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Sex-specific correlates of valvular and arterial calcification burden in patients with moderate aortic stenosis

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ABSTRACT

Introduction There are significant sex differences in the prevalence and severity of cardiac calcifying processes. Women harbour more severe mitral annular calcification (MAC), while men exhibit worse aortic valve (AVC) and coronary artery (CAC) calcification. To better understand these differences, we investigated the correlates of cardiac calcification according to sex.

Methods We conducted a cross-sectional study of 406 patients with ≥mild aortic stenosis (AS) defined by an aortic valve area ≤1.5 cm^2, a peak aortic jet velocity >2.0 m/s, or a mean transvalvular gradient >15 mm Hg. Doppler-echocardiography and non-contrast multidetector CT were performed concomitantly to assess AS and cardiac calcifications.

Results Mean age was 71±11 years and 33% were women. The AS haemodynamics were not significantly different between sexes (all p>0.50), with a mean indexed aortic valve area of 0.59±0.21 cm^2/m^2, peak aortic jet velocity of 2.78 (2.37–3.68) m/s, and mean gradient of 17.9 (12.8–31.3) mm Hg for the whole cohort. Compared with men, women harboured lower AVC (480 (222–1191) vs 1003 (484–2329) Agatston unit, AU; p<0.0001) and CAC (366 (50–914) vs 618 (167–1357) AU; p=0.007), but more severe MAC (60 (1–887) vs 48 (0–351) AU; p=0.08) and ascending aorta calcification (227 (43–863) vs 142 (7–493) AU; p=0.03). After comprehensive adjustment, sex remained an independent predictor of each cardiac calcification subtype (all p<0.02) except for the ascending aorta (p=0.32). In multivariable analysis, certain variables, like age or bicuspid aortic valve, were associated with the calcification scores in both sexes. Sex-specific predictors of calcification burden were absence of angiotensin receptor blockers (β=−0.26; p=0.007) and renal impairment (β=0.26; p=0.003) for AVC, and bisphosphonates (β=0.20; p=0.05) for CAC in women; coronary artery disease (β=0.25; p=0.001) for AVC, and angiotensin receptor blockers (β=0.19; p=0.02) and calcium/vitamin D (β=0.15; p=0.02) for MAC in men.

Conclusion In AS, factors associated with cardiac valvular and arterial calcification differ between sexes, suggesting an important contributory role of sex in the pathophysiology of these calcifying processes.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The prevalence and severity of calcification burden affecting the cardiac valves and arteries differs between women and men.

WHAT THIS STUDY ADDS

⇒ Certain predictors of cardiac calcification involving the aortic valve, mitral annulus and coronary arteries were found to be common to both sexes, whereas other predictors were specific to either women or men.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study highlights sex differences in predictors of cardiac calcifications, thus suggesting potentially different mechanistic pathways involved in these calcifying processes.

INTRODUCTION

Calcific aortic stenosis (AS) is the most prevalent valvular heart disease in developed countries,[1] and the second most common indication for cardiac surgery after coronary artery bypass grafting.[2] Studies demonstrate that women reach the same haemodynamic severity of AS than men, but with lower aortic valve calcification (AVC) load, despite accounting for aortic size.[3–5] Indeed, female aortic valves present a more fibrotic remodelling pattern compared with men.[6 7] Recent literature suggests that the severity of calcification affecting the mitral annulus (MAC) and the coronary arteries (CAC) may be sex-dependent as well, with an enhanced prevalence and severity of MAC in women and a higher burden of CAC in men.[6 8 9]

Yet, other studies have presented contradictory results, making this correlation between sex and cardiac calcification still a subject of debate.[9–11] The severity and distribution of calcifications in the heart can vary greatly from one individual to the other, regardless of sex. Other patient-related factors, such as comorbidities, are likely involved in the development of cardiac calcification, some of which may interact specifically with sex.

