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Role of aldosterone in the mid- and long-term left ventricular remodelling after acute myocardial infarction: the REMI study

Luca Monzo,¹ Olivier Huttin,¹ João Pedro Ferreira,^{1,2} Zohra Lamiral,¹ Erwan Bozec,¹ Marine Beaumont,³ Emilien Micard,³ Guillaume Baudry,¹ Pierre-Yves Marie,⁴ Romain Eschalier,⁵ Patrick Rossignol,^{1,6} Faiez Zannad,¹ Nicolas Girerd¹

¹Université de Lorraine, Centre d'Investigations Cliniques Plurithématique 1433 and Inserm U1116, CHRU Nancy, FCRIN INI-CRCT (Cardiovascular and Renal Clinical Trialists), Nancy, France; ²Cardiovascular Research and Development Center, Department of Surgery and Physiology, Faculty of Medicine of the University of Porto, Portugal; ³Centre d'Investigations Cliniques IADI U947, Centre Hospitalier Universitaire de Nancy, Vandoeuvre les Nancy, France; ⁴CHRU-Nancy, Université de Lorraine, Nuclear Medicine & Nancyclotep Imaging Platform, Nancy, France; ⁵Cardiology Department, CHU Clermont-Ferrand, F-63000 Clermont-Ferrand, France; and Université Clermont Auvergne, CHU Clermont-Ferrand, CNRS, SIGMA Clermont, Institut Pascal, F-63000 Clermont-Ferrand, France. ⁶Department of Medicine and Nephrology-Hemodialysis, Princess Grace Hospital, and Monaco Private Hemodialysis Centre, Monaco, Monaco

Corresponding author: Pr Nicolas Girerd, Centre d'Investigations Cliniques Plurithématique, INSERM 1433, Rue du Morvan, CHRU de Nancy, Institut Lorrain du Coeur et des Vaisseaux, Nancy, France. Tel: +33 3 83157315, Fax: +33 3 83157324. Email: nicolas_girerd@yahoo.com

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Abstract

Aims Whether aldosterone levels after myocardial infarction (MI) are associated with medium and long-term left ventricular (LV) remodelling in the era of systematic use of renin-angiotensin system inhibitors is uncertain. We prospectively investigated the relationship between aldosterone levels and mid- and long-term LV remodelling in patients with acute MI.

Methods and results Plasma aldosterone was measured in 119 patients successfully treated by primary percutaneous coronary angioplasty for a first acute ST-elevated MI (STEMI) 2-4 days after the acute event. LV volumes were assessed by cardiac magnetic resonance (CMR) and transthoracic echocardiography (TTE) in the same timeframe and 6 months later. LV assessment was repeated by TTE 3-9 years after MI (N=80). The median aldosterone level at baseline was 23.1 [16.8; 33.1] pg/mL. Higher post-MI aldosterone concentration was significantly associated in multivariable model with more pronounced increase in LV end-diastolic volume index (TTE: $\beta \pm SE$: 0.113 ± 0.046 , $P=0.015$; CMR: $\beta \pm SE$: 0.098 ± 0.040 , $P=0.015$) and LV end-systolic volume index (TTE: $\beta \pm SE$: 0.083 ± 0.030 , $P=0.008$; CMR: $\beta \pm SE$: 0.064 ± 0.032 , $P=0.048$) at 6-month follow-up, regardless of the method of assessment. This result was consistent also in patient with a LV ejection fraction (LVEF) >40%. The association between baseline plasma aldosterone and adverse LV remodelling did not persist at the 3-9 years follow-up evaluation.

Conclusion Aldosterone concentration in the acute phase was associated with adverse LV remodelling in the mid-term, even in the subgroup of patients with LVEF >40%, suggesting a potential role of the mineralocorticoid system in post-MI adverse remodelling. Plasma aldosterone was no longer associated with LV remodelling in the long-term. (NCT01109225)

Keywords: cardiovascular diseases; left ventricular remodelling; myocardial infarction; aldosterone; long-term follow-up

Introduction

Adverse left ventricular (LV) remodelling is an adaptive process following cardiac damage and is characterised by morphological changes in LV and deterioration of cardiac function.¹ The acute loss of myocardium results in the activation of neurohormonal compensatory mechanisms aimed at maintaining systemic perfusion such as the sympathetic nervous and renin-angiotensin systems. This neuro-hormonal overdrive leads to structural changes in LV over time, including an increase in ventricular volumes, a rightward shift of the end-diastolic pressure-volume relationship and development of a more spherical shape.² The resulting adverse ventricular remodelling represents a prevailing cause of heart failure (HF) in the current era.³

Several previous observations showed that aldosterone blood levels are significantly higher after acute myocardial infarction (MI) and promotes a range of deleterious effects on the cardiovascular system, including sodium and water retention, myocardial and perivascular fibrosis, baroreceptor and endothelial dysfunction, and cardiomyocyte necrosis,⁴ further exacerbating postinfarct ventricular remodelling and increasing the risk of cardiovascular events.^{5, 6} This evidence actually represented the trigger for developing drugs targeting the renin-angiotensin-aldosterone system. Modulation of the aldosterone pathway in patients with acute myocardial infarction complicated by LV dysfunction has been demonstrated to reduce mortality and morbidity.⁷ The potential effect of mineralocorticoid receptor antagonists (MRAs) on LV remodelling, a significant determinant of outcomes in post-MI patients, remains a subject of ongoing debate. In a cardiac magnetic resonance study on patients with recent MI and LV dysfunction, eplerenone therapy was associated with a modest antiremodelling effect at 12 and 24 months, but only after covariate adjustment.⁸ On the contrary, MRAs have demonstrated to improve post-MI remodelling in both a small mid-term follow-up scale echocardiographic study that enrolled patients with an anterior transmural thrombolised MI and in another short-term follow-up study that used LV ventriculography to examine anterior MI patients following revascularization.^{9, 10} Notably, aldosterone levels after acute MI has been showed to be associated with LV remodelling in the medium-term,¹¹ but data on the long-term association are lacking. Whether aldosterone levels are still associated with remodelling

in the era of systematic use of renin-angiotensin system (RAS) inhibitors following MI is also uncertain. In this study we prospectively investigated the relationship between baseline aldosterone levels and mid- and long-term LV remodelling in the current therapeutic era among patients with acute MI.

