tissue components, as well as tissue composition expressed as % [(tissue component volume/total tissue volume) $\times 100\%$], were calculated.¹⁸ Total tissue volume was the sum of calcific and non-calcific tissue volumes. The processing time for aortic valve ranged between 3 and 6 min.

Aortic valve calcium score was calculated using a standard Agatston methodology for all available non-contrast CT scans, with a threshold for calcium detection set at 130 HU and 3-mm slice thickness. Analysis was performed offline on dedicated workstations with validated software (Vitrea Software; Vital Images, Inc., Minnetonka, MN, USA).

All tomographic analyses were performed at the Cedars-Sinai Medical Center core laboratory by an expert reader (K.G.) blinded to clinical data.

Transcatheter aortic valve implantation

Adjudication of AS severity for TAVI eligibility was performed by a team encompassing an experienced echocardiographer, two cardiac interventionalists, and a radiologist. Patients with symptomatic severe AS (aortic valve area $< 1 \text{ cm}^2$, aortic valve area indexed to body surface area $< 0.6 \text{ cm}^2$) were classified as HG-AS with mean transvalvular pressure gradient $\geq 40 \text{ mmHg}$ or LFLG-AS with mean gradient $< 40 \text{ mmHg}$ and stroke volume index $< 35 \text{ mL/m}^2$. Patients with LFLG-AS were further divided by their left ventricular ejection fraction (LVEF) into low-LVEF (LVEF $< 50\%$) and preserved-LVEF (LVEF $\geq 50\%$). Among patients with low LVEF, LFLG-AS was distinguished from pseudo-AS with previously described criteria using transthoracic echocardiography, dobutamine stress echocardiography and cardiac CTA.¹²

Clinical endpoints

The primary outcome was a major adverse cardiovascular event (MACE) within 30 days following the procedure that included cardiovascular death, all-stroke, and myocardial infarction. All clinical events were evaluated in accordance with Valve Academic Research Consortium

(VARC)-2 criteria.¹⁹ Any death attributable to a proximate cardiac cause or death of an unknown cause was classified as cardiac death.

Statistical analysis

Data were tested for normality using Shapiro–Wilk test. Continuous data are expressed as mean (standard deviation) or median (interquartile range, IQR) dependent on the distribution and compared using the Student's *t*-test or non-parametric Mann–Whitney *U*-test as appropriate. Categorical variables are presented as absolute numbers (percentage) and were compared using a χ^2 test. Control patients were matched with the AS group in a 1:2 manner utilizing propensity score and a method of the nearest neighbour without replacement using gender, age, body mass index, and year of CT scan.²⁰ Discriminatory performance of different aortic valve tissue composition parameters was determined by the C-statistic, and compared using the method of DeLong et al.²¹ Receiver operating characteristic (ROC) curves were generated for different aortic calcium parameters alone and their combinations with non-calcific tissue. Optimal cut-offs for tissue parameters were identified by using the Youden index. Net reclassification improvement was calculated using the method described by Pencina et al.²² The correlation between two continuous variables was measured with the bivariate Pearson correlation. Multivariable logistic regression analysis was performed to evaluate the association of aortic valve composition with 30-day MACE and adjusted

Figure 2 Workflow for analysis of aortic valve tissue composition. First, region of interest is set between the lower coronary ostium and the virtual basal ring formed by the hinge points of each aortic valve cusp (A and B) and its contours are manually adjusted if necessary (C). Tissue components are identified using HU thresholds as calcific (>650 HU; yellow) or non-calcific (-30 to 350 HU; red) tissues (D and E); and aortic valve is reconstructed in three-dimensional model (F).

for the significant risk factors established in prior studies.^{23,24} Following clinical predictors were entered into backward stepwise multivariable logistic regression analysis: age, gender, diabetes mellitus, glomerular filtration rate, history of myocardial, history of stroke, LVEF, and non-femoral access site. Inter-observer variability was measured in a sample of 50 random AS patients using an interclass correlation coefficient (ICC) and Bland–Altman plots with mean bias and limits of agreement. Log-transformed values for aortic valve tissue indices were used in the statistical analyses. All probability values were two-tailed, and a *P*-value of <0.05 was considered statistically significant. Data were processed using the SPSS software, version 23 (IBM SPSS Statistics, New York, USA).

