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ORIGINAL PAPER

Association of aortic valvular complex calcification burden with procedural and long-term clinical outcomes after transcatheter aortic valve replacement

Euihong Ko[1†], Do-Yoon Kang[1†], Jung-Min Ahn[1], Tae Oh Kim[1], Ju Hyeon Kim[1], Junghoon Lee[1], Seung-Ah Lee[1], Dae-Hee Kim[1], Ho Jin Kim[2], Joon Bum Kim[2], Suk Jung Choo[2], Seung-Jung Park[1], and Duk-Woo Park [1*]

[1]Division of Cardiology, Department of Internal Medicine, Asan Medical Center, University of Ulsan College of Medicine, 88, Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Republic of Korea; and [2]Department of Thoracic and Cardiovascular Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

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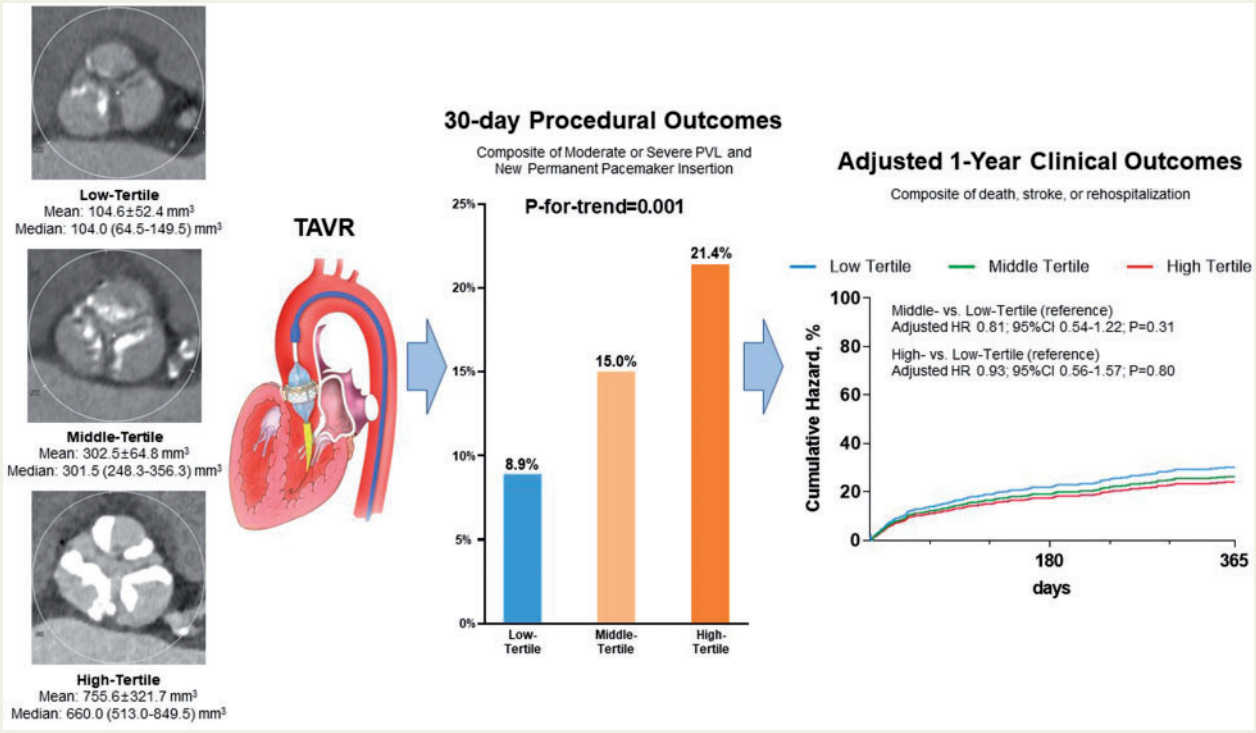
Aims This study aimed to assess the impact of valvular/subvalvular calcium burden on procedural and long-term outcomes in patients undergoing transcatheter aortic valve replacement (TAVR) for severe aortic stenosis (AS).

Methods and results In this prospective observational cohort study, we included patients with AS undergoing TAVR between March 2010 and December 2019. Calcium burden at baseline was quantified using multidetector computed tomography and the patients were classified into tertile groups according to the amount of calcium. Procedural outcomes [paravalvular leakage (PVL) or permanent pacemaker insertion (PPI)] and 12-month clinical outcomes (composite of death, stroke, or rehospitalization, and all-cause mortality) were assessed. A total of 676 patients (age, 79.8 ± 5.4 years) were analysed. The 30-day rates of moderate or severe PVL (*P*-for-trend = 0.03) and PPI (*P*-for-trend = 0.002) proportionally increased with the tertile levels of calcium volume. The 12-month rate of primary composite outcomes was 34.2% in low-tertile, 23.9% in middle-tertile, and 25.8% in high-tertile groups (log-rank *P* = 0.02). After multivariable adjustment, the risk for primary composite outcomes at 12 months was not significantly different between the tertile groups of calcium volume [reference = low-tertile; middle-tertile, hazard ratio (HR) 0.81; 95% confidence interval (CI) 0.54–1.22; *P* = 0.31; high-tertile, HR 0.93; 95% CI 0.56–1.57; *P* = 0.80]. A similar pattern was observed for all-cause mortality.

Conclusion The rates of PVL and PPI proportionally increased according to the levels of valvular/subvalvular calcium volume, while the adjusted risks for composite outcomes and mortality at 12 months were not significantly different.

