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ORIGINAL RESEARCH

Myocardial Scar and Mortality in Chronic Aortic Regurgitation

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BACKGROUND: Chronic aortic regurgitation (AR) can be associated with myocardial scarring. It is unknown if scarring in AR is linked to poor outcomes and whether aortic valve replacement impacts this association. We investigated the relationship of myocardial scarring to mortality in chronic AR using cardiac magnetic resonance.

METHODS AND RESULTS: We enrolled patients with moderate or greater AR between 2009 and 2019 and performed a blinded assessment of left ventricle remodeling, AR severity, and presence and extent of myocardial scarring by late gadolinium enhancement. The primary outcome was all-cause mortality. We followed 392 patients (median age 62 [interquartile range, 51–71] years), and 78.1% were men, and 25.8% had bicuspid valves. Median aortic valve regurgitant volume was 39 mL (interquartile range, 30–60). Myocardial scar was present in 131 (33.4%) patients. Aortic valve replacement was performed in 165 (49.1%) patients. During follow-up, up to 10.8 years (median 32.3 months [interquartile range, 9.8–69.5]), 51 patients (13%) died. Presence of myocardial scar (hazard ratio [HR], 3.62; 95% CI, 2.06–6.36; $P<0.001$), infarction scar (HR, 4.94; 95% CI, 2.58–9.48; $P<0.001$), and noninfarction scar (HR, 2.75; 95% CI, 1.39–5.44; $P<0.004$) were associated with mortality. In multivariable analysis, the presence of scar remained independently associated with death (HR, 2.53; 95% CI, 1.15–5.57; $P=0.02$). Among patients with myocardial scar, aortic valve replacement was independently associated with a lower risk of mortality (HR, 0.34; 95% CI, 0.12–0.97; $P=0.03$), even after adjustment for confounders.

CONCLUSIONS: In aortic regurgitation, myocardial scar is independently associated with a 2.5-fold increase risk in mortality. Aortic valve replacement was associated with a reduction in risk of mortality in patients with scarring.

Key Words: aortic regurgitation ■ aortic valve replacement ■ cardiac magnetic resonance ■ myocardial scar

Chronic aortic regurgitation (AR) is a common form of valvular heart disease characterized by volume and pressure overload of the left ventricle (LV).[1–3] The natural history of AR is characterized by progressive LV dilatation and hypertrophy with increased wall stress and eventual LV dysfunction.[4–6] Current guidelines for AR recommend aortic valve replacement (AVR) in the presence of symptoms or in asymptomatic patients with LV dysfunction and/or dilatation.[7] The development of symptoms or other guideline triggers for surgery can imply LV decompensation associated with residual risk, even after AVR.[8,9] As a result, predictors of poor outcomes in patients with asymptomatic AR continue to be investigated with the objective of improving long-term survival.[10]

Myocardial fibrosis in AR has been described in myocardial biopsy samples of patients undergoing AVR[11–14] and in animal models of AR.[15] The late gadolinium enhancement technique using cardiac magnetic resonance (CMR) directly visualizes and quantifies myocardial replacement fibrosis (scarring), with strong histopathology validation in a variety of myocardial disease states including aortic valve disease.[13,16,17] In addition, CMR is an accurate and reproducible

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CLINICAL PERSPECTIVE

What Is New?

- We found that presence of myocardial scar on cardiac magnetic resonance was associated with mortality in patients with moderate or greater aortic regurgitation.
- Both infarction and noninfarction scar were independently associated with mortality.
- In patients with myocardial scarring, aortic valve replacement was independently associated with a lower risk of mortality.

What Are the Clinical Implications?

- Our findings suggest that myocardial scar assessment by cardiac magnetic resonance may help in risk stratifying patients with aortic regurgitation and potentially identify patients with more advanced remodeling or with limited reserve where earlier surgery may confer benefit.
- Further studies in larger multicenter cohorts of patients not meeting guideline triggers for surgery are needed to assess if earlier intervention in patients with myocardial scarring is associated with improved outcomes, particularly in patients not meeting guideline triggers for surgery.

Nonstandard Abbreviations and Acronyms

AR	aortic regurgitation
AVR	aortic valve replacement
LVESD	left ventricular end-systolic diameter
RF	regurgitant fraction
RVol	regurgitant volume

noninvasive method to quantify ventricular volumes, mass, and regurgitant volume (RVol) and regurgitant fraction (RF). The impact of myocardial scarring on survival in chronic AR has not been well established. In an earlier study with a small number of patients with AR,[13] the presence of scar was associated with all-cause mortality. However, the effect of AVR on this association and patient outcome has not been previously studied. We hypothesized that myocardial scarring detected by CMR would be independently associated with mortality in patients with moderate or severe chronic AR by CMR. A second aim was to investigate whether AVR impacts this association.

METHODS

Patient Selection

Between 2009 and 2019, we identified patients who were prospectively enrolled in the DEBAKEY-CMR registry (NCT04281823) and found to have moderate or severe AR on CMR. The typical indication for CMR was quantification of AR severity, assessment of cardiac remodeling, or aortic aneurysm evaluation. We included patients with a RVol ≥30 mL or a RF ≥30% measured by CMR. We performed a thorough baseline patient interview and review of medical records at the time of imaging. The ascertained clinical data were demographic characteristics, cardiovascular risk factors, comorbidities, coronary artery disease (CAD) or prior myocardial infarction, New York Heart Association (NYHA) functional class, and Euroscore (European System for Cardiac Operative Risk Evaluation) II. Patients were excluded if they had other confounding causes of LV scarring by clinical history or imaging findings: (1) cardiomyopathy deemed unrelated to AR (eg, hypertrophic cardiomyopathy, amyloidosis, sarcoidosis); (2) prosthetic valves; (3) complex congenital heart disease; or (4) other concomitant left sided valve disease greater than moderate in severity (eg, aortic stenosis or mitral regurgitation) determined by CMR. Patients with severe renal insufficiency precluding gadolinium contrast administration were also excluded. The patient enrollment process is summarized in Figure 1. The study was approved by the institutional review board at Houston Methodist Research Institute, and patients gave written informed consent. Because of confidentiality issues, data sets and study materials are safeguarded by the Houston Methodist Research Institute and cannot be made available to outside parties.

CMR Study Protocol

CMR studies were acquired using either 1.5-T or 3.0-T clinical scanners (Siemens Avanto, Aera, Verio, and Skyra; Siemens, Erlangen, Germany) with a phased-array coil system. A CMR examination for aortic valve assessment began with cine-CMR for anatomic and functional assessment in a short-axis stack and standard 2-chamber, 3-chamber, and 4-chamber views using a steady-state free-precession sequence with a typical flip angle of 65° to 85°; repetition time of 3.0 ms; echo time of 1.3 ms; in-plane spatial resolution of 1.7 to 2.0 mm × 1.4 to 1.6 mm; slice thickness of 6 mm, with 4 mm interslice gap; and temporal resolution of 35 to 40 ms.

Anatomic assessment of the aortic valve was performed with the use of cine steady-state free-precession sequences. The 3-chamber view and coronal left ventricular outflow views were used to prescribe a parallel series of at least 3 thin (4–5 mm) slices in short axis to provide assessment of the aortic valve's morphology.

Phase-contrast CMR was performed at the levels of the sinotubular junction, left ventricular outflow tract, and the pulmonary artery. The typical parameters were flip angle of 25 to 30°, repetition time of ≈5 ms, echo

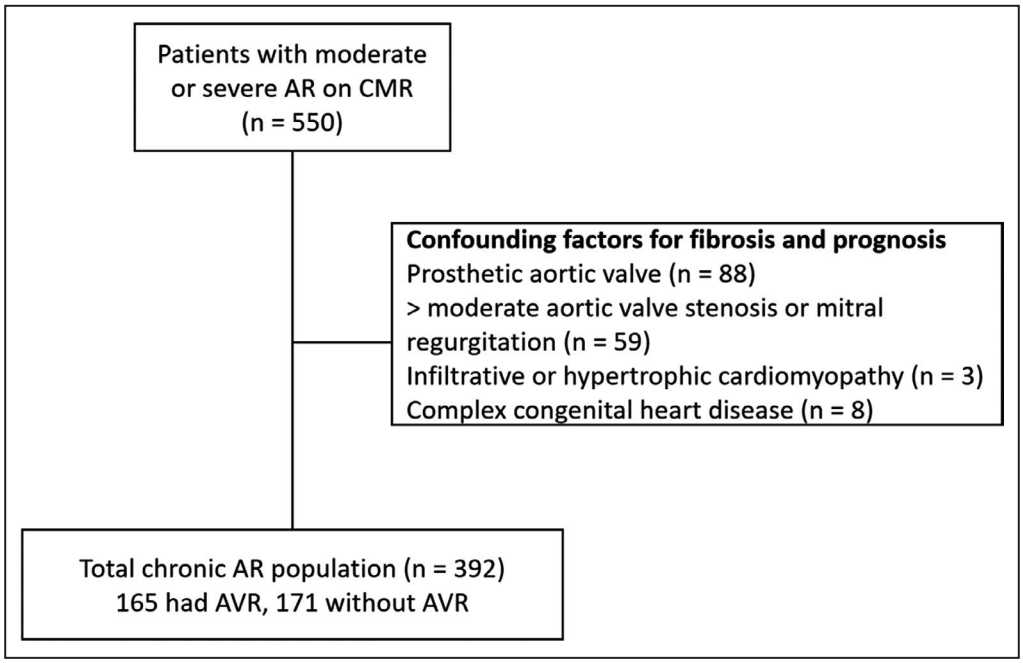

Figure 1. Detailed description of patient enrollment.
AR indicates aortic regurgitation; AVR, aortic valve replacement; and CMR, cardiac magnetic resonance.

time of 2.4 ms, reconstructed in-plane spatial resolution of ≈2.0×2.4 mm, slice thickness of 6 mm, and temporal resolution of ≈40 to 50 ms.

