



Sex Differences in Severe Aortic Stenosis — Clinical Presentation and Mortality —

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on behalf of the CURRENT AS Registry Investigators

Background: There is a paucity of data on the sex differences in the prevalence, clinical presentation, and prognosis of aortic stenosis (AS).

Methods and Results: A total of 3,815 consecutive patients with severe AS were enrolled in the multicenter CURRENT AS registry between January 2003 and December 2011. The registry included 1,443 men (38%) and 2,372 women (62%). Women were much older than men (79±10 vs. 75±10 years, $P<0.0001$), and the ratio of women to men increased with age. The cumulative 5-year incidence of all-cause death was significantly higher in men than in women (47% vs. 41%, $P=0.003$), although women were more symptomatic and much older. The 5-year mortality was similar between men and women at age <65 years (16% vs. 15%, $P=0.99$), whereas it was significantly higher in men than in women at age ≥65 years (65–74 years, 38% vs. 19%, $P<0.0001$; 75–84 years, 55% vs. 34%, $P<0.0001$; ≥85 years: 82% vs. 72%, $P=0.03$).

Conclusions: A large Japanese multicenter registry of consecutive patients with severe AS included a much higher proportion of women than men, with the female:male sex ratio increasing with age. The 5-year mortality rate of women was lower than that of men. Lower 5-year mortality rates in women were consistently seen across all age groups >65 years.

Key Words: Aortic stenosis; Aortic valve replacement; Mortality; Sex difference

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Aortic stenosis (AS) has become the most common valvular heart disease in the developed countries.^{1,2} The prevalence of rheumatic heart disease has declined, and the type of AS has shifted from rheumatic to non-rheumatic etiology.³ The lesion, referred to as degeneration, is now predominantly found in older patients. AS

progresses more rapidly in patients with degenerative calcification than in those with congenital or rheumatic disease;⁴ furthermore, older patients have a trend toward more rapid progression than younger patients.⁵ The progressive aging of the population in the developed countries will result in increasing number of patients presenting with clinically

Table 1. Subject Characteristics vs. Sex

	Men (n=1,443)	Women (n=2,372)	P value
Clinical characteristics			
Age (years) [†]	75.2±9.5	79.3±9.6	<0.0001
≤64	189 (13.1)	157 (6.6)	<0.0001
65–74	427 (29.6)	484 (20.4)	<0.0001
75–84	608 (42.1)	996 (42.0)	0.94
≥85	219 (15.2)	735 (31.0)	<0.0001
Symptoms of aortic stenosis	713 (49.4)	1,292 (54.5)	0.002
Chest pain	204 (14.1)	294 (12.4)	0.12
Syncope	72 (5.0)	126 (5.3)	0.70
HF	547 (37.9)	1,056 (44.5)	<0.0001
NYHA II	306 (21.2)	540 (22.8)	0.28
NYHA III	129 (8.9)	232 (9.8)	0.42
NYHA IV	102 (7.1)	271 (11.4)	<0.0001
NYHA NA	10 (0.7)	13 (0.6)	0.67
Admission for HF at index echocardiography [†]	244 (16.9)	546 (23.0)	<0.0001
Initial AVR strategy [†]	507 (35.1)	690 (29.1)	0.0001
≤64 years	91 (48.2)	69 (44.0)	0.45
65–74 years	194 (45.4)	214 (44.2)	0.74
75–84 years	191 (31.4)	330 (33.1)	0.51
≥85 years	24 (11.0)	58 (7.9)	0.17
BMI (kg/m ²)	22.2±3.7	21.5±3.9	<0.0001
<22 [†]	790 (54.8)	1,536 (64.8)	<0.0001
BSA (m ²)	1.60±0.15	1.37±0.15	<0.0001
Hypertension [†]	1010 (70.0)	1,657 (69.9)	0.93
Current smoking [†]	670 (46.4)	160 (6.8)	<0.0001
Diabetes mellitus	399 (27.7)	498 (21.0)	<0.0001
Receiving insulin [†]	85 (5.9)	103 (4.3)	0.03
Prior MI [†]	163 (11.3)	160 (6.8)	<0.0001
Prior open heart surgery	136 (9.4)	180 (7.6)	0.05
Prior stroke [†]	238 (16.5)	265 (11.2)	<0.0001
Atrial fibrillation or flutter [†]	306 (21.2)	522 (22.0)	0.56
Aortic/peripheral vascular disease	164 (11.4)	118 (5.0)	<0.0001
Serum creatinine (mg/dL) [†]	1.01 (0.83–1.68)	0.80 (0.62–1.1)	<0.0001
Hemodialysis [†]	242 (16.8)	163 (6.9)	<0.0001
Hemoglobin (g/dL)	12.2±2.2	11.1±1.9	<0.0001
Anemia ^{†,‡}	770 (53.4)	1,347 (56.8)	0.04
Liver cirrhosis (Child-Pugh B or C) [†]	16 (1.1)	22 (0.9)	0.58
Malignancy	259 (18.0)	258 (10.9)	<0.0001
Current treatment [†]	79 (5.5)	70 (3.0)	0.0001
Chest wall irradiation	10 (0.7)	15 (0.6)	0.82
Immunosuppressive therapy	36 (2.5)	95 (4.0)	0.01
Chronic lung disease	217 (15.0)	183 (7.7)	<0.0001
Moderate-severe [†]	49 (3.4)	63 (2.7)	0.19
Coronary artery disease [†]	553 (38.3)	591 (24.9)	<0.0001
Logistic Euroscore (%)	7.5 (4.5–13.9)	10.9 (7.0–18.3)	<0.0001
Euroscore II (%)	2.2 (1.3–4.0)	3.3 (2.0–5.4)	<0.0001
STS score (PROM) (%)	3.2 (1.8–5.9)	4.1 (2.6–6.8)	<0.0001

