CAR21-2571-R1

# Association of Myocardial Fibrosis And Stroke Volume By Cardiovascular Magnetic Resonance and Outcome in Severe Aortic Stenosis After Valve Replacement: Data from the BSCMR AS700 Study

## Subtitle: Myocardial Fibrosis, Stroke Volume by CMR and Outcome in Severe AS After Valve Replacement

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Word Count: 2448 (Excluding title, abstract, acknowledgements, references, figure legends, tables)

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Date of Revision: 06/02/2022

## KEY POINTS

**Question:** Are myocardial fibrosis and left ventricular indexed stroke volume by CMR ($SVi_{CMR}$) associated with outcome after valve replacement?

**Findings:** In a longitudinal observational cohort study of 674 patients, extent of late gadolinium enhancement and $SVi_{CMR}$ were independently associated with cardiovascular mortality, with risk increasing more rapidly below $SVi_{CMR}$ 45ml/m$^2$.

**Meaning:** $SVi_{CMR}$ is an important marker of risk after valve intervention, and should be considered alongside myocardial fibrosis in future risk models for predicting outcomes after surgery.

## ABSTRACT (350/350 WORDS)

**Importance:** Low flow severe aortic stenosis (LF-AS) has higher mortality than severe AS with normal flow. The conventional definition of LF-AS is an indexed stroke volume by echocardiography ($SVi_{ECHO}$) <35ml/m$^2$. Cardiovascular magnetic resonance (CMR) is the reference standard for quantifying left ventricular volumes and function, from which $SVi_{CMR}$ can be derived.

**Objective:** We sought to determine the association of left ventricular $SVi_{CMR}$ with myocardial remodeling and survival.

**Design:** A multicenter longitudinal outcome study conducted between January 2003 and May 2015. Patients were followed up for a median of 3.6 years.

**Setting:** A multicenter study across six UK cardiothoracic centers.

**Participants:** Patients with severe AS listed for either surgical (SAVR) or transcatheter aortic valve replacement (TAVR). Patients underwent preprocedural echocardiography and CMR. Patients were stratified by echocardiography derived aortic valve mean and/or peak gradient and $SVi_{CMR}$ into four AS endotypes: low flow low gradient, low flow high gradient, normal flow low gradient and normal flow high gradient AS.

**Exposures:** Surgical or Transcatheter Aortic Valve Replacement.

**Outcome Measures:** All-cause and cardiovascular (CV) mortality after aortic valve intervention.

**Results:** 674 patients with severe AS (age 75, IQR 66-80; 63% male, aortic valve area index 0.4, IQR 0.3-0.44 cm$^2$/m$^2$) were included. LF-AS endotypes (low gradient

and high gradient) had lower left ventricular ejection fraction (LVEF), mass, wall thickness, and importantly increased all-cause and CV mortality than normal-flow AS: HR[all-cause] 2.08 (95% CI 1.37-3.14, p<0.001); HR[cardiovascular] 3.06 (95% CI 1.79-5.25, p<0.001). Independent associations of CV mortality were lower $SVi_{CMR}$ (HR 1.64, 95%CI 1.08-2.5, p=0.04), age (HR 2.54, 95% CI 0.4-0.93, p=0.001) and higher quantity of LGE (HR 2.93, 95%CI 1.68-5.09, p<0.001). CV mortality hazard increased more rapidly below $SVi_{CMR}$ 45ml/$m^2$. $SVi_{CMR}$ was independently associated with age, atrial fibrillation, focal scar (LGE) and parameters of cardiac remodeling (LV mass, LA volume).

**Conclusion and Relevance:** SVi by CMR is associated with CV mortality after AVR, independent of age, scar and ejection fraction. The unique capability of CMR to quantify myocardial scar, combined with other prognostically important imaging biomarkers such as $SVi_{CMR}$ may enable comprehensive stratification of post-operative risk in severe symptomatic AS.

