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ORIGINAL RESEARCH

Excess Mortality and Undertreatment of Women With Severe Aortic Stenosis

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BACKGROUND: Although women represent half of the population burden of aortic stenosis (AS), little is known whether sex affects the presentation, management, and outcome of patients with AS.

METHODS AND RESULTS: In a cohort of 2429 patients with severe AS (49.5% women) we aimed to evaluate 5-year excess mortality and performance of aortic valve replacement (AVR) stratified by sex. At presentation, women were older (P<0.001), with less comorbidities (P=0.030) and more often symptomatic (P=0.007) than men. Women had smaller aortic valve area (P<0.001) than men but similar mean transaortic pressure gradient (P=0.18). The 5-year survival was lower compared with expected survival, especially for women (62±2% versus 71% for women and 69±1% versus 71% for men). Despite longer life expectancy in women than men, women had lower 5-year survival than men (66±2% [expected-75%] versus 68±2% [expected-70%], P<0.001) after matching for age. Overall, 5-year AVR incidence was 79±2% for men versus 70±2% for women (P<0.001) with male sex being independently associated with more frequent early AVR performance (odds ratio, 1.49; 1.18–1.97). After age matching, women remained more often symptomatic (P=0.004) but also displayed lower AVR use (64.4% versus 69.1%; P=0.018).

CONCLUSIONS: Women with severe AS are diagnosed at later ages and have more symptoms than men. Despite prevalent symptoms, AVR is less often performed in women and 5-year excess mortality is noted in women versus men, even after age matching. These imbalances should be addressed to ensure that both sexes receive equivalent care for severe AS.

Key Words: aortic stenosis ■ aortic valve replacement ■ gender differences ■ outcome ■ sex

Aortic stenosis (AS) is the most common valvular heart disease treated in developed countries,[1] and its prevalence is increasing with the aging of the population.[2] Although the population burden of AS is similar in men and women and current guidelines do not distinguish between the sexes in regard to AS symptoms, cardiac repercussions, or management,[3,4] there are increasingly recognized pathophysiological differences between men and women with AS. These involve the role of aortic valvular calcifications in relation to AS severity[5,6] and the left ventricular (LV) response to AS hemodynamic burden.[7,8] Conversely, the clinical differences between men and women with AS and their link to management and outcomes remain poorly defined.

Indeed, the mostly studied end point is clinical outcome after aortic valve replacement (AVR), surgical[9,10] or transcatheter,[11,12] reported alternatively as similar or different between the sexes although generally considered beneficial in both.[13] However, studies of the outcome after diagnosis have been more tenuous and contradictory. AS hemodynamic progression has been reported most generally similar in men and women[14,15] but some studies

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CLINICAL PERSPECTIVE

What Is New?

- Women with severe aortic stenosis are diagnosed at later ages than men; despite similar aortic stenosis severity, women have more symptoms and higher left atrial volumes and pulmonary pressures than men.
- Even after matching for age, women with severe aortic stenosis incur higher mortality than men despite their longer life expectancy in the general population.
- Men are more likely than women to undergo aortic valve replacement during follow-up, although the outcome of early aortic valve replacement is similar in men and women.

What Are the Clinical Implications?

- These imbalances in survival and management should be addressed to ensure that both sexes receive equivalent care for severe aortic stenosis.
- It is crucial to bring to the attention of the cardiology community the disparities in treatment and outcome of severe aortic stenosis between the sexes to ensure a prompt consideration to these deadly disparities.
- Future studies should be conducted prospectively to clarify the reasons for the operative or conservative management in order to provide specific corrective measures to the differences observed between men and women.

Nonstandard Abbreviations and Acronyms

AS	aortic stenosis
AVA	aortic valve area
AVR	aortic valve replacement
TAVR	transcatheter aortic valve replacement

are discordant and suggest a faster progression in women.[16] Conversely, very few data exist regarding clinical outcome after AS diagnosis. Studies in other valve diseases, although remaining quite limited, have suggested remarkable differences between the sexes. Among patients with mitral regurgitation, women tend to receive surgical treatment less frequently and later than men.[17,18] In patients with AS, potential differences in cardiac surgery indications are undefined, but US national data compile many more cases of AVR in men than women[10] discrepantly from the AS prevalence.[1] Furthermore, potential differences between the sexes in survival after diagnosis have not been clearly analyzed in the major AS outcome studies.[19–22] Prospective AS cohorts,[16,19,23] which enrolled mostly people with mild AS, were not geared toward routine clinical care and reported alternatively similar clinical progression[19,23] or excess complications[16] in women and therefore did not resolve the issue of sex-specific outcomes. Previous studies in aortic regurgitation emphasized the importance of accounting for differences between men and women[24,25] in managing the disease, but in AS, although recent reviews attempt to attract attention toward sex differences,[26,27] unavailability of sizable data specifically analyzing sex-specific outcome after severe AS clinical diagnosis prevents evaluating potential gaps in clinical care and remedies.

To address these gaps of knowledge, we gathered a large retrospective cohort of consecutive patients diagnosed in routine clinical practice with severe AS by echocardiography at 2 French tertiary care centers of northern France (Amiens and Lille). The aims of the study were 4-fold: (1) to evaluate 5-year mortality, by sex, in a large cohort of patients with severe AS managed in routine clinical practice relative to their specific life expectancy[28]; (2) to evaluate 5-year mortality, by sex after age matching; (3)to evaluate AVR timing and use according to sex before and after age matching; and (4) to evaluate 5-year mortality by sex after AVR.

