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CLINICAL RESEARCH
Interventional cardiology

Impact of sex on the management and outcome of aortic stenosis patients

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Objective The aim of this study was to assess the impact of sex on the management and outcome of patients according to aortic stenosis (AS) severity.

Introduction Sex differences in the management and outcome of AS are poorly understood.

Methods Doppler echocardiography data of patients with at least mild-to-moderate AS [aortic valve area (AVA) ≤1.5 cm^2 and peak jet velocity (V_{Peak}) ≥2.5 m/s or mean gradient (MG) ≥25 mmHg] were prospectively collected between 2005 and 2015 and retrospectively analysed. Patients with reduced left ventricular ejection fraction (<50%), or mitral or aortic regurgitation >mild were excluded.

Results Among 3632 patients, 42% were women. The mean indexed AVA (0.48 ± 0.17 cm^2/m^2), V_{Peak} (3.74 ± 0.88 m/s), and MG (35.1 ± 18.2 mmHg) did not differ between sexes (all $P \geq 0.18$). Women were older (72.9 ± 13.0 vs. 70.1 ± 11.8 years) and had more hypertension (75% vs. 70%; $P = 0.0005$) and less coronary artery disease (38% vs. 55%, $P < 0.0001$) compared to men. After inverse-propensity weighting (IPW), female sex was associated with higher mortality (IPW-HR: 1.91 [1.14–3.22]; $P = 0.01$) and less referral to valve intervention (competitive model IPW-HR: 0.88 [0.82–0.96]; $P = 0.007$) in the whole cohort. This excess mortality in women was blunted in concordant non-severe AS initially treated conservatively (IPW-HR = 1.03 [0.63–1.68]; $P = 0.88$) or in concordant severe AS initially treated by valve intervention (IPW-HR = 1.25 [0.71–2.21]; $P = 0.43$). Interestingly, the excess mortality in women was observed in discordant low-gradient AS patients (IPW-HR = 2.17 [1.19–3.95]; $P = 0.01$) where women were less referred to valve intervention (IPW-Sub-HR: 0.83 [0.73–0.95]; $P = 0.009$).

Conclusion In this large series of patients, despite similar baseline hemodynamic AS severity, women were less referred to AVR and had higher mortality. This seemed mostly to occur in the patient subset with discordant markers of AS severity (i.e. low-gradient AS) where women were less referred to AVR.

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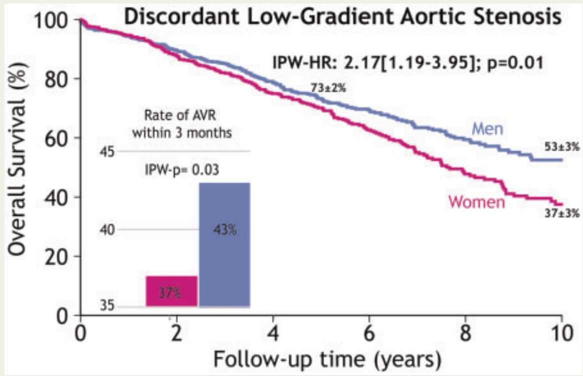
Graphical Abstract



Compared to men, women with low-gradient aortic stenosis have a worse survival, which could be partly explained by a lower rate of aortic valve replacement in women. IPW-HR, inverse-probability weighted hazard ratio.

Keywords Sex differences • Aortic stenosis • Aortic valve replacement • Aortic valve replacement • Survival • Low gradient

Introduction

Aortic stenosis (AS) is the third most frequent cardiovascular disease and the most common valvular heart disease in high-income countries.[1,2] Male sex is usually recognized as an important risk factor of AS and is associated with a higher risk of hemodynamic progression.[3,4] However, although congenital AS is more frequent in men (ratio 3:1), fibrocalcific degenerative AS seems to have a similar prevalence in both sexes after the age of 75 years.[1] Interestingly, men with AS exhibit more calcification within their aortic valve,[5,6] while women have more valvular fibrosis.[7] Nevertheless, the haemodynamic and overall fibrocalcific progression of the disease remains not significantly different between both sexes.[8,9]

The left ventricular (LV) remodelling and adaptative response to pressure overload related to AS seem guided by sex. LV remodelling tends to be more concentric in women, with increased myocardial fibrosis and a longer preservation of LV ejection fraction (LVEF).[10,11] This sex-specific LV remodelling pattern may lead to different clinical presentations and may influence the echocardiographic and global assessment of AS. This is especially the case in patients with concomitant low gradient and small valve area, which is a more frequent haemodynamic state in women.[12] All these specificities of AS related to sex may affect subsequent patient survival.[13,14] Indeed, published results regarding the impact of sex on survival after surgical aortic valve replacement (AVR) are conflicting, though they seem to lean towards worse survival in women.[15–19] On the other hand, following transcatheter AVR, women have better survival rates.[20–22] Globally, women may be referred later for AVR when compared to men, explaining an older age, more severe symptoms, and more severe AS at the time of AVR, despite fewer comorbidities.[19,20] However, the data are scarce in the literature to confirm this hypothesis, and the overall impact of sex on the course of AS remains poorly understood.

