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Left ventricular remodelling patterns after MitraClip implantation in patients with severe mitral valve regurgitation: Mechanistic insights and prognostic implications

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ABSTRACT

Aim: The effect of MitraClip implantation on left ventricular (LV) remodelling has been shown to be highly variable. The present study wants to assess patterns of LV remodelling and its relationship with outcome.

Methods and results: Serial echocardiography before, one month and 6 months after MitraClip implantation was performed in 79 pts with severe MR (age 74 ± 10 yrs, NYHA III/IV 80%, LV ejection fraction $38 \pm 13\%$, logistic EuroSCORE I 21 ± 15 , functional MR 81%). LV reverse / adverse remodelling was defined as a $>15\%$ decrease/ $>10\%$ increase in LV end-diastolic volume (LVEDV), respectively. Patients were followed over a period of 32 ± 16 months with all-cause mortality as the primary endpoint.

A sustained (6 month) reduction of $MR \leq 2$ post MitraClip implantation was observed in 83% of patients. The average decrease in LVEDV 6 months after intervention was $13\% \pm 16\%$. Reverse remodelling at six months occurred in 40 patients (51%), and adverse remodelling occurred in 6 (8%) patients. Patients with adverse remodelling showed, on average, a 38% increase of LVEDV at one month versus no early change in LVEDV in patients with reverse remodelling. During follow-up, a total of 25 (32%) patients died. Patients with adverse remodelling died more frequently than patients with reverse remodelling (67% vs 27%, adjusted odds ratio of 5.6 (95% CI 1.5-21)).

Conclusion: The majority of patients undergoing MitraClip implantation for severe MR showed LV reverse remodelling. However, there was a small group in whom afterload mismatch resulted in sustained adverse remodelling with subsequent high mortality.

Keywords: mitral regurgitation; MitraClip; left ventricular remodelling; heart failure; mitral valve repair; afterload mismatch

Introduction

Chronic severe mitral regurgitation (MR) imposes an important volume overload on the left heart, which in turn causes dilation of the left ventricle (LV) and left atrium (LA) as well as progressive adverse LV remodelling.¹ The negative impact of MR on prognosis has been linked to this progressive adverse LV remodelling as a result of ongoing volume overload.² Mitral valvular repair of severe MR, either surgically or percutaneously, has been shown to prevent and even reverse adverse remodelling, improve cardiac function and functional status and reduce the risk of heart failure.³⁻⁷ The effect of MR repair on LV remodelling is, however, highly variable.⁸

Previous surgical studies of chronic mitral regurgitation have highlighted the risk of afterload mismatch produced by the operation with a sharp decrease in the LV ejection fraction after the operation.^{9, 10} This response appears to reflect the unmasking of decreased myocardial contractility by mitral valve replacement, with ejection of the total stroke volume into the high impedance of the aorta. This risk was particularly high in patients with depressed LV function and/or in patients with dilated LV dimensions and a subsequent limited preload reserve.¹¹

The issue of afterload mismatch has also been encountered after percutaneous mitral valve treatment. Melisurgo et al. showed that in more than one-quarter of patients with severe functional mitral regurgitation, a significant reduction of the ejection fraction was observed early after MitraClip implantation, but this decrease in left ventricular function was temporary and was completely recovered by hospital discharge.¹² The effect on left ventricular remodelling (at 6 months), however, was not studied.

The process of reverse remodelling has also been reported in non-valvular cardiomyopathy treated with cardiac resynchronization therapy (CRT).¹³ Reverse remodelling post CRT was shown to be mainly dependent on the initial extent of the LV conduction delay and on the LV scar volume and has been shown to be associated with reduced heart failure morbidity and mortality.¹⁴ Data on the predictors of LV remodelling post MitraClip and on the clinical correlates of different patterns of LV remodelling are still limited, but this information may impact the selection of patients who are suitable for percutaneous mitral valve repair as well as their subsequent management.

Therefore, this study was designed to describe different patterns of LV remodelling post MitraClip implantation and to determine the predictors and clinical correlates of left ventricular remodelling after percutaneous mitral repair.

