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CLINICAL RESEARCH
Valvular heart disease

Concomitant mitral annular calcification and severe aortic stenosis: prevalence, characteristics and outcome following transcatheter aortic valve replacement

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Aims Calcified aortic stenosis (AS) and mitral annular calcification (MAC) have certain similar etiology and pathophysiological mechanisms. MAC is frequently encountered in pre-procedural computed tomography (CT) imaging of patients that undergo transcatheter aortic valve replacement (TAVR), but its prognostic implications for these patients have not been thoroughly investigated. This study sought to evaluate the prevalence of MAC among patients with severe AS and to assess the clinical implications of MAC on these patients during and following TAVR.

Methods and results Consecutive patients that underwent TAVR were compared according to the existence of MAC and its severity in pre-TAVR CT scans. From the entire cohort of 761 patients, 49.3% had MAC, and 50.7% did not have MAC. Mild MAC was present in 231 patients (30.4%), moderate MAC in 72 patients (9.5%), and severe MAC in 72 patients (9.5%). Thirty-day mortality and major complications were similar between patients with and without MAC. In a multivariable survival analysis, severe MAC was found to be an independent strong predictor of overall mortality following TAVR (all-cause mortality: hazards ratio [HR] 1.95, 95% confidence interval [CI] 1.24–3.07, $P = 0.004$; cardiovascular mortality: HR 2.35, 95% CI 1.19–4.66; $P = 0.01$). Severe MAC was also found to be an independent strong predictor of new permanent pacemaker implantation (PPI) after TAVR (OR 2.83, 95% CI 1.08–7.47; $P = 0.03$).

Conclusion Half of the patients with severe AS evaluated for TAVR were found to have MAC. Severe MAC is associated with increased all-cause and cardiovascular mortality and with conduction abnormalities following TAVR and should be included in future risk stratification models for TAVR.

Keywords Mitral annulus calcification • Transcatheter aortic valve implantation • TAVR • TAVI

Introduction

Mitral annular calcification (MAC) is a chronic degenerative process of the fibrous support structure of the mitral valve.[1] The reported prevalence of MAC in the general population is between 8% and 15%, but it significantly increases with age and in patients with multiple cardiovascular risk factors, chronic renal failure, or aortic stenosis (AS).[1–3] There is growing evidence that identification of calcified mitral annulus can be related independently to higher risk of cardiovascular events, conduction abnormalities, mitral valve disease, and mortality.[1,4–7] Previously, echocardiography was considered the best method to demonstrate MAC, but cardiac computed

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tomography (CT) is superior for evaluating the extent and location of MAC and for quantifying MAC objectively in order to assess its severity.[1,8]

Calcified AS and MAC have certain similar etiology and pathophysiological mechanisms.[1] Both conditions may be initiated by endothelial injury at foci of increased mechanical stress and progress to an atherosclerotic calcification.[9] They are, therefore, observed most commonly in the presence of significant atherosclerosis in the elderly. Transcatheter aortic valve replacement (TAVR) has emerged as a treatment option for inoperable or high-risk surgical patients with severe AS.[10,11] During recent years, there has been a substantial increase in the utilization of cardiac CT of patients with severe AS being evaluated for TAVR[12]. MAC is frequently encountered in these CT examinations but its prognostic implication in these patients has not been thoroughly investigated.

In our study, we sought to evaluate the prevalence of MAC among a large cohort of patients with severe AS and to assess the clinical implications of MAC on patients being treated with TAVR.

Methods

We retrospectively examined 761 patients with severe symptomatic AS that underwent TAVR during a three year period at the Cedars-Sinai Heart Institute. The study was approved by the institutional review board (IRB) and informed consent was obtained from all subjects. All patients had congestive heart failure with New-York Heart Association (NYHA) class II–IV symptoms. They underwent pre-procedural coronary angiography to assess the need for revascularization. Aortic valve disease was assessed with transthoracic echocardiography performed by experienced echocardiographers. Evaluation of AS severity was performed based on peak velocity, mean gradient, and calculation of the aortic valve area (AVA) using the continuity equation as recommended by current guidelines.[13] All patients had an AVA of <1 cm^2 and indexed AVA (AVA/body surface area) of <0.6 cm^2/m^2. Mitral regurgitation (MR) was evaluated pre- and post-TAVR on the basis of the integration of color Doppler jet area, vena contracta, and proximal isovelocity surface area and graded as no/trivial, mild, moderate, or severe.[14] Mitral valve gradients were determined from the Doppler diastolic mitral flow and considered significant if the mean gradient was ≥5 mmHg.[15]

Patients were also evaluated by an ECG-gated, multi-slice CT angiography study using a second-generation dual-source CT system (Siemens SOMATOM Definition Flash; Siemens Healthcare, Erlangen, Germany). Acquisition was in the cranio-caudal direction from the aortic arch to the diaphragm. CT was performed with a collimation of 128 × 0.625 mm and maximum tube current ranged was automated for each patient using Caredose (Siemens Healthcare, Erlangen, Germany) with a fixed tube potential of 100–120 kV. Images were reconstructed at 0.6 mm slices with 0.3 mm overlap with iterative reconstruction for evaluation at 10% intervals within the 0–90% RR range. CT images were reconstructed using 3mensio Valves Version 7.0 or 7.1 (3mensio Medical Imaging BV, Bilthoven, The Netherlands). Several views including axial and double oblique view at the mitral annular level as well as maximal intensity projection (MIP) reconstruction were used to assess the presence of MAC and its severity. MAC was defined by presence of dense calcium deposits at the base of mitral leaflets between the left atrium and ventricle. MAC severity was qualitatively determined by the circumferential involvement of the mitral ring[5,16]: mild = less than 1/3 of the annulus involved; moderate = between 1/3 and 1/2; and severe = calcification in more than half of the mitral annulus circumference (*Figure 1*). From a repeated measurement for a subset of 25 randomly selected patients, intra- and inter-observer variability for MAC severity grading was satisfactory (intra-observer: intra-class correlation coefficient: 0.97, $P < 0.001$; inter-observer: intra-class correlation coefficient: 0.94, $P < 0.001$). MAC was also quantified using 3mensio Valves software with threshold of 850 Hounsfield Units (HU) used to detect areas of calcium in the region of interest as previously validated in our institute for aortic valve calcium quantification in TAVR patients.[17] Maximal calcification thickness was also measured.

Left ventricular outflow tract (LVOT) calcification was defined as any calcification between the aortic valve annulus plane and 5 mm inferior to this plane. This was performed by one of the physician readers experienced in the assessment of pre-TAVR CT scans, blinded to the clinical data. Aortic valve calcium was quantified by 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.[18]

All patients were considered high-risk for valve surgery by our institutional heart team. Prosthetic valve size selection was based on CT or immediate pre-procedural three-dimensional transesophageal echocardiography. TAVR was performed under general anesthesia in all cases. The vascular access approach was chosen on the basis of the individual patient's risk profile. Baseline clinical, echocardiographic and procedural details for TAVR were recorded for all patients including 1 month clinical and echocardiographic evaluation during a follow-up visit. TAVR endpoints, device success, and adverse events were recorded using the Valve Academic Research Consortium (VARC)-2 definitions.[19] Post-TAVR paravalvular regurgitation (PVR) was assessed in line with VARC-2 criteria with peri-procedural transesophageal echocardiography examinations reviewed retrospectively.