## BACKGROUND

Current guidelines recommend intervention in severe aortic stenosis (AS) due to adverse prognosis. Life expectancy is improved, but not normalized, by aortic valve replacement (AVR)[1,2]. Identifying severe AS can be difficult if the peak velocity across the aortic valve is <4 m/sec, which can occur when the flow volume across the aortic valve is low. Stroke volume index (SVi) can be reduced in severe AS due to two mechanisms: small chamber size due to concentric hypertrophy with normal systolic function but diastolic dysfunction (paradoxical low flow), or secondary to reduced left ventricular (LV) function (classical low) [3]. Patients with 'paradoxical low-flow' severe AS, have also been shown to have worse outcomes that those with high gradient AS, suggesting that SVi may be an important marker of risk regardless of LV ejection fraction [4]. Current guidelines define low SVi by echocardiographic Doppler assessment as <35ml/m$^2$ [5]. However, SVi by echocardiography may be incrementally associated with mortality, representing a continuum of mortality hazard rather than a binary threshold [6,7].

While echocardiography remains the first line investigation for both quantification of AS severity and assessment of flow status, cardiovascular magnetic resonance (CMR) is increasingly recognized as a powerful adjunct to echocardiographic assessment of AS. CMR is the reference standard for evaluating cardiac volumes and function [8], redefining our understanding of the differing myocardial phenotypes [9], and it allows the detection of focal myocardial scar and diffuse fibrosis, which are both prognostic [10,11].

Whether $SVi_{CMR}$ is independently associated with mortality after valve intervention, and how this applies to different AS endotypes is less well defined. $SVi_{CMR}$ is most

frequently derived by a volumetric approach, differing from echo, which uses the left ventricular outflow tract velocity time integral (LVOT VTI) and estimated LVOT area[12]. Previous work has demonstrated good agreement between $SV_{CMR}$ and SV by echocardiography, provided that the LVOT VTI is measured in close proximity to the valve annulus[13].

We hypothesized that $SVi_{CMR}$ is independently associated with mortality in patients with severe AS and is associated with other parameters of myocardial remodeling.

## METHODS

AS700 was designed by the British Society of Cardiovascular Magnetic Resonance [BSCMR] Valve Consortium as a longitudinal observational cohort study performed in six UK cardiothoracic centers, to examine patients with severe symptomatic AS. As previously described [10], patients with severe AS (AVmax ≥4m/s, mean gradient ≥40mmHg, peak gradient ≥ 64mmHg or AVA < 1.0cm$^2$) awaiting valve intervention were prospectively recruited between January 2003 and May 2015. 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. The primary endpoint was all-cause mortality after valve replacement; the secondary endpoint was cardiovascular (CV) mortality, both determined from death certificate information and via the NHS Spine. The study was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for the reporting of observational studies.

### IMAGING DATA ACQUISITION AND ANALYSIS

Echocardiographic parameters were acquired following standard guidelines for AS severity assessment [14]. CMR was performed using standardized protocols, as

previously described [10]. Scans were anonymized, centralized and analyzed using CVI42 software (Circle Calgary, Alberta, Canada) in a distributed core-lab approach by experienced readers blinded to clinical parameters[10].

### Categorization by Stroke Volume and AS Endotype

The primary analysis focused on $SVi_{CMR}$ as a continuous variable. The secondary analysis divided the cohort into two groups: high flow ($SVi_{CMR}$ ≥35ml/m$^2$) and low flow ($SVi_{CMR}$ <35ml/m2) and then further into four AS endotypes by velocity, peak and mean AV gradient (by echocardiography) and $SVi_{CMR}$, as follows:

