CLINICAL STUDY

Sex-Related Differences in Cardiac Remodeling and Reverse Remodeling After Transcatheter Aortic Valve Implantation in Patients with Severe Aortic Stenosis in a Japanese Population

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Summary

Left ventricular (LV) remodeling with aortic stenosis (AS) appears to differ according to sex, but reverse remodeling after transcatheter aortic valve implantation (TAVI) has not been elucidated in a Japanese population. This study aims to determine whether any sex-related differences in LV or reverse remodeling after TAVI exist in the context of severe AS.

Of 208 patients who received TAVI for severe AS in our institution, 100 (men, 42; mean age, 83.0 ± 4.9 years) underwent transthoracic echocardiography before and 3 months after TAVI. Despite similar valvular gradients, women with severe AS had lower indexed LV mass (LVMi) than did men (152.3 ± 35.4 versus 173.2 ± 44.6 g/m^2, P = 0.005), with smaller indexed LV end-diastolic (LVEDVi) (50.2 ± 13.3 versus 61.4 ± 20.7 mL/m^2, P = 0.001) and end-systolic (LVESVi; 17.9 ± 8.7 versus 24.3 ± 13.8 mL/m^2, P = 0.006) volumes. After TAVI, women (−6.0% ± 14.4%) had higher reduction in the rate of change of relative wall thickness (RWT) than did men (4.4% ± 19.0%, P = 0.003). Men (−8.9% ± 3.9%) had higher reduction in the rate of change of LVEDVi than did women (1.5% ± 3.3%, P = 0.045). Incidence of LV reverse remodeling defined as a reduction in LVESV of >15% was significantly higher in men (50%) than in women (26%, P = 0.013).

In addition to sex differences in the pattern of LV remodeling with AS, reverse LV remodeling after TAVI also differed between sexes.

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Key words: Heart valve diseases, LV hypertrophy, Left ventricular remodeling

Aortic stenosis (AS) is a common disease that develops regardless of race, and sex differences in this disease have been reported in various populations.[1)] There is no difference in progression or prevalence by sex, but the manner of cardiac remodeling, especially left ventricular (LV) remodeling for AS, differs between the sexes.[2-4)] LV remodeling is heterogeneous, with four main geometric patterns: normal geometry, concentric remodeling, concentric hypertrophy, and eccentric hypertrophy.[5)] These patterns are based on LV mass (LVM), cavity size, and the ratio of these two factors. It is well known that many concentric hypertrophy changes are seen in females, while eccentric hypertrophy changes are seen in males.[6-10)] Meanwhile, LV reverse remodeling after surgical aortic valve replacement (SAVR) is an important indicator related to long-term prognosis and tends to be seen in males after SAVR.[9)]

Transcatheter aortic valve implantation (TAVI) has been introduced in Japan and is suitable for the treatment of elderly and frail patients. The myocardial response resulting from the improvement of AS is seen clearly and quickly after TAVI.[11)] However, the difference between the sexes in the change of cardiac morphology after TAVI in patients who were not indicated for SAVR has not been elucidated in a Japanese population. Therefore, this study aims to determine whether any sex-related differences exist in severe AS in terms of cardiac and reverse remodeling after TAVI in a Japanese population.

Methods

Study population and design: Between December 2013 and May 2018, 208 patients (men, 76 [36.5%]; mean age, 83.7 ± 4.8 years) with severe AS undergoing TAVI at Iwate Medical University Hospital were prospectively recruited (Figure 1). During the study period, patients un-

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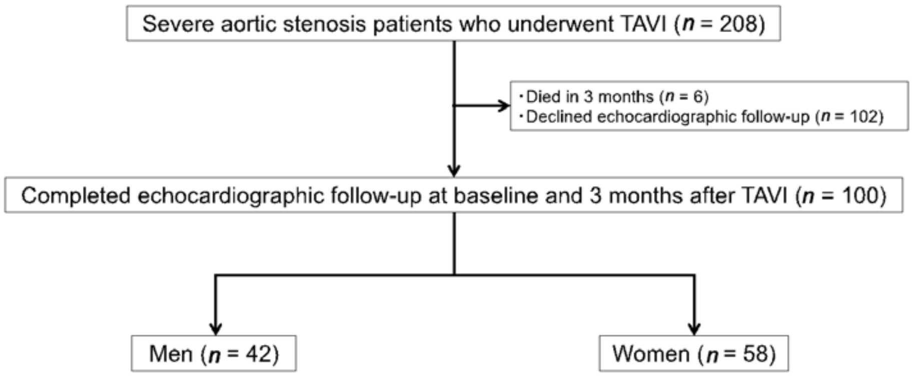

Figure 1. Patient recruitment pathway. TAVI indicates transcatheter aortic valve implantation.

derwent TAVI if they had severe AS with an aortic valve area (AVA) of < 1.0 cm^2 or < 0.6 cm^2/m^2 and were deemed inoperable or at a high risk for SAVR based upon the evaluations of a dedicated multidisciplinary team. Patients were evaluated by transthoracic echocardiography before TAVI and 3 months after the procedure.

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in an *a priori* approval by the institution's human research committee (MH2018-503), and written informed consent for data collection was obtained from each patient prior to TAVI.