Materials and methods

Patient population

The Relation Between Aldosterone and Cardiac Remodelling After Myocardial Infarction (REMI) study was a prospective single-centre cohort study (Nancy University Hospital) designed to determine whether aldosterone level was predictive of cardiac remodelling in the mid- (6 months) and long-term (3-9 years) after acute MI.

Patients successfully treated by primary percutaneous coronary angioplasty (PCI) for a first acute ST-segment elevation myocardial infarction (STEMI) between April 2010 and December 2013 were prospectively included. In order to be retained, acute STEMI had to be associated with a significant rise in cardiac enzymes and with an initial occlusion or sub-occlusion of the MI-related artery at angiography (Thrombolysis In Myocardial Infarction [TIMI] flow grade 0 to 1). As additional inclusion criteria, all patients had to show a TIMI flow 3 in the culprit artery after PCI.

Main exclusion criteria were: 1) previous history of MI; 2) any significant cardiac disease (including > grade-2 mitral regurgitation); 3) any contraindication to cardiac magnetic resonance (CMR); 4) atrial flutter or atrial fibrillation; 5) multivessel disease at coronary angiography and 6) ≥ 12 h delay-time between the onset of chest pain and reperfusion treatment.

Study protocol

After signing informed consent, patients underwent a clinical history review, physical examination, echocardiography, electrocardiogram, and blood sampling for laboratory analysis (lying down). Within 2 to 4 days after PCI, all eligible patients underwent CMR and transthoracic

echocardiography (TTE).

For the 6-month and long-term follow-up, all participants were scheduled to attend the Centre d'Investigation Clinique Plurithématique Pierre Drouin at the Nancy University Hospital at 8 AM after a 12- to 14-h fast. All subjects underwent blood sampling for laboratory analysis. Medical history, medications, anthropometric parameters were also recorded. Six months after the cardiac revascularisation procedure, a follow-up CMR and TTE were performed. Only TTE and clinical visit with blood sampling were repeated at the long-term follow-up visit. Medical treatment in the acute phase and at follow-up (included mineralocorticoid receptor antagonists) was left at the discretion of the treating physician.

The study was conducted according to the Declaration of Helsinki. The protocol was approved by the local Ethics Committee (CPP agreement n° 2009- A00537-50) and was registered at ClinicalTrials.gov identifier NCT01109225. All subjects provided signed informed consent before participation.

Cardiac magnetic resonance

CMR was performed using a GE 3T system (General Electric 3T signa HDxt) equipped with a dedicated phased-array cardiac coil. All examinations were performed with ECG gating and in breath-holding expiration. Cine imaging for cardiac morphology and function was performed using the steady-state free precession technique. The endocardial contours of the left and right ventricle were traced manually on all phases and slices using standard software (Mass Analysis +, version 4, Medis, Netherlands). Late gadolinium-enhanced (LGE) imaging was acquired 10 - 15 min after a cumulative total dose of 0.3 mmol/kg gadolinium contrast in matched short and long-axis planes with a T1-weighted 2D segmented inversion recovery gradient-echo sequence during diastolic standstill. The LGE imaging parameters included a 4.8/1.3 ms repetition time/echo time with a 200 - 300 ms inversion time adjusted to null normal myocardium. Transmural LGE extent was assessed visually and scored on a 17-segment model on 3 matched short-axis slices (basal, mid, apical). The

segmental extent of the LGE was considered as non-infarcted if there was no LGE. In case of hyperenhancement, infarcted segments were classified as transmural if LGE \geq 75% of mural extent. The size of the transmural myocardial infarction was determined as the percent of LV segments (17-segment model) showing a LGE \geq 75% of myocardial thickness.

Echocardiography

Complete TTE was performed with patients in the left lateral decubitus position within 48 hours after the CMR examination. Images were obtained with ECG gating, using a commercially available system (Vivid 7 or Vivid E9; GE Vingmed Ultrasound AS, Horten, Norway). M-mode and 2D images were acquired in cine-loop format from three consecutive beats. Echocardiographic images were obtained from the parasternal long-axis view, from short-axis views at the basal, median, and apical levels, and from the three standard LV apical views (four-chamber [4C], two-chamber [2C], and three-chamber views). All 2D images were acquired at a frame rate of 50 to 70 frames/sec. LV volumes and LV ejection fraction were calculated using the biplane Simpson technique. Measurements and analysis of echocardiographic images were performed offline using a commercially available workstation (EchoPAC version 110.1.0; GE Vingmed Ultrasound AS) in accordance with current guidelines,¹² blinded to clinical and CMR results. LV global longitudinal peak systolic strain (GLS) was assessed using automated function imaging from apical 4C and 2C views and the long-axis view.

Laboratory assays

Aldosterone (normal value [NV] 20-140 pg/mL) and renin (NV 1.5-17 pg/mL) were measured by radioimmunoassay (Siemens TKAL2 kit and CIS BIO kit). Type III procollagen amino-terminal peptide (PIIINP; NV 2.3-6.4 μ g/L), type I procollagen amino-terminal peptide (PINP; NV 69-163 ng/mL) and serum carboxy-terminal telopeptide of type I collagen (ICTP; NV 2.1-5.6 μ g/L) were

determined by radioimmunoassay (Orion Diagnostica, Finland). Ultrasensitive C-reactive protein (hsCRP) was measured by immunoturbidimetry. B-type natriuretic peptide (BNP) was measured by electro-chemiluminescence (Elecsys 2010 analyser, Roche Diagnostics, Mannheim, Germany). All intra-assay variations were <10%.

Statistical analysis

Continuous variables are presented as means \pm standard deviation (SD) or median and [25th–75th interquartile range (IQR)], categorical variables as frequencies (percentages), odds ratios as estimate and 95% confidence interval [OR (95% CI)]. Comparisons of baseline characteristics were carried out using Student or Mann Whitney tests for continuous variables and Pearson's Chi-Square or Fisher exact tests for categorical variables, as appropriate. Comparisons of characteristics between baseline and V2/V3 were performed using paired T-test or Signed rank test as required. Primary outcome was adverse LV remodelling expressed as change in LV end-diastolic volume (LVEDV) from baseline (V1) to 6-month visit (V2). Based on the literature data^{13, 14} we calculated that 200 patients would provide around 80% power to detect a difference between baseline and 6-month follow-up of 20% in LVEDV (α level, 0.05). A total sample size of 250 patients was therefore chosen to allow an anticipated 20% discontinuation rate due to dropouts.¹³ However, the trial was not able to reach the prespecified sample size due to slow enrolment, which resulted in a substantial reduction in power to test the primary end point. In addition, the main outcome measure initially planned for the study (baseline to follow-up change in LVEDV \geq 20%) was modified during the interim analysis to LVEDV change \geq 15% due to the low incidence of adverse remodelling using the initial threshold. To further cope with these difficulties, an additional visit was performed at 3-9 years. The outcomes related to these visits (LV remodelling from baseline to long-term visit) were considered as secondary. Sensitivity analysis considered adverse remodelling in the subgroup of patients with LVEF >40%. The main exploratory variable was aldosterone; the a priori defined adjustment variables based on the existing literature were the baseline value of LV

volumes (LVEDVi or LVESVi), anterior STEMI and baseline BNP. Further adjustment variables tested were RAS inhibitors use and incident MI.