Late gadolinium enhancement imaging was performed using a magnitude and phase-sensitive segmented inversion-recovery sequence, ≈10 minutes after intravenous gadolinium contrast administration (gadopentetate dimeglumine or gadoterate meglumine, 0.15 mmol/kg). Parameters were in-plane spatial resolution of 1.8×1.3 mm and slice thickness of 6 mm, with inversion time adjusted to null normal myocardium. Cine-CMR and late gadolinium enhancement-CMR images were obtained in matching short-axis and long-axis planes. Shimming and delta frequency adjustments were applied to minimize off-resonance artifacts.

CMR Analysis

LV and right ventricle (RV) end-diastolic volume and end-systolic volume, left ventricular ejection fraction (LVEF), right ventricular ejection fraction, and LV mass were measured according to guidelines.[18] RVol was calculated using the direct method from phase-contrast imaging at the level of the sinotubular junction or via the difference between LV outflow tract forward flow and net pulmonary artery flow. RF was calculated as reverse volume/forward volume×100%.[19]

The presence and extent of myocardial scar was assessed in all LV segments according to the 17-myocardial-segment model by a consensus of 2 readers who were blinded to clinical history and other imaging information. To mitigate the effect of imaging artifacts, scar was only considered present if it was visually identified on 2 contiguous or orthogonal slices and seen on both magnitude and phase-sensitive image reconstruction.[18] Our previously described semiquantitative method was used to rapidly calculate burden of myocardia scar (as a percentage of the left ventricle) by summing segmental scores, weighted by the midpoint of the range of late gadolinium enhancement, and dividing by the total number of LV regions.[20,21] Figure 2 shows patient examples of observed scar patterns and AR severity assessment. All analysis was done on the same software (Precession, Heart Imaging Technologies).

Follow-Up

Clinical follow-up was initiated from the time of CMR imaging. Event data were gathered from medical record review; telephone interviews with the patients, relatives, and/or their healthcare providers; and the social security death index database. Management plans including AVR or medical therapy was ascertained. The primary outcome was all-cause mortality. The event status (censor date) for all patients was checked until April 25, 2019. M.M. and D.J.S. had full access to all the data in the study and take responsibility for its integrity and the data analysis.

Statistical Analysis

Descriptive data were reported as median (interquartile range [IQR]) for continuous variables and as

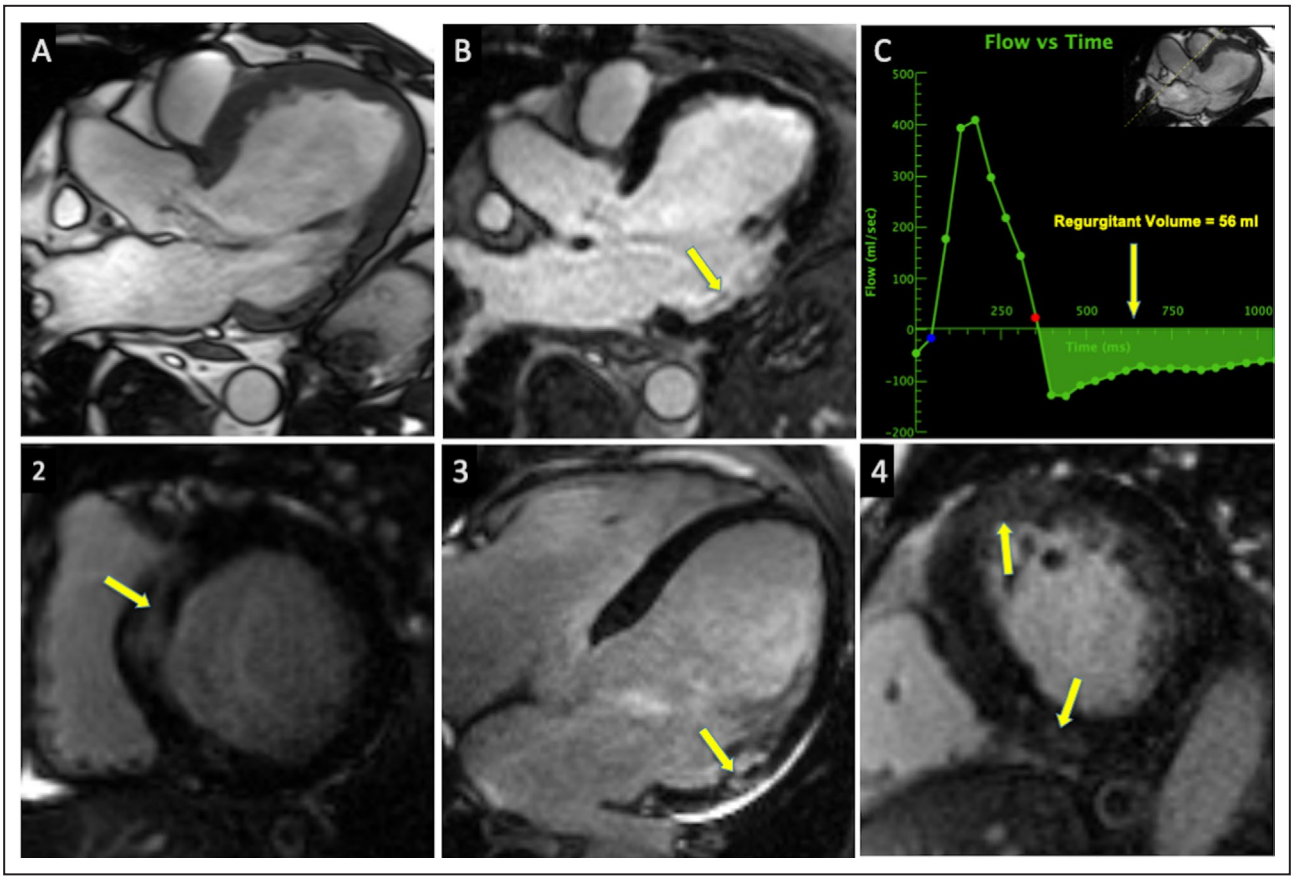

Figure 2. Patient examples.
A through C, A patient example with severe aortic regurgitation, regurgitant volume 56 mL, regurgitant fraction 55%, with associated subendocardial infarction scar in the inferolateral wall (arrow). Images 2, 3, and 4 show other examples of noninfarction pattern scar (arrows).

frequencies and proportions for categorical variables. Differences between groups (stratified by presence of scar, scar type, and AVR-scar subgroups) were compared using the χ^2 or Fisher exact tests for categorical variables and Kruskal–Wallis test for continuous variables.

Patient survival was presented using Kaplan–Meier curves. Differences between groups were compared using the log-rank test. Forest plots presented the adjusted mortality hazard ratios (HRs) of scar and other covariates of interest such as congestive heart failure, AVR, LVEF <50%, and left ventricular end-systolic diameter (LVESD) >5.0 cm.

Cox proportional hazards modeling was used to determine the contribution of potential prognostic variables to the patient outcome. The selection of covariates was conducted using Stata's Lasso command with the cross-validation selection option[22,23] and also based on clinical importance. The Euroscore II, which encompasses many of the factors associated with long-term mortality,[24] was used instead of its individual components to avoid overfitting. Schoenfeld residuals (using Stata's *phtest* command) and deviance residuals were used to test for proportional hazards and nonlinearity assumptions to ensure that these assumptions were met in all final models.

Three models were developed. In addition to other selected variables, model 1 also included the presence or absence of scar and models 2 and 3 also included the scar type or the AVR-scar subgroups, respectively.

Sensitivity analysis in subgroups without CAD and without LVEF <50% were performed. All analyses were performed on Stata version 16.1 (StataCorp LLC, College Station, TX). A *P*-value of <0.05 was considered statistically significant.

