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# Early eplerenone treatment in patients with acute ST-elevation myocardial infarction without heart failure: The Randomized Double-Blind Reminder Study

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## Aims

We aimed to assess the impact of eplerenone on cardiovascular (CV) outcomes in STEMI without known heart failure, when initiated within 24 h of symptom onset.

## Methods and results

In this randomized, placebo-controlled, double-blind trial, we assigned 1012 patients with acute STEMI and without a history of heart failure to receive either eplerenone (25–50 mg once daily) or placebo in addition to standard therapy. The primary endpoint was the composite of CV mortality, re-hospitalization, or, extended initial hospital stay, due to diagnosis of HF, sustained ventricular tachycardia or fibrillation, ejection fraction  $\leq 40\%$ , or elevated BNP/NT-proBNP at 1 month or more after randomization. BNP elevation was defined as BNP levels or values above 200 pg/mL or NT-proBNP values above 450 pg/mL (in patients aged below 50); above 900 pg/mL (age 50–75 years) or above 1800 pg/mL (patients older than 75). After a mean follow-up of 10.5 months, the primary endpoint occurred in 92 patients (18.2%) in the eplerenone group and in 149 patients (29.4%) in the placebo group [adjusted hazard ratio (HR), 0.58; 95% confidence interval (CI), 0.45–0.76;  $P < 0.0001$ ]. The primary endpoint was driven by a high BNP/NT-proBNP level (adjusted HR, 0.60; 95% CI, 0.45–0.79;  $P < 0.0003$ ). Adverse event rates were similar in both groups. Serum potassium levels exceeded 5.5 mmol/L in 5.6 vs. 3.2% ( $P = 0.09$ ) and were below 3.5 mmol/L in 1.4 vs. 5.6% of patients ( $P = 0.0002$ ), in the eplerenone and placebo groups, respectively.

## Conclusion

The addition of eplerenone during the acute phase of STEMI was safe and well tolerated. It reduced the primary endpoint over a mean 13 months follow-up mostly because of significantly lower BNP/NT-proBNP levels. Additional studies are needed to clarify the role of early use of MRAs in STEMI patients without heart failure.

## Clinical trial registration:

NCT01176968.

## Keywords

Myocardial infarction • Mineralocorticoid receptor antagonists • Eplerenone • B-type natriuretic peptide • Potassium

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<sup>†</sup> The 'A Double-Blind, Randomized, Placebo-Controlled Trial Evaluating The Safety And Efficacy Of Early Treatment With Eplerenone In Patients With Acute Myocardial Infarction' (REMINDER) investigators are listed in the Appendix.

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## Introduction

The short-term prognosis of patients undergoing revascularization for acute myocardial infarction (MI) has improved substantially over the past decade.<sup>1,2</sup> Despite current standard therapies, there is considerable increase in aldosterone, which is at its highest level shortly after the onset of acute MI. Aldosterone promotes a number of deleterious short- and long-term effects including sodium retention and potential arrhythmogenesis possibly due to potassium and magnesium depletion, as well as endothelial dysfunction, increased vascular tone, inhibition of neuronal re-uptake of catecholamines, cardiac myocyte necrosis, collagen deposition, and cardiac remodelling.<sup>3,4</sup> Furthermore, it has been found to predict poor outcomes.<sup>5–7</sup>

Current guidelines recommend the use of mineralocorticoid receptor antagonists (MRA) in patients presenting with heart failure post MI,<sup>8</sup> based on the results of the Eplerenone Post-AMI Heart Failure Efficacy and Survival Study (EPHESUS).<sup>9</sup> The benefits observed were more pronounced in patients with early administration of eplerenone (within 3–7 days) when compared with a later administration (7–14 days).<sup>10</sup> Furthermore, there is a potential for benefit even in those presenting without symptoms of heart failure or low left ventricular ejection fraction.<sup>11,12</sup>

The aim of the present study was to investigate the safety and efficacy of an early initiation of eplerenone, within the first 24 h of symptom onset when acute reperfusion is delivered to patients presenting STEMI without known heart failure.

## Methods

### Study oversight

The Executive Steering Committee (see Appendix) designed and oversaw the conduct of the trial and data analysis in collaboration with representatives of the study sponsor (Pfizer). The trial was monitored by an independent data and safety monitoring committee. Data were collected, managed, and analysed by a clinical research organization, contracted by the sponsor, according to the protocol and a predefined statistical analysis plan. Endpoints were adjudicated by an independent endpoint adjudication committee (see Appendix). The manuscript was prepared by the Study Steering Committee, whose members had unrestricted access to the data, and was subsequently revised by all authors. All the authors made the decision to submit the manuscript for publication and assume responsibility for the accuracy and completeness of the data and analyses.

