difference in prevalence of attenuated plaques or calcific nodules among any of the groups.

We divided patients into: 1) ST-segment elevation myocardial infarction (STEMI); 2) non-STEMI or unstable angina; and 3) stable coronary artery disease. In patients <65 years of age (but not ≥65 years of age), a difference in plaque rupture and TCFA prevalence was seen in patients with STEMI or non-STEMI/unstable angina but not in patients with stable coronary artery disease, with a similar trend in the prevalence of TCFA (**Figure 1**).

Multivariate analysis showed that male sex was an independent predictor for plaque rupture (odds ratio: 1.85 [95% confidence interval: 1.26, 2.71]; $p = 0.0017$) and for TCFA (odds ratio: 1.41 [95% confidence interval: 1.01, 1.96]; $p = 0.045$) after adjustment of other variables. However, age as a continuous variable was not an independent predictor for plaque rupture or TCFA.

The present study demonstrated that ruptured plaques and TCFA were more common in men than in women <65 years of age, but these differences disappeared in older patients (≥65 years of age). Some selection bias is expected because these patients were referred for coronary intervention. IVUS use was per operator discretion; IVUS was not performed in all coronary arteries; and pre-intervention IVUS was only performed in a subset. Nevertheless, we included the entire cohort of patients in the IVUS substudy of the ADAPT-DES study with pre-intervention imaging.

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Sex Differences in the Progression of Aortic Stenosis and Prognostic Implication

The COFRASA-GENERAC Study

In patients with aortic stenosis (AS), degree of aortic valve calcification (AVC) measured using multislice computed tomography is closely related to hemodynamic severity as assessed using transthoracic echocardiography (1); but for similar hemodynamic severity, AVC load is lower in females than in males and AS progresses faster as hemodynamic or anatomic severity increases (2,3). The impact of sex on AS progression accounting for baseline AS (hemodynamic or anatomic) severity has never been specifically evaluated.

Patients enrolled between November 2006 and September 2013 in 2 ongoing prospective studies, COFRASA (Aortic Stenosis in Elderly: Determinant of Progression) (NCT00338676) and GENERAC (Genetic of Aortic Valve Stenosis-Clinical and Therapeutic Implications) (NCT00647088) with at least 2 years of follow-up constituted our study population. Population and methodology has been described elsewhere (3). Briefly, all participants had pure, isolated, at least mild, asymptomatic, degenerative AS and underwent, the same day, a comprehensive clinical, transthoracic echocardiography, and multislice computed tomography evaluation at inclusion and yearly thereafter. The degree of AVC was quantitatively assessed according to the Agatston method (calcium score) expressed in arbitrary units (AU). Correlations

TABLE 1 Characteristics of the Population Overall and According to Sex

	Overall (N = 203)	Male (n = 152)	Female (n = 51)	p Value
Age, yrs	73 ± 9	73 ± 9	73 ± 10	0.78
Male	152 (75)	–	–	–
Sinus rhythm	190 (94)	141 (93)	49 (96)	0.38
Diabetes	50 (25)	40 (26)	10 (20)	0.33
Hypertension	139 (68)	104 (68)	35 (69)	0.98
Smoker	105 (52)	88 (58)	17 (33)	0.002
Body surface area, m^2	1.91 ± 0.22	1.97 ± 0.18	1.74 ± 0.24	<0.0001
Body mass index, kg/m^2	29 ± 5	29 ± 4	29 ± 7	0.81
Coronary artery disease	73 (36)	63 (41)	10 (20)	0.005
Stroke	17 (8)	13 (9)	4 (8)	0.87
Peripheral vascular disease	18 (9)	18 (11)	0	0.01
Pulmonary disease	41 (20)	29 (19)	12 (24)	0.49
Total cholesterol, mmol/l	4.71 ± 1.12	4.52 ± 1.07	5.28 ± 1.06	0.0001
Low-density lipoprotein cholesterol, mmol/l	2.65 ± 0.92	2.51 ± 0.88	3.08 ± 0.93	0.0002
Statins therapy	133 (66)	105 (69)	28 (55)	0.07
Serum creatinine, µmol/l	92 ± 28	98 ± 28	73 ± 15	0.0001
Trileaflet aortic valve	163 (80)	123 (81)	40 (78)	0.70
Ejection fraction, %	63 ± 5	64 ± 5	63 ± 6	0.63
Left ventricular mass index, g/m^2	114 ± 27	118 ± 27	103 ± 23	0.0003
Left ventricular hypertrophy	112 (55)	82 (54)	30 (59)	0.54
Baseline AS severity				
Mild AS	96 (47)	68 (45)	28 (55)	
Moderate AS	89 (44)	73 (48)	16 (31)	0.08
Severe AS	18 (9)	11 (7)	7 (14)	
Baseline aortic valve area, cm^2	1.39 ± 0.37	1.44 ± 0.36	1.25 ± 0.37	0.002
Baseline indexed aortic valve area, cm^2/m^2	0.73 ± 0.19	0.73 ± 0.18	0.72 ± 0.20	0.84
Baseline mean pressure gradient, mm Hg	23 ± 11	23 ± 11	23 ± 13	0.28
Baseline peak aortic velocity, cm/s	303 ± 65	305 ± 62	297 ± 74	0.29
Baseline aortic valve calcification score, AU	1168 ± 984	1256 ± 969	906 ± 989	0.0002
Follow-up AS severity				
Mild AS	49 (24)	35 (23)	14 (28)	
Moderate AS	94 (46)	76 (50)	18 (35)	0.18
Severe AS	60 (30)	41 (27)	19 (37)	
Mean pressure gradient increase, mm Hg/yr	3 ± 4	3 ± 3	5 ± 5	0.04
Peak velocity increase, cm/s/yr	17 ± 16	14 ± 14	23 ± 19	0.004
Aortic valve area decrease, $cm^2/m^2/yr$	−0.08 ± 0.07	−0.08 ± 0.08	−0.08 ± 0.07	0.96
Indexed Aortic valve area decrease, $cm^2/m^2/yr$	−0.04 ± 0.04	−0.04 ± 0.04	−0.05 ± 0.04	0.20
Aortic valve calcification increase, AU/yr	218 ± 226	215 ± 193	228 ± 307	0.30

