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# Sex Differences in Aortic Valve Calcification Measured by Multidetector Computed Tomography in Aortic Stenosis

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**Background**—Aortic valve calcification (AVC) is the intrinsic mechanism of valvular obstruction leading to aortic stenosis (AS) and is measurable by multidetector computed tomography. The link between sex and AS is controversial and that with AVC is unknown.

**Methods and Results**—We prospectively performed multidetector computed tomography in 665 patients with AS (aortic valve area,  $1.05 \pm 0.35$  cm<sup>2</sup>; mean gradient,  $39 \pm 19$  mm Hg) to measure AVC and to assess the impact of sex on the AVC–AS severity link in men and women. AS severity was comparable between women and men (peak aortic jet velocity:  $4.05 \pm 0.99$  versus  $3.93 \pm 0.91$  m/s,  $P=0.11$ ; aortic valve area index:  $0.55 \pm 0.20$  versus  $0.56 \pm 0.18$  cm<sup>2</sup>/m<sup>2</sup>;  $P=0.46$ ). Conversely, AVC load was lower in women versus men ( $1703 \pm 1321$  versus  $2694 \pm 1628$  arbitrary units;  $P<0.0001$ ) even after adjustment for their smaller body surface area or aortic annular area (both  $P<0.0001$ ). Thus, odds of high-AVC load were much greater in men than in women (odds ratio, 5.07;  $P<0.0001$ ). Although AVC showed good associations with hemodynamic AS severity in men and women (all  $r>|0.67|$ ;  $P<0.0001$ ), for any level of AS severity measured by peak aortic jet velocity or aortic valve area index, AVC load, absolute or indexed, was higher in men versus women (all  $P \leq 0.01$ ).

**Conclusions**—In this large AS population, women incurred similar AS severity than men for lower AVC loads, even after indexing for their smaller body size. Hence, the relationship between valvular calcification process and AS severity differs in women and men, warranting further pathophysiological inquiry. For AS severity diagnostic purposes, interpretation of AVC load should be different in men and in women. (*Circ Cardiovasc Imaging*. 2013;6:40-47.)

**Key Words:** aortic valve calcification ■ aortic valve stenosis ■ Doppler echocardiography ■ multidetector computed tomography ■ sex differences

Aortic stenosis (AS) is common in elderly people, affecting 2% of the population  $\geq 65$  years old and 4.6% of population  $\geq 75$  years old based on Doppler echocardiographic or community studies.<sup>1,2</sup> Nowadays, the most common cause of AS is degenerative, and aortic valve calcification (AVC) is the intrinsic mechanism of valvular stiffening and obstruction.<sup>3-6</sup> Although degenerative AS has long been considered age related, recent studies have demonstrated that it is an active process involving biological pathways with many similarities to atherosclerosis.<sup>7,8</sup> Epidemiological studies identified similar risk factors for calcific AS and coronary atherosclerosis such as age, smoking, elevated cholesterol levels, diabetes mellitus, metabolic syndrome, hypertension, and increase in lipoprotein-a levels.<sup>9</sup> Male sex was also touted as an independent risk factor for AS similar to atherosclerosis,<sup>9</sup> but studies linking valve tissue alterations<sup>10,11</sup> and calcification to AS<sup>12</sup> have not differentiated between men and women. Moreover, studies of aortic valve weight as a surrogate for calcification load showed discordant results with regard to

sex,<sup>13,14</sup> and clinically, guidelines do not differentiate between men and women for AS pathophysiology and management.<sup>6</sup>

**Editorial see p 8**  
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However, the analogy to atherosclerosis suggests that there may be important, yet thus far undefined, sex-related differences in the development of AVC and the transition to AS. This issue can now be analyzed because cardiac computed tomography (CT) provides accurate and reproducible quantification of AVC load,<sup>15</sup> and multidetector CT (MDCT) may prove to be a useful adjunct tool for the evaluation of AS severity. However, previous studies suggested a single set of cutoff values for detecting severe AS regardless of sex,<sup>16</sup> so the impact of sex on the relation between aortic cusp calcification measured by MDCT and hemodynamic severity of AS remains uncertain. The aim of the present study was to determine the differential physiological relationship between AVC

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load and AS hemodynamic severity between men and women. We hypothesized that women reach thresholds for severe AS for lower calcification loads than men and that when MDCT is used for the diagnosis of AS severity, criteria of AVC load would need to be adjusted specifically for each sex.

