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ORIGINAL RESEARCH

Sex-Specific Functional Status Decline and Outcomes in Mild-to-Moderate Aortic Stenosis

Results From the PROGRESSA Study

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ABSTRACT

BACKGROUND Little is known about the effect of sex on functional status decline in aortic valve stenosis (AS) patients.

OBJECTIVES The purpose of this study was to examine the changes in functional status according to sex in patients with mild-to-moderate AS and its association with the composite of death or aortic valve replacement (AVR).

METHODS We included patients with mild-to-moderate AS prospectively recruited in the PROGRESSA (Metabolic Determinants of the Progression of Aortic Stenosis) study (NCT01679431). Functional status was assessed using the New York Heart Association classification and the Duke Activity Status Index (DASI).

RESULTS A total of 244 patients (mean age 64 ± 14 years, 29% women) were included. The mean follow-up was 4.3 ± 2.4 years. Women with intermediate-to-fast AS progression rate (median change in peak aortic jet velocity ≥0.11 m/s/year) had significantly faster decline in DASI score compared to men with similar progression rate ($P < 0.05$). In linear mixed analysis adjusted for several clinical and echocardiographic factors, female sex and change in peak aortic jet velocity remained strongly associated with the worsening of New York Heart Association class and the decline of DASI score (all, $P < 0.001$). The composite of death or AVR occurred in 115 patients (16 deaths and 99 AVRs). In multivariable Cox regression analyses, functional status decline during follow-up remained significantly associated with the composite of death or AVR (HR: 2.13; 95% CI: 1.22-3.73; $P = 0.008$).

CONCLUSIONS In patients with mild-to-moderate AS at baseline, intermediate-to-fast progression rate of AS was associated with a more rapid decline of functional status during follow-up, particularly in women. Functional status decline during follow-up was strongly associated with the incidence of death or AVR, with comparable effect in both women and men. (JACC Adv. 2024;3:101267) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

AS = aortic valve stenosis

AVA = aortic valve area

AVR = aortic valve replacement

BNP = brain natriuretic peptide

BSA = body surface area

DASI = Duke Activity Status Index

Lp(a) = lipoprotein(a)

LV = left ventricular

LVEF = LV ejection fraction

NT-proBNP = N-terminal pro b-type natriuretic peptide

V_{peak} = peak aortic jet velocity

Calcific aortic valve stenosis (AS) is a leading cause of morbidity and mortality in high-income countries.[1] Due to the growing number of older people, the health care and socioeconomic burden related to AS is expected to increase dramatically in the next 2 decades.[1] There are no proven pharmacotherapies to prevent the development or the progression of AS, thus, surgical or transcatheter aortic valve replacement (AVR) remains the only effective therapeutic treatment for patients with severe AS.[2,3]

In patients with severe AS, AVR is recommended (Class I) in presence of symptoms and/or left ventricular (LV) systolic dysfunction (LV ejection fraction [LVEF] <50%).[2,3] In asymptomatic patients with severe AS, AVR may be considered (class IIa or IIb) in presence of very severe AS, fast progression rate of valve stenosis, markedly elevated brain natriuretic peptide (BNP), or decline in LVEF below 60%.[2,3] However, in current guidelines, the progression or decline in functional/health-related parameters are not considered as triggers for AVR in asymptomatic patients with AS.[2,3] Moreover, previous studies have reported sex-based differences in the clinical presentation and outcomes of severe AS, including more heart failure symptoms, late referral for AVR, and worse outcomes following surgical AVR in female patients.[4-7] However, it remains unclear whether the decline in functional status during the course of AS differs between women and men.

In this prospective observational study including patients with mild-to-moderate AS at baseline, we investigated: 1) the association of hemodynamic AS progression rate with changes in functional status according to sex; and 2) the association of functional status decline with the composite of death or AVR according to sex.

METHODS

STUDY POPULATION. The purpose and design of the PROGRESSA (Metabolic Determinants of the Progression of Aortic Stenosis, NCT01679431) study were previously described.[8,9] Briefly, patients with age ≥18 years and at least mild AS (ie, peak aortic jet velocity [V_{peak}] ≥2.0 m/s) were prospectively recruited and undergo a comprehensive Doppler echocardiography annually. For the present analysis, patients were excluded if they had: 1) severe and/or symptomatic AS, and/or indication for AVR; 2) moderate or greater aortic regurgitation, or significant mitral valve disease (stenosis or regurgitation); 3) LVEF <50%; and 4) if they are pregnant or lactating. The study was approved by the Ethics Committee of the Institut universitaire de cardiologie et de pneumologie de Québec, and all patients signed a written informed consent at the time of enrollment. Among the 345 patients recruited until October 31, 2018, 244 patients with mild-to-moderate AS had completed at least one follow-up with comprehensive clinical and imaging evaluation, and thus were included in the present subanalysis of the PROGRESSA study.

CLINICAL AND LABORATORY DATA. Clinical data included age, sex, height, weight, body surface area (BSA), body mass index, systolic and diastolic blood pressures, documented diagnoses of comorbidities (Supplemental Methods). Plasma levels of glucose, creatinine, N-terminal pro b-type natriuretic peptide (Nt-proBNP), standard lipid profile, apolipoprotein B, apolipoprotein A-I, and lipoprotein(a) [Lp(a)] were measured (Supplemental Methods). Furthermore, we calculated the ratio of Nt-proBNP between the measured serum level and the maximal normal level of Nt-proBNP for age and sex, as previously described.[10] A NT-proBNP ratio >1 indicates an abnormal/elevated serum level of Nt-proBNP.[10]

FUNCTIONAL STATUS DATA. Functional status was assessed at baseline and then annually using the NYHA functional class [11] and the Duke Activity Status Index (DASI).[12] The DASI is a self-administered questionnaire developed for assessment of functional status, which includes a 12-item questionnaire related to physical function and daily activities of living (ie self-care, ambulation, household tasks, sexual function, and recreational activities).[12,13] The sum of the points provided by each weighted item composes the DASI score, ranging from 0 to 58.2. Higher scores indicate better functional capacity. Metabolic equivalent was estimated as previously described.[12] Functional status data were prospectively collected by experienced nurses and trained clinical research personnel.