1. Normal Flow High gradient (NFHG) AS
    a. Peak gradient ≥64mmHg **or** mean gradient ≥40mmHg
    b. SVi ≥35ml/m$^2$
2. Low flow high gradient (LFHG) AS
    a. Peak gradient ≥64mmHg **or** mean gradient ≥40mmHg
    b. SVi <35ml/m$^2$
3. Low flow low gradient (LFLG) AS
    a. Peak gradient <64mmHg **and** mean gradient <40mmHg
    b. SVi <35ml/m$^2$
4. Normal flow low gradient AS (NFLG)
    a. Peak gradient <64mmHg **and** mean gradient <40mmHg
    b. SVi ≥35ml/m$^2$

We performed further exploratory analysis dividing the cohort by different flow thresholds in 10ml/m$^2$ increments: 35ml/m$^2$, 45ml/m$^2$, 55ml/m$^2$ and 65ml/m$^2$.

### Statistical Analysis

Continuous variables are expressed as median and interquartile range (IQR); categorical variables as counts and percent. Baseline characteristics of participants were compared using Kruskal-Wallis, $\chi^2$ or Fisher's exact tests as appropriate.

Univariable associations of all-cause and CV mortality were established via the Kaplan-Meier method. The index date was the date of CMR. Cox proportional hazards models were fitted for all-cause and CV mortality. The proportional hazards assumption was checked with Schoenfeld residuals. We additionally assessed the association of relevant clinical and CMR biomarkers with SVi in a proportional odds ordinal logistic regression model. Odds ratios and Hazard ratios are presented over the interquartile range of continuous variables.

### Model Selection

Spearman's $\rho^2$ –the square of Spearman's rho rank correlation coefficient for each variable was calculated, to approximate the potential predictive ability of each variable. A multivariable model was built including clinically relevant variables and incorporating restricted cubic splines to variables with the highest $\rho^2$ and to variables of interest (i.e. SVi). Variables with significant missing data were excluded. Variance Inflation Factors (VIFs) were calculated to ensure no significant collinearity.

The predictive information contained within each covariate was expressed by the Information Index, which is a chance corrected version of the adequacy index, proposed by Harrell[15]. This was calculated as the likelihood ratio chi-square minus the degrees of freedom (d.f.) or each added variable, divided by the total model likelihood ratio chi-square minus the d.f. for the total model. This allows for factors with different d.f. to be compared. The information index thus represents the percentage of explained variation in survival that is explained by the addition of the

specified predictor, though due to correlation between variables this need not necessarily add up to 100%. Evidence for incremental predictive value is assessed using the likelihood ratio chi-square test (but without the d.f. correction).

Statistical analyses were performed using software R version 3.5.2, with R studio interface © R Studio, Inc. using the 'rms' package, graphs were plotted in 'ggplot2'.

## RESULTS

### BASELINE CLINICAL AND IMAGING CHARACTERISTICS

The AS700 study comprised a total of 674 patients with severe AS. Baseline characteristics of the whole cohort are in Table S1. Median age was 75 (IQR 66-80); 63% male with a median aortic valve area index 0.4 $cm^2/m^2$ (IQR 0.3-0.44) and mean gradient of 46 mmHg (IQR 38-56). At a median follow up of 3.6 years (IQR 2.6-5.9), 145 patients died, of whom 70 had a cardiovascular cause ascribed. The median time from CMR to SAVR was 44 days (IQR 11-103 days) and to TAVR was 13 days (IQR 1-61 days). All deaths were post-intervention.

560 out of a total of 674 patients had sufficient flow and gradient data available to be stratified by flow and gradient: 412 patients had NFHG, 77 NFLG, 51 LFHG and 20 LFLG-AS. Baseline characteristics by AS endotype are shown in Table 1. Patients with LFLG had a greater incidence of AF than other endotypes. Patients with low flow AS (LFLG and LFHG) had lower LV and RV ejection fraction and lower LV mass and maximum wall thickness compared to high flow AS patients. LFHG patients had smaller LV cavity size compared with other groups (median LV EDV 57ml/$m^2$ for LFHG vs median 77-80ml/$m^2$ in other groups).