Statistical analysis

Continuous variables were tested for distribution normality with the Shapiro–Wilk test and expressed as mean ± SD or median and interquartile range. These variables were compared using two-sided Student's *t*-test or Wilcoxon rank sum test, as appropriate. Categorical variables are expressed as number (percentage) and were compared using the Pearson χ^2 test or Fisher exact test, as appropriate. Kaplan–Meier survival plot significance was estimated using the log-rank test and event rates computed as number of events divided by person-time. Schoenfeld residuals were used to assess the proportional hazards assumption for all Cox models. Their goodness of fit was tested using the Groennesby and Borgan test, and Harrell's *C*-statistic was computed to further evaluate the multivariable models. The likelihood ratio test was used to test the incremental value of MAC in predicting mortality. Cox multivariable regression analysis was performed to assess independent predictors of overall all-cause and cardiovascular mortality in patients who underwent TAVR. The multivariable model was built by selecting baseline variables that were significantly different between patients with and without MAC and/or those that satisfied the entry criterion of $P < 0.1$ in a univariate overall and/or 1-year mortality analysis: patient age, body mass index, gender, diabetes mellitus, coronary artery disease, chronic lung disease, previous stroke/transient ischemic attack, peripheral artery disease, frailty, prior cardiac surgery, chronic renal failure (glomerular filtration rate <30 mL/min/m^2), alternative access, Society of Thoracic Surgeons (STS) score, left ventricular ejection fraction, mean aortic valve gradient, CT mean annulus diameter, LVOT

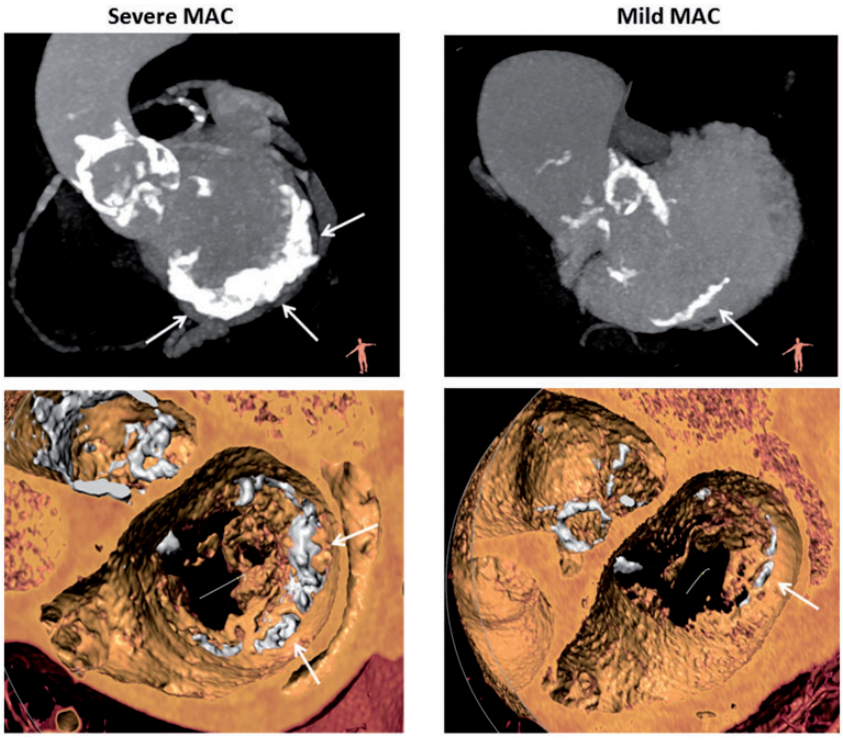


Figure 1 Grading of MAC severity in pre-TAVR CT scans. (Left top panel) Cardiac CT with double oblique view at the mitral annular level demonstrating a 220° circumferential severe MAC (arrows) and (right top panel) 90° circumferential mild MAC (arrow). (Bottom panels) Volume rendering images at the mitral annular level of the same patients.

calcification, and MAC. A multivariable logistic regression analysis was performed to assess independent predictors of 1-year all-cause and cardiovascular mortality in patients that underwent TAVR. This multivariable model was built by selecting variables that satisfied the entry criterion of $P < 0.1$ in a univariate 1-year mortality analysis: body mass index, chronic lung disease, peripheral artery disease, frailty, chronic renal failure, alternative access, STS score, left ventricular ejection fraction, and MAC. In order to assess predictors of new permanent pacemaker implantation (PPI) we performed a logistic regression analysis including baseline atrial fibrillation, post-dilatation (balloon aortic valvuloplasty following valve deployment), left bundle branch block, right bundle branch block, MAC, LVOT calcification, aortic valve calcification, valve type (self-expandable vs. balloon expandable), and valve size (23 mm/26 mm vs. 29 mm/31 mm). Patients who had PPI before TAVR were excluded from this analysis. This model was evaluated using Hosmer–Lemeshow goodness of fit test and *C*-statistics. All of the analyses were considered significant at a two-tailed *P* value of less than 0.05. The SPSS statistical package, version 20.0 was used to perform all statistical evaluation (SSPS Inc. Chicago, IL, USA).

Results

Overall, 761 out of 782 patients with severe AS that underwent TAVR at our institution during the study period had pre-TAVR CT scan available for analysis. From this cohort, 375 (49.3%) had MAC and 386 (50.7%) did not have MAC. Mild MAC was present in 231/761 patients (30.4%), moderate MAC in 72/761 patients (9.5%) and severe MAC in 72/761 patients (9.5%) (*Figure 2*).

Baseline characteristics

The baseline clinical patient characteristics and pre-TAVR imaging details of the study population are shown in *Table 1*. The average age was 81.2 ± 9.0 for patients with no MAC compared to 83.0 ± 8.5 for patients with MAC ($P = 0.004$). Patients with no MAC had male predominance (70.2%), compared with 1:1 male:female ratio among patients with MAC ($P < 0.001$). Chronic renal failure was more prevalent in patients with MAC (21.9% vs. 14.2%; $P = 0.01$). Patients with severe MAC had similar chronic renal failure prevalence as patient with no MAC (13.9%). The STS score was significantly higher for patients with MAC (8.8 ± 5.7 vs. 7.5 ± 4.3; $P < 0.001$). The MAC group had significantly higher baseline left ventricular ejection fraction, and higher aortic valve mean/peak echo gradients (59.5% and 46.7/77.9 mmHg vs. 54.3% and 44.3/74.6 mmHg, respectively; $P < 0.05$ for all). Baseline MR grades were similar between both groups (*Table 1*). CT scan analysis demonstrated significantly higher prevalence of LVOT calcification (51.2% vs. 39.9%; $P = 0.002$) and lower mean annulus diameter and area for patients with MAC. The mean MAC volume with HU-850 threshold was 117 ± 107 mm^3, 532 ± 245 mm^3, and 2247 ± 1520 mm^3 for the mild,

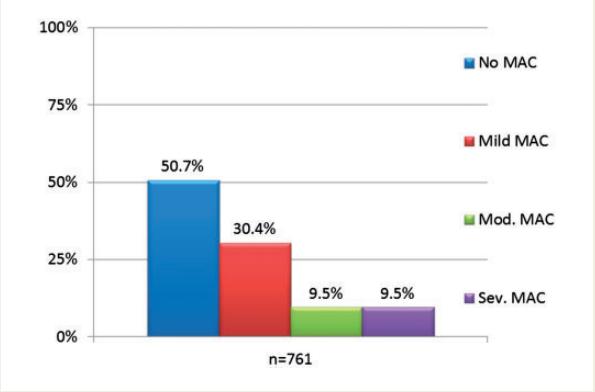


Figure 2 Prevalence of MAC classified to severity grades with CT in patients with severe AS.

moderate, and severe MAC groups, respectively ($P < 0.001$). The mean MAC maximal thickness was 5.1 ± 1.9 mm, 7.7 ± 1.7 mm, and 11.4 ± 3.6 mm for the mild, moderate, and severe MAC groups, respectively ($P < 0.001$).