Results

The study population included 447 patients, who underwent TAVI for severe AS. Mean age was 79.3 ± 7.1 years, 211 (47.3%) of patients were males and median Logistic EuroSCORE was 7.87 (IQR 4.77–15.8).²⁵ All patients were treated with second-generation transcatheter heart valves and 362 (81.0%) of patients received self-expandable valves. LFLG-AS was diagnosed in 119 (26.6%) patients: 47 (10.5%) had low and 72 (16.1%) had preserved LVEF. Detailed baseline and procedural characteristics are shown in Table 1. For the 224 control patients without known aortic valve disease, who underwent CTA for assessment of chest pain, mean age was 79.1 ± 6.8 and 107 (47.8%) were males.

Aortic valve composition in high-gradient vs. low-flow low-gradient AS

HG-AS patients had significantly higher aortic tissue volume compared to LFLG-AS (1672.7, IQR 1262.9–2161.5 vs. 1395.3, IQR 1062.2–1796 mm³, *P* < 0.001; Figure 3A) patients. Volume of calcific tissue was higher in HG-AS than LFLG-AS (724.2, IQR 434.9–1165.2 vs. 328.6, IQR 143.2–619.3 mm³, *P* < 0.001), as opposed to the volume of the non-calcific that was lower in HG-AS patients compared to LFLG-AS (860.2, IQR 684.9–1067.6 vs. 1063.6, IQR 789.1–1295.6 mm³, *P* < 0.001). Tissue composition was characterized by increased calcific component in patients with HG-AS compared to LFLG-AS (45.1% vs. 26.1%, *P* < 0.001). Proportion of the valve that was comprised of non-calcific tissue was, however, higher in LFLG-AS than HG-AS (73.9% vs. 54.9% *P* < 0.001).

Sensitivity analysis comparing the composition of aortic valve between LFLG-AS patients with low and preserved LVEF showed no differences in total aortic tissue volume (1395.3, IQR 1160.1–2023.0 vs. 1390.0, IQR 1035.8–1746.3 mm³, *P* = 0.430). Calcific tissue volume was lower in LFLG-AS patients with preserved LVEF than low LVEF (280.1, IQR 136.9–476.1 vs. 467.2, IQR 186.5–791.4 mm³, *P* = 0.030); however, volumes of non-calcific tissue did not differ between two LFLG-AS groups (1092.1, IQR 782.1–1336.6 vs. 981.3, IQR 814.0–1210.5 mm³, *P* = 0.624). Tissue composition was characterized by increased calcific component in patients with low as compared to preserved LVEF (30.3% vs. 23.3%, *P* = 0.024; Figure 3B).

Concurrent non-contrast CT was available in 254 (56.7%) of AS and 224 (100%) control patients. Aortic valve calcium score was

Table 1 Baseline clinical, imaging, and procedural characteristics

	High-gradient (N = 328)	Low-gradient (N = 119)	P-value
Baseline characteristics			
Age, years	79.8 ± 6.9	78.1 ± 7.6	0.032
Men	145 (44.2)	66 (55.5)	0.035
Body mass index	27.8 ± 4.8	26.9 ± 4.8	0.142
Logistic EuroSCORE	8.44 (5.45–17.50)	7.10 (4.2–15.46)	0.352
Hypertension	275 (83.8)	105 (88.2)	0.250
Diabetes mellitus	120 (36.6)	45 (37.8)	0.812
Hyperlipidaemia	279 (85.1)	103 (86.5)	0.692
Chronic obstructive pulmonary disease	99 (30.2)	29 (24.4)	0.229
Peripheral artery disease	47 (14.3)	21 (17.6)	0.388
Atrial fibrillation	124 (37.8)	49 (41.2)	0.518
History of myocardial infarction	83 (25.3)	41 (34.5)	0.056
Prior percutaneous coronary intervention	107 (32.6)	38 (31.9)	0.890
Prior coronary artery bypass grafting	50 (15.2)	34 (28.6)	0.001
History of stroke	46 (14.0)	14 (11.8)	0.384
Glomerular filtration rate (mL/min/1.73 m ²)	55 (42–69)	56 (45–74)	0.337
Echocardiographic data			
Ejection fraction (%)	60 (55–62)	54 (40–60)	<0.001
Aortic valve area (mm ²)	0.67 (0.55–0.78)	0.80 (0.65–0.90)	<0.001
Mean aortic gradient (mmHg)	50 (44–59)	33 (27–37)	<0.001
Maximal aortic gradient (mmHg)	84 (73–98)	55 (49–64)	<0.001
Peak jet velocity (m/s)	4.62 ± 0.57	3.68 ± 0.49	<0.001
Tomographic data			
Annulus mean diameter (mm)	24.6 (22.9–26.8)	25.0 (22.4–27.5)	0.888
Annulus perimeter (mm)	79 (74–86)	81 (72–89)	0.748
Annulus area (mm ²)	466 (401–550)	487 (383–592)	0.675
Aortic valve calcium score (AU)	3224 (2284–4335)	2001 (1132–3354)	<0.001
Procedural data			
Bicuspid valve	32 (9.7)	8 (6.7)	0.320
Self-expandable valve	267 (81.4)	95 (79.8)	0.708
Transfemoral access site	298 (90.9)	107 (89.9)	0.764
Post-dilatation	52 (15.9)	18 (15.1)	0.852