## Methods

### Study Population

We prospectively enrolled patients with at least mild calcific AS in whom we performed noncontrast MDCT scan for the evaluation of AVC and comprehensive transthoracic echocardiography within 90 days of each other between 1999 and 2010 in 2 large academic centers: Mayo Clinic, Rochester (MN), and Hôpital Bichat, Paris (France). AS severity was defined as recommended in the guidelines<sup>6</sup>: mild (aortic valve area [AVA] <1.5 cm<sup>2</sup>; mean gradient [MG] <25 mm Hg; or peak aortic jet velocity [VPeak] <3.0 m/s), moderate (AVA, 1.0–1.5 cm<sup>2</sup>; MG, 25–40 mm Hg; or VPeak, 3.0–4.0 m/s), or severe (AVA≤1.0 cm<sup>2</sup>; MG≥40 mm Hg; or VPeak≥4.0 m/s). The mean interval of time between echocardiographic and MDCT examination was 4±11 days (range, 0–68 days). Patients with overt rheumatic valve disease (defined history of rheumatic disease, mitral rheumatic valvulitis), endocarditis, or prior aortic valve replacement were excluded. Clinical history, symptoms, and examination were collected by the personal physicians of patients within each institution. Creatinine clearance was calculated by the Cockcroft–Gault formula:

$$\text{Creatinine Clearance} = \frac{(140 - \text{age}) \times \text{Weight [kg]}}{72 \times \text{Creatinine Level [mg/dl]}} \times (0.85 \text{ if women}) \quad (1)$$

Patients from the Bichat Hospital were enrolled in 2 ongoing prospective studies on aortic valve calcification/stenosis (COFRASA; www.clinicaltrials.gov, No. NCT-00338676 and; www.clinicaltrials.gov, No. NCT-00647088). Mayo's patients were enrolled for the present cross-sectional study. An informed consent was obtained from all patients, and the present study was approved by both institutional review boards.

### MDCT Scans

Noncontrast MDCT scans were performed with 16 (in 298 patients) or 64 (in 367 patients) detectors, single source CT scans (Sensation, Siemens Medical Systems, Forthheim, Germany; MX8000-IDT16, Philips Medical Systems, Andover, MA). The same methodology of image acquisition and interpretation was used in both centers. A scan run consisted of contiguous transverse slices with a thickness of 2.5 to 5 mm for the 64-detector and 43 mm for the 16-detector scanner. These were performed with a tube current of 42 to 1312 A and a voltage of 120 to 130 kV. Acquisition was triggered by EC at 75% to 80% of the ECG R-to-R-wave interval. No contrast enhancement was needed, nor was β-blocker administered for the purpose of the examination. Calcification was defined as 4 adjacent pixels with density >130 Hounsfield units. AVC was scored with the Agatston scoring method<sup>17</sup> using commercially available software (Aquarius iNtuition, TeraRecon, Heart Beat Calcium Scoring, Philips Medical Systems) as the average of 2 separate runs. Calcium scoring was performed by an investigator blinded to the echocardiographic data detecting AVC as the calcium present on the valvular leaflets and annulus. The aortic valve was visualized in multiple planes to accurately exclude contiguous calcium in the mitral valve annulus or aortic wall. AVC load was summated from all contiguous MDCT planes and was expressed as an absolute value or as a value indexed to body surface area (AVCi) or to cross-sectional area of the aortic annulus (AVCdensity). Radiation exposure was typically 2 to 3 mSV.

Thirty patients were randomly selected, and measurements of AVC were assessed by both the same and another investigator blinded to previous scoring and Doppler echocardiographic data and repeated

at least after 3 months after the original measurement. Then intraobserver and interobserver variabilities were calculated by dividing the absolute value of the difference between 2 measurements by the average value of the 2 measurements. Intraobserver variability was 4.1±5.8%, and interobserver variability was 6.6±7.0%.

