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Acute reverse remodelling following Trans-catheter Aortic Valve Implantation: a link between myocardial fibrosis and left ventricular mass regression

Short title: Acute reverse remodelling following TAVI

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BRIEF SUMMARY

Favourable reverse remodelling occurs following trans-catheter aortic valve implantation (TAVI) but the timeline of these changes and the relationship to myocardial fibrosis is unknown. This prospectively designed cardiovascular magnetic resonance imaging follow-up study of 57 patients undergoing TAVI has shown that left ventricular mass regression occurs early and is greater in those without myocardial fibrosis. Less favourable reverse remodelling may explain the reduced survival seen in patients with severe aortic stenosis and myocardial fibrosis.

ABSTRACT

Background: Despite the wealth of data demonstrating the positive effects on cardiac reverse remodelling in the long term, the immediate effects of trans-catheter aortic valve implantation (TAVI) on the left ventricle are yet to be comprehensively described using Cardiovascular Magnetic Resonance (CMR) imaging. Also, the link between myocardial fibrosis and acute left ventricular (LV) mass regression is unknown.

Methods: Fifty-seven patients with severe aortic stenosis awaiting TAVI underwent paired CMR scans prior to and early post-procedure (4 (IQR 1) days). LV mass, volume and function were measured. Late gadolinium enhancement (LGE) imaging was performed to assess for the presence of and pattern of myocardial fibrosis.

Results: Post-procedure, fifty-three (95%) patients experienced an immediate (10.1±7.1%) reduction in LV mass (LVMi) from 76±15.5 to 68.4±14.7g/m^2 (p=<0.001). Those with no LGE experienced the greatest LVMi regression (13.9±7.1%) compared to those with mid-wall/focal fibrosis pattern LGE (7.4±5.8%) and infarct pattern LGE (7.2±7.0%) (p=0.005). There was no overall change in LV ejection fraction (LVEF) (55.1±12.1 to 55.5±10.9%, p=0.867), however a significant improvement in LVEF was seen in those with abnormal (<55%, n=24 (42%)) baseline LVEF (43.2±8.9 to 46.7±10.5%, p=0.027). Baseline LVMi (p=0.005) and myocardial fibrosis (p<0.001) were strong independent predictors of early LVMi regression.

Conclusions: LV reverse remodelling occurs immediately following TAVI, with significant LV mass regression in the total population and an improvement in LVEF in those with pre-existing LV impairment. Those without myocardial fibrosis at baseline experience greater LV mass regression than those with fibrosis.

Keywords: Aortic Valve Stenosis, Ventricular Remodeling, Fibrosis, Trans-catheter Aortic Valve Implantation, Magnetic Resonance Imaging, left ventricular ejection fraction

INTRODUCTION

Left ventricular (LV) hypertrophy is almost ubiquitous in severe aortic stenosis (AS), reflecting myocardial adaptation to chronic elevation of afterload, in an attempt to normalise wall stress[1, 2]. Surgical aortic valve replacement (SAVR) and trans-catheter aortic valve implantation (TAVI) result in significant LV mass regression at medium and long term follow up[3, 4], with TAVI having a superior mass reduction compared with SAVR at 6 months[3]. TAVI results in an immediate, greater improvement in aortic pressure gradient[5]. This early improvement may be responsible for the greater degree of mass regression seen at mid and long term, which remains important as LV mass regression is a positive prognostic indicator[6] and is associated with reduced hospitalisation[7]. The acute effects of the reduction of afterload on the LV afforded by TAVI have not been described using Cardiovascular Magnetic Resonance (CMR) imaging. Studies to date investigating early mass regression following TAVI have used echocardiographic evaluation[8] and hence are underpowered[9]. The relationship between baseline myocardial fibrosis and early LV reverse remodelling remains poorly understood[10]. CMR imaging allows accurate assessment of LV mass regression and myocardial fibrosis. This may allow us to predict which patients are most likely to derive an immediate benefit from TAVI.

