JAMA Cardiology | Original Investigation

Sex-Specific Association of Myocardial Fibrosis With Mortality in Patients With Aortic Stenosis

Soongu Kwak, MD; Anvesha Singh, MBChB, PhD; Russell J. Everett, MD, PhD; Thomas A. Treibel, MD, PhD; Jaehyun Lim, MD; Sungho Won, PhD; Michelle C. Williams, MD, PhD; Krithika Loganathan, MD; Rong Bing, MD; Neil Craig, MD; Trisha Singh, BM; Shruti Joshi, MBBS; Heesun Lee, MD; Whal Lee, MD, PhD; Yong-Jin Kim, MD, PhD; Calvin W. L. Chin, MD, PhD; Miho Fukui, MD, PhD; Tarique Al Musa, MD; Marzia Rigolli, MD; Lionel Tastet, MSc; Laura E. Dobson, MD; Stephanie Wiesemann, MD; Vanessa M. Ferreira, MD, DPhil; Gabriella Captur, MD, PhD; Sahmin Lee, MD, PhD; Jeanette Schulz-Menger, MD; Erik B. Schelbert, MD; Marie-Annick Clavel, DVM, PhD; Sung-Ji Park, MD, PhD; Costanza Pellegrini, MD; Martin Hadamitzky, MD; Bernhard L. Gerber, MD, PhD; David E. Newby, MD, PhD; Saul G. Myerson, MD; Phillipe Pibarot, DVM, PhD; João L. Cavalcante, MD; Gerry P. McCann, MBChB, MD; John P. Greenwood, MD, PhD; James C. Moon, MD; Marc R. Dweck, MD, PhD; Seung-Pyo Lee, MD, PhD

IMPORTANCE Myocardial fibrosis in aortic stenosis (AS) may exhibit sex differences. However, its prognostic significance in women with AS remains unclear.

OBJECTIVE To investigate sex differences in myocardial fibrosis assessed by cardiovascular magnetic resonance (CMR) and evaluate its prognostic value in women and men with AS.

DESIGN, SETTING, AND PARTICIPANTS Patients with severe AS who underwent CMR before aortic valve replacement (AVR) were prospectively enrolled from 13 international sites between March 2011 and September 2021. Myocardial fibrosis was evaluated using extracellular volume fraction (ECV%) and late gadolinium enhancement (LGE). The main analysis was conducted on patients without obstructive coronary artery disease (CAD), defined as those with no history of myocardial infarction and no concomitant coronary artery bypass grafting. Data were analyzed from December 2023 to February 2024.

EXPOSURES Surgical or transcatheter AVR.

MAIN OUTCOMES AND MEASURES The primary outcome was post-AVR all-cause mortality and the secondary outcome was cardiovascular mortality.

RESULTS Of 822 patients, 670 were without obstructive CAD (368 men [55%] and 302 women [45%]). Among these, women and men had a similar age (median, 72 years vs 71 years, respectively), comorbidities, and AS severity. ECV% was similar between sexes; however, women had less LGE (both infarct and noninfarct LGE). After a median follow-up of 3.7 (IQR, 2.1-4.7) years, there were 76 deaths (11.3%), including 29 adjudicated cardiovascular deaths, in patients without obstructive CAD. Increasing ECV% and LGE were associated with higher all-cause and cardiovascular mortality in both sexes. Cox analyses demonstrated that both ECV% and LGE were associated with higher all-cause mortality without significant interaction by sex (women: adjusted hazard ratio [HR], 1.08 per 1% ECV% increase; 95% CI, 1.04-1.12; $P < .001$; men: adjusted HR, 1.01; 95% CI, 0.96-1.06; $P = .66$; P for interaction by sex = .09 and women: adjusted HR, 2.49 for the presence of LGE; 95% CI, 1.07-5.80; $P = .03$; men: adjusted HR, 1.82; 95% CI, 1.00-3.32; $P = .04$; P for interaction by sex = .68). In the entire population (n = 822), both noninfarct and infarct-related LGE were associated with increased mortality without significant interaction by sex.

CONCLUSIONS AND RELEVANCE In this study, patients with severe AS who underwent AVR exhibited similar ECV% between sexes, while women had lower LGE. Increased myocardial fibrosis provided important prognostic value for both sexes.

JAMA Cardiol. doi:10.1001/jamacardio.2024.5593
Published online February 19, 2025.

Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Seung-Pyo Lee, MD, PhD, Division of Cardiology, Department of Internal Medicine, Seoul National University Hospital, 101, Daehak-ro, Jongno-gu, Seoul 03080, South Korea (sproll1@snu.ac.kr); Marc R. Dweck, MD, PhD, British Heart Foundation Centre for Cardiovascular Science, University of Edinburgh, 47 Little France Crescent, Edinburgh EH16 4TJ, United Kingdom (marc.dweck@ed.ac.uk).

Aortic stenosis (AS) contributes to major morbidity and mortality globally.[1] Chronic pressure overload by valvular stenosis induces left ventricular (LV) hypertrophy, thus, maintaining cardiac performance. Over time, this hypertrophic response decompensates due to progressive myocyte death and myocardial fibrosis, ultimately leading to the development of symptoms, heart failure, and adverse events.[2,3]

Cardiovascular magnetic resonance (CMR) allows the noninvasive detection and quantification of myocardial fibrosis in patients with AS. Replacement fibrosis associated with AS can be detected by the presence of noninfarct late gadolinium enhancement (LGE) and quantified as the percentage of myocardial mass comprising LGE (LGE%). Noninfarct LGE represents a distinctive form of replacement fibrosis in AS, differing from the fibrosis pattern observed in myocardial ischemia.[2] Alternatively, diffuse interstitial fibrosis and noninfarct replacement fibrosis can be assessed with extracellular volume fraction (ECV%) using precontrast and postcontrast T1-mapping. Both ECV% and LGE provide prediction of subsequent mortality in patients with AS.[4-9] There is considerable interest in using these CMR assessments of myocardial fibrosis as objective markers of LV decompensation in AS,[10] which could be used to trigger decisions regarding early aortic valve replacement (AVR). Indeed, this strategy has been recently evaluated in a randomized trial,[11] with continued efforts to further assess its potential.

Sex-related differences in myocardial remodeling and fibrosis in patients with AS remain poorly defined. Existing LGE and T1-mapping studies in patients with AS have included relatively few women[12-14] and have provided contrasting results regarding whether women develop more or less myocardial fibrosis than men.[12-16] More importantly, large outcome studies investigating the prognostic role of fibrosis in women with AS are lacking.[15] Considering the significant sex differences in AS and its outcomes following AVR,[17-19] larger data that have the power to establish the prognostic role of these markers, in women as well as men, are required.

This international multicenter study aimed to address these issues in a large population of male and female patients with severe AS undergoing CMR prior to AVR. The aims were to investigate sex differences in myocardial fibrosis and LV remodeling in patients with severe AS and the prognostic role of ECV% and LGE in women.

Key Points

Question Are there sex-related differences in the extent of myocardial fibrosis in aortic stenosis (AS) and does myocardial fibrosis provide important prognostic information in both women and men?

Findings In this study, women with severe AS had a similar extracellular volume fraction but less replacement fibrosis compared with men. Both extracellular volume fraction and replacement fibrosis were associated with increased post–aortic valve replacement mortality in women as well as in men.

