Title: Redefining adverse and reverse left ventricular remodeling by cardiovascular magnetic resonance following ST-segment elevation myocardial infarction and their implications on long-term prognosis

Brief Title: LV remodeling by CMR post-STEMI and prognosis

Authors:

*Dr Heerajnarain Bulluck PhD.[1,4] *Dr Jaclyn Carberry MBChB,[2] Dr David Carrick MRCP,[1,2] Dr Margaret McEntegart MRCP,[1] Professor Mark C. Petrie MBChB,[1] Dr Hany Eteiba FRCP FACC,[1] Dr Stuart Hood FRCP,[1] Dr Stuart Watkins FRCP,[1,2] Dr Mitchell Lindsay FRCP,[1] Dr Ahmed Mahrous MBChB,[1] Professor Ian Ford PhD,[3] Professor Keith G. Oldroyd FRCP,[1] Professor Colin Berry FRCP FACC.[1,2]

*These authors contributed equally.

Affiliations:

[1]West of Scotland Heart and Lung Centre, Golden Jubilee National Hospital, Clydebank, Scotland

[2]British Heart Foundation Glasgow Cardiovascular Research Centre, Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, Scotland

[3]Robertson Centre for Biostatistics, University of Glasgow, Glasgow, Scotland

[4]Norfolk and Norwich University Hospital, Norwich, England

Correspondence: Professor Colin Berry, BHF Glasgow Cardiovascular Research Centre, Institute of Cardiovascular and Medical Sciences, 126 University Place, University of Glasgow, Glasgow, G12 8TA, Scotland, UK. Telephone: +44 (0) 141 330 1671 or +44 (0) 141 951 5000. Fax +44 (0) 141 330 6794 Email: colin.berry@glasgow.ac.uk

Author email addresses: Dr Heerajnarain Bulluck PhD h.bulluck@gmail.com, Dr Jaclyn Carberry MBChB, Dr David Carrick MRCP davidcarrick@nhs.net, Dr Margaret McEntegart MRCP margaret.mcentegart@nhs.net, Professor Mark C. Petrie MRCP Mark.Petrie@glasgow.ac.uk, Dr Hany Eteiba FRCP Hany.Eteiba@glasgow.ac.uk, Dr Stuart Hood FRCP Stuart.Hood@glasgow.ac.uk, Dr Stuart Watkins MRCP stuart.watkins@nhs.net, Dr Mitchell Lindsay MRCP mitchell.lindsay@nhs.net, Dr Ahmed Mahrous amahrous2003@gmail.com, Professor Ian Ford PhD Ian.Ford@glasgow.ac.uk, Professor Keith G. Oldroyd FRCP keith.oldroyd@nhs.net, Professor Colin Berry FRCP FACC Colin.Berry@glasgow.ac.uk.

Acknowledgements: We thank the patients and the staff in the Cardiology and Radiology Departments. We thank Peter Weale and Patrick Revell (Siemens Healthcare, UK).

Funding: British Heart Foundation Grant (RE/18/6134217; PG/11/2/28474) and the Chief Scientist Office. Professor Berry was supported by a Senior Fellowship from the Scottish Funding Council.

Disclosures: This project was supported by a research agreement with Siemens Healthcare.

Word count: 2667

Journal subject term: Magnetic Resonance Imaging

Abstract

Background: Cut-off values for change in left ventricular end-diastolic volume (LVEDV) and LV end-systolic volume (LVESV) by cardiovascular magnetic resonance (CMR) following ST-segment elevation myocardial infarction (STEMI) have recently been proposed and 4 patterns of LV remodeling were described. We aimed to assess their long-term prognostic significance.

Methods: A prospective cohort of unselected STEMI patients with paired acute and 6-month CMR, with the 5-year composite endpoint of all-cause death and hospitalization for heart failure was included. The prognosis of the following groups [Group 1: reverse LV remodeling (≥12% decrease in LVESV); Group 2: no LV remodeling (changes in LVEDV and LVESV <12%); Group 3: adverse LV remodeling with compensation (≥12% increase in LVEDV only); and Group 4: adverse LV remodeling (≥12% increase in both LVESV and LVEDV)] was compared.

Results: 285 patients were included with a median follow-up was 5.8 years. The composite endpoint occurred in 9.5% in Group 1, 12.3% in Group 2, 7.1% in Group 3 and 24.2% in Group 4. Group 4 had significantly higher cumulative event rates of the composite endpoint (log-rank test p=0.03) with the other 3 groups showing similar cumulative event rates (log-rank test p=0.51). Cox proportional hazard for Group 2 [HR 1.3 (95% CI 0.6-3.1), p=0.53] and Group 3 [HR 0.6 (95% CI 0.2-2.3), p=0.49] were not significantly different but was significantly higher in Group 4 [HR 3.0 (95% CI (1.2-7.1), p=0.015] when compared to Group 1.