* Corresponding author. Tel: +82 2 3010 3995; Fax: +82 2 475 6898. E-mail: dwpark@amc.seoul.kr
† These authors contributed equally to this work.

Graphical Abstract



Keywords aortic valves • calcium • mortality • transcatheter aortic valve replacement

Introduction

Transcatheter aortic valve replacement (TAVR) has been established as the standard treatment for symptomatic severe aortic stenosis (AS) across the diverse spectrum of operative risk.[1] For optimal procedural planning of TAVR, multidetector computed tomography (MDCT) is routinely performed and provides valuable information on valvular and/or subvalvular morphology including distribution and amount of valvular/subvalvular calcification.[2] In this context, further researches evaluating the association between CT morphology and the procedural and clinical outcomes are needed to define the most optimal candidates and develop a risk-stratification strategy for TAVR procedures.

Among several anatomic considerations, valvular/subvalvular calcification remains a particular challenge as it is associated with procedural complications including aortic root injury, paravalvular leakage (PVL), permanent pacemaker implantation (PPI), coronary obstruction, and residual post-implant gradient.[3,4] A detailed evaluation of calcium amount and distribution may contribute to reduce procedural complications and improve long-term outcomes of TAVR. Nevertheless, there is still a paucity of data regarding the impact of severity and distribution of valvular/subvalvular calcium on adverse clinical outcomes. Therefore, we sought to systematically assess the impact of valvular/subvalvular calcium amount on clinically relevant outcomes in patients with symptomatic severe AS undergoing TAVR.

Methods

Study population

The ASAN-TAVR registry is a prospective, single-centre, real-world registry that includes consecutive patients who underwent TAVR procedures for symptomatic severe AS at Asan Medical Center (Seoul, Republic of Korea) (ClinicalTrials.gov; NCT03298178). The present analysis included all consecutive patients who underwent TAVR between March 2010 and November 2019. Patients with preprocedural MDCT data for systematic evaluation of the aortic valvular complex were included in the analysis. This study was approved by the institutional review board of Asan Medical Center, and all patients provided written informed consent for participation. Following TAVR, the patients were prescribed dual antiplatelet therapy with aspirin and clopidogrel for at least 6 months or oral anticoagulants if clinically indicated.

MDCT and calcium measurement

MDCT examinations were performed as previously described[5,6] and independently evaluated by two investigators, who were blinded to the clinical outcomes, using a software specifically customized for valve analysis (3mensio Structural Heart, 3mensio Medical Imaging BV, Bilthoven, The Netherlands). For annular and aortic valve complex dimensions,

curved multiplanar reconstruction analyses were performed. A centreline was generated through the centre-point of the proximal ascending aorta, aortic valve, annulus, and left ventricular outflow tract (LVOT). The basal annular plane or ring was defined using this software as a cross-sectional plane connecting the nadir of each of the three leaflets by employing curved multiplanar reconstruction analyses.

The amount and distribution of calcium in aortic valve complexes were quantified using the 3mensio. The regions of interest for calcium quantification were drawn from the LVOT (5 mm into the left ventricle from the basal annular plane) to the higher height of the coronary ostia, while excluding coronary calcium from quantification (Supplementary data online, *Figure S1*). A threshold of 850 Hounsfield units for the contrast-enhanced data sets was used to detect calcium in the region of interest as previously described.[7] All the measurements were performed in the end-systolic phase. Calcium quantification using the Agatston score requires a non-linear weighting factor in its derivation and thus might have been shown to exhibit greater variability than the volumetric quantification of calcium. Accordingly, we quantified valvular/subvalvular calcium in cubic millimetres instead of using the Agatston score.[8]

Study outcomes and follow-up

The primary objective of the study was to evaluate the short-term (30 days) and long-term (12 months) outcomes of TAVR according to the severity of valvular/subvalvular calcium volume. The principal procedural outcomes were the incidences of moderate or severe PVL or PPI at 30 days. The primary long-term outcome was the incidence of major adverse cardiac or cerebrovascular events, which was defined as a composite of death from any cause, stroke, or rehospitalization at 12 months. All adverse outcomes were defined using the Valve Academic Research Consortium-2 definitions.[9] All events were independently reviewed and adjudicated by an independent group of clinicians who were blinded to the study purpose.

Baseline clinical data, procedural characteristics, and follow-up outcome data were prospectively recorded in a dedicated database, which is independently held and maintained at the Clinical Research Coordinating Center, CardioVascular Research Foundation, Asan Medical Center (Seoul, Republic of Korea). Clinical follow-up was performed via clinic visit and/or telephone interview at 1, 6, and 12 months and every 6 months thereafter. At each follow-up contact, data pertaining to the patients' clinical status and occurrence of any adverse clinical events were collected.

Statistical analysis

Continuous variables were compared using one-way analysis of variance or the Kruskal–Wallis test and are presented as mean ± standard deviation. Categorical variables were compared using the χ^2 test or Fisher's exact test and are presented as counts (percentages). The short-term (30 days) outcomes are reported as counts and percentages, and the differences between the tertile groups of calcium volume were assessed using the χ^2 test for trend. The long-term (12 months) cumulative event rates and incidence curves of the primary outcomes were estimated using the Kaplan–Meier estimates and compared using the log-rank test.