ECHOCARDIOGRAPHIC DATA. Comprehensive Doppler echocardiography exams were performed using commercially available ultrasound systems and images were analyzed in a core laboratory by experienced readers (Supplemental Methods). The aortic valve phenotype (ie, bicuspid versus tricuspid) was recorded. Stroke volume was calculated by multiplying the LV outflow tract area by the flow velocity-time integral and was indexed to BSA (SVi). The Doppler-echocardiographic indices of AS severity included V_{peak}, mean pressure gradient, aortic valve area (AVA) calculated by the standard continuity

equation and indexed AVA to BSA as recommended by guidelines.[14] The grading of AS severity and other echocardiographic measures were detailed in the Supplemental Methods.

STUDY ENDPOINTS. The study primary endpoint was defined as the composite of death from any cause or AVR throughout the study period (from baseline to the last follow-up). The decision of AVR was left to the discretion of the treating physician. The outcome data were collected prospectively through review of medical records and patient interviews. All patients included in the present study had at least one follow-up visit (≥1 year) and no patients were lost at follow-up prior to the occurrence of clinical outcome or study completion.

STATISTICAL ANALYSIS. Continuous variables were presented as mean ± SD or median (IQR) for non-normally distributed variables. Continuous variables were compared between groups with Student's *t*-test or with Wilcoxon-Mann-Whitney test. Categorical variables were presented as frequencies and percentages and were compared with chi-square test or Fisher's exact test. Changes in functional-related instruments over time were compared with baseline visit within each AS progression group using paired Student's *t*-test or Wilcoxon matched-pairs signed-rank test, as appropriate. Mixed model for repeated measures was used to compare the changes in DASI score at each follow-up time point.

Linear mixed models were used to determine the association of sex and hemodynamic progression rate of AS with the change of continuous dependent variables over time, specifically the change in DASI score. Linear generalized mixed models were used to determine the association of sex and hemodynamic progression rate of AS with the change of categorical dependent variables over time, specifically the change in NYHA functional class. The fixed effect included sex, hemodynamic parameters of AS severity (ie, V_{peak} measured at each visit), and the number of annual visits. The random effects included patients' study identification numbers and a random intercept to account for inherent variability among individual. The models were adjusted for age, body mass index, hypertension, diabetes, metabolic syndrome, coronary artery disease, history of atrial fibrillation, stroke volume index, and E/e' ratio as fixed factors. Results were presented as OR or coefficients, standard error, and 95% CIs.

Time-to-event analyses were performed between the baseline and last follow-up study visits. To account for missing data during the study period (11% of missing DASI score), multiple imputations by predictive mean matching using chained equations were conducted.[15] Time-to-events data were analyzed by averaging the parameter estimates across the imputed data sets and pooling individual results using Rubin's combination rules.[16] The estimates of cumulative incidence of death or AVR according to functional status decline were calculated using the Kaplan-Meier method and compared using the log-rank test. Univariable and multivariable Cox proportional hazards models were performed to determine the association between functional status decline with the composite of death or AVR. All survival analyses were performed both on the imputed and nonimputed data sets to ensure the robustness of our findings. Results were presented as HR with 95% CIs. Multivariable Cox proportional hazards models were adjusted for age, sex, hypertension, diabetes, plasma level of Lp(a), bicuspid aortic valve, LV mass index, E/e' ratio, and included NYHA class, DASI score, and peak aortic jet velocity as time-dependent measures. The variables selected for multivariable analyses were clinically relevant variables or variables associated with risk of events in univariable analyses (ie, $P < 0.10$). A 2-tailed P value < 0.05 was considered significant. Statistical analyses were performed with Stata software, version 18.0 (StataCorp).

RESULTS

STUDY POPULATION. Among the 244 patients (mean age 64 ± 14 years, 29% female) included in the present study, most had no or mild symptoms (98% NYHA functional class I or II) at baseline. Four (2%) patients with mild AS had more than mild symptoms (NYHA functional class III), with concurrent comorbidities, including obesity, which may have contributed to their symptoms. DASI was available for 219 (89%) patients, with a mean score of 41.2 ± 14.1 points, suggesting moderately good functional status at baseline.

Table 1 describes the baseline characteristics of the study population according to sex. Compared to men, women were younger and had a lower prevalence of hypertension, history of smoking, coronary artery disease, and atrial fibrillation, along with significantly lower plasma levels of Nt-proBNP ratio and high-sensitivity troponin T (all, $P \leq 0.01$) (Table 1). Despite the lower prevalence of comorbidities, women had worse functional status at baseline, characterized by a higher NYHA class ($P = 0.01$) and lower DASI score compared to men ($P = 0.006$) (Table 1). The degree of AS severity was comparable between women and men (V_{Peak}: 2.6 ± 0.4 m/s vs 2.7 ± 0.5 m/s; $P = 0.08$) (Table 1). As expected, LV