Conclusions: Patients with STEMI developing adverse LV remodeling at 6 months, defined as ≥12% increase in both LVESV and LVEDV by CMR, was associated with worse long-term clinical outcomes than those with adverse LV remodeling with compensation, reverse LV remodeling and no LV remodeling, with the latter 3 groups having similar outcomes in a cohort of stable reperfused STEMI patients.

Clinical Trial Registration Information: BHF MR-MI study, https://clinicaltrials.gov/ct2/show/NCT02072850

Key words: ST-segment elevation myocardial infarction, magnetic resonance imaging, left ventricular remodeling

Short Commentary

In a prospective cohort of 285 STEMI patients with paired acute and 6-month CMR, patients with adverse LV remodeling defined as ≥12% increase in both LVESV and LVEDV was associated with worse 5-year clinical outcomes in terms of all-cause death and hospitalization for heart failure than those with adverse LV remodeling with compensation (≥12% increase in LVEDV only) , reverse LV remodeling (≥12% decrease in LVESV) and no LV remodeling (changes in LVEDV and LVESV <12%), with the latter 3 groups having similar outcomes. Firstly, this definition for adverse LV remodeling of ≥12% increase in both LVESV and LVEDV at 6 months could be used as a screening tool to identify high-risk patients who could benefit from therapies such as mineralocorticoid receptor antagonist or neprilysin inhibitor/ angiotensin receptor blocker combination therapy to improve long term outcomes. Secondly, ≥12% increase in both LVESV and LVEDV could also be used as a new surrogate endpoint at 6 months for proof-of-concept studies targeting post-infarct LV remodeling. Our findings need to be validated in a larger cohort of patients as well as in those with echocardiographic parameters of LVEDV and LVESV.

Introduction

Despite reperfusion of the infarct-related artery by primary percutaneous coronary intervention (PPCI), adverse left ventricular (LV) remodeling occurs in a significant proportion of patients with ST-elevation myocardial infarction (STEMI)[1]. This is associated with the development of heart failure[2] and poor clinical outcomes[3]. Conversely, reverse LV remodeling post-STEMI has been shown to be associated with good clinical outcomes [4].

Cardiovascular magnetic resonance (CMR) is established as the gold standard modality not only for quantifying myocardial infarct (MI) size[5, 6] and microvascular obstruction (MVO)[7], but also for measuring LV volumes and LV ejection fraction (LVEF)[5, 8]. As a result, CMR is increasingly being used to assess surrogate clinical end-points following STEMI in cardioprotection studies.[9] By echocardiography, adverse LV remodeling following STEMI has been conventionally defined as ≥20% increase in LV end-diastolic volume (LVEDV) from baseline[10, 11] and reverse LV remodeling has been defined as ≥10% decrease in LV end-systolic volume (LVESV)[12].

Recently, cut-off values for the change in LVEDV and LVESV by CMR have been proposed based on a minimal detectable change of 12%. Four patterns of post-STEMI LV remodeling were defined: Group 1: reverse LV remodeling (≥12% decrease in LVESV); Group 2: no LV remodeling (changes in LVEDV and LVESV within <12%); Group 3: adverse LV remodeling with compensation (≥12% increase in LVEDV only); and Group 4: adverse LV remodeling (≥12% increase in both LVEDV and LVESV)[13]. However, these were not linked to clinical outcomes.

Therefore, we aimed to determine the prognostic value of the above 4 groups of LV remodeling defined by CMR at 6 months in a large cohort of STEMI survivors [14-16]. We

hypothesized that among survivors of STEMI, different patterns of LV remodeling at 6 months by CMR would carry different prognosis; Group 1 would have the best long-term outcome and Groups 2, 3 and 4 would have incrementally worse long-term clinical outcomes.

Methods

The data that support the findings of this study are available from the corresponding author upon reasonable request.

The study design has been reported (BHF MR-MI: NCT02072850) [14, 16-18] and is detailed in the Supplementary Methods. In brief, this was a prospective study with consecutive eligible patients recruited from a single centre between May 2011 and November 2012 following informed consent. The eligibility criteria included an indication for PPCI or thrombolysis for STEMI and exclusion criteria were standard contraindications to CMR or inability to tolerate a CMR scan (e.g. claustrophobia, inability to lie flat due to decompensated heart failure or mechanical complications, hemodynamic instability due to ventricular arrhythmias or cardiogenic shock). The study received ethics approval (reference 10-S0703-28) and was registered on clinicaltrials.gov (NCT02072850). Only patients with paired CMR data on LV volumes at baseline and at 6 months follow-up were included in this study.

CMR image analysis

Cardiac magnetic resonance imaging (CMR) analysis was performed on a Siemens workstation. LV volumes and LV ejection fraction were assessed using computer assisted planimetry (Syngo MR®, Siemens Healthcare, Erlangen, Germany) on the short-axis cine images with minimal manual adjustment when required and the LVEDV, LVESV, LV mass and LVEF were quantified by following standard recommendations[5]. Percentage change (%Δ) in LVEDV and LVESV were calculated as the difference between the follow-up

parameters and the corresponding baseline parameters and expressed as a percentage of the baseline parameters.