Meaning These results demonstrated that noninvasive fibrosis assessment using cardiovascular magnetic resonance may improve risk stratification and decision-making in both women and men with AS.

Methods

Cohort Characteristics

Our prospective cohort study consisted of patients with severe AS awaiting AVR across 13 different international sites in Belgium, Canada, Germany, South Korea, the United Kingdom, and the US. The cohort characteristics have been previously described[5,6] and the details of each site's enrollment period, inclusion criteria, and type of intervention are summarized in eTable 1 in Supplement 1. At all sites, patients scheduled for surgical or transcatheter AVR for severe AS between 2011 and 2021 were prospectively enrolled and all patients underwent CMR with T1-mapping shortly before their scheduled AVR (median time interval, 8 days). Patients were included irrespective of whether the aortic valve was tricuspid or bicuspid. Exclusion criteria were severe kidney dysfunction (estimated glomerular filtration rate less than 30 mL/min/1.73 m^2), presence of an implantable cardiac device, any prior heart valve surgery or intervention, and confirmed diagnosis of infiltrative cardiomyopathy, including cardiac amyloidosis.

The study complies with the Declaration of Helsinki, and the local institutional review boards approved the protocol. This study adheres to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines. Written informed consent was obtained from all participants.

Data Collection and Variable Definitions

Patients' clinical and echocardiography data were collected at the time of recruitment. Body surface area was calculated by the Mosteller formula. The predicted surgical mortality risk of AVR was calculated by the Society of Thoracic Surgeons score.[20,21] AS severity was assessed using echocardiography and according to contemporary guidelines.[22-24]

CMR

All participants underwent CMR shortly before AVR. Details of the scanners, T1-mapping pulse sequences, and field strengths by each participating center have been summarized (eTable 2 in Supplement 1). As previously reported,[5,6] standard long-axis views and short-axis cine stacks were acquired. LGE images were acquired 10 to 20 minutes after intravenous gadolinium contrast administration. Short-axis T1-mapping sequences were acquired at the midcavity level before and 10 to 20 minutes after contrast injection.

CMR images were transferred to the central core laboratory via a web-based storage cloud or an external hard drive. All images were analyzed with cvi42 software (Circle Cardiovascular Imaging), following a prespecified protocol by experienced cardiologists and technicians. All observers were blinded to the patients' clinical information and outcomes. Detailed methods of CMR image analysis are described in the eMethods in Supplement 1.

T1-mapping analysis was performed in the midinferoseptum of the LV as previously described.[5] Any infarct-related LGE

Table 1. Baseline Characteristics by Sex in Patients Without Obstructive Coronary Artery Disease

Characteristic	Median (IQR)		*P* value
	Women (n = 302)	Men (n = 368)	
Age, y	72 (64-79)	71 (64-78)	.34
Body mass index[a]	26.1 (23.5-30.3)	26.3 (23.7-29.4)	.87
Body surface area, m^2	1.69 (1.56-1.83)	1.91 (1.76-2.06)	<.001
Systolic blood pressure, mm Hg	130 (118-141)	128 (116-140)	.45
Diastolic blood pressure, mm Hg	72 (65-80)	72 (64-80)	.64
NYHA functional class, No. (%)[b]			
I	53 (19.6)	99 (30.1)	.02
II	113 (41.7)	129 (39.2)	
III	93 (34.3)	92 (28.0)	
IV	12 (4.4)	9 (2.7)	
Hematocrit, %	38.0 (35.5-40.2)	40.4 (37.6-43.0)	<.001
STS score	1.7 (1.2-2.5)	1.2 (0.8-1.8)	<.001
Medical history, No. (%)			
Atrial fibrillation	33 (10.9)	45 (12.2)	.69
Diabetes	66 (21.9)	80 (21.7)	>.99
Hypertension	161 (53.3)	178 (48.4)	.35
Aortic valve indices			
Mean pressure gradient, mm Hg	49.0 (41.0-63.0)	50.0 (40.2-62.0)	.95
Peak aortic jet velocity, m/s	4.6 (4.1-5.1)	4.5 (4.1-5.0)	.89
Aortic valve area index, cm^2/m^2	0.4 (0.3-0.5)	0.4 (0.3-0.5)	.91
Bicuspid aortic valve, No. (%)[c]	83 (32.8)	119 (39.9)	.10
Intervention received, No. (%)			
Isolated surgical AVR	225 (74.5)	283 (76.9)	.53
Transcatheter AVR	77 (25.5)	85 (23.1)	
Left heart structure and function			
Left atrial volume,[d] mL/m^2	46.4 (36.1-57.6)	46.8 (36.6-59.7)	.81
LV end-diastolic volume, mL/m^{2d}	61.7 (47.3-77.7)	69.3 (51.8-89.7)	<.001
LV end-systolic volume, mL/m^{2d}	16.1 (10.3-27.3)	20.8 (13.4-36.3)	<.001
LV stroke volume, mL/m^{2d}	42.3 (32.5-50.8)	44.7 (33.1-55.0)	.05
LV ejection fraction, %	71.8 (61.8-79.0)	65.6 (56.0-76.0)	<.001
Maximal wall thickness, mm	15.0 (13.0-17.0)	17.0 (14.8-19.0)	<.001
LV mass, g/m^{2d}	79.1 (67.4-98.5)	94.8 (79.8-119.0)	<.001
LV mass/volume ratio	1.35 (1.05-1.64)	1.43 (1.14-1.77)	.01
Right heart structure and function			
RV end-diastolic volume, mL/m^{2d}	54.7 (44.1-65.7)	62.4 (49.8-74.8)	<.001
RV end-systolic volume, mL/m^{2d}	21.1 (15.6-27.0)	26.0 (19.7-33.4)	<.001
RV stroke volume, mL/m^{2d}	34.2 (23.4-42.7)	35.3 (21.5-46.7)	.16
RV ejection fraction, %	62.7 (49.2-70.0)	57.0 (43.2-67.0)	<.001
Myocardial characteristics, No. (%)			
ECV%	27.5 (24.8-29.8)	26.8 (24.7-29.4)	.55
Any LGE	90 (29.8)	184 (50.0)	<.001
Noninfarct LGE	80 (26.5)	156 (42.4)	<.001
Infarct-related LGE	10 (3.3)	28 (7.6)	.03
LGE% among patients with LGE	0.8 (0.3-2.2)	1.2 (0.5-2.4)	.07

Abbreviations: AVR, aortic valve replacement; ECV%, extracellular volume fraction; LGE, late gadolinium enhancement; LGE%, late gadolinium enhancement percentage; LV, left ventricle; NYHA, New York Heart Association; RV, right ventricle; STS, Society of Thoracic Surgery.

[a] Calculated as weight in kilograms divided by height in meters squared.