Procedural details

Procedural details are shown in *Table 2*. Overall, the transfemoral approach was used in 86.6% of the cases, transapical approach in 5.1%, transaortic approach in 7.4%, and subclavian approach in 0.9%. Device success rate was 95.6% (369 of 386) for patients with no MAC compared with 94.9% (356 of 375) for patients with MAC ($P = 0.67$). Total fluoroscopy time and total contrast used were similar between groups. There were similar rates of post-procedural PVR and aortic valve gradients in patients with and without MAC (*Table 2*).

Table 1 Baseline patient characteristics

	No MAC ($n = 386$)	MAC ($n = 375$)	*P*-value	Mild/moderate MAC ($n = 303$)	Severe MAC ($n = 72$)
Age (years)	81.2 ± 9.0	83.0 ± 8.5	0.004	83.1 ± 9.0	82.5 ± 9.0
Male	271 (70.2)	188 (50.1)	<0.001	160 (52.8)	28 (38.9)
BMI (kg/m^2)	26.7 ± 5.6	26.9 ± 5.8	0.50	26.9 ± 5.7	27.4 ± 6.6
Hypertension	347 (89.9)	346 (92.3)	0.25	278 (91.7)	68 (94.4)
Diabetes mellitus	125 (32.4)	119 (31.7)	0.85	97 (32.0)	22 (30.6)
CAD	260 (67.4)	228 (60.8)	0.06	185 (61.1)	43 (59.7)
Previous CABG	127 (32.9)	76 (20.3)	<0.001	64 (21.1)	12 (16.7)
PAD	144 (37.3)	128 (34.1)	0.36	101 (33.3)	27 (37.5)
Previous Stroke/TIA	80 (20.7)	75 (20)	0.80	50 (16.5)	25 (34.7)
Chronic lung disease	153 (39.6)	132 (35.2)	0.21	104 (34.3)	28 (38.9)
Chronic renal failure[a]	55 (14.2)	82 (21.9)	0.01	72 (23.8)	10 (13.9)
Previous pacemaker	91 (23.6)	73 (19.5)	0.17	55 (18.2)	18 (25.0)
Atrial fibrillation	123 (31.9)	133 (35.5)	0.29	106 (35.0)	27 (37.5)
Frailty	130 (33.7)	136 (36.3)	0.45	105 (34.7)	31 (43.1)
STS score (%)	6.3 (4.5-9.2)	7.1 (5.0-10.6)	0.001	7.2 (4.9-11.0)	6.8 (5.4-9.4)
LV ejection fraction (%)	54.3 ± 15.5	59.5 ± 13.8	<0.001	58.7 ± 14.0	62.8 ± 12.3
LV end systolic diameter (cm)	3.3 ± 0.9	3.0 ± 0.8	<0.001	3.1 ± 0.8	2.8 ± 0.7
LV end diastolic diameter (cm)	4.6 ± 0.8	4.4 ± 0.7	0.01	4.5 ± 0.7	4.3 ± 0.8
LV mass index (g/m^2)	112.3 ± 36.4	111.2 ± 32.8	0.71	110.0 ± 32.3	115.9 ± 34.6
AVA (cm^2)	0.64 ± 0.16	0.63 ± 0.16	0.35	0.63 ± 0.16	0.64 ± 0.17
AV mean gradient (mmHg)	44.3 ± 13.5	46.7 ± 13.7	0.02	46.5 ± 14.0	47.3 ± 12.4
AV maximal gradient (mmHg)	74.6 ± 21.1	77.9 ± 21.7	0.03	77.5 ± 22.1	79.5 ± 19.9
MV mean gradient (mmHg)	0.4 ± 1.3	1.9 ± 2.8	<0.001	1.3 ± 2.3	4.3 ± 3.7
Pre-procedural mitral regurgitation:					
None/trace	108 (28.0)	95 (25.3)	0.82	78 (25.7)	17 (23.6)
Mild	150 (38.9)	148 (39.5)		122 (40.3)	26 (36.1)
Moderate	98 (25.4)	104 (27.7)		84 (27.7)	20 (27.8)
Severe	30 (7.8)	28 (7.5)		19 (6.3)	9 (12.5)
CT mean annulus diameter (mm)	24.7 ± 2.5	23.8 ± 2.8	<0.001	24.0 ± 2.8	23.4 ± 2.8
CT mean annulus area (mm^2)	478 ± 96	452 ± 98	0.001	456 ± 97	435 ± 102
CT mean AV Agatston calcification score (AU)	3473 ± 2151	3783 ± 2161	0.18	3772 ± 2060	3826 ± 2543
CT LVOT calcification	154 (39.9)	192 (51.2)	0.002	147 (48.5)	45 (62.5)

Values are mean ± SD or *n* (%), or median (interquartile range).
[a]Creatinine clearance < 30 mL/min/m^2.
AU, Agatston units; AV, aortic valve; AVA, aortic valve area; BMI, body mass index; CAD, coronary artery disease; CABG, coronary artery bypass graft; CT, computed tomography; LV, left ventricular; LVOT, left ventricular outflow tract; MAC, mitral annular calcification; MV, mitral valve; PAD, peripheral artery disease; STS, Society of Thoracic Surgeons; TIA, transient ischemic attack.

Table 2 Procedural data

	No MAC (n = 386)	MAC (n = 375)	P-value	Mild/moderate MAC (n = 303)	Severe MAC (n = 72)
Implanted valve type					
Edwards-SAPIEN	97 (25.1)	100 (26.7)	0.88	82 (27.1)	18 (25.0)
Sapien-XT	169 (43.8)	165 (44.0)		138 (45.5)	27 (37.5)
Sapien 3	89 (23.1)	78 (20.8)		60 (19.8)	18 (25.0)
Corevalve	31 (8.0)	32 (8.5)		23 (7.6)	9 (12.5)
Implanted valve size					
23 mm	83 (21.5)	135 (36.0)	<0.001	101 (33.3)	34 (47.2)
26 mm	176 (45.6)	164 (43.7)		137 (45.2)	27 (37.5)
29 mm	116 (30.1)	67 (17.9)		58 (19.1)	9 (12.5)
31 mm	11 (2.8)	9 (2.4)		7 (2.3)	2 (2.8)
Vascular access					
Transfemoral	333 (86.3)	326 (86.9)	0.30	264 (87.1)	62 (86.1)
Transapical	23 (6.0)	16 (4.3)		14 (4.6)	2 (2.8)
Transaortic	29 (7.5)	27 (7.2)		19 (6.3)	8 (11.1)
Subclavian	1 (0.3)	6 (1.6)		6 (2.0)	0
Device success	369 (95.6)	356 (94.9)	0.67	290 (95.7)	66 (91.7)
2nd valve	14 (3.6)	15 (4.0)	0.79	9 (3.0)	6 (8.3)
Post-dilatation	37 (9.6)	44 (11.7)	0.62	36 (11.9)	8 (11.1)
Valve embolization	4 (1.0)	2 (0.5)	0.69	1 (0.3)	1 (1.4)
Fluoroscopy time (min)	15.8 ± 8.9	16.8 ± 8.4	0.12	17.1 ± 8.7	15.6 ± 7.0
Total contrast used (mL)	83.4 ± 44.6	85.4 ± 39.1	0.54	86.8 ± 39.8	79.9 ± 35.8
TEE Post-procedural PVR					
None/trace	300 (77.7)	268 (71.5)	0.19	217 (71.6)	51 (70.8)
Mild	88 (22.8)	92 (24.5)		71 (23.4)	21 (29.2)
Moderate-severe	8 (2.1)	15 (4.0)		15 (5.0)	0
Post-procedural AV gradient (mmHg)	5.7 ± 5.0	5.7 ± 5.1	0.94	5.7 ± 5.2	5.6 ± 5.0

Values are mean ± SD or n (%).
AV, aortic valve; MAC, mitral annular calcification; PVR, paravalvular regurgitation; TEE, transesophageal echocardiography.