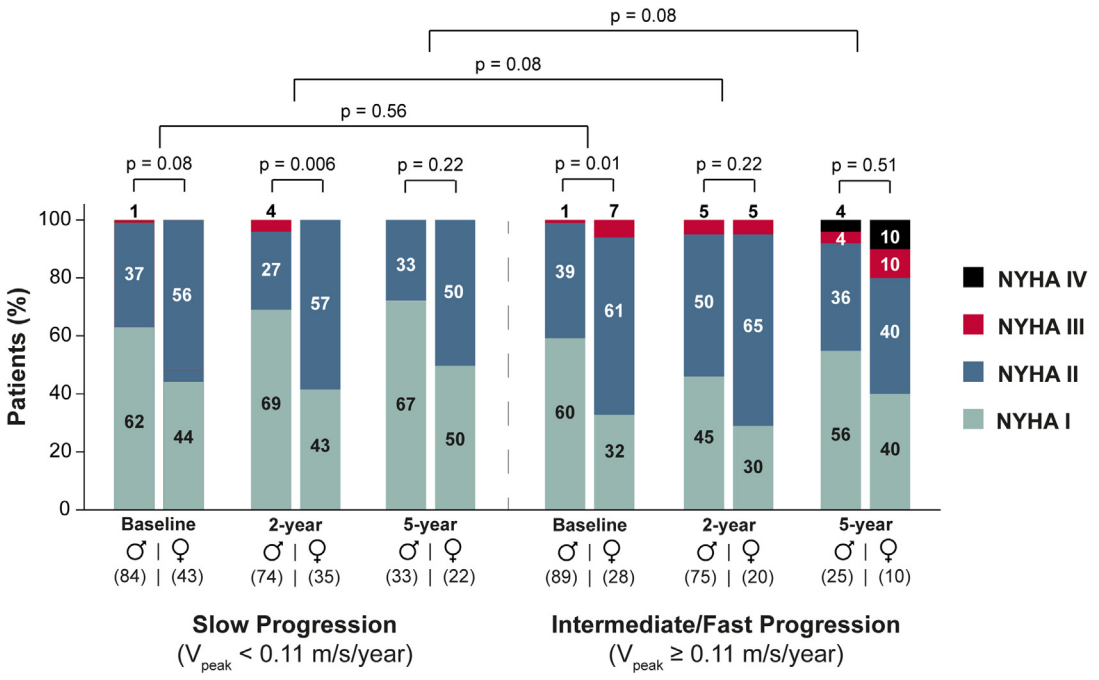
TABLE 1 Baseline Characteristics of the Study Population

	All Patients (N = 244)	Women (n = 71, 29%)	Men (n = 173, 71%)	*P* Value
Clinical data				
Age, y	64 ± 14	61 ± 16	66 ± 12	**0.03**
Body surface area, m^2	1.90 ± 0.21	1.69 ± 0.13	1.98 ± 0.18	**<0.001**
Body mass index, kg/m^2	29 ± 5	28 ± 5	29 ± 4	**0.009**
NYHA functional class				**0.009**
I	133 (55)	28 (39)	105 (61)	
II	107 (44)	41 (57)	66 (38)	
III	4 (2)	2 (3)	2 (1)	
Duke Activity Status Index score	41.2 ± 14.1	37.4 ± 14.5	42.8 ± 13.7	**0.01**
Metabolic equivalents	7.8 ± 1.7	7.3 ± 1.8	8.0 ± 1.7	**0.01**
Systolic blood pressure, mm Hg	138 ± 19	133 ± 20	139 ± 18	**0.01**
Diastolic blood pressure, mm Hg	77 ± 9	76 ± 9	77 ± 9	0.59
Hypertension	191 (78)	48 (68)	143 (83)	**0.01**
Diabetes mellitus	59 (24)	13 (18)	46 (27)	0.17
Metabolic syndrome	53 (22)	16 (23)	37 (22)	0.88
History of smoking	154 (63)	27 (38)	127 (73)	**<0.001**
Coronary artery disease	74 (30)	11 (15)	63 (36)	**0.001**
History of atrial fibrillation	32 (13)	4 (6)	28 (16)	**0.03**
Medication data				
ACE inhibitors	71 (29)	12 (17)	59 (34)	**0.007**
ARBs	74 (30)	26 (37)	48 (28)	0.17
Beta-blockers	73 (30)	14 (20)	59 (34)	**0.03**
Lipid-lowering agents	159 (65)	38 (54)	121 (70)	**0.01**
Anticoagulants	15 (6)	1 (1)	14 (8)	**0.04**
Laboratory data				
LDL-C, mmol/L	2.20 (1.76-2.75)	2.42 (1.83-3.15)	2.14 (1.75-2.59)	**0.001**
apoB, g/L	0.80 (0.69-0.99)	0.84 (0.72-1.07)	0.79 (0.69-0.96)	**0.02**
apoA-I, g/L	1.49 (1.32-1.67)	1.62 (1.43-1.77)	1.44 (1.28-1.59)	**<0.001**
HDL-C, mmol/L	1.38 (1.19-1.61)	1.54 (1.36-1.72)	1.32 (1.15-1.54)	**<0.001**
Lp(a), mg/dL (n = 177)	14 (6-45)	15 (5-56)	14 (5-45)	0.71
Triglycerides, mmol/L	1.27 (0.89-1.77)	1.23 (0.88-1.75)	1.27 (0.89-1.78)	0.72
Fasting glucose, mmol/L	5.3 (5.0-6.1)	5.1 (4.8-5.7)	5.4 (5.0-6.2)	**0.002**
Creatinine clearance, mL/min	84 (70-97)	88 (71-102)	83 (70-94)	0.14
NT-proBNP, pg/mL	80 (39-196)	90 (43-178)	76 (37-207)	0.45
NT-proBNP ratio	0.7 (0.4-1.6)	0.5 (0.3-0.9)	0.9 (0.4-2.1)	**<0.001**
High-sensitivity troponin T, ng/L	8.1 (5.4-12.7)	5.8 (3.0-7.9)	9.1 (6.0-13.7)	**<0.001**
Echocardiographic data				
Bicuspid aortic valve	58 (24)	23 (32)	35 (20)	**0.04**
Stroke volume index, mL/m^2	42 ± 6	42 ± 6	42 ± 6	0.92
Peak aortic jet velocity, m/s	2.6 ± 0.4	2.6 ± 0.4	2.7 ± 0.5	0.08
Mean gradient, mm Hg	16 ± 5	15 ± 5	16 ± 5	0.10
Aortic valve area, cm^2	1.31 ± 0.24	1.20 ± 0.22	1.36 ± 0.23	**<0.001**
Indexed aortic valve area, cm^2/m^2	0.69 ± 0.12	0.71 ± 0.14	0.69 ± 0.12	0.25
Mild AS	198 (81)	60 (76)	138 (67)	0.39
LV mass index, g/m^2	104 ± 21	95 ± 19	108 ± 21	**<0.001**
LV hypertrophy	91 (39)	36 (51)	55 (33)	**0.008**
E/e' ratio	11.1 ± 3.8	11.3 ± 3.7	11.0 ± 3.8	0.60
LV ejection fraction, %	65 ± 5	66 ± 5	64 ± 6	**0.003**

Values are mean ± SD, n (%), or median (25th–75th percentiles). **Bold** values indicates a significant *P*-value ($P < 0.05$).