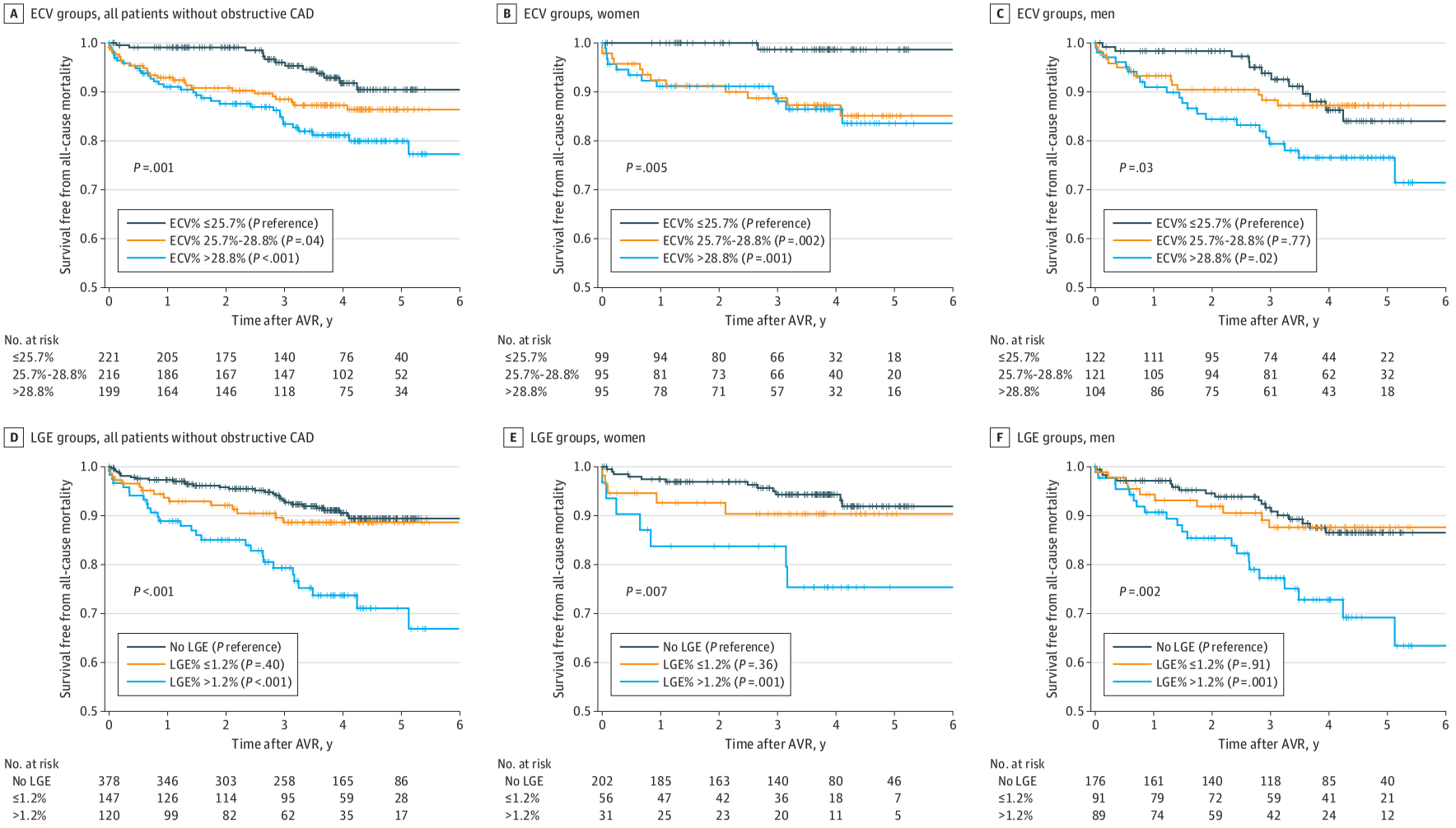
[b] Data available in 90% of study patients.

[c] Data available in 82% of study patients.

[d] Indexed to body surface area.

regions were excluded, but noninfarct LGE was included in the T1-mapping analysis, according to guideline recommendations.[25] The ECV% was calculated conventionally using the hematocrit and blood and myocardial T1 values as follows: ECV% = (100 − hematocrit [%]) × (T1 postmyocardium^{-1} − T1 premyocardium^{-1}) / (T1 postblood^{-1} − T1 preblood^{-1}). ECV% has been shown to have reliable reproducibility in patients with AS[26] and favorable interobserver variability for ECV% measurements in this cohort has been previously reported.[5] The presence of LGE was recorded across the entire short-axis stacks of the LV and

Figure 1. All-Cause Mortality After Aortic Valve Replacement (AVR) Stratified by Myocardial Fibrosis and Sex in Patients Without Obstructive Coronary Artery Disease (CAD)



Cumulative survival after AVR according to extracellular volume fraction (ECV%) groups (25.7% or less, more than 25.7 and 28.8 or less, and more than 28.8%) in all patients without obstructive CAD (A), women (B), and men (C). Cumulative survival after AVR according to late gadolinium enhancement (LGE) groups (no LGE; LGE percentage [LGE%]) 1.2% or less and LGE% more than 1.2%) in all patients without obstructive CAD (D), women (E), and men (F). The *P* value for pairwise comparison with the ECV% 25.7% or less group or no LGE group is shown.

Table 2. Association of Extracellular Volume Fraction (ECV%) and Late Gadolinium Enhancement (LGE) With the Risk of Mortality After Aortic Valve Replacement According to Sex in Patients Without Obstructive Coronary Artery Disease (CAD)

	All patients without obstructive CAD (n = 670)		Women (n = 302)		Men (n = 368)		*P* value for interaction by sex
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	
ECV%, per 1% increase							
Univariable analysis	1.05 (1.02-1.08)	<.001	1.06 (1.03-1.10)	<.001	1.03 (0.99-1.07)	.19	.20
Multivariable analysis[a]	1.04 (1.01-1.08)	.01	1.08 (1.04-1.12)	<.001	1.01 (0.96-1.06)	.66	.09
Presence of LGE							
Univariable analysis	2.16 (1.37-3.42)	.001	2.40 (1.08-5.34)	.03	1.81 (1.03-3.19)	.04	.55
Multivariable analysis[b]	2.25 (1.39-3.65)	<.001	2.49 (1.07-5.80)	.03	1.82 (1.00-3.32)	.04	.68
LGE%, per 1% increase							
Univariable analysis	1.11 (1.04-1.17)	<.001	1.13 (1.01-1.27)	.04	1.09 (1.02-1.16)	.02	.58
Multivariable analysis[b]	1.04 (0.99-1.10)	.14	1.10 (0.98-1.25)	.11	1.04 (0.97-1.11)	.31	.61

Abbreviations: HR, hazard ratio; LGE%, late gadolinium enhancement percentage; LV, left ventricle.

[a] Adjusted for age (years), type of intervention received, LV ejection fraction (less than 50%), and the presence of LGE.

[b] Adjusted for age (years), type of intervention received, LV ejection fraction (less than 50%), and extracellular volume fraction.

the LGE pattern was classified as either noninfarct LGE or infarct-related LGE when present. LGE was considered infarct related when located in the subendocardial or transmural myocardium, aligning with a coronary artery territory. Conversely, noninfarct LGE was defined as LGE not compatible with infarct-related LGE, typically presenting as focal, patchy, or diffuse patterns in the mid-wall of the LV (eFigure 1 in Supplement 1).[2] In this study, a small number of patients (n = 23 [2.8%]) had both noninfarct LGE and infarct-related LGE, and these patients were classified as having noninfarct LGE to focus on the prognostic role of AS-related replacement fibrosis. Regions of LGE were delineated using a semiautomated process, identifying pixels within the myocardium with a signal intensity exceeding 5 SDs of the normal remote myocardium. LGE% was calculated as the percentage of the total LGE mass divided by the myocardial mass.