RESULTS

Study Population

Baseline characteristics are displayed in Table 1. The median (IQR) age was 62 (51–71) years, and 78.1% were men. Patients were followed for up to 10.8 years, median 32.3 (9.8–69.5) months. Median aortic valve

Table 1. Baseline Characteristics

	Total (N=392)	No Myocardial Scar (n=261)	Myocardial Scar (n=131)	*P* Value
Clinical findings				
Age, y	62.0 (51.0–71.0)	59.0 (48.0–70.0)	64.0 (57.0–74.0)	<0.001
Sex				0.74
Female	86 (21.9)	56 (21.5)	30 (22.9)	
Male	306 (78.1)	205 (78.5)	101 (77.1)	
White patients	325 (82.9)	214 (81.9)	111 (84.7)	0.64
Body mass index	27.6 (24.4–31.3)	27.4 (24.4–30.9)	28.2 (24.7–32.0)	0.12
SBP, mm Hg	132.0 (120.0–146.0)	133.0 (122.0–146.0)	130.0 (118.0–147.0)	0.14
DBP, mm Hg	69.0 (62.0–78.0)	70.0 (62.0–78.0)	67.0 (61.0–79.0)	0.32
Heart rate, bpm	68.0 (60.0–78.0)	66.0 (60.0–76.0)	70.0 (61.0–80.0)	0.04
Atrial fibrillation or flutter	26 (6.5)	13 (4.9)	13 (9.6)	0.08
Congestive heart failure	114 (29.7)	44 (17.1)	70 (55.1)	<0.001
Diabetes mellitus	46 (11.9)	19 (7.3)	27 (21.1)	<0.001
Hyperlipidemia	198 (51.0)	113 (43.5)	85 (66.4)	<0.001
Hypertension	276 (71.1)	175 (67.6)	101 (78.3)	0.03
Smoking	147 (37.5)	85 (32.6)	62 (47.3)	0.004
Coronary artery disease	78 (22.3)	37 (15.1)	41 (39.4)	<0.001
History of myocardial infarction	45 (11.7)	15 (5.8)	30 (23.4)	<0.001
Chest pain	44 (11.4)	31 (11.9)	13 (10.2)	0.62
Dyspnea	159 (41.0)	90 (34.6)	69 (53.9)	<0.001
NYHA class				<0.001
I	244 (62.2)	176 (67.4)	68 (51.9)	
II	99 (25.3)	65 (24.9)	34 (26.0)	
III	42 (10.7)	16 (6.1)	26 (19.8)	
IV	7 (1.8)	4 (1.5)	3 (2.3)	
Chronic kidney disease				0.002
None	182 (46.4)	136 (52.1)	46 (35.1)	
Moderate, GFR 50–85 mL/min	181 (46.2)	111 (42.5)	70 (53.4)	
Severe, GFR 30–50 mL/min	29 (7.4)	14 (5.4)	15 (11.5)	
Thoracic aortic aneurysm	66 (16.8)	54 (20.7)	12 (9.2)	0.004
Pulmonary hypertension				<0.001
Moderate, PASP 31–55 mm Hg	63 (16.1)	35 (13.4)	28 (21.4)	
Severe, PASP >55 mm Hg	29 (7.4)	10 (3.8)	19 (14.5)	
Euroscore II	1.4 (0.7–2.8)	1.1 (0.7–2.2)	2.0 (1.0–3.4)	<0.001
Medications				
Aspirin	156 (40.4)	79 (30.5)	77 (60.6)	<0.001
β-blocker	208 (53.7)	118 (45.4)	90 (70.9)	<0.001
ACE inhibitor	112 (29.0)	65 (25.0)	47 (37.3)	0.01
Angiotensin receptor blocker	82 (21.5)	55 (21.2)	27 (22.0)	0.87
Mineralocorticoid receptor antagonist	31 (8.1)	19 (7.4)	12 (9.7)	0.44
Statin	160 (41.5)	88 (33.8)	72 (57.1)	<0.001
Warfarin	21 (5.5)	11 (4.2)	10 (8.1)	0.12
Novel oral anticoagulant	20 (12.7)	9 (8.6)	11 (21.2)	0.03
Nitrates	20 (5.2)	5 (1.9)	15 (11.9)	<0.001
Diuretic	139 (36.0)	72 (27.7)	67 (53.2)	<0.001
Insulin	14 (3.7)	3 (1.2)	11 (8.8)	<0.001

(*Continued*)

Table 1. Continued

	Total (N=392)	No Myocardial Scar (n=261)	Myocardial Scar (n=131)	*P* Value
Calcium channel blocker	78 (20.3)	54 (20.8)	24 (19.2)	0.72
Amiodarone	24 (6.3)	12 (4.6)	12 (9.6)	0.06
CMR findings				
LVEF	58.0 (47.6–65.0)	61.0 (54.0–66.0)	49.0 (38.3–61.0)	<0.001
Indexed LVEDV	113.8 (89.5–143.6)	112.5 (89.3–139.7)	114.6 (89.6–151.9)	0.34
Indexed LVESV	47.7 (31.9–68.5)	43.9 (30.7–63.6)	55.0 (39.3–89.4)	<0.001
Indexed LV mass	91.9 (73.5–113.6)	87.4 (71.3–107.3)	104.7 (82.8–130.5)	<0.001
Indexed LA volume	56.2 (43.8–70.8)	54.5 (42.9–67.9)	62.6 (47.8–79.9)	0.004
LVEDD	5.8 (5.2–6.4)	5.8 (5.2–6.3)	6.0 (5.2–6.5)	0.19
LVESD	4.0 (3.4–4.9)	3.9 (3.3–4.6)	4.5 (3.6–5.3)	<0.001
RVEF	52.0 (46.0–56.5)	53.0 (48.0–57.0)	49.0 (41.3–55.0)	<0.001
Indexed RVEDV	80.3 (64.8–96.0)	80.8 (66.7–96.9)	78.9 (62.9–91.8)	0.17
Indexed RVESV	38.3 (29.7–49.3)	38.0 (29.6–47.7)	38.6 (29.9–53.1)	0.43
Leaflet morphology				<0.001
Bicuspid aortic valve	101 (25.8)	81 (31.0)	20 (15.3)	
Trileaflet aortic valve	291 (74.2)	180 (69.0)	111 (84.7)	
Aortic RVol	39.5 (30.0–60.0)	43.0 (31.0–65.0)	35.0 (26.0–47.0)	<0.001
Aortic RF	38.0 (32.0–45.0)	38.0 (32.0–46.0)	37.0 (33.0–43.0)	0.66
Scar size, %	0.0 (0.0–2.0)	0.0 (0.0–0.0)	4.0 (2.0–8.0)	<0.001
Aortic valve replacement	165 (42.1)	115 (44.1)	50 (38.2)	0.26

Values are presented as number (percentage) or median (interquartile range). ACE indicates angiotensin-converting enzyme; bpm, beats per minute; CMR, cardiac magnetic resonance; DBP, diastolic blood pressure; GFR, glomerular filtration rate; LA, left atrium; LV, left ventricle; LVEDD, left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVESV, left ventricular end-systolic volume; NYHA, New York Heart Association; PASP, pulmonary artery systolic pressure; RF, regurgitant fraction; RVEDV, right ventricular end-diastolic volume; RVEF, right ventricular ejection fraction; RVESV, right ventricular end-systolic volume; RVol, regurgitant volume; and SBP, systolic blood pressure.

RVol was 39 (30–60) mL, and median RF was 38% (32%–45%). Leaflet morphology was bicuspid in 101 (25.8%) patients. LV myocardial scar was present in 131 (33.4%) patients. The median scar extent was 4% (2–8) of LV mass. A noninfarction pattern scar was present in 54% of those patients, and infarction pattern scar was present in 46%. The median Euroscore II was 1.4% (0.7–2.8).

New York Heart Association class II or greater was present in 148 (37.8%) patients. A reduced LVEF of <50% was present in 108 (27.6%) of cases, and 80 (20%) patients had an LVESD of >5.0 cm (20.6% with indexed LVESD >2.5 cm/m^2 and 51% with indexed LVESD >2 cm/m^2). LV dilatation when determined by LV end-diastolic diameter >6.5 cm was present in 18.7% of patients.

Patient Characteristics According to Myocardial Scar

Patients with scar were older (64 years [57–74] versus 59 years [48–70], *P*<0.001), had a higher prevalence of hypertension (78.3% versus 67.6%; *P*<0.001), diabetes mellitus (21.1% versus 7.3%; *P*<0.001), smoking (47.3% versus 32.6%; *P*<0.001), CAD (29.3% versus 13.1%; *P*<0.001), and a higher Euroscore II (2% [1–3.4] versus 1.1% [0.7–2.2]; *P*<0.001). With regard to aortic regurgitant severity or LV remodeling parameters, patients with scar had a lower RVol (35 mL [26–47] versus 43 mL [31–65]; *P*<0.001), similar RF (37% [33–43] versus 38% [32–46]; *P*=0.66), and similar left ventricular end-diastolic volume (114.6 [89.6–151.9] versus 112.5 [89.3–139.7]; *P*=0.34), but a lower LVEF (49% [38.3–61] versus 61% [54–66]; *P*<0.001) along with higher indexed LV mass and higher indexed left ventricular end-systolic volume. Other differences are noted in Table 1.

Outcome Analysis

During a median follow-up of 32.3 (IQR, 9.8–69.5) months, 51 patients (13%) died. The annualized mortality in the entire cohort was 3.8% per year. On univariate analysis, multiple clinical and CMR variables were associated with death (Table S1). Patients with myocardial scar had a significantly higher hazard of mortality (HR, 3.62; 95% CI, 2.06–6.36; *P*<0.001; Figure 3). Both infarction scar (HR, 4.94; 95% CI, 2.58–9.48; *P*<0.001)

and noninfarction pattern scar (HR, 2.75; 95% CI, 1.39–5.44; *P*<0.004) were independently associated with mortality. Quantitatively, every 2% increase in LV myocardial scar burden was associated with a 9% increase of relative risk of mortality (HR, 1.09; 95% CI, 1.04–1.14; *P*<0.001). Multivariable analysis was done adjusting for Euroscore, leaflet morphology, CAD, RVol, heart failure, AVR, hypertension, smoking, and presence of scar (Table 2, model 1). Scar, heart failure, smoking, CAD, and AVR were selected based on the Lasso. The other variables were included based on clinical importance. The likelihood ratio test comparing the models with and without the added variables had a significant *P* value, which indicated that variables selected for clinical importance should be included in the final models.