The aim of this study was to determine the acute changes seen in the left ventricle within the first week following TAVI and assess the significance of myocardial fibrosis.

METHODS

Study design and patients

In this prospective study, sixty-five patients with severe symptomatic AS awaiting TAVI were enrolled between December 2012 and April 2015 at a single tertiary centre (Leeds General Infirmary, Leeds, UK). Patients with a contraindication to CMR or TAVI implantation were excluded. Patients provided

informed written consent to take part in the study. The study was approved by the institutional ethics committee and complied with the Declaration of Helsinki.

TAVI procedure

Patients underwent Medtronic CoreValve or Evolut R (Medtronic Inc., Minneapolis, Minnesota) or Boston Lotus (Boston Scientific Corporation, Natick, MA) valve implantation. Trans-femoral was the default approach with other techniques (subclavian and direct aortic) chosen in the case of unsuitable femoral access. All procedures were performed by 2 experienced operators. Left ventricular end diastolic pressure (LVEDP) was measured invasively at the beginning and end of the procedure.

CMR acquisition

Details of the CMR pulse sequence have been previously published[3]. Briefly, CMR was performed pre-procedure (median 1 day, IQR 0 days) and prior to hospital discharge (median 4 days, IQR 1 day) using the same 1.5T scanner (Philips Healthcare, Best, The Netherlands). Multi-slice, multi-phase cine imaging was performed using a standard steady-state free procession (SSFP) pulse sequence in the short axis (10mm thickness, 0mm gap, 30 phases, matrix 192x192, typical field of view 340mm) to cover both ventricles. Standard 2, 3 and 4 chamber SSFP cine images were also acquired. Through-plane velocity encoded phase contrast (VENC) imaging was performed perpendicular to the aortic valve jet at the aortic sinotubular junction (typical VENC 250-500cm/sec, retrospective gating, slice thickness 6mm, 40 phases). LGE imaging (10-12 short axis slices, 10mm thickness, 0mm gap, matrix 240x240, 320-460mm field of view) was performed for the baseline scan only, with inversion time (TI) individually adjusted according to TI scout, 10-15 minutes after the administration of 0.2mmol/kg of gadoteric acid (Dotarem, Guerbet, Villepinte).

Image analysis

Offline quantitative analysis was performed with dedicated computer software (CVI[42], Circle Cardiovascular Imaging, Calgary, Alberta, Canada). Endocardial and epicardial borders were manually contoured by a single experienced operator (LED), blinded to clinical and procedural data, at end-diastole and end-systole with papillary muscles and trabeculations excluded to allow the calculation of left and right ventricular volumes (summation of discs methodology) and LV mass (epicardial volume – endocardial volume multiplied by myocardial density (1.05g/cm^3)). All values were indexed to body surface area. Aortic flow was quantified using cross-sectional phase contrast images with contouring of the aortic lumen to provide a peak forward flow velocity (m/sec) and regurgitant fraction (%). Significant aortic regurgitation was defined as an aortic regurgitant fraction >16%[11]. For analysis of the LGE images, each slice was visually inspected by two experienced independent observers, blinded to clinical and procedural data, for the presence or absence of LGE, which was then categorised as either infarct pattern or mid-wall/focal fibrosis pattern. Any discrepancy between the two operators was reviewed by a third operator to reach a consensus decision. Phase swap, cross cut and other geometry images were used in order to assist in decision making where required. Fibrosis mass was calculated via the semi-automated threshold of 5 standard deviation technique. Patients with a mixed pattern of LGE were assigned to the group according to the predominant pattern of LGE. Left atrial volume was calculated as previously described[12]. LV and RV longitudinal function was measured using the maximum length of mitral and tricuspid annular excursion between end diastole and end systole[13].