Outcome Assessment

Patients were followed up with from the date of AVR to the last clinical follow-up visit or death. The primary outcome was all-cause mortality after the AVR. Mortality data were ascertained by the official national death records or official medical records obtained by each study center, as well as reports from family members, where available, to ensure validity. The secondary outcome was cardiovascular death, defined as death attributed to sudden cardiac arrest, myocardial infarction, heart failure, infective endocarditis, or cerebrovascular events.

Statistical Analysis

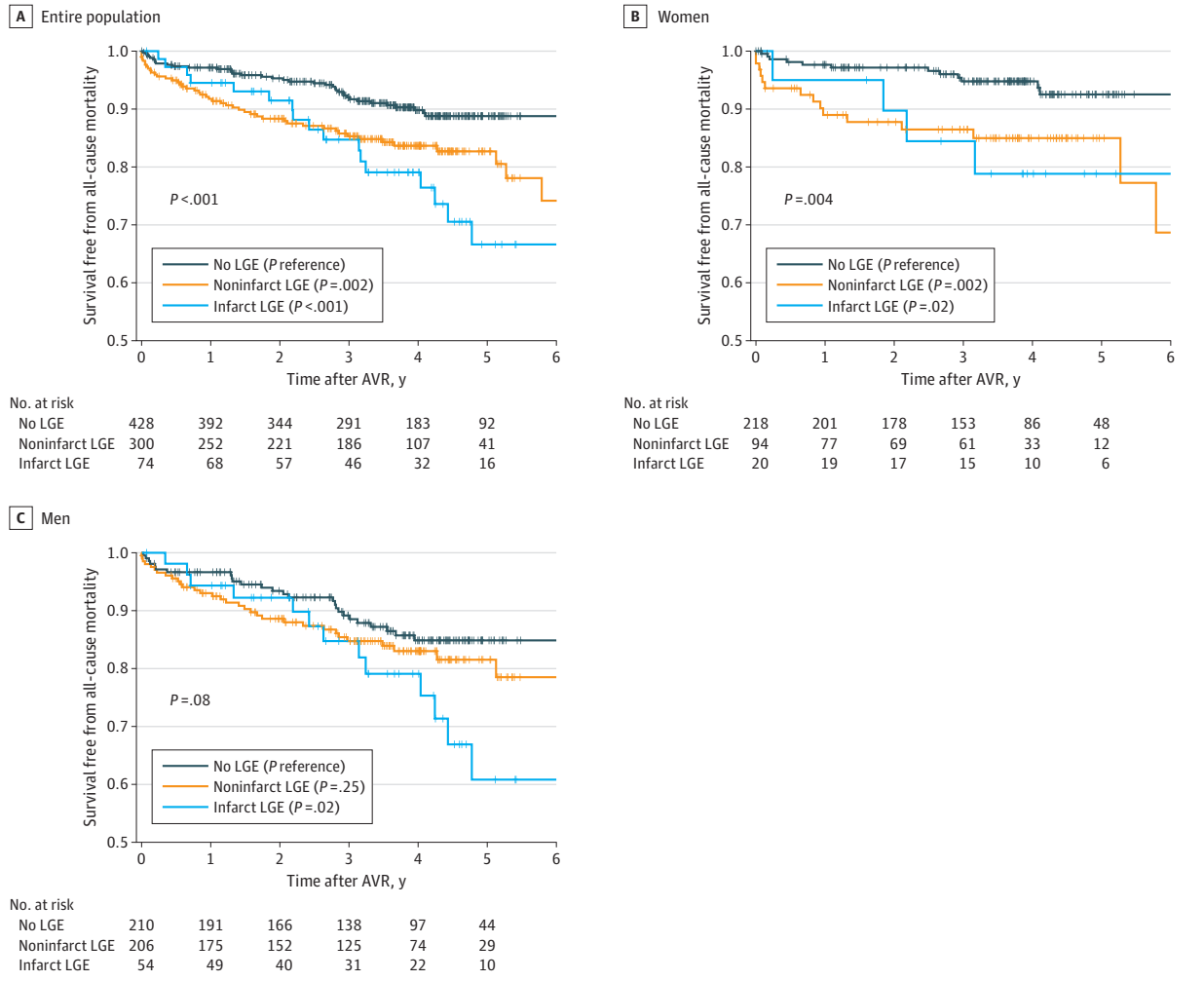
The main study analysis was conducted specifically in patients without evidence of obstructive coronary artery disease (CAD) (n = 670), defined as those with no history of myocardial infarction and no concomitant coronary artery bypass grafting (CABG), to minimize the potential influence of obstructive CAD. For the analysis of LGE types (infarct and noninfarct), the entire population was used to evaluate both types.

Continuous variables were expressed as median values with IQRs and categorical variables as counts and percentages. Comparisons between the groups were performed using the Kruskal-Wallis test for continuous variables and the χ^2 test for categorical variables. Kaplan-Meier survival curves were plotted by groups of ECV% and LGE. ECV% was categorized into 3 groups according to the tertile values across the entire population (25.7% or less, more than 25.7% and 28.8% or less, and more than 28.8%). For LGE, patients were categorized according to its presence and those with LGE were again dichotomized according to the median value of LGE% (1.2% or less and more than 1.2%). Given that ECV% and LGE% already account for body size, indexing was not required for these parameters. The comparison of survival between groups was performed using the log-rank test. Cox proportional hazards regression analysis was used to evaluate the association of ECV% and LGE with mortality risk, that was reported as a hazard ratio (HR) and 95% CI. Multivariable Cox analysis for ECV% was adjusted for age, type of intervention, LV systolic dysfunction (ejection fraction less than 50%), and the presence of LGE. Similarly, the analysis for the presence of LGE or LGE% was adjusted for age, type of intervention, LV systolic dysfunction, and ECV%. The difference in risks between men and women was tested in the Cox models using the interaction term. For the analysis of the cardiovascular mortality end point, we performed 2 separate analyses, in which nonadjudicated causes of death were either censored or classified as cardiovascular mortality, respectively.

A sensitivity analysis was performed after excluding patients with an LV ejection fraction less than 50% among those without obstructive CAD. Another sensitivity analysis was conducted after excluding patients with infarct-related LGE from the entire cohort. Subgroup analyses were also performed based on the interventions received.

A 2-tailed $P < .05$ was considered statistically significant. All analyses were performed using R version 4.3.0 (The R Project).

Figure 2. All-Cause Mortality After Aortic Valve Replacement (AVR) According to Patterns of Late Gadolinium Enhancement (LGE) and Sex in the Entire Study Population



Cumulative survival after AVR according to the patterns of LGE (no LGE, noninfarct LGE, infarct-related LGE) in the entire population (A), women (B), and men (C). The *P* value for pairwise comparison with no LGE group is shown.

Results

Clinical Characteristics by Sex

The entire population comprised a total of 822 patients with severe AS undergoing AVR, including 342 women (41.6%) and 480 men (58.4%) (eTable 3 in Supplement 1). Patients underwent isolated surgical AVR (n = 537 [65.3%]), surgical AVR with CABG (n = 109 [13.3%]), or transcatheter AVR (n = 176 [21.4%]). Women and men had similar AS severity, age, and body mass index. Women were more symptomatic compared with men. The proportions of women and men with atrial fibrillation, diabetes, and hypertension were also similar, although women had higher Society of Thoracic Surgeons Predicted Risk of Mortality scores (median, 1.8 vs 1.3; $P < .001$).