In this context, our study aimed (1) to confirm the role of sex as a predictor of location-specific cardiac calcification burden (AVC, CAC, MAC and ascending aorta calcification) and (2) to identify for each sex the factors that correlate with cardiac calcification location and burden.

METHODS

Study population

We conducted a cross-sectional study of patients with at least mild AS (defined as an aortic valve area ≤1.5 cm^2, a peak aortic jet velocity >2.0 m/s, or a mean gradient >15 mm Hg,) on transthoracic echocardiogram, between years 2010 and 2015. Patients were included only if they had concomitantly undergone a non-contrast multidetector CT (MDCT) within 3 months of their comprehensive Doppler echocardiography. Patients with missing MDCT aortic valve calcium scoring, rheumatic AS, infective endocarditis, cervical or thoracic radiotherapy-induced valvular lesions, reduced left ventricular ejection fraction (<50%), more than mild aortic or mitral regurgitation, and previous aortic valve procedure were excluded.

Clinical data

Clinical data were collected from the patients' charts and included age, sex, body surface area (BSA), body mass index (BMI), obesity (BMI ≥30 kg/m^2), blood pressure, smoking history, hypertension (defined as clinical diagnosis attributed by a physician or use of antihypertensive medication), diabetes mellitus (patients on oral hypoglycaemic or insulin medications or fasting glucose ≥7 mmol/L), hyperlipidaemia (patients on lipid-lowering medication or documented plasma low-density lipoprotein (LDL) ≥3.5 mmol/L), coronary artery disease (CAD; history of myocardial infarction, significant coronary artery stenosis—ie, >50% on coronary angiography and/or regional wall motion abnormality on echocardiogram), arrhythmia, previous myocardial infarction, chronic obstructive pulmonary disease, renal failure (estimated glomerular filtration rate (eGFR) <60 mL/min), thyroid dysfunction, and liver disease. eGFR was calculated using the Cockcroft-Gault formula. A medication list was obtained for each patient.

Multidetector CT Scan and Calcification Score assessment

The protocol for multidetector CT (MDCT) image acquisition and interpretation was previously published.[6 12] Briefly, MDCT scans without contrast were performed using a 64 slices helical scanner (Somaton Definition, Siemens AG Medical Solution, Germany) with a tube potential at 120 kV and a tube current-time product at 60–80 mAS. Operators blinded to patient clinical and echocardiographic data performed all MDCT analyses.

For each patient, four different cardiac calcification scores were measured: AVC, CAC, MAC and ascending aorta calcification. All scores were quantified with the Agatston method[13] using a commercially available and validated software (Aquarius iNtuition from TeraRecon, San Mateo, California, USA). All calcification score data are expressed in Agatston unit (AU). In patients with previous mitral valve replacement, angioplasty or coronary artery bypass graft surgery or pacemaker inducing artefacts, the respective scores for MAC, CAC or ascending aorta calcification were not considered in the analyses (online supplemental figure S1). The aortic valve was visualised in multiple planes, and careful measurement section by section aimed to accurately distinguish contiguous calcium in coronary arteries, mitral valve annulus or aortic wall. In 40 randomly selected patients, calcification measurements were assessed by both the same and another investigator blinded to previous imaging data, and repeated ≥3 months after the original measurement. Intraobserver and interobserver variabilities were evaluated by intraclass correlation, and presented with a Bland-Altman graph (online supplemental figures S2 and S3). Intraclass correlation intraobserver variability (0.998 for AVC, 0.996 for CAC, 0.993 for MAC, 0.988 for ascending aorta calcification) and interobserver variability (0.996 for AVC, 0.818 for CAC, 0.990 for MAC, 0.980 for ascending aorta calcification) were excellent.