Methods

Study population

The study population consisted of 79 patients who underwent percutaneous mitral valve repair with the MitraClip because of severe symptomatic mitral valve regurgitation in six Belgian centres and for whom serial 6 month echocardiographic evaluation data were available. All of these patients were deemed to have too high of a surgical risk based upon a global clinical assessment and heart-team evaluation. In case of a severe coronary stenosis percutaneous coronary intervention was performed at least six weeks before the mitral valve intervention). The clinical characteristics of the patients were extracted from the Belgian MitraClip database, which prospectively gathers clinical information on all MitraClip procedures in Belgium.¹⁵ At the time of the evaluation, there were 140 mitraclip patients included in the Belgian MitraClip database. A total of 61 patients were excluded because of early death (n=12 patients), early surgical mitral valve intervention (n=11) or because adequate echocardiographic images at baseline and at 1/6 month follow-up were not available (n=38). The ethical committee of Antwerp University Hospital approved the study protocol, and all patients gave written informed consent. The database is registered with clinicaltrials.gov (NCT02506387).

MitraClip procedure

All procedures were performed under general anaesthesia using transoesophageal echocardiography (TOE) and fluoroscopic guidance. A comprehensive description of the procedure is has been previously described^{15,16}. Post-procedural pharmacologic management included a three-month prescription of 75 mg of clopidogrel daily on top of aspirin or an anticoagulant and optimal heart failure treatment consistent with heart failure guidelines.

Procedural success was defined as a non-complicated placement of ≥ 1 clip coinciding with a per-procedural estimated MR reduction to \leq grade 2+.

Echocardiographic evaluation

All of the echocardiographic examinations were carried out by trained sonographers using high-quality cardiovascular ultrasound systems.

MR severity was graded according to the American Society of Echocardiography guidelines based on a validated multi-integrative method.¹⁷ Both qualitative (colour flow mapping) as

well as quantitative measurements (proximal isovelocity surface area whenever feasible) were used to grade the MR severity from grade 0 to grade 4 (grade 0: no/trace; grade 1: mild; grade 2: moderate; grade 3: moderate-to-severe; grade 4: severe).

Systolic pulmonary arterial pressure could be obtained in 75 patients from the summation of the trans-tricuspidalis regurgitation gradient and the estimated central venous pressure.

Serial LV and left atrial volumes adjusted for body surface area were calculated off-line by one expert using Simpson's biplane method. LV remodelling and LA remodelling were assessed by calculating the percentage of volume changes over time (6 months post intervention volume minus baseline volume). LV reverse remodelling was defined as a >15 % decrease in LV end-diastolic volume index (LVEDVi). LV adverse remodelling was defined as a > 10% increase in LV end-diastolic volume index. No LV remodelling was defined as a change between -15% and +10 % in LV end-diastolic volume index.

Early adverse remodelling, as a marker of afterload mismatch, was defined as a > 10% increase in LV end-diastolic volume index at one month post intervention.

Global longitudinal strain (GLS) was obtained from standard three-, four-, and two-chamber apical views by an automated measurement tool using speckle tracking (AutoStrain, Tomtec Imaging Systems GMBH, Unterschleissheim, Germany), with manual editing of the contours if necessary.

(There was strong agreement between LV volumes as assessed by echocardiography and cardiac MRI (56 LV volume data sets available, correlation coefficient 0.84), although there was an underestimation of volumes by echo, which is in agreement with previous studies.¹⁸ zou deze zin verplaatsen naa results)

Cardiovascular magnetic resonance imaging and analysis

In a subgroup of 22 patients (single centre Antwerp University Hospital), cardiovascular magnetic resonance imaging (CMR) was performed the day before the MitraClip intervention. Patients were examined using a Skyra 3 Tesla CMR scanner with a dedicated bodymatrix 18-channel coil and 32-channel spine coil (Siemens, Erlangen, Germany). The entire heart was imaged in the short-axis orientation by breath-hold TrueFISP imaging. Late gadolinium enhancement of the myocardium was studied 10 minutes after intravenous bolus injection of 0.2 mmol/kg gadolinium (Dotarem®, Guerbet, The Netherlands) and imaging the whole heart in short-axis orientation using TrueFISP Phase-Sensitive Inversion Recovery sequence.

CMR analysis was performed offline using Qmass software (MEDIS, Leiden, The Netherlands) to measure ventricular volumes, mass and myocardial scar tissue. Late gadolinium enhancement was defined by signal threshold values versus reference of 6 standard deviations above the mean signal intensity (SI) of reference (remote) myocardium.¹⁹

Electrocardiographic analysis

ECG quantification of the LV volume was calculated using a 32 point Selvester QRS score on a 12 lead ECG at baseline. This QRS score was validated in AMI patients and was also used to assess the extent of fibrosis in CRT studies both in patients with and without a conduction delay.^{20, 21} The QRS score was scaled according to the size of Q waves and R and S amplitudes.