METHODS

Inclusion and Exclusion Criteria

The data that support the findings of this study are available from the corresponding author on reasonable request. Between 2000 and 2017, consecutive patients of at least 18 years of age diagnosed with AS (aortic leaflet calcification with a reduction of systolic movements and peak aortic jet velocity [Vmax] >2.5 m/s) were identified and included in an electronic database. Patients presenting the following criteria were excluded: (1) aortic and/or mitral regurgitation of more than mild severity; (2) prosthetic valves, congenital heart disease (with the exception of bicuspid valve), supravalvular or subvalvular AS, or dynamic LV outflow tract obstruction; (3) mitral stenosis; and (4) refusal to participate in the study. This analysis was based on a study of 2429 patients with severe AS (aortic valve area [AVA] <1 cm^2 or indexed AVA <0.6 cm^2/m^2). The clinical and demographic baseline characteristics were retrospectively recorded and included cardiovascular risk factors, the presence of symptoms, comorbidity status, and the presence of coronary artery disease. The study was approved by an independent ethics committee and conducted in accordance with institutional policies, national legal requirements, and the revised principles of the Declaration of Helsinki.

Echocardiography

All patients underwent comprehensive Doppler-echocardiographic assessment with commercially available ultrasound systems. Aortic flow was systematically recorded by continuous-wave Doppler, from several views. The view identifying the highest velocities was used to determine Vmax. Three consecutive measurements in this view, for patients in sinus rhythm or 5 for patients in atrial fibrillation, were systematically averaged. LV outflow tract velocity was recorded using pulsed Doppler in the apical 5-chamber view with the sample volume situated 5 mm proximal to the plane of the aortic valve. The alignment of both pulsed- and continuous-wave Doppler was optimized to be parallel with flow. AVA was calculated with the continuity equation.

Follow-Up and End Points

Given the retrospective nature of the study, informed consent was waived, and all of the patients agreed to participate in the study when contacted each year for follow-up. Median follow-up was 42.0 (interquartile range 21–78) months. Patients were followed by clinical consultations and echocardiography at the outpatient clinics of the 2 tertiary care centers. A few patients were followed at public hospitals or private practices by referring cardiologists working in collaboration with the tertiary centers. Events were ascertained by direct patient interview and clinical examination and/or by repeated follow-up letters, questionnaires, and telephone calls to physicians, patients, and (if necessary) next of kin. Follow-up was complete until death or 2019 for 95% of patients. Clinical decisions regarding medical management and referral for AVR were made by the cardiology team including cardiologists and cardiac surgeons, with the approval of the patient's physician in accordance with current practice guidelines and the operative risk. The study primary end point was 5-year all-cause mortality and the study secondary end points were AVR performance and 5-year survival post AVR (early and late). Early AVR was defined as AVR performed within 3 months after inclusion. Perioperative mortality was defined as death occurring within 30 days of AVR or during the hospitalization if the patient was hospitalized for a longer period.

Statistical Analysis

SPSS version 18.0 software (IBM, Armonk, NY) was used for statistical analysis. The study population was split into 2 groups on the basis of sex. Continuous variables are expressed as mean values±1 SD or medians (interquartile range), and categorical variables are summarized as frequency percentages and counts. The relationships between baseline continuous variables and groups were explored by Student *t* test (for normally distributed variables) or Mann-Whitney *U* test (for nonnormally distributed variables). We used Pearson's χ^2 statistic or Fisher's exact test to assess the association between group and baseline categorical variables. Estimated survival rates±1 SE were estimated by Kaplan-Meier method and compared by 2-tailed log-rank tests. To assess the survival of men with severe AS relative to the expected survival of men of the same age in the general population, each man with severe AS was matched for the average survival (per year) of all men of the same age and same sex from our region (Somme, department of 555 551 inhabitants, northern France). To assess the survival of women with severe AS relative to the expected survival of women of the same age in the general population, each woman with severe AS was matched for the average survival (per year) of all women of the same age and same sex from our region. Control data were obtained from Somme life tables established on the basis of the 1999 population census, performed by the French Institute of National Statistics, and they represent the survival of the entire Somme general population.[29] Survival rates of patients with AS were compared with the expected survival of people of the same age and sex in the Somme department. Relative survival was computed as the ratio of estimated/expected survival (estimated number of survivors in the population with severe AS/expected number of survivors in the general population). Survival was also analyzed stratified by the presence of high or low-gradient severe AS.

Predictors of mortality in women were identified using Cox proportional hazards models. All significant variables in univariate analysis with $P<0.1$ were included in the multivariable Cox analysis. Given the large number of comparisons, alpha risk inflation was controlled according to the Hochberg method. Outcome comparison was also performed after age matching in order to have a group of men and a group of women comparable in terms of age. Matching with age was performed using the "Match" function from the package "Matching" of R software (R project for Statistical Computing, version 3.3.3). Each male patient was matched to a female patient with a caliper width of 0.1 year on age. We analyzed determinants of early AVR in the overall study population by classical multivariate logistic regression analysis after adjustment to age, symptoms, hypertension, Charlson comorbidity index (not including age), atrial fibrillation, coronary artery disease, AVA, mean pressure gradient, and LV ejection fraction (LVEF) and in the age-matched population by conditional multivariate logistic regression analysis after adjustment to the same variables (except age). We considered $P<0.05$ to be significant. All tests were 2-tailed.