Values are presented as n (%), mean ± SD or median (interquartile range).

Figure 3 Comparison of (A) respective tissue volumes and (B) tissue composition between high-gradient aortic stenosis, low-flow low-gradient (LFLG) aortic stenosis and control groups.

Table 2 Predicting severe aortic stenosis using different aortic valve tissue indices

Aortic tissue parameter	AUC (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	P-value*
Aortic valve calcium score	0.989 (0.981–0.996)	99% (97–100%)	93% (89–96%)	
Total tissue volume	0.993 (0.988–0.998)	98% (97–99%)	95% (91–97%)	0.009
Calcific tissue volume	0.986 (0.977–0.995)	98% (96–99%)	92% (88–95%)	0.076
Non-calcific tissue volume	0.914 (0.893–0.935)	79% (75–83%)	89% (85–93%)	<0.001

AUC, area under the curve; CI, confidence interval.

*P-value to compare AUC between reference aortic valve calcium score and different aortic valve tissue parameters derived from computed tomography angiography.

significantly higher for HG-AS than LFLG-AS (3224, IQR 2284–4335 vs. 2001, IQR 1132–3354 AU, $P < 0.001$) patients. There was very strong correlation of aortic valve calcium score with calcific tissue volume ($r = 0.899$, $P < 0.001$), moderate correlation with non-calcific tissue volume ($r = 0.616$, $P < 0.001$), and no correlation with low-attenuating tissue volume ($r = 0.071$, $P = 0.123$). Figure 4 depicts representative examples of aortic valves for HG-AS, LFLG-AS and control patients captured in non-contrast CT as well as CTA.

Accuracy of quantitative tissue parameters for detection of severe AS

Table 2 displays accuracy of different aortic tissue parameters for predicting severe AS. Total tissue volume quantified from CTA presented the highest predictivity towards severe AS with an AUC of 0.993, while the AUC for non-calcific aortic tissue volume alone was 0.914. Addition of non-calcific tissue volume to calcium parameters derived from non-contrast CT as well as CTA improved significantly

Figure 5 Additive value of non-calcific tissue volume for predicting severe aortic stenosis using different aortic valve calcium measurements: (A) calcium score, (B) calcium score thresholds ≥ 1274 AU for women and ≥ 2065 AU for men, (C) calcific tissue volume.

their predictive value (Figure 5).²⁶ Using ROC curve analysis, the optimal cut-off for non-calcific aortic tissue was $>700.9\text{ mm}^3$ (sensitivity of 83% and specificity of 92%) and for total tissue volume was $>877.3\text{ mm}^3$ (sensitivity of 94% and specificity of 97%). Applying above non-calcific tissue volume threshold in addition to the calcium score up-classified additional 32 (12.5%) stenotic and 17 (7.6%) control patients with a net reclassification index of 0.058 ($P=0.048$). Total tissue volume (representing overall valvular fibro-calcific burden) compared to the reference approach using aortic calcium score thresholds up-classified 24 (9.5%) stenotic and 1 (0.5%) control patients with a net reclassification index of 0.09 ($P<0.001$). Therefore adding the new CTA measures allow correct reclassification of patients beyond traditional calcium score. [Supplementary data online, Table S2](#) presents sensitivity analysis for accuracy of CTA-derived tissue indices in a group of patients with concurrent non-contrast CT only.