ACE = angiotensin-converting enzyme; apoB = apolipoprotein B; apoA-I = apolipoprotein A-I; ARBs = angiotensin receptor blockers; AS = aortic valve stenosis; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; Lp(a) = lipoprotein (a); LV = left ventricular; NT-proBNP = N-terminal pro B-type natriuretic peptide.

FIGURE 1 NYHA Functional Class According to Sex and AS Progression Rate



Comparison of NYHA functional class at baseline, 2-year, and 5-year follow-up between women and men, and according to hemodynamic progression rate of AS. Intermediate-to-fast versus slow progression rate of AS was defined as annualized change in V_{peak} ≥11 or <0.11 m/s/year. ♀ = Women; ♂ = Men. AS = aortic valve stenosis; V_{peak} = peak aortic jet velocity.

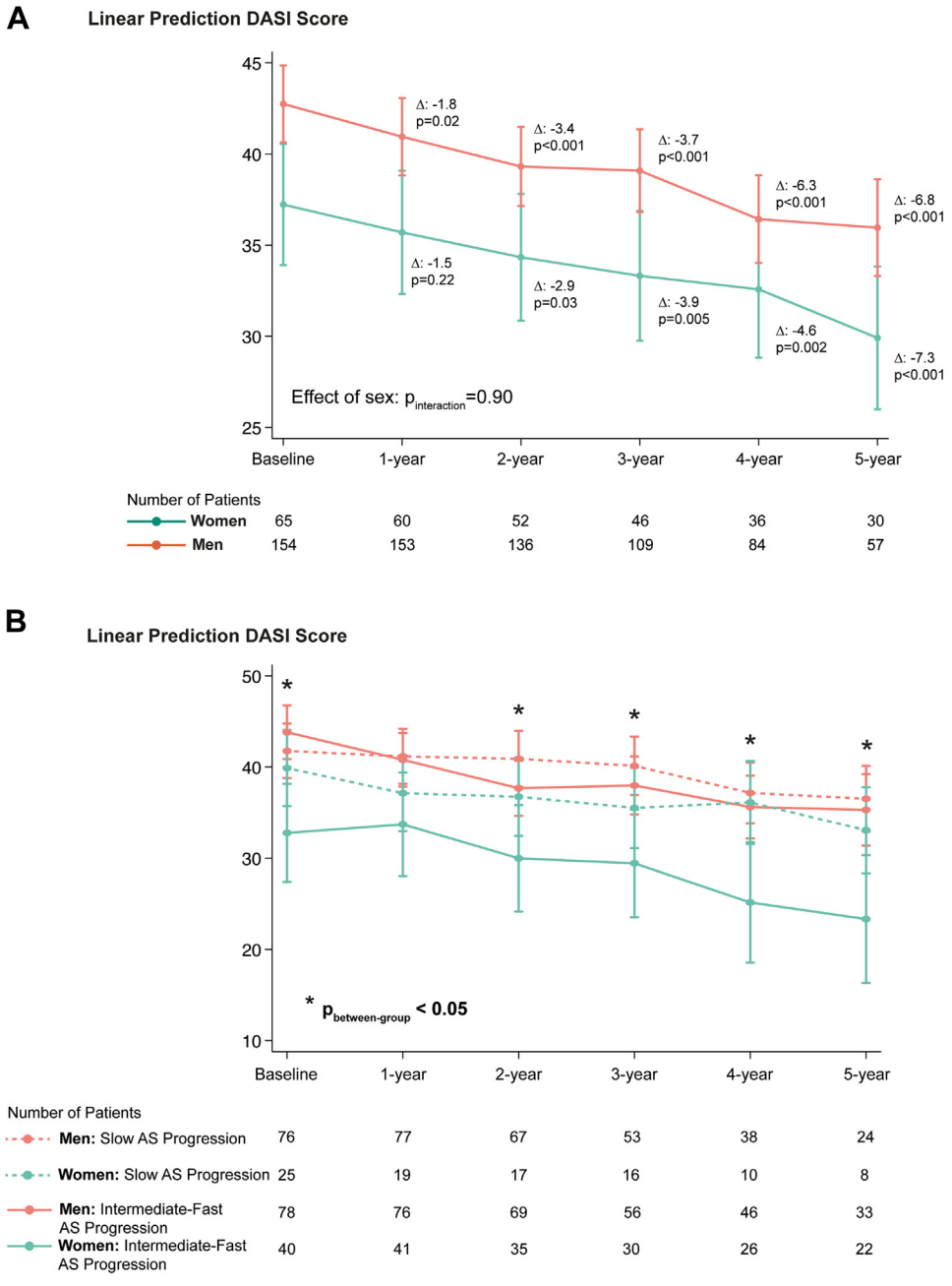
mass index was significantly lower in women than in men ($P < 0.001$), but women had more LV hypertrophy (51% vs 33%; $P = 0.008$) (Table 1).