Thus, we aimed to assess in a large cohort of patients with at least mild-to-moderate AS the impact of sex on: (i) clinical presentation and echocardiographic hemodynamic pattern of AS; (ii) clinical management according to AS pattern; and (iii) overall patient survival.

Methods

Patient population

We included in the study all consecutive adult patients with at least mild-to-moderate AS (aortic valve area: AVA $\leq$1.5 cm^2 and peak aortic jet velocity: V_{Peak} $\geq$2.5 m/s or mean gradient: MG $\geq$25 mmHg) who underwent comprehensive transthoracic Doppler echocardiography imaging studies at rest at the Institut Universitaire de Cardiologie et de Pneumologie de Québec (IUCPQ) between 2005 and 2015. Patients with only available stress, dobutamine or transesophageal echocardiography, incomplete echocardiographic study, depressed LVEF (<50%), previous valvular intervention, or concomitant significant mitral or aortic regurgitation (> mild) were excluded. All clinical and echocardiographic data were prospectively collected in an institutional database and retrospectively analysed. The date of the first transthoracic echocardiographic examination was defined as the baseline visit. The study was approved by the ethics committee of the IUCPQ who waived the necessity of a written consent according to the nature of the study.

Clinical data

Baseline clinical data included age, sex, body surface area (BSA), body mass index (BMI), diagnosis of hypertension [patients on antihypertensive medications or having known but untreated hypertension (blood pressure $\geq$140/90 mmHg)], diabetes (patients on oral hypoglycaemic or

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insulin medications or, in the absence of such medications, having a fasting glucose ≥7 mmol/L), hyperlipidaemia (patients on lipid-lowering medication or, in the absence of such medication, documented plasma LDL cholesterol ≥3.5 mmol/L), coronary artery disease [history of myocardial infarction, significant coronary artery stenosis (i.e. >50%) on coronary angiography, and/or regional wall motion abnormality on echocardiogram], chronic kidney disease (estimated glomerular filtration rate <60 mL/min/1.73 m^2), and chronic obstructive pulmonary disease. The presence of symptoms related to AS at baseline was defined by the presence of dyspnoea of NYHA class ≥II, angina, pre-syncope or syncope, deemed to be related to AS.

Echocardiographic data

LV geometry parameters included LV end-diastolic diameter, interventricular septal thickness (IVST), and LV posterior wall thickness (PWT). LV mass was calculated with the corrected formula from the American Society of Echocardiography,[23] and indexed to BSA. The relative wall thickness ratio was calculated by dividing the sum of PWT and IVST by LV end-diastolic diameter.[23] LVEF was calculated by the biplane Simpson method. LV stroke volume was calculated using the LV outflow tract diameter (measured at the insertion of the aortic valve leaflets) and the LV outflow tract velocity time integral and then indexed to BSA. AS severity assessment included the evaluation of V_{Peak}, MG calculated with the simplified Bernoulli equation, and AVA calculated with the continuity equation and indexed to BSA (AVAi).[24]

Patients were divided into four hemodynamic patterns according to AVAi and MG as follows:

- Non-severe AS: MG <40 mmHg and AVAi >0.6 cm^2/m^2 (>0.55 cm^2/m^2 for patients with BMI ≥30 kg/m^2).
- Severe AS: MG ≥40 mmHg and AVAi ≤0.6 cm^2/m^2 (≤0.55 cm^2/m^2 for patients with BMI ≥30 kg/m^2).
- Discordant high-gradient AS: MG ≥40 mmHg and AVAi >0.6 cm^2/m^2 (>0.55 cm^2/m^2 for patients with BMI ≥30 kg/m^2).
- Discordant low-gradient AS: MG <40 mmHg and AVAi ≤0.6 cm^2/m^2 (≤0.55 cm^2/m^2 for patients with BMI ≥30 kg/m^2).

