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RAPID COMMUNICATIONS
Imaging

Myocardial scar and remodelling predict long-term mortality in severe aortic stenosis beyond 10 years

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Introduction

Aortic stenosis (AS) is characterized by the narrowing of the aortic valve and compensatory myocardial remodelling.[1] However, ultimately the left ventricle decompensates, leading to heart failure and death, and intervention is advised for severe AS accompanied by either symptoms or left ventricular (LV) dysfunction.[2] Yet, over half of patients receiving aortic valve replacement (AVR) have irreversible myocardial scarring.[3] Our multicentre UK consortium linked pre-operative myocardial scarring, detected by late gadolinium enhancement (LGE) on cardiovascular magnetic resonance (CMR) with increased all-cause and cardiovascular (CV) mortality, regardless of intervention type, after a median of 3.5 years.[4] With the integration of machine learning for CMR analysis, we achieve 40% greater precision than human assessment, potentially uncovering patterns obscured by human variability.[5] We now examine whether the association of myocardial scar with mortality persists over longer-term follow-up.

Methods

The British Society of CMR Valve Consortium AS700 study is a longitudinal multicentre observational cohort study of patients with severe symptomatic AS. As previously described,[4] patients with severe AS (peak velocity ≥4 m/s, mean gradient ≥40 mmHg, peak gradient ≥ 64 mmHg or aortic valve area < 1.0 cm^2) awaiting surgical or transcatheter AVR (SAVR or TAVR) were recruited between 2003 and 2015. The study was approved by the UK National Research Ethics Service (13/NW/0832). The primary endpoint was all-cause mortality; the secondary endpoint was CV mortality, determined from death certificates. CMR followed standardized protocols with anonymization and central core lab analysis; LGE images for the assessment of myocardial scar were evaluated using CVI42 v5.6 (CircleCVI/Canada) by experienced readers blinded to clinical parameters.[4] A validated machine learning algorithm was used for LV volumetric parameters.[5]

Statistical analyses were performed using R (version 4.1.3). Cox models evaluated all-cause and CV mortality risks, setting the CMR date as the index. Multivariable models were pre-specified to include clinically relevant variables, incorporating restricted cubic splines to variables with the highest univariable predictive value. A complete cases approach was employed. Hazard ratios (HR) for continuous variables are presented over the interquartile range (IQR) in multivariable models. The Information Index (I_i) quantified the predictive contribution of each covariate to survival.[6]

Results

The AS700 study comprised a total of 674 patients with severe AS. The baseline characteristics of the whole cohort were previously