Of 670 patients without evidence of obstructive CAD, 302 were women and 368 were men (**Table 1**). Similar to the entire cohort, women had a similar age and comorbidities compared with men, with women having more advanced symptoms and higher Society of Thoracic Surgeons scores.

CMR Assessment of Myocardial Remodeling by Sex

The distribution of ECV% and LGE% showed little variation across the participating centers (eFigure 2 in Supplement 1). Despite similar burdens of comorbidities and AS severity, the maximal LV wall thickness, LV mass index, and LV mass to volume ratio were lower in women than in men, both in the entire population and in patients without obstructive CAD (eTable 3 in Supplement 1; Table 1). Compared with men, women had smaller LV volumes, higher LV ejection fractions, and consequently similar LV stroke volume indices, with similar patterns seen for right ventricular assessments. Although ECV% was similar between women and men, LGE was less frequently observed in women than in men irrespective of its pattern in the entire population (eTable 3 in Supplement 1). Similar findings were observed in patients without obstructive CAD

Table 3. Association of the Patterns of Late Gadolinium Enhancement (LGE) With Mortality Risk After Aortic Valve Replacement According to Sex in the Entire Population

	Entire population (n = 822)		Women (n = 342)		Men (n = 480)		*P* value for interaction by sex
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	
Univariable analysis							
No LGE	1 [Reference]	NA	1 [Reference]	NA	1 [Reference]	NA	NA
Noninfarct LGE	1.95 (1.27-2.99)	.002	3.17 (1.48-6.78)	.003	1.38 (0.82-2.32)	.22	.08
Infarct-related LGE	2.66 (1.50-4.71)	<.001	3.36 (1.08-10.43)	.04	2.09 (1.08-4.07)	.03	.47
Multivariable analysis[a]							
No LGE	1 [Reference]	NA	1 [Reference]	NA	1 [Reference]	NA	NA
Noninfarct LGE	1.80 (1.16-2.80)	.01	2.77 (1.25-6.12)	.01	1.30 (0.76-2.23)	.34	.18
Infarct-related LGE	1.76 (0.95-3.26)	.07	3.83 (1.19-12.33)	.02	1.17 (0.56-2.42)	.68	.21

Abbreviations: HR, hazard ratio; NA, not applicable.

[a] Adjusted for age (years), type of intervention received, LV ejection fraction (less than 50%), and extracellular volume fraction.

(women vs men: ECV% median, 27.5% vs 26.8%; *P* = .55; any LGE, 29.8% vs 50.0%; *P* < .001; noninfarct LGE, 26.5% vs 42.4%, *P* < .001; infarct-related LGE, 3.3% vs 7.6%, *P* = .03) (Table 1).

In both the entire population and patients without obstructive CAD, higher ECV% and LGE were associated with other markers of LV decompensation in both sexes, including increased LV end-systolic volume index, decreased LV ejection fraction, and increased LV mass index (eFigure 3 and eFigure 4 in Supplement 1).

Myocardial Fibrosis and Mortality

During a median of 3.7 (IQR, 2.1-4.7) years follow-up, there were 103 deaths in the entire population (12.5%). Among these, a definitive cause of death was available in 75 cases with 39 attributed to cardiovascular causes. Overall survival was higher in women (32 deaths [9.4%]) than in men (71 deaths [14.8%]; *P* = .02), while survival rate free from cardiovascular mortality was similar between sexes (eFigure 5 in Supplement 1). Among patients without obstructive CAD, there were 76 deaths (11.3%), including 29 adjudicated cardiovascular deaths. Similarly, survival was higher in women, but cardiovascular mortality remained comparable between sexes (eFigure 5 in Supplement 1).

All-cause and cardiovascular mortality increased with higher levels of ECV% or LGE in both sexes in the entire population (eFigure 6 and eFigure 7 in Supplement 1). Among patients without obstructive CAD, higher ECV% and LGE were again associated with a greater incidence of all-cause mortality in both sexes (**Figure 1**), as well as cardiovascular mortality (eFigure 8 in Supplement 1). A similar trend was consistently observed after further excluding patients with reduced LV ejection fraction (less than 50%) (eFigure 9 in Supplement 1).

In the univariable Cox analysis, both ECV% and LGE were associated with mortality in the entire population, with no significant interaction by sex (*P* > .05) (eTable 4 in Supplement 1). Similar findings were observed for cardiovascular mortality (eTable 5 in Supplement 1). The prognostic association persisted in women after adjustment for multiple covariates, without significant interaction by sex. The Cox analyses for patients without obstructive CAD are shown in **Table 2**. Both ECV% and LGE were consistently associated with a higher risk of all-cause mortality across all patients, even after adjustment for multiple covariates, without significant interaction by sex (women: adjusted HR, 1.08 per 1% increase in ECV%; 95% CI, 1.04-1.12; *P* < .001; men: adjusted HR, 1.01; 95% CI, 0.96-1.06; *P* = .66; *P* for interaction by sex = 0.09) (women: adjusted HR, 2.49 by the presence of LGE; 95% CI, 1.07-5.80; *P* = .03; men: adjusted HR, 1.82; 95% CI, 1.00-3.32; *P* = .04; *P* for interaction by sex = 0.68) (Table 2).

In the entire population, categorization of LGE by its cause demonstrated higher mortality in women with an infarct or noninfarct pattern and men with an infarct pattern compared with those without LGE (**Figure 2**). Noninfarct LGE was a significant risk factor for mortality in the multivariable Cox model, without significant interaction by sex (women: adjusted HR, 2.77; 95% CI, 1.25-6.12; *P* = .01; men: adjusted HR, 1.30; 95% CI, 0.76-2.23; *P* = .34; *P* for interaction by sex = .18) (**Table 3**).

Sensitivity and Subgroup Analysis

Among 306 women and 399 men without infarct-related LGE, ECV% was comparable between the sexes, while the prevalence of noninfarct LGE was significantly higher in men (eTable 6 in Supplement 1). In this population, a higher ECV% and LGE% were again associated with a higher mortality rate in women as well as men (eTable 7 and eFigure 10 in Supplement 1).

A subgroup analysis by type of intervention was performed (eTable 8 in Supplement 1) and showed similar prognostic associations in patients undergoing surgical AVR with or without CABG (eTable 9 in Supplement 1). In patients who underwent transcatheter AVR, ECV% was significantly associated with mortality, but LGE was not (eTable 10 in Supplement 1).

Discussion

In this large international multicenter study of patients with severe AS undergoing AVR, we demonstrated that, in a cohort well-balanced for age and comorbidities, women had similar ECV%, less replacement fibrosis, and lower overall mortality than men. The extent of fibrosis was associated with LV decompensation and increased mortality in both sexes, with-

out significant interaction by sex. These findings remained consistent after excluding those with evidence of obstructive CAD. We concluded that assessments of myocardial fibrosis are of major interest as markers of LV decompensation and prognosis, irrespective of sex, and may help optimize the timing of valve replacement in women as well as men.

