Comparison of the Quantity of Calcium in the Aortic Valve and the Coronary Arteries in Men Versus Women Who Underwent Transcatheter Aortic Valve Implantation

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Several studies have shown an association between aortic stenosis (AS) and coronary atherosclerosis. This study aimed to evaluate the gender differences in aortic valve calcium (AVC) and coronary artery calcium (CAC) and the association between CAC and all-cause mortality in patients with severe AS. A total of 260 patients (80 ± 7 years, 39% men) with severe AS who were scheduled for transcatheter aortic valve implantation (TAVI) were included. AVC and CAC before TAVI were assessed by noncontrast cardiac computed tomography. Patients with coronary intervention or aortic valve replacement before cardiac computed tomography were excluded. Standard reference values of CAC score were used to classify the percentile groups and the distribution of AVC was assessed. The primary end point was all-cause mortality. In men, the AVC score was 3,911 Hounsfield units (HUs) (interquartile range [IQR] 2,525 to 5,259) and in women, 2,409 HU (IQR 1,588 to 3,359) (p <0.001). CAC score in men was 824 HU (IQR 328 to 1,855) and in women, 478 HU (IQR 136 to 962) (p <0.001). In men, the AVC score increased along with the CAC score, whereas in women, the AVC score was similar across the CAC percentile groups. During a median follow-up of 1,095 days, 59 patients (23%) died. No significant gender-difference was seen in all-cause mortality for CAC score (p = 0.187). Men with severe AS show higher AVC and CAC scores than women. Although the pattern of CAC distribution was similar between men and women, the AVC score increased along with the CAC score in men; whereas, in women, the AVC score remained similar across the various percentiles. CAC score was not associated with cumulative mortality in patients with severe AS who underwent TAVI. **(Am J Cardiol 2022;182:83−88)**

Calcific aortic stenosis (AS) valve is the most common valvular heart disease in the aging population.[1,2] Although the underlying pathophysiologic process of calcification of the aortic valve remains incompletely understood, several studies have shown an association between calcific AS, atherosclerosis, and the presence of cardiovascular risk factors.[1−4] Therefore, it has been hypothesized that calcific AS and coronary atherosclerosis share similar pathophysiologic mechanisms. Interestingly, various studies evaluating the aortic valve and coronary artery calcium (CAC) score with cardiac computed tomography (CT) have shown important gender differences.[5−7] Men tend to have higher loads of aortic valve calcium (AVC) and CAC than women. CAC measured on CT has also been considered as a risk marker for cardiovascular events, with patients showing a CAC score >400 Hounsfield units (HUs) having a significantly increased risk for an adverse event.[8,9] However, there are limited studies that explored the gender differences of the interaction between AVC and CAC and the association between CAC and all-cause mortality in patients with severe AS. Therefore, the present study evaluated the distribution of AVC and CAC in men and women with severe AS. In addition, the prognostic value of CAC in this population was evaluated.

Methods

A total of 260 patients with severe AS who underwent transcatheter aortic valve implantation (TAVI) were included. Patients with coronary artery bypass grafting, percutaneous coronary intervention, or aortic valve replacement before cardiac CT were excluded. The AVC and CAC scores were assessed using noncontrast-enhanced CT. The standard reference values of the CAC score for men and women were used to divide the population in percentile groups, and the distribution of AVC scores across those percentiles of CAC score was assessed.[10] Clinical and

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0002-9149/

https://doi.org/10.1016/j.amjcard.2022.07.008

demographic data were collected from the electronic patient records (EPD Vision, version 12.3.5.0, Leiden, The Netherlands). For this retrospective analysis, the institutional review board waived the need for patient written informed consent.

Transthoracic echocardiography was performed in patients at rest, before TAVI. With the patient in the left lateral decubitus position, 2-dimensional, color, and continuous- and pulsed wave Doppler data were obtained in the parasternal and apical views, using commercially available ultrasound systems (E9 and E95, GE Healthcare, Horten, Norway), equipped with M5S transducers. Data were stored digitally for offline analysis using the EchoPac software (version BT13; GE Medical Systems, Horten, Norway). Left ventricular (LV) volumes were measured on apical 2- and 4-chamber views and indexed to body surface area (BSA).[11] LV ejection fraction was calculated using the Simpson method.[11] LV dimensions were measured on the parasternal long-axis view and LV mass was calculated according to Devereux formula.[11] The aortic valve morphology was assessed on the parasternal short-axis images to identify the number of cusps (tricuspid vs bicuspid).[12] On the 3- and 5-chamber apical views, the peak aortic jet velocity was measured using continuous-wave Doppler and, according to the Bernoulli equation, the aortic valve mean and peak gradients were calculated. The pulsed wave Doppler images of the LV outflow tract were obtained from the same apical views and the aortic valve area (AVA) was calculated using the continuity equation. AVA was also indexed to BSA. Severe AS was defined an AVA <1.0 cm^2 or indexed AVA <0.6 cm^2/m^2.[12]