Both aortic valve calcium score and calcific tissue volume, but not non-calcific tissue volume, correlated with the different echocardiographic measures of AS severity ([Supplementary data online, Table S3](#)). When subdivided by type of AS, a higher correlation between tissue indices and echocardiographic parameters was found for HG-AS than LFLG-AS patients.

Impact of aortic valve composition on 30-day MACE

In the first 30 days after TAVI, MACE occurred in 28 out of 445 (6.2%) patients, who survived the procedure and there were: 16 (3.5%) cardiovascular deaths, 9 (2.0%) strokes, and 4 (0.9%) myocardial infarctions. Patients with MACE were found to have increased total volume of aortic tissue as compared to patients without such complications (2071.8, IQR 1697.2–2212.7 vs. 1588.9, IQR 1208.5–2053.2 mm^3 , $P=0.010$), which was driven primarily by higher volume of non-calcific tissue (1144.9, IQR 902.7–1329.8 vs. 891.6, IQR 707.1–1137.5 mm^3 , $P<0.001$). In the multivariable analysis of clinical and quantitative CT parameters of aortic valve tissue, non-calcific tissue volume [odds ratio (OR) 5.2, 95% confidence interval (CI) 1.8–

Table 3 Association of clinical and CT aortic valve tissue parameters with risk of 30-day major adverse cardiovascular event in multivariable logistic regression^a

	OR (95% CI)	P-value
Age		
Male sex		
Diabetes mellitus		
History of myocardial infarction		
History of stroke	2.6 (1.6–6.6)	0.037
Glomerular filtration rate		
Left ventricular ejection fraction		
Non-femoral access site		
Calcific tissue volume		
Non-calcific tissue volume ^b	5.2 (1.8–15.4)	0.003

^aFinal model based on backward stepwise selection of variables at a Wald P-value of 0.1.
^bOdds ratios are per two-fold increase/doubling of the variable.

15.4, $P=0.003$] and history of stroke (OR 2.6, 95% CI 1.1–6.5, $P=0.037$) were independent predictors of 30-day MACE (Table 3).

Reproducibility of aortic valve composition assessment

There was an excellent intraobserver repeatability for calcific tissue volume measurement with an ICC of 0.999 (Table 4), coefficient of repeatability of 35.1, and bias of -0.5 ($P=0.834$). Similarly, intraobserver repeatability for non-calcific tissue volume was characterized with an ICC of 0.967, coefficient of repeatability of 273.8 and mean bias of -19.9 ($P=0.318$) (Figure 6).

Comparable to intraobserver analysis, there was also excellent interobserver repeatability for calcific tissue volume measurements with an ICC of 0.997, coefficient of repeatability of 56.8 and mean bias of 3.3 ($P=0.423$). Non-calcific tissue volume was characterized

Table 4 Intra- and inter-observer reproducibility of different tomographic aortic valve tissue parameters

	Intra-observer		Inter-observer	
	ICC (95% CI)	P-value	ICC (95% CI)	P-value
Total tissue volume	0.988 (0.980–0.994)	<0.001	0.982 (0.940–0.990)	<0.001
Calcific tissue volume	0.999 (0.998–0.999)	<0.001	0.998 (0.997–0.999)	<0.001
Non-calcific tissue volume	0.967 (0.942–0.981)	<0.001	0.945 (0.903–0.967)	<0.001

Figure 6 Intraobserver and interobserver repeatability for calcific and non-calcific tissue volumes measurements.

with an ICC of 0.945, repeatability coefficient of 334.9 and mean bias of -2.5 ($P = 0.918$) (Figure 6).

Discussion

The study presents the first comprehensive cardiac CTA-based evaluation of aortic valve tissue composition in patients treated with TAVI for severe AS. The main findings of this study were the following: (i) both HG-AS and LFLG-AS are characterized by an increase in aortic valve volumes compared to non-stenotic aortic valves; (ii) higher non-calcific tissue indices were noted in patients with LFLG-AS compared to HG-AS; (iii) addition of non-calcific tissue to the aortic valve calcium parameters improves their predictive value towards

severe AS; and (iv) non-calcific tissue is predictive of MACEs following TAVI.