Clinical follow-up

The primary study endpoint was freedom from all-cause death. The secondary endpoint was rehospitalisation for heart failure. All of the endpoints were obtained from patient records or from telephone calls with the patient or the patient's family if the patient was deceased.

Statistical analysis

Continuous variables are presented as the mean \pm standard deviation. Categorical variables are presented as counts and percentages. Characteristics were compared across groups with chi-square tests for categorical variables and ANOVA for continuous variables with post hoc Bonferroni testing. Comparisons of LV volume index changes for the different study subgroups were carried out by ANOVA for repeated measurements. For the identification of independent factors of LV remodelling, multiple stepwise regression analysis was performed with stepwise inclusion of the following factors: age, baseline LV ejection fraction, baseline LV end-diastolic dimension, log Euroscore 1, GLS, Systolic PAP, and MR grade at follow-up. Receiving Operating Characteristic (ROC) analysis was applied to define the optimal cut-off value to predict adverse remodelling.

Cumulative event-free survival estimates were plotted using the Kaplan-Meier technique. Differences between the survival curves of the different LV remodelling patterns were tested with the log-rank test. The Cox proportional hazards model was applied to identify independent predictors of mortality. The following baseline factors were included in the model: age, gender, BMI, baseline poor LV function (LVEF \leq 30%), baseline NYHA classification, renal function (glomerular filtration rate in ml/min/1.73 m²), diabetes, aetiology of mitral regurgitation, baseline LV end-diastolic dimension, baseline NYHA classification, Selvester QRS score, logistic Euroscore 1, GLS, Systolic PAP, MR grade at 6 month, and LV remodelling pattern (adverse-no remodelling- reverse remodelling).

A two-tailed p-value <0.05 was considered statistically significant. Statistical analyses were performed using MedCalc for Windows, version 15.0 (MedCalc Software, Ostend, Belgium).

Results

Study population

The study population consisted of 79 patients (54% male) with a mean age of 74 ± 10 yrs. The majority of patients had severe functional MR (81%) or mixed functional-degenerative MR (6%) and were highly symptomatic (NYHA class >2 in 80% of the patients). The study patients were at high surgical risk as evidenced by a high logistic Euroscore 1 (mean 21 ± 15), depressed left ventricular function (mean LV EF: 38 ± 13 %, mean GLS: -12 ± 4 %), and impaired renal function (mean GFR 51 ± 23 ml/min/1.73 m²). The majority (72%) had coronary artery disease, 42% had a history of coronary bypass graft surgery (CABG), 16% had chronic obstructive pulmonary disease and 42% had atrial fibrillation. Patients received standard heart failure medication: 82% received beta blockers, 62% received an angiotensin-converting-enzyme inhibitor (ACEI)/angiotensin receptor blocker (ARB), and 25% received aldosterone antagonists. Cardiac resynchronisation therapy was present in 13% of patients.

Percutaneous mitral valve repair with MitraClip was successful in 91% of patients; an average of 1.4 MitraClips were used. The severity of the mitral regurgitation decreased from a mean grade of 3.6 ± 0.5 to a mean grade of 1.6 ± 0.7 ($p < 0.0001$). After 6 months, the average MR was 1.8 ± 0.8 with MR grade $>2/4$ in 17% of the patients.

Ventricular remodelling patterns post MitraClip

Table 1 describes the evolution of the left ventricular and left atrial volume as well as LV ejection fraction pre, 1 month and 6 months after intervention. Both the LV end diastolic and LV end systolic volume indices show a biphasic pattern with an early increase and subsequent decrease of the volumes. The left atrial volumes showed a steady decrease over the 6 month period, whereas there was no significant change in LVEF%.

The average LV remodelling 6 months after intervention was $-13\% \pm 16\%$. Reverse remodelling occurred in 40 patients (51%), no remodelling occurred in 33 patients (42%) and adverse remodelling occurred in 6 patients (8%).

The extent of early LV remodelling (1 month after intervention) was on average $6.7 \pm 17\%$. Early adverse LV remodelling ($>10\%$) was present in 24 patients (30%), particularly in patients who showed adverse remodelling at six months. In those patients, the LV volume increased by 38% at one month.