### Study patients

REMINDER was a multi-centre, randomized, double-blind, placebo-controlled, two-arm, parallel group study. The trial randomized subjects at a 1 : 1 ratio of active treatment with eplerenone or placebo in addition to standard of care. The trial was approved by each centre's ethics committee. All patients provided written informed consent.

Eligible subjects were identified for inclusion following emergency room/ambulance evaluation and diagnosis of acute STEMI in the absence of a clinical diagnosis of HF. Randomization had to take place as early as possible following diagnosis and the first dose of study drug administered within 24 h of the onset of symptoms of acute MI and preferably within 12 h. It was not mandatory to obtain serum potassium values prior to treatment initiation or wait for BNP/NT-proBNP determinations prior to randomization and treatment initiation because of the

narrow time windows characteristic for an acute STEMI undergoing coronary reperfusion.

Key exclusion criteria included a previously known LVEF below 40% or a prior history of HF, an implanted cardiac defibrillator (ICD), haemodynamically relevant aortic or mitral valve stenosis, a diagnosis of hypertrophic cardiomyopathy, cardiac surgery within 30 days prior to randomization, an estimated glomerular filtration rate (eGFR) of less or equal to 30 mL per minute per 1.73 m<sup>2</sup> of body surface area (MDRD formula) (because of the contraindication for eplerenone use in these patients) or serum creatinine greater or equal to 220 µmol/L, and a need for potassium-sparing diuretics.

Prohibited concomitant medications included aldosterone antagonists, spironolactone, potassium canrenoate, potassium-sparing diuretics, potent cytochrome p450 3A4 (CYP3A4) inhibitors and inducers.

### Study procedures

A computerized randomization system (24 h interactive voice randomization system) with concealed study-group assignment was used to randomly (block size 4) assign patients to receive eplerenone (Inspra, Pfizer) or matching placebo. Eplerenone was started at a dose of 25 mg once daily and was to be increased to 50 mg once daily starting on day 2 if serum potassium concentration was below 5.0 mmol/L, eGFR was above 50 mL/min/1.73 m<sup>2</sup> (MDRD), and subjects were not taking mild to moderate inhibitors of CYP3A4.

Efficacy and safety assessments were performed at weeks 1 and 4 as well as at months 6, 12, 18, and the end of study visit. BNP/NT-proBNP concentrations were assessed locally at week 4 and at months 6, 12, 18 and the end of study visit. Transthoracic echocardiogram was performed at the 6 months follow-up and at the end of study visit.

### Study outcomes

The primary composite endpoint was the time to first occurrence of cardiovascular (CV) mortality, re-hospitalization, or extended initial hospital stay due to diagnosis of HF or sustained ventricular tachycardia (lasting at least 30 s at a rate of 100 bpm or more) or ventricular fibrillation, as well as LVEF equal or below 40% at 1 month or later post-randomization or BNP above 200 pg/mL or NT-proBNP above 450 pg/mL (in patients aged below 50); above 900 pg/mL (age 50–75 years), or above 1800 pg/mL (patients older than 75) after 1 month.<sup>13</sup> Heart failure was diagnosed based on at least one of the following criteria: (i) rehospitalization for the treatment of CHF supported by a discharge report or clinical summary in which 'Congestive Heart Failure' appeared as the principal or secondary diagnosis. (ii) Emergency room visit for CHF requiring treatment for oedema or dyspnoea with intravenous diuretic therapy resulting in clinical improvement and obviating the need for immediate hospitalization. Supporting data include, when available, chest X-rays, Swan Ganz catheterization, left ventricular function assessment, and discharge medications. Heart failure was adjudicated by a clinical endpoint committee. The main pre-specified secondary endpoints (Table 2) included all components of the primary endpoint; ICD or cardiac resynchronization therapy (CRT); second or subsequent non-fatal MI. The composite of CV mortality, re-hospitalization, or extended initial hospital stay due to diagnosis of HF, or sustained ventricular tachycardia or fibrillation was a secondary composite endpoint pre-specified in the statistical analysis plan.

### Statistical analysis

Based on the literature data,<sup>6,14,15</sup> the anticipated 6-month event rate for the primary endpoint was estimated to be 42% in the placebo group and 33% in the eplerenone group (representing a 22% improvement in favour of eplerenone). With a two-sided log-rank test on the time to first occurrence of the primary endpoint, at a 5% level of significance, with 80%

power and assuming a 5% non-evaluable dropout rate, the randomized sample size required was 306 subjects per group (i.e. 612 in total). However, based on a blinded review of data (resulting in no unblinding penalty) as of 28th August 2011, the observed overall event rate was 21% per 6 months and most of the events occurred within the first 3 months of enrolment. With no evidence of a changed assumption on the 22% improvement with eplerenone, the corresponding estimated event rates were 18.4 and 23.6% (per 6 months) for eplerenone and placebo, respectively. This resulted in an increase of the final sample size to 1012 randomized subjects or 506 per treatment arm. With this sample size, the trial had an at least 76% power for a durations of 3 months to detect the expected treatment effect.