Both absolute and relative changes in LV volumes were analysed in different models. Adverse LV remodelling was analysed in both continuous (linear increase) and dichotomous (< or $\geq 15\%$) scales via 3 nested models: A) Model 0 (M0): univariate model including only aldosterone; B) Model 1 (M1): included variables in M0 plus anterior STEMI; C) Model 2 (M2): included variables in M1 plus baseline BNP. Models were based on a generalised linear model (for continuous outcomes) and logistic regression (for dichotomous outcomes). All analyses were performed using SAS version 9.4 (TS1M1) (SAS Institute Inc., Cary, N.C., USA). The two-tailed significance level was set at $p < 0.05$.

Results

Patient characteristics

Baseline population characteristics are listed in **Table 1**. From April 2010 to March 2014, 145 patients were screened and 119 were enrolled in this study (**Figure 1**). Mean age was 56 ± 10 years, 86% were male, mean BMI was 27.2 ± 3.9 kg/m² and mean estimated glomerular filtration rate was 81.7 ± 18.4 ml/min/1.73 m². The vast majority of patients were treated with RAS inhibitors and beta-blockers at visit 2 (91% and 89%, respectively) and visit 3 (90% and 80%, respectively). None of the patients was treated with mineralocorticoid receptor antagonists (MRA) at visit 2, and only few at visit 3 (14%). At long term follow-up, 5 patients had a recurrence of MI (1 STEMI and 4 non-STEMI).

Fifty-six patients (47%) had anterior STEMI, with a median delay from symptoms onset to PCI of 90 [55; 118] minutes. At baseline echocardiography, mean LVEF was $50.5 \pm 8.8\%$, with 14% of the population showing a value $\leq 40\%$ (**Table 2**). As expected, the acute phase was characterised by high levels of cardiac damage and inflammation markers. The median blood concentration of aldosterone at baseline was 23.1 [16.8; 33.1] pg/mL. Baseline characteristics were largely similar

between patients with higher ($>$ median) vs. lower (\leq median) aldosterone concentration (**Supplemental Table 1**).

Left ventricular assessment at follow-up

At 6-month (mean 182.8 ± 13.9 days) follow-up, echocardiographic assessment showed a borderline but significant reduction in the mean LV end-systolic volume index (LVESVi; -3.4 mL/m², $P = 0.001$) compared to baseline, whereas LV end-diastolic volume index (LVEDVi) remained unchanged. This resulted in a concurrent improvement in mean LVEF ($+5.4\%$) and GLS (-3.1) (all $P < 0.001$). Similarly, CMR imaging showed a significant increase in mean LVEF ($+7.2\%$) due to a reduction in LVESVi (mean -4.2 mL/m²) and a slight increase in LVEDVi (mean $+4.2$ mL/m²) compared to baseline. Total myocardial infarction area significantly decreased at 6-month follow-up (-13.2%) ($P < 0.001$ for all CMR measurements). The prevalence of patients with an LVEF $\leq 40\%$ was significantly lower at 6-month follow-up in both echocardiographic (from 14% to 6%) and CMR (from 39% to 14%) assessments (**Table 2**).

Among the 80 patients who attended the long-term follow-up (mean 6.6 ± 0.6 years), a persistent reduction in mean LV volumes was observed compared to baseline (LVEDVi: -9.5 mL/m²; LVESVi: -7.2 mL/m²) and visit 2 (LVEDVi: -9.1 mL/m²; LVESVi: -3.9 mL/m²) (all $P < 0.001$). The LVEF improvement remained stable compared to the 6-month assessment.

There were no significant differences in terms of LV remodelling between patients with baseline aldosterone below or higher than the median (23.1 pg/mL). The only exception was that patients with higher-than-median aldosterone levels had no significant improvement in systolic LV volumes measured by echocardiography at 6 months whereas patients with lower aldosterone levels did show an improvement ($P = 0.007$) (**Supplemental Table 2**).

Markers of fibrosis

Among markers of collagen metabolism, only ICTP showed increased concentration in the post-MI

(10.8 ± 6.5 ng/mL), while both PINP (102.5 ± 40.5 μ g/L) and PIIINP (2.7 ± 1.2 μ g/L) were in the normal range (**Table 1**). No significant differences were found between patients with aldosterone above or below the median (**Supplemental Table 1**).

Both serum PINP and PIIINP showed non significantly changes during 6-month follow-up, with a median difference from baseline of 11.2 μ g/L (95% CI, -3.5 to 25.9; P=0.134) and 0.15 μ g/L (95% CI, -0.06 to 0.36; P=0.169), respectively. On the contrary, serum ICTP concentration was significantly reduced at 6-month follow-up compared with baseline (median difference - 2.1 [95% CI, -3.0 to -1.2] ng/mL; P <0.001). Overall, none of the explored markers of collagen metabolism was associated with post-MI aldosterone (all P>0.05), both considering their baseline values and their longitudinal changes (from baseline to V2) (**Supplemental Table 3**). Change in serum ICTP were inversely correlated with LV adverse remodelling at 6-month follow-up (LVEDVi: r - 0.22 [95% CI, -0.39; -0.3], P=0.03 and LVESVi: r -0.20 [95% CI, -0.38; -0.1], P=0.04).

Left ventricular remodelling and correlates

Overall, at 6-month follow-up 28% and 24% of patients showed an increase in LVEDVi $\geq 15\%$ by echocardiography and CMR, respectively; at long-term only 13% patients showed adverse remodelling (**Figure 2A**). The median relative change in LVEDVi between baseline and visit 2 was +0.1 [-16.1; 15.8] % by echocardiography and +2.0 [-5.2; 14.6] % by CMR, whereas from baseline to visit 3 was -15.6 [-28.7; -5.8] %. (**Figure 2B**). Post-MI aldosterone concentration was directly correlated with the change in LVEDVi at 6-month follow-up, irrespective of the method of assessment (echocardiography or CMR) (**Table 3**).