TAVI procedures: Patients were selected to undergo TAVI using a transfemoral (n = 83), trans-aortic (n = 2), or trans-apical (n = 15) approach, depending on the size, calcification, and tortuosity of the iliofemoral arterial access. Edwards valves (Sapien-XT, Sapien 3; Edwards Lifesciences, Irvine, CA, USA) and CoreValves, Evolut-R (Medtronic, Minneapolis, MN, USA) were used, and the device size was selected according to the area derived from the mean annulus diameter calculated using multidetector computed tomography and transesophageal echocardiography. The procedures were performed by experienced interventional cardiologists according to our standard operating procedures with the patients under general anesthesia. Hemodynamic and echocardiographic parameters were continuously monitored during the procedure.

Pre- and postprocedural echocardiography: All patients underwent echocardiography before TAVI and 3 months after TAVI. All echocardiograms were performed and analyzed by the same operator on an EPIQ 7 ultrasound machine (Philips Healthcare, Inc., Andover, MA, USA) and were digitally stored and later analyzed by a researcher who was completely blinded to all clinical data. Measurements and recordings were obtained according to the American Society of Echocardiography (ASE) guidelines.[12]

AVA was estimated with quantitative Doppler using the continuity equation.[12] The diameter of the LV outflow tract was measured 5 mm below the annulus from a zoomed image of the LV outflow tract obtained in the parasternal long-axis view. Peak flow velocity across the valve was determined in the apical window or the echocardiographic window, where the highest peak velocity could be obtained by placing the continuous wave Doppler cursor as close as possible to parallel with the flow across the valve. The peak transvalvular gradient was estimated using the Bernoulli equation.[12] Finally, the peak systolic flow velocity in the outflow tract was estimated with pulsed-wave Doppler.

LV wall thickness and dimensions were estimated from the average of three consecutive two-dimensional images obtained in the parasternal long-axis view according to the ASE's guidelines.[12] AS patients were categorized into four patterns of LV geometric adaption: "normal geometry," "concentric remodeling," "concentric hypertrophy," and "eccentric hypertrophy." These patterns are based on relative wall thickness (RWT), LVM, and the ratio of these two factors, as previously described.[5] RWT was calculated as the ratio of twice the interventricular septum wall thickness at end-diastole (IVSd) to the LV end-diastolic dimension (LVDd).[13] RWT was used to categorize LV hypertrophy (LVH) as either concentric (RWT ≥ 0.42) or eccentric (RWT < 0.42). LVM was calculated as recommended by the ASE using the Devereux formula, which incorporates LVDd, posterior wall thickness at end-diastole (PWd), IVSd, and LVDd:

$$LVM = 0.8 \times (1.04\ [(LVDd + PWd + IVSd)^3 - (LVDd)^3]) + 0.6.$$

LVM was indexed to body surface area (BSA). LVH was defined as indexed LVM (LVMi) exceeding 110 g/m^2 in women and 125 g/m^2 in men.[12] LV concentric remodeling was defined as a normal LVMi with RWT ≥ 0.42, eccentric LVH as increased LVMi with RWT < 0.42, and concentric LVH as increased LVMI with RWT ≥ 0.42.[5]

The LV volume was measured using the biplane area length method and corrected for BSA. The LV ejection fraction (LVEF) was calculated using the biplane modified Simpson's method. Indexed left atrial volume (LAVi) was measured in LV end systole in the frame preceding mitral valve opening. Mitral inflow was assessed in the apical four-chamber view using pulsed-wave Doppler with the sample volume paced at the tips of the mitral leaflets during diastole. From the mitral inflow profile, the E- and A-wave peak velocities and deceleration time were measured. Paravalvular and transvalvular regurgitation were assessed according to the Valve Academic Research Consortium-2 criteria.[14] Severe patient-prosthesis mismatch (PPM) was defined as an indexed effective orifice area 0.65 cm^2/m^2 3 months after TAVI. We evaluated the changes in echocardiographic parameters before and after TAVI using the rate of change. The rate of change was calculated as (post-TAVI - pre-TAVI) / pre-TAVI × 100 (%). We defined LV reverse remodeling as a reduction in LVESV of > 15%.[15)]

Statistical analysis: All statistical analyses were performed using JMP® 13 (SAS Institute Inc., Cary, NC, USA). Normality was checked using the Shapiro-Wilk test. Continuous variables are expressed as mean ± SD or median and interquartile range as appropriate, whereas qualitative variables are expressed as numbers and percentages. Differences between means were evaluated using paired (for before and after comparisons) and unpaired (for independent group comparisons) Student t-tests for normally distributed data and Mann-Whitney or Wilcoxon signed-rank tests for nonparametric data. The chi-square test was used for categorical variables and Fisher exact test for categorical variables with low frequencies (expected cell count < 5). Pearson correlation coefficients were used to investigate the relationship of cardiac reverse remodeling parameters with baseline parameters. A two-tailed $P < 0.05$ was considered statistically significant.