### ASSOCIATIONS WITH $SVI_{CMR}$

The strongest associations with $SVi_{CMR}$ (per 1ml/m$^2$ increase) were parameters of LV remodeling including LV mass (OR 2.65, 95%CI 1.98-3.54, Information index 32%, p<0.001) and LA volume (OR 2.27, 95% CI 1.73-2.99, Information index 26%, p<0.001). Other weaker associations with $SVi_{CMR}$ included age (OR 0.62, 95% CI 0.46-0.84, Information index 6.6%, p=0.002, history of atrial fibrillation (OR 0.36, 95%CI 0.21-0.62, Information index 9.21%, p<0.001) and the presence of myocardial LGE, likely representing pockets of scar tissue (OR 0.89, 95% CI 0.82-0.97, Information index 5%, p=0.006)(Table 2). LVEDVi and LVESVi were not included in the multivariable model as they are used to calculate stroke volume.

### Association with Outcome

Univariable associations with outcome are summarized in Table S2 (all-cause mortality) and Table S3 (cardiovascular mortality). Low flow AS was associated with increased all-cause and cardiovascular mortality compared to normal flow AS (HR[all-cause] 2.08, 95% CI 1.37-3.14, p<0.001; HR[cardiovascular] 3.06, 95% CI 1.79-5.25, p<0.001)(Figure 1). By AS endotype, both LFLG and LFHG AS were associated with CV mortality (LFLG HR 3.75, 95%CI 1.45-9.71, p=0.006; LFHG HR 2.56, 95% CI 1.21-5.42, p=0.014, NFLG AS HR 0.79, 95%CI 0.31-2.06, p=0.64), but not all-cause mortality. Mean and peak AV gradients were not associated with either all-cause or cardiovascular mortality in this group with already severe AS awaiting valve intervention. Examining different thresholds defining high and low $SVi_{CMR}$, there was a significant difference in mortality at thresholds of 35ml/m$^2$, 45ml/m$^2$ and 55ml/m$^2$ but not at 65ml/m$^2$ with progressive divergence of the curves, the lower the threshold (Figure S1).

Independent associations of all-cause mortality were increased age (HR 2.18, 95% CI 1.41-3.37, information index 22.73%, p<0.001), amount of LGE (HR 1.68, 95% CI 1.15-2.45, information index 11.49%, p=0.01) and maximum LV wall thickness (HR 0.75, 95% CI 0.57-0.98, information index 5%, p=0.03). Lower $SVi_{CMR}$ was not independently associated with all-cause mortality (HR 1.28, 95% CI 0.96-1.72, information index 1.47%, p=0.22), neither were indices of ventricular function (LVEF information index 0%, p=0.96; RVEF information index 0%, p=0.85)(Table 3).

Associations of CV mortality included increased age (HR 2.54, 95%CI 1.29-5.01, information index 13.3%, p=0.01), LGE (HR 2.93, 95% CI 1.68-5.09, information index 22.5%, p<0.001) and lower SVi (HR 1.64, 95%CI 1.08-2.5, information index 7.5%, p=0.04). The amount of LGE (even more than age) held the strongest association with CV mortality (with a greater hazard ratio than age).

The partial association between covariates (i.e. adjusted for other covariates within the model) and CV mortality can be seen in Figure 2 and all-cause mortality in Figure S2. Figure 2A shows that hazard of CV death increases continuously and in a non-linear fashion, increasing more rapidly below 45ml/$m^2$. Figure 2E demonstrates the strong non-monotonic relationship between CV mortality and quantity of LGE, with even very low volumes of LGE demonstrating significantly increased mortality risk.

Discussion

In patients with severe, symptomatic AS referred for SAVR or TAVR, $SVi_{CMR}$ is associated with cardiovascular mortality after valve replacement. The association of $SVi_{CMR}$ is independent of age, sex, LV ejection fraction and myocardial scar.