Mortality and major complications

Thirty-day clinical follow up was available for all patients. Thirty-day mortality and major complications were similar between patients with and without MAC (*Table 3*). NYHA functional class improvement of one grade or more was similar between groups (87.3% vs. 89.1% vs. 91.7% for the no MAC, non-severe MAC, and severe MAC, respectively; $P = 0.62$). There were 10/386 (2.6%, 1.42 per 100 person-years; 95% confidence interval [CI]: 0.76–2.64) cases of mortality within 30-days in the no MAC group vs. 15/375 (4.0%, 2.27 per 100 person-years; 95% CI: 1.37–3.77) in the MAC group (log rank $P = 0.28$). Mortality in patients with mild/moderate MAC was 3.3% (1.84 per 100 person-years; 95% CI: 0.99–3.41) at 30-days and 6.9% (4.35 per 100 person-years; 95% CI: 1.81–10.46) in patients with severe MAC (log-rank $P = 0.06$ for severe vs. no MAC). One-year mortality follow-up data were available for 750/761 patients (98.6%). The mean follow up period was 21.5 ± 11.3 months. One-year mortality was 47/381 (12.3%, 6.69 per 100 person-years; 95% CI: 5.03–8.91) in patients with no MAC vs. 56/368 (15.2%, 8.51 per 100 person-years; 95% CI: 6.55–11.06) in patient with MAC (log rank $P = 0.24$). Patients with mild/moderate MAC had 13.7% (7.54 per 100 person-years; 95% CI: 5.55–10.24) 1-year mortality rate and patients with severe MAC had 21.7% (13.16 per 100 person-years; 95% CI: 7.94–21.84) (log-rank $P = 0.03$ for severe vs. no MAC; *Summarizing Figure*). One-year cardiovascular mortality was 4.7%, 2.56 per 100 person-years; 95% CI: 1.61–4.07 (18/381) in patient with no MAC vs. 6.5%, 3.66 per 100 person-years; 95% CI: 2.45–5.46 (24/368) in patient with MAC (log-rank $P = 0.27$). Patients with mild/moderate MAC had 5.4%, 2.95 per 100 person-years; 95% CI: 1.81–4.82 1-year cardiovascular mortality rate and patients with severe MAC had 11.6%, 7.02 per 100 person-years; 95% CI: 3.51–14.04 (log-rank $P = 0.02$ for severe vs. no MAC). Kaplan–Meier all-cause survival analysis was performed for both groups up to 36 months after TAVR. There was similar survival between patients with and without MAC ($P = 0.13$, log-rank test; *Figure 3A*). Sub-group comparison showed that patients with non-severe (mild or moderate) MAC had similar mortality to patients with no MAC, while patients with severe MAC had increased mortality ($P = 0.046$, log-rank test; *Figure 3B*, see Supplementary material on line, *Figure S1*).

Multivariable analyses were performed to evaluate the independent effect of MAC on overall and 1-year mortality and cardiovascular mortality. Overall, there were 207 deaths (mortality event rate 151.8 per 1000 person-years, 95% CI 132.5–173.9) among the 761 patients

Table 3 Clinical outcome at 30-days

	No MAC (n = 386)	MAC (n = 375)	P-value	Mild/moderate MAC (n = 303)	Severe MAC (n = 72)
Mortality or major complication	43 (11.1)	45 (12.0)	0.71	34 (11.2)	11 (15.3)
Odds ratio (95% CI) vs. no MAC		1.09 (0.70–1.70)	0.71	1.01 (0.63–1.62)	1.44 (0.70–2.94)
Mortality	10 (2.6)	15 (4.0)	0.28	10 (3.3)	5 (6.9)
CVA/TIA	12 (3.1)	8 (2.1)	0.40	5 (1.7)	3 (4.2)
Myocardial infarction	1 (0.3)	3 (0.8)	0.37	3 (1.0)	0
Respiratory failure	10 (2.6)	12 (3.2)	0.62	11 (3.6)	1 (1.4)
Cardiogenic shock	7 (1.8)	6 (1.6)	0.82	5 (1.7)	1 (1.4)
Cardiac tamponade	1 (1.1)	2 (0.4)	0.42	2 (0.7)	1 (1.4)
Major bleeding	11 (2.8)	19 (5.1)	0.12	15 (5.0)	4 (5.6)
Major vascular complications	6 (1.6)	16 (4.3)	0.08	13 (4.3)	3 (4.2)
Minor vascular complications	35 (9.1)	32 (8.5)	0.80	30 (9.9)	2 (2.8)
New permanent pacemaker implantation[a]	37 (12.4)	33 (10.7)	0.53	19 (7.5)	14 (25.5)
Acute kidney injury stage 3	9 (2.3)	3 (0.8)	0.14	3 (1.0)	0

Values are n (%).
CI, confidence interval; CVA, cerebrovascular accident; MAC, mitral annular calcification; TIA, transient ischemic attack.
[a]155 patients with pacemaker implantation before TAVR were excluded.

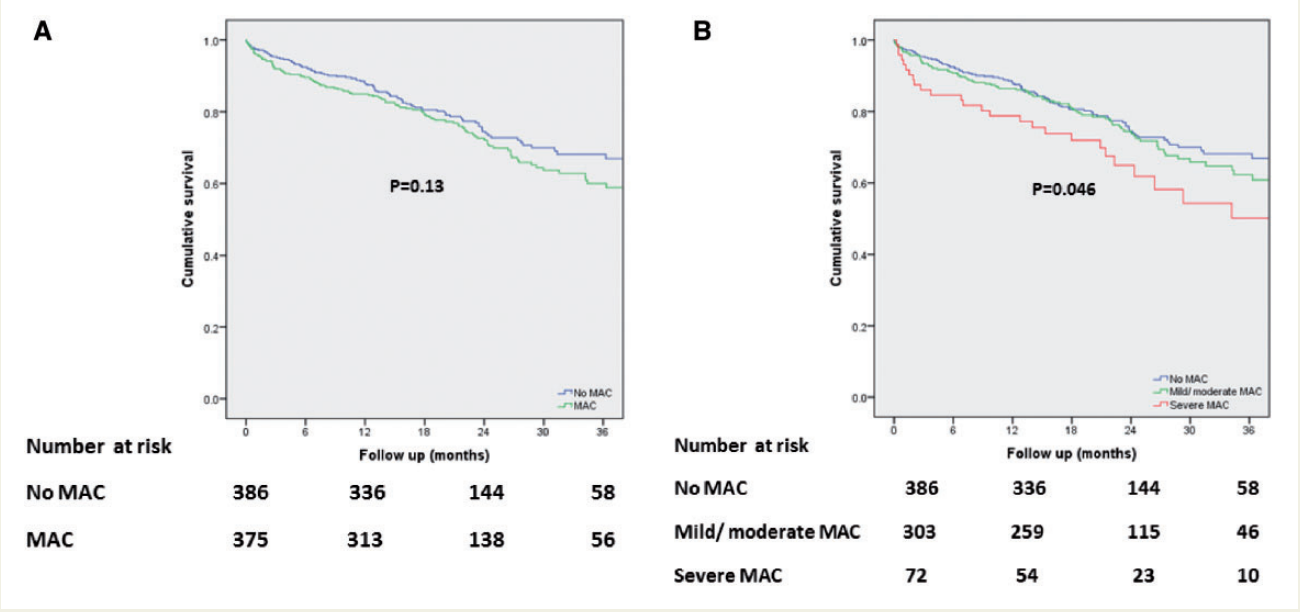


Figure 3 Overall survival during the study follow-up period. (*A*) Kaplan–Meier curves for overall survival in patients with no MAC compared with patient with MAC up to 36 months (P = 0.13, log-rank test). (*B*) Kaplan–Meier curves for overall survival in patients with no MAC vs. patients with mild or moderate MAC vs. patients with severe MAC up to 36 months (P = 0.046, log-rank test).