### Doppler Echocardiography

All patients underwent comprehensive Doppler echocardiography in each center, blinded to other clinical and MDCT data, with the use of standard ultrasound systems using the same methodology of image acquisition and interpretation in both centers. All measurements and calculations were performed as recommended by echocardiographic societies.<sup>18</sup> After measurement using multiple windows of the aortic annulus diameter, flow velocity, and time-velocity integral of left ventricular outflow tract (LVOT) and aortic jet, we calculated AVA by the continuity equation and MG by the modified Bernoulli equation. The AVA was calculated as an absolute value and indexed to body surface area (AVAi).

### Statistical Analysis

Results are expressed as mean±SD or percentages. Continuous variables were tested for distribution normality with the Shapiro–Wilk test. Differences between men and women were analyzed with the use of the 2-sided Student *t* test for continuous variables, Wilcoxon rank-sum test for ordinal variables, and the  $\chi^2$  test or Fisher exact test for categorical variables as appropriate. Associations between echocardiographic stenotic indexes (as independent variables) and AVC, AVCi, and AVCdensity (as dependent variables) were assessed with multiple regression models, and the equation providing the best fit was retained. The association between AVC and echocardiographic indexes of AS severity became linear after square root transformation of AVC. The impact of sex (as stratifying variable) was assessed by the interaction between sex and stenotic indexes in correlations using transformed and untransformed AVC. The impact of center or MDCT differences in these correlations was assessed by ANCOVA. Multivariable linear and logistic regressions were used to determine the associations between baseline characteristics and AVC load (as continuous variable, before and after square root transformation) or high AVC load (using the previously described AVC threshold of 1650 arbitrary units (AU)).<sup>16</sup> The odds ratios (ORs) of high AVC load and their 95% confidence interval (in brackets) were calculated unadjusted and adjusted in logistic models. Clinically relevant variables with a value of *P*<0.05 on univariable analysis were included in multivariable models with the focus of adjusting for independent correlates of AVC and examining the independent role of sex in determining AVC load as the main aim of the study. The final model retained included only the independent determinants of AVC, but extensive verification that no other variable inclusion affected the result was conducted in multiple models. Values of *P*<0.05 were considered statistically significant. Statistical analyses were performed with JMP 9.0.0 and Table Curve version 5.01 software programs.

## Results

### Population

In our cohort of 665 patients (Mayo Clinic, 503; Bichat Hospital, 162), there were 238 women and 427 men, and their baseline characteristics are presented in Table 1. The men:women ratio was not different between centers (64%:36% men:women in both centers; *P*=0.99) or between scanners (65%:35% men:women in 16-detector CT and 63%:37% men:women in 64-detector CT; *P*=0.45). As expected, there were slight clinical differences between men and women with AS: Women were slightly older, had a smaller body surface area, and were more often severely symptomatic. Men presented more frequently with a history of coronary disease, of hyperlipidemia, and, in

a borderline proportion, of diabetes mellitus. The renal function analysis was contrasted because men had higher creatinine, which, in view of a larger body, corresponded nevertheless to higher creatinine clearance. Importantly, men and women have equivalent AS severity (Table 1), measured by VPeak (4.05±0.99 versus 3.93±0.91;  $P=0.11$ ), MG (41±21 versus 39±18;  $P=0.09$ ), or AVAi (0.55±0.20 versus 0.56±0.18;  $P=0.46$ ).

### AVC Load

AVC load was lower in women compared with men (1703±1321 versus 2694±1628 AU;  $P<0.0001$ ). This difference remained significant even after accounting for the smaller body and heart size of women and normalizing the AVC load for body surface area (AVCi, 996±781 versus 1345±823 AU/m<sup>2</sup>;  $P<0.0001$ ) and for cross-sectional aortic annulus area (AVCdensity, 502±384 versus 633±399 AU/cm<sup>2</sup>;  $P<0.0001$ ; Table 1).