Previous studies have demonstrated an association between $SVi_{ECHO}$ and adverse outcomes after valve replacement[16]. Similarly, AS endotypes have classically been defined by echocardiography-derived SVi[5]. Calculation of stroke volume by echocardiography relies upon a number of geometric assumptions and accurate measurement of the LVOT anteroposterior diameter, which can be overcome through accurate volumetric analysis by CMR[17]. Using the same threshold by CMR, we see a marked survival penalty in low flow endotypes, driven by $SVi_{CMR}$ and not by gradient, with LFLG and LFHG AS following a similar adverse trajectory (Figure 1). We found that stroke volume itself was associated with parameters of cardiac remodeling, most strongly with LV mass and LA volume. Patients with LFLG and LFHG AS had lower LV mass and lower maximum wall thickness compared to HG-AS, though absolute differences were small.

Several studies have highlighted the importance of low SVi in predicting outcome in severe AS, and have supported the use of the 35ml/$m^2$ threshold proposed in current guidelines [5-7,18-21]. While a cut off is often clinically desirable, it lacks biological plausibility. In this cohort, CV mortality after valve replacement increases continuously with lower $SVi_{CMR,}$ more rapidly below of 45ml/$m^2$ (Figure 2A), raising the question as to whether reliance on a single threshold may be overly simplistic, and instead $SVi_{CMR}$ should be considered as a continuous variable in models of post-operative risk.

Previous work in mild-moderate AS has suggested that SVi is more than just a barometer of systolic function[22,23]. Our data (in severe AS) adds support to this hypothesis, in that while both LVEF and RVEF associated with $SVi_{CMR}$, neither

remained independent associations of outcome in a multivariable model incorporating $SVi_{CMR}$.

We have previously shown that women have different myocardial responses to severe AS than men, with less concentric remodeling and less scar[24-27]. Women also had higher cardiovascular mortality, but this was not borne out in multivariable analysis[9]. While sex itself was not associated with outcomes in this study, we found that low maximal wall thickness was independently associated with all-cause mortality and was more prevalent in low-flow AS endotypes.

Echo remains the first line technique for evaluation of AS severity and flow status. CMR is unlikely therefore to be routinely performed for the quantification of stroke volume alone. However, CMR provides an accurate assessment of AS severity, is the reference standard for quantification of ventricular mass and volumes and, perhaps most importantly, enables quantification of myocardial fibrosis by T1 mapping and late gadolinium enhancement imaging, all within the same scan [28]. $SVi_{CMR}$ offers additive prognostic information to that of myocardial tissue characterization. CMR may, in future, enable comprehensive multiparametric risk stratification of patients after valve replacement, through integration of multiple prognostically important biomarkers.

Using the Information index[15], we have demonstrated relative strength of association of different demographic and imaging biomarkers. LGE is by some margin the biomarker most strongly associated with cardiovascular outcome (Table 3), outperforming age and contributing more than three times the predictive information of indexed stroke volume. LGE demonstrates a non-monotonic relationship with outcome, with even small volumes of LGE being associated witha significantly

increased risk (Figure 2E). The relative strengths of these associations should be taken into consideration when evaluating the importance of different biomarkers in clinical risk models.

## LIMITATIONS

This is an observational study of patients at tertiary referral centers with cardiothoracic surgery and CMR focus, thus there the potential for selection bias. These patients were selected for inclusion after the decision for surgery/intervention had been made. These data therefore cannot inform on thresholds of risk on which to proceed to surgery, but rather reflect prognosis after valve intervention. Certain patient groups with contraindications to CMR were excluded as well as patients medically managed for aortic stenosis. Native T1 and extracellular volume (ECV) mapping techniques are not reported due to considerable variation in the values on different scanners at different institutions. The study was not initially designed to evaluate differences between AS endotypes, and thus is not powered for this purpose. Findings from this subgroup analysis are exploratory.