(Table 1 continued the next page.)

	Men (n=1,443)	Women (n=2,372)	P value
Etiology of aortic stenosis			
Degenerative	1259 (87.3)	2,120 (89.4)	<0.0001
Congenital (unicuspid, bicuspid, or quadricuspid)	133 (9.2)	125 (5.3)	
Rheumatic	38 (2.6)	112 (4.7)	
Infective endocarditis	2 (0.1)	5 (0.2)	
Other	11 (0.8)	10 (0.4)	
Echocardiograph characteristics			
Vmax (m/s)	4.1±0.9	4.2±1.0	0.07
Vmax ≥4 m/s†	822 (57.0)	1,363 (57.5)	0.76
Mean gradient (mmHg)	40.0±18.0	41.4±20.7	0.06
AVA (cm ²)	0.76±0.17	0.69±0.18	<0.0001
AVA index (cm ² /m ²)	0.48±0.11	0.51±0.14	<0.0001
LVEDD (mm)	48.8±7.1	44.2±6.3	<0.0001
LVESD (mm)	33.0±8.6	28.6±7.0	<0.0001
LVEF (%)†	60.1±14.1	64.4±12.9	<0.0001
Septal wall thickness (mm)	11.7±2.2	11.2±2.3	<0.0001
Posterior wall thickness (mm)	11.3±2.1	10.8±2.0	<0.0001
LVEF <40%	149 (10.3)	144 (6.1)	<0.0001
LVEF <50%	303 (21.0)	290 (12.2)	<0.0001
Any combined valvular disease (moderate-severe)†			
Moderate-severe AR	353 (24.5)	438 (18.5)	<0.0001
Moderate-severe MS	36 (2.5)	97 (4.1)	0.009
Moderate-severe MR	254 (17.6)	509 (21.5)	0.004
Moderate-severe TR	182 (12.6)	446 (18.8)	<0.0001
TR pressure gradient ≥40mmHg†	193 (13.4)	413 (17.4)	0.001

Data given as n (%), mean±SD, or median (IQR). †Potential independent variables selected for Cox proportional hazard models. ‡Defined according to World Health Organization criteria (hemoglobin <12.0g/dL in women and <13.0g/dL in men). AR, aortic regurgitation; AVA, aortic valve area; AVR, aortic valve replacement; BMI, body mass index; BSA, body surface area; HF, heart failure; LV, left ventricular; LVEDD, LV end-diastolic diameter; LVEF, LV ejection fraction; LVESD, LV end-systolic diameter; MI, myocardial infarction; MR, mitral regurgitation; MS, mitral stenosis; NA, not assessed; NYHA, New York Heart Association; PROM, predicted risk of mortality; STS, Society of Thoracic Surgeons; TR, tricuspid regurgitation; Vmax, peak aortic jet velocity.

significant AS in the near future.⁶

Sex differences have received increasing attention in cardiology.⁷ Women live longer than men, and longer life expectancy might influence the natural history of late-onset disease, but there is a paucity of data on the sex differences in the prevalence, clinical presentation, and prognosis of AS. The present study analyzed data from a large Japanese multicenter registry of consecutive patients with severe AS, focusing on comparison of the prevalence, clinical presentation and outcomes of severe AS between the sexes.