Study endpoints

The primary endpoint was all-cause mortality during follow-up. Outcome information related to mortality was confirmed for all patients by a provincial governmental statistical institution (Institut de la Statistique du Québec); thus, follow-up was 100% complete. To maximize the interrogation of this central database, a list with multiple demographics (including first and last names, dates of birth, and social security numbers) and a delay of 1 year between interrogation and closing follow-up dates were used.

The secondary endpoint was the occurrence of AVR, either surgical or transcatheter, with or without concomitant interventions. This information was retrospectively retrieved from the patients' charts. Initial treatment strategy was defined according to the choice of management in the first 3 months of follow-up as initial intervention (≤3 months) and initial conservative management (no intervention or intervention ≥3 months).

Statistical analysis

Continuous data were tested for the normality of distribution and homogeneity of variance with the Shapiro–Wilk and Levene tests, respectively. They are presented as mean ± standard deviation and were compared between men and women using Student's *t*-test. Categorical data are expressed as a percentage and compared using Chi-square or Fisher's exact tests, as appropriate. To adjust for covariates between men and women, a propensity score inverse-probability weighting (IPW) estimation was computed for each patient. All baseline characteristics (*Table 1*) were used to calculate the propensity score IPW for each patient. Survival rates were calculated using the Kaplan–Meier analysis and weighted univariate Cox proportional hazard regression (presented as hazard ratio: IPW-HR [95% confidence interval], *P*-value). The proportional hazard assumption was verified in all Cox analyses based on inspection of the Schoenfeld residual temporal trends (all $P > 0.46$). The interaction between sex and AVR was assessed by interaction term. The occurrence of AVR during follow-up was assessed in the whole cohort and in low-gradient AS patients using competing-risks regression based on Fine and Gray's proportional sub-hazards model (presented as sub-hazard ratio: IPW-SHR [95% confidence interval], *P*-value). Statistical analyses were performed with JMP version 14.0 and Stata version 14.0 software. A *P*-value of <0.05 was considered to be statistically significant.

Results

Baseline characteristics

A total of 3632 patients were included, 1518 (42%) women and 2114 (58%) men. Women were older and smaller than men (mean age: 72.9 ± 13.0 vs. 70.1 ± 11.8 years; BSA: 1.70 ± 0.19 vs. 1.95 ± 0.18 m^2, both $P < 0.0001$) and had a higher prevalence of hypertension (75% vs. 70%; $P = 0.0005$) but less coronary artery disease (38% vs. 55%, $P < 0.0001$). Prevalence of chronic pulmonary disease, diabetes, and chronic renal failure at baseline was not significantly different between sexes (*Table 1*). More women presented symptoms than men (76% vs. 72%; $P = 0.008$) (*Table 1*).

In the whole cohort, mean AVAi, V_{Peak}, and MG were 0.48 ± 0.17 cm^2/m^2, 3.74 ± 0.88 m/s, and 35.1 ± 18.2 mmHg, respectively, without sex-specific differences (all $P > 0.18$) (*Table 1*). The proportion of different hemodynamic AS severity patterns in the whole cohort was 24% for concordant non-severe AS, 36% for concordant severe AS, 1% for discordant high-gradient AS, and 39% for discordant low-gradient AS, without significant differences between women and men ($P = 0.99$). Compared to men, women had smaller LV dimensions, with more concentric remodelling and a slightly more elevated LVEF, resulting in similar stroke volume index (38.78 ± 10.34 vs. 39.03 ± 9.32 mL/m^2, $P = 0.46$).

Impact of sex on clinical outcomes in the entire cohort

During a mean follow-up of 4.05 ± 3.17 years, there were 1055 (29%) deaths and 2547 (70%) AVR (2239 surgical and 308 transcatheter). After IPW, women had a higher risk of death compared to men (IPW-HR: 1.91 [1.14-3.22]; $P = 0.01$; *Figure 1A*). Compared to men, women had 12% less chance of undergoing AVR (surgical or transcatheter) (IPW-SHR: 0.88 [0.82–0.96]; $P = 0.007$) (*Figure 1B*). There was no interaction between sex and AVR with regard to survival ($P = 0.16$).