RESULTS

Baseline Characteristics

The study population consisted of 2429 consecutive patients (1251 men [51.5%] and 1178 women [49.5%]). Women were older (P<0.001) with a smaller body surface area (P<0.001) and were more likely to be symptomatic (P=0.007) than men, and a higher proportion of women than of men were in New York Heart Association classes III and IV (P=0.005). Hypertension was more common in women (P=0.012) whereas men more frequently had diabetes mellitus (P=0.023) or a history of coronary artery disease or myocardial infarction (both P<0.001) and higher Charlson comorbidity index (P=0.030). Atrial fibrillation did not differ between men and women (P=0.19) (Table 1).

Women had a smaller AVA (P<0.001) and a smaller AVA indexed to height (P<0.001) than men. No difference was observed between men and women in terms of AVA indexed to body surface area (P=0.53), Vmax (P=0.14), or transaortic mean pressure gradient (P=0.18). Stroke volume (P=0.027) and LV end-diastolic (P<0.001) and end-systolic (P<0.001) diameters were greater in men whereas LVEF was lower (P<0.001) in men than in women. Concentric remodeling and concentric hypertrophy were more frequent in women than in men (P<0.001). Left atrial volumes (P=0.050) and pulmonary pressures (P=0.001) were greater in women than in men (Table 1).

Association of Sex With Survival

During follow-up, 860 deaths (35.4%) occurred. Estimated 5-year survival was 69±1% for men and 62±2% for women (P<0.001) (Figure S1). Ninety-four percent of transcatheter AVR (TAVR) were performed after 2012 in our study population. Estimated 5-year survival was 64±2% for men versus 60±2% for women; (P=0.030) in patients included before 2013 and 75±2% for men versus 65±3% for women; (P=0.001) for those included since 2013. Stratified by gradient, differences in 5-year survival between men and women persisted, 58±3% for low-gradient AS (mean pressure gradient<40 mm Hg) and 75±2% for high-gradient (men pressure gradient ≥40 mm Hg) AS in men versus 50±3% for low-gradient AS and 71±2% for high-gradient AS in women (P<0.001). The 5-year relative survival (estimated number of survivors/expected number of survivors in the general population) was 97% in men (estimated: 69±1%; expected: 71%) and only 87% in women (estimated: 62±2%, expected 71%) (Figure 1). Predictors of mortality in women with severe AS identified by Cox analyses are displayed in Table 2.

Baseline characteristics of the age-matched population are reported in Table 3. After the age-matching procedure, as expected, age was comparable between men and women (76.5±9.7 versus 76.4±9.8 years old; P=0.91). AS severity (indexed aortic valve area, peak aortic jet velocity, transaortic mean pressure gradient) was also comparable between the sexes. However, women still presented with lower Charlson comorbidity index (P=0.002), more symptoms (P=0.004), higher New York Heart Association stages (P=0.026), larger left atrial volumes (P=0.040), higher pulmonary pressures (P=0.014), and lower frequency of coronary artery disease (P<0.001). Estimated 5-year survival after age matching was 68±2% for men (expected: 70%, relative survival of 97%) and 66±2% for women (expected: 75%, relative survival of 88%) (P=0.039) (Figure 2).

Aortic Valve Replacement

Overall, 1557 patients (863 men and 694 women) underwent AVR (414 TAVR: 198 men [47.8%] and 216 women [52.2%]). Thirty-nine patients (2.5%) died in the perioperative period (20 men [2.5%] and 19 women [2.6%], P=0.55). The 5-year cumulative incidence of AVR was 79±2%, for men and 70±2% for women (P<0.001) (Figure 3). Stratified by gradient, lower AVR rate persisted in women, 59±3% for low-gradient AS and 90±1% for high-gradient AS in men versus 50±4% for low-gradient AS and 83±2% for high-gradient AS in women (P<0.001). The time between inclusion and AVR was longer for women than for men (16±25 months versus 14±23 months respectively, P=0.030) (Table 1), even after exclusion of patients with low-gradient AS (11±23 versus 8±18 months, P=0.041). In patients who underwent early AVR (n=1095), 5-year survival was similar for men and women (82±2% for men versus 85±2% for women; P=0.27), whereas women were older with smaller AVA (both P<0.001). Results were similar for patients who underwent late (>3 months within baseline echocardiography, n=462) AVR (85±2% for men versus 83±3% for women; P=0.46). On multivariate logistic regression analysis, being male was identified as an independent predictor of early AVR in the overall study population (adjusted odds ratio [OR], 1.49; 1.18–1.97; P=0.011), whereas low LVEF, lower mean pressure gradients, age, atrial fibrillation, higher Charlson score and the absence of symptoms were independently associated with lower performance of early AVR (all P<0.025). After age matching, despite more frequent symptoms, AVR (P=0.018) was still less performed in women than in men with a longer time between inclusion and AVR for women (P=0.005) (Table 3). On multivariate logistic regression analysis, being male remained an independent predictor of early AVR in this age-matched population (adjusted OR, 1.37; 1.11–1.69; P=0.003).