The analyses of the adjudicated primary and secondary endpoints were conducted on data from all patients who had undergone randomization, according to the intention-to-treat principle, with the use of a Cox proportional-hazards model. Hazard ratios (HR), 95% confidence intervals (95%CI), and *P*-values were adjusted for the following pre-specified baseline prognostic factors in model 1: baseline eGFR, previous MI, time (in hours) of first dose administered post onset of index symptom, and location of index MI anterior or non-anterior. For model 2, age, body mass index, haemoglobin, heart rate, systolic blood pressure, diabetes (yes/no), hypertension (yes/no), atrial fibrillation (yes/no), and the presence of either baseline left bundle branch block (LBBB) or QRS > 130 ms (yes/no) were included in addition to the covariates of model 1. Sensitivity analyses were also performed using unadjusted Cox models.

The consistency of the treatment effect was assessed among pre-specified subgroups. The effect in each subgroup was analysed with the use of a Cox proportional-hazards model, without adjustment for

covariates. The treatment-by-subgroup interaction was evaluated by means of a Cox proportional-hazards model with terms for treatment, subgroup, and their interaction.

Change from baseline in vital signs and clinically relevant laboratory values such as serum creatinine, serum potassium, and eGFR were assessed by analysis of covariance, with the corresponding baseline value as a covariate. Additionally, the incidence rates of the serum potassium value < 3.5 and > 5.5 mmol/L were summarized by treatment groups and Fisher's exact tests were performed. Adverse events were tabulated according to randomized group assignment and analysed by means of Fisher's exact test.