Figure 1 and table 3 show the % evolution of the LV end diastolic volume indices for the three different LV remodelling patterns. Although regression of the LV volumes was observed between 1 and 6 months for all LV patterns, this effect was insufficient to compensate for the afterload mismatch related early increase in LVED volumes observed in the groups without reverse remodelling ($p < 0.001$). Receiving Operating Characteristic (ROC) analysis was applied to assess whether LV remodelling at one month

could predict adverse remodelling at 6 months. An optimal cut-off value of -11% was calculated with a sensitivity of 100% and specificity of 80% to predict LV adverse remodelling at 6 months (Area Under the Curve of 0.91, $p < 0.0001$).

Ventricular remodelling predictors

Table 2 compares the characteristics between the three LV remodelling patterns. No significant differences were found except for lower BMI in the adverse remodelling group. There was a clear trend of less reverse remodelling in patients with high systolic pulmonary pressure). In a multivariate regression model, high systolic pulmonary pressure was the only independent correlating factor for the extent of LV remodelling ($r^2=0.07$, $p=0.02$). An optimal cut-off value of 50 mmHg was calculated with a sensitivity of 80 % and specificity of 69% to predict LV adverse remodelling at 6 months (Area Under the Curve of 0.66, $p=0.2$).

With regard to the relationship between fibrosis and LV remodelling, restriction of the patient population to patients without pacing did not change the relationship between the QRS score and LV remodelling ($p=0.8$, $r^2=0.001$). Also, in the subpopulation of patients with MRI data, no correlation was found between the amount of fibrosis as assessed by LGE cardiac MRI and LV remodelling ($p=0.9$, $r^2=0.0005$).

Ventricular remodelling patterns and clinical outcome

Over a period of 32 ± 16 months, there were 25 deaths (32%) and 40 (51%) re-hospitalizations for heart failure, with an average number of heart failure hospitalizations of 0.5 ± 0.9 for the total population. The relationship between different LV remodelling patterns and outcome is depicted in Figure 2 and Table 4. Patients with adverse remodelling died earlier and more frequently (log-rank p value= 0.005). Mortality occurred at 20 ± 9 months in patients with adverse remodelling versus at 32 ± 16 months in patients without adverse remodelling ($p=0.1$). There was also a trend towards more hospitalisations for heart-failure in the patient group with adverse remodelling.

Cox regression analysis revealed that adverse remodelling and high logistic Euroscore were the only independent predictors of mortality, with adjusted odds ratios of 5.6 (95% CI 1.5-21, $p=0.01$) and 1.05 (95%CI 1.02-1.08, $p=0.0004$), respectively.

Discussion

The present study demonstrates that the majority of patients undergoing percutaneous mitral valve repair for severe MR showed reverse remodelling. However, in a small group of patients (8%), adverse remodelling was documented which was associated with a high mortality rate.

Previous work, particularly from the EVEREST trials substudies, evaluated changes in LV volumes and demonstrated a 10 % decrease, on average, in LVEDV for the subgroup with functional MR and, on average, 14% for the subgroup with degenerative MR.^{6, 8} Our study data (average of 13%) are consistent with these findings. The high proportion (>50%) of patients with reverse remodelling is reassuring and promising for the percutaneous repair technique of mitral valve regurgitation and reflects the unloading effect of mitral valve repair even in severely diseased hearts. Similar high rates of reverse remodelling were also observed following restrictive surgical mitral annuloplasty in ischaemic mitral regurgitation.⁴ However, Braun et al. observed fading out of reverse remodelling in cases of severely dilated hearts (cut-off values of 65 mm LV end diastolic diameter).¹¹ Other factors that have been associated with attenuation of reverse remodelling include the magnitude of post intervention mitral regurgitation. Grayburn et al. showed that LVEDV improved proportionally to the degree of MR reduction but that for severe residual MR, no significant reverse remodelling post MitraClip was observed.⁸ In our study, baseline systolic pulmonary arterial pressure was the only independent predictor for reverse remodelling. Patients with high pulmonary pressure showed less reverse remodelling. Pulmonary arterial pressure might reflect diastolic dysfunction on top of the severe MR in our study population. After percutaneous mitral valve correction, severely impaired diastolic function together with reduced systolic dysfunction might have attenuated reverse remodelling. Pre-existing poor left ventricular function (both systolic and diastolic) puts patients at high risk for developing afterload mismatch and subsequent impairment of cardiac performance early after mitral valve repair. In our study population, 30% of patients showed evidence of afterload mismatch one month after intervention. Although recovery of adverse remodelling was observed in the majority of our patients, there was a small subgroup in whom adverse remodelling persisted after 6 months; that subgroup showed a high level of early adverse remodelling (40% increase in LV ED volume) and was associated with a high mortality rate. To our knowledge, this is the first report which identifies a subgroup of patients who show adverse remodelling post MitraClip. This might be partially explained by the limited data regarding LV remodelling after MR correction, and partially by the exclusion or marginal representation of patients with poor baseline LV function in previous studies. In the study of Grayburn et al., the average LV ejection fraction in FMR patients was 52% (versus 39% in our study population).⁸ Although LV ejection fraction assessment is well known to underestimate cardiac function in the presence of severe mitral regurgitation, it is unlikely that these patients would not have had enough cardiac reserve to compensate for the initial effect of afterload mismatch in contrast to the patients