Health outcomes

Adverse health outcomes that are implicated in the pathophysiology and natural history of STEMI were pre-specified. The primary composite outcome all-cause death and hospitalization for heart failure (HHF) at 5 years following discharge from hospital, independently adjudicated as per the event adjudication charter in the online appendix.

Statistical analysis

Statistical analysis was performed using SPSS version 25 (IBM Corporation, Illinois, US). Continuous data was expressed as mean ± standard deviation (SD) or median (interquartile range) and categorical data was reported as frequencies and percentages. Groups were compared using one-way analysis of variance/ Kruskal-Wallis or Fisher's exact test where appropriate. Cumulative hazard curves were used to assess survival at 5 years per group of LV remodeling and were compared using log-rank test. The primary analysis for the cumulative incidence of all-cause death and HHF at 5 years per group was performed using Cox proportional hazard (with censoring of data to the date of occurrence of the primary endpoint, lost to follow-up, withdrawal from the study or at 5 years) and the hazard ratios (HRs) were computed with 95% confidence interval. Adjusted HRs were also calculated after accounting for acute MI size, MVO and LVEF on the initial scan, the latter three factors being known prognostic CMR markers[19] and also accounting for baseline Global Registry of Acute Coronary Events (GRACE) score. All statistical tests were two-tailed, and $P<0.05$ was considered statistically significant.

Results

Of 391 patients referred for PPCI or urgent PCI following thrombolysis, 324 underwent the acute CMR at 2.2±1.9 days and 300 patients returned for the 6-month follow-up scan. 293 patients had matching LV volumes data and were included in this study (Figure 1). The median follow-up duration was 2120 days (5.8 years) with a range of 233 to 2456 days.

Patient characteristics

The majority of patients (46.8%) had reverse LV remodeling (Group 1) followed by 24.9% with no LV remodeling (Group 2). 14.3% with adverse LV remodeling and compensation (Group 3) and 11.3% with adverse LV remodeling (Group 4). There were 8 patients (2.7%) with ≥12% increase in LVESV only who did not fall in any of the above 4 groups (Figure 2).

The characteristics of these 285 patients are shown in Table 1. The mean age was 59±11 years and 74% were male. There were no differences in baseline characteristics including baseline comorbidities, drugs on discharge, pain onset-to-balloon time, angiographic characteristics and ST-segment resolution among the 4 groups.

Acute and follow-up CMR findings

The CMR findings are summarized in Table 2. Acute MI size was significantly different among the 4 groups ($p<0.001$). Group 4 had significantly larger MI size than Group 1 ($p=0.001$) but there was no statistically significant difference when compared to Group 2 ($p=0.66$) or Group 3 ($p=1.0$). The proportion of patients with MVO was lowest in Group 1

(38%) but similar in Groups 2 to 4 (MVO: 59%, 62% and 61%, respectively). However, among those with MVO, the extent of MVO was largest in Group 4 (11.7% LV mass). Acute LVESV was significantly lower in Group 2 (62ml) when compared to Group 1 (72ml, p=0.036). Acute LVEF was significantly higher in Group 2 (59%) when compared to Group 1 (54%, p=0.007) and Group 3 (51%, P<0.001). All other pairwise comparison did not reach statistical significance. Acute LVEDV and LV mass were similar among the 4 groups (P=0.31 and P=0.24, respectively) (Table 2).

At 6 months, those in Group 1 and Group 2 had significantly smaller chronic MI size (9% LV mass and 12% LV mass, respectively) than Group 4 (19% LV mass, P<0.001 and P=0.044, respectively) (Table 2). Group 4 had the lowest LVEF at follow-up (52%) when compared to Groups 1 to 3 (P<0.001 for pairwise comparison). However, LVEDV and LVESV were similar between Groups 3 and 4 (P=1.0 and P=0.24, respectively), but Groups 1 and 2 had significantly smaller LVEDV and LVESV than Group 4 (LVEDV: P<0.001 and P=0.004; LVESV: P<0.001 and P=0.001, respectively) (Table 2). Follow-up LV mass were similar among the 4 groups (P=0.19) (Table 2).