AS PROGRESSION, DECLINE OF FUNCTIONAL STATUS, AND EFFECT OF SEX. During a mean follow-up time of 4.3 ± 2.4 years, the proportion of patients with mild symptoms (NYHA functional class II) remained consistent from 43.9% to 42.2%. Conversely, the proportion of moderate (NYHA functional class III) and severe (NYHA functional class IV) symptoms increased from 1.6%, and 0% to 4.1%, and 1%, respectively. The deterioration in functional capacity was also apparent with a decrease in mean DASI score from 41.2 ± 14.1 to 34.6 ± 13.1 points. The AS progression rate, that is the annualized change in V_{peak}, in the whole cohort was: 0.11 m/s/year (range: 0.03-0.21). Thirty-six (15%) patients had fast (V_{peak} ≥0.30 m/s/year), 88 (36%) intermediate (V_{peak} 0.11-0.29 m/s/year), and 120 (49%) slow (V_{peak} <0.11 m/s/year) progression rate. There was no significant difference between men and women in AS progression rate based on V_{peak} ($P = 0.06$). However, the disease progression rate based on mean gradient was significantly faster in men compared to women ($P = 0.02$) (Supplemental Figure 1A and 1B). In addition, the annualized changes in indexed AVA and SVi were comparable between women and men (both, $P \geq 0.18$) (Supplemental Figure 1C and 1D). There was also evidence of more severe AS in women and men at last follow-up, with more incidence of low-gradient severe AS in women versus men (35% vs 27%) and more high-gradient severe AS in men versus women (13% vs 7%) (Supplemental Figure 2).

Figure 1 shows the change in NYHA functional class between baseline and 5 years of follow-up according to sex. The proportion of symptomatic patients (NYHA functional class ≥II) remained higher in women at 5 years, although there were no statistically significant differences (Figure 1). For the same degree of AS hemodynamic progression rate, women had more symptoms than men from baseline to 5 years (Figure 1).

There was a significant decline in DASI score in both women and men ($P < 0.05$), with no significant

FIGURE 2 Change in DASI Score According to Sex and AS Progression Rate



Linear prediction of the change in DASI score from baseline to 5-year follow-up between women and men (A), and according to sex and AS progression rate (B). *Indicates significant between-group difference (ie $P < 0.05$). *P* values were obtained after linear mixed analyses. ΔIndicates the change from baseline visit. DASI = Duke Activity Status Index; other abbreviation as in Figure 1.

difference in the rate of decline between two groups ($P = 0.90$) (Figure 2A). Although the slope of decline in DASI was comparable between women and men, DASI score remained significantly lower in women vs men from baseline to 5 years (Figure 2A). When analyzed according to AS progression rate, women with intermediate-to-fast hemodynamic progression rate (V_{peak} increase ≥0.11 m/s/year) had a significantly

TABLE 2 Association Between Sex, Change in Hemodynamic Severity of AS, and Worsening of NYHA Functional Class

	Change in NYHA Functional Class (n = 244)					
	Unadjusted Model			Adjusted Model[a]		
	OR	SE	95% CI	OR	SE	95% CI
Female	4.96	2.08	2.18-11.3[b]	14.8	6.08	6.64-33.1[b]
Peak aortic jet velocity, (per 1 m/s increase)	1.86	0.47	1.13-3.05[c]	4.19	1.19	2.41-7.31[b]

[a]Adjusted model including age, body mass index, hypertension, diabetes, metabolic syndrome, coronary artery disease, history of atrial fibrillation, stroke volume index, E/e' ratio, and follow-up time. OR is the odds ratio which indicates the risk of increase in NYHA functional class for each per-unit change in variables (ie female sex, NYHA class, and peak aortic jet velocity). SE is the standard error. [b]$P < 0.001$. [c]$P \leq 0.01$.

DASI = Duke Activity Status Index; other abbreviation as in Table 1.

faster decline in DASI score compared to other groups (Figure 2B).

In multivariable analysis, female sex remained significantly associated with the increase in NYHA functional class during follow-up (OR: 14.8; $P < 0.001$) (Table 2). The increase in hemodynamic severity of AS (ie V_{peak}) during follow-up remained significantly associated with the increase in NYHA functional class (OR: 4.19; $P < 0.001$) (Table 2). Female sex and AS hemodynamic severity remained significantly associated with the decline in DASI score during follow-up ($P < 0.001$) (Table 3). Of note, bicuspid aortic valve ($P = 0.20$) and LV mass index ($P = 0.08$) were not significantly associated with the increase in NYHA functional class, or the decline in DASI score (all, $P \geq 0.67$). The analysis including Lp(a) measurement is detailed in the Supplemental Results.

RISK OF CLINICAL EVENTS ACCORDING TO FUNCTIONAL STATUS DECLINE AND SEX. During the mean follow-up of 4.3 ± 2.4 years, the primary endpoint occurred in 115 (47%) patients, which included 16 (14%) deaths (without AVR) and 99 (86%) AVRs. Additionally, 106 (43%) patients had a decline in functional status, defined as an increase in NYHA functional class (≥1 class) and/or a faster decline in DASI score (annualized score decline <-2 points/year, ie, median of the entire cohort) during follow-up.

Functional status decline was significantly associated with an increased rate of the composite of death or AVR ($P < 0.001$) (Figure 3A). When stratified by sex, there was a significant difference between groups ($P = 0.004$), with a higher rate of the composite of death or AVR in women and men having functional status decline (Figure 3B).

In univariable Cox analysis, the change in functional status was significantly associated with the primary endpoint (HR: 1.88; 95% CI: 1.29-2.74; $P = 0.001$) (Table 4). Similarly, when analyzed according to sex and using men without functional status decline as a reference group, there was a significant association with the primary endpoint for women (HR: 1.93; 95% CI: 1.06-3.54; $P = 0.03$) and men (HR: 1.58; 95% CI: 1.02-2.45; $P = 0.03$) with functional status decline (Table 4). In multivariable Cox analyses, functional status decline remained significantly associated with the composite of death or AVR (HR: 2.13; 95% CI: 1.22-3.73; $P = 0.008$) (Table 4). Furthermore, after multivariable adjustment, functional status decline remained significantly associated with the composite of death or AVR both in women (HR: 2.25; 95% CI: 1.09-4.65; $P = 0.02$) and men (HR: 2.02; 95% CI: 1.07-3.83; $P = 0.03$) (Table 4). However, there was no significant difference between women and men with functional status decline in the adjusted composite risk of death or