## CONCLUSION

Indexed stroke volume by CMR ($SVi_{CMR}$) is associated with cardiovascular mortality in severe, symptomatic AS after valve replacement, independent of age, sex, left ventricular ejection fraction and scar. The unique capability of CMR to quantify myocardial scar, combined with other prognostically important imaging biomarkers such as $SVi_{CMR}$ may enable comprehensive stratification of post-operative risk in severe symptomatic AS.

## Acknowledgements

## Sources of Funding

This study was in part supported by the British Heart Foundation (University of Leeds, Greenwood JP [PG/11/126/29321]; University of Leicester, McCann GP [PG/07/068/2334]; University of Oxford, Myerson SG [FS/10/015/28104]; University of Edinburgh, Dweck MR [FS/10/026]; University College London, Moon JC [FS/08/028/24767]), Treibel TA [FS/19/35/34374] and Thornton GD [FS/CRTF/21/24128], the UK National Institute for Health Research via its Biomedical Research Centre and Clinical Research Facility (Leeds and Oxford) programmes, as well as Rosetrees Trust. Funding supported design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.The views expressed are those of the authors and not necessarily those of the UK National Health Service, National Institute for Health Research or Department of Health.

## Disclosures

No conflicts of interest to disclose.

## Access to Data and Analysis

Dr Thomas Treibel (lead author) acknowledges full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis

Dr George Thornton (UCL) conducted and is responsible for the data analysis.

## TABLE 1 BASELINE CHARACTERISTICS BY AS ENDOTYPE

| Characteristic | **High Flow, High Gradient**, N = 412[1] | **High Flow, Low Gradient**, N = 77[1] | **Low Flow, High Gradient**, N = 51[1] | **Low Flow, Low Gradient**, N = 20[1] | **p-value**[2] |
|---|---|---|---|---|---|
| **Age** | 74 (66, 81) | 70 (62, 78) | 77 (70, 82) | 74 (67, 80) | **0.015** |
| **Male Sex** | 252 (61%) | 54 (70%) | 31 (61%) | 15 (75%) | 0.3 |
| **Atrial Fibrillation** | 42 (10%) | 9 (12%) | 8 (16%) | 7 (35%) | **0.015** |
| **BMI** | 27.0 (24.3, 30.4) | 27.3 (24.5, 31.8) | 27.8 (24.5, 31.2) | 28.8 (25.7, 29.7) | 0.5 |
| **Type 2 Diabetes** | 83 (20%) | 15 (19%) | 17 (33%) | 3 (15%) | 0.2 |
| **Hypertension** | 227 (55%) | 40 (52%) | 30 (59%) | 12 (60%) | 0.9 |
| **NYHA class** | | | | | |
| I | 57 (14%) | 12 (16%) | 5 (10%) | 1 (5.0%) | |
| II | 160 (40%) | 45 (58%) | 16 (32%) | 6 (30%) | |
| III | 175 (43%) | 19 (25%) | 24 (48%) | 12 (60%) | |
| IV | 13 (3.2%) | 1 (1.3%) | 5 (10%) | 1 (5.0%) | |
| **Bicuspid valve** | 94 (23%) | 24 (32%) | 8 (16%) | 3 (15%) | 0.2 |
| **Coronary Artery Disease** | 65 (17%) | 9 (12%) | 10 (21%) | 4 (22%) | 0.4 |
| **History of MI** | 47 (11%) | 7 (9.1%) | 5 (9.8%) | 4 (20%) | 0.6 |
| **STS score** | 1.80 (1.09, 3.20) | 1.23 (0.83, 2.06) | 2.39 (1.46, 3.79) | 1.90 (1.24, 2.40) | **<0.001** |
| **Mean gradient (mmHg)** | 50 (42, 60) | 32 (27, 34) | 49 (40, 57) | 29 (26, 35) | **<0.001** |
| **Peak gradient (mmHg)** | 83 (73, 100) | 54 (46, 58) | 81 (70, 96) | 50 (45, 57) | **<0.001** |
| **Valve area ($cm^2/m^2$)** | 0.37 (0.30, 0.43) | 0.42 (0.36, 0.50) | 0.33 (0.26, 0.42) | 0.42 (0.37, 0.46) | **<0.001** |
| **LA volume ($ml/m^2$)** | 54 (43, 67) | 52 (43, 66) | 41 (33, 54) | 58 (39, 81) | **0.001** |
| **LV EDV (ml/m2)** | 80 (69, 95) | 78 (67, 94) | 57 (51, 87) | 77 (51, 115) | **<0.001** |