Characteristics associated with high AVC load (>1650 AU) in univariable analysis were age (OR, 1.35 [1.25–1.45] per 10-year increase;  $P<0.0001$ ), male sex (OR, 3.06 [2.21–4.26];  $P<0.0001$ ), New York Heart Association functional class ≥III (OR, 2.97 [2.07–4.27];  $P<0.0001$ ), history of coronary artery disease (OR, 1.87 [1.35–2.59];  $P=0.0001$ ), history of atrial fibrillation (OR, 1.85 [1.24–2.76];  $P=0.002$ ), chronic obstructive pulmonary disease (OR, 1.55 [1.03–2.33];  $P=0.03$ ), body surface area (OR, 1.20 [1.12–1.28];  $P<0.0001$ ), LVOT diameter (OR, 1.22 [1.17–1.27] per 0.1-cm increase;

$P<0.0001$ ), AVAi (OR, 2.29 [2.14–2.46] per 0.1-cm<sup>2</sup> decrease;  $P<0.0001$ ), MG (OR, 2.63 [2.43–2.85] per 10-mm Hg increase;  $P<0.0001$ ), VPeak (OR, 5.57 [4.85–6.40] per 1-m/s increase;  $P<0.0001$ ), left ventricular ejection fraction (OR, 1.35 [1.26–1.45] per 10% decrease;  $P<0.0001$ ), and creatinine level (OR, 1.84 [1.48–2.29];  $P=0.002$ ). After adjustment for age, LVOT diameter, VPeak, and AVAi as other independent determinants of AVC, men compared with women had higher odds of severe valve calcification (Table 2). Further adjustment for left ventricular ejection fraction, creatinine (or creatinine clearance), and history of coronary disease did not affect the independent determinants of severe AVC or the female sex–lower AVC link (both  $P<0.0001$ ). The model was confirmed when MG replaced VPeak with similarly high OR of severe AVC attached to male sex (OR, 5.40 [2.94–10.19];  $P<0.0001$ ). The model was also confirmed with AVC as a continuous variable by using multiple linear regression models, showing that, adjusting for age, VPeak, LVOT diameter, and AVAi, women had independently lower AVC load than men ( $P<0.0001$ ; Table 3). Moreover, the interaction term (ie, interaction between sex and AS severity documented by Doppler echocardiography) was highly significant ( $P<0.004$  with or without the use of square root–transformed AVC; Table 3). Similarly, with the use of normalized AVC (AVCi or AVCdensity), women independently had lower normalized AVC load than men, adjusted for the same

**Table 1. Baseline Characteristics**

Variables	Whole Cohort (n=665)	Female (n=238)	Male (n=427)	P
<b>Clinical data</b>				
Age, y	75±11	76±11	74±11	0.003
Body mass index, kg/m <sup>2</sup>	28.3±6.1	28.6±7.8	28.1±5.0	0.31
Body surface area, m <sup>2</sup>	1.91±0.24	1.73±0.22	2.01±0.19	<0.0001
NYHA functional class ≥III, n (%)	218 (33)	93 (39)	125 (29)	0.009
History of CAD, n (%)	279 (42)	71 (30)	208 (49)	<0.0001
Hypertension, n (%)	453 (68)	171 (72)	282 (66)	0.15
Diabetes mellitus, n (%)	158 (24)	47 (20)	111 (26)	0.07
History of atrial fibrillation, n (%)	151 (23)	52 (22)	99 (23)	0.61
COPD, n (%)	142 (21)	55 (23)	87 (20)	0.42
Hyperlipidemia, n (%)	444 (67)	148 (62)	296 (69)	0.07
Creatinine level, mg/dL	1.17±0.50	1.04±0.42	1.23±0.52	<0.0001
Creatinine clearance, mL/min	66±28	58±28	70±28	<0.0001
<b>Echocardiographic data</b>				
Peak aortic jet velocity, m/s	3.97±0.94	4.05±0.99	3.93±0.91	0.11
Mean gradient, mm Hg	39±19	41±21	39±18	0.09
Aortic valve area, cm <sup>2</sup>	1.05±0.35	0.94±0.34	1.11±0.34	<0.0001
Aortic valve area index, cm <sup>2</sup> /m <sup>2</sup>	0.55±0.19	0.55±0.20	0.56±0.18	0.46
LV outflow tract diameter, cm	2.2±0.2	2.1±0.1	2.3±0.2	<0.0001
LV ejection fraction, %	60±13	62±12	59±13	0.002
<b>MDCT data</b>				
AVC, AU	2339±1597	1703±1321	2694±1628	<0.0001
AVCi, AU/m <sup>2</sup>	1220±825	996±781	1344±823	<0.0001
AVC density, AU/cm <sup>2</sup>	586±398	502±384	633±399	<0.0001