Comparison of treatment strategies between sexes according to AS severity patterns and initial treatment strategy

In non-severe AS patients (*Table 2*), 414 patients were initially treated conservatively. Among them, during a mean follow-up of 4.33 ± 2.53 years, there were 149 deaths. After IPW, women and

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Table 1 Characteristics of the whole study cohort

	Whole cohort (*n* = 3632)	Women, *n* = 1518 (41.8%)	Men, *n* = 2114 (58.2%)	*P*-value
Clinical data				
Age, years	71.27 ± 12.39	72.93 ± 13.02	70.08 ± 11.77	<0.0001
Body surface area, m^2	1.84 ± 0.22	1.70 ± 0.19	1.95 ± 0.18	<0.0001
Body mass index, kg/m^2	27.95 ± 5.49	27.85 ± 6.17	28.02 ± 4.95	0.36
Hypertension, %	72.44	75.49	70.25	0.0005
Atrial fibrillation/flutter, %	15.72	17.25	14.63	0.05
Diabetes, %	29.60	28.26	30.56	0.13
Hyperlipidaemia, %	65.23	59.62	69.25	<0.0001
Coronary artery disease, %	47.72	37.88	54.78	< 0.0001
Chronic pulmonary disease, %	15.34	14.62	15.85	0.31
Renal disease, %	16.41	17.13	15.89	0.32
Symptoms, %	73.84	76.22	72.15	0.008
Echocardiographic data				
LVOT diameter, cm	2.15 ± 0.23	2.02 ± 0.20	2.25 ± 0.20	<0.0001
LVED diameter, cm	4.50 ± 0.56	4.26 ± 0.50	4.68 ± 0.54	<0.0001
LV mass index, g/m^2	135.13 ± 39.13	126.92 ± 36.98	141.09 ± 39.58	<0.0001
Relative wall thickness ratio	0.51 ± 0.12	0.52 ± 0.13	0.50 ± 0.11	0.0009
Peak aortic jet velocity, m/s	3.74 ± 0.88	3.75 ± 0.90	3.74 ± 0.86	0.89
Mean aortic gradient, mmHg	35.09 ± 18.17	35.10 ± 18.71	35.07 ± 17.78	0.95
Indexed aortic valve area, cm^2/m^2	0.48 ± 0.17	0.48 ± 0.18	0.48 ± 0.16	0.26
Indexed stroke volume, mL/m^2	38.93 ± 9.76	38.78 ± 10.34	39.03 ± 9.32	0.46
LV ejection fraction, %	61.57 ± 6.34	62.17 ± 6.16	61.13 ± 6.36	<0.0001
AS severity groups				0.99
Concordant non-severe AS, %	24	24	24	
Concordant severe AS, %	36	35	36	
Discordant high-gradient AS, %	1	1	1	
Discordant low-gradient AS, %	39	40	39	

AS, aortic stenosis; LV, left ventricular; LVED, left ventricular end-diastolic; LVOT, left ventricular outflow tract.

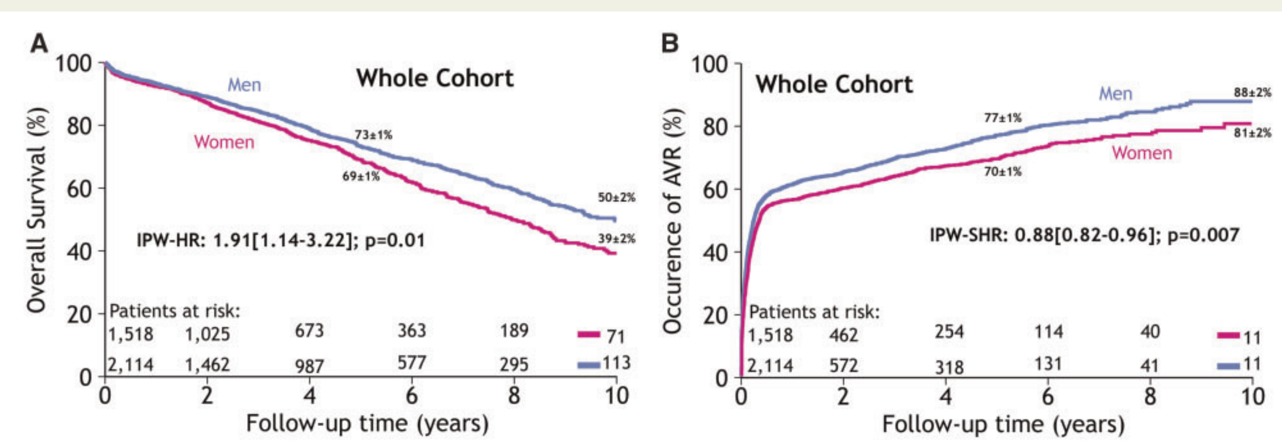

Figure 1 Management strategy for aortic stenosis in women and men and its impact on mortality. (*A*) Kaplan–Meier survival curves showing that women have lower survival than men. (*B*) Kaplan–Meier time-to-event curves showing that women are less treated with aortic valve replacement than men. IPW-HR, inverse-probability weighted hazard ratio; IPW-SHR, inverse-probability weighted sub-hazard ratio (competitive model analysis).