A subset of patients had CMR data on intramyocardial hemorrhage (IMH) on the acute scan (218) and residual iron at follow-up (n = 243). The incidence of IMH was lowest in Group 1 (24%) but those in Groups 2 to 4 had similar incidences (53%, 55% and 54%, respectively). Residual iron was significantly higher in Group 4 (40%), similar between Groups 2 (32%) and 3 (28%), and lowest in Group 1 (10%), P<0.001 for trend

LV remodeling at 6 months and clinical outcomes

The composite endpoint of all-cause death and HHF occurred in 9.5% in Group 1, 12.3% in Group 2, 7.1% in Group 3 and 24.2% in Group 4. The breakdown of the individual endpoints in each group is provided in Table 3. Cumulative hazard plot analysis showed that those in

Group 4 had significantly higher cumulative event rates of the composite endpoint (log-rank test p=0.03) when compared to the 3 other groups, with the latter 3 groups showing similar cumulative event rates (log-rank test P=0.51) (Figure 3). Using Group 1 as reference, the Cox proportional hazard for Groups 2 [HR 1.3 (95% CI 0.6-3.1), P=0.53] and 3 [HR 0.6 (95% CI 0.2-2.3), P=0.49] were not significantly different but significantly higher for those in Groups 4 [HR 3.0 (95% CI (1.2-7.1), P=0.015]. These findings remained consistent after adjusting for acute MI size, MVO and initial LVEF with Group 4 having the worse prognosis [adjusted HR 2.5 (95% 1.0-6.3), P=0.044], whereas those in Groups 2 [adjusted HR 1.3 (95% 0.5-3.0), P=0.61] and 3 [adjusted HR 0.5 (95% 0.1-1.8), P=0.28] had similar prognosis to Group 1. Similar findings were obtained after adjusting for GRACE score with Group 4 having the worse prognosis [adjusted HR 2.7 (95% 1.0-7.4), P=0.049], whereas those in Groups 2 [adjusted HR 1.7 (95% 0.7-4.2), P=0.2] and 3 [adjusted HR 0.8 (95% 0.2-2.7), P=0.67] had similar prognosis to Group 1.

Discussion

We have shown that in a cohort of unselected STEMI patients with paired acute and 6-month CMR data, those with adverse LV remodeling, defined as the combination of a ≥12% increase in both LVEDV and LVESV from baseline (Group 4), have significantly worse prognosis in terms of the composite endpoint of all-cause mortality and HHF after a median follow-up of 5.8 years, when compared to patients with any of the 3 other patterns of LV remodeling. Of note, those with an isolated ≥12% increase in LVEDV only (Group 3) had a similar prognosis to those with reverse LV remodeling (Group 1) or no LV remodeling (Group 2). Our findings extend and validate prior work in a derivation cohort.[13]

Our findings are relevant for clinical practice and therapeutic trials. We have provided evidence that adverse LV remodeling following STEMI should be defined as a ≥12% increase in both LVEDV and LVESV and this approach clearly identified a high-risk group of patients at 6 months. The implications are two-fold: firstly, this definition could be used as a screening tool to identify high-risk patients and they could be targeted with further potential therapies such as mineralocorticoid receptor antagonist or neprilysin inhibitor/ angiotensin receptor blocker combination therapy; secondly, this definition could be used as a new surrogate endpoint at 6 months for proof-of-concept studies targeting post-infarct LV remodeling.

LV remodeling is usually assessed using echocardiography[10,11,12] but has also been assessed using single-photon computed tomography (SPECT) and CMR[20]. Computed tomography (CT) is another modality to assess serial LV volumes[21]. Although assessment of LV volumes by SPECT and CT are highly reproducible, they utilize ionized radiation. Recently, the use of CMR to assess LV remodeling has gathered momentum. Reindl et al[22]

recently proposed a cut-off of ≥10% increase in LVEDV at 4 months to define adverse LV remodeling by CMR based on a study of 224 patients. However their follow-up time was only 2 years and their composite endpoints included stroke, non-fatal myocardial re-infarction together with all-cause mortality and HHF, the former 2 endpoints being not directly related to the development of adverse LV remodeling[22]. The number of events was small (n=13), which make their analysis prone to statistical fragility. Furthermore, the cumulative hazard curves for health outcomes indicates that events occurring prior to the 4-month CMR may not have been excluded[22]. Most recently, Rodriguez-Palomares et al[23] in a larger cohort of 374 patients, showed that the optimal definition for adverse LV remodeling that predicted outcomes after a mean follow-up of 6 years was a combination of a 15% increase in LVEDV and a 3% reduction in LVEF at 6 months. LVEDV was used to estimate LVEF therefore given this association (and inverse correlation) it is not surprising that those with both and increase in LVEDV and a decrease in LVEF had worse prognosis. However, those with a 15% increase in LVEDV alone or a 3% decrease in LVEF alone also showed some prognostic significance when compared to those with neither of those changes and therefore their definition for adverse LV remodeling does not identify all the high risk patients[23].

Reverse LV remodeling is prognostic in chronic heart failure, including in patients undergoing cardiac resynchronization therapy[24, 25]. In the STEMI setting, Funaro et al showed that reverse LV remodeling occurred in 39% of their study population and was prognostic [4]. However, there were only 110 patients in their study and the follow-up period was 2 years only [4]. They only compared their patients into two groups, without differentiating those who developed adverse LV remodeling to those with no LV remodeling [4]. Their events included 9 HHF, 3 cardiac deaths and 4 non-fatal MI, the latter unlikely to be directly linked to the development of adverse LV remodeling [4]. Our study, included a larger number of patients

and had a follow-up duration period of 5-year with clinical outcomes assessed blind to the baseline data. We suggest our findings provide substantive evidence for this combinatory approach to prognostication.