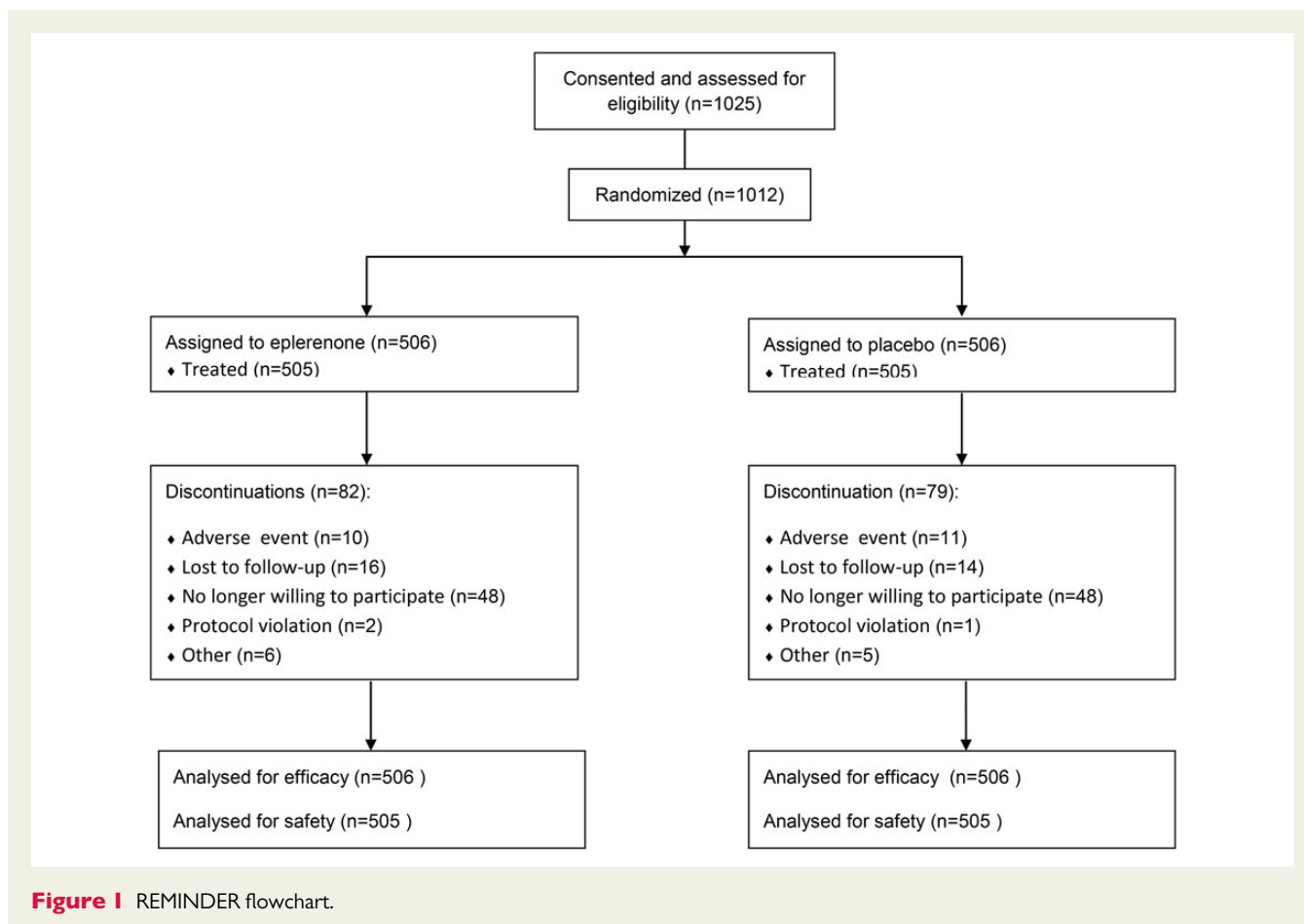
## Results

### Study patients

Between 28 September 2010 and 28 October 2012, 1012 patients at 65 centres in 11 countries were recruited. Of these patients, 506 were randomly assigned to eplerenone and 506 to placebo (Figure 1). The two groups were balanced with respect to baseline characteristics (Table 1).

### Study drug administration and follow-up

One patient in each group did not start study medication and was not included in the safety analysis. Patients received the first dose of eplerenone after a mean duration of  $16.4 \pm 7.2$  h (range 0.5–73.2 h) and the first dose of placebo at  $15.4 \pm 6.6$  h (range 0–34.5 h) following



**Table 1** Baseline characteristics of the patients, according to the study group<sup>a</sup>

Characteristics	Eplerenone (n = 506)	Placebo (n = 506)
Age, year	58.5 ± 10.8	57.8 ± 11.0
Female sex, no. (%)	86 (17.0)	103 (20.4)
Race, no. (%) <sup>b</sup>		
White	475 (93.9)	471 (93.1)
Black	1 (0.2)	1 (0.2)
Asian	0	5 (1.0)
Other	30 (5.9)	29 (5.7)
Heart rate (bpm)	73 ± 13	74 ± 13
Blood pressure (mmHg)		
Systolic	125.7 ± 18.7	126.7 ± 17.0
Diastolic	76.0 ± 12.5	76.8 ± 11.5
Body-mass index (kg/m <sup>2</sup> )	27.9 ± 4.5	28.2 ± 4.2
Serum creatinine (mg/dL)	0.91 ± 0.20	0.91 ± 0.21
Estimated GFR, mL/min/1.73 m <sup>2</sup> of body-surface area	86.5 ± 28.2	86.4 ± 24.9
Estimated GFR < 60 mL/min/1.73 m <sup>2</sup> , no. (%)	34 (6.8)	50 (10.0)
Serum potassium (mmol/L)	4.07 ± 0.46	4.04 ± 0.45
Myocardial infarction		
Anterior MI	180 (35.6)	205 (40.5)
Medical history, no. (%)		
Hypertension	241 (47.6)	260 (51.4)
Diabetes	65 (12.8)	78 (15.4)
History of MI	33 (6.5)	23 (4.5)
Atrial fibrillation	8 (1.6)	9 (1.8)
Concomitant treatments at randomization		
ACE inhibitors/ARBs	418 (82.6)	421 (83.2)
Beta-blockers	445 (87.9)	447 (88.3)
Diuretics	54.7 (10.7)	51 (10.1)
Lipid lowering agents	492 (97.2)	493 (97.4)
Acetylsalicylic acid	497 (98.2)	496 (98.0)
P2Y12 antagonists	498 (98.4)	498 (98.4)
Heparins and fondaparinux	395 (78.1)	401 (79.2)
Oral anticoagulants	7 (1.4)	5 (1.0)
GP IIb/IIIa inhibitors	148 (29.2)	148 (29.2)
Bivalirudin	13 (2.6)	12 (2.4)
Fibrinolytics	31 (6.1)	21 (4.2)
PCI/thrombolysis at randomization		
PCI	431 (85.2)	440 (87.0)
Thrombolysis	32 (6.3)	21 (4.2)
No reperfusion	43 (8.5)	45 (8.9)

Percentages may not total 100 because of rounding. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; GFR, glomerular filtration rate; GP, glycoprotein; MI, myocardial infarction; PCI, percutaneous coronary intervention.