Results

Population: Of 208 patients referred for possible enrollment into this study, 108 were excluded: 6 patients died within 3 months of causes unrelated to the TAVI procedure and echocardiography was not able to be performed at the 3-month follow-up in 102 patients. The remaining 100 patients (male, 42; female, 58) fulfilled the study criteria and were enrolled accordingly (Figure 1). There were no significant differences between the group that completed the 3-month echocardiography and that did not in age (83.0 ± 4.9 versus 84.3 ± 5.2 years, $P = 0.077$), baseline indexed AVA (AVAi) (0.50 ± 0.13 versus 0.49 ± 0.12 cm/m^2, $P = 0.561$), Logistic Euro score (8.3 [2.3-29.3] versus 7.4 [2.2-44.0], $P = 0.445$), or STS risk score (5.2 [1.4.-18] versus 5.0 [1.7-12.7], $P = 0.887$). There were no significant differences among the groups with regard to other baseline characteristics, indicating that the demographics of the analyzed patients were representative of the larger population.

Baseline patient characteristics and echocardiographic parameters are shown in Tables I, II. The BSA was significantly higher in men (1.6 ± 0.1 m^2) than in women (1.4 ± 0.2 m^2, $P < 0.001$), and the serum creatinine was significantly higher in men (1.1 [0.5-2.1] mg/dL) than in women (0.8 [0.5-1.6] mg/dL, $P = 0.005$). The proportion of patients with the chronic obstructive pulmonary disease (COPD) was significantly higher in men (14%) than in women (2%, $P = 0.015$). The New York Heart Association (NYHA) class was significantly lower in men (2.0 ± 0.5) than in women (2.4 ± 1.8, $P = 0.026$).

Baseline echocardiographic measurements: At baseline, although the AVAi was significantly lower in men (0.46 ± 0.02 cm^2/m^2) than in women (0.53 ± 0.12 cm^2/m^2, P = 0.013), there were no significant differences between the groups in aortic maximum and mean pressure gradient (Table II). Women with severe AS had higher RWT (0.73 ± 0.15 versus 0.64 ± 0.11, $P < 0.001$) than men, with smaller indexed LV end-diastolic (LVEDVi) (50.2 ± 13.3 versus 61.4 ± 20.7 mL/m^2, $P = 0.001$) and end-systolic (LVESVi; 17.9 ± 8.7 versus 24.3 ± 13.8 mL/m^2, P = 0.006) volumes (Figure 2). In contrast, men with severe AS had higher LVMi (173.2 ± 44.6 versus 152.3 ± 35.4 g/m^2, $P = 0.005$) and lower A-wave peak velocities (1.0 ± 0.2 versus 1.2 ± 0.3 m/second, $P < 0.001$) than women (Table II). There were no marked sex differences in patterns of remodeling ($P = 0.070$): concentric hypertrophy (81% of males and 95% of females) was seen in both sexes, but concentric remodeling tended to be seen more in men (17%) than in women (3%). Aortic regurgitation (AR) > grade 3 was seen significantly more in men (17%) than in women (2%, $P = 0.005$). There was no significant difference between men and women in terms of LVEF (62.4 ± 9.3 versus 65.5 ± 8.1, $P = 0.075$), mitral regurgitation (MR) (> grade 3) (2% versus 8%, $P = 0.182$), or tricuspid max pressure gradient (28.3 ± 8.7 versus 27.2 ± 7.3, $P = 0.537$).

Echocardiographic assessment 3 months after TAVI: There was a marked improvement in aortic valve obstruction in both men and women (AVA 0.46 ± 0.02 to 1.21 ± 0.30 cm^2/m^2 in men, 0.53 ± 0.12 to 1.25 ± 0.34 cm^2/m^2 in women; mean pressure gradient 53.9 ± 18.1 to 10.6 ± 2.0 mmHg in men, 54.8 ± 19.6 to 12.2 ± 5.5 mmHg in women; peak pressure gradient 91.9 ± 30.0 to 21.3 ± 7.2 mmHg in men, 91.4 ± 27.0 to 24.8 ± 11.2 mmHg in women; $P < 0.001$) (Table II) 3 months after TAVI. No patients of either sex had severe PPM. The rate of changes in echocardiographic parameters are presented in Table II. Women (−6.0% ± 14.4%) had higher reduction in the rate of change of RWT than did men (4.4% ± 19.0%, $P = 0.003$). Men had higher reduction in the rate of change of LVDd (−4.5% ± 10.2% in men versus 2.6% ± 10.7% in women, $P = 0.001$) and LVEDVi (−8.9% ± 3.9% in men versus 1.5% ± 3.3% in women, $P = 0.045$) than did women. LV volume reduction occurred regardless of the baseline level of the LV volume, although LV volume reduction was greatest in those patients with the highest LVEDVi and LVESVi at baseline (Figure 2). Improvement of LVEF occurred regardless of the baseline level of LVEF, although LVEF improvement was greatest in those patients with lower LVEF at baseline. Incidence of LV reverse remodeling was significantly higher in men (50%) than in women (26%, $P = 0.013$). Men (58.2 ± 45.2 mL/m^2) had lower LAVi than women (62.1 ± 22.9 mL/m^2, $P = 0.007$) 3 months after TAVI. There were no marked sex differences in the pattern of remodeling after TAVI ($P = 0.291$): concentric hypertrophy (male, 76%; female, 88%) was predominantly seen in both sexes, but one male and four females changed from concentric hypertrophy to concentric remodeling. There was no sex-related difference in paravalvular leakage (PVL) score (9.4% ± 6.4% in men versus 12.2% ± 7.4% in women, P = 0.096). Figure 3 shows representative echocardiography images before and after TAVI in each group.