DISCUSSION

This study, based on a large cohort of patients with severe AS managed in routine clinical practice, demonstrates that there are considerable clinical and

Table 1. Baseline Characteristics of the Study Population

Variables	Male (n=1251)	Female (n=1178)	*P* Value	Hochberg Adjusted *P* Value
Demographics, baseline data, and symptoms				
Age, y	74±11	79±10	<0.001	<0.016
Body surface area, m^2	1.96±0.2	1.76±0.2	<0.001	<0.016
New York Heart Association class, n (%)			0.005	0.075
I–II	953 (76.2%)	842 (71.5%)		
III–IV	298 (23.8%)	336 (28.5%)		
Symptoms related to AS, n (%)	923 (73.8%)	930 (78.1%)	0.007	0.098
Medical history and risk factors				
Hypertension, n (%)	917 (73.3%)	911 (77.3%)	0.012	0.156
Diabetes mellitus, n (%)	421 (33.7%)	351 (29.8%)	0.023	0.270
Dyslipidemia, n (%)	660 (52.8%)	602 (51.1%)	0.219	0.438
Coronary artery disease, n (%)	689 (55.5%)	480 (40.7%)	<0.001	<0.016
Prior myocardial infarction, n (%)	110 (8.8%)	59 (5.0%)	<0.001	<0.016
Prior atrial fibrillation, n (%)	437 (34.9%)	391 (33.2%)	0.195	0.438
Charlson comorbidity index (without age)	2.25±1.83	2.09±1.79	0.030	0.270
Serum creatinine, µmol/L	93 (79–116)	81 (65–106)	<0.001	<0.0160
Echocardiography and Doppler parameters				
Aortic valve area, cm^2	0.81 (0.67–0.97)	0.72 (0.60–0.86)	<0.001	<0.016
Indexed to body surface area, cm^2/m^2	0.41 (0.34–0.49)	0.41 (0.33–0.49)	0.530	0.530
Indexed to size, cm^2/m	0.47 (0.39–0.56)	0.45 (0.37–0.54)	<0.001	<0.016
Doppler parameters				
Peak aortic jet velocity, m/s	4.20 (3.60–4.70)	4.10 (3.50–4.60)	0.142	0.438
Transaortic mean pressure gradient, mm Hg	44 (33–56)	43 (31–55)	0.181	0.438
Indexed stroke volume, mL/m^2	40 (33–46)	39 (32–46)	0.027	0.207
AS severity				
High-gradient severe AS	781 (62.4%)	701 (59.5%)	0.076	0.438
Low-gradient severe AS	470 (37.6%)	477 (40.5%)		
LV end-diastolic diameter, mm	52 (47–56)	47 (42–51)	<0.001	<0.016
Indexed to body surface area, mm/m^2	26 (24–29)	26 (23–29)	0.019	0.193
Indexed to size, mm/m	30 (27–33)	29 (26–32)	<0.001	<0.016
LV end-systolic diameter, mm	33 (29–38)	29 (25–34)	<0.001	<0.016
Indexed to body surface area, mm/m^2	17 (14–19)	17 (14–19)	0.138	0.412
Indexed to size, mm/m	19 (17–22)	18 (15–21)	<0.001	<0.016
LV end-diastolic volume, mL	135 (106–171)	101 (80–130)	<0.001	<0.016
Indexed to body surface area, mL/m^2	70 (54–85)	57 (46–72)	<0.001	<0.016
Indexed to size, mL/m	79 (62–99)	63 (50–81)	<0.001	<0.016
Ejection fraction, %	60 (54–65)	62 (56–68)	<0.001	<0.016
LV mass, g	265 (212–320)	214 (176–263)	<0.001	<0.016
Indexed to body surface area, g/m^2	135 (109–162)	123 (101–147)	<0.001	<0.016
Indexed to size, g/m	154 (124–186)	134 (111–164)	<0.001	<0.016
V remodeling			<0.001	<0.016
Normal, n (%)	220 (17.6%)	145 (12.3%)		
Concentric remodeling, n (%)	232 (18.5%)	260 (22.1%)		
Concentric hypertrophy, n (%)	510 (40.8%)	550 (46.7%)		
Eccentric hypertrophy, n (%)	289 (23.1%)	223 (18.9%)		
Indexed left atrial volume, mL/m^2	42 (33–54)	43 (34–57)	0.050	0.400
Pulmonary artery systolic pressure, mm Hg‡	33 (29–41)	35 (29–44)	0.001	0.061

(*Continued*)

Table 1. Continued

Variables	Male (n=1251)	Female (n=1178)	*P* Value	Hochberg Adjusted *P* Value
Management				
AVR, n (%	863 (69.0%)	484 (58.9%)	<0.001	<0.016
Early AVR, n (%)	601 (48%)	494 (41.9%)	0.001	0.016
Time to AVR, mo	14±23	16±25	0.030	0.270
Combined procedure, n (%)[§]	204 (23.2%)	150 (21.3%)	0.200	0.530

