



# Myocardial Scar and Mortality in Severe Aortic Stenosis

## Data From the BSCMR Valve Consortium

Editorial, see p 1948

**BACKGROUND:** Aortic valve replacement (AVR) for aortic stenosis is timed primarily on the development of symptoms, but late surgery can result in irreversible myocardial dysfunction and additional risk. The aim of this study was to determine whether the presence of focal myocardial scar preoperatively was associated with long-term mortality.

**METHODS:** In a longitudinal observational outcome study, survival analysis was performed in patients with severe aortic stenosis listed for valve intervention at 6 UK cardiothoracic centers. Patients underwent preprocedural echocardiography (for valve severity assessment) and cardiovascular magnetic resonance for ventricular volumes, function and scar quantification between January 2003 and May 2015. Myocardial scar was categorized into 3 patterns (none, infarct, or noninfarct patterns) and quantified with the full width at half-maximum method as percentage of the left ventricle. All-cause mortality and cardiovascular mortality were tracked for a minimum of 2 years.

**RESULTS:** Six hundred seventy-four patients with severe aortic stenosis (age,  $75 \pm 14$  years; 63% male; aortic valve area,  $0.38 \pm 0.14$  cm<sup>2</sup>/m<sup>2</sup>; mean gradient,  $46 \pm 18$  mm Hg; left ventricular ejection fraction,  $61.0 \pm 16.7\%$ ) were included. Scar was present in 51% (18% infarct pattern, 33% noninfarct). Management was surgical AVR (n=399) or transcatheter AVR (n=275). During follow-up (median, 3.6 years), 145 patients (21.5%) died (52 after surgical AVR, 93 after transcatheter AVR). In multivariable analysis, the factors independently associated with all-cause mortality were age (hazard ratio [HR], 1.50; 95% CI, 1.11–2.04;  $P=0.009$ , scaled by epochs of 10 years), Society of Thoracic Surgeons score (HR, 1.12; 95% CI, 1.03–1.22;  $P=0.007$ ), and scar presence (HR, 2.39; 95% CI, 1.40–4.05;  $P=0.001$ ). Scar independently predicted all-cause (26.4% versus 12.9%;  $P<0.001$ ) and cardiovascular (15.0% versus 4.8%;  $P<0.001$ ) mortality, regardless of intervention (transcatheter AVR,  $P=0.002$ ; surgical AVR,  $P=0.026$  [all-cause mortality]). Every 1% increase in left ventricular myocardial scar burden was associated with 11% higher all-cause mortality hazard (HR, 1.11; 95% CI, 1.05–1.17;  $P<0.001$ ) and 8% higher cardiovascular mortality hazard (HR, 1.08; 95% CI, 1.01–1.17;  $P<0.001$ ).

**CONCLUSIONS:** In patients with severe aortic stenosis, late gadolinium enhancement on cardiovascular magnetic resonance was independently associated with mortality; its presence was associated with a 2-fold higher late mortality.

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## Clinical Perspective

### What Is New?

- In patients with severe aortic stenosis, focal myocardial fibrosis (scar) determined by cardiovascular magnetic resonance was present in >50% of patients and was associated with a 2-fold higher late mortality.
- Focal scar (both infarct and noninfarct patterns) was independently associated with all-cause and cardiovascular mortality after both surgical and transcatheter aortic valve replacement.

### What Are the Clinical Implications?

- In severe aortic stenosis, late gadolinium enhancement appears to be a useful biomarker of left ventricular remodeling, and its presence is associated with worse long-term outcomes after aortic valve intervention.
- This raises the hypothesis that, for some patients, timing of aortic valve intervention may be too late once scar has developed and that randomized trials of earlier intervention are now required.

**A**ortic stenosis (AS) is the most common valvular heart disease.<sup>1</sup> It is characterized by progressive narrowing of the aortic valve and by hypertrophic remodeling of the left ventricular (LV) myocardium.<sup>2</sup> This process maintains wall stress and cardiac performance for many years, but ultimately the LV decompensates, heralding the transition to heart failure, symptom development, and death.<sup>3</sup> The treatment for AS is valve replacement, with the goal of reducing both symptoms and mortality.

Current guidelines recommend aortic valve intervention by surgical aortic valve replacement (SAVR) or transcatheter aortic valve replacement (TAVR) in symptomatic severe AS or for asymptomatic severe AS in the presence of LV dysfunction or exercise-invoked symptoms.<sup>4</sup> However, symptoms can be difficult to interpret, especially in the elderly, who may be less active or have multiple comorbidities, and reduction in ejection fraction is often irreversible and associated with increased risk of heart failure and death.<sup>5</sup>

Although the primary insult is valve stenosis, the cardiac response to this may be equally important. Therefore, there is growing interest in objective and early markers of cardiac decompensation. Histological and imaging studies have suggested that focal myocardial fibrosis is a key driver in the transition from hypertrophy to heart failure.<sup>6–10</sup> Myocardial replacement fibrosis (scar) can be detected by cardiovascular magnetic resonance (CMR) with the late gadolinium enhancement (LGE) technique. From single-center studies, focal fibrosis has been associated with increased levels of myocar-

dial injury, diastolic and systolic dysfunction, electrocardiographic changes, and adverse clinical outcomes.<sup>7–10</sup> Focal scar by LGE is irreversible at 9 and 12 months after SAVR.<sup>5,11</sup> CMR-detected myocardial fibrosis therefore appears to be a useful and objective biomarker of LV decompensation in AS.

Prior studies have been too small to evaluate the independent association of imaging biomarkers and demographic factors with total and cardiovascular mortality in patients with severe AS.<sup>7–10</sup> We established a UK consortium to determine which preoperative factors were most strongly associated with long-term postoperative mortality in patients with severe AS on conventional management pathways, which could potentially be used to time surgery better in the future. We hypothesized that myocardial scarring detected by LGE-CMR would be independently associated with mortality in patients with severe AS undergoing aortic valve intervention.

## METHODS

The data, analytical methods, and study materials will be made available to other researchers for purposes of reproducing the results or replicating the procedure. The data are available from the corresponding author on reasonable request.

### Patients and Study Design

A longitudinal, observational outcome study in patients with severe AS referred to 6 UK cardiothoracic surgical centers and listed for valve intervention (Brompton Hospital and Barts Heart Center in London; Edinburgh Heart Center; Glenfield Hospital in Leicester; Leeds Teaching Hospitals National Health Service Trust; John Radcliffe Hospital in Oxford). Between January 2003 and May 2015, patients were prospectively recruited after evaluation by the multidisciplinary heart team. The study was approved by the UK National Research Ethics Service (13/NW/0832) and conformed to the principles of the Declaration of Helsinki, and all patients gave written informed consent. The primary end point was all-cause mortality. The secondary end point was cardiovascular disease–related mortality as defined by diagnosis on the UK death certificate. Patients >18 years of age with severe AS (1 of the following: aortic valve area <1 cm<sup>2</sup>, peak pressure gradient >64 mmHg, mean pressure gradient >40 mmHg, or peak velocity >4 m/s) who had undergone CMR imaging for research purposes were included.