Discussion

To the best of our knowledge, this study is the first to demonstrate the influence of sex on differences in car-

Table I. Baseline Clinical Characteristics

	Total (*n* = 100)	Men (*n* = 42)	Women (*n* = 58)	*P* value
Age, years	83.2 ± 5	82.4 ± 6	83.1 ± 4	0.139
Length of hospital stay, days	20 [9-208]	16 [9-143]	23 [9-208]	0.900
BSA, m^2	1.5 ± 0.2	1.6 ± 0.1	1.4 ± 0.2	< 0.001
HF hospitalization, *n* (%)	37 (37)	14 (33)	23 (40)	0.518
NYHA class (median)	2.2 ± 0.7	2.0 ± 0.5	2.4 ± 1.8	0.026
Comorbidities				
Dyslipidemia, *n* (%)	52 (52)	18 (43)	34 (59)	0.119
Diabetes, *n* (%)	43 (43)	22 (52)	21 (36)	0.107
Hypertension, *n* (%)	83 (83)	34 (80)	49 (84)	0.642
CKD, *n* (%)	54 (54)	26 (62)	28 (48)	0.177
Atrial fibrillation, *n* (%)	27 (27)	12 (29)	15 (26)	0.763
CAD, *n* (%)	40 (40)	13 (31)	27 (47)	0.116
Previous myocardial infarction, *n* (%)	4 (4)	1 (2)	3 (5)	0.482
CABG, *n* (%)	4 (4)	3 (7)	1 (2)	0.172
PAD, *n* (%)	23 (23)	11 (26)	12 (21)	0.519
Carotid stenosis > 50%, *n* (%)	8 (8)	5 (12)	3 (5)	0.207
Cerebrovascular disease, *n* (%)	24 (24)	8 (19)	16 (28)	0.324
COPD, *n* (%)	7 (7)	6 (14)	1 (2)	0.015
Drug history				
ACE-I/ARB, *n* (%)	65 (65)	28 (67)	37 (64)	0.766
Beta-blocker, *n* (%)	52 (52)	22 (52)	30 (52)	0.948
Calcium channel blocker, *n* (%)	43 (43)	15 (36)	28 (48)	0.211
Diuretics, *n* (%)	47 (47)	18 (43)	29 (50)	0.480
Risk scores				
Logistic Euro score, %	8.3 [2.3-29.3]	7.0 [2.3-26.1]	9.8 [3.6-29.3]	0.106
STS score, %	5.2 [1.4-18]	4.9 [1.4-16.0]	5.3 [2.8-18]	0.501
Blood				
Hemoglobin, g/dL	11.3 ± 1.6	11.6 ± 1.9	11.1 ± 11.3	0.187
Platelet, × 10^4/µL	18.6 ± 6.0	17.9 ± 5.8	19.1 ± 6.2	0.323
HbA1C, %	6.0 ± 0.7	6.0 ± 0.6	6.1 ± 0.8	0.456
Creatinine, mg/dL	0.9 [0.5-2.1]	1.1 [0.5-2.1]	0.8 [0.5-1.6]	0.005
BNP, pg/mL	292 [24-2834]	341 [24-2834]	271 [41-2084]	0.140
Pulmonary hypertension, *n* (%)	23 (23)	9 (22)	14 (24)	0.662
Type of approach				
Transfemoral, *n* (%)	83 (83)	35 (82)	48 (83)	0.817
Trans-apical, *n* (%)	15 (15)	6 (14)	9 (15)	0.865
Trans-aortic, *n* (%)	2 (2)	1 (2)	1 (2)	0.818
Type of biological valve				0.766
SAPIEN	83 (83)	36 (86)	47 (81)	0.539
CoreValve/Evolut	17 (17)	6 (14)	11 (19)	

BSA indicates body surface area; HF, heart failure; NYHA, New York Heart Association classification; CKD, chronic kidney disease; CAD, coronary artery disease; CABG, coronary artery bypass graft; PAD, peripheral artery disease; COPD, chronic obstructive pulmonary disease; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; STS, society of thoracic surgeons predicted risk of mortality; and BNP, brain natriuretic peptide.

diac remodeling in AS and in reverse remodeling after TAVI in a Japanese population. We found that women had higher RWT with a smaller LV volume, whereas men were prone to the development of a larger LV volume and increased LVM. After TAVI, LV volume reduction was observed only in men and RWT regression was seen only in women.