Doppler echocardiography measurements

Transthoracic Doppler echocardiography was performed using a commercially available ultrasound system and image analysis was performed as recommended by the American Society of Echocardiography.[14 15] Left ventricular ejection fraction was measured by the biplane Simpson method. Stroke volume was calculated by multiplying the left ventricular outflow tract area by the flow velocity-time integral, and then indexed to BSA. Haemodynamic severity of AS was assessed with the standard parameters: peak aortic jet velocity was measured from the transaortic jet continuous-wave Doppler, mean gradient was calculated by the Bernoulli formula and aortic valve area by the standard continuity equation. Aortic valve area was calculated as an absolute value and indexed to BSA. Aortic and mitral regurgitation severity was assessed by an integrated multiparameter approach, as recommended by the current guidelines,[16] and graded as (1) trivial, (2) mild, (3) moderate and (4) severe.

Statistical analyses

Continuous variables were tested for normality with the Shapiro-Wilk test and are expressed as mean±standard deviation or median (percentile 25 and 75) as appropriate. All cardiac calcification scores were not normally distributed. Differences between women and men were assessed using the Student's-t test for continuous normally distributed variables, or the Wilcoxon rank sum test for non-normally distributed variables. Categorical variables are presented as absolute numbers and percentages, and were compared with the use of the χ^2 test or Fisher's exact test as appropriate.

For each cardiac calcification subtype, multivariable linear regression analysis was performed to identify the correlation between patients' characteristics and the

degree of calcification load detected by MDCT. Traditional cardiovascular risk factors (age, male sex, smoking history, hypertension, hyperlipidaemia and diabetes) and clinically relevant variables with a p<0.20 on univariable analysis were included in the multivariable models. We included BSA to account for smaller heart size in women. Final models were adjusted in order to retain only independent predictors of each calcification subtype. Multivariable models were then performed for each sex, in order to identify the sex-specific correlates of cardiac calcification subtypes. Collinear variables were not entered in the same model, and we considered an acceptable variance inflating factor if <2.0. A two-sided p<0.05 was considered statistically significant. Statistical analyses were performed with JMP V.14.0.0 software program.

RESULTS

Patient characteristics

Four hundred and six patients (134 women (33%)) were included in this study (flow chart presented in online supplemental figure S1). Their baseline characteristics

Table 1 Characteristics of the study population

Variables	Whole cohort (n=406)	Men (n=272, 67%)	Women (n=134, 33%)	P value
Clinical data				
Age, years	71±11	**70±11**	**73±12**	**0.02**
Body surface area, m^2	1.93±0.23	**2.01±0.19**	**1.76±0.22**	**0.0001**
Hypertension, n (%)	336 (83)	223 (82)	113 (84)	0.61
Coronary artery disease, n (%)	233 (58)	165 (61)	68 (51)	0.05
Diabetes, n (%)	135 (33)	89 (33)	46 (34)	0.77
Hyperlipidaemia, n (%)	321 (79)	218 (80)	103 (77)	0.40
Thyroid dysfunction, n (%)	76 (19)	**32 (12)**	**44 (33)**	**0.0001**
eGFR, mL/min	68.4 (50.6–90.4)	**74.7 (57.3–94.8)**	**59.3 (43.6–75.9)**	**0.0001**
eGFR <60 mL/min, n (%)	142 (36)	**75 (29)**	**67 (51)**	**0.0001**
Current smoker, n (%)	49 (12)	34 (13)	15 (11)	0.68
Medication				
ACE inhibitor, n (%)	127 (31)	**96 (35)**	**31 (23)**	**0.01**
ARB, n (%)	136 (34)	89 (33)	47 (35)	0.65
Statin, n (%)	306 (76)	212 (78)	94 (70)	0.08
Vitamin K antagonist, n (%)	65 (16)	**36 (13)**	**29 (22)**	**0.03**
Bisphosphonate, n (%)	48 (12)	**15 (6)**	**33 (25)**	**0.0001**
Echocardiographic data				
Bicuspid aortic valve, n (%)	76 (19)	57 (21)	19 (14)	0.10
Mean gradient, mm Hg	17.9 (12.8–31.3)	17.0 (13.0–29.9)	18.8 (12.1–34.5)	0.93
Peak aortic jet velocity, m/s	2.78 (2.37–3.68)	2.76 (2.41–3.60)	2.83(2.34- 3.84)	0.73
Aortic valve area, cm^2	1.14±0.42	**1.18±0.39**	**1.06±0.45**	**0.006**
Indexed aortic valve area, cm^2/m^2	0.59±0.21	0.59±0.19	0.60±0.24	0.56
Indexed stroke volume, mL/m^2	37.1 (31.8–42.7)	36.5 (31.5–41.5)	38.0 (32.0–43.5)	0.21
LV ejection fraction, %	62.3±7.1	**61.3±6.9**	**64.3±7.2**	**0.0001**
Mitral regurgitation severity	1 (1–2)	**1 (0.6–2)**	**1 (1–2)**	**0.04**
Aortic regurgitation severity	1 (0–2)	1 (0–2)	1 (0–2)	0.34
MDCT data				
AVC, AU	853 (349–1945)	**1003 (484–2329)**	**480 (222–1191)**	**0.0001**
MAC, AU	49 (0–432)	48 (0–351)	60 (1 – 887)	0.08
CAC, AU	503 (118–1238)	**618 (167–1357)**	**366 (50–914)**	**0.007**
Asc. aorta calcification, AU	156 (14–634)	**143 (7–493)**	**227 (43–863)**	**0.03**