<sup>a</sup>Plus–minus values are means ± SD.

<sup>b</sup>Race was reported by the investigators.

the index MI. On day 2, the majority of patients (96.5%) was uptitrated to 50 mg eplerenone daily and 88.6% received the higher dose at the end of the study.

## Study outcomes

After a mean follow-up of 10.5 months, the primary endpoint occurred in 92 (18.2%) patients in the eplerenone group when compared with 149 (29.4%) in the placebo group (Figure 2 and Table 2) [Adjusted HR 0.58 (95% CI, 0.45–0.76;  $P < 0.0001$ )] and in an unadjusted analysis (HR 0.58; 95%CI 0.45–0.75;  $P < 0.0001$ ).

An elevation of BNP/NT-proBNP after 1 month was observed less frequently in the eplerenone group than in the placebo group. This effect was consistent at months 6, 12, and 18. There was no significant difference in any of the other components of the primary endpoint (Table 2). The composite clinical endpoint of CV mortality, HF episode, or sustained ventricular arrhythmia was not statistically different with eplerenone ( $n = 9$ , 1.8%) than with placebo ( $n = 16$ , 3.2%) (adjusted HR 0.55; 95% CI, 0.23–1.35,  $P = 0.19$ ).

The effect was consistent in all major subgroups (Figure 3) except for heart rate ( $P$ -value for interaction 0.021), and timing of acute reperfusion ( $P$ -value for interaction 0.008).

## Safety

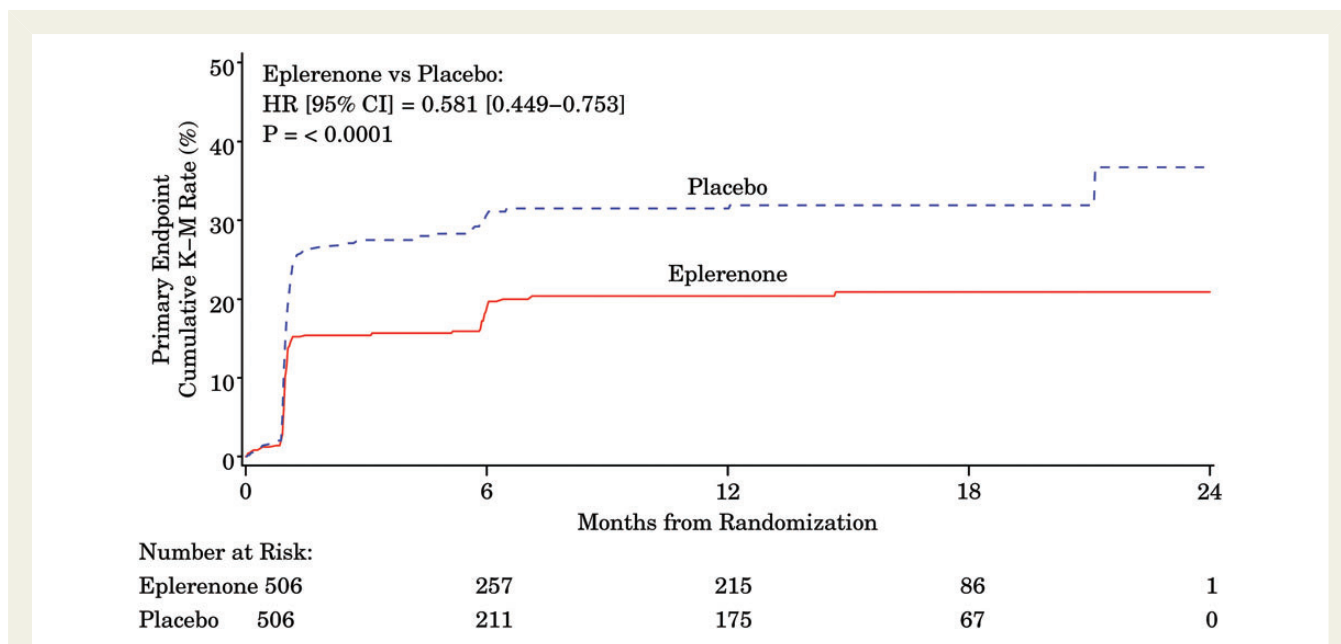
During the course of the study, 28 patients (5.5%) receiving eplerenone and 24 patients (4.8%) receiving placebo discontinued the study because of an adverse event ( $P = 0.48$ ). Relevant safety variables are summarized in Table 3. Overall mortality was low with death reported in 3 of 506 patients (0.6%) in the eplerenone group and 3 of 506 patients (0.6%) in the placebo group.