Variables independently associated with all-cause mortality were heart failure (HR, 2.26; 95% CI, 1.04–4.93; *P*=0.04) and presence of scar (HR, 2.53; 95% CI, 1.15–5.57; *P*=0.02), whereas AVR was associated with reduced mortality (HR, 0.27; 95% CI, 0.1–0.71; *P*=0.01). Both infarction scar and noninfarction scar were independently associated with mortality (Table 2, model 2). The scar burden as percentage of the LV was not associated with mortality after the same multivariable adjustments. AVR as a time-varying covariate was not significantly associated with survival in the first model.

Outcomes According to Management Strategy

Follow-up data on AVR status were available in 336 (85.7%) of the cohort. AVR was performed in 165 (49.1%) patients (158 surgical AVR and 7 transcatheter AVR), and the remainder were managed medically. The median duration from the CMR exam to AVR was 1.02 (IQR, 0.2–3.3) months. There were 31 (18.1%) deaths in the medical therapy group and 17 (10.3%) deaths in the AVR group. The annualized mortality rate was 2.4% per year in the AVR group and 7.4% per year in the medical therapy group. In the 165 patients who underwent AVR, there were 114 with class I indications for surgery and 48 with

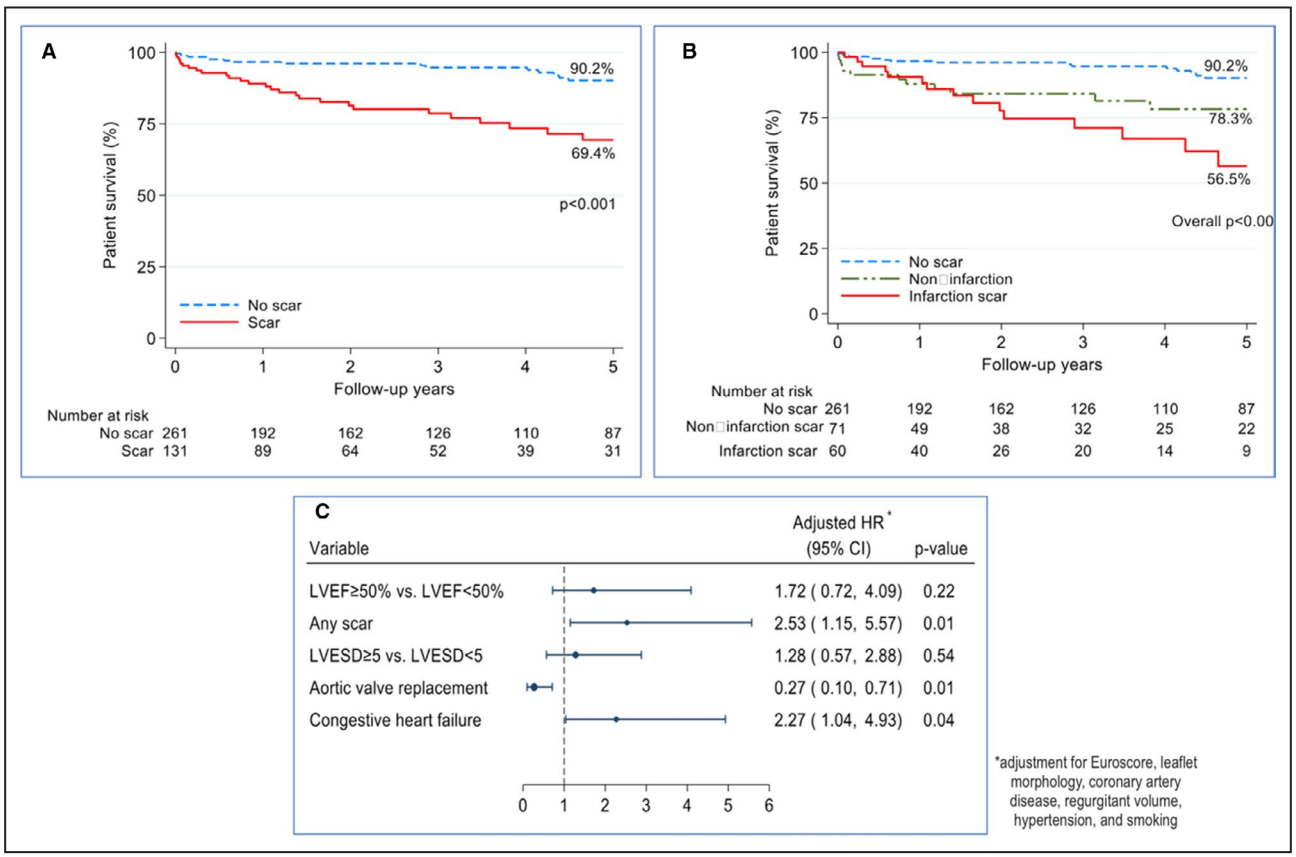

Figure 3. Survival according to presence or absence of scar.
Kaplan Meier curves for survival by presence of scar (**A**) and scar type (**B**). **C**, Forest plot for the adjusted hazard ratios for mortality of late gadolinium enhancement, aortic valve replacement, and traditional guidelines triggers for aortic valve replacement in aortic regurgitation (adjustment for Euroscore, leaflet morphology, coronary artery disease, regurgitant volume, hypertension, and smoking). LVEF indicates left ventricular ejection fraction; and LVESD, left ventricular end systolic diameter.

Table 2. Multivariable Cox Proportional Hazard Models for Predictors of Mortality

	Clinical Variables and Presence of Scar		Clinical Variables and Scar Type		Clinical Variables and Scar/AVR Subgroups	
	Adjusted HR (95% CI)	*P* Value	Adjusted HR (95% CI)	*P* Value	Adjusted HR (95% CI)	*P* Value
Euroscore	1.01 (0.97–1.05)	0.72	1.02 (0.99–1.06)	0.24	1.01 (0.97–1.05)	0.72
Trileaflet vs bicuspid valve	1.76 (0.60–5.16)	0.31	2.52 (0.88–7.25)	0.09	1.76 (0.60–5.16)	0.31
CAD	1.63 (0.74–3.59)	0.22	…	…	1.63 (0.74–3.59)	0.22
Aortic RVol, per 5 mL increase	1.05 (0.97–1.15)	0.24	1.04 (0.98–1.12)	0.21	1.05 (0.97–1.15)	0.24
AVR	0.27 (0.10–0.71)	0.01	0.40 (0.20–0.82)	0.01	…	…
CHF	2.26 (1.04–4.93)	0.04	1.91 (1.00–3.65)	0.049	2.26 (1.03–4.96)	0.04
Hypertension	1.50 (0.60–3.72)	0.38	1.69 (0.70–4.10)	0.24	1.50 (0.60–3.73)	0.38
Smoking	1.62 (0.79–3.36)	0.19	1.65 (0.88–3.09)	0.12	1.62 (0.79–3.36)	0.19
Presence of scar	2.53 (1.15–5.57)	0.02	…	…	…	…
Scar type						
None	…	…	(Reference)		…	…
Noninfarction scar	…	…	2.24 (1.05–4.75)	0.04	…	…
Infarction scar	…	…	2.19 (1.03–4.64)	0.04	…	…
AVR-scar subgroup						
AVR (+)/scar (–)	…	…	…	…	(Reference)	
AVR (–)/scar (–)	…	…	…	…	3.76 (1.00–14.09)	0.049
AVR (+)/scar (+)	…	…	…	…	2.55 (0.64–10.12)	0.18
AVR (–)/scar (+)	…	…	…	…	9.48 (2.36–38.03)	0.002

AVR indicates aortic valve replacement; CAD, coronary artery disease; CHF, congestive heart failure; HR, hazard ratio; and RVol, regurgitant volume.

class II indications for surgery (12 based on LV diameter criteria and 36 based on concomitant surgery criteria). There were 3 patients who underwent AVR for complicated endocarditis. In the medical therapy group of patients who met class I indications for AVR based on the CMR results (RVol ≥45 or RF ≥40% with symptoms or LVEF <50%), there were 12 patients who did not undergo surgery after multidisciplinary discussion, usually because of a small regurgitant volume ≈30 to 40 mL with a high regurgitant fraction >40%, as a result of a small stroke volume and thus were considered to have moderate AR.

In patients who met class II indications for AVR (RVol ≥45 or RF ≥40% with LVESD >5 cm or LVESD >2.5 cm/m^2 or left ventricular end-diastolic diameter >6.5 cm), there were 2 patients who were treated medically: 1 had atypical symptoms (currently being monitored) and 1 who was deemed moderate AR. No other surgical indications (aortic aneurysm or coronary bypass surgery) were evident in these patients.

A comparison between the AVR and medical management groups is presented in Table S2. Patients who underwent AVR were younger (age 59 [49–65] versus 66 [55–75] years; *P*<0.001), had higher Euroscore II (1.8% [0.7–3.6] versus 1.3% [0.7–2.5]; *P*=0.02), and were more likely to have a bicuspid valve (30.9% versus 21.2%; *P*=0.04) compared with the medical management group. The AVR group had a higher RVol (53 [38–80] versus 32 [26–42]; *P*<0.001), higher RF (43% [35–51] versus 35% [31–40]; *P*<0.001), and greater left ventricular remodeling.