The relationship between the amount of valvular/subvalvular calcium and the 12-month clinical outcomes was investigated using crude and multivariable Cox proportional-hazards models. To determine the independent association between the calcium amount and clinical outcomes, multivariable models were fully adjusted with relevant clinical, anatomic, and procedural characteristics including age, sex, body mass index, the Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) score, the Logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE) II, diabetes, congestive heart failure, previous percutaneous coronary intervention (PCI), previous stroke, chronic kidney disease, atrial fibrillation, ejection fraction, mean aortic-valve gradient, low-flow low-gradient (LF-LG) AS, aortic regurgitation (moderate or severe), bicuspid aortic valve, type of valve (balloon-expandable vs. self- and mechanically expandable), access route (transfemoral vs. non-transfemoral), and type of anaesthesia (general vs. non-general). Stratified analyses with regard to distribution pattern and clinical impact of calcium volume by sex were performed. Finally, key subgroup analyses were performed in patients with LF-LG AS and those with bicuspid AS.

All reported *P*-values are two-sided and those <0.05 were considered statistically significant. No adjustment for multiple testing was undertaken. Because of the potential for type I error due to multiple comparisons, all findings of this study should be interpreted as exploratory. All statistical analyses were performed using IBM SPSS Statistics for Windows, version 25.0 (IBM, Armonk, NY, USA).

Results

Study population and calcium amount/distribution

Between March 2010 and November 2019, consecutive 700 patients with severe AS who underwent TAVR were enrolled in the ASAN-TAVR registry. Among them, 15 patients with a valve-in-valve procedure, 5 without pre-TAVR MDCT screening, and 3 with low-quality pre-TAVR MDCT imaging were excluded from the present analysis. A total of 676 patients were included in the analysis. The mean ± SD age of patients was 79.8 ± 5.4 years and 50.3% were men. The mean STS-PROM score and logistic EuroSCORE II were 4.1 ± 0.3 and 14.7 ± 1.0, respectively.

The median calcium volume of the patients as a whole was 301.0 mm^3 [inter-quartile range (IQR): 148.0–513.0]; the median volume of calcium in the low-, middle-, and high-tertile group was 104.0 mm^3 (IQR: 64.5–149.5), 301.5 mm^3 (IQR: 248.3–356.3), and 660.0 mm^3 (IQR: 513.0–849.5), respectively (*Table 1*). Overall, 76 (11.2%) patients had bicuspid AS. The median volume of calcium was significantly higher in patients with bicuspid AS than those with tricuspid AS (570.4 vs. 282.5 mm^3; $P < 0.001$). The frequency histogram of calcium in patients with tricuspid AS showed a right-skewed distribution, while those in patients with bicuspid AS showed a multimodal distribution (Supplementary data online, *Figure S2*).

Baseline clinical, anatomic, and procedural characteristics

Baseline clinical, anatomic, and procedural characteristics according to tertile groups of valvular/subvalvular calcium volume are summarized in *Table 1*. The proportion of male patients ($P < 0.001$) and mean body mass index ($P = 0.005$) were higher in higher-tertile groups, while the STS-PROM score was lower in higher tertile groups ($P = 0.02$). On echocardiography, peak aortic-valve velocity and mean pressure gradient were higher in higher-tertile groups (both $P < 0.001$), while the proportion of LF-LG AS was significantly higher in the low-tertile group ($P < 0.001$). Higher-tertile groups had a larger annulus diameter, larger annulus area, higher amount of LVOT calcium, and a higher proportion of bicuspid AS (all $P < 0.001$).

Table 1 Baseline patient and procedural characteristics according to the valvular/subvalvular calcium volume tertile