Limitations

We included a cohort of relatively low-risk STEMI survivors who could tolerate a CMR scan acutely and at 6 months. We included all-cause mortality rather than cardiac mortality as not all causes of deaths could be adjudicated with adequate certainty. We used CMR to assess LV remodeling. The number of patients in each group was relatively small and the number of events were also low at only 33 (11.6%). Future research should assess external validity in other post-MI populations assessed with different imaging methods.

Conclusion

In a cohort of unselected, stable reperfused STEMI patients who could tolerate a CMR scan, those with a 12% increase in both LVEDV and LVESV (adverse LV remodeling) by CMR at 6 months was associated with worse clinical outcomes after a median follow-up of 5 years than those with a 12% increase in LVEDV alone (adverse LV remodeling with compensation), those with a 12% reduction in LVESV (reverse LV remodeling) and those with no changes to their LVESV and LVESV (no LV remodeling). Therefore, a 12% increase in both LVEDV and LVESV at 6 months by CMR could be considered as a definition for adverse LV remodeling in the setting of STEMI. Reverse LV remodeling did not carry prognostic significance in our study. The findings could be relevant for risk stratification of patients post-MI and the design of clinical trials.

References

1. Westman PC, Lipinski MJ, Luger D, Waksman R, Bonow RO, Wu E and Epstein SE. Inflammation as a Driver of Adverse Left Ventricular Remodeling After Acute Myocardial Infarction. *J Am Coll Cardiol*. 2016;67:2050-2060.

2. Cheng S and Vasan RS. Advances in the epidemiology of heart failure and left ventricular remodeling. *Circulation*. 2011;124:e516-519.

3. St John Sutton M, Pfeffer MA, Plappert T, Rouleau JL, Moye LA, Dagenais GR, Lamas GA, Klein M, Sussex B, Goldman S and et al. Quantitative two-dimensional echocardiographic measurements are major predictors of adverse cardiovascular events after acute myocardial infarction. The protective effects of captopril. *Circulation*. 1994;89:68-75.

4. Funaro S, La Torre G, Madonna M, Galiuto L, Scara A, Labbadia A, Canali E, Mattatelli A, Fedele F, Alessandrini F et al. Incidence, determinants, and prognostic value of reverse left ventricular remodelling after primary percutaneous coronary intervention: results of the Acute Myocardial Infarction Contrast Imaging (AMICI) multicenter study. *Eur Heart J*. 2009;30:566-575.

5. Schulz-Menger J, Bluemke DA, Bremerich J, Flamm SD, Fogel MA, Friedrich MG, Kim RJ, von Knobelsdorff-Brenkenhoff F, Kramer CM, Pennell DJ, et al. Standardized image interpretation and post processing in cardiovascular magnetic resonance: Society for Cardiovascular Magnetic Resonance (SCMR) board of trustees task force on standardized post processing. *J Cardiovasc Magn Reson*. 2013;15:35.

6. Ibanez B, Aletras AH, Arai AE, Arheden H, Bax J, Berry C, Bucciarelli-Ducci C, Croisille P, Dall'Armellina E, Dharmakumar R et al. Cardiac MRI Endpoints in Myocardial Infarction Experimental and Clinical Trials: JACC Scientific Expert Panel. *J Am Coll Cardiol*. 2019;74:238-256.

7. Niccoli G, Montone RA, Ibanez B, Thiele H, Crea F, Heusch G, Bulluck H, Hausenloy DJ, Berry C et al. Optimized Treatment of ST-Elevation Myocardial Infarction. *Circ Res*. 2019;125:245-258.

8. Grothues F, Smith GC, Moon JC, Bellenger NG, Collins P, Klein HU and Pennell DJ. Comparison of interstudy reproducibility of cardiovascular magnetic resonance with two-dimensional echocardiography in normal subjects and in patients with heart failure or left ventricular hypertrophy. *Am J Cardiol*. 2002;90:29-34.

9. Bulluck H, Hammond-Haley M, Weinmann S, Martinez-Macias R and Hausenloy DJ. Myocardial Infarct Size by CMR in Clinical Cardioprotection Studies: Insights From Randomized Controlled Trials. *JACC Cardiovasc Imaging*. 2017;10:230-240.

10. Bolognese L, Cerisano G, Buonamici P, Santini A, Santoro GM, Antoniucci D and Fazzini PF. Influence of infarct-zone viability on left ventricular remodeling after acute myocardial infarction. *Circulation*. 1997;96:3353-3359.

11. Cerisano G, Bolognese L, Carrabba N, Buonamici P, Santoro GM, Antoniucci D, Santini A, Moschi G and Fazzini PF. Doppler-derived mitral deceleration time: an early strong predictor of left ventricular remodeling after reperfused anterior acute myocardial infarction. *Circulation*. 1999;99:230-236.