In bold statistically significant results.
ACE, angiotensin-converting enzyme; ARB, angiotensin-II receptor blocker; Asc, ascending; AU, Agatston unit; AVC, aortic valve calcification; CAC, coronary artery calcification; eGFR, estimated glomerular filtration rate; LV, left ventricular; MAC, mitral annular calcification; MDCT, multidetector CT.

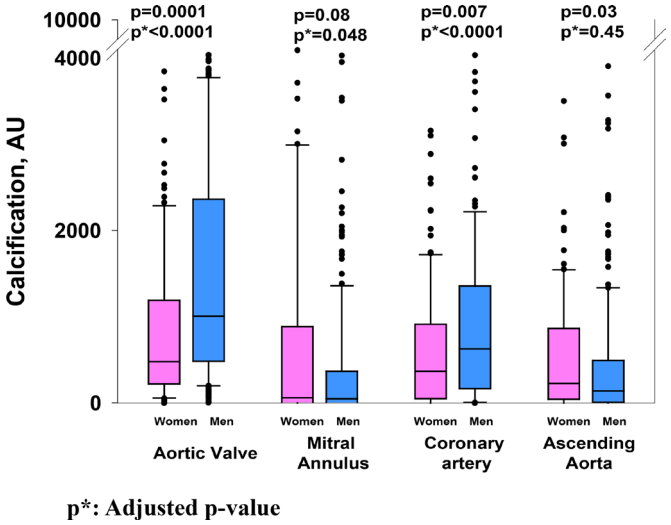

Figure 1 Calcification load on multidetector CT according to location and sex. AU, agatston unit.

are presented in table 1. Compared with men, women were slightly older (73±12 vs 70±11 years; p=0.02), had smaller BSA (1.76±0.22 vs 2.01±0.19 m^2; p<0.0001) and a higher prevalence of thyroid dysfunction (33 vs 12%; p<0.0001) and renal failure (51 vs 29%; p<0.0001). History of CAD was less prevalent in women than men (51 vs 61%, p=0.05). Haemodynamic AS severity, determined by the Doppler echocardiographic parameters, was similar between sexes (all p≥0.56), with a mean indexed aortic valve area=0.59 ± 0.21 cm^2/m^2, a median peak aortic jet velocity=2.78 (2.37–3.68) m/s and a median mean gradient=17.9 (12.8–31.3) mm Hg.

On MDCT, women harboured lower AVC (480 (222–1191) vs 1003 (484–2329)AU; p<0.0001), and CAC scores (366(50-914) vs 618 (167–1357)AU; p=0.007). Conversely, they had higher MAC (60(1–887) vs 48 (0–351)AU; p=0.08) and ascending aorta calcification scores (227(43–863) vs 142(7–493)AU; p=0.03) compared with men (figure 1). These differences persisted after adjustment and indexation for BSA (all p≤0.04), except for calcification of the ascending aorta (p=0.13).