### Image Acquisition

Echocardiographic parameters were acquired as part of the clinical workup following the guidelines for assessment of AS severity recommended by the American and European societies of echocardiography.<sup>12</sup> Global hemodynamic load was measured by calculating the valvulo-arterial impedance index, defined as the ratio of the estimated LV systolic pressure (sum of systolic arterial pressure and mean pressure gradient) to the stroke volume indexed for body surface area. CMR was performed on 1.5- and 3-T scanners using standardized

protocols. In brief, cine images were acquired in long-axis planes and contiguous short-axis slices for ventricular volumes, mass, and function. Phase-contrast velocity-encoded images were acquired for valve hemodynamics, and the LGE technique was used to identify myocardial scar, as previously described.<sup>13</sup> All participating centers have previously published single-center mechanistic data in AS in which image quality and specific CMR pulse sequence parameters can be reviewed.<sup>10,14–17</sup>

## Data Management and Outcomes

Anonymized clinical and imaging data were collected and managed with REDCap (Research Electronic Data Capture) software<sup>18</sup> hosted at Barts Heart Center/University College London. All deaths were identified through the UK National Health Service National Spine Database. Cardiovascular mortality was established in all deceased individuals from the official death certificates, which in the United Kingdom list up to 3 causes of death and were adjudicated by 2 readers (P.B., J.P.G.) blinded to all clinical data. Cardiovascular mortality was defined as death attributable to myocardial ischemia and infarction, heart failure, cardiac arrest resulting from arrhythmia or unknown cause, or cerebrovascular accident.

## Data Analysis

All CMR scans were centralized and rereported in core laboratory fashion by experienced readers blinded to clinical parameters using CVI42 software (Circle Calgary). Each center analyzed a single component of the CMR scan for the entire study population, according to a prespecified standard operating procedure ([online-only Data Supplement](#)) and after a period of training and reproducibility evaluation. LV volume and mass analysis was performed by manual contouring of the endocardial and epicardial borders at end diastole and end systole.<sup>19</sup> Left atrial area and length at end systole were measured in the horizontal (4-chamber) and vertical long-axis (2-chamber) views for calculation of left atrial volumes by the biplane area length method and indexed.<sup>19</sup> Aortic flow for regurgitant volume and fraction was quantified from phase-contrast velocity-encoded images.<sup>20</sup> LGE was categorized by 2 observers into 3 patterns (none, infarct, or noninfarct patterns) and quantified with the full width at half-maximum method as percentage of the LV.<sup>13</sup> Examples of typical echocardiographic and CMR images are shown in Figure 1. Further technical details of the image analysis can be found in the [online-only Data Supplement](#).

## Statistics

Statistical analysis was performed in R (version 3.0.1; The R Foundation for Statistical Computing). Distribution of data was assessed on histograms and with the Shapiro-Wilk test. Continuous variables are expressed as mean±SD or as median and interquartile range; categorical variables, as counts and percent. Baseline characteristics of participants were compared with the unpaired Student *t* test, Mann-Whitney-Wilcoxon test,  $\chi^2$  test, or Fisher exact test as appropriate. The primary end point was all-cause mortality. The secondary end point was cardiovascular disease-related mortality. In addition, we computed early postintervention

(TAVR/SAVR) mortality (defined as 30-day or in-hospital mortality). Survival in patients with and without LGE was evaluated with the Kaplan-Meier method and compared among groups with the log-rank test. The index date was the date of CMR. Hazard ratios (HRs) were expressed as mean±95% CIs.

All clinical parameters were proposed for inclusion in a univariate Cox proportional hazards model. The most predictive candidate variable was selected from each of 3 domains if applicable (clinical, echocardiography, CMR) to avoid colinearity and then entered into the final model. Unique, clinically relevant predictor variables with a value of  $P<0.10$  in univariate analysis were entered into final multivariable models; a forward stepwise procedure was used. The incremental value between steps was measured by the  $\chi^2$  method. The proportional hazards assumption was tested with the use of log-log plots and examination of Schoenfeld residuals. All tests were 2-sided; values of  $P<0.05$  were considered significant.

## Role of the Funding Source

No additional funding was obtained for this consortium study beyond that of the original single-center research funding. Funders provided financial support for the original data collection but had no role in the consortium study design, data collection, data analysis, data interpretation, or writing of the report. All authors had access to the primary data and have final responsibility for publication.