of the present study. Early adverse remodelling in the present study most likely revealed the true severity of underlying cardiac dysfunction (both systolic and diastolic), which was not fully captured by baseline LV ejection fraction or GLS. Severe pre-existing LV dysfunction with a limited cardiac reserve is most likely also the reason for the observed high mortality rate. Adverse remodelling has also been linked with higher mortality in other non-valvular interventions, such as post CRT. ²²

It would be very useful to identify patients who are at increased risk for adverse remodelling post intervention, and in whom a valve intervention might be futile.

From our study two markers emerged as potential risk factors: first, baseline systolic pulmonary artery pressure which had a moderate value to predict adverse remodelling and secondly, assessment of early adverse remodelling at one month with a higher predictive value. If the increase in LV volume at one month was more than 10%, the chance of developing adverse remodelling at six months was high as was the risk of dying within two years. This could alert the treating physician to optimize medical heart failure therapy and/or seek other heart failure treatments, such as cardiac transplantation/CRT. Whether assessment of contractile reserve with low dose dobutamine or with exercise might better predict the development of adverse remodelling post MitraClip is still unknown but is worthy of investigation while considering the appropriate selection of patients for mitral valve repair.

The results of this study should be considered in the context of the following limitations.

The study population was selected, as patients who died before 6 months were excluded (cf. inclusion required the availability of echo data at six months), which may generate some bias, particularly towards the relationship between LV remodelling and outcome. Therefore, the proportion of patients with LV adverse remodelling might be greater than we have presented. In addition, the relatively small number of patients may impede thorough multivariate analysis of the different risk factors of LV remodelling. Finally, we performed late gadolinium enhancement technique to assess localized heart fibrosis. Additional T1 mapping may provide more information on diffuse heart fibrosis, which may reflect better the degree of underlying myocardial dysfunction (both systolic and diastolic).

In conclusion, although the majority of patients undergoing percutaneous mitral valve repair for severe MR showed reverse remodelling, there was a small group in whom afterload mismatch resulted in sustained adverse remodelling and subsequent high mortality, which was most likely related to severe underlying cardiac systolic and diastolic dysfunction.

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Table 1: Cardiac remodelling post MitraClip

	Pre	1 month post	6 month post	P value
MR grade	3.6 ± 0.5	1.8 ± 0.8*	1.8 ± 0.8*	<0.0001
LV EDVi, ml	95 ± 39	100 ± 40*	82 ± 35*	<0.001
LV ESVi, ml	60 ± 31	65 ± 34*	52 ± 29*	<0.001
LV EF,%	38 ± 13	38 ± 14	39 ± 12	0.2
LA VI, ml	70 ± 21	67 ± 26	58 ± 19*	<0.001

* p value<0.005 (Bonferroni correction)

Data presented as the mean value (standard deviation).

LAVI: left atrium volume index; LV EF: left ventricular ejection fraction; LV EDVI: left ventricular end-diastolic volume index; LV ESVI: left ventricular end-systolic volume index; MR: mitral regurgitation.

Table 2: Characteristics of different LV remodelling patterns.