12. Yu CM, Bleeker GB, Fung JW, Schalij MJ, Zhang Q, van der Wall EE, Chan YS, Kong SL and Bax JJ. Left ventricular reverse remodeling but not clinical improvement predicts long-term survival after cardiac resynchronization therapy. *Circulation*. 2005;112:1580-1586.

13. Bulluck H, Go YY, Crimi G, Ludman AJ, Rosmini S, Abdel-Gadir A, Bhuva AN, Treibel TA, Fontana M, Pica S et al. Defining left ventricular remodeling following acute ST-segment elevation myocardial infarction using cardiovascular magnetic resonance. *J Cardiovasc Magn Reson*. 2017;19:26.

14. Carberry J, Carrick D, Haig C, Ahmed N, Mordi I, McEntegart M, Petrie MC, Eteiba H, Hood S, Watkins S et al. Persistent Iron Within the Infarct Core After ST-Segment Elevation Myocardial Infarction: Implications for Left Ventricular Remodeling and Health Outcomes. *JACC Cardiovasc Imaging*. 2018;11:1248-1256.

15. Carrick D, Haig C, Rauhalammi S, Ahmed N, Mordi I, McEntegart M, Petrie MC, Eteiba H, Hood S, Watkins S et al. Prognostic significance of infarct core pathology revealed by quantitative non-contrast in comparison with contrast cardiac magnetic resonance imaging in reperfused ST-elevation myocardial infarction survivors. *Eur Heart J*. 2016;37:1044-1059.

16. Carrick D, Haig C, Rauhalammi S, Ahmed N, Mordi I, McEntegart M, Petrie MC, Eteiba H, Lindsay M, Watkins S et al. Pathophysiology of LV Remodeling in Survivors of STEMI: Inflammation, Remote Myocardium, and Prognosis. *JACC Cardiovasc Imaging*. 2015;8:779-789.

17. Carrick D, Haig C, Ahmed N, McEntegart M, Petrie MC, Eteiba H, Hood S, Watkins S, Lindsay MM, Davie A et al. Myocardial haemorrhage after acute reperfused ST-elevation myocardial infarction: temporal evolution, relation to microvascular obstruction and prognostic significance. *Circ Cardiovasc Imaging*. 2016;9:e004148.

18. Carrick D, Haig C, Ahmed N, Rauhalammi S, Clerfond G, Carberry J, Mordi I, McEntegart M, Petrie MC, Eteiba H et al. Temporal Evolution of Myocardial Hemorrhage and Edema in Patients After Acute ST-Segment Elevation Myocardial Infarction: Pathophysiological Insights and Clinical Implications. *J Am Heart Assoc*. 2016;5:e002834.

19. Stiermaier T, Jobs A, de Waha S, Fuernau G, Poss J, Desch S, Thiele H and Eitel I. Optimized Prognosis Assessment in ST-Segment-Elevation Myocardial Infarction Using a Cardiac Magnetic Resonance Imaging Risk Score. *Circ Cardiovasc Imaging*. 2017;10:e006774.

20. Oh JK, Velazquez EJ, Menicanti L, Pohost GM, Bonow RO, Lin G, Hellkamp AS, Ferrazzi P, Wos S, Rao V, Berman D, Bochenek A, Cherniavsky A, Rogowski J, Rouleau JL, Lee KL, Investigators on behalf of the S. Influence of baseline left ventricular function on the clinical outcome of surgical ventricular reconstruction in patients with ischaemic cardiomyopathy. *Eur Heart J* 2013;34:39–47.

21. Shudo Y, Taniguchi K, Takeda K, Sakaguchi T, Funatsu T, Kondoh H, Sawa Y. Serial multidetector computed tomography assessment of left ventricular reverse remodeling, mass, and regional wall stress after restrictive mitral annuloplasty in dilated cardiomyopathy. *J Thorac Cardiovasc Surg*. 2012;143:S43–S47.

22 Reindl M, Reinstadler SJ, Tiller C, Feistritzer HJ, Kofler M, Brix A, Mayr A, Klug G and Metzler B. Prognosis-based definition of left ventricular remodeling after ST-elevation myocardial infarction. *Eur Radiol*. 2019;29:2330-2339.

23. Rodriguez-Palomares JF, Gavara J, Ferreira-Gonzalez I, Valente F, Rios C, Rodriguez-Garcia J, Bonanad C, Garcia Del Blanco B, Minana G, Mutuberria M et al. Prognostic Value of Initial Left Ventricular Remodeling in Patients With Reperfused STEMI. *JACC Cardiovasc Imaging*. 2019;12:2445-2456.