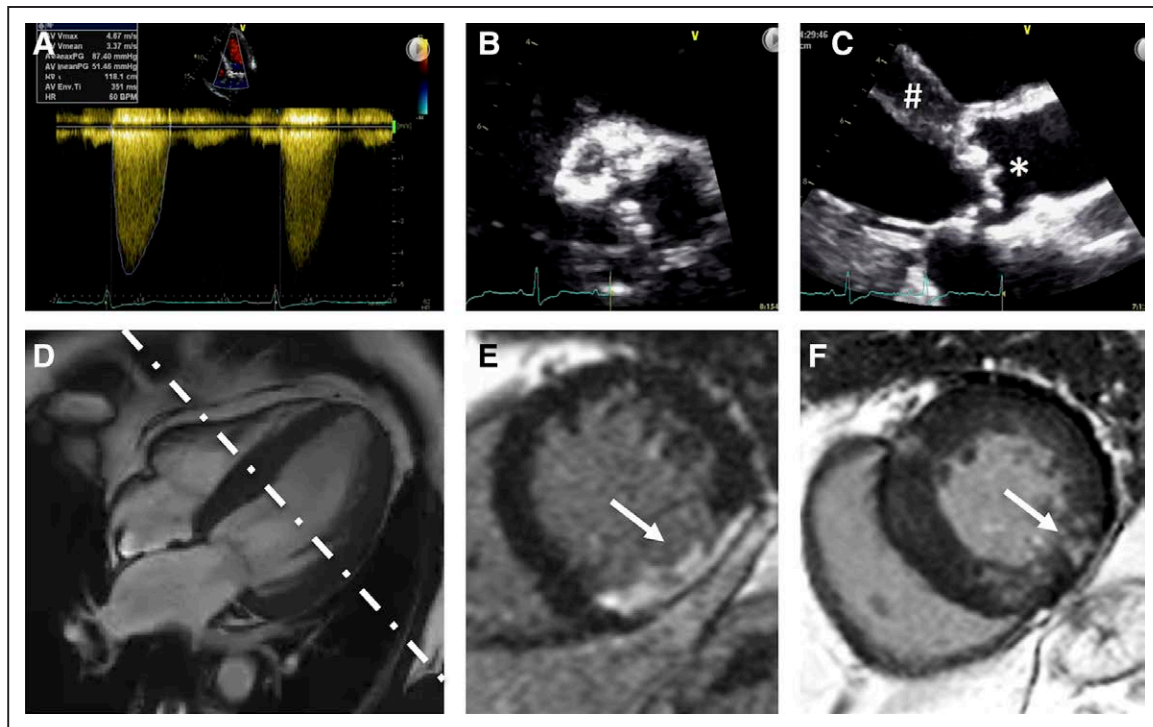
## RESULTS

### Baseline Characteristics

Baseline characteristics of the 674 patients included are shown in Table 1 and [Figure 1 in the online-only Data Supplement](#) (study flowchart). Mean age was 75±14 years (63% male) with a mean aortic valve area of 0.38±0.14 cm<sup>2</sup>/m<sup>2</sup> and mean gradient of 46±18 mm Hg. Median aortic valve regurgitant fraction was 8.0% (interquartile range, 2.7%–17.3%); 16% of patients had at least moderately elevated pulmonary arterial systolic pressure (defined as 30–55 mm Hg by echocardiography). LV myocardial scar, as assessed by LGE, was present in 51% of patients in a 2:1 ratio between noninfarct (33%) and infarct (18%) pattern scar.

### Management by Surgical Replacement Versus Transcatheter Replacement

Management was SAVR (n=399) or TAVR (n=275). Median time from CMR to SAVR was 44 days (interquartile range, 11–103 days) and to TAVR was 13 days (interquartile range, 1–61 days). Compared with SAVR, patients managed with TAVR were older (79.2±7.8 versus 68.6±10.3 years;  $P<0.001$ ) and more likely female (48% versus 29%;  $P<0.001$ ) with more atrial fibrillation (21.1% versus 6.5%;  $P<0.001$ ), more coronary artery disease (39.3% versus 19.5%;  $P<0.001$ ), less hypertension (42.6% versus 59.5%;



**Figure 1. Multimodality assessment of aortic stenosis (AS).**

Assessment of AS by transthoracic echocardiography (TTE; **A–C**) and cardiovascular magnetic resonance (**D–F**). **A**, Continuous Doppler trace across the aortic valve in the apical 5-chamber demonstrating hemodynamic parameters consistent with severe AS (peak velocity, 4.67 m/s; peak gradient, 87 mmHg; mean gradient, 51 mmHg). **B**, Short-axis TTE image of a severely calcified aortic valve. **C**, Parasternal long-axis image demonstrating left ventricular hypertrophy (#) and a calcified aortic valve (\*). **D**, Four-chamber balanced steady-state free precession cine image demonstrating left ventricular hypertrophy; white dotted line demonstrates the axis of acquisition of the short axis (**E** and **F**). **E**, Late gadolinium enhancement (LGE) image in a midventricular short axis showing transmural LGE of a full-thickness myocardial infarct (arrow). **F**, LGE image in a midventricular short axis showing patchy nonischemia LGE in the mid inferolateral segment (arrow) and more subtle LGE in the infoseptum and right ventricular insertion points.

$P < 0.001$ ), and fewer bicuspid aortic valves (5.5% versus 33.8%;  $P < 0.001$ ). Patients undergoing TAVR had higher peak aortic valve gradients and smaller aortic valve area. Furthermore, patients undergoing TAVR had larger LV volumes and lower LV ejection fraction and had more severe symptoms; LV mass and LGE prevalence were not different between groups, although infarct pattern scar was more prevalent in the TAVR group and noninfarct scar was more prevalent in the SAVR group.

### Patient Characteristics According to LGE Status

LGE positive patients were more likely to be male (72.7 versus 54.4%;  $P < 0.001$ ) and to have had a previous myocardial infarct (17.0% versus 4.0%;  $P < 0.001$ ) and had larger indexed LV end-diastolic volume, higher indexed LV mass, and lower LV ejection fraction (all  $P < 0.001$ ) than LGE negative patients (Table 1). In the SAVR cohort only, men also had higher New York Heart Association functional class ( $P = 0.006$ ) and higher systolic blood pressure ( $138.5 \pm 20.5$  versus  $134.0 \pm 17.8$  mm Hg;  $P = 0.036$ ).

### Outcome

During a median 3.6 years of follow-up (interquartile range, 2.6–5.9 years), 145 patients (21.5%) died (52 after SAVR and 93 after TAVR). This equated to 52 deaths per 1000 patient-years (27 and 104 for SAVR and TAVR groups, respectively). A cardiovascular cause of death was ascribed to 70 patients (10.4% of whole cohort; 19 after SAVR [4.8%], 51 after TAVR [18.5%]). At 30 days after the intervention, overall mortality was 1.8% ( $n = 12$ ), with 1.3% ( $n = 5$ ) for SAVR and 2.5% ( $n = 7$ ) for TAVR. At 1 year, overall mortality was 6.2% ( $n = 42$ ), with 3.0% ( $n = 12$ ) for SAVR and 10.9% ( $n = 30$ ) for TAVR (Table 1 in the online-only Data Supplement).

### Predictors of Outcome

Fifty-two variables were compared with outcome (including demographic, comorbidities, therapies, Society of Thoracic Surgeons score, and imaging [echocardiography/CMR] parameters). In univariate analysis (Table 2 and Tables II and III in the online-only Data Supplement for all, SAVR, and TAVR, respectively), 28 of them were associated with outcome. In multivariable analysis (Table 3 and Tables IV and V in the online-only Data Supplement for all, SAVR, and TAVR, respectively), the factors