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Table 2 Characteristics of patients with concordant non-severe aortic stenosis and initial conservative management and patients with concordant severe aortic stenosis and initial valve intervention

	Patients with concordant non-severe AS and initial conservative management (n = 414)			Patients with concordant severe AS and initial intervention (n = 1107)		
	Women, n = 183 (44%)	Men, n = 231 (56%)	P-value	Women, n = 453 (41%)	Men, n = 654 (59%)	P-value
Clinical data						
Age, years	71.81 ± 16.23	70.23 ± 14.2	0.29	72.86 ± 11.56	69.4 ± 11.1	<0.0001
Body surface area, m^2	1.67 ± 0.14	1.94 ± 0.17	<0.0001	1.68 ± 0.16	1.94 ± 0.15	<0.0001
Body mass index, kg/m^2	26.79 ± 5.16	27.86 ± 4.5	0.02	27.62 ± 5.58	27.65 ± 4.21	0.93
Hypertension, %	69.95	71.43	0.74	78.59	67.28	<0.0001
Atrial fibrillation/flutter, %	16.39	46.88	0.89	14.13	10.86	0.10
Diabetes, %	25.14	32.03	0.12	30.91	28.59	0.41
Hyperlipidemia, %	53.01	67.97	0.002	58.06	68.96	0.0002
Coronary artery disease, %	37.16	50.22	0.008	35.32	50.00	< 0.0001
Chronic pulmonary disease, %	19.13	19.05	0.98	10.82	14.53	0.07
Renal disease, %	16.94	17.32	0.92	15.89	14.37	0.49
Symptoms, %	46.99	44.59	0.63	91.88	86.63	0.007
Echocardiographic data						
LVOT diameter, cm	2.03 ± 0.21	2.30 ± 0.26	<0.0001	2.02 ± 0.18	2.25 ± 0.17	<0.0001
LVED diameter, cm	4.29 ± 0.51	4.73 ± 0.51	<0.0001	4.21 ± 0.46	4.64 ± 0.51	<0.0001
LV mass index, g/m^2	121.75 ± 32.61	130.71 ± 33.1	0.01	133.17 ± 36.7	152.61 ± 42.99	<0.0001
Relative wall thickness ratio	0.49 ± 0.16	0.46 ± 0.1	0.03	0.54 ± 0.13	0.54 ± 0.12	0.57
Peak aortic jet velocity, m/s	2.77 ± 0.29	2.85 ± 0.31	0.01	4.73 ± 0.52	4.66 ± 0.53	0.04
Mean gradient, mmHg	16.5 ± 3.93	17.71 ± 4.76	0.01	55.96 ± 13.17	54.65 ± 13.19	0.10
Indexed aortic valve area, cm^2/m^2	0.73 ± 0.18	0.71 ± 0.16	0.30	0.34 ± 0.08	0.36 ± 0.08	<0.0001
Indexed stroke volume, mL/m^2	42.90 ± 10.21	43.39 ± 11.21	0.65	38.67 ± 8.77	39.34 ± 8.01	0.19
LV ejection fraction, %	61.34 ± 6.16	61.47 ± 5.89	0.83	62.9 ± 6.03	61.79 ± 6.14	0.003

LV, left ventricular; LVED, left ventricular end-diastolic; LVOT, left ventricular outflow tract.

men had a similar risk of mortality (IPW-HR: 1.03 [0.63–1.68]; P = 0.88) (*Figure 2A*).

In severe AS patients (*Table 3*), most of the patients (94%) underwent AVR within 3 months without differences between women and men (93% vs. 95%; P = 0.16). During a mean follow-up post-AVR of 3.5 ± 3.0 years, there were 234 deaths. The risk of death post-AVR did not differ between sexes (IPW-HR: 1.25 [0.71–2.21]; P = 0.43) (*Figure 2B*).

In patients with discordant low-gradient AS, women showed a higher risk of death (IPW-HR: 2.17 [1.19-3.95]; P = 0.01) (*Figure 3A* and *Graphical Abstract*). Among the 786 patients who underwent initial medical management, women seemed to be at higher risk of mortality than men (IPW-HR: 1.88 [1.00–3.57]; P = 0.05), but not among the 533 patients who underwent initial intervention (IPW-HR: 1.74 [0.68–4.46]; P = 0.24). In discordant low-gradient AS, a major difference between sexes was the lower rate of AVR in women than in men at 3 months (37% vs. 43%; P = 0.03) (*Graphical Abstract*) and during the entire follow-up (IPW-SHR: 0.83 [0.73–0.95]; P = 0.009) (*Figure 3B*).