Multidetector row CT scans were performed using a 320-slice CT scanner (Aquilion ONE, Toshiba Medical Systems, Tochigi-ken, Japan) or with a 64-slice CT scanner (Aquilion 64, Toshiba Medical Systems).[13] The multidetector CT acquisition protocol started with a prospective calcium scan (collimation 4 × 3.0 mm, tube voltage and current of 120 kV and 200 mA), followed by the contrast-enhanced CT.[13] From the noncontrast-enhanced images, the Agatston AVC and CAC scores were assessed. Offline analysis of the data was performed in a remote workstation with dedicated CT software (Vitrea, Vital Images, Minnetonka, Minnesota).

The primary end point was all-cause mortality. Survival data were collected from the departmental Cardiology Information System (EPD version 12.6.2.0) and were complete for all patients.

Continuous variables are presented as mean ± SD if normally distributed and were analyzed using the unpaired Student's *t* test. Continuous variables that were not normally distributed are presented as median and interquartile range (IQR) and were analyzed using the Mann-Whitney *U* test. Categoric data are presented as frequencies and percentages and were analyzed using the chi-square test. Kaplan−Meier curves were performed for survival analysis, and differences between groups were analyzed using the log-rank test. A Cox proportional hazards model was conducted with gender and CAC >400 HU as co-variates. The groups were divided according to gender and CAC score < or >400 HU.[8,9] A 2-sided p <0.05 was considered statistically significant. Statistical analysis was performed using the SPSS software (version 25.0; IBM, Armonk, New York).

Results

Clinical characteristics of the patient population are shown in Table 1. A total of 260 patients, 102 men (mean age 79 ± 7 years) and 158 women (mean age 81 ± 7 years), were included. Women were significantly older, had a lower BSA, and less impaired renal function than men. Except for smoking, cardiovascular risk factors were not significantly different between both genders. There was no significant difference in medication use.

Echocardiographic and CT characteristics of the patient population are shown in Table 2. Women had significantly smaller LV end-systolic and end-diastolic volumes indexed than men. There was no significant difference between men and women regarding the morphology of the aortic valve. The AVC score was significantly higher in men than women (2,409 HU [IQR 1,588 to 3,359], p <0.001). Similarly, the CAC score was significantly higher in men (824 HU [IQR 328 to 1,855]) than in women (478 HU [IQR 136 to 962], p <0.001). The distribution of AVC and CAC scores in the patient population are shown in Fig. 1. Men had higher AVC and CAC scores compared with women. In men, the AVC score increased along with the CAC score, whereas in women the AVC scores were similar across the various percentiles of CAC score.

The Kaplan-Meier curve for all-cause mortality is shown in Fig. 2. During a median follow-up of 1,095 (IQR 581 to 1,095) days, 59 patients (23%) died. There was no significant difference in mortality rates between men and women for each of the CAC score groups (p = 0.187). The hazard ratio was increased for mortality in men and CAC score >400 HU; although, this did not reach statistical significance (Supplementary Table 1).

Discussion

The present study showed that there is a discordance between the interaction of CAC and AVC between gender, whereas the cumulative mortality was similar in men and women.

In both men and women, AVC and CAC scores have been associated with an increased risk of atherosclerotic cardiovascular events and all-cause mortality.[9,14−17] However, studies investigating the interaction between AVC and CAC scores in patients with severe AS are limited. Patients with severe AS tend to be older than the participants included in population-based studies, from which the categories of CAC score have been derived.[18] In addition, they frequently present with concomitant coronary artery disease.[19,20] Therefore, we investigated the interaction between these 2 CT-derived scores in a selected population, excluding patients with previous coronary artery or aortic valve intervention. Similar to previous studies, the present study demonstrated that men have higher AVC and CAC scores than women.[5−7] Importantly, men also showed an association between the CAC score and the AVC score (with both scores increasing in parallel), whereas women did not show an increase in the AVC score along with the