At 6-month follow-up, 18% and 11% of patients showed an increase in LVESVi $\geq 15\%$, by echocardiography and CMR, respectively; at long-term follow-up 11% patients had such remodelling (**Figure 2C**). The median relative change in LVESVi at 6 months was -8.3 [-29.5; 9.8] % and -8.9 [-20.7; 2.1] % by echocardiography and CMR, respectively, while was -25.5 [-41.8;

7.6] % at long-term follow-up (**Figure 2D**). Similar to LVEDVi analysis, post-MI aldosterone concentration was directly correlated with the echocardiographic-assessed change in LVESVi (independently whether assessed as continuous or dichotomic) at 6-month follow-up (**Table 4**). Adjustment for covariates most likely impacting adverse LV remodelling did not significantly change the predictive value of baseline aldosterone at medium term. The results were consistent also after adjustment for RAS inhibitors treatment and incident MI (**Supplemental Table 4**).

A higher baseline aldosterone level (\geq median) was associated with adverse LVESVi remodelling (change $\geq 15\%$ from baseline), but not with LVEDVi remodelling (**Supplemental Table 5 and Supplemental Table 6**). Post-MI aldosterone was not significantly associated with baseline LVEF and total infarct size. The association between post-MI aldosterone and LV adverse remodelling persisted also when only the subgroup of patients with LVEF $>40\%$ was considered (**Supplemental Table 7 and Supplemental Table 8**).

At long-term follow-up, aldosterone lost its ability to significantly predict adverse remodelling. At this timepoint, the most powerful predictor of change in both LVEDV and LVESV was their respective baseline values (**Table 3 and 4; Supplemental Table 5 and 6**).

Discussion

The key finding of the present study is that, in the current era of systematic use of RAS inhibitors post-MI, aldosterone concentration measured early after STEMI was associated with adverse LV remodelling in the mid-term, but not in the long-term. This was independent of the parameter used to define adverse LV remodelling (increase in LVEDV or LVESV), although higher baseline aldosterone concentrations (\geq median) were more likely to predict LVESV remodelling at mid-term follow-up. Interestingly, post-MI aldosterone level was associated in the mid-term to adverse LV remodelling even in patients with LVEF $>40\%$, a subset of patients without strong evidence for treatment with RAS inhibitors.

Adverse LV remodelling begins early after an acute MI and is characterised by stretching

and thinning of the infarcted myocardium, infarct expansion, progressive dilation of the ventricular cavity and distortion of the cavity shape.¹⁵ This maladaptive process leads to profound alterations in ventricular architecture that usually results in contractile dysfunction, a powerful marker of adverse prognosis in post-MI patients.¹⁶ The renin-angiotensin-aldosterone system plays a role in the pathophysiology of post-MI LV remodelling. In experimental models, the upregulation of the cardiac angiotensin II pathway after acute MI is correlated with an increase in myocardial fibrosis.¹⁷ The administration of ACE inhibitors and ARBs has been demonstrated to modulate these histopathologic changes and reduce post-MI cardiac remodelling,^{18, 19} improving long-term survival.^{20, 21} Aldosterone has also been primarily implicated in the post-MI fibroblast responses within the myocardium⁴ and its rise has been correlated with increased morbidity and mortality.⁵ Aldosterone level in the myocardium is partially under the control of angiotensin II via stimulation of myocardial aldosterone synthase,²² and is extracted in part from the bloodstream.²³ In the post-MI period, the activation of these mechanisms increases aldosterone concentration in the myocardium,^{23, 24} which in turn stimulates collagen types I and III synthesis.² Aldosterone and angiotensin II were also found to induce cardiac myocyte apoptosis in a rat model.²⁵ Altogether, these mechanisms lead to myocardial fibrosis and adverse LV remodelling.⁴ Aldosterone blockade has been shown to modulate fibrosis and adverse remodelling in the post-AMI setting,^{9, 10} with a significant improvement in early and long-term mortality.⁷

In keeping with previous observations, our study demonstrated that aldosterone concentration early after an acute MI could be implicated in LV dilatation at mid-term follow-up, irrespective of the classical variables associated with post-MI remodelling. Yet, the magnitude of this association seems modest to moderate in light of the approximately 20% higher risk in LV remodelling (i.e. LVESVi \geq 15%) per 10 pg/mL aldosterone increase observed in our study. This limited association questions whether treatments targeting aldosterone can have a sizeable impact of mid-term remodelling, in an era where virtually all patients receive RAS inhibitors following MI. Notably, higher concentrations of aldosterone at baseline appears to better predict LVESV

dilatation, one of the strongest prognostic indicators for survival in post-MI patients.²⁶ This result is not surprising since it has been demonstrated that treatment with mineralocorticoid receptor antagonists,²⁷ as well as other drugs acting on LV remodelling,²⁸⁻³⁰ is most effective on the change in LVESV as opposed to LVEDV. Whether this is a direct effect of anti-remodelling treatment or a mere reflection of haemodynamic changes (i.e. reduction in afterload) still remains a matter of debate. From a clinical perspective, the assessment of aldosterone concentration immediately after a STEMI could allow identifying patients at higher risk for adverse LV remodelling independent of LV ejection fraction, at least in the mid-term, and thus more prone to benefit from treatment with RAS inhibitors. It has been advocated that the role of aldosterone in adverse LV remodelling is in part mediated by its effect on collagen metabolism, mainly stimulating collagen synthesis and fibroblast proliferation via activation of local mineralocorticoid receptors.³¹ In line, treatment with eplerenone in EPHEBUS trial showed to consistently reduce serum procollagen type-I C-terminal pro-peptide (PICP) and PIIINP levels, two important markers collagen synthesis, with no apparent effect on ICTP, a marker of collagen degradation.³² High post-MI ICTP levels were previously associated with LV remodelling and likely reflect an intense breakdown of cicatricial zonal collagen after MI.³³ In our study, we showed that the longitudinal reduction of ICTP rather than the absolute post-MI value was associated with LV adverse remodelling. This difference could be more likely ascribed to the different study population (small infarct sizes with relatively preserved LV function vs large MI with low LVEF³³) enrolled in our study.