**Table 1. Baseline Characteristics**

Variable	All Patients* (n=674)	+LGE (n=341)†	-LGE (n=272)‡	P Value
Age (IQR), y	74.6 (14.4)	74.3 (14.6)	75.0 (14.5)	0.44
Intervention				
SAVR, n (%)‡	399 (59.2)	194 (56.9)	176 (64.7)	0.05
TAVR, n (%)	275 (40.8)	147 (43.1)	96 (35.3)	
Male, n (%)	425 (63.1)	248 (72.7)	148 (54.4)	<0.001
BMI, kg/m <sup>2</sup>	27.6±5.1	27.8±5.1	27.3±4.8	0.20
Atrial fibrillation, n (%)	84 (12.5)	49 (14.4)	28 (10.3)	0.13
Diabetes mellitus, n (%)	146 (21.7)	77 (22.6)	58 (21.3)	0.71
Hypertension, n (%)	358 (53.1)	184 (54.0)	155 (57.0)	0.46
Systolic BP, mmHg	135.0±20.4	133.4±20.3	137.3±20.2	0.03
Diastolic BP, mmHg	72.7±12.2	72.2±11.8	74.0±11.8	0.10
Bicuspid aortic valve, n (%)§	149 (22.1)	80 (23.5)	53 (19.4)	0.23
Known CAD, n (%)	197 (29.2)	123 (36.1)	74 (27.2)	0.16
No previous PCI/CABG, n (%)§	533 (79.1)	260 (76.2)	220 (80.9)	0.65
Previous PCI, n (%)	57 (8.5)	38 (11.1)	16 (5.9)	0.07
Previous CABG, n (%)	58 (8.6)	31 (9.1)	22 (8.1)	0.92
History of MI, n (%)§	73 (10.8)	58 (17.0)	11 (4.0)	<0.001
STS Mortality Risk score (IQR), %	1.75 (1.89)	1.74 (1.79)	1.76 (1.69)	0.78
EuroSCORE II, %	1.81 (2.40)	1.87 (2.85)	1.64 (1.69)	0.07
NYHA functional class, n (%)§				
I	81 (12.0)	33 (9.7)	47 (17.3)	0.03
II	258 (38.3)	138 (40.5)	90 (33.1)	
III	248 (36.8)	127 (37.2)	98 (36.0)	
IV	22 (3.3)	10 (2.9)	8 (2.9)	
Baseline medications, n (%)§				
ACE inhibitor or ARB	262 (38.9)	139 (40.8)	107 (39.3)	0.56
β-Blocker	240 (35.6)	130 (38.1)	92 (33.8)	0.27
Aldosterone antagonist*	36 (5.3)	21 (6.1)	11 (4.0)	0.12
Statin	406 (60.2)	224 (65.7)	162 (59.6)	0.23
Echocardiographic data				
Mean aortic valve gradient (IQR), mmHg	46.0 (18.0)	46.0 (19.0)	46.0 (17.0)	0.20
Peak aortic valve gradient (IQR), mmHg	78.0 (30.0)	78.0 (30.0)	79.5 (30.0)	0.34
AVA (IQR), cm <sup>2</sup>	0.70 (0.31)	0.70 (0.21)	0.70 (0.17)	0.98
Indexed AVA (to BSA) (IQR), cm <sup>2</sup> /m <sup>2</sup>	0.38 (0.14)	0.41 (0.13)	0.40 (0.13)	0.94
Estimated PASP, n (%)				
Normal§	316 (46.9)	159 (46.6)	138 (50.7)	0.85
Moderate (31–55 mmHg)	80 (11.9)	43 (12.6)	30 (11.0)	
Severe (>55 mmHg)	30 (4.5)	16 (4.7)	11 (4.0)	
CMR data				
LV end-diastolic volume index (IQR), mL/m <sup>2</sup>	79.5 (29.3)	85.4 (33.4)	73.3 (23.1)	<0.001
LV stroke volume index (IQR), mL/m <sup>2</sup>	46.2 (14.5)	46.0 (14.9)	45.8 (14.2)	0.80
LV ejection fraction (IQR), %	61.0 (16.7)	58.0 (21.0)	64.0 (12.0)	<0.001
Maximal LV wall thickness (IQR), mm	14.0 (4.0)	14.0 (4.0)	13.0 (3.0)	<0.001
LV mass index (IQR), g/m <sup>2</sup>	81.0 (31.0)	87.1 (31.3)	74.9 (28.5)	<0.001
RV end-diastolic volume index (IQR), mL/m <sup>2</sup>	67.4 (22.2)	68.5 (22.5)	66.8 (19.8)	0.015

(Continued)

**Table 1. Continued**

Variable	All Patients* (n=674)	+LGE (n=341)†	–LGE (n=272)‡	P Value
RV ejection fraction (IQR), %	65.0 (13.0)	63.8 (15.0)	65.0 (11.0)	0.026
Indexed left atrial volume (IQR), mL/m <sup>2</sup>	52.8 (25.7)	53.3 (24.4)	51.4 (25.4)	0.19
CMR aortic valve regurgitant fraction (IQR), %	8.0 (14.7)	8.9 (16.2)	7.7 (12.2)	0.12
Valvulo-arterial impedance (IQR)	3.93 (1.4)	3.93 (1.3)	3.98 (1.5)	0.20
LGE present, n (%)	341 (50.6)	341 (100)	0	NA
Noninfarct pattern	222 (32.9)	222 (65.1)	0	NA
Infarct pattern	119 (17.7)	119 (34.9)	0	NA
LGE mass (IQR), %	0.53‡ (3.08)	2.72 (3.95)	0	NA

Normally distributed continuous variables are expressed as mean±SD; nonparametric continuous variables are expressed as median (IQR); and categorical variables are expressed as counts (percent).

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; AVA, aortic valve area; BMI, body mass index; BP, blood pressure; BSA, body surface area; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CMR, cardiovascular magnetic resonance; IQR, interquartile range; LGE, late gadolinium enhancement; LV, left ventricular; MI, myocardial infarction; NA, not available; NYHA, New York Heart Association; PASP, pulmonary artery systolic pressure; PCI, percutaneous coronary intervention; RV, right ventricular; SAVR, surgical aortic valve replacement; STS, Society of Thoracic Surgeons; and TAVR, transcatheter aortic valve replacement.

\*All patient groups: all SAVR+TAVR.

†For the LGE columns, 61 subjects (32 TAVR and 29 SAVR) did not undergo LGE imaging.

‡All SAVR: SAVR+SAVR/CABG.

§This variable of counts contains missing data—for example, 46 missing NYHA (incomplete data), 5 missing bicuspid aortic valve data points, 26 baseline CAD missing data points, and 1 missing MI data point.