Current guidelines require that, for consideration of SAVR or TAVI in patients with severe AS, symptoms related to the valvular disease be present.[16] TAVI has recently emerged as an alternative treatment for severe symptomatic AS in patients who are not suitable for surgery or are at high surgical risk. Among patients undergoing TAVI, women more commonly have insidious symptoms, resulting in late presentation and less frequent referral for intervention, as well as a greater prevalence of coexisting valve diseases such as severe MR, than males.[17] Differences also exist in other comorbidities; women with AS are older and frailer, with a porcelain aorta and a greater predicted risk using both the Logistic Euro and STS risk scores. In contrast, women have a lower rate of coronary artery disease, previous myocardial revascularization, atrial fibrillation, and diabetes.[17,18]

It has been reported that severe AS patients receiving TAVI in Japan are much older than those in Europe and the United States.[19,20] The population of patients in this trial had an average age approximately more than five years older than the populations in recent TAVI trials.[6,9,11] Moreover, in contrast to other studies evaluating sex in AS, our male and female groups were similar in terms of

Table II. Echocardiographic Data Before and After TAVI, Grouped according to Sex

	Total (n = 100)	Men (n = 42)	Women (n = 58)	P value for sex difference
Aortic maximum pressure gradient (mmHg)				
Preintervention	91.6 ± 28.1	91.9 ± 30.0	91.4 ± 27.0	0.939
Postintervention	23.2 ± 9.9	21.3 ± 7.2	24.8 ± 11.2	0.080
Rate of change (%)	−72.7 ± 14.4	−75.3 ± 10.6	−70.8 ± 16.4	0.121
Aortic mean pressure gradient (mmHg)				
Preintervention	54.4 ± 18.9	53.9 ± 18.1	54.8 ± 19.6	0.806
Postintervention	11.5 ± 4.9	10.6 ± 2.0	12.2 ± 5.5	0.107
Rate of change (%)	−76.7 ± 12.9	−78.6 ± 9.9	−75.3 ± 14.7	0.273
Aortic valve area index (cm^2/m^2)				
Preintervention	0.50 ± 0.13	0.46 ± 0.02	0.53 ± 0.12	0.013
Postintervention	1.23 ± 0.32	1.21 ± 0.30	1.25 ± 0.34	0.506
Rate of change (%)	158.3 ± 83.4	171.3 ± 89.7	148.7 ± 77.9	0.184
Aortic regurgitation > 3, n (%)				
Preintervention		7 (17)	1 (2)	0.005
PVL score (%)				
Postintervention		9.4 ± 6.4	12.2 ± 7.4	0.096
Septum wall thickness at end-diastole (mm)				
Preintervention	14.6 ± 1.8	14.8 ± 1.8	14.5 ± 1.8	0.545
Postintervention	14.2 ± 2.1	14.5 ± 2.2	13.9 ± 2.1	0.150
Rate of change (%)	−3.1 ± 10.2	−1.5 ± 10.2	−4.2 ± 10.1	0.177
Posterior wall thickness at end-diastole (mm)				
Preintervention	13.6 ± 1.5	13.7 ± 1.6	13.4 ± 1.4	0.336
Postintervention	13.0 ± 1.6	13.4 ± 1.7	12.7 ± 1.4	0.028
Rate of change (%)	−3.4 ± 10.0	−1.7 ± 10.4	−4.7 ± 9.7	0.148
RWT				
Preintervention	0.64 ± 0.12	0.64 ± 0.11	0.73 ± 0.15	< 0.001
Postintervention	0.62 ± 0.11	0.66 ± 0.13	0.69 ± 0.13	0.303
Rate of change (%)	−1.6 ± 17.2	4.4 ± 19.0	−6.0 ± 14.4	0.003
LVMi (g/m^2)				
Preintervention	161.3 ± 40.7	173.2 ± 44.6	152.3 ± 35.4	0.005
Postintervention	152.2 ± 38.5	157.2 ± 38.8	147.9 ± 38.1	0.230
Rate of change (%)	−4.5 ± 18.0	−8.1 ± 14.5	−1.9 ± 19.8	0.089
Pattern of remodeling (preintervention), n (%)				
Normal geometry	0	0	0	0.070
Concentric remodeling	9 (9)	7 (17)	2 (3)	
Concentric hypertrophy	89 (89)	34 (81)	55 (95)	
Eccentric hypertrophy	2 (2)	1 (2)	1 (2)	
Pattern of remodeling (postintervention), n (%)				
Normal geometry	0	0	0	0.291
Concentric remodeling	14 (14)	8 (19)	6 (10)	
Concentric hypertrophy	83 (83)	32 (76)	51 (88)	
Eccentric hypertrophy	3 (3)	2 (5)	1 (2)	
LVDd (mm)				
Preintervention	43.2 ± 6.5	47.1 ± 5.8	40.4 ± 5.6	< 0.001
Postintervention	42.7 ± 5.6	44.7 ± 5.4	41.2 ± 5.3	0.002
Rate of change (%)	−0.3 ± 11.0	−4.5 ± 10.2	2.6 ± 10.7	0.001
LVDs (mm)				
Preintervention	27.8 ± 6.7	30.7 ± 6.8	25.6 ± 5.8	< 0.001
Postintervention	26.1 ± 5.0	27.8 ± 4.8	24.8 ± 4.8	0.003
Rate of change (%)	−3.9 ± 15.9	−7.1 ± 17.8	−1.5 ± 14.0	0.081
LVEDVi (mL/m^2)				
Preintervention	54.9 ± 17.6	61.4 ± 20.7	50.2 ± 13.3	< 0.001
Postintervention	51.1 ± 16.4	53.3 ± 16.5	49.5 ± 12.5	0.194
Rate of change (%)	−2.9 ± 25.8	−8.9 ± 26.3	1.5 ± 24.8	0.045
LVESVi (mL/m^2)				
Preintervention	20.6 ± 11.5	24.3 ± 13.8	17.9 ± 8.7	0.006
Postintervention	17.9 ± 7.2	19.1 ± 7.4	17.1 ± 6.9	0.165
Rate of change (%)	−2.0 ± 35.8	−9.5 ± 37.8	3.4 ± 33.5	0.075
Reduction in LVESV of > 15%, n (%)	36 (36)	21 (50)	15 (26)	0.031
LVEF (%)				
Preintervention	64.2 ± 8.8	62.4 ± 9.3	65.5 ± 8.1	0.075