AVC indicates aortic valve calcification; AVCi, aortic valve calcification index to body surface area; AVC density, aortic valve calcification index to cross-sectional aortic annulus area; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; LV, left ventricular; MDCT, multidetector computed tomography; and NYHA, New York Heart Association.

background variables (all  $P < 0.005$ ), and the interaction term remained significant (all  $P < 0.01$ ). Adjusting the models further for serum creatinine level or creatinine clearance did not affect the significance of sex (all  $P < 0.0001$ ) or interaction term (all  $P < 0.009$ ) in the multivariable models of AVC, AVCi, and AVCdensity. Thus, regardless of the format of analysis, women have lower AVC, lower AVCi that accounts for smaller body size, and lower AVCdensity that accounts for smaller LVOT than men, warranting an analysis of the relation in AVC-hemodynamic severity of AS in both sexes.

**Contrasting Associations Between AVC and Hemodynamic Markers of AS Severity**

In Figure 1, we plotted AVC (x axis) versus VPeak (Figure 1A), MG (Figure 1B), and AVAi (Figure 1C). In all plots, AVC showed good associations with these hemodynamic markers of AS severity in men and in women (all  $r > |0.67|$  and  $P < 0.0001$ ). Despite these similar association strength, the regression curves were influenced by sex (all  $P < 0.0001$  by interaction analysis). In showing the full range of AS severity, there is an overlap between both sexes for low velocities, low gradients, and high AVAi, but with increasing AVC load, the regression curves in men and women separated, showing that for a higher but similar loads of calcium, hemodynamic severity of AS was worse in women than men. This difference in association between AS severity and AVC load remained significant when AVC was indexed to body surface area to account for lower body size in women (AVCi: all interaction  $P < 0.005$ ) or to LVOT area to account for smaller heart size in women (AVCdensity: all interaction  $P < 0.009$ ).

After patients were divided in to tertiles of normalized AVC (Figure 2), AVCi in Figure 2A, and AVCdensity in Figure 2B, women had a more severe AS, as documented by VPeak and AVAi in each tertile of normalized AVC (all  $P < 0.01$ ).

**Discussion**

The main findings of this prospective study are as follows.

1. Women, with similar AS severity as men, present with lower AVC load than men. Moreover, after taking into account that women have smaller bodies and smaller LVOT, AVC load normalization for body surface area and cross-sectional aortic annulus area shows that women present lower AVCdensity than men for similar AS severity.

2. The difference between sexes is related to a steeper slope of AS severity increase with any given AVC load or density increase in women than in men.
3. For diagnostic purposes, interpreting the AVC load link to severe AS should be different and lower for women as compared with men. Therefore, while valvular calcification is the mechanism of AS in both men and women, there are important pathophysiological differences between men and women that warrant specific clinical approaches and further research into disease mechanisms specific to each sex.

**AVC–AS Mechanism**

The link between aortic valve accumulation of calcification (ie, anatomic lesion of the valve) and AS (ie, hemodynamic burden of the lesion) has been long demonstrated in autopsy studies,<sup>19–21</sup> even at a very early stage of the disease.<sup>10</sup>

This anatomic link for AS calcification was confirmed in vivo casually during fluoroscopy<sup>22</sup> and more recently quantitatively by using CT in previous small studies.<sup>13,23–25</sup> In the present large, prospective, cross-sectional study with simultaneous CT scans and Doppler echocardiograms, we observed excellent correlations between hemodynamic severity of AS and severity of AVC load determined by MDCT.<sup>15,23,26,27</sup> However, although the general mechanism of more calcification associated with more severe AS holds true, this large series of patients provides the power to detect for the first time that the relation between AS severity and AVC load in men and women is significantly different (Figure 1). As expected, in patients with mild AVC and less severe AS, the difference between sexes is smaller (Figure 2), and obviously, at that relatively benign end of the spectrum, AVC load, peak aortic velocity, mean gradient, and indexed aortic valve area should be equal in men and women with normal or minimally affected aortic valves. Thus, there is an expected overlap with mild AS, but inclusion of a wide range of AS severity allows demonstration of the strong impact of sex on AVC load and the lower odds of severe AVC load in women compared with men regardless of any adjustment. Remarkably, the hemodynamic severity of AS was similar between men and women, but direct comparison or interaction analysis of AVC load emphasized the lesser calcification in women. The explanation of this difference is not in the body habitus because normalization for body surface area and cross-sectional area of the aortic annulus showed the same results. Differences between men and women with AS generally emphasized the ventricular