during the follow-up period, of which 85 were of cardiovascular cause. The mortality rates for the no MAC, any MAC, mild/moderate, and severe MAC in 1000 person-years were 136.3 (95% CI: 111.6–166.5), 168.3 (95% CI: 139.7–202.7), 154.2 (95% CI: 124.5–191.0), and 235.0 (95% CI: 161.2–342.7), respectively (log-rank P-value 0.046 for three groups and 0.01 for severe vs. no MAC groups). We performed a univariable analysis of predictors for overall and 1-year all-cause mortality (*Table 4* and see Supplementary material online, *Table S1*, respectively). Cox regression multivariable analysis included 19 different variables (see statistical analysis section), with Harrel's C-statistic of 0.7079. The assumption of proportional hazards was met for both overall and for the individual predictors; and the goodness of fit was excellent (P = 0.86). Severe MAC was found to be an independent strong predictor of overall all-cause mortality following

Table 4 Multivariable Cox proportional hazard analysis of overall mortality

Variable	Univariable analysis			Multivariable analysis		
	Hazard ratio	95% confidence interval	*P*-value	Hazard ratio	95% confidence interval	*P*-value
MAC						
MAC vs. no MAC	1.23	0.94–1.62	0.13			
Non-severe vs. no MAC	1.13	0.85–1.52	0.41	1.13	0.82–1.55	0.47
Severe vs. no MAC	1.71	1.12–2.62	0.01	1.95	1.24–3.07	**0.004**
Age	1.02	1.01–1.04	0.01	1.00	0.98–1.02	0.96
Gender (male)	1.12	0.85–1.49	0.42	1.66	1.10–2.50	**0.02**
Body mass index (kg/m^2)	0.97	0.94–0.99	0.01	0.99	0.96–1.02	0.63
Diabetes mellitus	1.43	1.08–1.89	0.01	1.62	1.20–2.19	**0.002**
Hypertension	0.71	0.46–1.11	0.13			
Coronary artery disease	0.97	0.73–1.28	0.82	0.78	0.56–1.08	0.13
Previous coronary artery bypass graft or valve surgery	0.91	0.68–1.20	0.55	0.72	0.50–1.05	0.09
Peripheral artery disease	1.25	0.95–1.64	0.12	1.22	0.90–1.64	0.20
Previous Stroke/TIA	1.20	0.87–1.67	0.27	1.07	0.76–1.50	0.72
Chronic lung disease	1.24	0.94–1.64	0.12	1.18	0.86–1.62	0.31
Chronic renal failure (glomerular filtration rate <30 mL/min/m^2)	2.61	1.96–3.50	<0.001	1.72	1.18–2.50	**0.01**
Previous pacemaker	1.29	0.94–1.77	0.11			
Atrial fibrillation	1.38	1.05–1.82	0.02	1.33	0.99–1.80	0.06
Frailty	1.78	1.35–2.34	<0.001	1.38	1.02–1.88	**0.04**
Society of Thoracic Surgeons score (%)	1.09	1.07–1.11	<0.001	1.06	1.03–1.09	**<0.001**
Left ventricular ejection fraction	0.99	0.98–0.99	0.002	0.99	0.98–1.00	**0.02**
AV mean gradient (mmHg)	0.99	0.98–1.00	0.01	0.99	0.98–1.00	0.14
AVA (cm^2)	0.50	0.20–1.26	0.14			
CT mean annulus diameter (mm)	0.99	0.94–1.04	0.68	0.97	0.90–1.04	0.39
CT AV Agatston calcification score	1.00	0.99–1.01	0.91			
CT LVOT calcification	1.12	0.85–1.47	0.41	1.08	0.81–1.46	0.60
Alternative access (transapical/transaortic/subclavian)	1.95	1.40–2.73	<0.001	1.87	1.28–2.73	**0.001**

AV, aortic valve; AVA, aortic valve area; CT, computed tomography; LVOT, left ventricular outflow tract; MAC, mitral annular calcification; TIA, transient ischemic attack.

TAVR (hazards ratio [HR] 1.95, 95% CI 1.24–3.07; $P = 0.004$) (*Table 4*, *Figure 4*). The incremental value of MAC group was significant, per the likelihood ratio test ($P = 0.03$). Other independent predictors of mortality in this model included diabetes mellitus (HR 1. 62), chronic renal failure (HR 1.72), frailty (HR 1.38), STS score (HR 1.06), left ventricular ejection fraction (1.01), and alternative access (HR1.87). Severe MAC was also found to be an independent strong predictor of overall cardiovascular mortality following TAVR (HR 2.35, 95% CI 1.19–4.66; $P = 0.01$). Overall there were 103 deaths at 1-year follow-up and 42 were of cardiovascular cause. Logistic regression multivariable analysis included nine variables (see statistical analysis section). Severe MAC was found to be an independent strong predictor of 1-year all-cause mortality following TAVR (Odds ratio [OR] 2.30, 95% CI 1.14–4.66; $P = 0.02$) (see Supplementary material online, *Table S1*). Other independent predictors of 1-year mortality in this model included chronic lung disease (OR 1.70), chronic renal failure (OR 2.29), STS score (OR 1.05), left ventricular ejection fraction (OR 1.01), and alternative access (OR 2.02). Severe MAC was also found to be an independent strong predictor of 1-year cardiovascular mortality following TAVR (OR 3.75, 95% CI 1.46–9.65; $P = 0.01$).

Need for new PPI

Overall there were 70 (11.6%) new PPI among the 606 patients that did not have pacemaker implanted prior to TAVR. New PPI was required in12.4% of the patients with no MAC vs. 10.7% of the patients with MAC ($P = 0.53$). Sub-group analysis revealed that patients with non-severe MAC had 7.5% (19/252) new PPI rate and patients with severe MAC had 25.5% (14/55) ($P = 0.01$ for severe MAC vs. no MAC; *Table 3*, *Summarizing Figure*). A univariable and multivariable analysis of predictors for new PPI was performed (*Table 5*). The *C*-statistic for the multivariable model was 0.7858, and the model's goodness of fit was $P = 0.56$. Severe MAC was found to be an independent strong predictor of new PPI after TAVR (OR 2.83, 95% CI

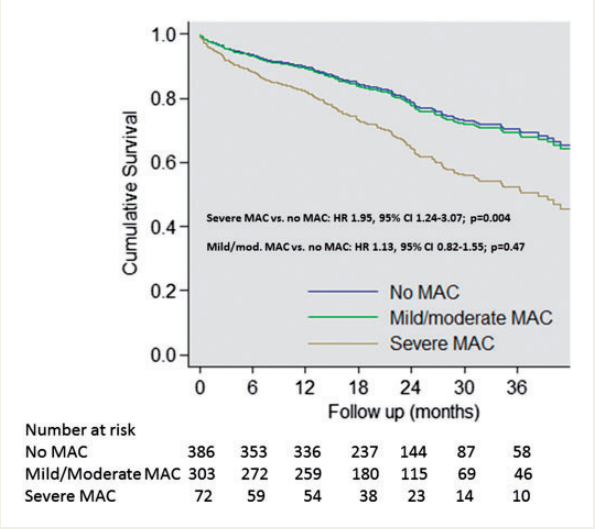


Figure 4 Cox regression multivariable survival curves up to 36 months according to MAC severity. Severe MAC was found to be an independent strong predictor of overall mortality following TAVR (HR 1.95 95% CI 1.24–3.07; P = 0.004). Non-severe MAC was not found to predict overall mortality following TAVR (HR 1.13 95% CI 0.82–1.55; P = 0.47). The model was adjusted to patient age, body mass index, gender, diabetes mellitus, coronary artery disease, chronic lung disease, previous stroke/transient ischemic attack, peripheral artery disease, frailty, prior cardiac surgery, chronic renal failure, alternative access, STS score, left ventricular ejection fraction, mean aortic valve gradient, CT mean annulus diameter, and LVOT calcification.