Recent studies have established aortic valve calcium assessed with CT as a robust tool for distinguishing severe AS patients especially in LFLG-AS and as a powerful marker in the prediction of both disease progression and clinical events.⁶ While calcification is seen in nearly all stenotic aortic valves, they are often preceded by fibrotic thickening of aortic valve leaflets.^{9–11} In fact, even mild fibrosis without presence of calcification has been found to impact the valvular function and increase cardiovascular mortality.²⁷ While younger patients with bicuspid valves comprise the vast majority of patients with more valvular thickening compared to calcification, cases of severe stenosis in tri-leaflet aortic valves with minimal calcification are also encountered.^{28–30} In up to 10% of patients with AS, valve leaflet calcification

by CT might underestimate severity of AS.^{4,31} In our study, we explored for the first-time a non-invasive characterization of aortic valve with quantitative CTA with measurement of both calcific and non-calcific components of valve tissue. We show that the addition of non-calcific tissue volume to aortic valve calcium score (derived from non-contrast CT) as well as calcific tissue volume (derived from CTA) improves their prediction of severe AS. Inclusion of non-calcific tissue indices into diagnostic scheme of AS might potentially expand the clinical utility of CTA for disease severity grading and might enable non-invasive monitoring of therapies aimed at reducing aortic valve thickening.³²

The increasing extent of aortic valve calcium is also known to portend adverse procedural outcomes following TAVI and the significance of different patterns of calcification on post-TAVI outcomes are being investigated. While previous studies attempted to associate specific locations of calcium deposits with procedural complications, we investigated the prognostic significance of volumetric quantification of valve tissue and its individual components.³³ Although aortic valve calcium was found to be associated with severe procedural complications, transcatheter aortic valves of second generations have been shown to remain less impacted by the extent of landing zone calcium.^{34,35} We extend these observations by demonstrating that both total aortic tissue volume and the volume of non-calcific aortic valve tissue, but not calcific tissue alone, can predict 30-day MACEs (composite of cardiovascular death, all-stroke, and myocardial infarction) post-TAVI. Interestingly, histopathological analysis of debris captured with cerebral protection device during TAVI showed different forms of non-calcific tissue and thrombus to compose the majority of the liberated material.³⁶ Whereas the association of CTA-defined non-calcific tissue with stroke requires further validation, it may be potentially applied for a personalized approach in TAVI. One approach could employ different pre-emptive measures such as application of cerebral protection devices and/or stronger antithrombotic therapy following procedure. Alternatively, in patients with native valve presenting extremely large deposits of non-calcific tissue, in whom another precautionary steps are precluded, referral for surgical aortic valve replacement rather than TAVI could be considered.

Furthermore, examination of aortic valve composition in HG and LFLG-AS patients revealed that patients with HG-AS had higher tissue volume compared to aortic valve in LFLG-AS. Interestingly, volumes of respective tissue components also differed between HG and LFLG cohorts with LFLG-AS patients having a greater non-calcific tissue volume and lower calcific tissue volume compared to HG-AS. It remains unknown whether these disparities impact transvalvular gradients or should be considered as their consequence. Increased shear stress along with the turbulent flow in HG-AS may lead to endothelial dysfunction and inflammation that ultimately promote tissue alterations through interleukin-1 β /6 pathways.³⁷ On the other hand, aortic valve leaflets containing more fibrous and fibro-fatty tissue might generate lesser resistance, leading to lower gradients across diseased valves. Indeed, our analysis demonstrated that only calcific tissue volume was correlated with elevated transaortic gradients and peak velocity. Our results complement findings of Abramowitz et al.,²⁸ who observed significantly fewer LFLG patients with heavily calcific valves and proposed an increase of non-calcific tissue within the valve leaflets as the potential cause of the discrepancy between aortic valve

calcium score and the haemodynamic severity of AS in this patient population.

The present study is subject to several limitations. Our novel CT-derived quantitative characterization of aortic valve tissue composition lacks gold-standard histopathological validation; therefore, our results should be interpreted as hypothesis-generating. Second, non-contrast CT scans were not available for all patients included in the study. Finally, only TAVI patients were studied, thus findings might not be applicable in the surgical cohorts.

In conclusion, quantitative CTA assessment of aortic valve tissue volume and composition can improve identification of severe AS, differentiation between HG and LFLG AS in patients referred for TAVI and prediction of 30-day MACEs post-TAVI, over the current clinical standard. Inclusion of quantitative measurement of non-calcific aortic valve tissues into tomographic work-up of patients referred for TAVI may improve classification of diseased valves and the prediction of adverse outcomes.

Supplementary data

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

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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