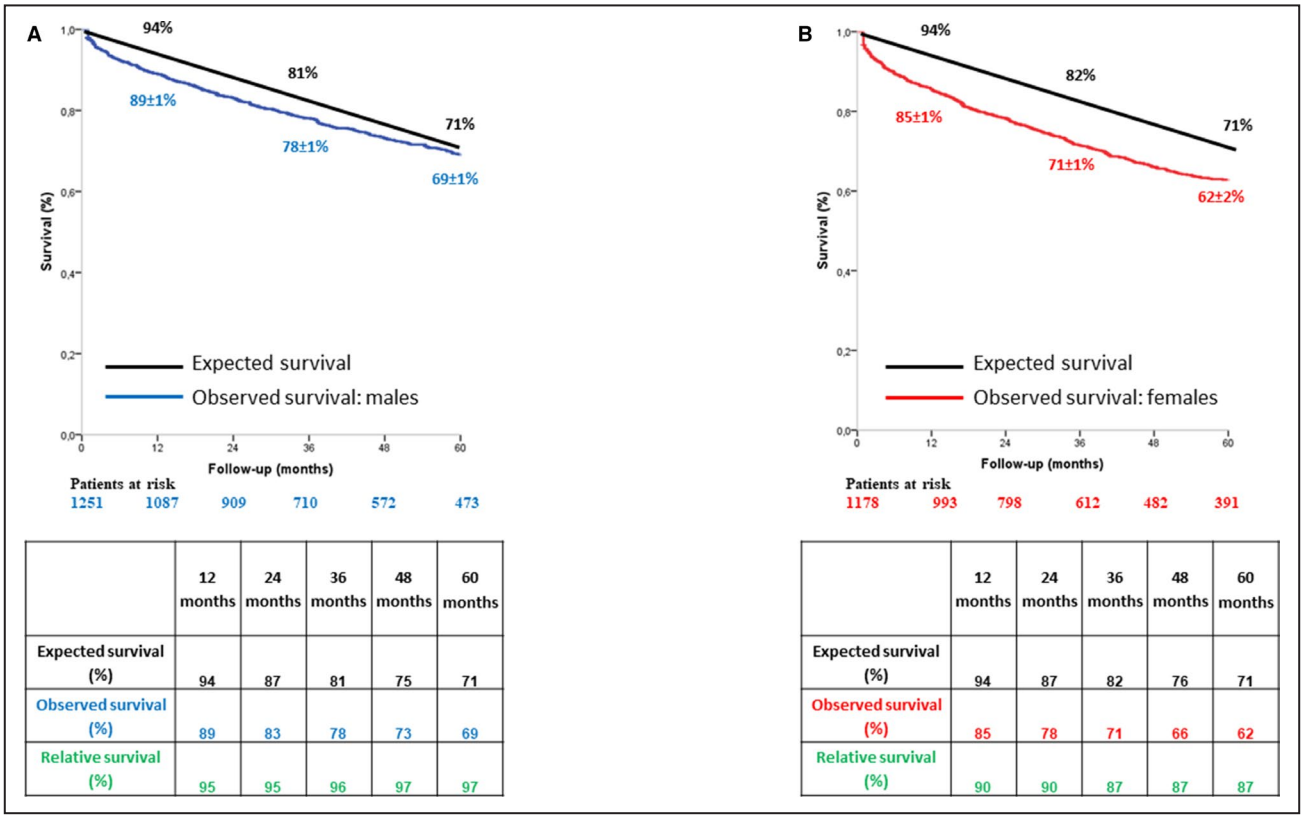
Continuous normally distributed variables are expressed as mean±1 SD, nonnormally distributed continuous variables are expressed as median (25th and 75th percentiles), and categorical variables as percentages and counts. AS indicates aortic stenosis; and LV, left ventricular.

[†]Available in 2287 patients.

[‡]Available in 2073 patients.

[§]Associated coronary bypass and/or ascending aorta replacement.

outcome differences between men and women with AS. Women are diagnosed at later ages, with less comorbidities, and have more symptoms than men, corroborated by larger left atrial volumes and higher pulmonary pressures than men despite similar gradients and AVAs normalized by body surface area and despite higher LVEF. After the diagnosis of severe AS, lower survival in women is confirmed by comparison with expected survival in the general population and by age matching. The other major finding observed in our cohort is that women are managed conservatively longer than men and are less frequently undergoing AVR despite their more frequent symptoms. Indeed, men are more likely to undergo early AVR and AVR at any time during follow-up than women. However, in women and men undergoing early AVR survival is not significantly different. These differences in management and outcome affecting women with severe AS should raise the attention of clinicians to eliminate potential biases and consider similarly, irrespective of sex, providing the powerful benefits of AVR for severe AS.



	12 months	24 months	36 months	48 months	60 months
Expected survival (%)	94	87	81	75	71
Observed survival (%)	89	83	78	73	69
Relative survival (%)	95	95	96	97	97

	12 months	24 months	36 months	48 months	60 months
Expected survival (%)	94	87	82	76	71
Observed survival (%)	85	78	71	66	62
Relative survival (%)	90	90	87	87	87

Figure 1. Five-year estimated survival of men (A) and women (B) with aortic stenosis compared with that of the age- and sex-matched general population.
Relative survival was computed as the ratio of the estimated/expected survival

Table 2. Factors Associated With Mortality in Women With Severe Aortic Stenosis

Variables	All-Cause Mortality			
	Univariate Cox Analysis		Multivariable Cox Analysis	
	HR (CI 95%)	*P* Value	HR (CI 95%)	*P* Value
Age (per y)	1.11 (1.09–1.12)	<0.001	1.05 (1.04–1.07)	<0.001
Body surface area (per 0.1 cm^2 decrease)	0.31 (0.19–0.51)	<0.001	0.55 (0.30–0.98)	0.044
Symptoms related to aortic stenosis (yes vs no)	1.86 (1.22–2.77)	<0.001	1.59 (1.27–1.99)	<0.001
Diabetes mellitus (yes vs no)	1.16 (0.95–1.42)	0.128		
Hypertension (yes vs no)	1.46 (1.15–1.87)	0.002	0.90 (0.68–1.19)	NS
Prior atrial fibrillation (yes vs no)	2.15 (1.78–2.59)	<0.001	1.47 (1.19–1.81)	<0.001
Coronary artery disease (yes vs no)	0.92 (0.76–1.11)	0.369		
Prior myocardial infarction (yes vs no)	2.10 (1.42–2.98)	<0.001	1.16 (0.79–1.72)	NS
Charlson comorbidity index (per unit)	1.20 (1.15–1.25)	<0.001	1.08 (1.03–1.14)	0.002
Aortic valve area (per 0.10 cm^2 decrease)	0.97 (0.95–0.98)	<0.001	0.99 (0.98–1.02)	NS
Mean pressure gradient (per mm Hg increase)	0.98 (0.97–0.99)	<0.001	0.99 (0.99–1.01)	NS
LV end diastolic diameter (per mm increase)	0.97 (0.95–0.99)	<0.001	1.01 (0.99–1.03)	NS
LV concentric hypertrophy (yes vs no)	1.41 (1.16–0.70)	<0.001	1.44 (1.17–1.77)	0.001
Left ventricular ejection fraction (per 10% decrease)	0.88 (0.81–0.96)	0.001	0.93 (0.85–0.99)	0.030
Indexed stroke volume (per mL/m^2 decrease)	0.97 (0.96–0.99)	<0.001	0.98 (0.97–0.99)	0.005
Aortic valve replacement (time-dependent variable)	0.14 (0.11–0.18)	<0.001	0.18 (0.14–0.24)	<0.001