1.08–7.47; P = 0.03). The incremental prediction value of the severe MAC group was significant (P = 0.003). Other independent predictors of new PPI included right bundle branch block (OR 6.99) and self-expandable valve (OR 4.89). LVOT calcification was significantly found to predict new PPI only in the univariable model.

Mitral valve disease

Pre-TAVR MR distribution was similar between groups (*Table 1*). Overall, improvement of one grade or more in MR between patients with and without MAC was similar (31.0% vs. 32.5% respectively, P = 0.70). Sub-group analysis revealed that 33.2% of patients with non-severe MAC had one grade or more MR improvement vs. 22.0% of patients with severe MAC (P = 0.14 for severe MAC vs. no MAC). MR improvement was not associated with 1-year or with overall mortality (1-year mortality: OR 0.67, 95% CI 0.32–1.40, P = 0.29; overall mortality: HR 0.86, 95% CI 0.58–1.29, P = 0.47). Patients with severe MAC had reduction in pulmonary artery systolic pressure (PASP) from 44.5 ± 15 mmHg to 40.5 ± 12 mmHg before and after TAVR, respectively. Patients with no MAC had reduction in PASP from 39.8 ± 15 mmHg to 34.9 ± 13 mmHg before and after TAVR, respectively. Pre- and post-TAVR gradients >10 mmHg were found in one patient with no MAC (0.26%), one patient with non-severe MAC (0.33%) and five patients with severe MAC (6.9%). Post-procedural mitral valve gradient ≥5 mmHg was found in 3.5% of the patients without MAC vs. 22.5% of the patients with MAC (P < 0.001). In the severe MAC sub-group, 50.7% had gradient ≥5 mmHg vs. 15.9% in the non-severe MAC sub-group (P < 0.001). Post-procedural mitral valve gradient ≥5 mmHg was not associated with overall mortality (HR 0.93, 95% CI 0.61–1.43, P = 0.75).

Discussion

Degenerative calcification of the mitral annulus is accelerated by conditions that increase mitral valve stress such as aortic valve stenosis.[1,20] Nonetheless, there is limited data on the prevalence of MAC among patients with severe AS and its influence on clinical outcomes following TAVR. The results of the present study indicate that half of the patients with severe AS evaluated for TAVR were found to have at least some degree of MAC in pre-TAVR cardiac CT. Severe MAC, defined as calcification in more than half of the mitral annulus circumference was found in 10% of the entire cohort. Similar short and mid-term clinical outcomes were found in patients with and without MAC, but severe MAC was a strong independent predictor of all-cause and cardiovascular mortality and of new PPI following TAVR. Severe MAC was also found to be strongly associated with significant gradient (≥5 mmHg) across the mitral valve post-TAVR.

The association between MAC and calcific AS was first established in 1954 by Simon and Liu,[21] who found AS in 27% of 59 autopsy specimens of patients with MAC. In a retrospective evaluation of echocardiograms, Movahed et al.[6] noted that MAC was present in 15% of patients with AS compared with only 6% of patients without AS. The prevalence of echocardiography diagnosed MAC was found to be 23% in 219 patients with mild to moderate AS.[22] A recent study examining CT scans of 106 patients with severe AS that underwent aortic valve replacement showed evidence of MAC in 53% of the patients.[16] The present study included a relatively large cohort of patient with severe AS (761 patients). It demonstrated MAC to be prevalent in 49.3% of the cases. Severity of MAC classified with pre-TAVR CT scans was mild in 30.4%, moderate in 9.5% and severe in 9.5%. Increased mitral valve stress is the underlying mechanism contributing to this high prevalence of MAC among a population of elder patients with severe AS and hypertension.[1] It is mediated by increased left ventricular peak systolic pressure and therefore increased mitral valve closing pressure resulting in excess annular tension and subsequently annulus degeneration.

Few previous studies have demonstrated correlation between MAC and increased cardiovascular and all-cause mortality.[4,23,24] Fox et al. examined the association between MAC assessed by echocardiography and the incidence of cardiovascular death and all-cause death among 169 subjects with MAC vs. 1028 subjects without MAC over 16 years of follow-up.[4] In multivariable adjustment for traditional cardiovascular risk factors, MAC was associated with an increased risk cardiovascular death (HR-1.6) and all-cause death (HR-1.3). Similar findings were demonstrated by Ramaraj et al. during 12 years of follow-up.[24] In the present cohort of patients with severe AS, MAC (including all grades of severity) was not found to increase mortality during a mean follow-up period of less than 2 years. Nonetheless, utilizing CT for MAC assessment and sub-dividing the patients according to MAC severity have enabled to recognize a strong independent

Table 5 Multivariable logistic regression analysis of new PPI following TAVR (at 30-days)

Variable	Univariable analysis			Multivariable analysis		
	Odds ratio	95% confidence interval	*P*-value	Odds ratio	95% confidence interval	*P*-value
MAC						
MAC vs. no MAC	0.85	0.52–1.41	0.53			
Non-severe vs. no MAC	0.58	0.32–1.03	0.07	0.74	0.35–1.58	0.44
Severe vs. no MAC	2.42	1.20–4.86	0.01	2.83	1.08–7.47	**0.03**
Left bundle brunch block	0.64	0.22–1.82	0.40	0.87	0.28–2.77	0.82
Right bundle brunch block	5.75	3.25–10.15	<0.001	6.99	3.34–14.62	**<0.001**
Atrial fibrillation	1.11	0.64–1.93	0.71	0.87	0.41–1.86	0.73
Post-dilatation	2.49	1.29–4.78	0.01	1.54	0.62–3.84	0.36
CT AV Agatston calcification score[a]	1.01	0.99–1.02	0.14	1.00	0.98–1.02	0.98
Valve size (29/31 mm vs. 23/26 mm)	2.13	1.27–3.57	0.004	1.67	0.79–3.50	0.18
CT LVOT calcification	1.92	1.15–3.20	0.01	1.88	0.92–3.86	0.09
Self-expandable valve	5.84	3.05–11.19	<0.001	4.89	1.42–16.91	**0.01**

AV, aortic valve; CT, computed tomography; LVOT, left ventricular outflow tract; MAC, mitral annular calcification.
[a]Odds ratio per 100 Agatston units increment.

correlation between severe MAC and mortality (both all-cause and cardiovascular) following TAVR. In both analyses of overall mortality up to 3-years and of 1-year mortality, severe MAC was determined to be a strong predictor of death and of cardiovascular death following this procedure (*Figures 3B and 4*, *Table 4* and Supplementary ma terial online, *Table S1*). Possible explanations for these findings are that MAC may be a marker for atherosclerotic disease burden and for end-organ damage or that other unmeasured factors such as metabolic, inflammatory and haemostatic risk factors might be responsible for the increase risk of mortality in patients with MAC and severe AS following TAVR.