Outcomes According to Management Strategy and Scar Presence

When stratifying patients according to the presence of scar and management strategy, patients with scar who underwent medical management had the highest hazard of mortality (Figure 4). In multivariable analysis, patients with scar and a medical management strategy had a significantly higher hazard of mortality (HR, 9.48; 95% CI, 2.36–38.03; *P*=0.002) compared with those who underwent AVR and had no myocardial scar (Table 2, model 3). Among patients with myocardial scar, AVR was independently associated with a lower hazard of mortality (HR, 0.34; 95% CI, 0.12–0.97; *P*=0.04) (Table 3). A comparison between AVR and medical management in patients with scar is presented in Table S3. We performed separate sensitivity analysis excluding patients with CAD (Table S4) and patients with LVEF <50% (Table S5), and the results remained consistent with the main findings. In the subgroup of patients who

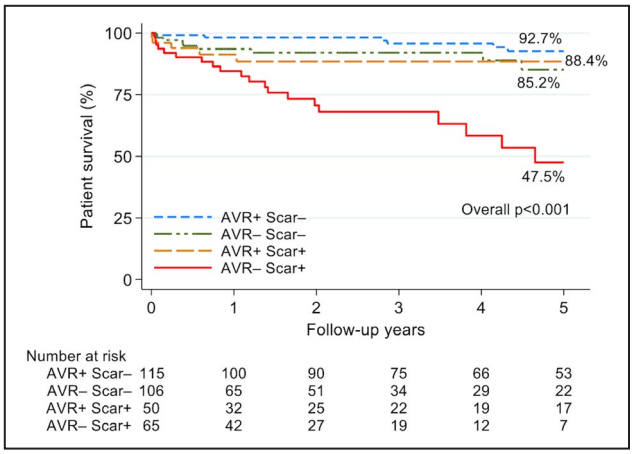

Figure 4. Kaplan—Meier curves for patient survival according to AVR and scar subgroups.
AVR indicates aortic valve replacement.

had LVEF ≥50%, there was no difference in LVEF between patients with and without scar (median [IQR] of 62.0% [57.0%–68.1%] and 61.2% [55.5%–65.3%], respectively; *P*=0.11). Although LVEF was not included in the final model, it was forced in the initial model, which turned out to be not statistically significant. Given that there was no significant difference in the performance of the model with and without LVEF and that LVEF is included within the Euroscore calculation, LVEF was removed from the final model to keep the number of covariates at a minimum. Therefore, LVEF is not likely to have a significant confounding effect in this subgroup of patients.

DISCUSSION

In patients with moderate or severe AR by CMR, the presence and extent of myocardial replacement fibrosis–or scar–were associated with an increased risk of mortality. Myocardial scar was present in a third of patients with AR, and both infarction and noninfarction pattern scar were associated with mortality in multivariable analysis. In patients with scar, we observed that AVR was associated with a lower mortality, the worst outcome being in patients with scar treated medically.

Outcome of Patients With AR and Fibrosis

Natural history studies of AR described a prolonged asymptomatic course characterized by progressive LV dilatation and low mortality rates before the onset of symptoms or LV dysfunction. However, patients included in these studies were generally younger, and outcomes might differ from current practice.[5,25–27] In our study, we investigated a contemporary cohort of patients with AR with multiple comorbidities, reflective

Table 3. Cox Proportional Hazards Models for Risk of Death in Patients With Scar

Hazard Ratio for AVR (vs Medical Management)	Hazard Ratio (95% CI)	*P* Value
Model 1: unadjusted	0.33 (0.14–0.77)	0.01
Model 2: adjusted for Euroscore	0.34 (0.14–0.79)	0.01
Model 3: adjusted for Euroscore, CAD, CHF, HTN, smoking, bicuspid vs trileaflet valve	0.34 (0.12–0.97)	0.04

AVR indicates aortic valve replacement; CAD, coronary artery disease; CHF, congestive heart failure; and HTN, hypertension.

of the increasing burden of valvular heart disease in older patients.[28] It has long been recognized that the pressure and volume overload exerted on the LV by AR results in cellular and extracellular structural changes, including myocardial fibrosis.[11,14,29–31] Animal models have shown that myocardial fibrosis in AR is related to increased fibronectin and glucosamine expression with altered collagen expression and organization.[15,30] Taniguchi et al[32] showed that excessive interstitial fibrosis was independently associated with myocardial contractile dysfunction in a hemodynamic study of patients with isolated AR. Interestingly, the percent interstitial fibrosis on biopsy had no significant correlation with ventricular volume or mass, suggesting that patients may differ in their maladaptive tissue remodeling to AR.

The detection of myocardial scar by CMR has identified high-risk cohorts in many cardiovascular diseases, including aortic valve stenosis[33] and AR in a smaller study.[34] Given its noninvasive nature and strong histopathologic correlation, CMR assessment of scar has emerged as a powerful modality to evaluate LV dysfunction and is being tested in a randomized trial in the early treatment of asymptomatic AS (EVOLVED-AS [Early Valve Replacement Guided by Biomarkers of LV Decompensation in Asymptomatic Patients With Severe AS] trial; NCT03094143). Our findings extend results from the pure pressure-overload state of aortic stenosis to the mixed pressure and volume overload state of AR, although the exact mechanisms and patterns of fibrosis development may not be the same between the 2 distinct lesions.[29,30] The scar size in our population was small and could be argued to not be significant. However, it should be noted that scar extent and outcomes are not linear. In dilated cardiomyopathy, the presence of scar was reported to be associated with a large increase in the risk of mortality and sudden death, even when the extent is small.[35] Furthermore, the extent of scar in aortic stenosis studies has been relatively small as well.[33]

Management of Patients With AR

Recent studies have demonstrated improved outcomes when treating AR in patients at lower LV

remodeling thresholds than using currently recommended guidelines. In a recent large study of patients with grade III–IV AR and preserved LV ejection fraction, 96% of deaths occurred in those with an indexed LV end-systolic dimension of <2.5 cm/m^2, although determining the cause of death has inherent challenges. In the group that did not meet the guidelines' criteria for intervention, AVR was associated with improved long-term survival.[9] However, the risk of surgery, although lower than in past decades, still has to be balanced against watchful waiting. Furthermore, percutaneous therapies for AR continue to be developed, and outcomes continue to improve with newer generation valves.[36] There remains a need for strong and reproducible biomarkers that could further risk-stratify patients. Our findings suggest that myocardial scar assessment by CMR may serve as one; and potentially identify patients with more advanced remodeling or with limited reserve where earlier surgery, at lesser degrees of AR, might confer benefit. A supportive finding to this hypothesis is that performing AVR appears to reduce the risk of mortality in those with myocardial scar independent of their surgical risk profile and comorbidities. Indeed, patients who underwent AVR had a higher Euroscore than those who were managed medically, and a small percentage of patients who were managed medically met guideline indications for AVR, arguing against patients in the medical therapy arm being selected out of surgical treatment. However, because patients who underwent AVR met the conventional guideline criteria for intervention, further investigation is required to determine if the presence of scar could identify patients in whom earlier surgery may confer benefit in the absence of another established indication. Other confounding factors may not be accounted for, and further confirmation in multicenter studies is warranted.

Limitations

This is an observational study from a single tertiary referral center, and this results in an inherent selection bias. Referral biases may affect the prevalence of disease and comorbidities in this study, and patients with end-stage renal disease were not included. We did not exclude patients with CAD so as to maintain generalizability of the study findings, especially in an older population with numerous comorbidities reflecting contemporary patients with AR. The prevalence of AR increases with advancing age reaching >16% in the elderly population aged >70 years.[28] Furthermore, not all patients underwent coronary angiography to determine coronary artery disease status, but clinical history and available diagnostic testing results were thoroughly evaluated. Other biomarkers such as extracellular volume fraction, brain natriuretic peptide, or echocardiographic speckle tracking parameters were not available, and cause of death was not ascertained. Although our models have <10 events per predictor as suggested by Harrell et al,[37] which might raise questions on overfitting, the selected variables are clinically important, and there is a growing number of publications suggesting that the rule of 10 events per predictor can be relaxed.[38,39]

CONCLUSIONS

In patients with moderate or severe AR, myocardial scar is independently associated with a 2.5-fold increase in mortality. Both infarction and noninfarction scar incur an increased risk of death, and AVR appears to mitigate the hazard in those with myocardial scar. Further confirmation is needed to determine if the prognostic value of CMR scar detection identifies patients with AR with maladaptive remodeling and whether earlier surgery leads to improved outcomes in patients with AR with myocardial scarring in the absence of conventional guideline criteria for surgery.

ARTICLE INFORMATION

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Supplementary Material

Tables S1–S5

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SUPPLEMENTAL MATERIAL

Table S1. Univariable Cox proportional hazard predictors of mortality.