HR indicates hazard ratio; LV, left ventricular; and NS, nonsignificant.

Impact of Sex on the Left Heart Response to AS

Some studies have suggested that the pathophysiology of AS at the valvular and ventricular levels may differ between men and women. First, for a similar severity of AS, women present a lower aortic valve calcification load, as measured by computed tomography or by aortic valve weight, than men.[5,6,16] Before AVR, men have more maladaptive LV hypertrophy with more fibrosis-associated genes than women and more fibrosis at surgery.[30] These findings concerning the pathophysiology of AS raise questions about its biological mechanism and the cellular and molecular effects of sex in AS appear to be a promising field of investigation.

The differences between men and women in AS also include LV response and adaptation to the increased afterload caused by AS. Indeed, for similar AS severity women have smaller end-systolic diameters,[7,8] lower indexed LV mass,[7,31] greater LVEF,[6–8,31] and a higher prevalence of diastolic dysfunction than men.[6] Thus, LV response and adaptation to AS appear to be heterogeneous and there may be sexual dimorphism in the myocardial response to AS. Accordingly, in our study, women had lower stroke volumes, indexed LV mass and end-systolic diameters and greater LVEF, left atrial volumes, and systolic pulmonary artery pressure than men with, however, smaller AVAs in women.

Impact of Differences of Management Between Sexes on Survival

Sex differences at presentation among patients with AS[23] showed higher frequency of hypertension in women, whereas coronary artery disease is more frequent in men.[23] Women presenting for transcatheter treatment of severe AS[11] have, similarly to our study, older age, with fewer comorbidities, more symptoms, smaller AVAs, more concentric hypertrophy known to be associated with increased mortality in women with AS,[32] and greater left atrial volumes and pulmonary pressures than men. However, disparities in the referral of men and women for surgery have been reported.[10,33] Among patients with AS, frequency of men and women is generally comparable,[34,35] but the frequency of surgical valve replacement differs by sex. Indeed, in a large contemporary US database containing information about patient discharges from about 1000 nonfederal hospitals in 45 states, 166 809 patients are reported to have undergone AVR between 2003 and 2014: 63% were male and only 37% were female.[10] The suggestion that TAVR may be particularly beneficial in women in clinical trials,[11] although never confirmed by a specific trial in women, may have led to their preferential referral to TAVR.[36] However, in our study, the cumulative incidence of AVR was lower for women than for men (70±2% versus 79±2%, respectively, at 5 years) and being male was an independent predictor of AVR, with the relative likelihood of surgery

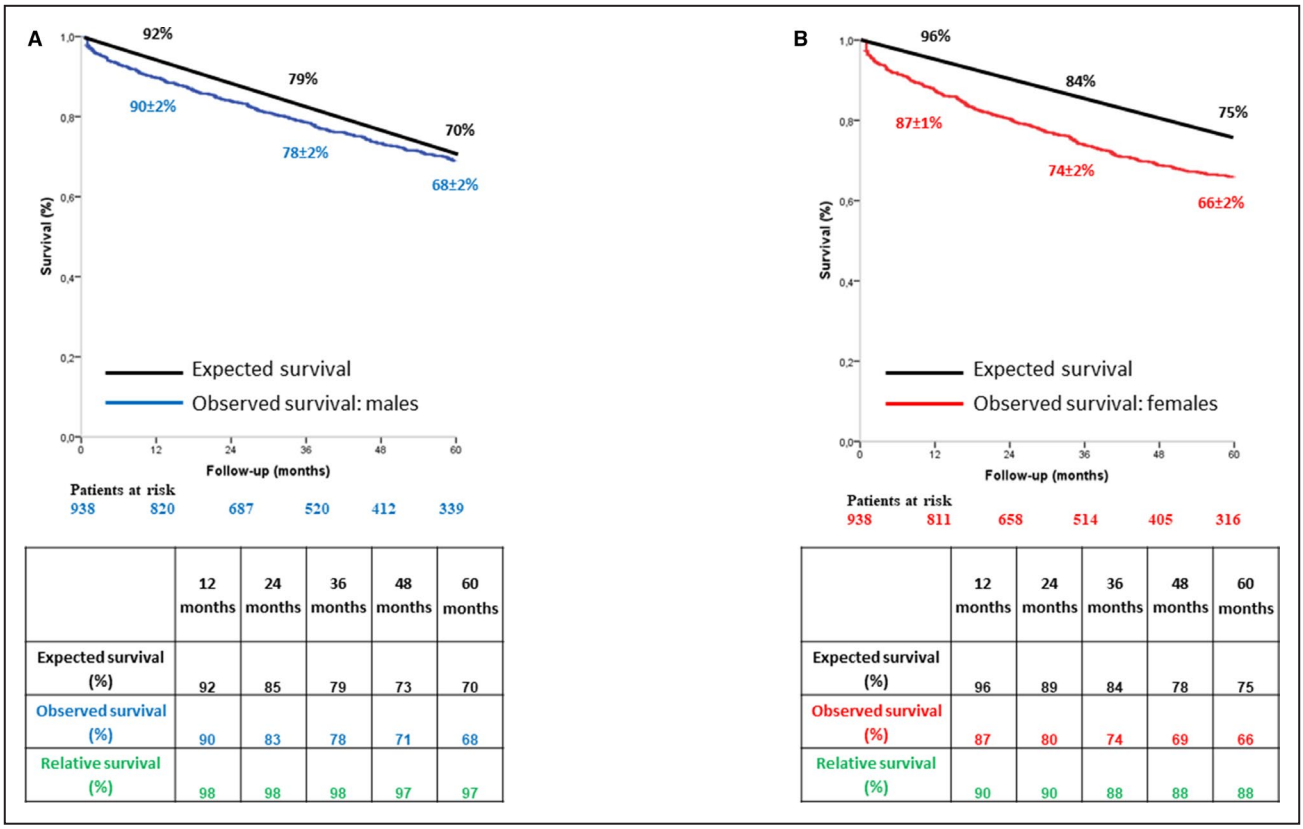
Table 3. Baseline Characteristics of Patients After Age Matching