Methods

Subjects

The study design and patient enrollment for the Contemporary outcomes after sURgery and medical tREatmENT in patients with severe Aortic Stenosis (CURRENT AS) registry have previously been described in detail.⁸ In brief, the CURRENT AS is a retrospective, multicenter registry that enrolled consecutive patients with severe AS at 27 centers in Japan between January 2003 and December 2011. We enrolled 3,815 consecutive patients who met the definition of severe AS (peak aortic jet velocity [Vmax] >4.0 m/s, mean aortic pressure gradient [PG] >40 mmHg, or aortic valve area [AVA] <1.0 cm²) for the first time during the study period.⁹ AVA was calculated using the standard continuity equation. Initial aortic valve replacement (AVR) strategy was chosen in 1,197 patients after index echocardiography, while

the remaining 2,618 patients were managed conservatively. The institutional review boards of all 27 participating centers approved the protocol. Written informed consent from each patient was waived for this retrospective study, because clinical information used in the study was obtained during routine clinical practice; no patient refused to participate when contacted for follow-up.

Definitions

Angina, syncope, or heart failure including dyspnea were regarded as symptoms related to AS. The primary outcome measure for the current analysis was all-cause death. Causes of death were classified according to the Valve Academic Research Consortium (VARC).^{10,11} Sudden death was defined as unexplained death in previously stable patients. Aortic valve-related death included aortic procedure-related death, sudden death, and death due to heart failure possibly related to the aortic valve. Heart failure hospitalization was defined as hospitalization due to worsening heart failure requiring i.v. drug therapy. Symptoms of AS were defined as chest pain, syncope or pre-syncope, and heart failure possibly related to the AS as judged by the attending physicians.

Statistical Analysis

Baseline clinical and echocardiographic characteristics, and 5-year clinical outcomes were compared between the sexes. A separate analysis was performed including only the initial

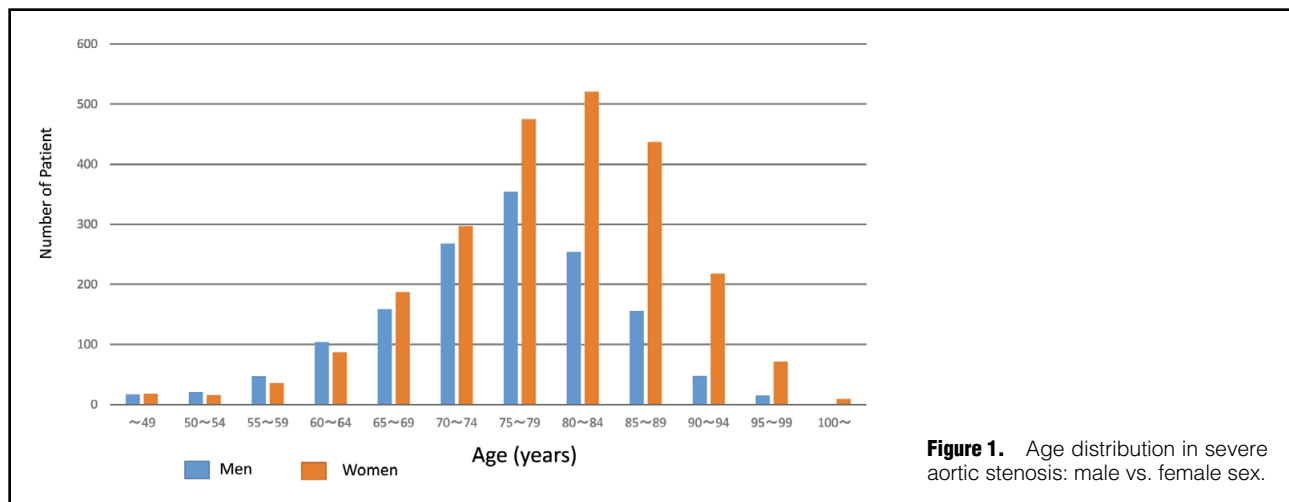


Figure 1. Age distribution in severe aortic stenosis: male vs. female sex.

AVR group to evaluate the sex-related differences in the outcomes of AVR.

Categorical variables are presented as numbers and percentages, and were compared using the chi-squared test or Fisher's exact test. Continuous variables are presented as mean \pm SD or median (IQR). Based on their distributions, continuous variables were compared using Student's t-test or Wilcoxon rank sum test. The Kaplan-Meier method was used to estimate the cumulative incidence, and differences were assessed using log-rank test. On multivariable adjusted analysis, we included the 21 clinically relevant factors listed in **Table 1** in the Cox proportional hazard models as the risk-adjusting variables, and the centers were incorporated as the stratification variable, consistent with a previous report.⁸ The continuous variables other than age were dichotomized by their medians or clinically meaningful reference values. Because the difference in age between men and women was too large to allow the dichotomous approach, age was treated as a continuous variable in the Cox proportional hazard models. The risks of male relative to female sex for the clinical endpoints were expressed as hazard ratios with 95% CI. All statistical analyses were conducted by physicians (M.T., T. Taniguchi) and a statistician (T. Morimoto) using either JMP 10.0.2 or 11.2.0 (SAS Institute, Cary, NC, USA) or SAS 9.4 (SAS Institute, Cary, NC, USA). Two-tailed $P < 0.05$ was considered to be statistically significant.