	Alive (*n*=341)	Dead (*n*=51)	Unadjusted HR (95% CI)	p-value
Clinical Variables				
Age (years), median (IQR)	61.0 (50.0, 70.0)	66.0 (57.0, 76.0)	1.03 (1.01, 1.05)	0.003
Female sex	69 (20.2)	17 (33.3)	1.73 (0.97, 3.10)	0.07
BMI, median (IQR)	27.5 (24.4, 31.2)	27.8 (24.2, 31.5)	1.02 (0.98, 1.07)	0.39
Heart rate (bpm), median (IQR)	66.0 (60.0, 75.0)	78.0 (63.0, 86.0)	1.04 (1.02, 1.06)	<0.001
SBP (mmHg), median (IQR)	133.0 (122.0, 146.0)	126.0 (112.0, 151.0)	1.00 (0.98, 1.01)	0.54
DBP (mmHg), median (IQR)	69.0 (61.5, 78.0)	68.5 (62.0, 82.0)	1.01 (0.99, 1.03)	0.40
Congestive heart failure	85 (25.5)	29 (56.9)	4.02 (2.30, 7.03)	<0.001
Diabetes	36 (10.7)	10 (20.0)	1.97 (0.99, 3.95)	0.06
Hyperlipidemia	164 (48.7)	34 (66.7)	2.33 (1.30, 4.18)	0.01
Hypertension	232 (68.8)	44 (86.3)	2.68 (1.21, 5.95)	0.02
Smoking	118 (34.6)	29 (56.9)	2.54 (1.46, 4.43)	0.001
Coronary artery disease	60 (19.2)	18 (48.6)	3.86 (2.02, 7.37)	<0.001
History of myocardial infarction	33 (9.8)	12 (24.0)	3.17 (1.65, 6.09)	0.001
Chest pain	39 (11.6)	5 (10.0)	1.01 (0.40, 2.55)	0.98
Dyspnea	129 (38.3)	30 (58.8)	2.12 (1.21, 3.71)	0.01
Euroscore, median (IQR)	1.2 (0.7, 2.5)	2.1 (1.3, 4.0)	1.07 (1.03, 1.10)	<0.001
Other components of Euroscore				
Insulin dependent diabetes	1 (0.3)	3 (5.9)	4.26 (1.32, 13.70)	0.02
Angina at rest	2 (0.6)	0 (0.0)	NA	NA
NYHA class				
I	222 (65.1)	22 (43.1)	(reference)	
II	85 (24.9)	14 (27.5)	1.66 (0.85, 3.25)	0.14
III	32 (9.4)	10 (19.6)	3.04 (1.44, 6.43)	0.004
IV	2 (0.6)	5 (9.8)	12.82 (4.83, 34.03)	<0.001
Chronic Kidney Disease				
None	164 (48.1)	18 (35.3)	(reference)	
Moderate (GFR 50-85 ml/min)	154 (45.2)	27 (52.9)	1.73 (0.95, 3.15)	0.07
Severe (GFR 30-50 ml/min)	23 (6.7)	6 (11.8)	2.92 (1.15, 7.38)	0.02
Thoracic aortic disease	60 (17.6)	6 (11.8)	0.66 (0.28, 1.55)	0.340
Pulmonary hypertension				
None or Not available	274 (80.4)	26 (51.0)	(reference)	
Moderate (PASP 31-55 mmHg)	46 (13.5)	17 (33.3)	3.56 (1.93, 6.59)	<0.001
Severe (PASP >55 mmHg)	21 (6.2)	8 (15.7)	4.76 (2.14, 10.57)	<0.001
Extracardiac arteriopathy	24 (7.0)	6 (11.8)	2.21 (0.94, 5.20)	0.07
Chronic lung disease	10 (2.9)	4 (7.8)	2.83 (1.02, 7.86)	0.046
Poor mobility	1 (0.3)	2 (3.9)	14.68 (3.47, 62.16)	<0.001
Redo surgery	37 (10.9)	6 (11.8)	1.10 (0.47, 2.57)	0.83

Active endocarditis	6 (1.8)	2 (3.9)	1.68 (0.41, 6.93)	0.47
Critical preoperative state	0 (0.0)	2 (3.9)	13.34 (3.20, 55.55)	<0.001
LV dysfunction				
None	249 (73.0)	28 (54.9)	(reference)	
Mild	78 (22.9)	16 (31.4)	2.01 (1.08, 3.73)	0.03
Moderate	10 (2.9)	2 (3.9)	2.03 (0.48, 8.56)	0.33
Severe	4 (1.2)	5 (9.8)	5.36 (2.06, 13.97)	0.001
Emergency/Urgent procedure	0 (0.0)	3 (5.9)	17.14 (5.26, 55.85)	<0.001
Number of interventions needed (*)				
1	255 (74.8)	39 (76.5)	(reference)	
2	76 (22.3)	6 (11.8)	0.52 (0.22, 1.23)	0.14
3	10 (2.9)	6 (11.8)	2.28 (0.96, 5.40)	0.06
Medications				
Aspirin	135 (40.2)	21 (42.0)	1.06 (0.60, 1.86)	0.84
Beta blocker	174 (51.6)	34 (68.0)	1.94 (1.07, 3.52)	0.03
ACE inhibitor	94 (28.0)	18 (36.0)	1.30 (0.73, 2.31)	0.38
Angiotensin receptor blocker	72 (21.6)	10 (20.4)	0.94 (0.47, 1.89)	0.87
Mineralocorticoid receptor antagonist	21 (6.3)	10 (20.8)	3.69 (1.83, 7.42)	<0.001
Warfarin	15 (4.5)	6 (12.2)	2.15 (0.91, 5.06)	0.08
Novel oral anticoagulant	20 (13.4)	0 (0.0)	NA	NA
Nitrates	14 (4.2)	6 (12.0)	3.59 (1.52, 8.46)	0.003
Diuretics	109 (32.4)	30 (60.0)	2.81 (1.60, 4.95)	<0.001
Insulin	8 (2.4)	6 (12.0)	2.92 (1.24, 6.87)	0.01
Calcium channel blocker	70 (20.9)	8 (16.0)	0.80 (0.37, 1.70)	0.56
Statin	135 (40.2)	25 (50.0)	1.51 (0.87, 2.64)	0.14
Amiodarone	20 (6.0)	4 (8.0)	1.55 (0.56, 4.31)	0.40
CMR Variables				
LVEF, median (IQR)	59.0 (49.7, 65.0)	52.0 (38.7, 62.0)	0.97 (0.95, 0.98)	<0.001
Indexed LVEDV, median (IQR)	113.8 (90.1, 143.3)	114.0 (76.7, 145.0)	1.00 (1.00, 1.01)	0.30
Indexed LVESV, median (IQR)	46.2 (31.7, 68.0)	51.4 (34.1, 77.5)	1.01 (1.00, 1.02)	0.004
Indexed LV mass, median (IQR)	89.9 (72.8, 113.6)	99.1 (74.1, 116.1)	1.00 (0.99, 1.01)	0.58
RVEF, median (IQR)	52.0 (47.0, 56.9)	51.0 (34.0, 55.0)	0.96 (0.94, 0.98)	0.001
Indexed RVEDV, median (IQR)	80.8 (66.0, 96.4)	75.3 (56.3, 92.9)	1.00 (0.99, 1.01)	0.76
Indexed RVESV, median (IQR)	38.3 (30.0, 49.0)	38.0 (25.1, 52.5)	1.01 (1.00, 1.02)	0.04
Leaflet morphology				
Bicuspid	97 (28.4)	4 (7.8)	(reference)	
Trileaflet	244 (71.6)	47 (92.2)	4.26 (1.53, 11.84)	0.01
Aortic RVol, per 5mL increase, median (IQR)	8.0 (6.0, 12.0)	7.0 (4.6, 12.0)	0.96 (0.90, 1.02)	0.20
Aortic RF, per 5% increase, median (IQR)	7.4 (6.4, 9.0)	7.6 (6.8, 9.0)	1.08 (0.95, 1.23)	0.26
Indexed LA volume, median (IQR)	56.0 (44.0, 69.7)	60.4 (41.2, 84.1)	1.01 (1.00, 1.02)	0.045

Scar parameters				
Scar size (%), median (IQR)	0.0 (0.0, 2.0)	2.0 (0.0, 5.0)	1.04 (1.02, 1.07)	<0.001
Scar size, per 2% increase, median (IQR)	0.0 (0.0, 1.0)	1.0 (0.0, 2.5)	1.09 (1.04, 1.14)	<0.001
Presence of scar				
No	241 (70.7)	20 (39.2)	(reference)	
Yes	100 (29.3)	31 (60.8)	3.62 (2.06, 6.36)	<0.001
Scar Pattern				
None	241 (70.7)	20 (39.2)	(reference)	
Non-infarction pattern	57 (16.7)	14 (27.5)	2.75 (1.39, 5.44)	0.004
Infarction pattern	43 (12.6)	17 (33.3)	4.94 (2.58, 9.48)	<0.001
Aortic Valve Replacement	148 (43.4)	17 (33.3)	0.48 (0.27, 0.86)	0.01
AVR-scar subgroup (N=343)				
AVR (+)/scar (-)	106 (36.8)	9 (18.8)	(reference)	
AVR (-)/scar (-)	96 (33.3)	10 (20.8)	2.03 (0.82, 5.03)	0.13
AVR (+)/scar (+)	42 (14.6)	8 (16.7)	2.56 (0.98, 6.63)	0.054
AVR (-)/scar (+)	44 (15.3)	21 (43.8)	7.93 (3.57, 17.60)	<0.001
AVR-scar subgroup (N=343)				
Other subgroups	244 (84.7)	27 (56.3)	(reference)	
AVR (-)/scar (+)	44 (15.3)	21 (43.8)	4.97 (2.77, 8.91)	<0.001

ACE=angiotensin converting enzyme, BMI=body mass index, BSA=body surface area, DBP=diastolic blood pressure, IQR=interquartile range, LA=left atrium, LVEF=left ventricular ejection fraction, LVEDV=left ventricular end-diastolic volume, LVESV= left ventricular end-systolic volume, LVEDD=left ventricular end-diastolic diameter, LVESD=left ventricular end-systolic diameter, RVEF=right ventricular ejection fraction, RVEDV=right ventricular end-diastolic volume, RVESV=right ventricular end-systolic volume, RVol=regurgitant volume, RF=regurgitant fraction, SBP=systolic blood pressure

(*) Interventions needed along with AVR could include coronary bypass grafting, aortic aneurysm repair, left atrial appendage resection or ligation.