Statistical analysis

Continuous variables were expressed as mean±SD or median (IQR) and discrete variables as frequency (percentage). Data were tested for normality using the Shapiro-Wilks test. For normally distributed data, paired and unpaired Student's *t* tests were used. For non-normally distributed data, the Related-Samples Wilcoxon Signed Rank Test and independent samples Mann-Whitney U test were used. The

Chi-squared test was used for comparing categories of data. To compare between groups analysis of variance (ANOVA) and Tukey *post-hoc* tests were used. Predictors of LV mass regression were calculated by a stepwise multiple linear regression model with baseline measurements entered as co-variate factors. Variables with a $p<0.05$ were entered into the multi-variable analysis. Pearson correlation coefficients were calculated to investigate the relationship of LV mass regression and LVEF with baseline factors. All statistical analyses were performed using the PASW software package (V.20.0, SPSS, IBM, Chicago, Illinois, USA). $P<0.05$ was considered statistically significant. Based on the published data[9], the group size required to detect a 3% change in LVEF is 15 and 9 to detect a 10g change in LV mass. For the assessment of inter-observer variability, two independent investigators analysed LV mass on a random selection of 10 patients both pre- and post- TAVR. For intra-observer variability a similar dataset from 10 patients was analysed twice by the author one month apart. The co-efficient of variation was calculated by dividing the standard deviation of the differences between measurements divided by their general mean and expressed as a percentage. Intra-and inter-observer variability for LV mass quantification was 4.5% and 5% respectively.

RESULTS

Of the recruited patients, 57 (88%) completed both pre-procedure and early post-procedure scan protocols. Reasons for non-completion of the study protocol included pacemaker implantation (n=3), peri-procedural death (n=2), poor image quality due to arrhythmia (n=1) and claustrophobia (n=2). The analysed study population did not differ from the non-completion population in terms of age (79±8 vs. 79±7yrs, p=0.916), baseline indexed aortic valve area (AVAi) (0.33±0.09 vs. 0.34±0.09cm/m^2, p=0.747) or EuroSCORE II (4.47±3.40 vs. 4.55±3.46%, p=0.891). Basic demographic, clinical and echocardiographic characteristics of the final study population can be seen in Table 1.

Baseline CMR characteristics

All studies were of diagnostic quality and the TAVI prosthesis did not cause significant artefact. Baseline LVEF was 55.1±12.1% and mean indexed LV mass (LVMi) was 76.2±15.5g/m^2 with an LV mass:LVEDV ratio of 0.80±0.15. LGE imaging was available for 53 patients. 4 (7%) patients did not receive a Gadolinium-based contrast agent due to pre-existing renal failure with an estimated glomerular filtration rate of <30ml/min/1.73m^2. 14 patients (26%) had evidence of myocardial infarction pattern LGE, 19 patients (36%) had mid-wall/focal fibrosis pattern LGE and the remaining 20 (38%) had no evidence of LGE. Examples of the differing patterns of LGE can be seen in Figure 1. Fibrosis distribution can be seen in Figure 2. Mean mass of infarct and mid-wall/focal fibrosis were 5.8±6.7 and 1.3±1.0g respectively accounting for 5.0±6.6 and 0.9±0.8% of baseline LV mass. Those with no fibrosis at baseline had a lower pre-procedure LVEDP (18±5mmHg) than those with infarct pattern LGE (21±8mmHg) and mid wall/focal fibrosis (24±8mmHg)(*F*=3.249, p=0.047) but there was no significant difference between the different fibrosis groups in terms of baseline LVMi (no LGE 74.3±15.7, mid-wall/focal fibrosis LGE 77.6±55.8, infarct pattern LGE 73.1±13.7g/m^2, *F*=0.390*, p*=0.679) or baseline LVEF (no LGE 57.8±10.7, mid-wall/focal fibrosis LGE 55.8±14.5, infarct pattern LGE 51.3±10.6%, *F*=1.162, p=0.321).