Results

Patient Characteristics

Among the 3,815 patients with severe AS enrolled in this registry, the prevalence of women (2,372 patients, 62.2%) was much higher than that of men (1,443 patients, 37.8%). Women were much older than men (79.3 ± 9.6 vs. 75.2 ± 9.5 years, $P < 0.0001$), and the female:male sex ratio in the population increased with age (**Table 1**; **Figure 1**). More than 50% of the AS patients diagnosed at ≤ 64 years were men, whereas $>60\%$ of severe AS patients diagnosed at ≥ 65 years were women. Notably, $>70\%$ of the severe AS patients diagnosed at ≥ 80 years were women (**Figure 1**).

Regarding the baseline clinical characteristics, a greater proportion of women than men had symptoms of AS at presentation (**Table 1**). Women more often had heart failure,

and their New York heart association (NYHA) functional class was greater than that of men. Initial AVR strategy, however, was planned more often in men than in women. When stratified by age, the proportion of patients with the initial AVR strategy was similar between men and women in each age category (**Table 1**). Women had a smaller body mass index and body surface area (BSA); they were more likely to have anemia, and to have received immunosuppressive therapy. A greater proportion of men had a prior history of atherosclerotic diseases, such as myocardial infarction, stroke, and aortic/peripheral artery disease. Men also had a higher prevalence of comorbidities such as renal disease, malignant disease, and chronic obstructive pulmonary disease. Regarding the etiology of AS, degenerative AS accounted for the majority of both male and female patients.

Regarding the echocardiographic characteristics, women had greater Vmax and PG at presentation, as well as smaller valve areas indexed to BSA (**Table 1**). Women had smaller and less hypertrophied left ventricles, while men often had depressed left ventricular systolic function as reflected by lower left ventricular ejection fraction. Women more often had pulmonary hypertension as indicated by tricuspid valve regurgitation PG ≥ 40 mmHg (**Table 1**).

Sex-Related Differences in Clinical Outcomes

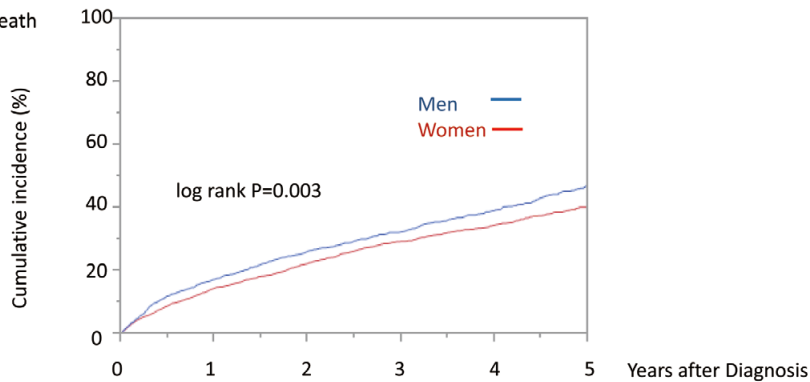
The cumulative 5-year incidence of all-cause death was significantly higher in men than in women (47% vs. 41%, $P = 0.003$), although women as compared with men were significantly older, and less often treated with initial AVR (**Figure 2**; **Table 2**). Even after adjusting for confounders, the excess mortality risk of male relative to female sex remained significant. Men were also associated with a significantly higher risk for sudden death and non-cardiovascular death than women. The adjusted risks of male relative to female sex were neutral for cardiovascular death and aortic valve-related death. Among patients initially treated with the conservative strategy, subsequent AVR was more often performed in men than in women during follow-up (**Table 2**).