Table 1
Clinical characteristics

Variable	Total population(n = 260)	Men(n = 102)	Women(n = 158)	p-Value
Age (years)	80 ± 7	79 ± 7	81 ± 7	0.030
Body mass index (kg/m^2)	26 ± 5	27 ± 4	26 ± 6	0.637
Creatinine (μmol/liter)	88 (70-109)	100 (82-129)	80 (65-99)	<0.001
Systolic blood pressure (mmHg)	138 ± 23	134 ± 24	141 ± 23	0.024
Diastolic blood pressure (mmHg)	69 ± 13	70 ± 13	69 ± 13	0.425
CAD	46 (18%)	19 (19%)	27 (17%)	0.751
Diabetes mellitus	74 (28%)	35 (34%)	39 (25%)	0.093
Hypertension	192 (74%)	73 (72%)	119 (75%)	0.502
Dyslipidemia	135 (52%)	54 (53%)	81 (51%)	0.792
Smoker	69 (27%)	36 (35%)	33 (21%)	0.010
Family history of CAD	32 (23%)	10 (19%)	22 (26%)	0.372
β-blockers	138 (53%)	50 (49%)	88 (56%)	0.292
ACE inhibitors or ARB	129 (50%)	49 (48%)	80 (51%)	0.683
Statins	119 (46%)	54 (53%)	65 (41%)	0.062
Diuretics	157 (60%)	62 (61%)	95 (60%)	0.916
Aspirin	95 (37%)	39 (38%)	56 (35%)	0.648
Oral anticoagulants	102 (39%)	46 (45%)	56 (35%)	0.120

Values are mean ± SD, median [IQR] or n (%). Diabetes mellitus was defined as having a history of diabetes mellitus and medical therapy with insulin, oral glucose-lowering drugs or diet; Hypertension was defined as a systolic blood pressure of >140 mmHg and/or a diastolic blood pressure of >90 mmHg or prior use of antihypertensive medication; dyslipidemia was defined as previous statin use and/or having a documented history of dyslipidemia.

ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker; CAD = coronary artery disease.

CAC score. The pathophysiologic mechanisms underlying this observation merit further investigation. A possible explanation could be the hormonal differences between men and women. It has been postulated that the female gender hormone (estrogen) plays a role in preventing the inflammatory process, which is associated with arterial and valvular calcification.[21] However, even in postmenopausal women (in whom estrogen concentrations are declining), gender differences in the degree of arterial and valvular calcification are still observed.[22] This might suggest that the protective effects of estrogen in younger female patients still remain in postmenopausal women. Nonetheless, irrespective of the hormonal status, studies have shown differences in vascular calcification in men and women despite the same severity of cardiovascular risk factors. These gender differences in calcification are also seen in the aortic valve. Simard et al[23] reported that for the same degree of AS severity, women had less valvular calcification but more fibrosis than men. Differences in coronary plaque composition between genders have also been described. Women are more likely to have less calcified plaques and more noncalcified plaques than men.[24,25] Moreover, the impact of various cardiovascular risk factors on coronary artery disease is different between genders, with diabetes mellitus and smoking being a stronger risk factor for coronary artery disease in women than men.[26,27] As such, underlying cardiovascular risk factors could perhaps also have a different impact on the development of AVC in men compared with women. Previous studies have suggested a possible correlation between AVC and CAC scores.[22,28] In a healthy population, Nasir et al[28] reported that the presence of AVC was independently associated with an increasing

Table 2
Echocardiography and computed tomography characteristics

Variable	Total population(n=260)	Men(n=102)	Women(n=158)	p-Value
Echocardiography	-	-	-	
Tricuspid AV morphology	254 (98%)	101 (99%)	153 (97%)	0.252
LVOT diameter (mm)	20.2 ± 2.8	21.2 ± 3.6	19.6 ± 1.9	<0.001
LV end systolic volume indexed (ml/m^2)	23 (15-42)	27 (18-49)	21 (14-37)	0.004
LV end diastolic volume indexed (ml/m^2)	51 ± 22	56 ± 23	48 ± 20	0.005
LV ejection fraction (%)	54 ± 14	53 ± 14	55 ± 14	0.291
Stroke volume index (ml/m^2)	37 ± 13	36 ± 11	36 ± 14	0.354
Mean aortic pressure gradient (mmHg)	45 ± 16	44 ± 15	46 ± 17	0.433
Peak aortic pressure gradient (mmHg)	72 ± 26	70 ± 25	73 ± 27	0.255
Aortic valve area (cm^2)	0.71 ± 0.20	0.76 ± 0.19	0.68 ± 0.19	0.001
Computed tomography	-	-	-	
Aortic valve calcium score (HU)	2776 (1786-4168)	3911 (2525-5259)	2409 (1588-3359)	<0.001
Coronary artery calcium score (HU)	617 (172-1392)	824 (328-1855)	478 (136-962)	<0.001

Values are mean ± SD, median [IQR] or n (%).