Variables	Male (n=938)	Female (n=938)	*P* Value
Demographics, baseline data, and symptoms			
Age, y	76±10	76±10	0.91
Body surface area, m^2	1.96±0.2	1.79±0.2	<0.001
New York Heart Association class, n (%)			0.026
I–II	708 (75.5%)	670 (71.4%)	
III–IV	230 (24.5%)	268 (28.6%)	
Symptoms related to aortic stenosis, n (%)	697 (74.3%)	746 (79.5%)	0.004
Medical history and risk factors			
Hypertension, n (%)	688 (73.3%)	718 (76.5%)	0.061
Diabetes mellitus, n (%)	315 (33.6%)	287 (30.6%)	0.091
Coronary artery disease, n (%)	540 (57.6%)	397 (42.3%)	<0.001
Prior myocardial infarction n (%)	95 (10.1%)	38 (4.1%)	<0.001
Prior atrial fibrillation, n (%)	349 (37.2%)	308 (32.8%)	0.026
Charlson comorbidity index (without age)	2.31±1.80	2.05±1.80	0.002
Serum creatinine, µmol/L	94 (78–120)	82 (64–109)	<0.001
Echocardiography and Doppler parameters			
Aortic valve area, cm^2	0.81 (0.68–0.95)	0.72 (0.60–0.87)	<0.001
Indexed aortic valve area to size, cm^2/m	0.41 (0.35–0.44)	0.40 (0.33–0.49)	0.525
Doppler parameters			
Peak aortic jet velocity, m/s	4.20 (3.60–4.70)	4.20 (3.60–4.70)	0.645
Transaortic mean pressure gradient, mm Hg	44 (33–55)	45 (32–56)	0.656
Indexed stroke volume, mL/m^2	40 (33–46)	40 (33–46)	0.970
LV end-diastolic diameter, mm	51 (47–55)	48 (43–52)	<0.001
Indexed to body surface area, mm/m^2	26 (23–28)	27 (24–29)	<0.001
Indexed to size, mm/m	30 (27–33)	30 (27–32)	0.210
LV end-systolic diameter, mm	33 (28–38)	30 (25–35)	<0.001
Indexed to body surface area, mm/m^2	17 (14–19)	16 (14–19)	0.395
Indexed to size, mm/m	19 (17–22)	18 (15–21)	<0.001
Ejection fraction (%)	60 (54–65)	63 (57–68)	<0.001
Indexed LV mass, g/m^2	127 (103–154)	120 (106–140)	<0.001
Indexed left atrial volume, mL/m^2	42 (33–53)	44 (33–58)	0.040
Pulmonary artery systolic pressure, mm Hg	33 (28–41)	34 (29–44)	0.014
Management			
AVR, n (%)	648 (69.1%)	604 (64.4%)	0.018
Early AVR, n (%)	456 (48.6%)	403 (43.0%)	0.008
Time to AVR, mo	13±20	16±25	0.005

Continuous normally distributed variables are expressed as mean±1SD, nonnormally distributed continuous variables are expressed as median (25th and 75th percentiles), and categorical variables as percentages and counts. AVR indicates aortic valve replacement; and LV, left ventricular.

49% higher than for women. Furthermore, the time between inclusion and AVR was longer for women than for men.

However, to the best of our knowledge, the repercussions of the patient's sex for 5-year mortality have never been studied before in a population of patients with severe AS managed in routine clinical practice. Few studies focused on outcome after AVR reported conflicting results.[9,37,38] Although some[37] reported that being female was the only independent predictor of 30-day mortality in patients undergoing isolated surgical AVR, others[38] found that operative and postoperative long-term mortality was not higher in women than in men. Interest in the differences between male and female patients with AS has been revived by the introduction and widespread adoption of TAVR, which appears to be associated with better outcomes in women than in men. Large meta-analyses have shown survival after TAVR to be better for women than for men.[12,39] In the PARTNER trial, a randomized trial evaluating TAVR against surgical AVR, TAVR yielded survival benefits over surgical AVR for women but not for



	12 months	24 months	36 months	48 months	60 months
Expected survival (%)	92	85	79	73	70
Observed survival (%)	90	83	78	71	68
Relative survival (%)	98	98	98	97	97

	12 months	24 months	36 months	48 months	60 months
Expected survival (%)	96	89	84	78	75
Observed survival (%)	87	80	74	69	66
Relative survival (%)	90	90	88	88	88

Figure 2. Five-year estimated survival of men (A) and women (B) of the age-matched cohort compared with that of the age- and sex-matched general population.
Relative survival was computed as the ratio of the estimated/expected survival

men.[11] However, the outcome after the diagnosis of severe AS has not been reported yet.