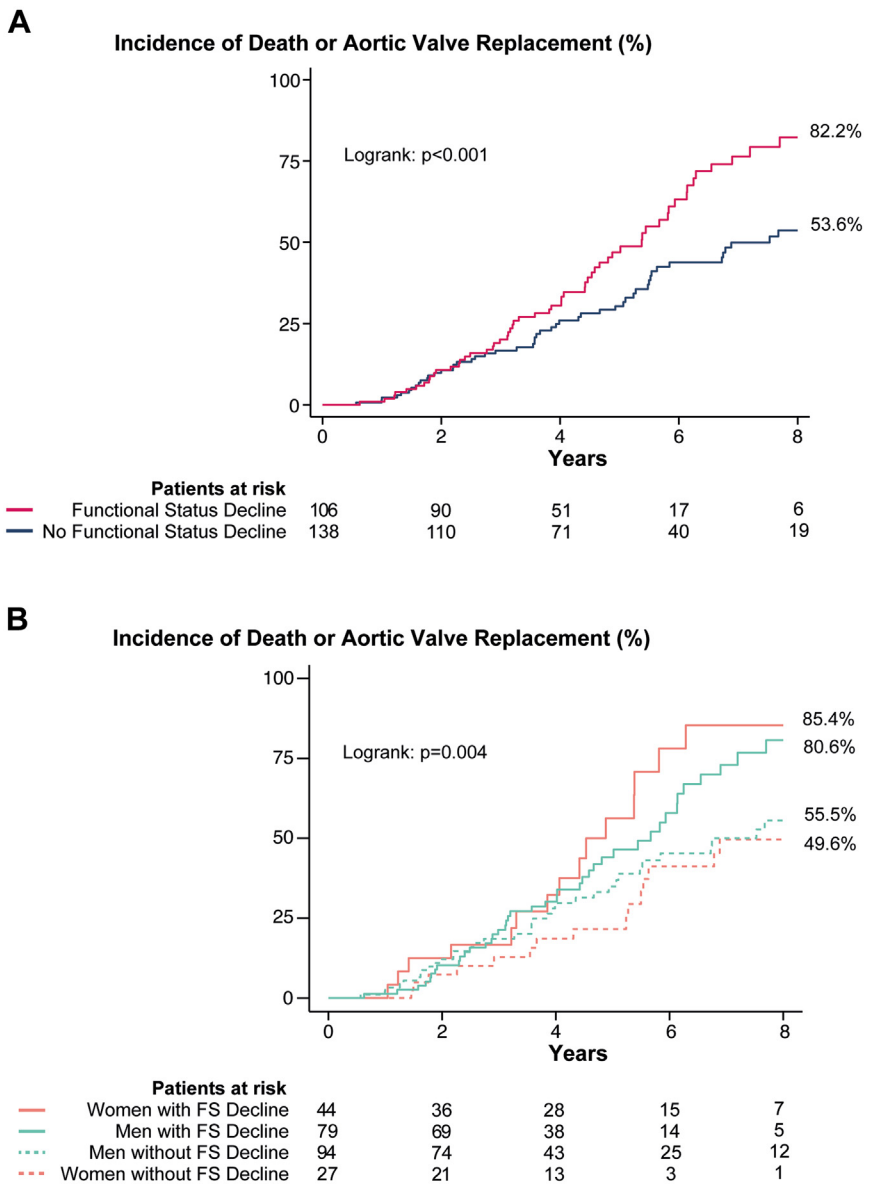
TABLE 3 Association Between Sex, Change in Hemodynamic Severity of AS, and Decline in DASI Score

	Change in DASI Score (n = 237)					
	Unadjusted Model			Adjusted Model[a]		
	Coefficient	SE	95% CI	Coefficient	SE	95% CI
Female	−5.54	1.87	−9.19 to −1.88[c]	−10.3	1.37	−12.9 to −7.56[b]
Peak aortic jet velocity, (per 1 m/s increase)	−6.21	0.82	−7.81 to −4.61[b]	−3.51	0.83	−5.13 to −1.89[b]

[a]Adjusted model including age, body mass index, hypertension, diabetes, metabolic syndrome, coronary artery disease, history of atrial fibrillation, stroke volume index, E/e' ratio, and follow-up time. Coeff. is the fixed effect, which indicates the change in DASI score for each per-unit change in variables (ie, female sex and peak aortic jet velocity). SE is the standard error of the estimate regression coefficient. [b]$P < 0.001$. [c]$P < 0.01$.

Abbreviation as in Tables 1 and 2.

FIGURE 3 Incidence of the Composite of Death or AVR According to Functional Status Decline



Kaplan-Meier curves of the cumulative incidence of death from any cause or AVR according to functional status decline (A), and functional status decline and sex (B). Functional status decline was defined as an increase in NYHA functional class (≥1 class) and/or a faster decline in DASI score (annualized score decline <-2 points/year, ie, median of the entire cohort) during follow-up. AVR = aortic valve replacement; FS = functional status; other abbreviations as in Figures 1 and 2.

AVR ($P = 0.76$). The analyses without imputation are reported in the Supplemental Results.

DISCUSSION

The main findings of this study are: 1) for the same degree of AS hemodynamic severity, and despite lower comorbidities at baseline, women have a worse functional status at baseline, which persisted during follow-up compared to men; 2) faster progression in AS severity was associated with a significant and rapid decline in functional status during follow-up, but with a greater impact in women than in men; and 3) functional status decline during follow-up was strongly related to the incidence of death or AVR, with comparable effect in both women and men.

DECLINE IN FUNCTIONAL STATUS DURING AS PROGRESSION. The development, validation, and application of patient-centered outcomes, such as functional status, are key to improve the patient care journey for patients with valvular heart disease.[17] There are, however, very few studies that examined the changes in patient's functional/health status instruments during follow-up in patients with AS and these studies were generally focused on symptomatic patients with severe AS undergoing AVR.[18,19] Arnold et al[19] previously validated the Kansas City Cardiomyopathy Questionnaire—a disease-specific self-administered questionnaire—to monitor the functional status and quality of life of symptomatic patients with severe AS. The present study is the first to document that decline in functional status occurs early in the course of aortic valve disease and is, in large part, determined by the progression rate of AS hemodynamic severity. Indeed, hemodynamic progression of AS severity was strongly associated with the worsening of NYHA functional class and decline of DASI score, and these associations persisted after adjustment for age, sex, cardiovascular risk factors, and baseline AS severity. Although advanced age and comorbidities may contribute to the deterioration in patient's functional status during the course of AS, our findings suggest that the progression of AS hemodynamic severity is the main driver of this deterioration. Therefore, serial assessment of functional status may help to adjust periodic clinical and imaging follow-up of patients with initially mild-to-moderate AS and an increased risk of rapid disease progression.