We presented, to our knowledge, the largest sex-specific CMR study in AS, investigating both ECV% and LGE in patients with severe AS undergoing AVR, representing the largest cohort of female participants reported to date. All patients were imaged just prior to AVR, ensuring that patients were studied at a similar time point in their disease course. An important strength in this study, compared with previous ones,[12,13,15] is that women and men were well balanced in terms of age, AS severity, and comorbidities, thereby minimizing the influence of many potential confounders and allowing us to compare patterns of remodeling and fibrosis by sex and link these observations with subsequent patient survival.

Similar to previous studies, we observed that women with AS have smaller hearts and lower wall thickness, LV mass, and LV mass to volume ratio than men but have higher LV ejection fractions.[12-16] A higher prevalence of LV hypertrophy in men than in women has been reported,[13,14] which may indicate more maladaptive LV remodeling associated with AS in men. Previous studies have provided conflicting data with respect to the extent of myocardial fibrosis by sex, particularly ECV%, probably due to a small sample size and variability in study populations and comorbidities.[12-14] Here, we investigated a large cohort that included 342 women with ages and comorbidity similar to those of men, demonstrating that women are less likely to have LGE than men at the time of AVR, whereas ECV%, a marker of both interstitial and noninfarct replacement fibrosis, was similar between the sexes. Both types of fibrosis markers are closely related to LV decompensation and increased mortality, irrespective of sex. Notably, even after excluding patients with evidence of obstructive CAD, the prevalence of LGE remained consistently lower in women. The exact mechanism underlying the sex differences in the extent of myocardial fibrosis remains unclear. Several studies have suggested a significant role of endogenous sex hormones and imbalances in these hormones, particularly testosterone, in the development of myocardial fibrosis in both animal and human models.[27,28] This may be one of the reasons why men have more hypertrophy and higher levels of replacement fibrosis.

There are very few studies investigating the association of myocardial fibrosis with hard clinical outcomes in women with AS. Replacement fibrosis, as assessed by LGE, was previously reported to be associated with worse post-AVR survival in 249 women with severe AS.[15] However, little is known about the prognostic power of ECV% in women with AS and existing T1-mapping studies that investigated sex differences did not have outcome data or included insufficient numbers of women.[12-14] Here, we demonstrated that both ECV% and LGE were prognostic in a large group of women (n = 342) and remained independent predictors of death after multivariable adjustments. Even a modest burden of ECV% (middle tertile) was associated with a higher incidence of mortality in women, while women in the lowest ECV% tertile exhibited a particularly favorable prognosis. Together, this implies that myocardial fibrosis markers may serve as particularly powerful and sensitive prognostic indicators in women with AS.

Our study has important potential clinical implications. Our data highlight important sex differences in LV remodeling in AS and provide a notable advance in our understanding of how the ventricle starts to decompensate in men and women with AS. In particular, we have demonstrated that women have more favorable patterns of remodeling and less replacement myocardial fibrosis than men while having similar degrees of ECV%. This lower burden of replacement fibrosis appeared to translate into a better prognosis for women than men, at least in this patient population where age, AS severity, and comorbidities were well balanced between the sexes. Indeed, we have here confirmed the prognostic information provided by myocardial fibrosis, not only in the cohort as a whole but also in women when considered in isolation. This confirms the findings of previous studies in populations that were dominated by men.[5,9,15] While the efficacy of early AVR in patients with asymptomatic severe AS with midwall LGE was not demonstrated in a recent randomized trial, potential benefits were suggested, including a reduction in unplanned AS-related hospitalizations and symptom improvement.[11] Notably, the trial included a limited number of women (28%), highlighting the need for a larger study with sufficient power to evaluate the efficacy of this strategy in both sexes. Considering the differing propensity for reversibility between the 2 types of fibrosis,[29,30] detailed myocardial phenotyping using both markers may help identify optimal candidates for early intervention in both sexes.

Limitations

Our study has several limitations. First, although, to our knowledge, this study is by far the largest CMR study of patients with severe AS to date, our findings could be influenced by potential selection bias and unmeasured confounders. Second, the mechanism underlying these sex differences cannot be examined in our study, which needs to be investigated in future studies. Third, more information on hard clinical outcomes, including heart failure hospitalizations, was not available, and the cause of mortality could be adjudicated in 73% of the mortality cases. Lastly, our cohort focused on patients with severe AS scheduled for AVR. While this facilitated comparisons between the sexes in patients with similar disease severity, our results may require further validation in patients with less severe AS.[31]

Conclusions

In patients with severe AS undergoing AVR, women have less wall thickening, hypertrophy, and replacement myocardial fibrosis than men, but have similar ECV%. Myocardial fibrosis provides significant prognostic information in both men and women with AS undergoing AVR. Noninvasive fibrosis assessment using CMR may improve risk stratification and decision-making in women as well as men with AS.

ARTICLE INFORMATION

Accepted for Publication: December 13, 2024.

Published Online: February 19, 2025. doi:10.1001/jamacardio.2024.5593

Author Affiliations: Department of Internal Medicine, Seoul National University Hospital, Seoul, South Korea (Kwak, Lim, H. Lee, Kim, S.-P. Lee); Department of Cardiovascular Sciences, University of Leicester and the NIHR Leicester Biomedical Research Centre, Glenfield Hospital, Leicester, United Kingdom (A. Singh, McCann); British Heart Foundation Centre for Cardiovascular Science, University of Edinburgh, Edinburgh, United Kingdom (Everett, Williams, Loganathan, Bing, Craig, T. Singh, Joshi, Newby, Dweck); Barts Health NHS Trust and University College London, London, United Kingdom (Treibel, Moon); Department of Public Health Sciences, Seoul National University, Seoul, South Korea (Won); Department of Radiology, Seoul National University Hospital, Seoul, Korea (W. Lee); Department of Internal Medicine, Seoul National University College of Medicine, Seoul, South Korea (Kim, S.-P. Lee); National Heart Center Singapore, Singapore (Chin); Cardiovascular Imaging Research Center and Core Lab, Minneapolis Heart Institute Foundation, Minneapolis, Minnesota (Fukui, Cavalcante); Leeds Institute for Cardiovascular and Metabolic Medicine, University of Leeds, Leeds, UK and Baker Heart and Diabetes Institute & Monash University, Melbourne, Australia (Al Musa, Dobson, Greenwood); University of Oxford Centre for Clinical Magnetic Resonance Research, BHF Centre of Research Excellence (Oxford), NIHR Biomedical Research Centre (Oxford), Oxford, United Kingdom (Rigolli, Ferreira, Myerson); Institut Universitaire de Cardiologie et de Pneumologie de Québec/Québec Heart and Lung Institute, Université Laval, Québec city, Québec, Canada (Tastet, Clavel, Pibarot); Charité Campus Buch ECRC and Helios Clinics Cardiology Germany, DZHK partner site, Berlin, Germany (Wiesemann, Schulz-Menger); Inherited Heart Muscle Disease Clinic, Department of Cardiology, Royal Free Hospital, NHS Foundation Trust, London, United Kingdom (Captur); Division of Cardiology, Asan Medical Center Heart Institute, University of Ulsan College of Medicine, Seoul, South Korea (S. Lee); Allina Health Minneapolis Heart Institute, Minneapolis, Minnesota (Schelbert, Cavalcante); Division of Cardiology, Department of Medicine, Cardiovascular Imaging Center, Heart Vascular Stroke Institute, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea (Park); Department of Cardiology, German Heart Center Munich, Munich, Germany (Pellegrini); Department of Radiology and Nuclear Medicine, German Heart Center Munich, Munich, Germany (Hadamitzky); Division of Cardiology, Department of Cardiovascular Diseases, Cliniques Universitaires St Luc and Institut de Recherche Cardiovasculaire (IREC), Université Catholique de Louvain (UCLouvain), Brussels, Belgium (Gerber); Center for Precision Medicine, Seoul National University Hospital, Seoul, South Korea (S.-P. Lee).