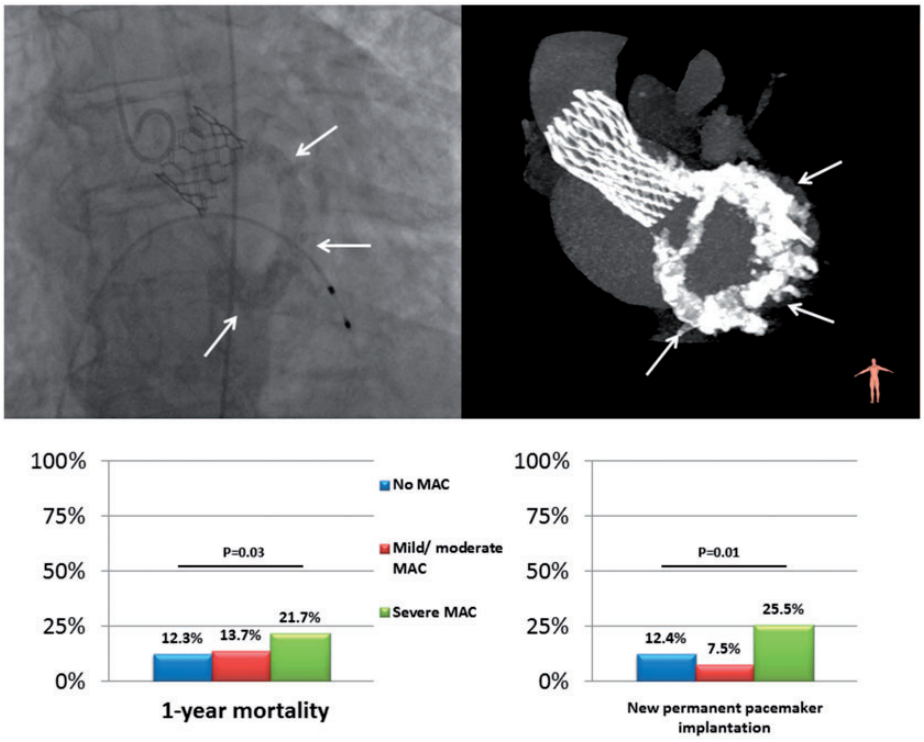
MAC generally has little or no impact on left ventricular inflow or mitral valve function because unlike in rheumatic mitral involvement, there is usual sparing of the leaflet commissures in these patients.[1] Nonetheless, severe calcification of the mitral annulus may occasionally cause MR or stenosis.[6,25] Movahed et al. examined 24 380 echocardiograms and found MAC to be present in 11.7% of patients with MR vs. 4.3% without MR.[6] A possible mechanism for this association is that calcium infiltration of the base of the posterior leaflet reduces leaflet mobility, increases traction on the chordae and elevates the leaflets, which facilitates chordal elongation or rupture, causing secondary MR. In a small study of 35 patients, Durst et al.[26] found MAC with encroaching onto the leaflets and restricting leaflet motion to be associated with a reduction in MR improvement after TAVR. In our current analysis, pre-TAVR MR distribution was similar between groups and improvement of one grade or more in MR between patients with and without MAC was similar at 1-month echocardiography follow-up. Longer-term follow-up may be needed to demonstrate changes in MR improvement rates following this procedure.

Interestingly, the present study revealed a strong association between MAC and significant gradients across the mitral valve. Half of the patients with severe MAC had at least 5 mmHg post-TAVR mitral valve gradient. Previously, the existence of significant mitral valve gradient in patients with MAC was reported to be rare.[1,25,27] Nonetheless, when MAC is extensive it may invade the inter-annular fibrosa and limit leaflets mobility. It should be highlighted, that with the current follow-up period, we could not demonstrate association between post-TAVR significant mitral valve gradient and mortality. Nonetheless, a careful assessment of mitral valve stenosis severity and post-TAVR symptomatic status may help to identify a subset of patients that can benefit from mitral valve intervention after TAVR.

Examining the short-term effect of MAC on the clinical outcomes after TAVR revealed no correlation between MAC and 30-day mortality or major complications. Nonetheless, severe MAC was found to be a strong predictor of new PPI following TAVR (OR 2.83, *Table 5*). Self-expandable valve implantation and pre-procedural right bundle branch block are both strong predictors for new PPI following TAVR in the present cohort as well as in previous reports.[28] MAC was previously found to be related to new PPI after TAVR in one relatively small cohort of patients that had self-expandable valve implantations.[29] In an analysis of 105 patients, Boerlage-Van Dijk et al. found MAC (OR 1.3) and preexisting right bundle branch block (OR 8.5) as independent predictors for PPI after TAVR. The association between MAC and conduction system abnormalities was noted in the earliest reports of this entity.[1] Patients with MAC have higher prevalence of atrioventricular block, bundle branch block and intra-ventricular conduction delay. Higher incidence of conduction disease may be due to direct extension of calcific deposits to the region of the atrioventricular node and the bundle of His or due to diffuse degenerative conduction system disease that is frequently associated with MAC.[1,30] The trauma inflicted by the valve stent frame and by the valvuloplasty balloon during pre or post-dilatation and during valve deployment is more likely to result in a high degree atrioventricular block in patients with severe MAC as demonstrated in the current analysis.

Study limitations

A main limitation of the present study is that it represents a retrospective, single-center experience with a limited follow-up period. The sub-group of patients with severe MAC was relatively small and likely had high degree of confounding. Nonetheless, despite the fact



Summarizing Figure Concomitant MAC and severe AS: influence on clinical outcomes following TAVR. (Top left panel) Cardiac fluoroscopy demonstrating circumferential severe MAC (white arrows) in a patient that underwent Sapien 3 TAVR. (Top right panel) Cardiac CT with maximal intensity projection (MIP) at the mitral annular and aortic valve level demonstrating circumferential severe MAC (white arrows) in a patient that underwent CoreValve TAVR. (Bottom left panel) Patients with severe MAC had increased 1-year all-cause mortality following TAVR. (Bottom right panel) Patients with severe MAC had increased rate of new permanent pacemaker implantation at 30-days following TAVR.

that half of the patients with severe AS have MAC, previous studies that examined predictors of mortality and clinical outcome for these patients did not include MAC in their analysis. Future multi-center studies with larger number of patients and longer follow-up may further clarify this subject. Although severe MAC was found to be a strong predictor of all-cause mortality in the present study, the mechanism attributing to these results could not be determined.

Conclusion

Half of the patients with severe AS evaluated for TAVR were found to have MAC. Severe MAC is a strong predictor of all-cause and cardiovascular mortality and of conduction abnormalities following TAVR and should be included in future risk stratification models for TAVR. Severe MAC is associated with significant gradient across the mitral valve.

Clinical perspective

There is limited data on the prevalence of MAC among patients with severe AS and its influence on clinical outcomes following TAVR. Our data suggest that half of the patients with severe AS evaluated for TAVR have at least some degree of MAC in pre-TAVR cardiac CT. A subset of patients with concomitantly severe MAC and AS has increased risk for mortality and conduction abnormalities following TAVR. Future studies are needed to determine if patients with severe MAC and AS may benefit from earlier intervention and from lower threshold for PPI during follow-up after TAVR.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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References

1. Abramowitz Y, Jilaihawi H, Chakravarty T, Mack MJ, Makkar RR. Mitral annulus calcification. *J Am Coll Cardiol* 2015;**66**:1934–1941.