| | | | | | |
|---|---|---|---|---|---|
| **Stroke volume (ml/m2)** | 49 (42, 55) | 46 (42, 56) | 30 (27, 33) | 29 (26, 32) | **<0.001** |
| **LVEF (%)** | 62 (55, 69) | 62 (54, 68) | 57 (31, 62) | 40 (24, 60) | **<0.001** |
| **EF < 50%** | 59 (14%) | 9 (12%) | 19 (37%) | 13 (65%) | **<0.001** |
| **RVEF (%)** | 65 (61, 72) | 65 (58, 73) | 57 (50, 66) | 48 (38, 63) | **<0.001** |
| **Max. wall thickness (mm)** | 14.0 (12.0, 16.0) | 14.0 (12.0, 15.0) | 13.0 (11.0, 15.5) | 13.0 (10.0, 14.0) | **0.002** |
| **LV mass (g/m2)** | 84 (68, 100) | 76 (62, 89) | 67 (53, 85) | 68 (55, 87) | **<0.001** |
| **LGE Present** | 205 (54%) | 40 (60%) | 23 (48%) | 13 (68%) | 0.39 |
| **LGE pattern** | | | | | |
| None | 176 (46%) | 27 (40%) | 25 (52%) | 6 (32%) | 0.192 |
| Non-infarct | 147 (39%) | 25 (37%) | 14 (29%) | 6 (32%) | |
| Infarct | 58 (15%) | 15 (22%) | 9 (19%) | 7 (37%) | |
| **LGE (g)** | 0.25 (0.00, 1.73) | 0.57 (0.00, 2.47) | 0.00 (0.00, 2.03) | 0.27 (0.00, 6.26) | 0.2 |

[1] 114 observations excluded due to missing data
[2] Kruskal-Wallis rank sum test; Pearson's Chi-squared test; Fisher's exact test

## TABLE 2. MULTIVARIABLE MODEL OF ASSOCIATIONS OF INDEXED STROKE VOLUME

| Per 1ml/m$^2$ increase in $SVi_{CMR}$ | **Odds ratio[a]** | **95% CI** | **Information Index (%)** | **Likelihood ratio test of nested model without variable (p-value)** |
|---|---|---|---|---|
| **Age** | **0.62** | **0.46-0.84** | **6.65** | **0.002** |
| Male Sex | 1.00 | 0.7-1.43 | 0.00 | 0.995 |
| **LV mass (g/m2)** | **2.65** | **1.98-3.54** | **32.09** | **<0.001** |
| **LA volume (ml/m2)** | **2.27** | **1.73-2.99** | **25.56** | **<0.001** |
| STS score | 0.94 | 0.8-1.1 | 0.00 | 0.435 |
| **Atrial Fibrillation** | **0.36** | **0.21-0.62** | **9.21** | **<0.001** |
| **LGE (g)** | **0.89** | **0.82-0.97** | **5.02** | **0.006** |
| Bicuspid valve | 1.17 | 0.75-1.81 | 0.00 | 0.486 |
| Mean gradient (mmHg) | 1.02 | 0.84-1.24 | 0.00 | 0.830 |
| Coronary Artery Disease | 1.19 | 0.76-1.87 | 0.00 | 0.732 |