Table II. Echocardiographic Data Before and After TAVI, Grouped according to Sex (Continued)

	Total (n = 100)	Men (n = 42)	Women (n = 58)	P value for sex difference
Postintervention	65.4 ± 6.4	64.5 ± 6.5	66.1 ± 6.3	0.237
Rate of change (%)	3.3 ± 13.9	5.4 ± 17.2	1.7 ± 10.9	0.346
LAVi (mL/m^2)				
Preintervention	63.5 ± 35.6	61.9 ± 43.9	64.8 ± 28.4	0.223
Postintervention	60.7 ± 33.3	58.2 ± 45.2	62.1 ± 22.9	0.007
Rate of change (%)	−1.1 ± 25.2	−4.1 ± 27.6	1.1 ± 23.2	0.312
E (m/second)				
Preintervention	0.9 ± 0.3	0.9 ± 0.3	0.9 ± 0.3	0.908
Postintervention	0.9 ± 0.3	0.9 ± 0.3	0.9 ± 0.3	0.504
Rate of change (%)	10.8 ± 37.6	8.1 ± 36.5	12.8 ± 38.5	0.544
A (m/second)				
Preintervention	1.1 ± 0.3	1.0 ± 0.2	1.2 ± 0.3	< 0.001
Postintervention	1.2 ± 0.3	1.1 ± 0.2	1.3 ± 0.3	0.002
Rate of change (%)	8.1 ± 34.6	9.7 ± 45.3	7.1 ± 26.3	0.751
E/A				
Preintervention	0.8 ± 0.5	0.9 ± 0.6	0.7 ± 0.4	0.246
Postintervention	0.8 ± 0.3	0.8 ± 0.3	0.8 ± 0.3	0.718
Rate of change (%)	6.3 ± 46.7	−4.7 ± 45.2	13.3 ± 46.8	0.098
Deceleration time (ms)				
Preintervention	303.2 ± 113.2	292.6 ± 116.4	311.4 ± 111.4	0.367
Postintervention	316.4 ± 100.1	315.3 ± 113.5	316.4 ± 90.85	0.592
Rate of change (%)	8.5 ± 39.6	10.4 ± 39.9	7.1 ± 39.6	0.682
Mitral regurgitation > 3, n (%)				
Preintervention	5 (5)	1 (2)	4 (8)	0.182
Postintervention	4 (4)	1 (2)	3 (5)	0.637
Tricuspid max pressure gradient (mmHg)				
Preintervention	27.7 ± 7.9	28.3 ± 8.7	27.2 ± 7.3	0.537
Postintervention	26.1 ± 7.7	26.3 ± 7.7	26.0 ± 7.8	0.844
Rate of change (%)	−4.3 ± 33.1	−9.8 ± 38.8	−0.2 ± 27.8	0.172

PVL indicates paravalvular leakage; RWT, relative wall thickness; LVMi, indexed left ventricular (LV) mass; LVDd, LV end-diastolic diameter; LVDs, LV end-systolic diameter; LVEDVi, indexed LV end-diastolic volume; LVESVi, indexed LV end-systolic volume; LVEF, LV ejection fraction; and LAVi, indexed left atrial volume.

age, comorbidity, cardiac risk score, and aortic valve gradients. Only AVAi, NYHA classification, baseline AR, creatinine, and, expectedly, COPD prevalence and BSA differed between the two groups. The advanced symptomatic status of women with AS has been attributed to more severe LV diastolic dysfunction, a higher prevalence of pulmonary hypertension, severity of AS, and older age.[21,22] Although age, severity of AS, LV diastolic dysfunction, and tricuspid max pressure gradient were similar in this study, higher RWT and smaller LV volume in women might be associated with advanced symptomatic status. It is well known that smoking history is significantly higher in men with AS.[22] Although smoking status was not recorded in this study, a high history of smoking in men might be related to having a history of COPD. Higher LV cavity size and mass in men may contribute to higher prevalence of baseline AR, but the PVL after TAVI was similar between sexes in this study.

It is still debated whether sex-specific factors influence and modify the clinical course of AS over time and whether hormonal changes, including history of pregnancy and age of menopause, can impact TAVI outcomes.[23-25] Myocardial response to pressure overload is different in women and men,[6,7,26] and it has been reported that female patients have a higher prevalence of normal geometry and concentric remodeling, while male patients show a higher rate of maladaptive remodeling (including concentric hypertrophy and eccentric hypertrophy) that eventually leads to LV dilation.[6,8] Women also typically have higher LVEF; however, little is known about the role of gender in LV remodeling in extreme age in the Japanese population.