2. Kanjanauthai S, Nasir K, Katz R, Rivera JJ, Takasu J, Blumenthal RS, Eng J, Budoff MJ. Relationships of mitral annular calcification to cardiovascular risk factors: the Multi-Ethnic Study of Atherosclerosis (MESA). *Atherosclerosis* 2010;**213**:558–562.
3. Foley PW, Hamaad A, El-Gendi H, Leyva F. Incidental cardiac findings on computed tomography imaging of the thorax. *BMC Res Notes* 2010;**3**:326.
4. Fox CS, Vasan RS, Parise H, Levy D, O'donnell CJ, D'agostino RB, Benjamin EJ. Framingham Heart StudyMitral annular calcification predicts cardiovascular morbidity and mortality: the Framingham Heart Study. *Circulation* 2003;**107**:1492–1496.
5. Barasch E, Gottdiener JS, Larsen EKM, Chaves PHM, Newman AB, Manolio TA. Clinical significance of calcification of the fibrous skeleton of the heart and atherosclerosis in community dwelling elderly. The Cardiovascular Health Study (CHS). *Am Heart J* 2006;**151**:39–47.
6. Movahed M-R, Saito Y, Ahmadi-Kashani M, Ebrahimi R. Mitral annulus calcification is associated with valvular and cardiac structural abnormalities. *Cardiovasc Ultrasound* 2007;**5**:14.
7. Nair CK, Runco V, Everson GT, Boghairi A, Mooss AN, Mohiuddin SM, Sketch MH. Conduction defects and mitral annulus calcification. *Br Heart J* 1980;**44**:162–167.
8. Higgins J, Mayo J, Skarsgard P. Cardiac computed tomography facilitates operative planning in patients with mitral calcification. *Ann Thorac Surg* 2013;**95**:e9–11.
9. Johnson RC, Leopold JA, Loscalzo J. Vascular calcification: pathobiological mechanisms and clinical implications. *Circ Res* 2006;**99**:1044–1059.
10. Makkar RR, Fontana GP, Jilaihawi H, Kapadia S, Pichard AD, Douglas PS, Thourani VH, Babaliaros VC, Webb JG, Herrmann HC, Bavaria JE, Kodali S, Brown DL, Bowers B, Dewey TM, Svensson LG, Tuzcu M, Moses JW, Williams MR, Siegel RJ, Akin JJ, Anderson WN, Pocock S, Smith CR, Leon MB. PARTNER Trial InvestigatorsTranscatheter aortic-valve replacement for inoperable severe aortic stenosis. *N Engl J Med* 2012;**366**:1696–1704.
11. Kodali SK, Williams MR, Smith CR, Svensson LG, Webb JG, Makkar RR, Fontana GP, Dewey TM, Thourani VH, Pichard AD, Fischbein M, Szeto WY, Lim S, Greason KL, Teirstein PS, Malaisrie SC, Douglas PS, Hahn RT, Whisenant B, Zajarias A, Wang D, Akin JJ, Anderson WN, Leon MB. PARTNER Trial InvestigatorsTwo-year outcomes after transcatheter or surgical aortic-valve replacement. *N Engl J Med* 2012;**366**:1686–1695.
12. Nguyen G, Leipsic J. Cardiac computed tomography and computed tomography angiography in the evaluation of patients prior to transcatheter aortic valve implantation. *Curr Opin Cardiol* 2013;**28**:497–504.
13. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, Guyton RA, O'gara PT, Ruiz CE, Skubas NJ, Sorajja P, Sundt TM, Thomas JD. American College of Cardiology/American Heart Association Task Force on Practice Guidelines2014 AHA/ACC guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014;**63**:2438–2488.
14. Zoghbi WA, Enriquez-Sarano M, Foster E, Grayburn PA, Kraft CD, Levine RA, Nihoyannopoulos P, Otto CM, Quinones MA, Rakowski H, Stewart WJ, Waggoner A, Weissman NJ. American Society of Echocardiography. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. *J Am Soc Echocardiogr* 2003;**16**:777–802.
15. Baumgartner H, Hung J, Bermejo J, Chambers JB, Evangelista A, Griffin BP, Iung B, Otto CM, Pellikka PA, Quiñones M. American Society of Echocardiography, European Association of Echocardiography. Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice. *J Am Soc Echocardiogr* 2009;**22**:1–23–102.
16. Takami Y, Tajima K. Mitral annular calcification in patients undergoing aortic valve replacement for aortic valve stenosis. *Heart Vessels* 2016;**31**:183–188.
17. Jilaihawi H, Makkar RR, Kashif M, Okuyama K, Chakravarty T, Shiota T, Friede G, Nakamura M, Doctor N, Rafique A, Shibayama K, Mihara H, Trento A, Cheng W, Friedman J, Berman D, Fontana GP. A revised methodology for aortic-valvar complex calcium quantification for transcatheter aortic valve implantation. *Eur Heart J Cardiovasc Imaging* 2014;**15**:1324–1332.
18. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol* 1990;**15**:827–832.
19. Kappetein AP, Head SJ, Généreux P, Piazza N, Mieghem NM. V, Blackstone EH, Brott TG, Cohen DJ, Cutlip DE, Es G-A, van Hahn RT, Kirtane AJ, Krucoff MW, Kodali S, Mack MJ, Mehran R, Rodés-Cabau J, Vranckx P, Webb JG, Windecker S, Serruys PW, Leon MB. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. *J Am Coll Cardiol* 2012;**60**:1438–1454.
20. Silbiger JJ. Anatomy, mechanics, and pathophysiology of the mitral annulus. *Am Heart J* 2012;**164**:163–176.
21. Simon MA, Liu SF. Calcification of the mitral valve annulus and its relation to functional valvular disturbance. *Am Heart J* 1954;**48**:497–505.
22. Jassal DS, Tam JW, Bhagirath KM, Gaboury I, Sochowski RA, Dumesnil JG, Giannoccaro PJ, Jue J, Pandey AS, Joyner CD, Teo KK, Chan KL. Association of mitral annular calcification and aortic valve morphology: a substudy of the aortic stenosis progression observation measuring effects of rosuvastatin (ASTRONOMER) study. *Eur Heart J* 2008;**29**:1542–1547.
23. Ramaraj R, Manrique C, Hashemzadeh M, Movahed MR. Mitral annulus calcification is independently associated with all-cause mortality. *Exp Clin Cardiol* 2013;**18**:e5–e7.
24. Völzke H, Haring R, Lorbeer R, Wallaschofski H, Reffelmann T, Empen K, Rettig R, John U, Felix SB, Dörr M. Heart valve sclerosis predicts all-cause and cardiovascular mortality. *Atherosclerosis* 2010;**209**:606–610.
25. Muddassir SM, Pressman GS. Mitral annular calcification as a cause of mitral valve gradients. *Int J Cardiol* 2007;**123**:58–62.
26. Durst R, Avelar E, McCarty D, Poh K-K, Friera LF, Llano MF, Chu J, Anumandla AKR, Rodriguez LL, Mack MJ, Hanzel G, Kodali SK, Hung J, Picard MH. Outcome and improvement predictors of mitral regurgitation after transcatheter aortic valve implantation. *J Heart Valve Dis* 2011;**20**:272–281.
27. Nestico PF, Depace NL, Morganroth J, Kotler MN, Ross J. Mitral annular calcification: clinical, pathophysiology, and echocardiographic review. *Am Heart J* 1984;**107**:989–996.
28. Siontis GCM, Jüni P, Pilgrim T, Stortecky S, Büllesfeld L, Meier B, Wenaweser P, Windecker S. Predictors of permanent pacemaker implantation in patients with severe aortic stenosis undergoing TAVR: a meta-analysis. *J Am Coll Cardiol* 2014;**64**:129–140.
29. Boerlage-Van Dijk K, Kooiman KM, Yong ZY, Wiegerinck EMA, Damman P, Bouma BJ, Tijssen JGP, Piek JJ, Knops RE, Baan J. Predictors and permanency of cardiac conduction disorders and necessity of pacing after transcatheter aortic valve implantation. *Pacing Clin Electrophysiol PACE* 2014;**37**:1520–1529.
30. Takamoto T, Popp RL. Conduction disturbances related to the site and severity of mitral annular calcification: a two-dimensional echocardiographic and electrocardiographic correlative study. *Am J Cardiol* 1983;**51**:1644–1649.