Table S2. Baseline characteristics according to management strategy.

	Total (N=336)	Medical Management (*n*=171)	AVR (*n*=165)	p-value
Clinical Findings				
Age (years), median (IQR)	62.0 (52.0, 71.0)	66.0 (55.0, 75.0)	59.0 (49.0, 67.0)	<0.001
Sex				0.52
Female	70 (20.8)	38 (22.2)	32 (19.4)	
Male	266 (79.2)	133 (77.8)	133 (80.6)	
Body mass index, median (IQR)	27.6 (24.4, 31.4)	27.0 (24.2, 31.4)	28.2 (24.4, 31.8)	0.15
SBP (mmHg), median (IQR)	132.5 (120.0, 146.0)	134.0 (121.5, 148.0)	130.0 (120.0, 143.0)	0.15
DBP (mmHg), median (IQR)	68.5 (61.0, 78.0)	70.0 (62.0, 80.0)	67.5 (60.0, 76.0)	0.06
Heart rate (bpm), median (IQR)	68.0 (60.0, 78.0)	68.0 (60.0, 80.0)	68.0 (60.0, 77.0)	0.59
Congestive heart failure	99 (29.8)	55 (32.5)	44 (27.0)	0.27
Diabetes	41 (12.3)	26 (15.2)	15 (9.2)	0.10
Hyperlipidemia	174 (52.1)	94 (55.3)	80 (48.8)	0.23
Hypertension	243 (72.8)	129 (75.4)	114 (69.9)	0.26
Smoking	130 (38.7)	74 (43.3)	56 (33.9)	0.08
Coronary artery disease	64 (21.2)	42 (26.9)	22 (15.1)	0.01
Prior myocardial infarction	37 (11.1)	27 (16.0)	10 (6.1)	0.004
Chest pain	39 (11.6)	22 (12.9)	17 (10.4)	0.48
Dyspnea	144 (43.0)	69 (40.4)	75 (45.7)	0.32
NYHA class				<0.001
I	198 (58.9)	120 (70.2)	78 (47.3)	
II	92 (27.4)	36 (21.1)	56 (33.9)	
III	39 (11.6)	11 (6.4)	28 (17.0)	
IV	7 (2.1)	4 (2.3)	3 (1.8)	
Chronic Kidney Disease				0.30
None	154 (45.8)	72 (42.1)	82 (49.7)	
Moderate (GFR 50-85 ml/min)	159 (47.3)	88 (51.5)	71 (43.0)	
Severe (GFR<50 ml/min)	23 (6.8)	11 (6.4)	12 (7.3)	
Thoracic aortic disease	61 (18.2)	18 (10.5)	43 (26.1)	<0.001
Pulmonary hypertension				0.96
Moderate (PASP 31-55 mmHg)	57 (17.0)	28 (16.4)	29 (17.6)	
Severe (PASP >55 mmHg)	27 (8.0)	14 (8.2)	13 (7.9)	
Euroscore, median (IQR)	1.5 (0.7, 3.0)	1.3 (0.7, 2.5)	1.8 (0.7, 3.6)	0.02
Medications				
Aspirin	135 (40.5)	73 (42.9)	62 (38.0)	0.36
Beta blocker	178 (53.3)	97 (56.7)	81 (49.7)	0.20
ACE inhibitor	96 (28.8)	49 (28.8)	47 (28.8)	1.00
Angiotensin receptor blocker	71 (21.5)	41 (24.3)	30 (18.6)	0.21
Mineralocorticoid receptor antagonist	28 (8.5)	17 (10.1)	11 (6.9)	0.30
Warfarin	18 (5.4)	9 (5.3)	9 (5.5)	0.94
Novel oral anticoagulant	15 (11.4)	10 (12.2)	5 (10.0)	0.70
Nitrates	19 (5.7)	10 (5.9)	9 (5.5)	0.88
Diuretic	122 (36.6)	57 (33.5)	65 (39.9)	0.23
Insulin	13 (3.9)	7 (4.2)	6 (3.7)	0.81
Calcium channel blocker	66 (19.9)	38 (22.4)	28 (17.3)	0.25

Statin	138 (41.4)	83 (48.5)	55 (34.0)	0.01
Amiodarone	21 (6.3)	11 (6.5)	10 (6.2)	0.92
CMR Findings				
LVEF, median (IQR)	58.0 (46.7, 64.9)	58.1 (46.0, 64.0)	57.0 (48.0, 65.0)	0.55
indexed LVEDV, median (IQR)	116.3 (90.3, 145.9)	105.4 (86.2, 135.8)	127.0 (96.6, 157.3)	<0.001
Indexed LVESV, median (IQR)	48.9 (32.7, 71.3)	44.7 (31.6, 65.6)	54.8 (35.7, 76.0)	0.03
Indexed LV mass, median (IQR)	94.3 (74.1, 115.2)	87.4 (69.0, 110.4)	102.6 (85.8, 120.8)	<0.001
LVEDD, median (IQR)	5.9 (5.2, 6.4)	5.6 (5.1, 6.2)	6.1 (5.5, 6.8)	<0.001
LVESD, median (IQR)	4.0 (3.4, 5.0)	3.8 (3.3, 4.9)	4.3 (3.6, 5.1)	0.004
RVEF, median (IQR)	51.0 (46.0, 56.0)	52.0 (45.0, 56.0)	50.2 (46.0, 56.0)	0.54
Indexed RVEDV, median (IQR)	80.5 (66.0, 97.1)	80.2 (66.4, 97.5)	81.0 (66.0, 94.7)	0.89
Indexed RVESV, median (IQR)	38.5 (30.0, 50.3)	38.0 (30.0, 50.0)	39.0 (30.0, 50.4)	0.75
Indexed LA volume, median (IQR)	56.6 (44.4, 70.7)	53.7 (41.2, 69.8)	60.5 (47.5, 72.0)	0.04
Leaflet morphology Bicuspid Trileaflet	 87 (25.9) 249 (74.1)	 36 (21.1) 135 (78.9)	 51 (30.9) 114 (69.1)	0.04
Aortic RVol, median (IQR)	40.0 (30.0, 61.0)	32.0 (26.0, 42.0)	53.0 (38.0, 80.0)	<0.001
Aortic RF, median (IQR)	38.0 (33.0, 46.0)	35.0 (31.0, 40.0)	43.0 (35.0, 51.0)	<0.001
Any scar	115 (34.2)	65 (38.0)	50 (30.3)	0.14
Scar size (%), median (IQR)	0.0 (0.0, 2.0)	0.0 (0.0, 3.0)	0.0 (0.0, 2.0)	0.12

Values are in number (%) unless otherwise indicated. ACE=angiotensin converting enzyme, BMI=body mass index, BSA=body surface area, DBP=diastolic blood pressure, IQR=interquartile range, LA=left atrium, LVEF=left ventricular ejection fraction, LVEDV=left ventricular end-diastolic volume, LVESV= left ventricular end-systolic volume, LVEDD=left ventricular end-diastolic diameter, LVESD=left ventricular end-systolic diameter, RVEF=right ventricular ejection fraction, RVEDV=right ventricular end-diastolic volume, RVESV=right ventricular end-systolic volume, RVol=regurgitant volume, RF=regurgitant fraction, SBP=systolic blood pressure

Table S3. Baseline characteristics according to management strategy in patients with scar.