‖LGE mass (percent) as the median of all patients, including those without LGE.

independently associated with all-cause mortality were age (HR, 1.50; 95% CI, 1.11–2.04;  $P=0.009$ , scaled by epochs of 10 years), Society of Thoracic Surgeons score (HR, 1.12; 95% CI, 1.03–1.22;  $P=0.007$ ), and scar presence (HR, 2.39; 95% CI, 1.40–4.05;  $P=0.001$ ). The incremental effect of adding age, Society of Thoracic Surgeons score, and LGE presence to the risk stratification model is demonstrated in [Figure II in the online-only Data Supplement](#); global Wald  $\chi^2$  is shown for separate Cox regression models predicting all-cause death. For cardiovascular mortality, the factors independently associated with all-cause mortality were age (HR, 1.94; 95% CI, 1.44–2.60;  $P<0.0001$ , scaled by epochs of 10 years), female sex (HR, 2.17; 95% CI, 1.28–3.70;  $P<0.001$ ), LGE presence (HR, 3.14; 95% CI, 1.65–5.99;  $P<0.001$ ), and reduced LV ejection fraction (HR, 0.98; 95% CI, 0.96–1.00;  $P=0.013$ ). Pulmonary artery systolic pressure was not included in the main model because data were available in only 63.3% (SAVR, 82.7%; TAVR, 49.5%), but when included, the presence of severely elevated pulmonary arterial systolic pressure (>55 mm Hg) was an independent predictor of all-cause mortality (HR, 2.73; 95% CI, 1.21–6.17;  $P=0.016$ ; [Table VI in the online-only Data Supplement](#)). Neither coronary artery disease nor previous coronary revascularization (percutaneous coronary intervention or coronary artery bypass graft surgery) was an independent predictor of mortality ([Table VII in the online-only Data Supplement](#)). Furthermore, no echocardiographic or CMR markers of aortic valve stenosis severity were independently predictive of mortality.

Patients with myocardial scar had higher (double) all-cause mortality (26.4% versus 12.9%;  $P<0.001$ ) and 3

times the cardiovascular mortality (15.0% versus 4.8%;  $P<0.001$ ), regardless of valve intervention type (TAVR,  $P=0.002$ ; SAVR,  $P=0.026$ ; [Figure 2](#)) and scar type, with both infarct and noninfarct scar being associated with similarly adverse outcomes ( $P<0.001$  for both; [Figure 3](#))—for example, all-cause mortality, 25.2% noninfarct pattern LGE, 28.6% infarct pattern, and 12.9% no LGE. Quantitatively, every 1% increase in LV myocardial scar burden was associated with an 11% higher all-cause mortality hazard (HR, 1.11; 95% CI, 1.05–1.17;  $P<0.001$ ) and an 8% higher cardiovascular mortality hazard (HR, 1.08; 95% CI, 1.01–1.17;  $P<0.001$ ; [Table VIII in the online-only Data Supplement](#)). There was no significant change in results when events within 30 days of intervention were excluded or the index date was changed from time of CMR to time of intervention ([Tables IX and X in the online-only Data Supplement](#)).

## DISCUSSION

In patients with severe AS, in terms of disease-based parameters, we have shown that myocardial fibrosis (scar) is independently associated with mortality. This was the case for all-cause and cardiovascular mortality, after both surgical and transcatheter intervention, and for both infarct and noninfarct scar patterns. Specifically, every 1% increase in scar burden increased mortality hazard by 11% and cardiovascular mortality hazard by 8%. Given that most of this scar is AS-related and that scar was present in half of the patients, we postulate that, for many patients, AS surgery is potentially occurring too late and leaving patients with residual risk.

**Table 2. Univariate Parameters**

Parameter	All Patients (n=674)							
	All-Cause Mortality (n=145)				Cardiovascular Mortality (n=70)			
	HR	z	P Value	95% CI	HR	z	P Value	95% CI
Baseline demographics								
Age*	1.92	7.04	<0.0001	1.60–2.31	2.24	5.75	<0.0001	1.70–2.95
Male sex	0.77	–1.58	0.115	0.55–1.07	0.55	–2.47	0.014	0.35–0.88
BMI	0.98	–1.40	0.161	0.94–1.01	0.97	–1.21	0.227	0.92–1.02
Atrial fibrillation	2.33	4.202	<0.001	1.57–3.45	3.37	4.57	<0.0001	2.01–5.67
Diabetes mellitus	1.32	1.48	0.139	0.91–1.90	1.93	2.63	0.009	1.18–3.14
Hypertension	1.06	0.37	0.715	0.77–1.47	1.02	0.08	0.940	0.64–1.63
Bicuspid AoV	0.28	–4.43	<0.0001	0.16–0.50	0.25	–3.23	0.001	0.11–0.58
Previous CAD	1.69	3.02	0.003	1.20–2.38	1.98	2.77	0.006	1.22–3.20
Previous PCI or CABG	1.51	2.09	0.037	1.03–2.24	1.82	2.17	0.030	1.06–3.11
Previous MI	0.74	–1.17	0.244	0.44–1.23	0.67	–1.10	0.271	0.33–1.36
Baseline NYHA functional class								
II	2.70	2.12	0.034	1.08–6.80	2.82	1.39	0.163	0.66–12.17
III	4.16	3.05	0.002	1.66–10.40	5.60	2.35	0.019	1.33–23.52
IV	8.75	4.01	<0.0001	3.03–25.21	15.28	3.40	<0.001	3.17–73.67
Baseline medications								
ACE inhibitor or ARB	1.37	1.78	0.076	0.97–1.94	1.50	1.61	0.107	0.92–2.44
β-Blocker	1.19	1.04	0.300	0.85–1.67	1.45	1.53	0.127	0.90–2.32
Aldosterone antagonist	0.82	–0.52	0.607	0.38–1.76	1.44	0.85	0.398	0.62–3.34
Statin	1.16	0.83	0.408	0.82–1.65	1.30	1.01	0.314	0.78–2.15
STS score	1.18	7.78	<0.0001	1.13–1.23	1.22	7.15	<0.0001	1.15–1.28
EuroSCORE	1.10	5.20	<0.0001	1.06–1.13	1.12	5.35	<0.0001	1.08–1.17
Echocardiography data								
Mean AoV gradient	1.00	0.84	0.402	0.99–1.02	0.99	–0.66	0.509	0.97–1.01
Peak AoV gradient	1.00	0.83	0.407	1.00–1.01	1.00	–0.33	0.740	0.99–1.01
AoV area	0.33	–2.30	0.021	0.13–0.85	0.23	–2.05	0.040	0.06–0.94
AoV area indexed to BSA	0.30	–1.36	0.173	0.05–1.70	0.26	–1.03	0.301	0.02–3.32
Estimated PA pressure								
Moderate	2.10	2.73	0.006	1.23–3.58	3.07	2.86	0.004	1.42–6.63
Severe	4.09	3.98	<0.0001	2.04–8.20	7.10	4.28	<0.0001	2.90–17.41
CMR data								
LV end-diastolic volume index	1.00	1.17	0.242	1.00–1.01	1.00	0.91	0.366	1.00–1.01
Indexed LV stroke volume	0.97	–4.27	<0.0001	0.95–0.98	0.96	–4.11	<0.0001	0.94–0.98
LV ejection fraction	0.98	–4.87	<0.0001	0.97–0.99	0.97	–5.06	<0.0001	0.95–0.98
Maximal LV wall thickness	0.93	–2.45	0.014	0.88–0.99	0.91	–2.22	0.026	0.84–0.99
Indexed LV mass	1.00	–0.29	0.769	0.99–1.01	1.00	–0.24	0.811	0.99–1.01
RV end-diastolic volume index	1.00	–0.48	0.628	0.99–1.01	1.00	–0.15	0.878	0.98–1.01
RV ejection fraction	0.98	–3.29	0.001	0.96–0.99	0.96	–3.68	0.002	0.95–0.98
Indexed LA volume	1.01	3.17	0.002	1.00–1.02	1.02	3.66	<0.001	1.01–1.03
CMR AoV regurgitant fraction	0.99	–0.82	0.412	0.98–1.01	0.98	–1.32	0.186	0.96–1.01
Valvulo-arterial impedance	1.17	1.93	0.054	1.00–1.37	1.21	1.62	0.106	0.96–1.51
LGE								
LGE presence/absence	2.22	4.00	<0.0001	1.50–3.28	3.38	3.92	<0.0001	1.84–6.22