AV = aortic valve; LV = left ventricular; LVOT = left ventricular outflow tract; HU = Hounsfield unit.

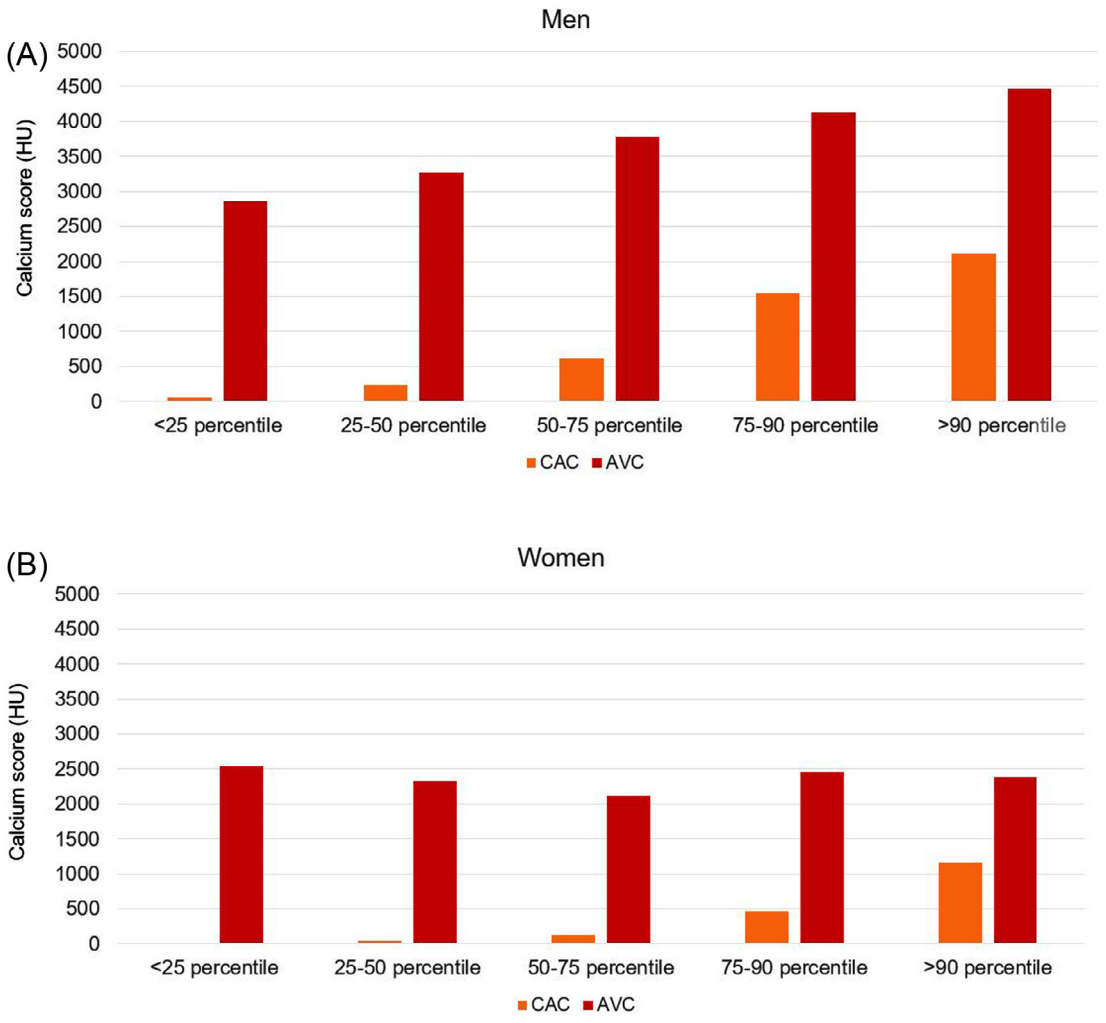


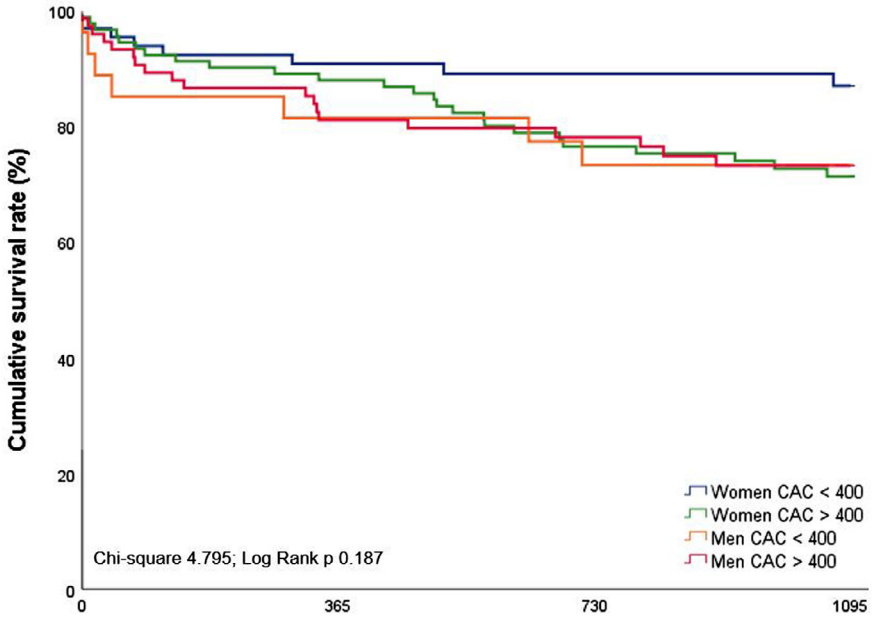
Figure 1. AVC and CAC in men (*A*) and women (*B*) categorized by percentiles using the standard reference of CAC score.

severity of coronary atherosclerosis. In contrast, Liyanage et al[22] reported no correlation between AVC and CAC in elderly patients with severe AS. The present study provides more insights in this topic and shows that the AVC score increases in parallel with the CAC score in men but not in women.

Several studies have reported that patients with an increased CAC score have an increased risk of cardiovascular events and mortality.[9,14,17] A study in 13,092 asymptomatic participants that was performed by Nakanishi et al[9] reported a strong association between the CAC score and long-term mortality, with the highest risk being observed in participants with a CAC score ≥400. This finding was confirmed by Miedema et al[17] in a much larger study (22,346 patients) and showed that patients with a CAC score >100 already had a fivefold increased risk for mortality because of coronary heart disease and a threefold increased risk for mortality related to cardiovascular disease, compared with patients with a CAC score of 0. When specifically looking at gender differences, Nakanishi et al[9] did not find any significant difference in the risk of all-cause mortality between men and women at any level of CAC. Similarly, in our study with patients with severe AS who underwent TAVI, we did not detect any significant difference between men and women with a CAC score >400 compared with a CAC score <400. These findings suggest that although most patients with severe AS who underwent TAVI receive a preprocedural cardiac CT, CAC score cannot be used to risk stratify these patients or assess their risk for future events. Larger prospective trials are needed to confirm these results.