There were numerically more cases of hyperkalaemia (serum potassium concentration above 5.5 mmol per litre) and severe hyperkalaemia (serum potassium concentration above 6.0 mmol per litre) in patients treated with eplerenone compared with placebo; however, this did not reach statistical significance. In contrast, patients with hypokalaemia (serum potassium concentration below 3.5 mmol per litre) were significantly more frequently found with placebo than with eplerenone (Table 3). There were no deaths associated with the development of hyperkalaemia in patients randomized to eplerenone.

There were no other clinically significant differences between the two groups with respect to changes in laboratory variables, reported adverse events, or adverse events leading to permanent withdrawal of the study drug.

## Discussion

We evaluated the effect of an early addition of eplerenone 25–50 mg once daily to recommended treatment in patients with acute STEMI and no history of heart failure or low left ventricular ejection fraction. Patients were at low risk of clinical events as evidenced by the 0.4% CV mortality rate for the duration of the trial. The safety of the early administration of eplerenone was excellent, while the rate of the primary outcome was significantly reduced in the eplerenone group when compared with the placebo group. This effect of eplerenone



**Figure 2** Cumulative Kaplan–Meier estimates of rates of the primary outcome according to study group.

**Table 2** Primary outcome, component events, and key secondary outcomes<sup>a</sup>

Outcome	Eplerenone (n = 506) No. of patients (%)	Placebo (n = 506) No. of patients (%)	Adjusted Hazard Ratio (95% CI)	Adjusted P Value	Unadjusted Hazard Ratio (95% CI)	Unadjusted P Value
Primary outcome	92 (18.2)	149 (29.4)	0.58 (0.45–0.76)	<0.0001	0.58 (0.45–0.75)	<0.0001
Cardiovascular mortality	2 (0.4)	2 (0.4)	0.56 (0.05–6.31)	0.64	0.99 (0.14–7.04)	0.99
Re-hospitalization or extended initial hospital stay due to diagnosis of HF	7 (1.4)	11 (2.2)	0.73 (0.27–1.99)	0.53	0.64 (0.25–1.64)	0.35
Sustained ventricular tachycardia or ventricular fibrillation	0	3 (0.6)	–	–	–	–
EF ≤40% (≥1 month post randomization)	20 (4.0)	19 (3.8)	1.08 (0.58–2.04)	0.81	1.01 (0.54–1.89)	0.98
BNP > threshold <sup>b</sup> (≥1 month post randomization)	81 (16.0)	131 (25.9)	0.60 (0.45–0.79)	0.0003	0.59 (0.45–0.78)	0.0002
Secondary outcomes						
Implantation of ICD or CRT	3 (0.6)	3 (0.6)	1.07 (0.21–5.37)	0.94	0.99 (0.20–4.91)	0.99
Second or subsequent non-fatal MI	10 (2.0)	6 (1.2)	1.60 (0.57–4.53)	0.38	1.66 (0.60–4.58)	0.32
CV death, heart failure and arrhythmia combined <sup>c</sup>	9 (1.8)	16 (3.2)	0.55 (0.23–1.35)	0.19	0.56 (0.25–1.27)	0.16

<sup>a</sup>Hazard ratio, 95% confidence interval (CI) of hazard ratio, and P-value for the primary analysis (adjusted model #1) were based on a Cox proportional hazard (PH) model.

<sup>b</sup>BNP >200 pg/mL or NT-proBNP >450 (age <50 years), >900 (age 50–75 years), or >1800 pg/mL (age >75 years).

<sup>c</sup>The time to first occurrence of cardiovascular (CV) mortality, re-hospitalization, or extended initial hospital stay due to diagnosis of heart failure (HF), or sustained ventricular tachycardia or fibrillation.

was consistent across major pre-specified subgroups, but was particularly obvious in patients undergoing rapid reperfusion within 6 h of symptom onset. The improvement in the primary outcome was mainly driven by a significant reduction of BNP/NT-proBNP.

Eplerenone has been shown to reduce mortality in patients with HF, particularly in those with a recent MI and left ventricular dysfunction and in those with chronic heart failure with low LVEF and mild symptoms. Surprisingly, its use in populations after AMI where they