In this first study of the impact of sex on outcome after the diagnosis of severe AS, we found that the risk of 5-year mortality after diagnosis of severe AS was greater in women than in men, with a worse relative survival compared with the general population than men. This excess mortality appears to be due in part to women being seen at a more advanced stage of the disease probably related to a combination of late diagnosis because they wait longer before visiting a doctor or because it takes longer for them to be diagnosed and experience a less frequent and later referral for AVR. Moreover, after age matching, when age was comparable as expected between women and men, AVR was still less frequently performed in women than in men, and mortality was still greater in women despite better life expectancy in women than in men.[28] Women with severe AS receive medical attention or at least are referred for severe AS at an older age, as suggested by small pilot studies.[33,34] In our referral centers, despite a similar diagnosis of severe AS, and more symptoms, women receive an indication for AVR less frequently and later than men. Hence, this potential link between the more conservative AS management in women and their excess mortality needs to be further investigated and proactive measures aimed at addressing these imbalances should be tested.

Limitations

Our study presents the major limitations inherent to retrospective analyses. Patients with classical low-flow low-gradient AS had a dobutamine stress echo to search for a flow (contractile) reserve and to exclude a pseudosevere AS. Confirmation of the severity of AS in patients with paradoxical low-flow, low-gradient AS was achieved by left heart catheterization in the early 2000s and more recently, by a calcium scoring using computed tomography, sometimes supplemented by dobutamine stress echo or cardiac catheterization in difficult cases. Even with this careful evaluation of AS severity, we cannot be excluded that some of these patients were suffering from pseudosevere AS. The higher frequency of low-gradient AS in women may have affected later AVR referral of women. Referral of patients to 2 tertiary care centers may have resulted in a selection bias but there is no large-scale systematic

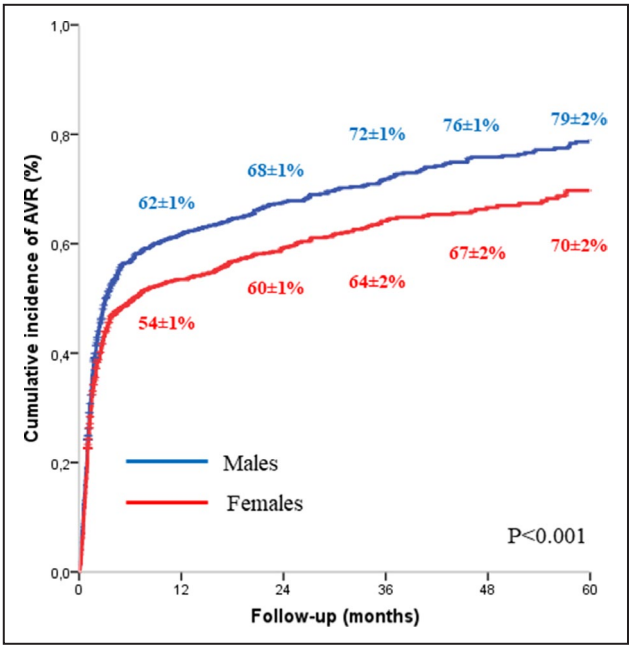


Figure 3. Cumulative incidence of surgery during follow-up, by sex.
AVR indicates aortic valve replacement.

diagnosis of AS in the general population. It would have been interesting to have characteristics of patients with undiagnosed AS or with AS diagnosed but not referred to our center. However, short of performing echocardiograms on the entire population, these patients remain unknown and by nature their characteristics are unknown. Future larger sampling of the general population for screening AS should be conducted in view of the magnitude of undiagnosed valve diseases in the few studies available.[2,40] The study is contemporary to the initial application of TAVR for severe AS in routine practice, which may have evolved but the proof that clinical practice in women may have changed remains elusive. Hence, it is essential to bring to the attention of the cardiology community the disparities in treatment and outcome of severe AS between the sexes to ensure a prompt attention to these deadly disparities. The specific indications for AVR or lack thereof were not recorded in our database. Therefore, future studies should be conducted prospectively to specify the reasons for the operative or conservative management to provide specific corrective actions to the differences observed between men and women in the present study.

CONCLUSIONS

In this large first study of sex differences in the management and outcome of severe AS, we observed that in routine clinical practice, women are diagnosed at a later age than men, and despite similar AS severity, have more symptoms and higher left atrial volumes and pulmonary pressures than men. Most important, even after age matching, women presenting with severe AS incur greater mortality than men despite their longer life expectancy. Furthermore, during follow-up, men are more likely than women to undergo AVR although the outcome of early AVR is similar in men and women. Hence, it is crucial to raise the awareness of the medical community regarding these sex-related differences in treating severe AS, to reach equivalent quality of care for each patient regardless of their sex.

ARTICLE INFORMATION

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Supplementary Material

Figure S1

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SUPPLEMENTAL MATERIAL

Figure S1. Kaplan-Meier survival curves in patients with aortic stenosis, by sex.