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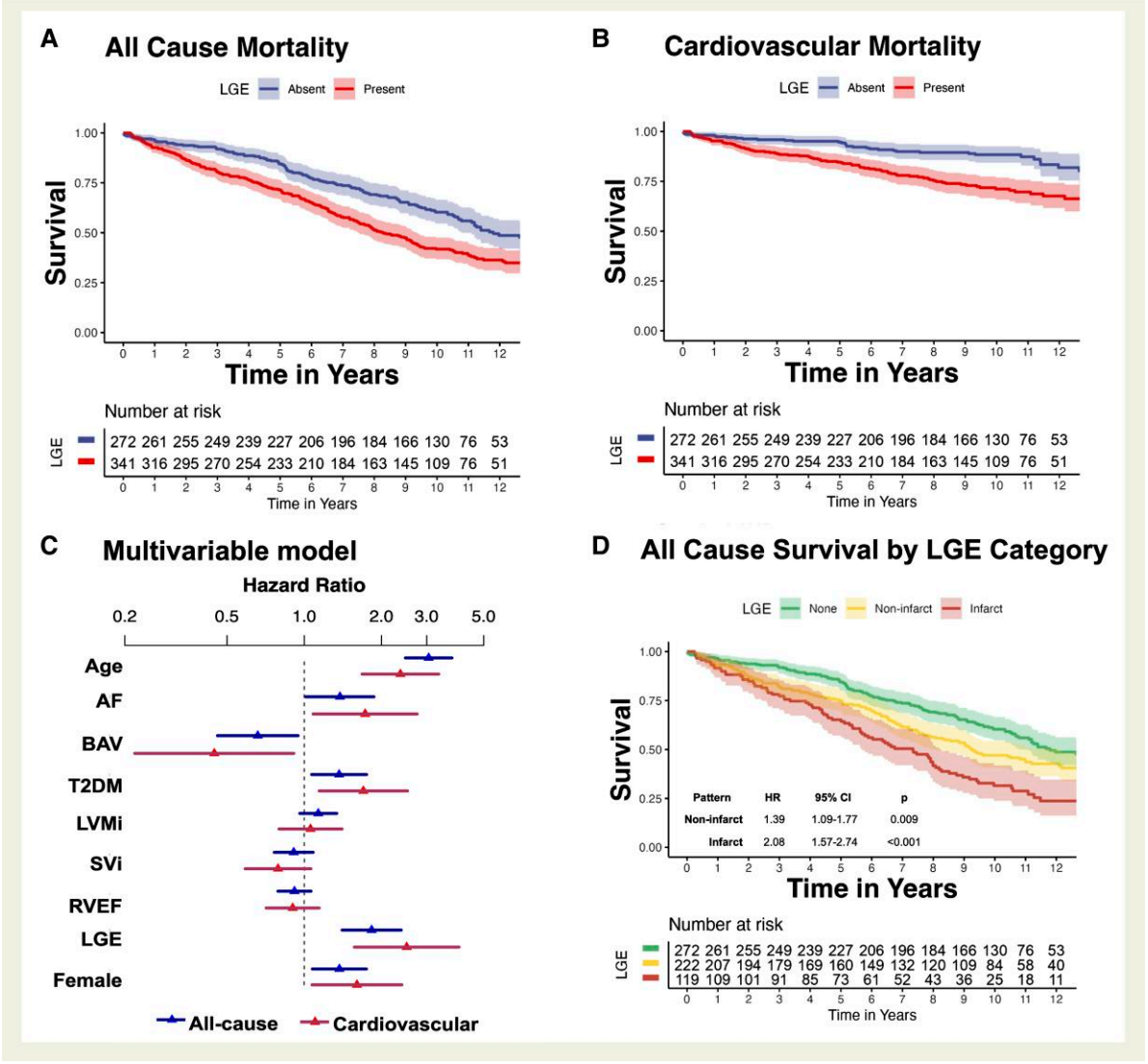

Figure 1 (*A*) Kaplan–Meier curve of all-cause mortality stratified by the presence or absence of late gadolinium enhancement. (*B*) Kaplan–Meier curve of cardiovascular mortality stratified by the presence or absence of late gadolinium enhancement. (*C*) Forest plot of hazard ratios and 95% confidence intervals for all-cause and cardiovascular mortality. Continuous variables are presented over the interquartile range of the variable. Age (years) hazard ratio over interquartile range 66–81 years. AF, atrial fibrillation; BAV, bicuspid aortic valve; T2DM, type 2 diabetes mellitus; LVMi, left ventricular mass index- hazard ratio presented over IQR 58–81 g/m^2; Svi, stroke volume index- hazard ratio presented over 37–52 mL/m^2, RVEF, right ventricular ejection fraction- HR presented over IQR 58%–71%; LGE, Late gadolinium enhancement- hazard ratio presented over interquartile range 0–2.1 g. (*D*) Kaplan–Meier curve of all-cause mortality stratified by pattern of late gadolinium enhancement (none, non-infarct pattern, infarct pattern). Results of univariable association of all-cause mortality and pattern of late gadolinium enhancement are presented in the table

described.[4] Median age was 75 years; 63% were male with a mean aortic valve area index of 0.4 cm^2/m^2 and median peak velocity of 4.4 m/s. A total of 613 patients had LGE data available. LGE was present in 56% (19% infarct and 36% non-infarct pattern). Those with LGE were more likely male, with larger LV volumes and mass and lower ejection fraction. At a median of 11.3 (IQR 11.0–11.8) years of follow-up, 377 (56%) patients died; 154 (39%) post-SAVR and 223 (81%) post-TAVR. A total of 130 had a CV cause ascribed (45 SAVR; 85 TAVR). The median survival was 10 years. Patients with LGE had a reduced median survival of 3.5 years (8.3 vs. 11.8 years), regardless of scar pattern or mode of operative intervention.