[a]Odds ratios are reported over the interquartile range of the variable

## TABLE 3. COX PROPORTIONAL HAZARDS MODEL – ALL-CAUSE AND CV MORTALITY

| ALL-CAUSE MORTALITY | Hazard Ratio[a] | 95% CI | Information Index (%) | Likelihood ratio test of nested model without variable (p-value) |
|---|---|---|---|---|
| Lower $SVi_{CMR}$ (ml/m2) | 1.28 | 0.96-1.72 | 1.47 | 0.22 |
| **Age** | **2.18** | **1.41-3.37** | **22.73** | **<0.001** |
| STS score | 0.85 | 0.47-1.52 | 2.49 | 0.16 |
| **LGE (g)** | **1.68** | **1.15-2.45** | **11.49** | **0.01** |
| Bicuspid valve | 0.52 | 0.25-1.07 | 3.74 | 0.06 |
| Atrial Fibrillation | 1.44 | 0.86-2.41 | 1.23 | 0.17 |
| LVEF (%) | 1.01 | 0.75-1.35 | 0.00 | 0.96 |
| RVEF (%) | 1.03 | 0.78-1.35 | 0.00 | 0.85 |
| **Max. wall thickness (mm)** | **0.75** | **0.57-0.98** | **5.03** | **0.03** |
| Male Sex | 0.93 | 0.6-1.44 | 0.00 | 0.74 |
| **CV MORTALITY** | **Hazard Ratio[a]** | **95% CI** | **Information Index (%)** | **Likelihood ratio test of nested model without variable (p-value)** |
| **Lower $SVi_{CMR}$ (ml/m2)** | **1.64** | **1.08-2.5** | **7.48** | **0.04** |
| **Age** | **2.54** | **1.29-5.01** | **13.26** | **0.01** |
| STS score | 0.81 | 0.36-1.81 | 5.34 | 0.07 |
| **LGE (g)** | **2.93** | **1.68-5.09** | **22.47** | **<0.001** |
| Bicuspid valve | 0.84 | 0.33-2.18 | 0.00 | 0.72 |
| Atrial Fibrillation | 1.94 | 0.99-3.76 | 4.26 | 0.06 |
| LVEF (%) | 1.12 | 0.75-1.69 | 0.00 | 0.58 |
| RVEF (%) | 1.08 | 0.74-1.58 | 0.00 | 0.70 |
| Max. wall thickness (mm) | 0.60 | 0.47-1.02 | 4.29 | 0.06 |
| Male Sex | 0.57 | 0.30-1.07 | 3.41 | 0.08 |

[a]Hazard ratios are reported over the interquartile range of the variable

# FIGURE TITLES & LEGENDS

## FIGURE 1 KAPLAN-MEIER SURVIVAL CURVES FOR CARDIOVASCULAR MORTALITY

Unadjusted Kaplan-Meier estimates of all-cause and cardiovascular survival by flow status (Panels A& B) and by AS endotype (Panels C & D). Tables below each plot describe number of patients at risk. Tables below each plot describe number of patients at risk. Low stroke volume refers to a $SVi_{CMR} < 35ml/m^2$, High stroke volume to $SVi_{CMR} \geq 35ml/m^2$

## FIGURE 2 PARTIAL ASSOCIATION PLOTS OF HAZARD RATIO OF CARDIOVASCULAR DEATH

Partial association plots demonstrating the relationship between individual variables and CV mortality after multivariable adjustment. A, Indexed stroke volume by CMR; B, Left ventricular ejection fraction (LVEF); C, Right ventricular ejection fraction (RVEF); D, STS score; Late gadolinium enhancement (LGE); E, Age. The red line in each plot delineates a hazard ratio of 1. The blue dashed line in Panel A is to illustrate the $SVi_{CMR}$ at which cardiovascular hazard begins to increase more rapidly. The shaded area represents the 95% confidence interval.

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