(Continued)

Table 2. Continued

Parameter	All Patients (n=674)							
	All-Cause Mortality (n=145)				Cardiovascular Mortality (n=70)			
	HR	z	P Value	95% CI	HR	z	P Value	95% CI
LGE pattern								
Noninfarct	2.08	3.40	<0.001	1.36–3.17	2.80	3.06	0.002	1.45–5.40
Infarct	2.49	3.79	<0.001	1.55–4.00	4.54	4.36	<0.0001	2.30–8.97
LGE mass, per 1% increase	1.07	4.00	<0.0001	1.04–1.11	1.09	3.78	<0.001	1.04–1.13

ACE indicates angiotensin-converting enzyme; AoV, aortic valve; ARB, angiotensin receptor blocker; BMI, body mass index; BSA, body surface area; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CMR, cardiac magnetic resonance; HR, hazard ratio; LA, left atrial; LGE, late gadolinium enhancement; LV, left ventricular; MI, myocardial infarction; NYHA, New York Heart Association; PA, pulmonary artery; PCI, percutaneous coronary intervention; RV, right ventricular; and STS, Society of Thoracic Surgeons.

\*Using age variable scaled by epochs of 10.

AS is important, because it is the most common valvular heart disease in the developed world (>3% of those >75 years of age), and the advent of TAVR now offers a treatment option for many of those with significant comorbidities who were previously deemed inoperable. Current guidelines recommend valve intervention to improve survival and symptom status when AS is severe and ventricular decompensation is present, suggested by the onset of symptoms or a reduction in LV ejection fraction.<sup>4</sup> We have highlighted in this study an addition-

al component of this risk-benefit analysis that has been underrecognized: silent irreversible scar is very common and is associated with increased mortality. Moreover, the greater the scar burden, the higher the mortality. Previous studies have suggested that operating earlier may be beneficial for patients, but identifying which patients are likely to benefit is difficult given that many will remain asymptomatic for years. Our findings suggest that scar burden might be used to optimize the timing of surgical intervention, with half of patients demonstrating

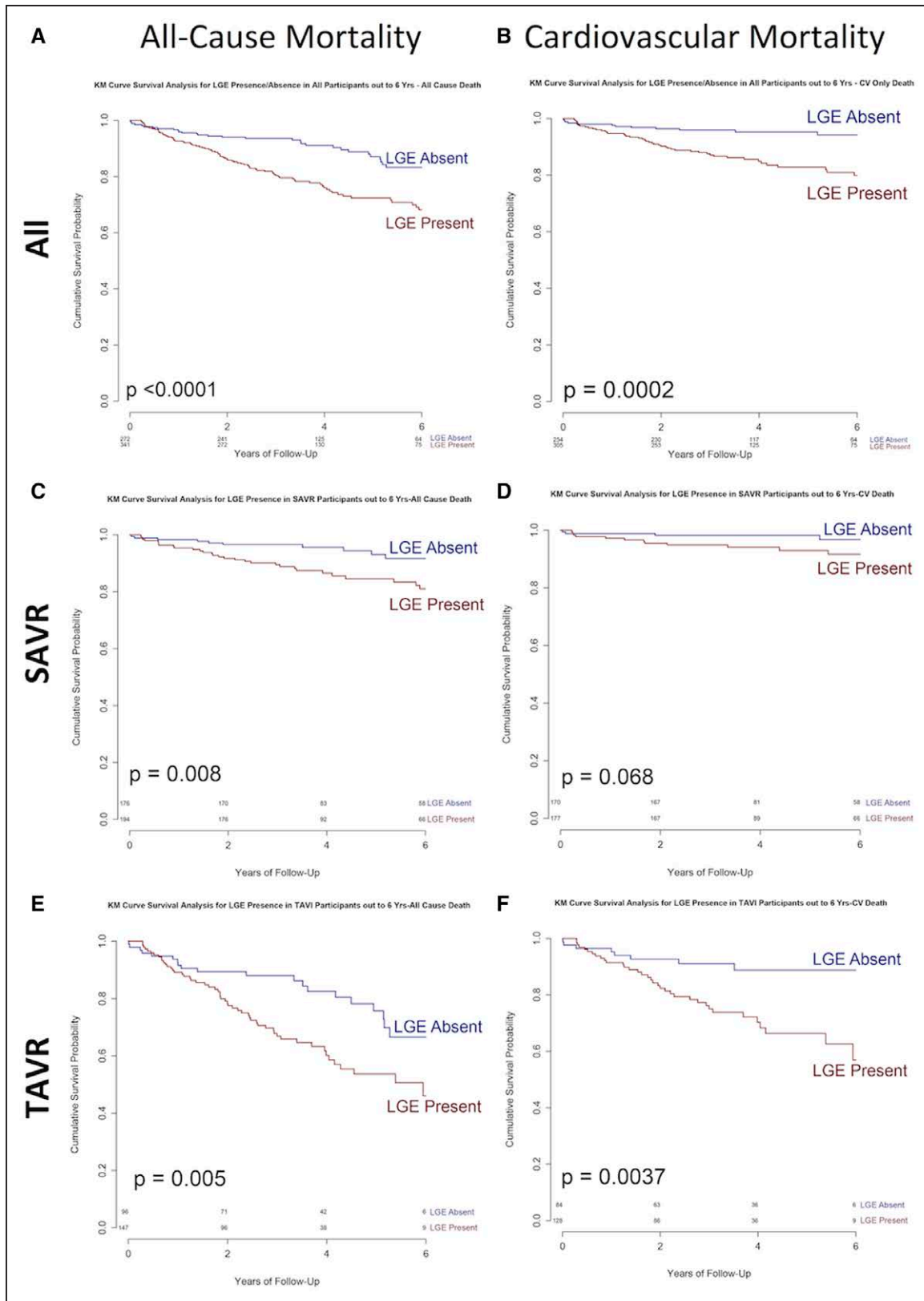
Table 3. Multivariable Model: All-Cause and Cardiovascular Mortality