Another interesting finding of our study is that post-MI aldosterone levels were associated with adverse LV remodelling even in the subset of patients with LVEF >40%. According to the results of the EPHEBUS trial,⁷ in the post-MI setting MRA are recommended only in patients who develop LV dysfunction. Nevertheless, recent evidence showed that MRA could be potentially beneficial event in patients presenting without low LVEF or HF symptoms. The REMINDER trial (N=1012) shows that the early (within 24h from STEMI) addition of eplerenone to standard therapy was safe and effective on BNP reduction in patients presenting with acute STEMI without known

HF or LVEF <40%.³⁴ In the ALBATROSS trial (N=1603, MRA vs. placebo in patients with acute MI irrespective of the presence of HF or LV dysfunction), MRA use reduced the odds of death (HR 0.20; [95% CI: 0.06 - 0.70]; P =0.0044) and showed a trend in reduction (P for interaction =0.08) of the primary endpoint (composite of death, resuscitated cardiac arrest, significant ventricular arrhythmia, indication for implantable defibrillator, or new or worsening HF at 6-month follow-up) in the STEMI subgroup (N=1.229).³⁵ Our findings might provide further evidence and biological plausibility for the showed clinical results and for extending the use of MRA in patients with STEMI irrespective of the presence of HF or LV dysfunction.

We also show, for the first time, that aldosterone concentration was not able to predict adverse LV remodelling at very long-term follow-up. Concurrently, the number of patients experiencing post-MI adverse remodelling at this timepoint was quite low. These findings are probably interrelated and likely due to the combination of the large use of anti-remodelling therapies and the timely percutaneous intervention in our cohort. Restoring blood flow in the culprit artery early after the onset of pain reduces infarct size and improves clinical outcomes in patients with STEMI.^{36, 37} Several studies have demonstrated a benefit from early myocardial reperfusion on both adverse LV remodelling and improvement in ventricular function.² In our study, the median time from symptoms onset to PCI was 90 minutes, which is much shorter compared with other studies. For example, in a large observational study involving 5243 patients with STEMI from 20 tertiary hospitals with the capability of primary PCI in Korea, the median symptom onset-to-balloon time was 179 minutes.³⁸ In another study investigating 2345 patients admitted in a 24/7 primary PCI service, the mean symptom onset-to-balloon time in early-comers with STEMI (i.e. <6 hours from symptoms onset) was 148 minutes.³⁹ The larger myocardial salvage obtained with early revascularisation might therefore play a crucial role in determining our findings in the long-term analysis.

Limitations

Our study has certain limitations which should be acknowledged. First, the study did not reach the prespecified recruitment: consequently, the sample size was relatively small and the number of events relatively few (also influenced by the single-centre design), resulting in a substantial reduction in power to test the primary end point. In addition, the threshold for the definition of LV remodelling (i.e. baseline to follow-up percentage change in LV volumes) was adjusted from 20% to 15% in order to cope with the low incidence of events. Therefore, larger, multi-centre studies are required to confirm our findings and to provide more precise assessment of the association between post-MI aldosterone levels and mid to long-term cardiac remodelling. The association between post-MI aldosterone level and change in LV volumes was statistically significant, yet with a modest to moderate strength. Given the magnitude of this association, the clinical implications of these findings remain uncertain. This may actually suggest that only patients at highest risk of remodelling may have a sizeable clinical benefit from treatment targeting renin-angiotensin-aldosterone system. Nearly all patients were treated with renin-angiotensin-system inhibitors; therefore, the effect of aldosterone on LV remodelling was likely mitigated. Nevertheless, this represents the current standard of practice, and assessing the association of aldosterone with outcome in the current therapeutic era could conversely be perceived as the strength of our study. Finally, our cohort was characterised by small infarct sizes with relatively preserved LV function. However, this reflects the effectiveness of an appropriate STEMI management in a tertiary hospital with a 24/7 primary PCI service.

Conclusions

Aldosterone concentration measured early after a STEMI was an independent predictor of adverse LV remodelling in the mid-term. These results were consistent also in patients with LVEF >40%, suggesting a possible benefit from MRA treatment also in this population. Plasma aldosterone was no longer associated with LV remodelling in the long-term. The modern therapeutic approach to STEMI management with timely percutaneous revascularisation and the wide use of anti-

remodelling therapy could have contributed to this result.

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Conflicts of interest

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Figure Legends

Figure 1 Study flow diagram.