	Adverse LV remodelling N=6	No LV remodelling N=33	Reverse LV remodelling N=40	P value
Age	68 ± 13	73 ± 9	75 ± 10	0.3
Male gender,%	50	49	60	0.6
AHT,%	83	70	73	0.8
Diabetes,%	50	35	15	0.3
GFR, ml/min..	58 ± 45	51 ± 21	52 ± 21	0.7
BMI,	20 ± 2	26 ± 4	26 ± 4	0.004
Prior MI, %	83	52	48	0.26
EF,%	39 ± 17	35 ± 13	39 ± 13	0.3
LVEF≤ 30, %	35	40	28	0.5
GLS	-11± 4	-11± 4	-13± 4	0.3
CRT, %	17	18	8	0.4
NYHA class	2.7 ± 0.5	3.0 ± 0.5	2.8 ± 0.6	0.8
Log Euroscore 1	22 ± 17	23 ± 15	19 ± 15	0.6
QRS score	19 ± 11	17 ± 15	17 ± 10	0.9
MRI fibrose (n=22)	3.6 ± 6 (n=3)	10 ± 14 (n=7)	12 ± 12 (n=12)	0.6
Successful intervention,%	100	85	95	0.6
Aetiology: FMR	83	79	83	0.5
MR grade pre	3.8 ± 0.4	3.6 ± 0.5	3.6 ± 0.5	0.5
LVEDVi, pre, ml/m²	72 ± 24	100 ± 36	95 ± 39	0.2
LAVi, ml/m²	64 ± 15	71 ± 21	70 ± 23	0.76
SPAP, mmHg	56 ± 18	50 ± 12	45 ± 13	0.1
Estimated CVP	8 ± 4	10 ± 6	10 ± 6	0.2

Data presented as the mean value (standard deviation) or as a proportion (%).

AHT: arterial hypertension; BMI: body mass index; CRT: cardiac resynchronisation therapy; GFR: glomerular filtration rate; GLS: global longitudinal strain; FMR: functional mitral regurgitation; LV EF: left ventricular ejection fraction; LAVI: left atrial volume index; LV EDVI: left ventricular end-diastolic volume index; MI: myocardial infarction; MR: mitral regurgitation; MRI: magnetic resonance imaging; NYHA: New York Heart Association; SPAP: systolic pulmonary arterial pressure

Table 3: LV remodelling parameters

MR grade post 6 mo	2.0 ± 1.0	1.9 ± 1.0	1.7 ± 0.6	0.6
Severe MR post 6 mo, %	17	25	10	0.7
LVED remod 1 mo,%	38 ± 35	8 ± 15	1.2 ± 10	<0.001
LVED remod 6 mo,%	19 ± 12	-5 ± 8	-25 ± 8	<0.001

Data presented as the mean value (standard deviation) or as a proportion (%).

LVED remod: left ventricular remodelling; MR: mitral regurgitation

Table 3: Clinical outcome

	Adverse LV remodelling N=6	No LV remodelling N=33	Reverse LV remodelling N=40	P value
Death,%	67	30	27	0.15
Rehospitalisations For heart failure, n	0.8±1.6	0.6±0.9	0.4±0.6	0.3

Data presented as the mean value (standard deviation) or as a proportion (%).