Invasive pressure measurements

There was a positive correlation between pre-implant LVEDP and baseline LVMi (r=0.367, p=0.005), but no relationship between pre-implant LVEDP and LVEF (r=-0.067, p=0.619) or AVAi (r=0.002, p=0.986). TAVI was associated with a significant reduction in LVEDP from 21±8mmHg at the start of the procedure to 19±6mmHg following device deployment (p=0.009). Those with a significant reduction in LVEDP (defined as >5mmHg) had a greater baseline LVMi (LVEDP reduction 85.6±14.1 vs. no LVEDP reduction 72.2±14.5g/m^2 p=0.002) and had a significant reduction in LV cavity size (LVEDVi) post-procedure (LVEDP reduction: 8.7±16.0 vs. no LVEDP reduction 0.24±11.4ml/m^2, p=0.028). There was no relationship between post-procedure LVEDP and post-procedure aortic regurgitation (r=0.186, p=0.173).

Post-procedure CMR

CMR derived values pre and early post-procedure can be seen in Table 2. Fifty-three (95%) patients experienced an acute reduction in LV mass. LVMi regressed by 10.1±7.1% from 76±15.5 to 68.4±14.7g/m^2 (p=<0.001). Those in the highest quartile of baseline LVMi had more absolute LVMi regression than those in the lowest quartile (10.5±5.8 vs. 6.4±1.3g/m^2, p=0.045). LV mass regression did not differ according to gender (men 7.8±5.4 vs. women 7.7±6.0g/m^2, p=0.980) and was not associated with baseline AVAi (r=0.126, p=0.348,)post-procedural aortic regurgitation (AR) (r=-0.136, p=0.321), post-procedural valve gradient (r=-0.005, p=0.969), or systolic blood pressure (r=-0.041, p=0.767). Patients with a history of hypertension (n=24 (42%)) experienced greater LV mass regression than those with no hypertension (9.6±5.1 vs. 6.4±5.8g/m^2, p=0.038). Significant AR was present in nine (16%) patients. LVMi regression was similar according to post-procedure AR status (No significant AR 8.5±5.6 vs. significant AR 4.5±5.4g/m^2, p=0.066).

There was no overall change in LVEF (Table 2), however, when split according to baseline LVEF, classified as normal (baseline LVEF>55%, n=33 (58%)) and abnormal (baseline LVEF<55%, n=24 (42%)), a significant improvement in LVEF was seen in those with an abnormal baseline LVEF (43.2±8.9 to 46.7±10.5%, p=0.027), mainly driven by an increase in indexed left ventricular end systolic volume (LVESVi) (Figure 3).

Late Gadolinium Enhancement

Those with no LGE experienced the greatest LV mass regression (13.9±7.1%) compared to those with mid-wall/focal myocardial fibrosis (7.4±5.8%) or myocardial infarct (7.2±7.0%) (*F*=5.968, p=0.005) driven by a difference between those with no fibrosis and mid-wall/focal myocardial fibrosis (p=0.011) and those with no fibrosis and myocardial infarct(p=0.017). There was no difference in LV mass regression between those with mid-wall/focal fibrosis and infarct pattern LGE (p=0.997). Change in

LVEF was not different according to fibrosis status (no fibrosis 1.4±7.1%, mid-wall/focal fibrosis pattern LGE 0.3±7.1% and infarct pattern LGE -1.3±4.2%, *F*=0.688, p=0.507). Longitudinal LV function improved following TAVI in those with no fibrosis (9.68±1.99 to 11.17±2.77mm, p=0.046) whereas in those with mid-wall/focal fibrosis LGE (10.79±2.82 to 10.29±1.75mm, p=0.499) and infarct pattern LGE (10.69±3.78 to 11.69±3.15, p=0.161) there was no change.

Predictors of LV mass regression

Variables including patient demographics, relevant clinical history, procedural characteristics and baseline cardiac measurements were analysed to determine univariable predictors of LV mass regression (Table 3). Multivariable regression analysis revealed only baseline LVMi and the presence of LGE to be independent predictors of early LV mass regression.