**Table 2. Multivariable Predictors of an Aortic Valve Calcification >1650 AU**

	Increment Category	Odds Ratio (95% Confidence Interval)	Estimate±SD	P
Clinical data				
Age	+10 y	1.71 (1.38–2.13)	0.54±0.11	<0.0001
Male sex	Yes	5.07 (2.78–9.46)	1.62±0.31	<0.0001
Echocardiographic data				
Peak aortic jet velocity	+1 m/s	4.59 (2.97–7.33)	1.52±0.30	<0.0001
Indexed AVA	–0.1 cm <sup>2</sup> /m <sup>2</sup>	1.79 (1.44–2.24)	0.58±0.11	<0.0001
LV outflow tract diameter	+0.1 cm	1.4 (1.22–1.65)	0.35±0.07	<0.0001

AVA indicates aortic valve area; and LV, left ventricular.

**Table 3. Multivariable Predictors of Aortic Valve Calcification**

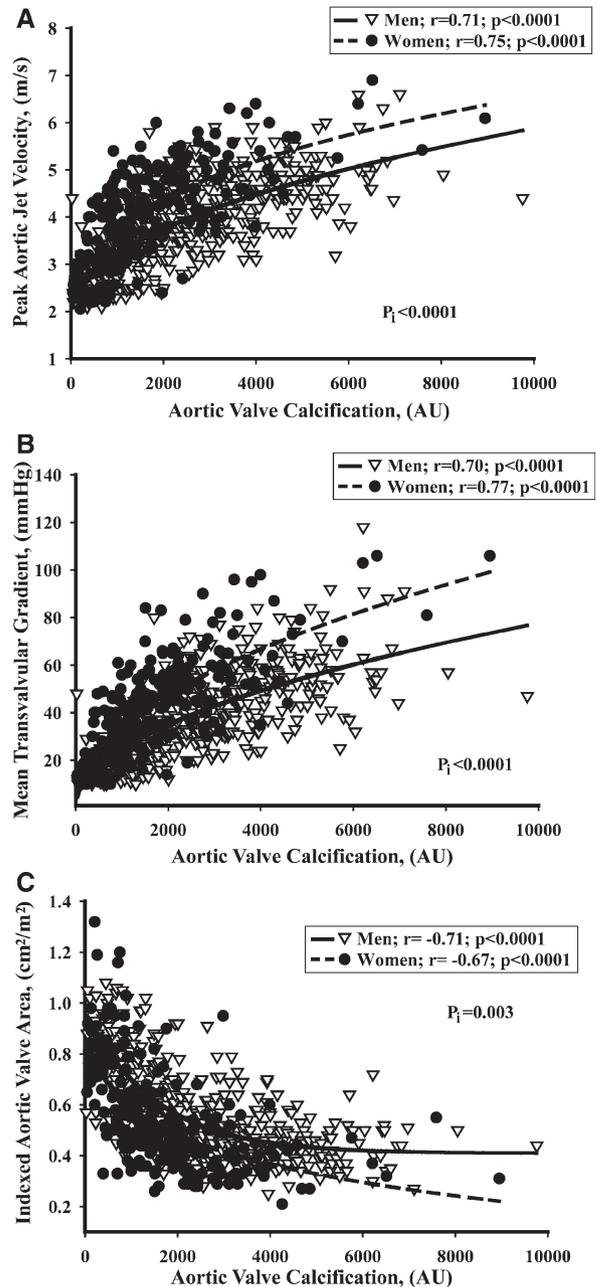
	Increment Category	Estimate±SD	P
Clinical data			
Age	+10 y	181±39	<0.0001
Male sex	Yes	719±45	<0.0001
Echocardiographic data			
Peak aortic jet velocity	+1 m/s	884±68	<0.0001
Indexed aortic valve area	-0.1 cm <sup>2</sup> /m <sup>2</sup>	166±36	<0.0001
LV outflow tract diameter	+0.1 cm	181±24	<0.0001
Interaction sex-indexed aortic valve area	...	175±45	<0.0001

LV indicates left ventricular.

response to the disease,<sup>24,25,28</sup> with differing hypertrophy patterns.<sup>29,30</sup> However, differences in the process of calcification have not been emphasized<sup>13</sup> because doing so requires large series with simultaneous quantitative measurements in vivo. This new insight into the pathophysiology of AS development raises the question of its biological mechanism. Whether factors that have been cited as affecting AS and AVC progression such as vitamin D receptors<sup>31</sup> or growth factors<sup>32</sup> are different in women and may lead to more extensive fibrosis is unclear and requires further research. Regardless of the new observation that AVC load is different in men and women with AS, AVC load has important and immediate diagnostic implications.