24. Hellawell JL and Margulies KB. Myocardial reverse remodeling. *Cardiovasc Ther*. 2012;30:172-181.

25. Stellbrink C, Breithardt OA, Franke A, Sack S, Bakker P, Auricchio A, Pochet T, Salo R, Kramer A, Spinelli J et al. Impact of cardiac resynchronization therapy using hemodynamically optimized pacing on left ventricular remodeling in patients with congestive heart failure and ventricular conduction disturbances. *J Am Coll Cardiol*. 2001;38:1957-1965.

Figure Titles and Legends

Figure 1: Flow diagram of the patients' screening and selection process

Of 391 patients screened, 324 underwent CMR at 2.2±1.9 days and 300 patients returned for a second scan at 6-months. Matching LV volumes data were available for 293 patients and they were included in this study.

Figure 2. Distribution of the patients in the 4 main groups according to their change in LVEDV and LVESV from baseline

This graph shows the distribution of the percentage change in LVESV against LVESV of the whole cohort of patients in this study and colour coded according to groups. A minority of patients (n=8) had an increase in LVESV only and were not classified.

Figure 3. Cumulative hazard curves of the cumulative event rates of the 4 groups of LV remodeling

The cumulative event rates of the composite endpoint of all-cause death and HHF for the 4 groups are shown in this cumulative hazard plot with their corresponding HRs. Those in Group 4 had had significantly higher cumulative event rates of the composite endpoint (log-rank test $P<0.001$) when compared to the 3 other groups.

402 **Table 1: Baseline demographics.**

	All N=293	Group 1 N=137	Group 2 N=73	Group 3 N=42	Group 4 N=33	P value
Age	59±11	60±11	58±12	57±12	59±11	0.45
Male Gender	216 (74%)	100 (73%)	49 (67%)	32 (76%)	28 (84%)	0.28
Diabetes Mellitus	33 (11%)	16 (12%)	7 (10%)	3 (7%)	5 (15%)	0.70
Hypertension	95 (32%)	45 (33%)	21 (29%)	12 (29%)	14 (43%)	0.52
Dyslipidaemia	84 (29%)	43 (31%)	21 (29%)	9 (21%)	9 (27%)	0.66
Smoking	176 (60%)	80 (58%)	46 (63%)	25 (60%)	21 (64%)	090
Previous MI	20 (7%)	10 (7%)	5 (7%)	0 (0%)	5 (15.2%)	0.09
GRACE risk score	141 (123-162)	143 (123-160)	136 (123-156)	147 (121-166)	150 (120-169)	0.46
Medications						
ACEI	289 (99%)	133 (97%)	73 (100%)	42 (100%)	33 (100%)	0.23
Beta-blocker	280 (96%)	129 (94%)	70 (96%)	40 (95%)	33 (100%)	0.55
MRA	6 (2%)	2 (1.5%)	1 (1.4%)	1 (2.4%)	2 (6.1%)	0.39
Statin	293 (100%)	137 (100%)	73 (100%)	42 (100%)	33 (100%)	1.0
Aspirin	292 (99%)	137 (100%)	72 (98%)	42 (100%)	33 (100%)	0.41
Clopidogrel	293 (100%)	135 (99%)	72 (98%)	42 (100%)	33 (100%)	0.78
SBP/ mmHg	136±25	136±26	135±23	136±22	143±23	0.43
DBP/ mmHg	79±14	79±13	80±14	80±15	83±17	0.43
Heart rate/ bpm	78±17	76±16	77±18	82±17	80±19	0.17

Onset-to-balloon time/ mins	171 (117-300)	161 (113-260)	172 (110-312)	225 (131-382)	166 (129-343)	0.10
IRA						
LMS	1 (0.3%)			1 (2%)		
LAD	109 (37%)	49 (36%)	25 (34%)	23 (55%)	12 (36%)	0.17
Cx	51 (17%)	26 (19%)	12 (16%)	6 (14%)	5 (15%)	
RCA	132 (45%)	62 (45%)	36 (49%)	12 (29%)	16 (49%)	
Pre-PCI TIMI flow						
0	190 (65%)	86 (63%)	46 (63%)	28 (67%)	25 (76%)	
1	24 (8%)	10 (7%)	8 (11%)	5 (12%)	0 (0%)	0.27
2	53 (18%)	23 (17%)	16 (22%)	6 (14%)	6 (18%)	
3	26 (9%)	18 (13%)	3 (4%)	3 (7%)	2 (6%)	
Post-PCI TIMI flow						
0	1 (0.3%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	
1	3 (1%)	0 (0%)	2 (3%)	1 (2%)	0 (0%)	0.68
2	9 (3%)	4 (3%)	2 (3%)	1 (2%)	2 (6%)	
3	280 (96%)	132 (96%)	69 (95%)	40 (95%)	31 (94%)	
STR						
Complete	135 (46%)	62 (46%)	38 (52%)	15 (36%)	14 (42%)	0.68
Partial	111 (38%)	51 (38%)	24 (33%)	21 (50%)	13 (39%)	
None	46 (16%)	23 (16%)	11 (15%)	6 (14%)	6 (18%)	
Multi-vessel Disease						0.80
2 vessel disease	85 (31%)	41 (31%)	24 (33%)	10 (24%)	10 (32%)	