	Total	AVR (-)/Scar (+)	AVR (+)/Scar (+)	P Value
Clinical Characteristics				
Age (years), median (IQR)	65.0 (57.0, 75.0)	68.0 (60.0, 76.0)	62.5 (57.0, 67.0)	0.01
Sex				0.06
Female	23 (20.0)	9 (13.8)	14 (28.0)	
Male	92 (80.0)	56 (86.2)	36 (72.0)	
Body mass index, median (IQR)	28.2 (24.8, 32.6)	28.1 (24.7, 31.5)	28.5 (26.3, 33.5)	0.26
SBP (mmHg), median (IQR)	129.5 (118.0, 146.0)	131.0 (117.0, 147.0)	128.0 (120.0, 144.0)	0.98
DBP (mmHg), median (IQR)	66.0 (60.0, 79.0)	67.0 (62.0, 81.0)	65.0 (58.0, 76.0)	0.20
Heart rate (bpm), median (IQR)	71.0 (60.0, 80.0)	74.0 (61.0, 82.0)	67.5 (60.0, 75.0)	0.11
Congestive heart failure	62 (54.9)	35 (54.7)	27 (55.1)	0.96
Diabetes	24 (21.2)	16 (24.6)	8 (16.7)	0.31
Hyperlipidemia	78 (69.0)	45 (70.3)	33 (67.3)	0.74
Hypertension	93 (81.6)	53 (81.5)	40 (81.6)	0.99
Smoking	56 (48.7)	36 (55.4)	20 (40.0)	0.10
Coronary artery disease	37 (38.9)	26 (48.1)	11 (26.8)	0.04
Myocardial infarction	26 (22.8)	18 (27.7)	8 (16.3)	0.15
Chest pain	12 (10.5)	5 (7.7)	7 (14.3)	0.26
Dyspnea	64 (56.1)	32 (49.2)	32 (65.3)	0.09
NYHA class				0.01
I	57 (49.6)	39 (60.0)	18 (36.0)	
II	30 (26.1)	18 (27.7)	12 (24.0)	
III	25 (21.7)	7 (10.8)	18 (36.0)	
IV	3 (2.6)	1 (1.5)	2 (4.0)	
CKD stage				0.11
None	37 (32.2)	18 (27.7)	19 (38.0)	
Moderate (GFR 50-85 ml/min)	65 (56.5)	42 (64.6)	23 (46.0)	
Severe (GFR 30-50 ml/min)	13 (11.3)	5 (7.7)	8 (16.0)	
Thoracic aortic disease	12 (10.4)	5 (7.7)	7 (14.0)	0.27
Pulmonary hypertension				0.43
Moderate	25 (21.7)	12 (18.5)	13 (26.0)	
Severe	18 (15.7)	9 (13.8)	9 (18.0)	
Euroscore, median (IQR)	2.2 (1.1, 3.7)	1.8 (1.1, 2.8)	3.1 (1.1, 4.5)	0.03
Medications				
Aspirin	68 (60.2)	40 (61.5)	28 (58.3)	0.73
Beta blocker	81 (71.7)	47 (72.3)	34 (70.8)	0.86
ACE inhibitors or ARBs	65 (58.0)	41 (64.1)	24 (50.0)	0.14
Mineralocorticoid receptor antagonist	11 (10.0)	7 (10.9)	4 (8.7)	0.70
Nitrates	15 (13.4)	9 (14.1)	6 (12.5)	0.81
Warfarin	8 (7.2)	5 (7.9)	3 (6.3)	0.73
Novel Oral Anticoagulant	9 (18.8)	5 (17.9)	4 (20.0)	0.85
Diuretic	59 (52.7)	31 (48.4)	28 (58.3)	0.30
Insulin	10 (9.0)	6 (9.5)	4 (8.3)	0.83
Calcium channel blocker	22 (19.8)	13 (20.3)	9 (19.1)	0.88
Statin	64 (57.1)	40 (61.5)	24 (51.1)	0.27

Amiodarone	10 (9.0)	6 (9.4)	4 (8.5)	0.88
CMR Findings				
LVEF, median (IQR)	49.0 (38.0, 60.0)	46.0 (35.4, 58.0)	52.5 (40.0, 62.0)	0.08
Indexed LVEDV, median (IQR)	117.6 (90.0, 155.4)	108.8 (87.6, 147.8)	131.8 (96.6, 162.7)	0.11
Indexed LVESV, median (IQR)	57.1 (40.7, 97.9)	54.5 (39.9, 96.1)	57.9 (41.3, 97.9)	0.78
Indexed LV mass, median (IQR)	106.3 (84.5, 130.8)	104.7 (83.3, 130.5)	106.8 (85.6, 131.1)	0.84
LVEDD, median (IQR)	6.0 (5.3, 6.7)	5.8 (5.1, 6.5)	6.1 (5.4, 6.8)	0.22
LVESD, median (IQR)	4.5 (3.6, 5.5)	4.5 (3.6, 5.5)	4.5 (3.8, 5.3)	0.99
Indexed LA volume, median (IQR)	61.9 (47.8, 73.7)	60.6 (43.0, 73.4)	63.4 (53.6, 75.9)	0.32
RVEF, median (IQR)	48.6 (40.0, 55.0)	47.0 (36.0, 53.0)	50.0 (44.0, 56.0)	0.08
Indexed RVEDV, median (IQR)	80.1 (64.1, 94.2)	75.3 (64.2, 85.7)	82.9 (63.9, 103.2)	0.20
Indexed RVESV, median (IQR)	39.3 (31.9, 55.2)	39.0 (32.1, 53.1)	41.0 (31.6, 57.8)	0.79
Leaflet morphology				0.03
Bicuspid	18 (15.7)	6 (9.2)	12 (24.0)	
Trileaflet	97 (84.3)	59 (90.8)	38 (76.0)	
Aortic RVol, median (IQR)	36.0 (26.0, 48.0)	31.0 (23.0, 38.0)	46.5 (32.0, 63.0)	<0.001
Aortic RF, median (IQR)	38.0 (33.0, 43.0)	36.0 (33.0, 39.0)	41.0 (35.0, 49.0)	0.001
Scar size (%), median (IQR)	4.0 (2.0, 8.0)	4.0 (3.0, 9.0)	3.0 (2.0, 7.0)	0.07

Values are in number (%) unless otherwise indicated. ACE=angiotensin converting enzyme, ARB= angiotensin receptor blocker, BMI=body mass index, DBP=diastolic blood pressure, IQR=interquartile range, LA=left atrium, LVEF=left ventricular ejection fraction, LVEDV=left ventricular end-diastolic volume, LVESV= left ventricular end-systolic volume, LVEDD=left ventricular end-diastolic diameter, LVESD=left ventricular end-systolic diameter, RVEF=right ventricular ejection fraction, RVEDV=right ventricular end-diastolic volume, RVESV=right ventricular end-systolic volume, RVol=regurgitant volume, RF=regurgitant fraction, SBP=systolic blood pressure

Table S4. Multivariable Cox proportional hazard models for predictors of mortality excluding patients with CAD.

	Clinical variables and presence of scar		Clinical variables and scar type		Clinical variables and scar/AVR subgroups	
	Adjusted HR (95% CI)	**p-value**	**Adjusted HR (95% CI)**	**p-value**	**Adjusted HR (95% CI)**	**p-value**
Euroscore	1.11 (1.01, 1.22)	0.02	1.12 (1.02, 1.23)	0.01	1.11 (1.01, 1.22)	0.03
Trileaflet versus bicuspid valve	2.97 (0.83, 10.6)	0.09	3.23 (0.89, 11.7)	0.074	2.8 (0.80, 10.0)	0.10
Aortic RVol, per 5mL increase	1.08 (1.01, 1.15)	0.01	1.08 (1.01, 1.15)	0.01	1.07 (1.007, 1.1)	0.03
AVR	0.47 (0.20, 1.11)	0.08	0.43 (0.17, 1.03)	0.059	-	-
Hypertension	2.35 (0.69, 8.00)	0.17	2.40 (0.7, 8.1)	0.16	2.36 (0.69, 8.06)	0.16
Smoking	1.34 (0.79, 2.25)	0.26	1.43 (0.84, 2.43)	0.17	1.32 (0.78, 2.25)	0.29
Presence of scar	2.78 (1.32, 5.86)	0.007	-	-	-	-
Scar type						
None			(reference)			
Non-infarction scar			3.51 (1.51, 8.1)	0.003		
Infarction scar			2.00 (0.72, 5.51)	0.17		
AVR-scar subgroup						
AVR (+)/scar (-)					(reference)	
AVR (-)/scar (-)					0.67 (0.19, 2.31)	0.53
AVR (+)/scar (+)					1.34 (0.36, 4.96)	0.65
AVR (-)/scar (+)					3.77 (1.29, 11.01)	0.01

CAD=coronary artery disease, AVR=aortic valve replacement, RVol=regurgitant volume.

Table S5. Multivariable Cox proportional hazard models for predictors of mortality excluding patients with LVEF<50%.

	Clinical variables and presence of scar		Clinical variables and scar type		Clinical variables and scar/AVR subgroups	
	Adjusted HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value
Euroscore	0.99 (0.83, 1.18)	0.91	1.00 (0.87, 1.16)	0.97	1.00 (0.84, 1.19)	0.97
Trileaflet versus bicuspid valve	1.40 (0.37, 5.32)	0.63	1.86 (0.52, 6.69)	0.34	1.37 (0.36, 5.24)	0.65
CAD	1.45 (0.50, 4.22)	0.49	--	--	1.43 (0.49, 4.15)	0.51
Aortic RVol, per 5mL increase	1.10 (0.99, 1.22)	0.08	1.09 (1.00, 1.19)	0.054	1.10 (0.99, 1.21)	0.08
AVR	0.22 (0.07, 0.71)	0.01	0.26 (0.10, 0.71)	0.01	--	--
Hypertension	2.90 (0.63, 13.30)	0.17	3.32 (0.75, 14.83)	0.12	2.98 (0.64, 13.77)	0.16
Smoking	2.74 (1.10, 6.87)	0.03	3.08 (1.38, 6.89)	0.01	2.75 (1.10, 6.90)	0.03
Presence of scar	4.77 (1.78, 12.78)	0.002	--	--	--	--
Scar type						
None	--	--	(reference)			
Non-infarction scar	--	--	4.23 (1.68, 10.63)	0.002	--	--
Infarction scar	--	--	4.56 (1.63, 12.74)	0.004	--	--
AVR-scar subgroup						
AVR (+)/scar (-)	--	--	--	--	(reference)	
AVR (-)/scar (-)	--	--	--	--	4.00 (0.96, 16.72)	0.06
AVR (+)/scar (+)	--	--	--	--	3.92 (0.88, 17.44)	0.07
AVR (-)/scar (+)	--	--	--	--	21.76 (4.15, 114.24)	<0.001

CAD=coronary artery disease, AVR=aortic valve replacement, CHF=congestive heart failure, RVol=regurgitant volume.