LV: left ventricular

Figure 1

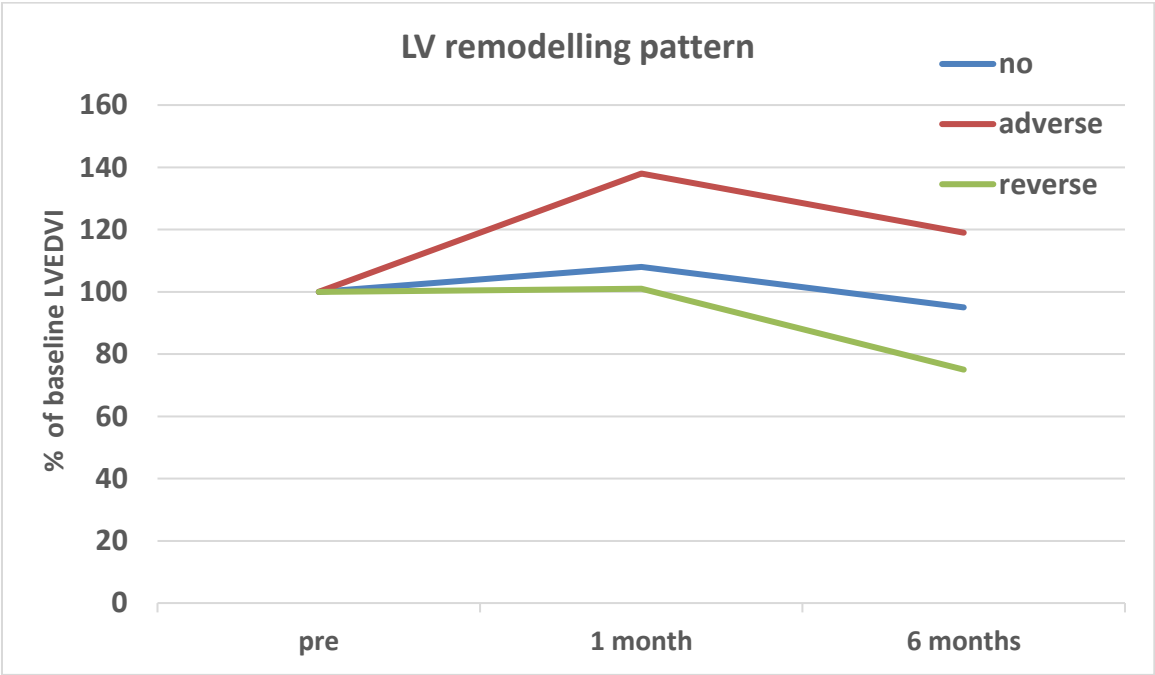


Figure 2

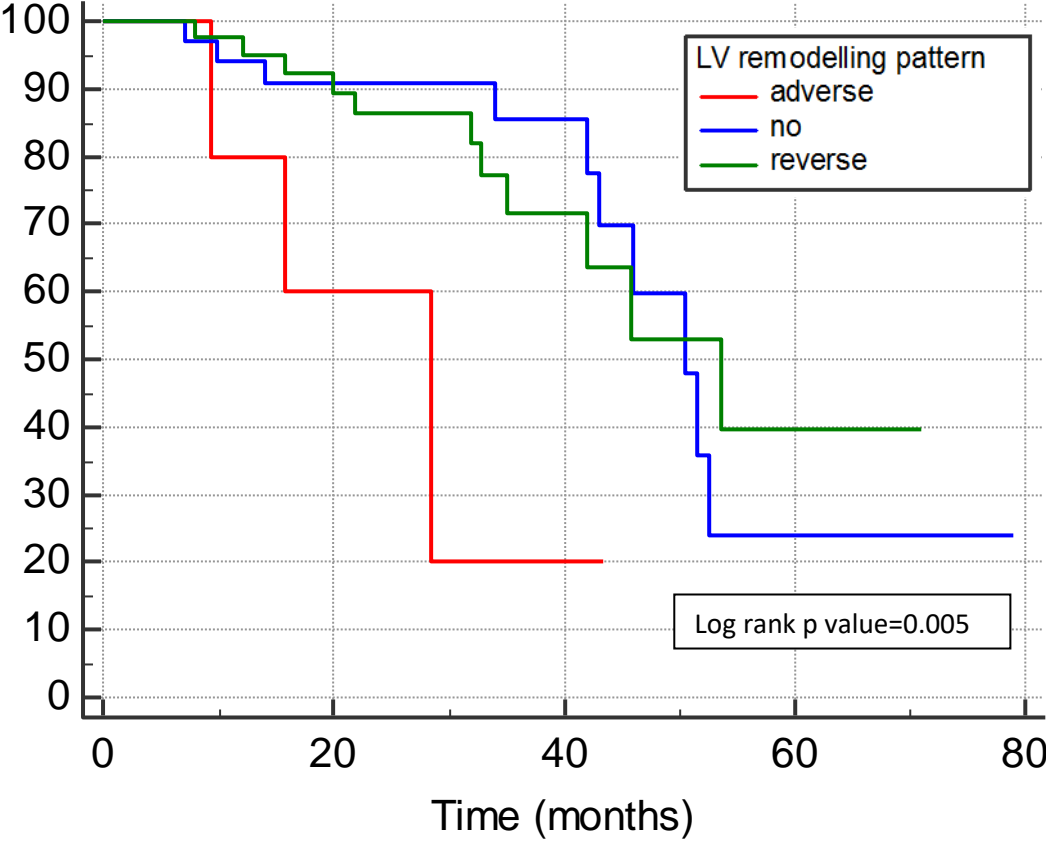


FIGURE LEGENDS

Figure 1

Line graph showing the change (at one and six months) in the average left ventricular end-diastolic volume index (LVEDVI) for the different left ventricular (LV) remodelling patterns. Changes expressed as % of the baseline LVEDVI

Figure 2

Kaplan-Meier curves representing cumulative event-free plot for all-cause death for the different left ventricular (LV) remodelling patterns.