Discussion

In this large cohort of AS patients, despite similar baseline AS severity patterns, management and clinical outcome were significantly different in women compared to men: (i) in patients with concordant non-severe AS initially treated conservatively (as recommended by guidelines), women and men had a similar risk of mortality; (ii) in severe AS patients, aortic valve intervention rates were similar in men and women and survival after intervention was similar between sexes; and (iii) in patients with discordant low-gradient AS, women were less referred to intervention and experienced higher mortality.

Women, who represented 42% of the study cohort, had the same degree of AS severity as men and were only 2.8 years older than men. This finding suggests that the dogma of a one-decade delay in the development of AS in women compared to men may not be true.[17]

In patients with concordant non-severe AS, current guidelines recommend a conservative follow-up, except if another cardiac surgery is performed. Thus, in our population, to only account for AS, we

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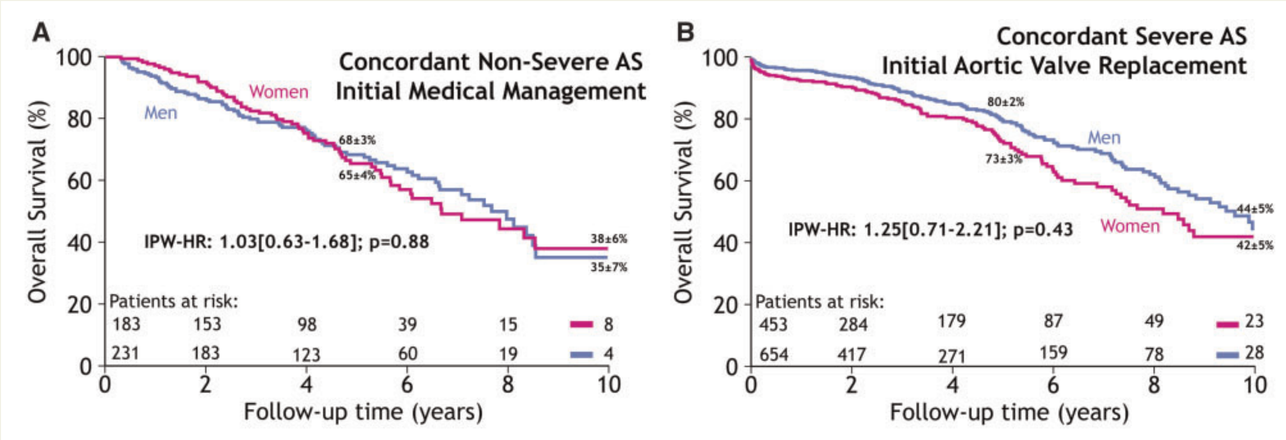

Figure 2 Kaplan–Meier survival curves of concordant aortic stenosis patients according to AS severity and treatment strategy. Kaplan–Meier curves showing no survival difference between women and men with concordant non-severe aortic stenosis receiving initial medical management (*A*) or with concordant severe aortic stenosis after initial aortic valve replacement (*B*). IPW-HR, inverse-probability weighted hazard ratio.

analysed only concordant non-severe AS patients undergoing initial conservative management. Interestingly, survival did not differ between men and women when AVR was not required. In a recent study, including a large number of patients without AVR, male sex was associated with long-term mortality,[25] which may be indeed explained by the longer life expectancy in women than in men.

Sex-specific reports of outcome after surgical AVR provided conflicting results. Female sex is often associated with higher 30-day and long-term mortality.[19,26] Several intrinsic features in women have been linked to more adverse events after surgical AVR, including smaller aortic annuli leading more frequently to prosthesis–patient mismatch, more concentric LV remodelling, and more myocardial fibrosis.[11] However, women present with a worse preoperative risk profile.[17,27,28] In our study, after carefully balancing baseline characteristics, survival after AVR was comparable between men and women. This could be explained by the grouping of surgical and transcatheter AVR, as the intrinsic clinical characteristics, especially small aortic annuli, appear to have less impact on outcome following transcatheter AVR.[29–31] However, other studies found that women and men had equivalent survival after surgical AVR, after adjusting for worse risk profile.[17,32]