Variable	All patients (*N* = 676)	Tertile of valvular/subvalvular calcium volume			*P*-Value
		Low-tertile (*N* = 225)	Middle-tertile (*N* = 226)	High-tertile (*N* = 225)	
Clinical data					
Age (years)	79.8 ± 5.4	79.5 ± 5.2	79.5 ± 5.7	80.4 ± 5.2	0.13
Male	340 (50.3)	69 (30.7)	111 (49.1)	160 (71.1)	<0.001
Body mass index (kg/m^2)	24.0 ± 3.4	24.5 ± 3.4	23.9 ± 3.3	23.5 ± 3.4	0.005
STS-PROM	3.9 ± 2.9	4.3 ± 3.6	3.9 ± 2.3	3.5 ± 2.4	0.019
EuroSCORE II	12.9 ± 10.6	14.1 ± 12.7	12.9 ± 9.6	11.9 ± 9.1	0.11
Hypertension	590 (87.3)	201 (89.3)	195 (86.3)	194 (86.2)	0.53
Diabetes	336 (49.7)	127 (56.4)	101 (44.7)	108 (48.0)	0.038
Dyslipidaemia	512 (75.7)	181 (80.4)	164 (72.6)	167 (74.2)	0.12
Congestive heart failure	108 (16.0)	35 (15.6)	27 (11.9)	46 (20.4)	0.047
Previous PCI	193 (28.6)	75 (33.3)	70 (31.0)	48 (21.3)	0.012
Previous stroke	80 (11.8)	35 (15.6)	24 (10.6)	21 (9.3)	0.10
Chronic kidney disease[a]	100 (14.8)	40 (17.8)	32 (14.2)	28 (12.4)	0.27
Bicuspid aortic valve	76 (11.2)	13 (5.8)	19 (8.4)	44 (19.6)	<0.001
Echocardiography data					
Ejection fraction (%)	58.3 ± 11.0	59.1 ± 11.1	58.1 ± 11.1	57.7 ± 10.7	0.35
Mean aortic-valve gradient (mmHg)	59.1 ± 21.3	47.3 ± 14.5	58.6 ± 19.3	71.4 ± 22.2	<0.001
Peak aortic-valve velocity (m/s)	4.90 ± 0.81	4.46 ± 0.66	4.87 ± 0.70	5.36 ± 0.80	<0.001
Low-flow low-gradient AS	45 (6.7)	32 (14.2)	10 (4.4)	3 (1.3)	<0.001
Aortic valve area (cm^2)	0.61 ± 0.16	0.67 ± 0.15	0.60 ± 0.16	0.55 ± 0.13	<0.001
Computed tomography data					
Annulus mean diameter (mm)	24.0 ± 2.3	23.0 ± 2.0	23.8 ± 2.2	25.1 ± 2.2	<0.001
Annulus area (mm^2)	443.5 ± 84.3	408.5 ± 72.7	437.5 ± 79.0	484.4 ± 83.2	<0.001
Annulus perimeter (mm)	75.9 ± 7.1	72.9 ± 6.3	75.4 ± 5.7	79.5 ± 6.8	<0.001
Median aortic root calcium volume (mm^3)	301.0 (148.0–513.0)	104.0 (64.5–149.5)	301.5 (248.3–356.3)	660.0 (513.0–849.5)	<0.001
Median LVOT calcium volume (mm^3)	20.0 (4.0–41.0)	2.0 (1.0–3.0)	19.0 (6.5–36.3)	23.0 (4.3–43.3)	<0.001
Presence of LVOT calcium	62 (9.2%)	2 (0.9%)	12 (5.3%)	48 (21.3%)	<0.001
Aortic valve density (mm^3/cm^2)[b]	69.4 (35.3–114.5)	24.8 (16.3–35.6)	69.5 (58.0–81.6)	139.3 (110.9–186.4)	<0.001
Procedural characteristics					
Balloon-expandable	519 (76.8)	179 (79.6)	181 (80.1)	159 (70.7)	0.029
Type of valve					0.018
SAPIEN	6 (0.9)	0	5 (2.2)	1 (0.4)	
SAPIEN XT	116 (17.2)	44 (19.6)	38 (16.8)	34 (15.1)	
SAPIEN 3	397 (58.7)	135 (60.0)	138 (61.1)	124 (55.1)	
CoreValve	83 (12.3)	18 (8.0)	23 (10.2)	42 (18.7)	
Evolut R	62 (9.2)	24 (10.7)	18 (8.0)	20 (8.9)	
Evolut Pro	7 (1.0)	3 (1.3)	1 (0.4)	3 (1.3)	
Lotus	5 (0.7)	1 (0.4)	3 (1.3)	1 (0.4)	
Transfemoral	652 (96.4)	218 (96.9)	215 (95.1)	219 (97.3)	0.80
Monitored anaesthesia care	440 (65.1)	150 (66.7)	149 (65.9)	141 (62.7)	0.64

Values are mean ± SD, median (IQR), or *n* (%).
[a]Chronic kidney disease was defined as creatine clearance < 30 mL/min.
[b]Aortic valve density was calculated by indexing aortic root calcium volume to cross-sectional annulus area.
AS, aortic stenosis; EuroSCORE, the European System for Cardiac Operative Risk Evaluation; IQR, inter-quartile range; LVOT, left ventricular outflow tract; PCI, percutaneous coronary intervention; STS-PROM, Society of Thoracic Surgeons Predicted Risk of Mortality.

TAVR was performed through transfemoral access in 96% of the patients and monitored anaesthesia care was used in 65% of the patients, without significant differences among the tertile groups ($P = 0.12$ and 0.64, respectively). Balloon-expandable valves and smaller-sized valve (≤23 mm) were less commonly used in higher-tertile groups ($P = 0.029$ and <0.0001, respectively).

Table 2 Observed rates of clinical outcomes at 30 days and 12 months according to the valvular/subvalvular calcium volume tertiles

Variable	All patients (*N* = 676)	Tertile of valvular/subvalvular calcium volume			*P*-Value
		Low-tertile (*N* = 225)	Middle-tertile (*N* = 226)	High-tertile (*N* = 225)	
30-Day outcomes[a]					
Moderate or severe paravalvular leakage	45/588 (7.7)	9/192 (4.7)	15/200 (7.5)	21/196 (10.7)	0.026
New permanent pacemaker implantation	58 (8.6)	10 (4.4)	20 (8.8)	28 (12.4)	0.002
Death	14 (2.1)	5 (2.2)	4 (1.8)	5 (2.2)	>0.99
Cardiovascular	9 (1.3)	3 (1.3)	3 (1.3)	3 (1.3)	>0.99
Non-cardiovascular	4 (0.6)	1 (0.4)	1 (0.4)	2 (0.9)	0.54
Stroke	27 (4.0)	14 (6.2)	6 (2.7)	7 (3.1)	0.09
Disabling	9 (1.3)	2 (0.9)	3 (1.3)	4 (1.8)	0.41
Non-disabling	16 (2.4)	11 (4.9)	2 (0.9)	3 (1.3)	0.013
Life-threatening or major bleeding	187 (27.7)	63 (28.0)	60 (26.5)	64 (28.4)	0.91
Coronary obstruction	2 (0.3)	0	0	2 (0.9)	0.08
Annular rupture or root injury	2 (0.3)	0	1 (0.4)	1 (0.4)	0.39
Bail out valve-in-valve	18 (2.7)	4 (1.8)	5 (2.2)	9 (4.0)	0.14
Device success	651 (96.3)	219 (97.3)	219 (96.9)	213 (94.7)	0.13
12-Month outcomes[b]					
Primary composite outcome	189 (28.0)	77 (34.2)	54 (23.9)	58 (25.8)	0.020
Death	48 (7.1)	21 (9.3)	12 5.3)	15 (6.7)	0.19
Cardiovascular	17 (2.5)	6 (2.7)	7 (3.1)	4 (1.8)	0.67
Non-cardiovascular	21 (3.1)	9 (4.0)	4 (1.8)	8 (3.6)	0.30
Stroke	42 (6.2)	18 (8.0)	11 (4.9)	13 (5.8)	0.32
Disabling	16 (2.4)	4 (1.8)	6 (2.7)	6 (2.7)	0.83
Non-disabling	21 (3.1)	12 (5.3)	4 (1.8)	5 (2.2)	0.052
Death or stroke	79 (11.7)	36 (16.0)	20 (8.8)	23 (10.2)	0.002
Life-threatening or major bleeding	199 (29.4)	68 (30.2)	64 (28.3)	67 (29.8)	0.71
Rehospitalization[c]	149 (22.0)	57 (25.3)	46 (20.4)	46 (20.4)	0.21
Moderate or severe paravalvular leakage	48/491 (9.8)	9/153 (5.9)	15/173 (8.7)	24/165 (14.5)	0.028
New PPI	62 (9.2)	11 (4.9)	23 (10.2)	28 (12.4)	0.017