Aortic valve calcification

In univariable analysis for the whole cohort (online supplemental table S2), higher AVC load was associated with age, male sex, CAD, eGFR <60 mL/min, bicuspid aortic valve, use of calcium and/or vitamin D supplements, CAC and MAC. In the stratified analysis according to sex, age, MAC and BSA remained associated with AVC load for both women and men, while eGFR <60 mL/min and CAC were associated with AVC load only in women.

After comprehensive multivariable adjustment (table 2), male sex remained strongly correlated with higher AVC load in the whole cohort (p≤0.0001). In the sex-specific analysis, age (both p≤0.03), bicuspid aortic valve (both p≤0.04) and higher MAC score (both p<0.0001) remained associated with higher AVC load in both sexes. However, CAD was independently associated with higher AVC load (p=0.001) only in men. In women, the absence of angiotensin-II receptor blocker drugs (beta=0.26, p=0.007) was strongly associated with higher AVC score.

Table 2 Multivariate analysis of AVC load in the whole cohort, in women and in men

	Whole cohort				Women		Men	
	Coef.	SE	Beta	P value	Beta	P value	Beta	P value
Male sex	**1014.92**	**217.18**	**0.3**	**<0.0001**	–	–	–	–
Age (per year)	**36.38**	**9.3**	**0.27**	**<0.0001**	**0.26**	**0.03**	**0.31**	**0.001**
Body surface area (per m^2)	−346.06	446.56	−0.05	0.44	−0.13	0.15	−0.05	0.49
Hypertension	338.33	283.3	0.09	0.23	0.11	0.38	0.09	0.35
Hyperlipidaemia	83.38	324	0.02	0.80	−0.16	0.23	0.14	0.28
Coronary artery disease	**531.06**	**189.29**	**0.16**	**0.01**	0.01	0.91	**0.25**	**0.001**
eGFR <60 mL/min	366.02	226.58	0.08	0.11	**0.26**	**0.003**	−0.03	0.64
Bicuspid aortic valve	**1342.59**	**239.95**	**0.35**	**<0.0001**	**0.22**	**0.04**	**0.42**	**<0.0001**
ARB	−398.86	223.24	−0.11	0.08	**−0.26**	**0.007**	−0.08	0.38
ACE inhibitor	−172.11	237.72	−0.05	0.47	−0.05	0.59	−0.04	0.67
Statin	100.01	299.23	0.03	0.74	0.1	0.45	−0.05	0.68
Calcium and/or vitamin D	−90.51	108.41	−0.05	0.41	−0.11	0.22	−0.04	0.55
MAC (per AU)	**0.28**	**0.06**	**0.25**	**<0.0001**	**0.42**	**<0.0001**	**0.27**	**<0.0001**
CAC (per AU)	−0.06	0.08	−0.04	0.48	–	–	–	–

In bold statistically significant results.
ACE, angiotensin-converting enzyme; ARB, angiotensin-II receptor blocker; AU, Agatston unit; AVC, aortic valve calcification; CAC, coronary artery calcification; eGFR, estimated glomerular filtration rate; MAC, mitral annular calcification; SE, Standard error.

Table 3 Multivariate analysis of MAC load in the whole cohort, in women and in men