Sex-Related Mortality Differences According to Age

We analyzed the 5-year outcomes for all-cause death, cardiovascular death, and non-cardiovascular death stratified

A

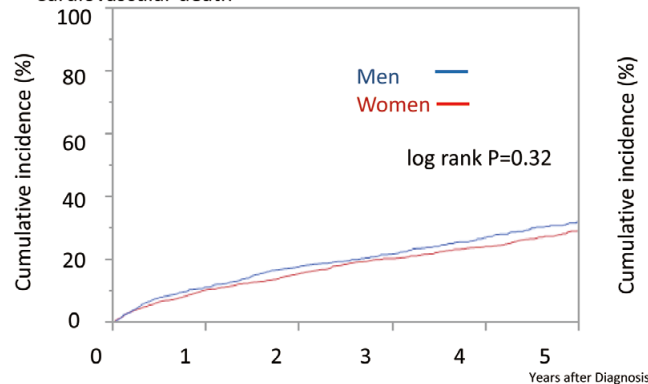
All cause Death



	0 day	30 days	1year	3 years	5 years
Men					
N of patients with event		42	246	444	548
N of patient at risk	1443	1379	1142	711	211
Cumulative incidence(%)		2.9	17.5	32.6	47.4
Women					
N of patients with event		61	338	653	780
N of patient at risk	2372	2269	1915	1262	396
Cumulative incidence(%)		2.6	14.7	29.5	40.5

B

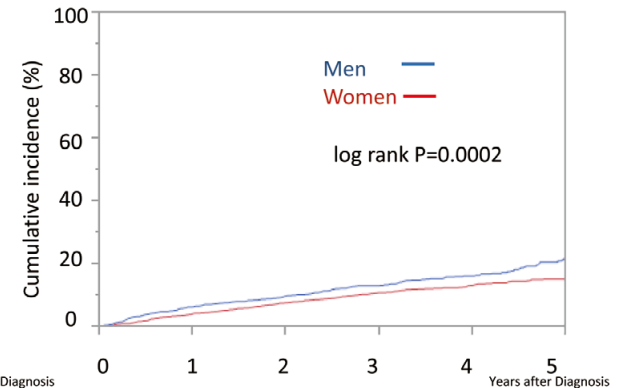
Cardiovascular death



	0 day	30 days	1year	3 years	5 years
Men					
N of patients with event		30	158	284	347
N of patient at risk	1443	1379	1142	711	211
Cumulative incidence(%)		2.1	11.6	22.2	32.7
Women					
N of patients with event		48	242	439	526
N of patient at risk	2372	2269	1915	1262	396
Cumulative incidence(%)		2.0	10.7	20.7	29.6

C

Non-cardiovascular death



	0 day	30 days	1year	3 years	5 years
Men					
N of patients with event		12	88	160	201
N of patient at risk	1443	1379	1142	711	211
Cumulative incidence(%)		0.8	6.7	13.4	21.9
Women					
N of patients with event		13	96	214	254
N of patient at risk	2372	2269	1915	1262	396
Cumulative incidence(%)		0.6	4.5	11.1	15.4

Figure 2. Kaplan-Meier curves for (A) all-cause death, (B) cardiovascular death, and (C) non-cardiovascular death in male vs. female patients.

by age and sex (Figure 3; Figures S1–S3). Male and female patients aged ≤ 64 years had similarly low 5-year mortality rates. In patients aged ≥ 65 years, the 5-year mortality was significantly higher in men than women across all age categories (Figure 3). Those sex-related mortality differences in the age groups >65 years remained significant even after adjusting for confounders (Table S1).

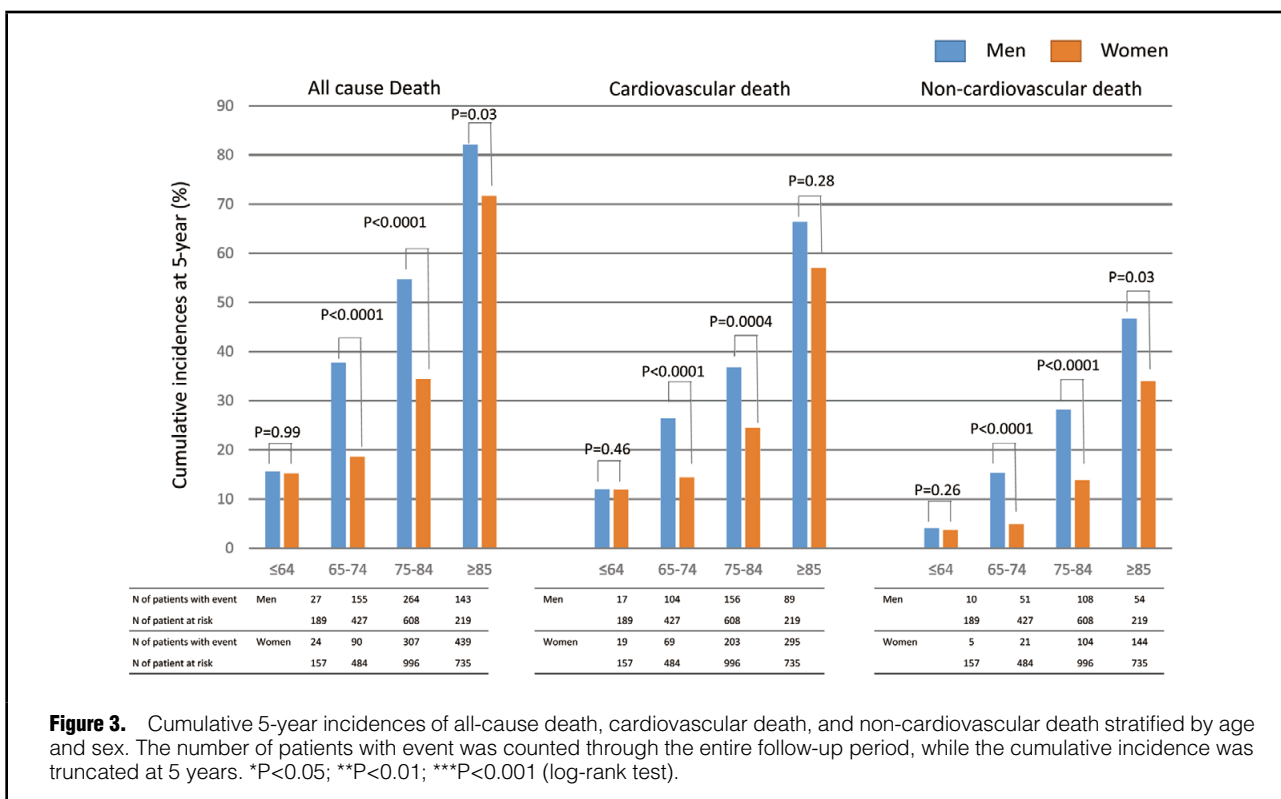
Sex-Related Differences in Outcome After AVR