DISCUSSION

This prospectively designed follow up study is the first using CMR, the reference standard technique for LV volume and mass quantification, to accurately describe the acute changes in LV mass and function early after TAVI and the relationship to myocardial fibrosis. We have shown that LV reverse remodelling begins immediately, with an absolute reduction of 10% of LV mass occurring within the first week and LVEF improving in those with a reduced baseline ejection fraction. Furthermore, we have demonstrated that those without fibrosis at baseline experience greater early LV mass regression and an improvement in longitudinal LV function.

Remodelling in aortic stenosis and acute reverse remodelling following TAVI

Our baseline characteristics were similar to other TAVI-based studies, representing a population with high levels of co-morbidity at elevated surgical risk[14]. Our rates of baseline mid-wall/focal and infarct fibrosis are consistent with other studies; Dweck et al[15] reported rates of mid-wall/focal fibrosis in 38% of patients and infarct pattern LGE in 28% of patients with moderate or severe AS.

Weidemann et al reported rates of fibrosis in 62% of patients undergoing aortic valve replacement for AS[10]. In our population, there was no association between baseline LVMi and presence or type of fibrosis, yet those with fibrosis had a higher pre-implant LVEDP. This suggests that those with fibrosis may have greater wall stress, with stiffer, less compliant left ventricles leading to elevated filling pressures but not necessarily greater hypertrophy. There was no overall acute change in LVEF which is in keeping with other CMR studies[16], however, those with a reduced baseline LVEF did derive a significant improvement, suggesting that acute afterload reduction does have a favourable effect on LVEF in those with an abnormality at baseline.

We have been able to offer further insight into the timeline of LV mass regression following TAVI. It is well described in the literature that most mass regression occurs within the first 6 months of TAVI, with rates of 18-22% reported[3, 17] with slower regression thereafter[4]. In this study we have been able to show that favourable reverse remodelling occurs almost immediately, with significant LV mass regression occurring within the first week post-TAVI. Similar findings been suggested by echo studies after TAVI[7] and SAVR[8] and has been associated with reduced re-hospitalisation[7]. An echocardiographic sub-study of the PARTNER A trial reported mass regression of 17% at one year following TAVI, with around half of this occurring within the first 30 days[7]. Assessment of LV mass by echocardiography is calculated on the basis of a number of anatomical and mathematical assumptions, reducing its accuracy[18]. Due to the excellent endocardial definition afforded by the technique, LV mass quantification using modern CMR SSFP pulse sequences have been shown to have an excellent correlation with autopsy studies[19]. CMR LV mass quantitation is also more reproducible than by echo[20], allowing smaller sample sizes to detect a treatment effect.

Evidence from animal models support the notion that LV mass regression occurs acutely; a regression in myocyte volume and myocyte cross sectional area has been demonstrated in hypertensive rats one week following the initiation of anti-hypertensive treatment[21]. It has previously been shown that

hearts subject to chronic pressure overload exhibit greater myocardial oedema[22], and it is plausible that the acute reduction in LV mass is due to an early regression of oedema rather than an actual change in myocyte size. Further study using pre- and post-contrast T1 mapping to estimate extracellular volume and cardiomyocyte size may help to further unravel this potential mechanistic effect[23, 24].