	Whole				Women		Men	
	Coef.	SE	Beta	p>t	Beta	p>t	Beta	p>t
Male sex	**−440.33**	**191.44**	**−0.14**	**0.02**	–	–	–	–
Age (per year)	9.18	8.04	0.07	0.25	0.16	0.18	0.01	0.86
Body surface area (per m^2)	616.34	389.11	0.09	0.11	0.1	0.26	0.06	0.30
Hypertension	−217.78	266.47	−0.05	0.41	−0.16	0.20	−0.06	0.50
Diabetes	**349.63**	**169.23**	**0.11**	**0.04**	0.17	0.09	0.09	0.14
Hyperlipidaemia	−75.94	209.99	−0.02	0.72	0.02	0.86	−0.04	0.57
Coronary artery disease	58	167.68	0.02	0.73	0.14	0.14	−0.08	0.25
eGFR<60 mL/min	163.19	191.23	0.04	0.39	−0.07	0.45	0.1	0.12
Current smoker	−60.82	225.63	−0.01	0.79	−0.07	0.45	0.02	0.70
ARB	262.35	199.44	0.08	0.19	0.04	0.72	**0.19**	**0.02**
ACE inhibitor	186.62	204.28	0.06	0.36	0.05	0.64	0.12	0.13
Vitamin K antagonist	261.33	206.56	0.06	0.21	−0.05	0.61	**0.14**	**0.02**
Bisphosphonate	282.01	256.64	0.06	0.27	0.03	0.72	0.06	0.33
Calcium and/or vitamin D	**266.58**	**99.12**	**0.15**	**0.01**	0.14	0.15	**0.15**	**0.02**
AVC (per AU)	**0.28**	**0.05**	**0.28**	**<0.0001**	**0.37**	**<0.0001**	**0.28**	**<0.0001**
Asc. aorta calcification (per AU)	−0.002	0.09	−0.002	0.98	–	–	–	–
CAC (per AU)	0.09	0.09	0.07	0.32	–	–	–	–

In bold statistically significant results.
ACE, angiotensin-converting enzyme; ARB, angiotensin-II receptor blocker; Asc, ascending; AU, Agatston unit; AVC, aortic valve calcification; CAC, coronary artery calcification; eGFR, estimated glomerular filtration rate; MAC, mitral annular calcification; SE, Standard error.

Mitral annulus calcification

In univariable analysis (online supplemental table S3), higher MAC score was associated with age, female sex, eGFR <60 mL/min, hypertension, CAD, diabetes, vitamin K antagonists, bisphosphonates, calcium and/or vitamin D supplements and AVC. After stratification by sex, the factors that remained significantly associated with MAC in both sexes were age, diabetes and AVC. In men, higher MAC load was also associated with eGFR <60 mL/min, angiotensin-II receptor blocker drugs (p=0.03), vitamin K antagonists (p=0.001) and calcium and/or vitamin D supplements (p=0.002), while, in women, it was specifically correlated with CAD (p=0.004) and CAC (p=0.002).

After comprehensive adjustment in the multivariable model (table 3), female sex remained significantly associated with higher MAC load (p=0.02). When analysing by sex, MAC remained correlated with AVC for both women and men (p≤0.0001). In men only, higher MAC load was also associated with the use of angiotensin-II receptor blockers, calcium and/or vitamin D supplements and vitamin K antagonists (all p=0.02).

Coronary artery calcification

Univariable analyses (online supplemental table S4) showed correlation of higher CAC load with age, male sex, hypertension, hyperlipidaemia, CAD, angiotensin-converting enzyme (ACE) inhibitors, statins, AVC and ascending aorta calcification scores. When stratified by sex, age (both p<0.0001), hypertension (both p≤0.003), CAD (both p<0.0001) and ascending aorta calcification (both p≤0.002) were associated with higher CAC load for both sexes. In women, higher CAC was also associated with hyperlipidaemia (p<0.0001), diabetes (p=0.03), ACE inhibitors (p=0.03), statins (p=0.03), bisphosphonates (p=0.01), calcium and/or vitamin D supplements (p=0.02), MAC (p=0.002) and AVC (p=0.02).

After comprehensive adjustment (table 4), male sex remained strongly and independently associated with higher CAC load (beta=0.20; p=0.005). Stratified multivariable analyses showed an association between CAC severity and older age in both sexes (p≤0.006), whereas its association with bisphosphonates (p=0.04) was only present in women, and its association with ascending aorta calcification (p=0.007) and calcium and/or vitamin D supplements (p=0.03) only in men.