In the initial AVR group, the sex differences in the patient characteristics were similar to those in the entire cohort, except that men and women had a similar symptomatic status at presentation (Table S2). Regarding the AVR procedural characteristics in the initial AVR group, the prosthetic valve size was smaller in women than in men, although the prevalence of type of valves used (prosthetic, biopros-

Table 2. Clinical Outcomes at 5-Years vs. Sex

	Men		Women		HR (95% CI)	P value†	Adjusted HR (95% CI)	P value†
	No. patients with ≥1 event (cumulative 5-year incidence, %) (n=1,443)	No. patients with ≥1 event (cumulative 5-year incidence, %) (n=2,372)	No. patients with ≥1 event (cumulative 5-year incidence, %) (n=1,443)	No. patients with ≥1 event (cumulative 5-year incidence, %) (n=2,372)				
Death	589 (47.4)	860 (40.5)	1.17	0.003	1.36	<0.0001	(1.20–1.54)	
Cardiovascular death	366 (32.7)	586 (29.6)	1.07	0.32	1.15	0.08	(0.98–1.33)	
Aortic valve-related death	232 (22.0)	377 (20.2)	1.05	0.55	1.20	0.06	(0.99–1.45)	
Sudden death	96 (9.7)	100 (5.7)	1.65	0.0005	1.65	0.003	(1.19–2.27)	
Non-cardiovascular death	223 (21.9)	274 (15.4)	1.40	0.0002	1.86	<0.0001	(1.52–2.29)	
HF hospitalization	268 (27.0)	544 (30.7)	0.83	0.01	0.96	0.60	(0.81–1.13)	
Composite of aortic valve-related death or hospitalization due to HF	387 (34.7)	685 (36.1)	0.95	0.38	1.01	0.93	(0.87–1.16)	
Surgical AVR or TAVI (initial AVR group)‡	492/507 (99.1)	671/690 (98.2)	NA		NA			
Surgical AVR or TAVI (conservative group)‡	224/936 (44.5)	317/1,682 (31.4)	NA		NA			

†Kaplan-Meier log rank. ‡TAVI performed during follow-up in 1 patient in the initial AVR group, and in 15 patients in the conservative group. The number of patients with at least 1 event was counted through the entire follow-up period, while the cumulative incidence was truncated at 5 years. TAVI, transcatheter aortic valve implantation; other abbreviations as in Table 1.



thetic and mechanical valves) did not differ by sex (Table S3). In the initial AVR group, 30-day mortality rate after AVR was not significantly different between men and women

(2.4% vs. 1.3%, $P=0.16$), but the cumulative 1-year and 5-year incidences of all-cause death was significantly higher in men than in women (10.5% vs. 5.6%, $P=0.003$, and 28.7%