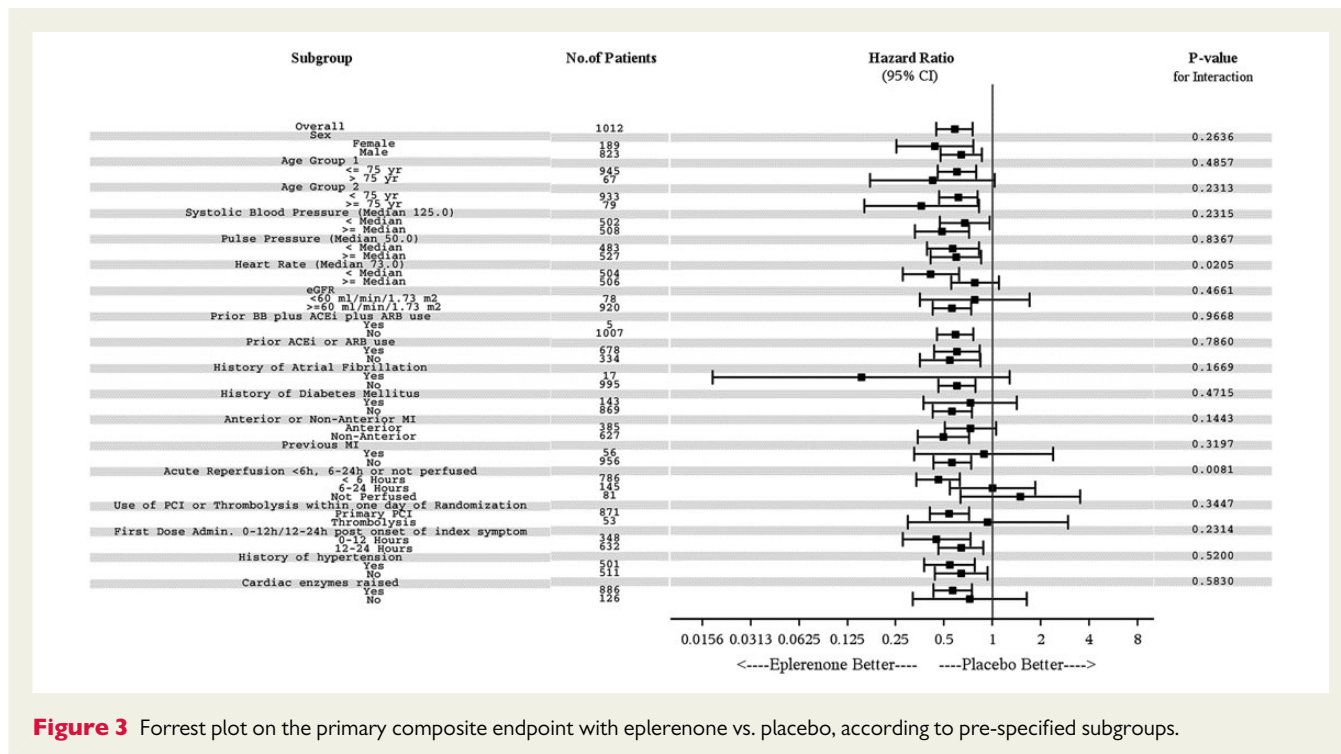


Figure 3 Forrest plot on the primary composite endpoint with eplerenone vs. placebo, according to pre-specified subgroups.

Table 3 Safety, according to the study group

	Eplerenone # of patients (%) / mean ± SD	Placebo # of patients (%) / mean ± SD	P-value
All adverse events	298/505 (59.0)	296/505 (58.6)	0.95
Adverse events leading to study drug discontinuation	28/505 (5.5)	24/505 (4.8)	0.48
Death	3/506 (0.6)	3/506 (0.6)	1.00
Serum creatinine mean change from baseline at 1 month (mg/dL)	0.06 ± 0.16	0.05 ± 0.16	0.42
Median (range)	0.07 (−0.7 to 0.7)	0.05 (−0.81 to 0.80)	
Potassium mean change from baseline at 1 month (mmol/L)	0.41 ± 0.56	0.32 ± 0.50	<0.0001
	0.40 (−1.24 to 2.46)	0.30 (−1.24 to 7.87)	
Hyperkalaemia (>6.0 mmol/L)	8/498 (1.6)	2/496 (0.4)	0.11
Hyperkalaemia (>5.5 mmol/L)	28/498 (5.6)	16/496 (3.2)	0.09
Hypokalaemia (<3.5 mmol/L)	7/498 (1.4)	28/496 (5.6)	0.0002
Systolic BP mean change at 1 week (mmHg)	−5.9 ± 20.7	−6.0 ± 19.5	0.38
	−5.0 (−92 to 65)	−5.5 (−80 to 55)	
Renal failure (eGFR <30 mL/min/1.73 m <sup>2</sup> )	2/490 (0.4)	3/491 (0.6)	1.00

are specifically recommended is extremely low, ranging between 9<sup>16</sup> and 55%.<sup>17</sup> Accumulating data suggested that a MRA given early in the course of an acute MI may improve patient prognosis because aldosterone rises in the early hours of MI potentially leading to acute adverse effects.<sup>6,7,18,19</sup> Furthermore, i.v. potassium canrenoate, the active metabolite of spironolactone, given within 12 h of the onset of acute MI followed by spironolactone on top of enalapril vs. enalapril alone was shown to reduce left ventricular dilation and collagen serum biomarker levels and improve LVEF.<sup>11</sup> Finally, in

experimental studies, the administration of eplerenone immediately post coronary artery ligation, but not 3 days thereafter, enhanced infarct neovascularization and reduced early left ventricular dilation and dysfunction.<sup>12</sup>