Ascending aorta calcification

Ascending aorta calcification and CAC were strongly correlated in univariable analysis (online supplemental table S5). They both also shared similar associated factors. After comprehensive adjustment (online supplemental table S1), female sex (p=0.32) did not remain statistically associated with ascending aorta calcification. However, stratified multivariable analyses suggested different predictive factors between sexes, with more severe ascending aorta calcification being associated with

Table 4 Multivariate analysis of CAC load in the whole cohort, in women and in men

	Whole cohort				Women		Men	
	Coef.	SE	Beta	p>t	Beta	p>t	Beta	p>t
Male sex	**447.96**	**166.95**	**0.20**	**0.008**	–	–	–	–
Age	**23.54**	**6.27**	**0.26**	**<0.0001**	**0.22**	**0.01**	**0.28**	**0.001**
Body surface area	85.09	342.07	0.02	0.80	0.03	0.77	0.33	0.67
Hypertension	162.45	182.87	0.06	0.38	−0.05	0.72	0.09	0.28
Diabetes	186.95	151.53	0.08	0.22	0.16	0.16	0.06	0.46
eGFR <60 mL/min	33.49	173.65	0.01	0.85	0.02	0.86	0.003	0.97
Current smoker	−19.64	189.91	−0.006	0.92	−0.02	0.80	0.01	0.892
Statin	152.15	225.73	0.07	0.50	0.14	0.13	0.05	0.52
Vitamin K antagonist	−117.52	184.24	−0.04	0.52	0.001	0.99	0.002	0.98
Bisphosphonate	230.93	230.31	0.07	0.32	**0.20**	**0.05**	−0.02	0.80
Calcium and/or vitamin D	−150.56	88.60	−0.12	0.09	0.01	0.78	**−0.17**	**0.03**
Asc. aorta calcification (per AU)	**0.18**	**0.07**	**0.17**	**0.006**	0.13	0.19	**0.20**	**0.009**
AVC (per AU)	−0.02	0.04	−0.02	0.72	–	–	–	–
MAC (per AU)	0.05	0.05	0.06	0.27	–	–	–	–

In bold statistically significant results.
Asc, ascending; AU, Agatston unit; AVC, aortic valve calcification; CAC, coronary artery calcification; eGFR, estimated glomerular filtration rate; MAC, mitral annular calcification; SE, Standard error.

the use of vitamin K antagonists (p=0.01) in women, and with the level of CAC (p=0.01) in men.

DISCUSSION

In this cross-sectional study, our results (1) confirmed that for comparable haemodynamic severity of AS and after comprehensive adjustment for potential confounders, women presented lower AVC and CAC burden, but more severe MAC than men, and (2) suggest that factors associated with valvular and arterial calcification differ between sexes. Men exhibited a higher AVC load when exposed to traditional cardiovascular risk factors, such as CAD, whereas the intake of angiotensin-II receptor antagonists was associated with lower AVC load in women. Regarding MAC, the use of vitamin K antagonists, calcium and/or vitamin D or angiotensin-II receptor antagonists were specifically associated with higher calcification scores only in men. Bisphosphonate use was specifically associated with CAC in women.

Despite prior studies reporting sex differences in cardiac calcification loads,[3–6 8] our study is the first to assess the specific factors associated with each site of cardiac calcification with respect to sex. Interestingly, the calcification sites correlated with each other in both sexes, despite a widely different distribution of calcification burden between women and men, which underlines the complex interrelationship of calcifying processes at the valvular and vascular levels. Despite relatively comparable baseline characteristics between women and men, most correlates of higher calcification loads were specific to sex. This suggests that the pathophysiology of valvular and vascular calcification may differ between women and men.