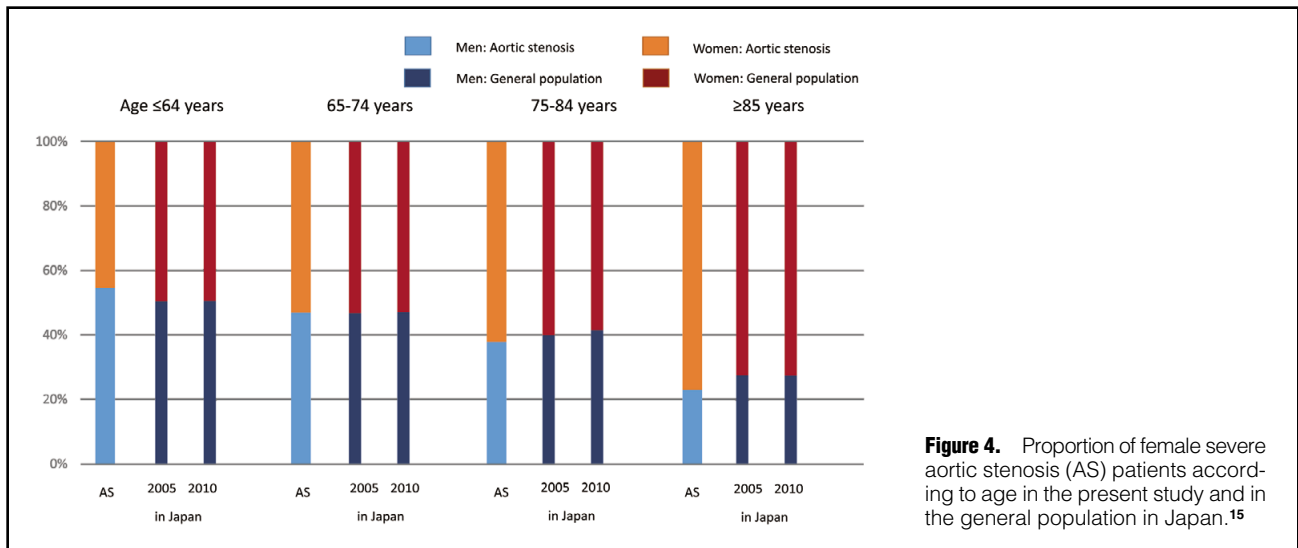


Figure 4. Proportion of female severe aortic stenosis (AS) patients according to age in the present study and in the general population in Japan.¹⁵

vs. 17.7%, $P=0.0001$, respectively; **Table S4**). The cumulative incidences of cardiovascular death, aortic valve-related death, and aortic valve procedure-related death were similar between men and women, while the cumulative incidences of non-cardiovascular death were much lower in women than in men (**Table S4**). After adjusting for confounders, the sex-related differences in all-cause death were attenuated, whereas the risk for non-cardiovascular death remained strongly related to sex, with a significantly higher risk in male than in female patients (**Table S5**).

Discussion

The main findings of the present analysis were as follows: First, in this large Japanese multicenter registry of consecutive patients with severe AS, the number of women was much greater than that of men, with greater prevalence of women with increasing patient age; Second, the 5-year mortality rate was lower in women than in men, even though women were much older, and more often symptomatic; Third, lower 5-year mortality rates in women were consistently seen across all the age groups >65 years.

In this study, the proportion of women was much greater than in the previous registries, including those of conservatively treated patients¹² or in the population based studies.^{6,13,14} In previous epidemiological studies on patients with late-onset AS,^{5,13,14} the number of women was equal to or greater than the number of men, but, after adjusting for age, the prevalence of AS was reported to be higher in men than in women.^{13,14} In the current study there were slightly more men than women in the <65 years age group, while in the >65 years group, there were more women than men, with the proportion of women increasing with age (**Figure 1**). The increase in the female:male sex ratio with aging in the present severe AS patients was similarly observed in the general population in Japan in 2005 and 2010 (**Figure 4**).¹⁵ Therefore, one explanation for the obvious female predominance in the present study would be the relatively longer life expectancy of women in Japan. Increasing prevalence of AS with age,^{1,5,13,16} and longer life expectancy of women might synergistically influence the predominance of elderly women with severe AS in the present study. Another explanation for the female predominance might be broader med-

ical attention for the elderly and for women in the present study than in the earlier studies. It has been hypothesized that women receive medical attention less frequently than men. A comparison between a population-based study for valve disease among randomly selected adults from the general population and a community study using clinical data on valve diseases suggested that there was no difference between men and women in the frequency of valve diseases, but that valve disease was diagnosed less often in women than in men in the community group, indicating an important diagnostic gap between men and women.¹ In contrast, the similar distribution of sex ratio by age between the present patients and the general population may indicate that any detection bias between men and women is small. Moreover, most Japanese adults receive periodical medical check-up, and this may be associated with the more frequent diagnosis of AS.¹⁷

Regarding the treatment strategies for AS, initial AVR was less frequently chosen in women than in men despite the greater prevalence of symptomatic patients in women. The prevalence of initial AVR, however, was similar between men and women when stratified by age categories, suggesting the absence of a large treatment gap between men and women in the decision for AVR.