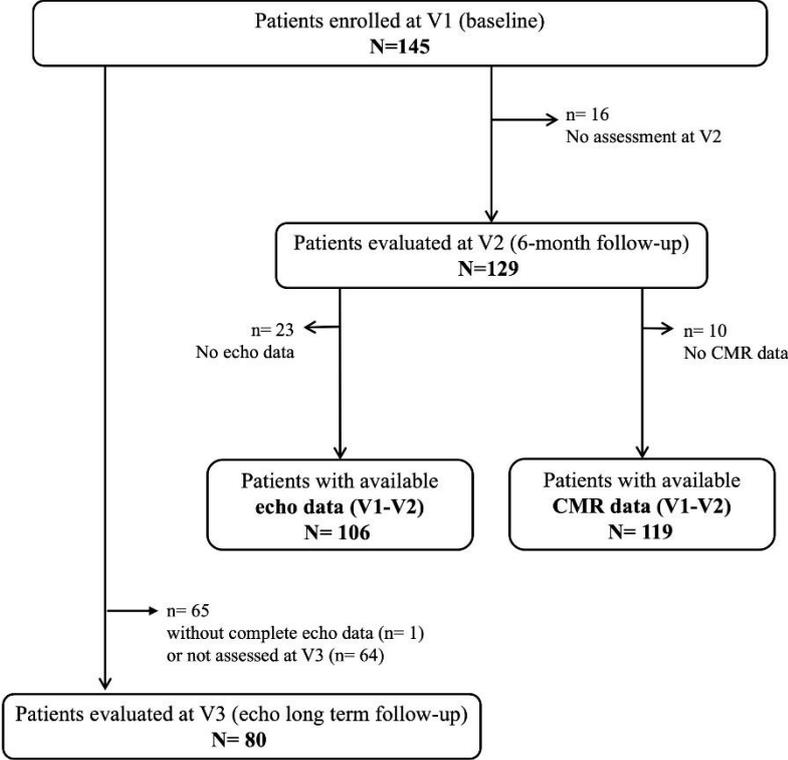
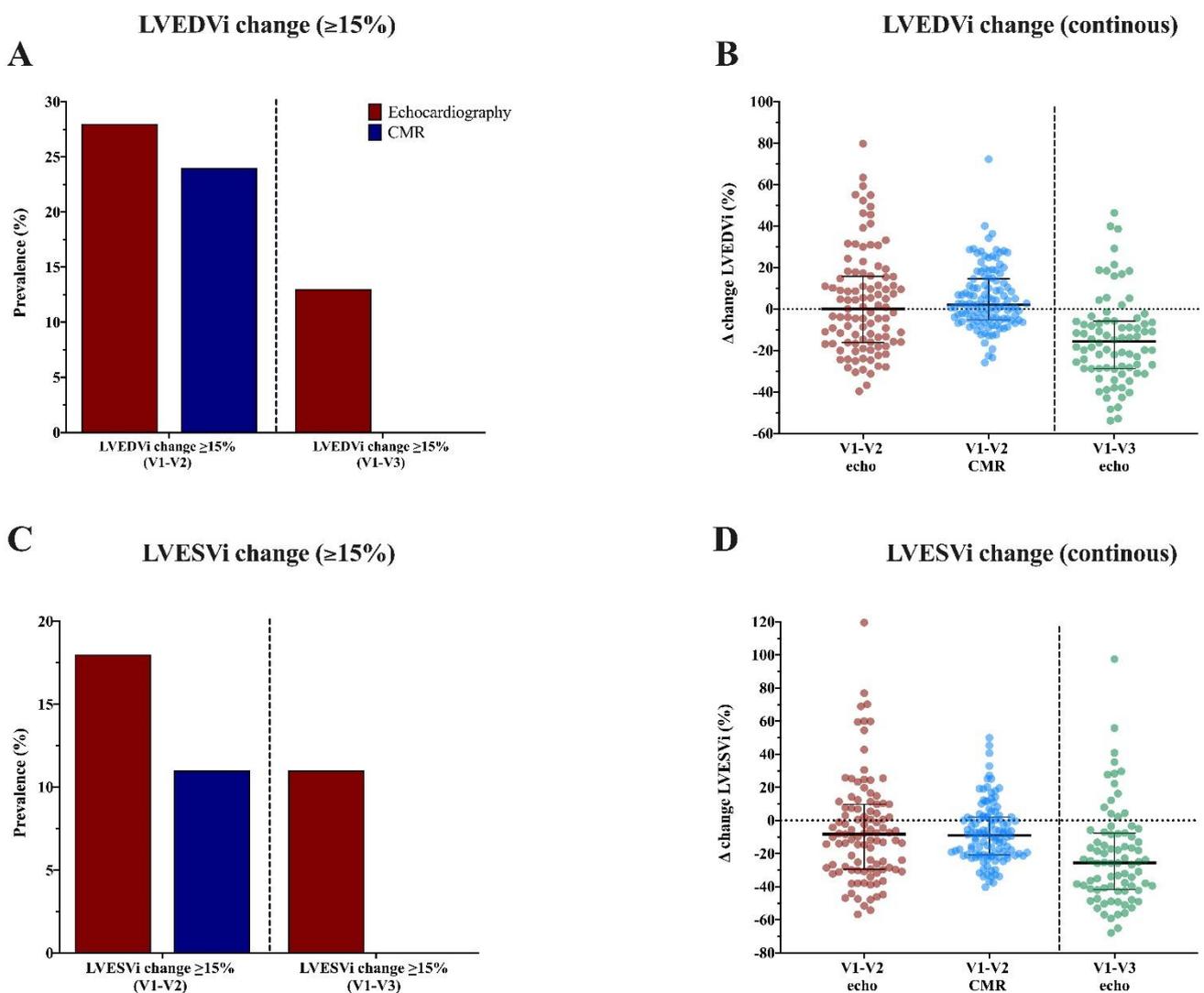


Figure 2 Prevalence of patients exhibiting an increase $\geq 15\%$ in **A)** left ventricular end-diastolic volume and **B)** left ventricular end-systolic volume at mid- (V2) and long-term (V3) follow-up by echocardiography and cardiac magnetic resonance. Relative change in left ventricular end-diastolic volume (**C)** and end-systolic volume (**D)**) between baseline (V1) and V2 and V3. Data are expressed as median and interquartile range. CMR - cardiac magnetic resonance; echo – echocardiography; LVEDVi - left ventricular end-diastolic volume index; LVESVi - left ventricular end-systolic volume index.



Graphical abstract Summary of the study design and key findings. Abbreviations: CMR, cardiac magnetic resonance; LV, left ventricle; LVEF, left ventricular ejection fraction; MI, myocardial infarction; pPCI, primary percutaneous coronary intervention; STEMI, ST elevated myocardial infarction.