### AVC-AS Diagnosis

Doppler echocardiography remains the gold standard technique to assess AS severity.<sup>33</sup> However, this technique has some significant limitations. Echocardiography can be challenging in patients with poor windows such as those suffering from obesity or chronic obstructive pulmonary disease. More important, assessment of AS severity can often be challenging<sup>34</sup> in patients with low AVA (in the severe range) and low gradient (in the moderate range) with or without low flow or low ejection fraction.<sup>35-38</sup> Affirming the severity of AS is crucial for clinical management and decision making.<sup>39-41</sup> Doppler echocardiography at rest is not conclusive in such patients, requiring additional testing to differentiate truly severe from pseudosevere AS.<sup>35,38,42,43</sup> Catheterization is often not helpful because of similar discrepancies in AS severity markers,<sup>44</sup> whereas crossing the aortic valve also carries a significant risk of cerebral embolism,<sup>45,46</sup> and stress Doppler echocardiography is not always conclusive.<sup>35</sup> Hence, CT has emerged as an adjunct to Doppler echocardiography in the determination of AS severity.<sup>47</sup> Indeed, although Doppler echocardiography quantifies the hemodynamic degree of AS, CT measures the intrinsic lesion of the valve and provides an additional parameter to evaluate calcified aortic valve disease severity. AVC measurement by MDCT is a fast, simple, noninvasive, highly feasible, widely available, and highly reproducible technique.<sup>15,16</sup> In these studies, intraobserver and interobserver variabilities were <7%. Moreover, for visualization of calcification, CT does not require contrast and can be performed in patients with arrhythmias. AVC may also have other interest in AS evaluation because it has been shown in transcatheter aortic valve implantation to predict aortic regurgitation after the procedure.<sup>48</sup> However, our study emphasizes

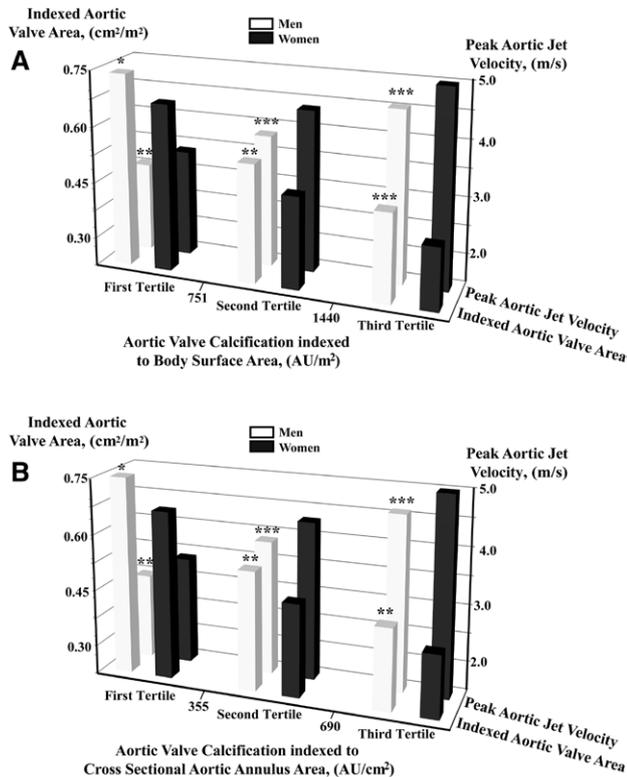


**Figure 1.** Associations between aortic valve calcification (AVC) load and hemodynamic markers of aortic stenosis (AS) severity according to sex. In all panels, AVC load expressed in arbitrary units (AU) is independent variable (x axis): **(A)** AS severity documented by peak aortic jet velocity (y axis); **(B)** AS severity documented by mean transvalvular gradient (y axis); and **(C)** AS severity documented by indexed aortic valve area (y axis). Note that although men and women have similarly low AVC for minimal valvular obstruction, increasing obstruction occurs for lower calcium loads in women compared with men for all measures of AS severity as denoted by the AVC-sex interaction ( $P:P$ ).

the necessity to interpret differently the link between AVC load values and AS severity in men and women.