Author Contributions: Drs Dweck and S.P. Lee had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs Dweck and S.P. Lee contributed equally as last co-author.

Concept and design: Kwak, Williams, H. Lee, W. Lee, Kim, Captur, Schulz-menger, Pellegrini, Pibarot, Moon, Dweck, SP Lee.
Acquisition, analysis, or interpretation of data: Kwak, A. Singh, Everett, Treibel, Lim, Won, Williams, Loganath, Bing, Craig, T. Singh, Joshi, W. Lee, Chin, Fukui, Musa, Rigolli, Tastet, Dobson, Wiesemann, Ferreira, Sahmin Lee, Schelbert, Clavel, Park, Pellegrini, Hadamitzky, Gerber, Newby, Myerson, Cavalcante, McCann, Greenwood, Moon, Dweck, S.P. Lee.
Drafting of the manuscript: Kwak, T. Singh, W. Lee, Pellegrini, Dweck, S.P. Lee.
Critical review of the manuscript for important intellectual content: Kwak, A. Singh, Everett, Treibel, Lim, Won, Williams, Loganath, Bing, Craig, Joshi, H. Lee, W. Lee, Kim, Chin, Fukui, Musa, Rigolli, Tastet, Dobson, Wiesemann, Ferreira, Captur, Sahmin Lee, Schulz-Menger, Schelbert, Clavel, Park, Hadamitzky, Gerber, Newby, Myerson, Pibarot, Cavalcante, McCann, Greenwood, Moon, Dweck, S.P. Lee.
Statistical analysis: Kwak, Lim, Won, Loganath, T. Singh, H. Lee, W. Lee.
Obtained funding: Treibel, Schulz-Menger, Hadamitzky, Gerber, Newby, Pibarot, Dweck.
Administrative, technical, or material support: Kwak, A. Singh, Everett, Lim, Williams, Loganath, Craig, T. Singh, W. Lee, Kim, Chin, Musa, Rigolli, Dobson, Wiesemann, Ferreira, Captur, Sahmin Lee, Schelbert, Clavel, Pellegrini, Hadamitzky, Myerson, Greenwood, Moon, Dweck.
Supervision: Lim, Williams, H. Lee, W. Lee, Kim, Fukui, Schulz-Menger, Schelbert, Park, Newby, Myerson, Pibarot, McCann, Greenwood, Moon, Dweck, S.P. Lee.

Conflict of Interest Disclosures: Dr Williams reported consultant fees from Canon, Feops, Novartis, and Siemens Healthineers outside the submitted work. Dr Fukui reported personal fees from Anteris Technologies and Edwards Lifescience outside the submitted work. Dr Rigolli reported employment from Bristol Myers Squibb outside the submitted work. Dr Ferreira reported salary from the University of Oxford from the British Heart Foundation during the conduct of the study and grants from GE Healthcare outside the submitted work; in addition, Dr Ferreira had a patent pending research license for WO/2020/161481 to GE Healthcare, a patent for WO/2021/044153 pending research license to GE Healthcare and a patent research license issued for US 11,747,426 B2 to GE Healthcare. Dr Schelbert reported personal fees from Haya Therapeutics outside the submitted work. Dr Clavel reported grants from Edwards Lifesciences, Medtronic, Pi-Cardia, Novartis, and Rednvia outside the submitted work. Dr Gerber reported personal fees from Bristol Myers Squibb and Novartis outside the submitted work. Dr Pibarot reported grants from Edwards Lifesciences Echo Corelab, Medtronic, Pi-Cardia, and Novartis outside the submitted work. Dr Cavalcante reported grants from Abbott Structural, Allina Health Foundation, JenaValve, the National Institutes of Health/National Heart, Lung, and Blood Institute, and honoraria or consultation fees from 4C Medical, Abbott Structural, Alleviant, Anteris, Boston Scientific, Circle Cardiovascular Imaging, Edwards Lifesciences, JenaValve, JC Medical, Medtronic, Novo Nordisk, Pie Medical, Siemens Healthineers, Shockwave, and Zoll outside the submitted work. Dr Moon reported stock holding from MyCardium outside the submitted work. No other disclosures were reported.

Funding/Support: This research was supported by grants from the Korea Health Technology Research and Development Project through the Korea Health Industry Development Institute, funded by the Ministry of Health and Welfare, Republic of Korea grant number (HI22C0154) and a grant from the National Research Foundation of Korea, Ministry of Science and ICT, Republic of Korea (RS-2023-00208947) to Dr S.P. Lee. The British Heart Foundation supports Dr Newby (CH/09/002, RG/16/10/32375, RE/18/5/34216), and Dr Dweck (FS/SCRF/21/32010). Dr Newby is the recipient of a Wellcome Trust Senior Investigator Award (WT103782AIA). Dr Dweck is the recipient of the Sir Jules Thorn Award for Biomedical Research 2015 (15/JTA). Dr Myerson acknowledges funding support from the Oxford National Institute for Health Research Biomedical Research Centre. Drs McCann and Singh are funded by the National Institute for Health Research (RP-08-ST2-007) and (Advanced Fellowship 300867), respectively. Dr Cavalcante has received consulting fees from 4C, Abbott Structural, Anteris, AriaCV, Boston Scientific, Edwards Lifesciences, Medtronic, VDyne, WL Gore, and Xylocor and has received research grant support from the Abbott Northwestern Hospital Foundation. Dr Pibarot has received institutional funding from Edwards Lifesciences, Medtronic, Pi-Cardia, and Cardiac Success for echocardiography core laboratory analyses and research studies in the field of interventional and pharmacologic treatment of valvular heart diseases, for which he received no personal compensation.

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Data Sharing Statement: See Supplement 2.

REFERENCES

1. Coffey S, Roberts-Thomson R, Brown A, et al. Global epidemiology of valvular heart disease. *Nat Rev Cardiol*. 2021;18(12):853-864. doi:10.1038/s41569-021-00570-z

2. Bing R, Cavalcante JL, Everett RJ, Clavel MA, Newby DE, Dweck MR. Imaging and impact of myocardial fibrosis in aortic stenosis. *JACC Cardiovasc Imaging*. 2019;12(2):283-296. doi:10.1016/j.jcmg.2018.11.026

3. Dweck MR, Boon NA, Newby DE. Calcific aortic stenosis: a disease of the valve and the myocardium. *J Am Coll Cardiol*. 2012;60(19):1854-1863. doi:10.1016/j.jacc.2012.02.093

4. Chin CWL, Everett RJ, Kwiecinski J, et al. Myocardial fibrosis and cardiac decompensation in aortic stenosis. *JACC Cardiovasc Imaging*. 2017;10(11):1320-1333. doi:10.1016/j.jcmg.2016.10.007

5. Everett RJ, Treibel TA, Fukui M, et al. Extracellular myocardial volume in patients with aortic stenosis. *J Am Coll Cardiol*. 2020;75(3):304-316. doi:10.1016/j.jacc.2019.11.032