In this study, aortic valve gradients, RWT, and LVMi were higher at baseline than those of the past studies.[6,11] Moreover, 89% of patients (male, 81%; female, 95%) displayed concentric hypertrophy before TAVI. One possible reason is that the patients' hearts in this Japanese cohort were small compared with the reference values in the ASE guidelines.[12,27] Moreover, concentric hypertrophy of the LV is considered to progress as AS patients grow older. We have demonstrated that men and women with severe AS and similar comorbidities remodel in different ways: women exhibited higher RWT with a smaller LV volume, while men were prone to the development of a larger LV volume and increased LVM. In the present study, we defined LV reverse remodeling as a reduction in LVESV of > 15%. The definition of LV reverse remodeling varies in the literature, but reduction in LVESV of > 15% after cardiac resynchronization therapy has been reported to be a valid measure of volume responders.[15] Incidence of LV reverse remodeling was significantly higher in men than in women after TAVI and was greatest in the patients with the highest LV volume at baseline. Similarly,

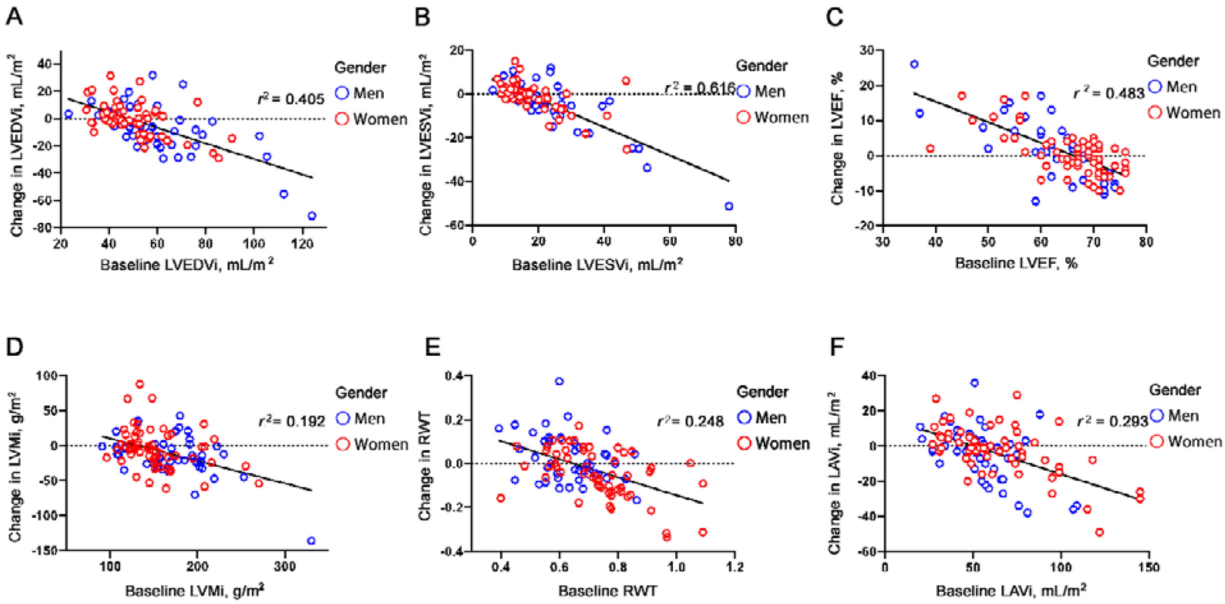

Figure 2. Relationship between cardiac reverse remodeling parameters after transcatheter aortic valve implantation and baseline parameters according to sex. **A:** Relationship between change in indexed left ventricular (LV) end-diastolic volume (LVEDVi) and baseline LVEDVi. **B:** Relationship between change in indexed LV end-systolic volume (LVESVi) and baseline LVESVi. **C:** Relationship between change in LV ejection fraction (LVEF) and baseline LVEF. **D:** Relationship between change in indexed LV mass (LVMi) and baseline LVMi. **E:** Relationship between change in relative wall thickness (RWT) and baseline RWT. **F:** Relationship between change in indexed left atrial volume (LAVi) and baseline LAVi.