	All Patients (n=674)				
	HR	z	P Value	95% CI	$\chi^2$ (P Value)
All-cause mortality (n=145)					
CMR RV ejection fraction	1.01	0.89	0.374	0.99–1.04	–862.7
CMR LV ejection fraction	1.00	–0.15	0.879	0.98–1.02	12.5 (<0.001)
CMR BSA-indexed LA volume	1.00	0.64	0.520	0.99–1.02	140.4 (<0.0001)
Atrial fibrillation	1.39	0.87	0.383	0.66–2.92	7.3 (0.007)
LV maximal wall thickness	0.93	–1.85	0.064	0.85–1.01	4.6 (0.032)
STS score	1.12	2.68	0.007	1.03–1.22	38.8 (<0.0001)
CMR BSA-indexed LV SV	1.00	–0.21	0.832	0.97–1.02	3.9 (0.050)
CAD	0.99	–0.05	0.963	0.59–1.65	11.3 (<0.001)
AVA (by echocardiography)	1.10	0.18	0.855	0.39–3.12	571.6 (<0.0001)
Age*	1.50	2.61	0.009	1.11–2.04	5.0 (0.026)
LGE presence	2.39	3.22	0.001	1.40–4.05	129.7 (<0.0001)
Bicuspid aortic valve	0.67	–1.01	0.315	0.31–1.46	1.95 (0.163)
Cardiovascular-only mortality (n=70)					
Female sex	2.17	–2.89	0.004	1.28–3.70	–89.4
Previous CAD	1.53	1.60	0.110	0.91–2.56	28.0 (<0.0001)
CMR LV EF	0.98	–2.50	0.013	0.97–1.00	22.8 (<0.0001)
Atrial fibrillation	1.43	1.17	0.240	0.79–2.58	8.2 (0.004)
Age*	1.94	4.41	<0.0001	1.44–2.60	21.3 (<0.0001)
LGE presence	3.14	3.47	<0.001	1.65–5.99	82.2 (<0.0001)

AVA indicates aortic valve area; BSA, body surface area; CAD, coronary artery disease; CMR, cardiac magnetic resonance; EF, ejection fraction; HR, hazard ratio; LA, left atrial; LGE, late gadolinium enhancement; LV, left ventricular; RV, right ventricular; STS, Society of Thoracic Surgeons; and SV, stroke volume.

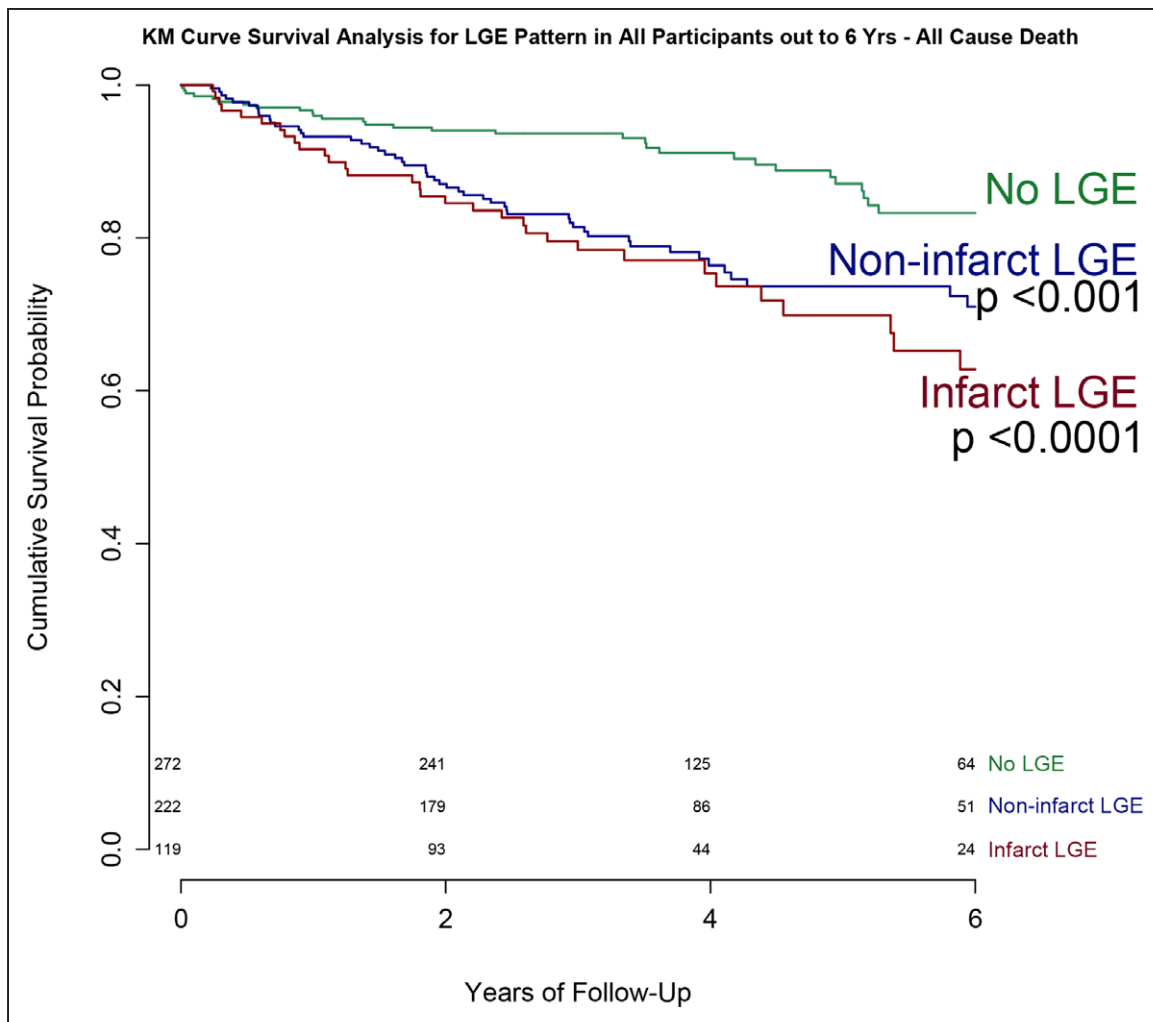
\*Using age variable scaled by epochs of 10.