TABLE 4 Association of Functional Status Decline With the Primary Endpoint

	Risk of Death or Aortic Valve Replacement (n_{events} = 115)			
	Univariable Analysis		Multivariable Analysis	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Model n° 1				
Decline of functional status	**1.88 (1.29-2.74)**	**0.001**	**2.13 (1.22-3.73)**	**0.008**
Model n° 2				
Men	Reference		Reference	
No decline in functional status				
Women	0.67 (0.37-1.22)	0.19	0.95 (0.50-1.83)	0.89
No decline in functional status				
Men	**1.58 (1.02-2.45)**	**0.03**	**2.02 (1.07-3.83)**	**0.03**
Decline of functional status				
Women	**1.93 (1.06-3.54)**	**0.03**	**2.25 (1.09-4.65)**	**0.02**
Decline of functional status				

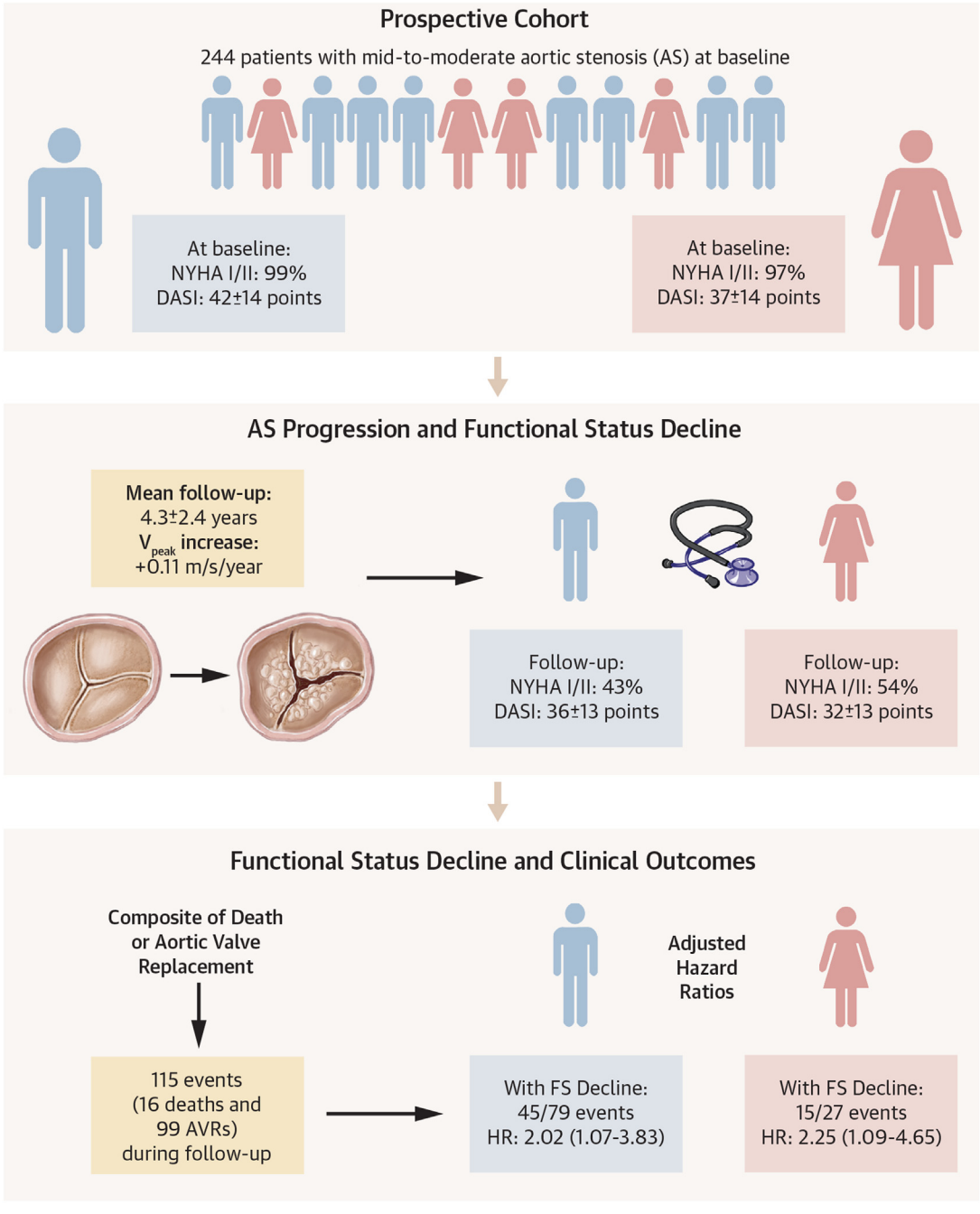
Multivariable *Model n°1* adjusted for age, sex, hypertension, diabetes, bicuspid aortic valve, LV mass index, E/e' ratio, peak aortic jet velocity (ie AS hemodynamic severity) as time-dependent, NYHA class as time-dependent, and DASI score as time-dependent. Multivariable *Model n°2* same as multivariable *Model n°1* excluding sex. **Bold** values indicate significant association.

Abbreviations as in Tables 1 and 2.