6. Kwak S, Everett RJ, Treibel TA, et al. Markers of myocardial damage predict mortality in patients

with aortic stenosis. *J Am Coll Cardiol*. 2021;78(6):545-558. doi:10.1016/j.jacc.2021.05.047

7. Lee H, Park JB, Yoon YE, et al. Noncontrast myocardial T1 mapping by cardiac magnetic resonance predicts outcome in patients with aortic stenosis. *JACC Cardiovasc Imaging*. 2018;11(7):974-983. doi:10.1016/j.jcmg.2017.09.005

8. Lee HJ, Lee H, Kim SM, et al. Diffuse myocardial fibrosis and diastolic function in aortic stenosis. *JACC Cardiovasc Imaging*. 2020;13(12):2561-2572. doi:10.1016/j.jcmg.2020.07.007

9. Musa TA, Treibel TA, Vassiliou VS, et al. Myocardial scar and mortality in severe aortic stenosis. *Circulation*. 2018;138(18):1935-1947. doi:10.1161/CIRCULATIONAHA.117.032839

10. Treibel TA, López B, González A, et al. Reappraising myocardial fibrosis in severe aortic stenosis: an invasive and non-invasive study in 133 patients. *Eur Heart J*. 2018;39(8):699-709. doi:10.1093/eurheartj/ehx353

11. Loganath K, Craig NJ, Everett RJ, et al; EVOLVED investigators. Early intervention in patients with asymptomatic severe aortic stenosis and myocardial fibrosis: the EVOLVED randomized clinical trial. *JAMA*. Published online October 28, 2024. doi:10.1001/jama.2024.22730

12. Singh A, Chan DCS, Greenwood JP, et al. Symptom onset in aortic stenosis: relation to sex differences in left ventricular remodeling. *JACC Cardiovasc Imaging*. 2019;12(1):96-105. doi:10.1016/j.jcmg.2017.09.019

13. Tastet L, Kwiecinski J, Pibarot P, et al. Sex-related differences in the extent of myocardial fibrosis in patients with aortic valve stenosis. *JACC Cardiovasc Imaging*. 2020;13(3):699-711. doi:10.1016/j.jcmg.2019.06.014

14. Treibel TA, Kozor R, Fontana M, et al. Sex dimorphism in the myocardial response to aortic stenosis. *JACC Cardiovasc Imaging*. 2018;11(7):962-973. doi:10.1016/j.jcmg.2017.08.025

15. Singh A, Musa TA, Treibel TA, et al. Sex differences in left ventricular remodelling, myocardial fibrosis and mortality after aortic valve replacement. *Heart*. 2019;105(23):1818-1824. doi:10.1136/heartjnl-2019-314987

16. Lee JM, Park SJ, Lee SP, et al. Gender difference in ventricular response to aortic stenosis: insight from cardiovascular magnetic resonance. *PLoS One*. 2015;10(3):e0121684. doi:10.1371/journal.pone.0121684

17. Cho L, Kibbe MR, Bakaeen F, et al. Cardiac surgery in women in the current era: what are the gaps in care? *Circulation*. 2021;144(14):1172-1185. doi:10.1161/CIRCULATIONAHA.121.056025

18. Chaker Z, Badhwar V, Alqahtani F, et al. Sex differences in the utilization and outcomes of surgical aortic valve replacement for severe aortic stenosis. *J Am Heart Assoc*. 2017;6(9):e006370. doi:10.1161/JAHA.117.006370

19. Saad M, Nairooz R, Pothineni NVK, et al. Long-term outcomes with transcatheter aortic valve replacement in women compared with men: evidence from a meta-analysis. *JACC Cardiovasc Interv*. 2018;11(1):24-35. doi:10.1016/j.jcin.2017.08.015

20. O'Brien SM, Shahian DM, Filardo G, et al; Society of Thoracic Surgeons Quality Measurement Task Force. The Society of Thoracic Surgeons 2008 cardiac surgery risk models: part 2–isolated valve surgery. *Ann Thorac Surg*. 2009;88(1)(suppl):S23-S42. doi:10.1016/j.athoracsur.2009.05.056

21. Shahian DM, O'Brien SM, Filardo G, et al; Society of Thoracic Surgeons Quality Measurement Task Force. The Society of Thoracic Surgeons 2008 cardiac surgery risk models: part 3–valve plus coronary artery bypass grafting surgery. *Ann Thorac Surg*. 2009;88(1)(suppl):S43-S62. doi:10.1016/j.athoracsur.2009.05.055

22. Baumgartner H, Hung J, Bermejo J, et al. Recommendations on the echocardiographic assessment of aortic valve stenosis: a focused update from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. *J Am Soc Echocardiogr*. 2017;30(4):372-392. doi:10.1016/j.echo.2017.02.009

23. Otto CM, Nishimura RA, Bonow RO, et al. 2020 ACC/AHA guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2021;143(5):e72-e227. doi:10.1161/CIR.0000000000000923

24. Vahanian A, Beyersdorf F, Praz F, et al; ESC/EACTS Scientific Document Group. 2021 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J*. 2022;43(7):561-632. doi:10.1093/eurheartj/ehab395

25. Moon JC, Messroghli DR, Kellman P, et al; Society for Cardiovascular Magnetic Resonance Imaging; Cardiovascular Magnetic Resonance Working Group of the European Society of Cardiology. Myocardial T1 mapping and extracellular volume quantification: a Society for Cardiovascular Magnetic Resonance (SCMR) and CMR Working Group of the European Society of Cardiology consensus statement. *J Cardiovasc Magn Reson*. 2013;15(1):92. doi:10.1186/1532-429X-15-92

26. Chin CW, Semple S, Malley T, et al. Optimization and comparison of myocardial T1 techniques at 3T in patients with aortic stenosis. *Eur Heart J Cardiovasc Imaging*. 2014;15(5):556-565. doi:10.1093/ehjci/jet245

27. Zwadlo C, Schmidtmann E, Szaroszyk M, et al. Antiandrogenic therapy with finasteride attenuates cardiac hypertrophy and left ventricular dysfunction. *Circulation*. 2015;131(12):1071-1081. doi:10.1161/CIRCULATIONAHA.114.012066

28. Chehab O, Shabani M, Varadarajan V, et al. Endogenous sex hormone levels and myocardial fibrosis in men and postmenopausal women. *JACC Adv*. 2023;2(3):100320. doi:10.1016/j.jacadv.2023.100320

29. Treibel TA, Kozor R, Schofield R, et al. Reverse myocardial remodeling following valve replacement in patients with aortic stenosis. *J Am Coll Cardiol*. 2018;71(8):860-871. doi:10.1016/j.jacc.2017.12.035

30. Everett RJ, Tastet L, Clavel MA, et al. Progression of hypertrophy and myocardial fibrosis in aortic stenosis: a multicenter cardiac magnetic resonance study. *Circ Cardiovasc Imaging*. 2018;11(6):e007451. doi:10.1161/CIRCIMAGING.117.007451

31. Lee HJ, Singh A, Lim J, et al. Diffuse interstitial fibrosis of the myocardium predicts outcome in moderate and asymptomatic severe aortic stenosis. *JACC Cardiovasc Imaging*. Published online September 25, 2024. doi:10.1016/j.jcmg.2024.08.003