Considering the dramatic improvement of prognosis in acute reperfusion of STEMI, it is challenging to assess the impact of new therapies on CV mortality and morbidity, especially when low-risk patients are enrolled.<sup>1,2</sup> Accordingly, the CV event rates in our study were too low to show statistically significant changes. Given

the observed overall event rate of fatal and non-fatal CV events of 2.5% per year, a sample size of over 10 000 patients per group would have been needed to demonstrate a 15–20% event reduction with 80% power at the 5% level of significance. Because of these anticipated limitations, rather than relying on hard outcomes only, we included markers of subclinical HF into the primary endpoint.

The overall outcome of the primary endpoint was strongly driven by a reduction of BNP/NT-proBNP. Natriuretic peptides have been shown to be a major prognostic factor for short-term and long-term prognosis in patients with MI and left ventricular dysfunction.<sup>13,20</sup> BNP, obtained within the first 40 h of the onset of ischaemic symptoms in patients with acute coronary syndromes, predicted death at 10 months with an OR of 5.8 (95% CI 1.7–19.7) in the highest quartile of BNP values.<sup>21</sup> Furthermore, it was associated with the risk for developing new or worsening HF. In another study, in patients with STEMI but no evidence of clinical HF, NT-proBNP remained a significant predictor of mortality after adjustment for age and LVEF [risk ratio 2.4 (95% CI 1.1–5.4)].<sup>22</sup>

Our study results are, however, in partial agreement with the results from the AVANT GARDE-TIMI 43 Trial,<sup>23,24</sup> where aliskiren and/or valsartan was tested against placebo to blunt the increase in natriuretic peptides in patients after ACS without heart failure. NT-proBNP declined significantly in each treatment arm, including placebo, by week 8, though there were no differences in the reduction between treatment strategies (42% in placebo, 44% in aliskiren, 39% in valsartan, and 36% in combination arm). Again no differences in clinical outcomes were observed.

A key value of this study is that it provides important new safety information about early treatment with eplerenone after myocardial infarction. Eplerenone was generally well tolerated in our low-risk population and only few patients discontinued treatment during the study. This good tolerance was obtained with 96.5% of patients in the eplerenone group being uptitrated to 50 mg on the second day of treatment. Initial concerns about starting the drug during the early course of MI proved not to be justified. The rate of hyperkalaemia (>5.5 mmol/L; 5.2%) was less than in EMPHASIS-HF (8.0%) and nominally higher than in EPHEMUS (3.4%), although not statistically different from placebo. Rates of severe hyperkalaemia (>6.0 mmol/L) were rare: 1.6% with eplerenone and 0.4% with placebo ( $P = 0.11$ ). This is reassuring given the instability of patients with acute STEMI within the first hours of hospitalization. It should also be emphasized that there were no deaths associated with the development of hyperkalaemia in patients randomized to eplerenone. On the other hand, rates of hypokalaemia were low (1.4%) and substantially less than in the placebo group (5.6%;  $P = 0.0002$ ). This is important because low serum potassium has been associated with an increased risk of arrhythmia and mortality.<sup>25</sup>

Our study has some limitations: it was not powered for hard clinical outcomes in this low-risk population of patients with STEMI without a history of HF. We enrolled low-risk subjects as eplerenone is already licensed for use in the higher risk patients with HF post AMI. We suspect that the benefit on clinical endpoints would be larger in a higher risk population. This concept is being tested in an ongoing study (Aldosterone Blockade Early After Acute Myocardial Infarction, ALBATROSS, NCT01059136). Although we excluded patients with a known LVEF < 40% or a prior history of HF or HF at admission, we did not evaluate the LVEF and BNP values at baseline

only allowing a comparison of values against the control group of patients receiving placebo.

In conclusion, this study shows that compared with placebo, the addition of eplerenone to standard therapy within 24 h of symptom onset is safe and reduces brain natriuretic peptide levels of patients presenting with acute STEMI without known HF or LVEF < 40%. A larger randomized trial is needed to finally assess the role of MRA in patients after acute STEMI not complicated by heart failure.

## Collaborator

Peter Bramlage (Mahlow, Germany).

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## Appendix

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