### Limitation

In this study, the type and length of use of medication cannot be assessed for each patient; thus, it is possible that some medication may influence the calcification of the aortic



**Figure 2.** Evaluation of peak aortic jet velocity and indexed aortic valve area according to aortic valve calcification (AVCi indexed to body surface area: **A**) or AVCdensity (AVC indexed to cross-sectional area of aortic annulus **B**) and sex. **A**, AVCi was divided in tertile: first tertile defined by  $AVCi \leq 751$  AU/m<sup>2</sup>; second tertile by  $751 < AVCi \leq 1440$  AU/m<sup>2</sup>; and third tertile by  $AVCi > 1440$  AU/m<sup>2</sup>. **B**, AVCdensity was divided in tertile: first tertile defined by  $AVCdensity \leq 355$  AU/cm<sup>2</sup>; second tertile by  $355 < AVCdensity \leq 690$  AU/cm<sup>2</sup>; and third tertile by  $AVCdensity > 690$  AU/cm<sup>2</sup>. Note that, for a given amount of AVC, women show a more severe aortic stenosis than men: \* $P < 0.01$ ; \*\* $P < 0.001$ ; \*\*\* $P < 0.0001$ .

valve. Nevertheless, no medication has been shown to differently modify AVC and hemodynamic severity, and because we focused on this relation, medication may have only a minor impact. Another limitation of the study is that the measurements were done in 2 institutions and with different echocardiographic and CT equipment. However, Doppler echocardiographic measurements are routinely used clinically, and methods of measurement are well defined. The MDCT quantification of calcification has been the subject of longstanding collaboration among our institutions<sup>15,16,49</sup> and is achieved by software that leaves limited operator interventions in defining calcification of interest. As shown, variability is low, and ANCOVA showed that the slope of the regression of velocity–AVC is similar between institutions in men ( $P=0.40$ ) and women ( $P=0.61$ ) and between scanners used in men ( $P=0.34$ ) and women ( $P=0.52$ ). Thus, the multicenter and multiscanner nature of our study further reinforces our main result.

## Conclusions

In this large prospective study of AVC by MDCT with simultaneous Doppler echocardiography–derived hemodynamics of AS, women reached similar AS severity as men for lower aortic

valve calcium loads, even after normalization for lower body surface area and smaller aortic annulus area. The differences between sexes are related to a steeper slope of AS severity increase for any given AVC load (or density) increase in women compared with men. For diagnostic purposes, linking AVC load to severe AS should be different and lower for women compared with men. Therefore, although valvular calcification is the mechanism of AS in both men and women, important pathophysiological differences between men and women warrant specific clinical approaches and further research in disease mechanisms specific to each sex.

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### CLINICAL PERSPECTIVE

Aortic stenosis (AS) in the adult is attributed to calcific deposits in the aortic leaflets tissue by a process similar to atherosclerosis. Differences in atherosclerotic lesions between men and women are well known, but it is unclear whether such differences exist for aortic valve calcification (AVC) load. New insights can be obtained by quantifying AVC load using multidetector computed tomography. In our study, which uses Doppler echocardiography and multidetector computed tomography during the same episode of care, men and women presented with the same AS hemodynamic severity, but AVC load was higher in men compared with women. After taking into account the smaller body surface area and smaller left ventricular outflow tract area in women compared with men, the difference in AVC load remained significant. Moreover, for a similar AS severity as documented by Doppler echocardiography, men had a 5-fold-higher chance of being considered as having a severe AVC load. Thus, our study shows a considerable physiological difference between men and women with AS in that women reach severe hemodynamic AS with a much smaller AVC load, absolute or size adjusted, than men. This difference warrants mechanistic investigation to relate AVC load progression to AS progression in women compared with men. Clinically, for diagnosis purposes, the link between AVC load values and AS severity should be interpreted differently in men and women.