**Figure 2.** All-cause and cardiovascular mortality in severe aortic stenosis by late gadolinium enhancement (LGE) status.

Kaplan-Meier (KM) survival plots showing all-cause (left) and cardiovascular (CV; right) mortality in all patients (**A** and **B**; n=674), patients treated with surgical aortic valve replacement (SAVR; **C** and **D**; n=399), and patients treated with transcatheter aortic valve replacement (TAVR; **E** and **F**; n=275), according to the presence or absence of LGE preoperatively. TAVI indicates transcatheter aortic valve implantation.



**Figure 3.** All-cause mortality in severe aortic stenosis (AS) by late gadolinium enhancement (LGE) pattern.

Kaplan-Meier (KM) survival plot showing all-cause mortality in all patients with severe AS ( $n=674$ ) by pattern of late gadolinium enhancement (no LGE, infarct LGE, noninfarct LGE; both  $P<0.001$ ). The plot summarizes 6-year follow-up data.

irreversible scar and a consequent doubling of postoperative medium-term mortality. Noninfarct pattern scar was twice as prevalent as infarct scar, and both predicted worse outcome, as previously suggested.<sup>8,9</sup> In asymptomatic severe AS, the risks of early surgery (1%–2% mortality) and prolonged risk of prosthesis-associated complications (eg, endocarditis, pacemaker dependency, bleeding, thrombosis, valve degeneration) need to be balanced against the “silent” risk of sudden cardiac death (1.5%/y) and increased risk of intervention and long-term outcome after symptoms have developed.<sup>21</sup> Our results may therefore provide a mechanism for better selection of appropriate patients for early surgery, but this remains to be tested.

### Potential Pathophysiology of Scar Formation

The ventricle in AS initially responds to pressure loading by LV hypertrophy resulting in adaptive LV remodel-

ing to maintain wall stress and cardiac performance. Despite compensatory capillary vasodilatation, over time, myocardial oxygen demand outstrips supply, leading to subendocardial ischemia and eventually LV decompensation.<sup>22–24</sup> The transition to LV decompensation occurs by fibrosis and myocyte degeneration with irreversible cell loss, mainly by autophagy and oncosis.<sup>6</sup> This process is driven by subendocardial ischemia and preceded by 2 phenomena: perfusion defects and troponin elevation (indicating myocardial cell death).<sup>25,26</sup> Replacement fibrosis ensues, which starts in the subendocardial layers first, then over time affects deeper myocardial layers,<sup>17</sup> and in turn contributes significantly to the progression of LV systolic dysfunction.<sup>6</sup> Diffuse myocardial fibrosis, with increased collagen I and III deposition around cardiomyocytes and bundles, occurs predominantly in the midmyocardium.<sup>17</sup> Patchy foci of fibrosis on LGE imaging can be indicative of widespread diffuse fibrosis. Diffuse fibrosis can be assessed by CMR  $T_1$  mapping<sup>17,27</sup> but was

not investigated in this study because it has become available only more recently.

Focal fibrosis identified by LGE is associated with adverse outcome across a wide range of myocardial pathologies<sup>28</sup> and has been shown in small single-center studies to be associated with outcome in AS.<sup>7–10</sup> The presented data place LGE-detected scar firmly as a key outcome predictor in AS and suggest that current timing of valve intervention (TAVR or SAVR), based on a combination of valve severity and symptoms, may be too late for optimal long-term outcomes. This was highlighted in a recently completed multicenter observational study in asymptomatic patients with moderate to severe AS (the PRIMID-AS study [Microvascular Dysfunction in Aortic Stenosis]; NCT01658345) showing that the presence of scar on LGE did not predict symptom onset.<sup>14</sup>

Earlier intervention, for example, in asymptomatic severe AS, may therefore warrant investigation. Despite numerous observational studies to assess risk prediction in asymptomatic AS, there have been no randomized trials of early intervention to improve outcome. Patients at risk of myocardial decompensation resulting from scar or myocardium in the process of developing scar can be identified early through the use of high-sensitivity troponin, perfusion defects, or CMR LGE techniques.<sup>15</sup> One study that will go some way in addressing this issue is the EVOLVED-AS trial (Early Valve Replacement Guided by Biomarkers of LV Decompensation in Asymptomatic Patients With Severe AS; NCT03094143), a parallel-group, multicenter, prospective randomized (open-label blinded end point) trial of early aortic valve intervention in asymptomatic patients with severe AS and evidence of LV decompensation, as evidenced by noninfarct pattern LGE. In the absence of prospective randomized trials, only registry data suggest the likely impact of early surgery.<sup>29,30</sup>

Stratifying intervention on the basis of the presence of LGE may be too late because even the small amount of scar detected in our cohort is associated with residual increased risk of all-cause and cardiovascular mortality, but until EVOLVED-AS and further studies report results, the role of, timing of, and intervals for CMR to guide decision making in patients with moderate to severe AS remain unclear.

Our study has limitations. This was an observational study of patients at surgical centers with an interest in CMR and echocardiography for clinical and research indications, potentially introducing selection bias. As a result of the contraindications for contrast-enhanced CMR, patients with severe renal impairment and preoperative pacemaker/defibrillators were not represented. Sixty-one patients did not undergo LGE imaging. There were no reported invasive measures of hemodynamics (during angiography), hematocrit, brain natriuretic peptides, or blood troponin; per clinical routine,

renal function was checked before LGE CMR but was not systematically captured or easily retrieved for this analysis. Furthermore, no routine imaging follow-up was performed. Although studies of other populations have shown that unrecognized infarct scar increases with age<sup>31</sup> and can be found in up to 10% of subjects, this would account for only a minority of the scar burden found in our population. Both TAVR and SAVR have been associated with de novo LGE, which may be associated with further myocardial decompensation.<sup>32,33</sup> Because of the lack of follow-up CMR data, the possibility of further periprocedural damage could not be excluded. Finally, multivariate analysis was not controlled for the type of intervention. This may have been important in TAVR in particular, for which the learning curve and patient selection have changed over the years.

## CONCLUSIONS

In patients with severe AS, preoperative focal myocardial scar is independently associated with mortality, its presence being associated with a 2-fold higher late mortality.

## ARTICLE INFORMATION

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## Disclosures

None.

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