The present study has limitations. First, this is a single-center, retrospective study with inherent limitations related to its retrospective design. Second, this study only included patients who underwent TAVI and not surgical aortic valve replacement. Third, only patients with noncontrast-enhanced CT to assess the coronary and AVC were included, which could have resulted in selection bias. Fourth, different CT scans were used (64-slice CT vs 320-CT). Fifth, the aortic valve morphology was only assessed by transthoracic echocardiography.

In conclusion, men with severe AS have higher AVC and CAC scores than women. Although the pattern of CAC distribution is similar between men and women, the AVC score increases along with the CAC score in men; whereas in



No. at risk				
Women CAC < 400	66	55	48	41
Women CAC > 400	92	79	65	52
Men CAC < 400	27	21	18	12
Men CAC > 400	75	59	49	41

Figure 2. Kaplan−Meier analysis of all-cause mortality according to gender and CAC score < or >400 Hounsfield units.

women, the AVC scores remained similar across the various percentiles. CAC score was not associated with cumulative mortality in patients with severe AS who underwent TAVI.

Disclosures

The department of Cardiology of the Leiden University Medical Center received research grants from Abbott Vascular, Bayer, Bioventrix, Biotronik, Boston Scientific, Edwards Lifesciences, GE Healthcare, and Medtronic. Dr. Delgado received speaker fees from Abbott Vascular, Edward Lifesciences, GE Healthcare, MSD, and Medtronic. Dr. Marsan received speaker fees from Abbott Vascular and GE Healthcare. Dr. Bax received speaker fees from Abbott Vascular. The remaining authors have no conflicts of interest to declare.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2022.07.008.

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