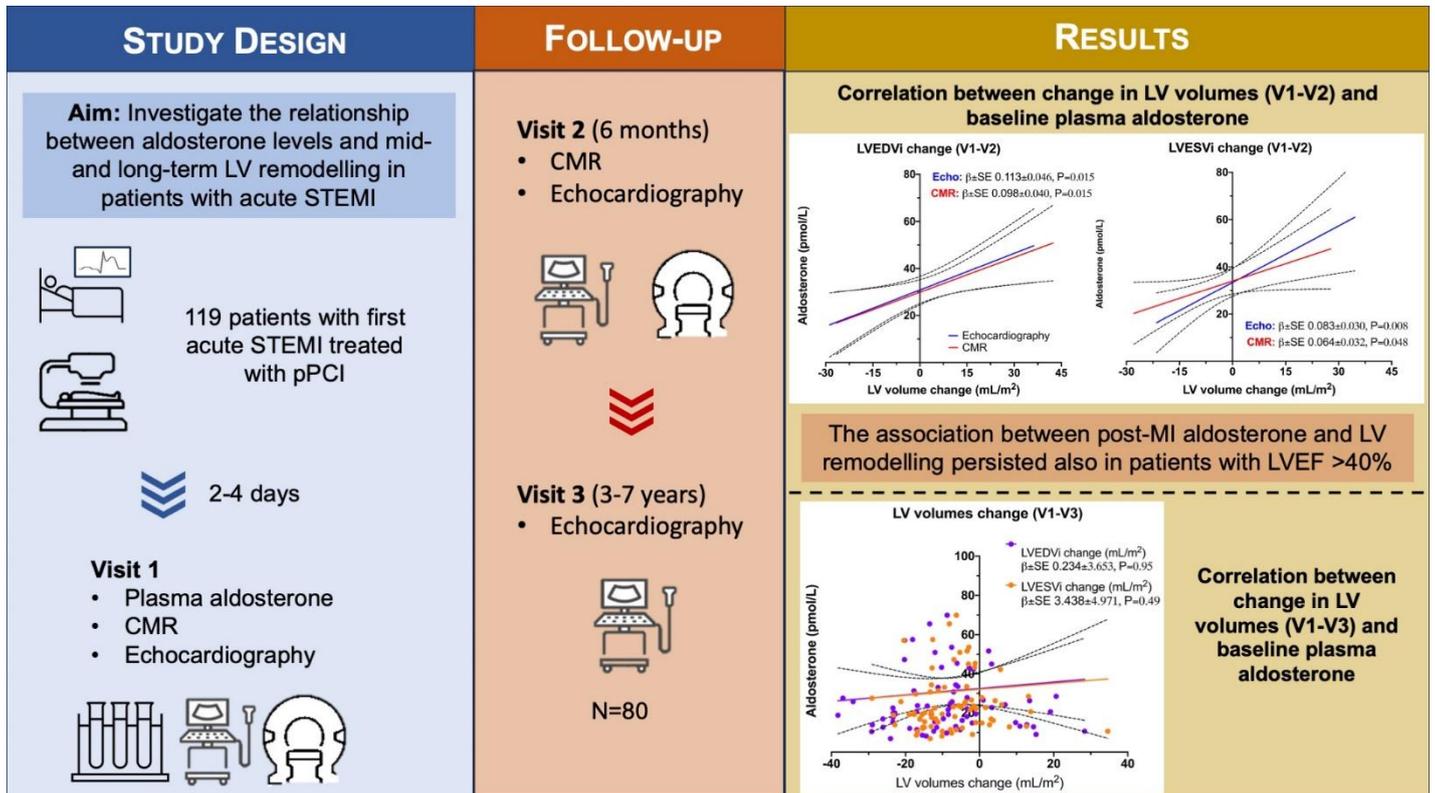


Table 1 Baseline characteristics of the study population

Demographics and clinical characteristics	
Age, years	56 ± 10
Male gender, n (%)	102 (86)
Body mass index, kg/m ²	27.2 ± 3.9
Current smoker, n (%)	54 (45)
Diabetes mellitus, n (%)	9 (8)
Hypertension, n (%)	39 (33)
Hypercholesterolemia, n (%)	46 (39)
Heart rate, bpm	72 ± 13
Systolic blood pressure, mmHg	126 ± 21
Diastolic blood pressure, mmHg	78 ± 14
Coronary intervention	
Time from pain onset to PCI, minutes	90 (55; 118)
Anterior STEMI, n (%)	56 (47)
MI-related coronary artery, n (%)	
- Left anterior descending artery	62 (52)
- Right coronary artery	44 (37)
- Left circumflex artery	13 (11)
Biomarkers	
Troponin I, µg/L	58.9 (21.1; 95.0)
CPK, UI/L	2514 (1173; 4018)
CK-MB, UI/L	226 (118; 331)
eGFR-MDRD, ml/min/1.73 m ²	81.7 ± 18.4
C-reactive protein, mg/L	13.7 (6.1; 25.7)
BNP, pg/mL	152 (79; 266)
Renin, µUI	14.9 (6.8; 34.8)
Aldosterone, pg/mL	23.1 (16.8; 33.1)
PINP, µg/L	102.5 ± 40.5
PIIINP, µg/L	2.7 ± 1.2
ICTP, ng/mL	10.8 ± 6.5
Medications at 6-month follow-up	
RASi, n (%)	108 (91)
Beta-blockers, n (%)	106 (89)
MRA, n (%)	0 (0)
Medications at long-term follow-up	
RASi, n (%)	72 (90)
Beta-blockers, n (%)	65 (80)
MRA, n (%)	11 (14)

Abbreviations: BNP, type-B natriuretic peptide; ICTP, type I collagen telopeptide; CPK, creatine phosphokinase; CK-MB, creatine-kinase MB; eGFR, estimated glomerular filtration rate; MRA, mineralocorticoid receptor antagonist; PCI, percutaneous coronary intervention; PINP, procollagen type-I N-terminal pro-peptide; PIIINP, procollagen type-III N-terminal pro-peptide; RASi, renin-angiotensin system inhibitors; STEMI, ST-segment elevated myocardial infarction.

Table 2 Echocardiographic and cardiac magnetic resonance characteristics at baseline and follow-up

	Baseline (V1)	6-month follow-up (V2)	p-value (V1 -V2)	Long-term follow-up (V3)	p-value (V1 -V3)
Echocardiography					
LVEDVi, mL/m ²	61.2 ± 14.5	62.7 ± 18.6	0.405	50.3 ± 15.0	<0.001
LVESVi, mL/m ²	30.8 ± 11.5	28.6 ± 13.1	0.015	22.5 ± 10.3	<0.001
LVEF, %	50.5 ± 8.8	55.5 ± 9.7	<0.001	56.2 ± 8.7	<0.001
LVEF ≤ 40%, n (%)	17 (14)	6 (6)	0.039	3 (4)	0.028
LV mass index, gr/m ²	115.4 ± 35.2	111.9 ± 33.3	0.849	96.4 ± 22.8	<0.001
GLS	-14.5 ± 3.4	-17.4 ± 3.5	<0.001		
Cardiac magnetic resonance					
LVEDVi, mL/m ²	93.0 ± 15.4	97.2 ± 17.9	<0.001		
LVESVi, mL/m ²	54.7 ± 14.8	50.5 ± 16.8	<0.001		
LVEF, %	41.7 ± 8.1	48.9 ± 8.7	<0.001		
LVEF ≤ 40%, n (%)	46 (39)	17 (14)	<0.001		
Total MI area, % of LV	39.3 ± 12.7	26.5 ± 11.1	<0.001		

Abbreviations: GLS, global longitudinal strain; LV, left ventricle; LVEDVi, left ventricular end-diastolic volume index; LVESVi, left ventricular end-systolic volume index; LVEF, left ventricular ejection fraction; MI, myocardial infarction.