Values are mean ± SD or n (%). Comparisons between sexes were performed using chi-square, Student *t* test, or Wilcoxon tests as appropriate.

AS = aortic stenosis; AU = arbitrary units.

between calcium score and AS hemodynamic severity were tested with linear and nonlinear regressions and the model using the square root of AVC was retained as providing the best fit. The impact of sex was assessed using analysis of covariance.

We prospectively enrolled 203 patients (Table 1). Mean pressure gradient (MPG) was 23 ± 11 mm Hg; 96 patients (47%) had mild AS (MPG <20 mm Hg), 89 patients (44%) had moderate AS (MPG 20 to 40 mm Hg), and 18 patients (9%) had severe AS (MPG >40 mm Hg). Mean AVC score was 1,168 ± 984 AU. AS hemodynamic severity was similar in females and males (MPG 23 ± 13 mm Hg vs. 23 ± 11 mm Hg, p = 0.28), but AVC load was significantly lower in females than males (906 ± 989 AU vs. 1,256 ± 969 AU, p = 0.0002). AVC correlated well to MPG both in males and females ($r = 0.70$, $p < 0.0001$ and $r = 0.74$, $p < 0.0001$, respectively) but the regression curves were different according to sex (p = 0.005) with lower loads of calcium in females than in males for the same hemodynamic severity.

Mean follow-up time was 3.2 ± 1.2 years. Mean MPG increased from 23 ± 11 mm Hg to 33 ± 17 mm Hg (+3 ± 4 mm Hg/year). Hemodynamic progression was different between females and males (5 ± 5 mm Hg vs. 3 ± 3 mm Hg, p = 0.04), and in multivariate analysis, after adjustment for age, valve anatomy, and MPG, sex was independently associated with hemodynamic progression (p = 0.0005). Final mean AVC score was 1,852 ± 1,502 AU (+218 ± 226 AU/year). Absolute AVC progression rate was not statistically different between females and males (228 ± 307 AU/year vs. 215 ± 193 AU/year, p = 0.30), but as baseline AVC was significantly lower at baseline in females compared to males, the annualized relative progression rate was significantly higher (33 ± 32% vs. 19 ± 16%, p = 0.004), and in multivariate analysis after adjustment for age and valve anatomy and baseline AVC score, female sex was an independent predictor of AVC progression (p = 0.002).

During follow-up, 41 patients developed AS-related symptoms (no death occurred). The AS-related events rate at 5 years was 44% in females and 23% in males (p = 0.03) and in multivariate analysis (Cox proportional-hazard analyses), after adjustment for age, valve anatomy, and baseline MPG, sex was an independent predictor of outcome (hazard ratio 2.60 [95% confidence interval: 1.32 to 5.02]; p = 0.007). The same results were observed when baseline AVC score was entered into the model instead of MPG (hazard ratio: 2.69 [95% confidence interval: 1.34 to 5.26]; p = 0.006).

We and others have demonstrated the excellent diagnostic value of AVC to assess AS severity. Although the general mechanism of more calcification is associated with more severe AS holds true in females and in males, females display lower AVC load than males for the same hemodynamic severity. The impact of sex on AS progression has been only evaluated in few studies and was negative (4). However, these studies enrolled highly selected patients, were

often retrospective, did not consider a complementary independent method for assessing AS progression, and do not always consider baseline AS severity. In the present study, AS progressed faster in females than in males after adjustment for baseline AS severity. This was true for both MPG and AVC progression, but no change in valve area was observed. The absolute AVC progression rate was not different between sexes, but as females presented with significantly lower AVC load, a lower progression rate would have been expected in the absence of sex impact. These finding underline the important pathophysiological differences between females and males and strongly support the development of future research in disease mechanisms specific to each sex. In addition, current recommendations advised a yearly follow-up of patients with moderate AS. Our findings with a faster progression and lower event-free survival in females than in males suggest that females may benefit from a closer follow-up time.

In a prospective cohort of AS patients, we found that female sex was an independent determinant of both AVC and MPG progression which translated into a higher AS-related events rate. These results support that AS pathophysiology may be different in females and in males and suggest that a closer follow-up time may be advised in females. However, these findings observed in a relatively small number of females deserve confirmation in further studies.

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