The study of sex differences in AS largely gained interest during these past 10 years, however, without any clear sex-specific pathophysiologic pathway being proposed. It is interesting to note that angiotensin-II receptor blockers, but not ACE inhibitors, were associated with a lower AVC score in women. Indeed, ACE and angiotensin II colocalise with LDL in the extracellular matrix of the aortic valve,[17] and have been associated with faster progression of AS.[18–22] Moreover, in addition to the ACE, chymase, another angiotensin II-forming enzyme, has been found in human AS lesions,[17 20] which may explain the inefficiency of ACE inhibitors to prevent or slow AS progression.[23] Since angiotensin II has several proinflammatory and profibrotic effects, blocking this cascade directly at the level of the angiotensin receptor may help limit the development of fibrosis within the aortic valvular tissue, and therefore, the development of calcification.[20] Finally, the impact of angiotensin-II receptor blockers may be more important in women given the increased preponderance of fibrosis in female stenotic valves compared with males.[6 7] Thus, the use of angiotensin-II receptor blockers could be of interest in the prevention of AS progression, which is currently under investigation in the Angiotensin Receptor Blockers in Aortic Stenosis ARBAS study (NCT04913870). Further, hypertension has been associated with AS and/or AVC progression, especially in women, adding more to the rationale of angiotensin-II receptor blockade therapy in this population.[24 25]

There is also growing interest around MAC, partly related to its clinical impact in transcatheter therapies.[26] Beside the higher prevalence and more severe burden of MAC found in women, data on risk factors leading to the development of MAC remain scarce. Hypertension, diabetes and hypercholesterolaemia have been previously associated with MAC.[27] In our study, the relationship between diabetes and MAC showed borderline significance in women. In men, however, the impact of calcium and/or vitamin D supplements is) interesting, as it could be consequent to the direct effect of calcium/vitamin D intake or could represent a surrogate of the impact of osteoporosis (calcification paradox, cf. below). In the male subgroup as well, the association of vitamin K antagonists with MAC could be caused by a reduction in active matrix gla protein (ie, carboxylated and phosphorylated), which is vitamin K-dependent and protective against ectopic calcification. Carboxylated and phosphorylated matrix gla protein has been previously associated with lower MAC but with an interaction with diabetes.[28] In our study (data not shown), this interaction was present in the whole cohort (p=0.02) but not in the sex-stratified analysis (p>0.30).

Risk factors for CAC are known to be strongly related to sex. Interestingly, diabetes represents a greater risk factor for CAD in women than men.[29 30] Our results did not suggest a stronger association between diabetes and CAC in women. This could be related to the fact that CAD is not only due to CAC, but also to lipid infiltration and plaque development which would not be captured via quantification of calcifying burden. In women, however, the use of bisphosphonates was associated with more severe CAC. This could be explained by the calcification paradox, meaning that it could be related to the underlying disease being treated (osteoporosis) more than to the use of the drug itself. As such, arterial mineralisation has been associated with reduced bone mineral density or disturbed bone turnover.[31] Osteoporosis being more prevalent in women, it is expected to have a larger impact in this population when compared with men. Statins were also more strongly associated with CAC in women than men. It is thought that statins increase CAC burden by increasing the calcific density of existing atherosclerotic plaques, thereby enhancing their stability.[32–34] As involved mechanisms are yet to be defined,[35 36] the interaction of statins with sex in CAC severity certainly deserves future scientific attention.

Limitations

The major limitation of this study is its cross-sectional design, where only correlations can be demonstrated. However, our study was performed on a relatively large population, which allowed analyses to be performed in women and men separately with sufficient power. Baseline characteristics were relatively similar between both sexes, allowing for adequate comparison. Given that our study was conducted in a population of patients with moderate AS in majority, our results may not directly apply to patients with aortic sclerosis, isolated mitral valve disease or isolated CAD.

CONCLUSION

In this series of patients with AS, after adjustment for potential confounding factors, men presented higher levels of AVC and CAC, while women had more severe MAC. When analysed separately, several parameters were associated with each type of cardiac calcification in both sexes, while others were found to be specific to sex. This suggests that both common and sex-specific pathways are involved in the development and severity of valvular and vascular calcification, thus emphasising the importance of considering sex and its interacting factors in the study of potential preventive and therapeutic avenues.

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