Table 3 Crude and adjusted correlations between change in LVEDVi (from baseline to 6-month and long-term follow-up) and baseline aldosterone concentration

Outcome	Model	Covariates	6-month follow-up				Long-term follow-up		
			Echocardiography		CMR		Echocardiography		
			Beta ± SE	P-value	Beta ± SE	P-value	Beta ± SE	P-value	
Absolute change in LVEDVi, mL/m ²	M0	Aldosterone (pg/mL)	0.113 ± 0.045	0.014	0.095 ± 0.040	0.020	2.409 ± 4.749	0.61	
		LVEDVi (mL/m ²)	-0.154 ± 0.092	0.095	-0.154 ± 0.075	0.042	-0.249 ± 0.113	0.031	
	M1	Aldosterone (pg/mL)	0.111 ± 0.045	0.016	0.093 ± 0.039	0.021	2.351 ± 4.684	0.62	
		LVEDVi (mL/m ²)	-0.170 ± 0.093	0.07	-0.170 ± 0.074	0.023	-0.313 ± 0.117	0.009	
		Anterior STEMI	2.863 ± 2.740	0.3	5.300 ± 2.254	0.02	5.325 ± 3.018	0.082	
	M2	Aldosterone (pg/mL)	0.113 ± 0.046	0.015	0.098 ± 0.040	0.015	3.438 ± 4.971	0.49	
		LVEDVi (mL/m ²)	-0.166 ± 0.094	0.08	-0.175 ± 0.074	0.02	-0.323 ± 0.119	0.008	
		Anterior STEMI	2.438 ± 2.791	0.38	4.973 ± 2.291	0.032	4.935 ± 3.091	0.11	
		BNP (ng/mL)	3.673 ± 8.515	0.67	10.067 ± 7.329	0.17	8.833 ± 12.182	0.47	
				OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)*	P-value
	Change in LVEDVi ≥ 15%	M0	Aldosterone (per 10 pg/mL increment)	1.064 (0.928 - 1.220)	0.37	1.089 (0.952 - 1.246)	0.22	0.504 (0.224 - 1.136)	0.099
M1		Aldosterone (per 10 pg/mL increment)	1.067 (0.930 - 1.224)	0.35	1.088 (0.947 - 1.249)	0.23	0.517 (0.226 - 1.184)	0.12	
		Anterior STEMI	0.749 (0.305 - 1.842)	0.53	2.570 (1.060 - 6.229)	0.037	2.511 (0.579 - 10.89)	0.22	
M2		Aldosterone (per 10 pg/mL increment)	1.075 (0.936 - 1.236)	0.30	1.087 (0.946 - 1.249)	0.24	0.555 (0.227 - 1.358)	0.20	
		Anterior STEMI	0.649 (0.256 - 1.646)	0.36	2.553 (1.032 - 6.316)	0.043	-	-	
		BNP (ng/mL)	1.001 (0.998 - 1.004)	0.44	0.999 (0.997 - 1.002)	0.73	1.006 (1.001 - 1.011)	0.025	

*Due to the low number of events (N = 10), models were adjusted for one variable at a time.

Abbreviations: BNP, type-B natriuretic peptide; CI, confidence interval; LVEDVi, left ventricular end-diastolic volume index; MI, myocardial infarction; OR, odds ratio; STEMI, ST-segment elevated myocardial infarction.

Table 4 Crude and adjusted correlations between change in LVESVi (from baseline to 6-month and long-term follow-up) and baseline aldosterone concentration

Outcome	Model	Covariates	6-month follow-up				Long-term follow-up	
			Echocardiography		CMR		Echocardiography	
			Beta ± SE	P-value	Beta ± SE	P-value	Beta ± SE	P-value
Absolute change in LVESVi, mL/m ²	M0	Aldosterone (pg/mL)	0.082 ± 0.030	0.008	0.062 ± 0.032	0.059	-0.046 ± 3.490	0.99
		LVESVi (mL/m ²)	-0.220 ± 0.077	0.005	-0.085 ± 0.062	0.18	-0.320 ± 0.108	0.004
	M1	Aldosterone (pg/mL)	0.080 ± 0.030	0.010	0.060 ± 0.032	0.062	-0.259 ± 3.461	0.94
		LVESVi (mL/m ²)	-0.239 ± 0.077	0.003	-0.108 ± 0.062	0.087	-0.375 ± 0.113	0.001
		Anterior STEMI	2.740 ± 1.837	0.14	3.793 ± 1.850	0.043	3.408 ± 2.211	0.13
	M2	Aldosterone (pg/mL)	0.083 ± 0.030	0.008	0.064 ± 0.032	0.049	0.234 ± 3.653	0.95
		LVESVi (mL/m ²)	-0.251 ± 0.079	0.002	-0.134 ± 0.066	0.043	-0.381 ± 0.116	0.002
		Anterior STEMI	2.410 ± 1.861	0.2	3.672 ± 1.886	0.054	3.399 ± 2.259	0.14
		BNP (ng/mL)	6.848 ± 5.754	0.24	8.382 ± 6.203	0.18	3.876 ± 9.020	0.67
			OR (95% CI)*	P-value	OR (95% CI)*	P-value	OR (95% CI)*	P-value
Change in LVESVi ≥ 15%	M0	Aldosterone (per 10 pg/mL increment)	1.201 (1.036 - 1.394)	0.015	1.150 (0.988 - 1.339)	0.072	0.793 (0.484 - 1.299)	0.36
	M1	Aldosterone (per 10 pg/mL increment)	1.202 (1.032 - 1.399)	0.018	1.147 (0.981 - 1.342)	0.085	0.798 (0.490 - 1.301)	0.37
		Anterior STEMI	2.133 (0.722 - 6.304)	0.17	2.855 (0.813 - 10.03)	0.10	1.270 (0.310 - 5.196)	0.74
	M2	Aldosterone (per 10 pg/mL increment)	1.230 (1.056 - 1.432)	0.008	1.160 (0.995 - 1.352)	0.059	0.876 (0.545 - 1.408)	0.58
		Anterior STEMI	-	-	-	-	-	-
		BNP (ng/mL)	1.003 (1.000 - 1.006)	0.056	1.002 (0.999 - 1.005)	0.29	1.005 (1.000 - 1.010)	0.075

*Due to the low number of events, models were adjusted for one variable at a time.

Abbreviations: BNP, type-B natriuretic peptide; CI, confidence interval; LVESVi, left ventricular end-systolic volume index; MI, myocardial infarction; OR, odds ratio; STEMI, ST-segment elevated myocardial infarction.