Myocardial fibrosis

Myocardial fibrosis manifests as a result of myocyte apoptosis and subsequent replacement fibrosis and expansion of the extra-cellular volume[25]. It is a well defined phenomenon in patients with severe AS[10] although the pathogenesis of the myocyte death remains unclear. Potential mechanisms include sub-endocardial ischaemia as a result of chronic supply demand mis-match in the context of LV hypertrophy, myocardial stretch as a result of increased systolic wall stress and angiotensin II related cell damage[15]. Myocardial fibrosis is important; it has been found to be an adverse prognostic marker in patients with AS, with a 6-8x risk of mortality, incremental to that of baseline LVEF[15]. Postulated mechanisms of this increase in mortality include ventricular arrhythmia and adverse ventricular reverse remodelling. In our study although LV mass regression was seen in all 3 groups of patients, those without fibrosis at baseline had greater acute LV mass regression than those with both focal/mid wall fibrosis and infarct pattern fibrosis. The favourable LV reverse remodelling demonstrated in those without fibrosis may allow a mechanistic explanation for this survival advantage. The lack of relationship between myocardial fibrosis and LVEF is perhaps not surprising, as LVEF is derived predominantly from radial contraction, which is not significantly contributed to by the sub-endocardial layers. Sub-endocardial fibres are the most sensitive to myocardial ischaemia (resulting from supply-demand mismatch) and systolic wall stress[26] and are responsible for longitudinal function[27]. This is therefore a plausible explanation for the improvement in longitudinal function seen in the group without fibrosis and the lack of improvement in both the mid-wall/focal and infarct pattern fibrosis groups.

Limitations

As with many studies investigating 'real world' patients, our study population was heterogeneous including those with and without coronary artery disease and differing baseline LVEF, which may have influenced the results. Although the dropout rate was low for a CMR based study and the recruited population did not appear to differ from the analysed population, there is still the potential for bias. Although we were careful to include all possible factors in the study that may have influenced LV reverse remodelling, there may have been other factors involved. Specifically, no echocardiographic data regarding post-procedure valve gradients was acquired as a part of this study. However, we were able to report CMR derived values for post-procedural valve gradient and did not find this to be a predictor of LV mass regression on univariate analysis. CMR derived flow gradients are less accurate than echocardiographically derived Doppler gradients and therefore an in-depth analysis of any influence of patient-prosthesis mismatch was not possible. This study was not designed as an outcome study, nonetheless, demonstrating a link between acute LV reverse remodelling and mortality would strengthen these data.

CONCLUSIONS

This prospective CMR study has demonstrated that important changes in LV reverse remodelling can be seen within the first week following TAVI, with significant LV mass regression in the total population and an improvement in LVEF in those with reduced pre-procedure LVEF. Those with no evidence of myocardial fibrosis at baseline experience more LV mass regression than those with fibrosis and also an acute improvement in longitudinal function, demonstrating a link between fibrosis and acute LV mass regression.

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RELATIONSHIP WITH INDUSTRY

JPG and SP have received an educational research grant from Philips Healthcare. DB and CJM are consultants and proctors for both Medtronic and Boston Scientific.

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FIGURE LEGENDS

Figure 1

Left ventricular (LV) short axis CMR images demonstrating the different types of late gadolinium enhancement (LGE). Panel A. The LV myocardium appears black with no evidence of LGE. Panel B: The red arrow depicts focal fibrosis at the anterior right ventricular insertion point. Panel C:A typical mid wall LGE pattern (red arrow). Panel D: Infarction pattern LGE, with the red arrow demonstrating an anterior myocardial infarction of around 50% trans-murality. LV: Left ventricle. RV: Right ventricle.

Figure 2

The distribution and frequency (%) of infarct pattern and non-infarct (focal/mid-wall) pattern late gadolinium enhancement (LGE) as represented on a 17 segment AHA model.

Figure 3

Bar graphs depicting change in LVEF, LVEDVi and LVESVi according to baseline LVEF pre and post-TAVI. The error bars depict the 95% Confidence Intervals. LVEF: Left ventricular ejection fraction. LVEDVi: Indexed left ventricular end diastolic volume. LVESVi: Left ventricular end systolic volume. TAVI: Trans-catheter aortic valve implantation.

TABLES

Table 1. Basic demographic, clinical and echocardiographic data.