Nevertheless, either if AVR is performed via transcatheter approach or surgically, women need to be referred for intervention at the most optimal time to better prevent adverse clinical outcomes. Many studies reported lower rates of referral to AVR in women compared to men.[19,33,34] As demonstrated in our study, when AS severity is concordant at echocardiography (i.e. concordant grading between AVA and MG or V_{Peak}), patient referral for AVR and survival are equivalent in women and men. However, when echocardiographic parameters of AS severity are discordant (discordance between small AVAi and low MG/V_{Peak}), women are less referred for intervention, despite having equivalent AVAi, MG and V_{Peak}, and similar or higher occurrence of symptoms compared to men. Unreported variables may be related to this lower referral rate in women, such as frailty and patient's refusal. However, unreported variables should have the same impact in severe AS and discordant AS, as age, BSA, BMI, etc., are similar. Thus, AS severity may be underestimated in women, especially since male sex has been described as a major risk factor for AS.[4] Indeed, in young (<50 years) AS patients, male sex is certainly an important risk factor as AS has been reported to be more frequently associated with bicuspid aortic valve in males with a ratio of three men for one women.[35,36] However, if male patients show an increased incidence of AS after 65 years of age (280 in men vs. 220/100 000 person-years in women), the crude number of AS patients is equivalent between sexes.[1]

Limitations

Our study was a retrospective analysis of prospectively collected data; thus, we cannot exclude the possibility of residual confounding, such as frailty. However, our design, routine clinical practice, and interrogation of the central provincial database limited enrolment and follow-up bias. The use of the AVAi to define AS severity patterns was mandatory to compare men and women due to significant BSA differences. To limit the overestimation of AS severity in obese patients, an AVAi of <0.55 cm^2/m^2 was considered for severe AS in obese patients.

Conclusion

In this large series of patients with mild-to-moderate and severe AS, women had a worse survival rate than men, especially when echocardiographic parameters of AS severity were discordant (i.e. low-gradient AS). Women with discordant low-gradient AS appeared to be

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Table 3 Characteristics of patients with discordant low-gradient aortic stenosis according to initial management

	Patients with discordant low-gradient AS ($n = 1319$)			Initial conservative management ($n = 786$)			Initial aortic valve intervention ($n = 533$)		
	Women, $n = 553$ (42%)	Men, $n = 766$ (58%)	*P*-value	Women, $n = 346$ (44%)	Men, $n = 440$ (56%)	*P*-value	Women, $n = 207$ (39%)	Men, $n = 326$ (61%)	*P*-value
Clinical data									
Age, years	73.86 ± 13.09	71.32 ± 11.32	<0.0001	73.85 ± 14.55	71.62 ± 12.35	0.02	73.76 ± 10.29	70.83 ± 9.82	0.001
Body surface area, m^2	1.68 ± 0.16	1.94 ± 0.16	<0.0001	1.67 ± 0.16	1.94 ± 0.17	<0.0001	1.70 ± 0.16	1.93 ± 0.16	<0.0001
Body mass index, kg/m^2	27.39 ± 5.34	27.67 ± 4.55	0.3	26.64 ± 5.20	27.41 ± 4.69	0.03	28.65 ± 5.33	28.02 ± 4.34	0.13
Hypertension, %	75.77	70.50	0.03	73.70	67.05	0.04	79.23	15.15	0.28
Atrial fibrillation/flutter, %	19.35	18.28	0.62	20.23	21.14	0.76	17.87	14.42	0.29
Diabetes, %	28.03	31.07	0.23	26.01	30.68	0.15	31.40	31.60	0.96
Hyperlipidemia, %	64.92	68.67	0.15	57.80	62.95	0.14	76.81	76.38	0.91
Coronary artery disease, %	38.16	58.75	< 0.0001	31.79	54.32	< 0.0001	48.79	64.72	0.0003
Chronic pulmonary disease, %	14.29	16.19	0.34	14.16	17.73	0.18	14.49	14.11	0.90
Renal disease, %	17.90	17.36	0.80	16.18	19.55	0.22	20.77	14.42	0.06
Symptoms, %	73.14	70.48	0.31	58.47	52.90	0.14	96.67	92.93	0.09
Echocardiographic data									
LVOT diameter, cm	1.98 ± 0.14	2.20 ± 0.17	<0.0001	1.97 ± 0.14	2.19 ± 0.17	<0.0001	2.00 ± 0.14	2.22 ± 0.17	<0.0001
LVED diameter, cm	4.23 ± 0.46	4.63 ± 0.52	<0.0001	4.23 ± 0.46	4.66 ± 0.53	<0.0001	4.22 ± 0.47	4.59 ± 0.5	<0.0001
LV mass index, g/m^2	121.7 ± 35.48	133.12 ± 35.29	<0.0001	120.75 ± 34.31	133.42 ± 37.01	<0.0001	123.08 ± 37.3	132.65 ± 32.97	0.002
Relative wall thickness ratio	0.51 ± 0.13	0.49 ± 0.11	0.03	0.50 ± 0.12	0.48 ± 0.11	0.02	0.51 ± 0.13	0.5 ± 0.11	0.31
Peak aortic jet velocity, m/s	3.36 ± 0.51	3.37 ± 0.48	0.81	3.25 ± 0.52	3.20 ± 0.45	0.21	3.57 ± 0.42	3.61 ± 0.41	0.35
Mean gradient, mmHg	26.30 ± 8.12	26.70 ± 7.72	0.37	23.81 ± 7.85	23.72 ± 7.19	0.87	30.45 ± 6.74	30.72 ± 6.49	0.65
Indexed aortic valve area, cm^2/m^2	0.45 ± 0.08	0.46 ± 0.08	<0.0001	0.47 ± 0.08	0.48 ± 0.08	0.01	0.42 ± 0.08	0.44 ± 0.08	0.002
Indexed stroke volume, mL/m^2	34.65 ± 6.76	35.42 ± 6.7	0.04	34.76 ± 7.02	35 ± 6.59	0.63	34.45 ± 6.3	36 ± 6.8	0.01
LV ejection fraction, %	61.90 ± 6.39	60.62 ± 6.40	<0.0001	62 ± 6.18	60.66 ± 6.60	<0.0001	61.76 ± 6.73	60.55 ± 6.14	0.03