Covariates independently associated with all-cause mortality included age [HR 3.05, 95% confidence interval (CI) 2.48–3.76, I_i 49%, $P < .001$], LGE extent (HR 1.83, 95% CI 1.42–2.39, I_i 11%, $P < .001$), female sex (HR 1.37, 95% CI 1.08–1.75, I_i 2%, $P = .01$), type 2 diabetes mellitus (T2DM) (HR 1.37, 95% CI 1.07–1.75, I_i 2%, $P = .01$), bicuspid aortic valve (BAV) (HR 0.66, 95% CI 0.46–0.95, I_i 2%, $P = .02$), and atrial fibrillation (AF) (HR 1.38, 95% CI 1.02–1.87, I_i 1%, $P = .04$) (*Figure 1*). Age and LGE had the strongest association with all-cause mortality regardless of the type of intervention. Associations with CV mortality mirrored this, though LGE contributed more to the predictive model (HR 2.51, 95% CI 1.57–4.00, I_i 22%,

$P < .001$ for CV mortality). The relationship between LGE and outcome was non-monotonic, with greatest increase in hazard between zero and 2 g of LGE.

Discussion

In patients with severe AS, myocardial scar diagnosed by CMR before AVR remains independently associated with mortality beyond 11 years of follow-up. This is the case for both all-cause and CV mortality, after both surgical and transcatheter intervention, and for both infarct and non-infarct scar patterns. Infarct scars had twice the mortality hazard of non-infarct scars. Patients with myocardial scarring have a 3.5-year reduction in median survival.

Our previous data showed that focal scar is present in half of patients before intervention, is irreversible and associated with mortality up to 3.5 years.[4,7] The magnitude and direction of this effect are sustained in the long term. The amount of LGE had the strongest association with all-cause and CV mortality aside from age (I_i for CV mortality 22%, for all-cause mortality 11%) and was far greater than co-morbidities. Other measures of myocardial remodelling and function did not contribute to the model. These data place LGE-detected scar as a key outcome predictor in AS and suggest that the current timing of valve intervention may be too late for some patients. We also show that T2DM is independently associated with outcome, its importance more apparent for CV mortality in the subgroup undergoing SAVR (I_i for T2DM of 14%, greater than age). T2DM is known to be associated with an increased risk of heart failure, persistent impairment of myocardial energetics, and myocardial perfusion after AVR;[8] dedicated trials of novel diabetic medications in this patient group should therefore be considered. We have previously shown that female sex was associated with CV mortality;[4] this effect remains significant with extended follow-up.

Limitations of the study include potential selection bias as patients were only recruited at tertiary referral centres with cardiothoracic surgery. Our data cannot inform on thresholds of risk on which to proceed to AVR, but rather prognosis after AVR. Whether LGE presence can be used as a threshold for intervention is being tested in the EVOLVED trial.[9] Diffuse fibrosis was not investigated in this cohort but has been reported by our group and others separately.[10]

Conclusion

In patients with severe AS undergoing valve replacement, the myocardial scar is independently associated with all-cause and CV mortality beyond 10 years of follow-up. The presence of scar reduces median survival by a third or 3.5 years, underscoring the importance of its evaluation for post-intervention risk assessment in this patient population.

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Prof Greenwood was the chief investigator of this study. Prof. Dweck, Prof. Moon, Prof. Myerson, Prof. McCann, and Prof. Prasad were the principal investigators at each site. Dr Treibel and Dr Thornton wrote this manuscript and performed the statistical analysis. Drs Greenwood, Musa, and Bijsterveld obtained ethics approval and coordinated the study. Dr Treibel, Dr Thornton, P. Bijsterveld, and Dr Greenwood adjudicated the outcomes. Dr Captur set up and maintained the REDCap database. Drs Aziminia, Craig, Dattani, Musa, Treibel, Vassiliou, Singh, Chin, and Rigolli performed the data collection, anonymization, and upload. Drs Musa, Foley, and Dobson performed the CMR LGE analysis. Drs Vassiliou and Malley performed the atrial volume analysis. Drs Singh and Foley performed the aortic flow analysis. Drs Treibel, Chin, Pica, Loudon, and Rigolli performed the original left and right ventricular volume and function analyses. Dr Davies performed the AI analysis. All authors have critically reviewed and approved the manuscript.

Declarations

Disclosure of Interest

George Thornton, Rhodri Davies, James Moon, and Thomas Treibel perform *ad hoc* consultancy and hold shares in Mycardium AI Ltd.

Data Availability

Data is available on request.

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Ethical Approval

The study was approved by the UK National Research Ethics Service (13/NW/0832), conformed to the principles of the Declaration of Helsinki and patients gave written informed consent.

Pre-registered Clinical Trial Number

Not applicable.

Appendix 1

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