	Analysed population (n=57)
Age, years	79±8
Length of stay, days	7.2±7.0
Gender, male	30 (53)
NYHA classification	3.0±0.4
EuroSCORE II, %	4.6±3.5
Atrial Fibrillation	11 (19)
Diabetes Mellitus	9 (16)
Hypertension	24 (42)
Previous myocardial infarction	15 (26)
Previous coronary artery bypass grafting	12 (21)
Prior percutaneous coronary intervention	17 (30)
Any coronary artery stenosis >50%	26 (46)
Echocardiographic data	
Indexed aortic valve area, cm/m^2	0.34±0.09
Peak aortic valve velocity, m/sec	4.7±0.6

Data expressed as mean ±SD or number (%)

NYHA: New York Heart Association .

Table 2. CMR-derived parameters pre and post-procedure.

	Pre-procedure	Post-procedure	P Value
Mitral annular displacement, mm	10.3±2.8	11.0±2.6	0.134
LVEDVi, ml/m^2	97.8±24.3	95.1±18.9	0.226
LVESVi, ml/m^2	45.7±22.6	43.6±18.3	0.268
LVEF, %	55.1±12.1	55.5±10.9	0.867
LVMi, g/m^2	76.2±15.5	68.4±14.7	<0.001
LV mass/LVEDV	0.76±0.15	0.73±0.15	<0.001
RVEDVi, ml/m^2	72.6±15.8	73.6±14.5	0.407
RVESVi, ml/m^2	33.1±11.4	33.0±10.0	0.834
RVEF, %	55.1±8.8	55.8±8.5	0.248
Tricuspid annular excursion, mm	20.2±7.0	19.5±6.9	0.356
Indexed left atrial volume, ml/m^2	75.4±24.7	70.4±23.1	0.042
Max pressure gradient, mmHg	44±15*	18±9	<0.001
Aortic regurgitation fraction, %	12.3±9.4	7.6±6.5	0.005

LVEDVi: Indexed left ventricular end diastolic volume. LVESVi: Indexed left ventricular end systolic volume. LVEF: Left ventricular ejection fraction. LVMi: Indexed left ventricular mass. RVEDVi: Indexed right ventricular end diastolic volume. RVESVi: Indexed right ventricular end systolic volume. RVEF: Right ventricular ejection fraction.

*CMR derived peak aortic valve gradients in severe AS are systematically lower than echocardiographically derived gradients.

Table 3. Univariate and multiple regression analysis for change in indexed left ventricular mass.

	B Coefficient	Standard Error	P Value	95% CI
Univariable analysis – change in LVMi				
Baseline LVMi	0.119	0.047	0.014	0.025 to 0.212
Gender	-0.037	1.514	0.980	-3.072 to 2.997
Age	0.032	0.097	0.747	-0.163 to 0.227
Hypertension	3.126	1.472	0.038	0.176 to 6.076
AVAi	7.968	8.426	0.348	-8.919 to 24.855
SBP	-0.010	0.033	0.767	-0.077 to 0.057
Reduction in LVEDP >5mmHg	1.740	1.609	0.284	-4.965 to 1.485
TAVI size	0.418	0.287	0.151	-0.158 to 0.993
Presence of fibrosis	-5.042	1.467	0.001	-7.987 to -2.097
Type of fibrosis	2.562	0.847	0.004	0.860 to 4.263
Post-procedural AR	-0.120	0.120	0.321	-0.360 to 0.120
Post-procedural aortic valve peak gradient	-0.004	0.091	0.969	-0.186 to 0.179
Multivariable regression analysis – change in LVMi				
Baseline LVMi	0.126	0.043	0.005	0.040 to 0.212
Presence of fibrosis	-5.190	1.362	<0.001	-7.926 to -2.454

LVMi: Indexed left ventricular mass. AVAi: Indexed aortic valve area. SBP: Systolic blood pressure. TAVI: Transcatheter aortic valve implantation. AR: Aortic regurgitation.