3 vessel disease	41 (14%)	19 (14%)	9 (12%)	6 (15%)	7 (23%)

MI: myocardial infarction; GRACE: Global Registry of Acute Coronary Events; ACEI: angiotensin converting enzyme inhibitor; MRA: mineralocorticoid receptor antagonist; SBP: systolic blood pressure; DBP: diastolic blood pressure; IRA: infarct related artery; LMS: left main stem; LAD: left anterior descending artery; Cx: circumflex artery; RCA: right coronary artery; PCI: percutaneous coronary intervention; TIMI: thrombolysis in myocardial infarction; STR: ST-segment resolution

409 **Table 2: CMR characteristics.**

	All N=293	Group 1 N=137	Group 2 N=73	Group 3 N=42	Group 4 N=33	P value
			Acute CMR			
MI size/ % LV mass	16 (7-27%)	13 (4-21)	15 (7-25)	25 (13-32)	29 (10-36)	<0.001
MVO/ %	146 (50%)	52 (38%)	43 (59%)	26 (62%)	20 (61%)	0.003
MVO/ % LV mass	4.7 (2.1-11.8) n=146	4.0 (1.7-9.0) n=52	3.6 (1.6-8.2) n=43	7.3 (2.9-14.3) n=26	11.7 (2.8-21.6) n=20	<0.001
IMH (n=218)	87/218 (40%)	24/101 (24%)	32/60 (53%)	17/31 (55%)	14/26 (54%)	<0.001
LVEF/%	55±10	54±8	59±10	51 ±10	55±12	<0.001
LVEDV/ ml	150 (127-175)	154 (133-179)	145 (123-169)	155 (115-170)	145 (120-173)	0.31
LVESV/ ml	66 (49-86)	72 (54-87)	62 (45-76)	73 (57-93)	64 (43-98)	0.036
LV mass/ g	133 (105-152)	134 (106-153)	128 (101-143)	142 (99-161)	133 (114-166)	0.24
			6-months CMR			
MI size/ % LV mass	11 (4-19)	9 (3-14)	12 (4-19)	19 (10-24)	19 (7-32)	<0.001
Residual iron (n=243)	52/243 (21%)	11/116 (10%)	21/66 (32%)	10/36 (28%)	10/25 (40%)	<0.001
LVEF/%	62±9	66±7	61±8	60±9	52±11	<0.001
LVEDV/ ml	154 (127-186)	146 (120-168)	154 (127-171)	182 (134-203)	185 (146-219)	<0.001

LVESV/ ml	57 (40-74)	47 (37-64)	58 (43-72)	74 (55-89)	79 (61-118)	<0.001
LV mass/ g	116 (96-137)	116 (95-135)	116 (95-132)	119 (96-141)	127 (111-143)	0.19

%Δ in LV parameters from baseline

%Δ MI size	ˉ29 (ˉ46-ˉ6)	ˉ33 (ˉ48-ˉ6)	ˉ29 (ˉ47-ˉ4)	ˉ27 (ˉ45-ˉ15)	ˉ21(ˉ45-0)	0.73
%ΔLVEDV	3 (ˉ5-13)	ˉ5 (ˉ13-2)	4 (ˉ1-7)	17 (14-21)	26 (17-33)	<0.001
%ΔLVESV	ˉ26 (ˉ12-4)	ˉ27 (ˉ38-ˉ19)	ˉ4 (ˉ9-4)	ˉ4 (ˉ13-5)	31 (18-53)	<0.001
%ΔLVEF	10 (3-18)	16 (11-23)	4 (0-7)	15 (9-21)	ˉ4 (ˉ19-4)	<0.001
%ΔLV mass	ˉ10 (ˉ17-ˉ2)	ˉ11 (ˉ19-ˉ4)	ˉ10 (ˉ16-ˉ2)	ˉ9(-20-ˉ3)	ˉ7(ˉ21-ˉ4)	0.51

410 MI: myocardial infarction; LV: left ventricular; MVO: microvascular obstruction; IMH:
411 intramyocardial hemorrhage; LVEF: left ventricular ejection fraction; LVEDV: left ventricular end-
412 diastolic volume; LVESV: left ventricular end-systolic volume; %Δ: percentage change

413

Table 3: Pre-specified clinical outcomes at 5-years.

	Group 1 N=137	Group 2 N=73	Group 3 N=42	Group 4 N=33	Total
Composite of all-cause death and HHF	13 (9.5%)	9 (12.3%)	3 (7.1%)	8 (24.2%)	33 (11.6%)
HHF	2 (1.5%)	0 (0%)	0 (0%)	3 (9.1%)	5 (1.8%)
All-cause death	11 (8.0%)	9 (12.3%)	3 (7.1%)	5 (15.2%)	28 (9.8%)

HHF: hospitalization for heart failure