In the present study, women were older and more often symptomatic than men at presentation. This is in agreement with previously published data.^{18,19} The advanced symptomatic status of women has been attributed to greater echocardiographic AS severity, as indicated by smaller AVA, as well as greater Vmax and mean PG.²⁰ Furthermore, pulmonary hypertension was more prevalent in women. Despite these high-risk features and lower prevalence of initial AVR in women, the 5-year mortality rate was significantly lower in women than in men. Aging was strongly related to the 5-year mortality in both men and women. Male and female patients aged <65 years had similarly low 5-year mortality rates. In those >65 years, the 5-year mortality rate was significantly higher in men than in women. In women, the increase in mortality with aging was delayed as compared with men. Higher prevalence of a prior history of atherosclerotic diseases, renal disease, malignant disease, and chronic obstructive pulmonary disease in men as compared with women might influence the sex-related mortal-

ity difference even after the adjustment for these factors as confounders. Most of the sex-related mortality difference was due to the difference in non-cardiovascular death, indicating that the generally longer life expectancy in women strongly influences the prognosis in AS. In contrast, the risk for AS-related outcomes such as aortic valve-related death and heart failure hospitalization was neutral between men and women.

There have been a number of reports on sex-related differences in surgical outcomes in patients with severe AS. Morris et al reported increased short-term mortality in women,¹⁹ whereas other reports have indicated better long-term survival in women²¹ or no sex-related differences in outcomes.²² These varying results may be explained by the differences in comorbidities contributing to mortality risks. In the present study evaluating a large number of patients with AVR, the crude 30-day mortality rate was not different between men and women, while the crude 5-year mortality rate was much lower in women than in men. The better crude survival in women was presumably due to longer life expectancy. Fuchs et al reported a lower mortality in women after AVR in the ≥ 79 -years age group.²¹ In the present study, sex-related differences in survival after AVR in the elderly were also observed in those aged ≥ 65 years (data not shown). Adjusted 5-year mortality risk of male relative to female patients, however, was neutral, suggesting that the better crude survival rate in women was related to the lower prevalence of measured morbidities in women.

Study Limitations

This study had several limitations. First, the comparison of the incidence of severe AS between men and women may have been affected by detection bias. Such bias cannot be fully excluded even though this was a large-scale multicenter registry and the female:male sex ratio stratified by age was similar between the present subjects and the general population. To further investigate this issue, a large-scale population-based study is required. Second, we enrolled patients who met the definition of severe AS for the first time during the study period. The mortality outcome after the enrollment may vary with duration from the onset of symptoms to enrollment in symptomatic patients.²³ Third, in this observational study, the possibility of residual confounding and selection bias could not be ruled out. Fourth, surgical treatment was performed more often in men than in women. We could not deny a possible selection bias between men and women in decisions about surgical treatment, although the prevalence of initial AVR was similar between male and female patients when stratified by age. Fifth, elderly patients often had complex comorbidities, significant physical or cognitive disabilities, and frailty. Such factors possibly could potentially influence patient detection and treatment decision making. Although we thoroughly reviewed all patient charts and the hospital databases to evaluate patient condition, factors specific to the elderly were not included in the pre-specified protocol. Finally, when interpreting the current study results, ethnicity, health-care systems, and social systems in Japan should be considered, because these could influence patient detection and outcomes.

Conclusions

A large Japanese multicenter registry of consecutive patients with severe AS had a much higher proportion of women than men, with the female:male sex ratio increasing with

age. The 5-year mortality rate of women was lower than that of men. Lower 5-year mortality rates in women were consistently seen across all age categories >65 years.

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Disclosures

The authors declare no conflict of interest.

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Supplementary Files

Supplementary File 1

Figure S1. Kaplan-Meier curves for all-cause death stratified by age: male vs. female sex.

Figure S2. Kaplan-Meier curves for cardiovascular death stratified by age: male vs. female sex.

Figure S3. Kaplan-Meier curves for non-cardiovascular death stratified by age: male vs. female sex.

Table S1. Crude and adjusted mortality risk of male relative to female sex vs. age

Table S2. Initial AVR group subject characteristics vs. age

Table S3. Initial AVR group: preoperative information and procedure characteristics

Table S4. Clinical outcome of initial AVR

Table S5. Crude and adjusted effects of male relative to female sex for clinical outcome of initial AVR

Please find supplementary file(s);
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