Values are *n* (%) or *n*/*N* (%).
[a]Thirty-day outcomes were compared with the χ^2 test for trend.
[b]The percentages are Kaplan–Meier estimates of the rates of the endpoints at 12 months, and *P*-values were compared with the log-rank test.
[c]Valve-related or procedure-related, and including heart failure (PARTNER-3 definition).
PPI, permanent pacemaker insertion.

Procedural and 12-month clinical outcomes

Early (procedural and 30 days) and late (12 months) clinical outcomes are summarized in *Table 2*. The rate of device success was 96.3% in the overall population, and there was not significantly different among the tertile groups (low-tertile, 97.3%; middle-tertile, 96.9%; high-tertile, 94.7%; *P*-for-trend = 0.13). The 30-day rates of moderate or severe PVL (4.7% in low-, 7.5% in middle-, and 10.7% in high-tertile; *P*-for-trend = 0.03) and PPI (4.4% in low-, 8.8% in middle-, and 12.4% in high-tertile; *P*-for-trend = 0.002) were proportionally higher in higher tertile groups (*Figure 1*).

At 12 months, the incidence of the primary composite outcome of death, stroke, or rehospitalization was significantly higher in the low-tertile group than in the middle- and high-tertile groups (34.2% vs. 23.9% vs. 25.8%, respectively; log-rank *P* = 0.02) (*Figure 2*). The incidence of the composite outcome of death or stroke at 12 months was also significantly higher in the low-tertile group. The crude and adjusted risks for the primary composite outcome and its individual components at 12 months are shown in *Table 3*. After multivariable adjustment of potential confounding covariates, there were no significant differences in the risks for primary composite outcomes at 12 months among the three tertile groups [reference = low-tertile; hazard ratio (HR) 0.81; 95% confidence interval (CI) 0.54–1.22; *P* = 0.31 for middle-tertile, and HR 0.93; 95% CI 0.56–1.57; *P* = 0.80 for high-tertile (low tertile group = reference)] (*Figure 2*). A similar pattern was observed for all-cause mortality.

Pattern and clinical impact of calcium volume by sex

The distribution of calcium volume according to sex is shown in Supplementary data online, *Figure S3*. With higher tertile levels of valvular/subvalvular calcium volume, the incidence of composite of

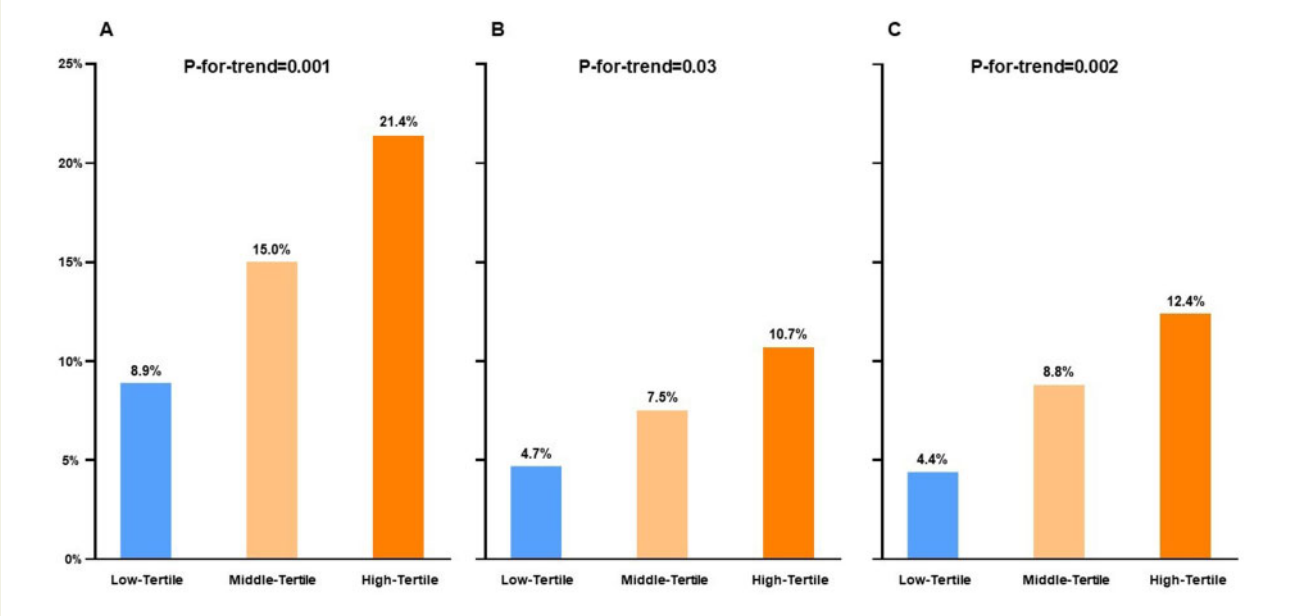


Figure 1 Incidence of moderate or severe paravalvular leakage at 30 days according to the tertile of valvular/subvalvular calcium volume.
(*A–C*) The 30-day rates of moderate or severe PVL or PPI, moderate or severe PVL, and PPI, respectively. PPI, permanent pacemaker insertion; PVL, paravalvular leakage.