AS, aortic stenosis; LV, left ventricular; LVED, left ventricular end-diastolic; LVOT, left ventricular outflow tract.

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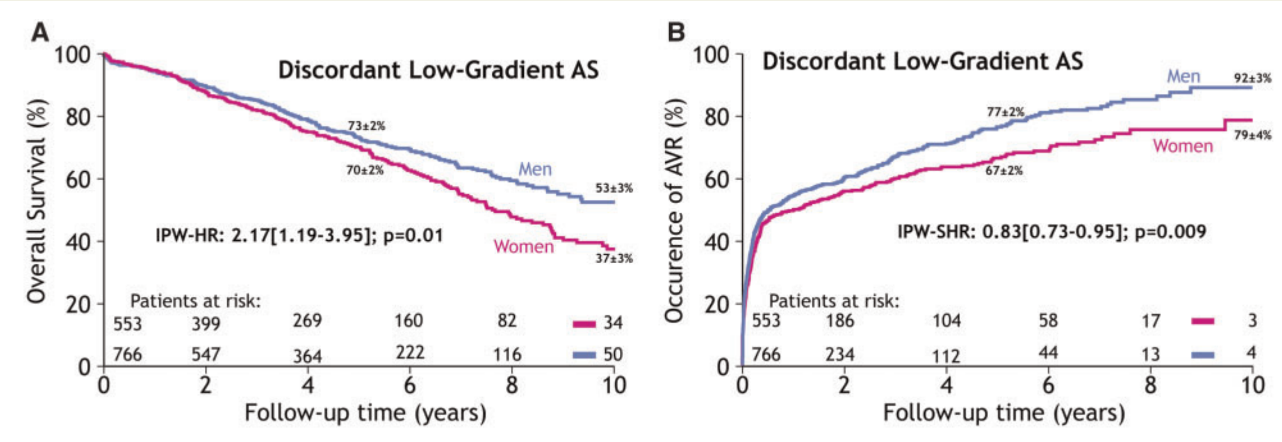

Figure 3 Kaplan–Meier survival curves of discordant low-gradient aortic stenosis patients. (*A*) Kaplan–Meier survival curves showing that women have lower survival than men. (*B*) Kaplan–Meier time-to-event curves showing that women are less treated with aortic valve replacement than men. IPW-HR, inverse-probability weighted hazard ratio; IPW-SHR, inverse-probability weighted sub hazard ratio (competitive model analysis).

less referred for AVR, resulting in increased mortality in women during follow-up.

Clinical perspectives

Although discordant low-gradient AS has the same prevalence in men and women, women are less often considered for AVR. AVR, either performed via transcatheter approach or surgically, should not be denied or delayed in women with symptomatic discordant AS, if AS has been shown to be severe by alternative imaging, e.g. computed tomography. The best intervention in women (i.e. transcatheter vs. surgical AVR) needs to be further investigated as women seem to have worse outcomes than men after surgical AVR while better outcomes after transcatheter intervention.

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Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request. The data are not publicly available due to ethical restrictions.

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