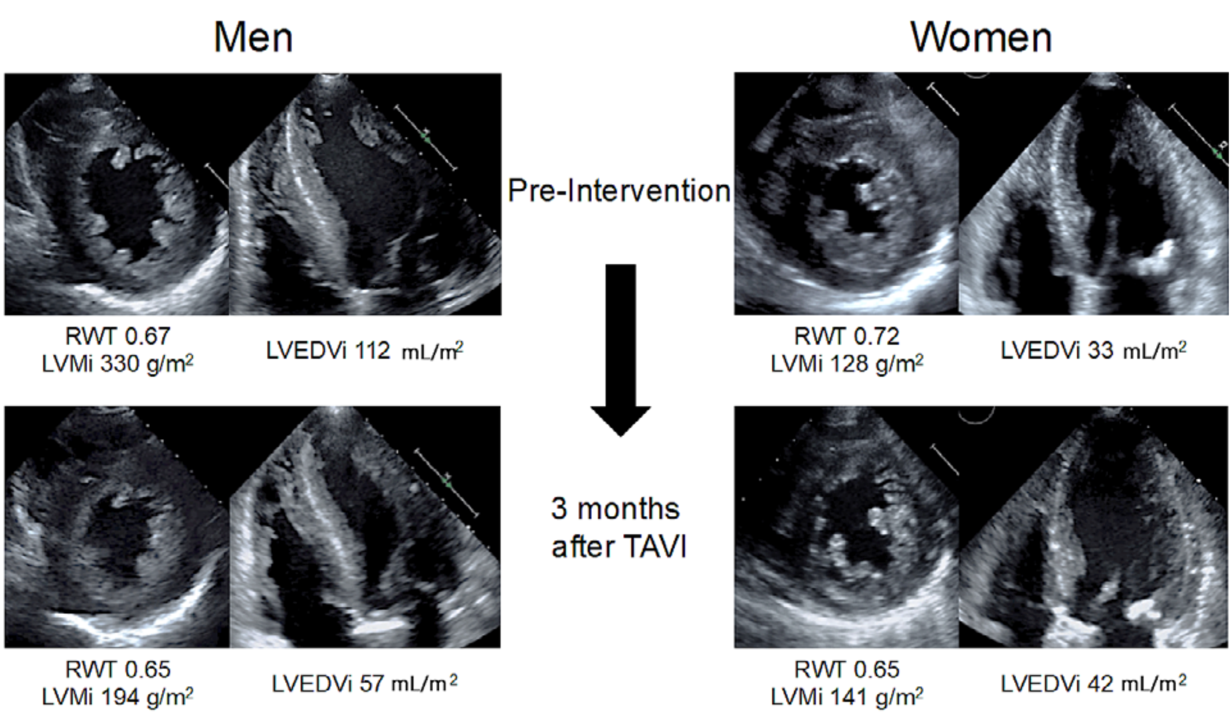

Figure 3. Short-axis and four-chamber echocardiographic images of the left ventricle before and after transcatheter aortic valve implantation (TAVI). The left-hand panel shows a typical male pattern of remodeling with increased left ventricular (LV) cavity size and greater LV mass at baseline (top image) and then reverse remodeling 3 months after TAVI (bottom image). The right-sided panel depicts a typical female ventricle in severe aortic stenosis (AS) with a lower LV mass and a small LV cavity size (top image) and subsequent large relative wall thickness (RWT) regression 3 months after TAVI (bottom image). LVEDVi, indexed LV end-diastolic volume; LVMi, indexed LV mass

the size of LA in men was significantly lower than that in women after TAVI. This may reflect a greater improvement in LV cavity pressure, transmitral gradient, and mitral valve tethering forces in men. On the other hand, RWT regression was seen only in women after TAVI. Thus, this study revealed that myocardial responses after TAVI differ between the sexes, as well as baseline characteristics.

Studies are currently underway to assess the benefits of expanding the use of TAVI to asymptomatic severe AS and moderate AS with reduced LVEF and are expected to have a positive outcome.[28,29] Cardiac and reverse remodeling will be different in the context of TAVI performed in these patient groups, which have a younger age. Our study results might be useful as a fundamental data in comparing reverse remodeling after the procedure for each indication of TAVI that can provide the most therapeutic effects in Japanese population.

Several limitations of our study must be considered. First, half (52%) of the original study population did not complete the study protocol, mainly due to geographical reasons. This may have introduced bias, although the analyzed population did not differ in terms of baseline characteristics from the original population. Further studies are needed to evaluate the LV reverse remodeling using the data of high follow-up rates. Second, echocardiography was performed for the assessment of LV remodeling instead of cardiac magnetic resonance (CMR), which is the golden standard for evaluating LV remodeling. Using an echocardiography-based approach to LV remodeling can lead to a potential underestimation of biological sex dimorphism in LV remodeling in AS.[6] However, CMR requires the suspension of respiration and gadolinium-based contrast agent. There are several factors that may limit the ability of the elderly patients to perform CMR, such as consistent breath-holds and renal dysfunction. Further studies are needed for evaluating LV remodeling using CMR. Third, the postprocedure scan was performed 3 months after TAVI. Although it is well documented that most of reverse remodeling occurs within the first 6 months,[30] this timepoint could still be too early to detect any subtle differences between the sexes. Stangl, *et al*. reported that LV reverse remodeling was observed both in men and women 3 months after TAVI, but improvement of LVEF was significant only in women.[11] Chen, *et al*. reported that women exhibited an early regression of LVMi.[31] In contrast, the regression of LVMi in men seemed to be more gradual and the significant regression of LVMi from baseline began to be observed since 3 months later after TAVI. Further studies are needed to evaluate the LV reverse remodeling using long-term follow-up data. Finally, because of the relatively small sample size, the study may be not sufficiently powered to assess all gender differences.

Conclusion

This study demonstrates that there are clear differences in the way that male and female hearts adapt to the pressure overload of AS despite similar comorbidities and valvular gradients. Sex-related differences of reverse remodeling after TAVI also differed, reflecting the pattern of remodeling in AS in extreme age in the Japanese population.

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The authors have no conflicts of interest to declare.

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