SEX DIFFERENCES IN DECLINE OF FUNCTIONAL STATUS. There is now compelling evidence supporting the presence of differences between women and men with respect to the fibro-calcific remodeling of the aortic valve and LV remodeling response in AS.[20-24] While these differences may contribute to different clinical manifestations of AS, sex-specific deterioration of health status during disease progression has been largely unexplored. Prior studies have reported worse symptomatic status in women undergoing AVR compared to men.[4,25-27] However, women were also older, had more preoperative risk factors and more severe AS.[4,25-27] In the present study, based on observational and prospective longitudinal data, we found that for the same degree of AS hemodynamic severity, women presented with worse functional status at baseline compared to men. The sex-related difference in functional status was accentuated during follow-up. Singh et al [5] previously reported that, for a given degree of AS severity, women had earlier onset of symptoms than men but they did not assess quality of life. Our findings underscore the need to develop sex-specific criteria/parameters when interpreting the anatomical and functional consequences of AS progression.

In our study population, women were significantly younger than men at baseline. The younger age in women may explain the lower prevalence of comorbidities as well as the higher proportion of bicuspid aortic valve. Despite lower comorbidities, women had a similar degree of AS severity and LV filling pressure, but a greater degree of LV hypertrophy, which may have contributed to their functional status at baseline and throughout AS progression. We previously reported that female sex was an independent determinant of higher interstitial and replacement myocardial fibrosis.[23] In women with AS, the LV hypertrophic remodeling may contribute to impaired coronary microcirculation leading to repetitive myocardial ischemia and the development of myocardial fibrosis.[23] Therefore, myocardial fibrosis expansion, as a result of pressure overload and LV remodeling, could lead to more advanced LV diastolic dysfunction and thus more symptoms in women. On the other hand, other parameters, in addition to AS severity and LV consequences, may influence the decline in functional status of patients with AS. Indeed, perceived health and functional status may differ between women and men due to several other conditions including social and cultural

CENTRAL ILLUSTRATION **Sex-Related Differences in the Decline of Functional Status in Patients With Mild-to-Moderate AS**



Tastet L, et al. JACC Adv. 2024;3(10):101267.

Among patients with mild-to-moderate AS at baseline, women present with more symptoms and have worse decline in health status for similar AS hemodynamic progression rate. Abbreviations as in Figures 1 to 3.

determinants.[28-30] This has been well illustrated in ischemic heart disease where poor social factors were associated with worse outcome in women.[31] Moreover, women typically have lower maximal oxygen consumption and shorter 6-minute walk test distances, independent of AS/symptoms, which may also explain the lower DASI score at baseline. However, in our study, women with faster AS progression experience a more rapid decline in functional status, even after adjustment for several confounding factors. Hence, these findings warrant further studies to better understand the sex-specific aspects of AS progression and management.

Prior studies have reported sex disparities in referral patterns for AVR.[4,26] Women with severe AS are less likely to be referred for surgical AVR or are referred at a more advanced stage of the disease versus men. This has been well documented in a recent large hospital network including more than 10,000 patients with severe AS.[32] Among patients with severe low-gradient AS, male sex was independently associated with higher likelihood of receiving AVR.[32] We have recently reported similar results in a large series of patients in whom women with severe low-gradient AS were less often referred to AVR, resulting in excess mortality among women.[7] Given that presence of severe AS and of symptoms are the primary triggers for intervention in AS, it is surprising to see that women are less often referred or referred later to AVR versus men. These findings may be related to the fact that both AS severity (probably because of high prevalence of low gradient AS) and of symptoms may be underestimated and/or misinterpreted to a larger extent in women vs men. However, these findings diverge from those of the present study, wherein women were not undertreated compared to men. The conflicting results are likely due to differences in the study population and endpoints. The present study included patients who were younger and at a less advanced disease stage, as evidenced by the significant age difference for women (>10 years), with yearly follow-up.

FUTURE PERSPECTIVES. AVR is up to now the only effective treatment for severe AS. However, several randomized trials have been initiated recently or will be launched in the near future to test whether pharmacotherapies are able to slow or block the progression of AS. For these trials, the primary outcomes are generally the progression of anatomic or hemodynamic severity of AS assessed by imaging. Recently, Lindman et al on behalf of the Heart Valve Collaboratory[33] emphasized the importance of also including patient-centered outcomes in the design of these trials. This recommendation is further buttressed by the present study (**Central Illustration**), which revealed an insidious decline in functional status parameters, affecting predominantly women in patients with initially mild or moderate AS.

STUDY LIMITATIONS. A causal relationship between faster AS progression rate and rapid decline in functional status could not be inferred. Notably, despite our effort to account for the effect of confounding factors, including underlying cardiovascular comorbidities and parameter of diastolic dysfunction, residual confounding effects may persist. Therefore, careful consideration is needed when interpreting these findings. However, compared to prior studies, we prospectively assessed patients' functional status on a yearly basis using well validated instruments. The DASI is not a cardiovascular disease (and so AS)-specific health status questionnaire and is limited by the lack of validated criteria to define the minimum decrease in DASI that can be considered clinically significant in terms of decline in functional status. Additionally, it is important to emphasize that the sex-specific analysis, aimed at determining the prognostic value of functional status decline, serves primarily as hypothesis-generating.

CONCLUSIONS

In this prospective observational study of patients with mild-to-moderate AS at baseline, women with intermediate-to-fast hemodynamic progression rate of AS had a greater decline in functional status compared to men. The decline in functional status during follow-up was associated with a higher rate of the composite of death or AVR in both women and men. These findings lend support for the use of patient-centered endpoint to monitor AS disease progression and enhance risk stratification. However, they also highlight the need for sex-specific symptoms assessment tools in patient care.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In patients with mild-to-moderate AS, for the same hemodynamic progression rate of AS, women have significantly faster decline of functional status.

TRANSLATIONAL OUTLOOK: In patients with initially mild-to-moderate AS and an intermediate-to-fast hemodynamic progression rate, active surveillance of rapid declines in functional status may help identify patients who may benefit from earlier elective intervention. Women require particular attention as the decline in functional status appears to be often underdetected and underestimated.

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KEY WORDS aortic valve stenosis, functional status, sex differences

APPENDIX For supplemental Methods, Results, tables, and figures, please see the online version of this paper.