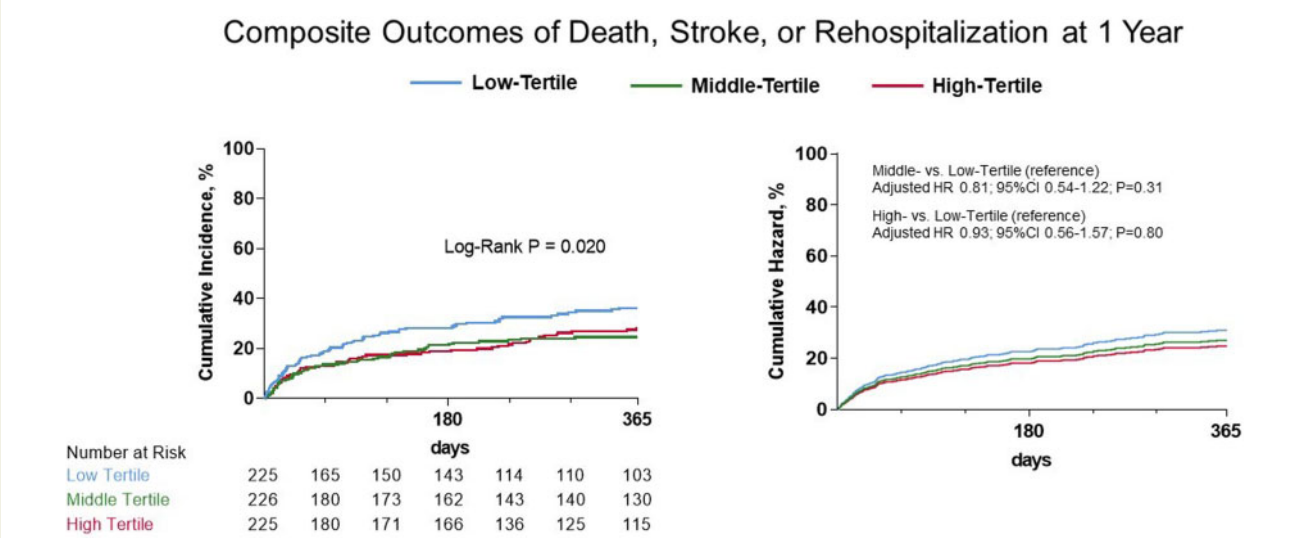


Figure 2 Unadjusted and adjusted incidence of primary composite outcome of death, stroke, or rehospitalization at 12 months according to the tertile of valvular/subvalvular calcium volume. Left panel shows the Kaplan–Meier estimates of the primary composite outcome of death, stroke, or rehospitalization at 12 months. Right panel shows the adjusted cumulative incidence curves for the primary composite outcome.

PVL and PPI proportionally increased in both men and women (Supplementary data online, *Figure S4*). The crude and adjusted risks for primary composite outcomes at 12 months according to sex are illustrated in Supplementary data online, *Figure S5*. There were no significant differences in the adjusted risks for primary composite outcomes according to the tertile groups of calcium volume in men, while high-tertile group had better adjusted risk for primary composite outcomes in women.

Key subgroup analysis

Patients with LF-LG AS had a significantly lower amount of valvular/subvalvular calcium than those with high-flow high-gradient AS

Table 3 Unadjusted and adjusted hazard ratios for clinical outcomes at 12 months according to the valvular/subvalvular calcium volume tertiles

	Unadjusted		Adjusted[a]	
12-Month outcomes	**HR (95% CI)**	***P*-Value**	**HR (95% CI)**	***P*-Value**
Composite of death, stroke, or rehospitalization				
Low-tertile	Referent		Referent	
Middle-tertile	0.64 (0.45–0.91)	0.01	0.81 (0.54–1.22)	0.31
High-tertile	0.69 (0.49–0.98)	0.04	0.93 (0.56–1.57)	0.80
Death				
Low-tertile	Referent		Referent	
Middle-tertile	0.53 (0.26–1.09)	0.08	0.53 (0.22–1.28)	0.16
High-tertile	0.69 (0.36–1.34)	0.28	0.34 (0.11–1.08)	0.07
Stroke				
Low-tertile	Referent		Referent	
Middle-tertile	0.58 (0.28–1.24)	0.16	0.94 (0.37–2.36)	0.89
High-tertile	0.70 (0.34–1.42)	0.32	1.75 (0.55–5.60)	0.18
Death or stroke				
Low-tertile	Referent		Referent	
Middle-tertile	0.52 (0.30–0.90)	0.02	0.59 (0.30–1.15)	0.12
High-tertile	0.61 (0.36–1.03)	0.07	0.60 (0.26–1.39)	0.23
Rehospitalization				
Low-tertile	Referent		Referent	
Middle-tertile	0.75 (0.51–1.10)	0.14	1.01 (0.64–1.59)	0.98
High-tertile	0.74 (0.50–1.10)	0.13	1.06 (0.59–1.91)	0.86

[a]Multivariable models were adjusted for age, sex, body mass index, STS-PROM score, EuroSCORE II, diabetes, congestive heart failure, previous PCI, previous stroke, chronic kidney disease, atrial fibrillation, ejection fraction, mean aortic-valve gradient, low-flow low-gradient AS, aortic regurgitation (moderate or severe), bicuspid aortic valve, type of valve (balloon-expandable vs. self- and mechanically expandable), access route (transfemoral vs. non-transfemoral), and type of anaesthesia (general vs. non-general).

AS, aortic stenosis; CI, confidence interval; EuroSCORE, the Logistic European System for Cardiac Operative Risk Evaluation; HR, hazard ratio; PCI, percutaneous coronary intervention; STS-PROM, Society of Thoracic Surgeons Predicted Risk of Mortality.

(0.07 ± 0.25 vs. 373.0 ± 325.9 mm^3, $P < 0.001$). The incidence of the primary composite outcome at 12 months was significantly higher in patients with LF-LG AS than those with high-flow high-gradient AS (48.9% vs. 26.5%, log-rank $P < 0.001$). However, the differential impact of valvular/subvalvular calcium volume on primary composite outcome at 12 months was not evident in patients with LF-LG AS (50.0% in low-tertile, 50.0% in middle-tertile, and 33.3% in high-tertile; log-rank $P = 0.76$).

Patients with bicuspid AS had similar 12-month incidence of primary composite outcomes with tricuspid AS (21.1% vs. 28.8%, log-rank $P = 0.17$). The differential impact of valvular/subvalvular calcium volume on primary composite outcome at 12 months was also not evident in patients with bicuspid AS (31.8% in low-tertile, 15.8% in middle-tertile, and 20.5% in high-tertile; log-rank $P = 0.65$). Among these subgroups, multivariable analysis was not performed owing to the limited number of patients and clinical events.

Discussion

In this prospective, real-world cohort of consecutive patients who underwent TAVR for severe AS, we evaluated the clinical impact of valvular/subvalvular calcium amount on procedural and long-term outcomes. The principal findings of the present analysis can be summarized as follows: (i) the distribution of valvular/subvalvular calcium showed a right-skewed pattern in patients as a whole, and compared with those with tricuspid AS, patients with bicuspid AS had a significantly higher calcium volume and a different distribution pattern of calcium volume; (ii) the rates of PVL and PPI proportionally increased with increasing tertile levels of valvular/subvalvular calcium volume; (iii) the rates of serious procedural complications including annulus rupture, coronary obstruction, and cardiac tamponade were low and comparable across the tertile groups of calcium volume; and (iv) there were no significant differences in the adjusted risks of primary composite of death, stroke, or rehospitalization, and all-cause mortality at 12 months according to the tertile groups of calcium volume (*Figure 3*).

Degenerative aortic valve calcification is the most common aetiology of AS, accounting for up to 80% of patients with severe AS.[10] Previous studies showed that the presence of aortic valve calcification as detected by MDCT was significantly associated with a more rapid progression of AS and higher rates of adverse events and mortality.[11,12] However, clinical information on the impact of valvular/subvalvular calcium burden on immediate procedural and long-term cardiovascular events after TAVR was lacking.[13,14] In this regard, our study may provide valuable clinical insights on the clinical impact of

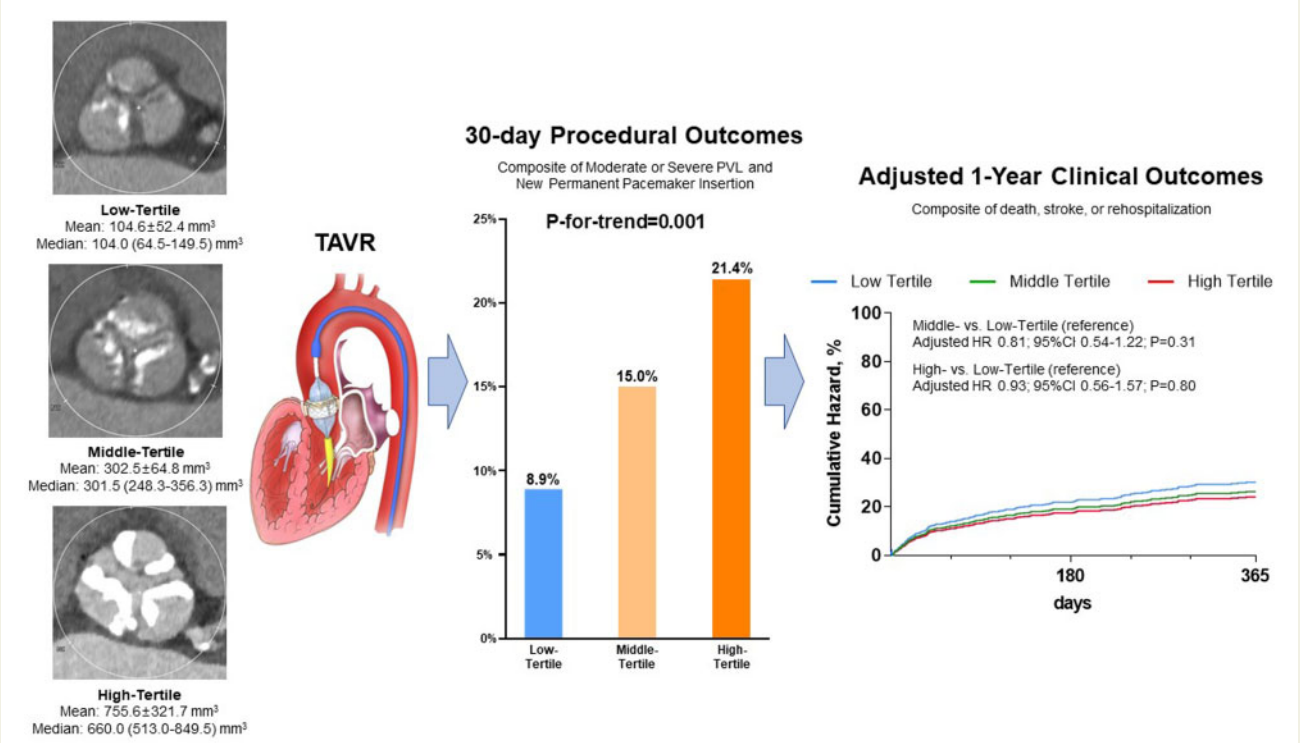


Figure 3 Association between valvular/subvalvular calcium amount and procedural complications and 12-month primary clinical outcome.
PPI, permanent pacemaker insertion; PVL, paravalvular leakage.

quantitatively defined annular calcium burden with respect to both immediate- and long-term outcomes following TAVR.

In previous randomized controlled trials of TAVR, AS combined with very severe calcification (including bicuspid AS) was either excluded or not fully evaluated.[15,16] The risk of suboptimal valve expansion in severely calcified aortic valve, higher incidence of PVL, aortic root injury, and PPI were the main reasons for such complex procedures.[14,17] The current analysis showed that the incidences of PVL and PPI proportionally increased according to the increasing amount of valvular and LVOT calcium, while the combined incidence of serious procedural complications (i.e. aortic root injury, aortic dissection, and conversion to surgery) was <1%. Asymmetrical calcification and predominant involvement of one aortic cusp, as well as the extent into the aortic root and to the LVOT, are also important parameter, which have been found to relate to procedural complications, such as PVL or PPI. Unfortunately, in our study, these changes were not systematically considered, since the LVOT calcium volume was too smaller than the valvular calcium volume [median, 20.0 (4.0–41.0) vs. 277.0 (134.3–459.3) mm^3]. Therefore, these factors should be further addressed through larger-sized clinical studies with adequate imaging information.

Previous studies examining the correlation between the severity of valvular/subvalvular calcium and clinical outcome following TAVR have yielded mixed results.[13,14] In our study, there were no significant differences in the adjusted risks for primary composite outcome and mortality between the tertile groups. The plausible explanations for the lack of a significant effect of baseline calcium volume on the long-term outcomes are as follows. First, substantial differences in the baseline characteristics including the higher prevalence of LF-LG AS and higher STS-PROM score in the low-tertile group may have led to the worse clinical outcomes compared with the middle- and high-tertile groups. After adjusting for these confounding variables, there were no significant differences in the long-term outcomes according to the amount of valvular/subvalvular calcium. Secondly, our findings represent not only the evolution of device technology but likely also operator experience, and procedural advancements, which might attenuate the long-term prognostic impact of baseline valvular/subvalvular calcium severity after optimal fixing AS with TAVR.

Similar to our study, prior study showed that LF-LG AS was more prevalent in patients with low aortic valve calcium.[18] Also, recent study showed that non-calcific tissue volume was an independent predictor of major adverse cardiovascular events following TAVR.[19] Higher non-calcific tissue indices were noted in patients with LF-LG AS compared with high gradient AS. Patients with non-rheumatic low calcified severe AS may have relatively more fibrous or fibro-fatty, rather than calcium deposition in the aortic valve, which could also contribute to valve stenosis and suggest a different pathogenesis for the progression of AS.[20] An increase of non-calcific tissue within the valve leaflets was the potential cause of the discrepancy between aortic valve calcium score and the haemodynamic severity of AS.[18,19] Also, these findings might partly explain the discrepancy between the amount of calcium and long-term clinical outcomes after TAVR and hence further research is needed in this area.

This study has several limitations. First, as our study is an analysis of non-randomized observational data, unmeasured confounders might have influenced the observed findings. Thus, the overall findings in our study should be considered exploratory and hypothesis-generating only. Secondly, although MDCT measurements were performed by experienced cardiologists and radiologists, the CT data were not adjudicated by an independent imaging core laboratory. Thirdly, although we adjusted valve type in our multivariable outcome analysis, the majority of patients in our study had been implanted balloon-expandable valves and a relatively small number of patients were implanted self-expandable and mechanically expandable valves, which might limit the generalizability of the current findings in the other clinical setting with different devices. Fourthly, given the relatively small sample size of patients and clinical events, our study might be underpowered for detecting the occurrence of devastating complications according to the severity of calcium. Fifthly, in our study, Agatston score was only available in limited patients, which might affect comparative outcomes. Lastly, the follow-up duration was somewhat short to evaluate the true long-term effect of calcium volume on clinically relevant outcomes.

Conclusions

In this real-world, prospective cohort of patients undergoing TAVR for severe AS, the rates of PVL and PPI proportionally increased according to increasing volume of valvular/subvalvular calcium. However, these differences did not lead to significant increases in the adjusted risks of the primary composite outcome of death, stroke, or rehospitalization or all-cause mortality at 12 months. Further investigation is warranted to define the optimal procedural planning and risk-stratification according to the degree of calcification in patients undergoing TAVR.

Supplementary data

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

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