Individual Participant Data Analysis of two Trials on Aldosterone Blockade in Myocardial Infarction

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Abstract

Background

Two recent randomized trials studied the benefit of Mineralocorticoid receptor antagonists (MRA) in ST-elevation myocardial infarction (STEMI) irrespective or in absence of heart failure. The studies were both undersized to assess hard clinical endpoints. A pooled analysis was pre-planned by the steering committees.

Methods

We conducted a pre-specified meta-analysis of patient-level data of STEMI patients recruited in 2 multicenter superiority trials, randomized within 72 hours after symptom onset. Patients were allocated (1:1) to 2 MRA regimens: 1. An intravenous bolus of potassium canrenoate (200 mg) followed by oral spironolactone (25 mg od) versus standard therapy; or 2. Oral Eplerenone (25 to 50 mg) in versus placebo. The primary and key secondary outcomes, all cause death and the composite of all cause death or resuscitated sudden death respectively, were assessed in the intention to treat population using a Cox model stratified on the study identifier.

Results

Patients were randomly assigned to receive (n=1118) or not the MRA regimen (n=1123). After a median follow-up time of 188 days, the primary and secondary outcomes occurred in 5(0.4%) and 17 (1.5%) patients (adjHR 0.31, 95%CI 0.11 to 0.86, p=0.03) and, 6(0.5%) and 22(2%) patients (adjHR 0.26; 95% CI 0.10-0.65, p=0.004) in the MRA and control groups respectively. There were also trends toward lower rates of cardiovascular death (p=0.06) and ventricular fibrillation (p=0.08) in the MRA group.

Conclusion

Our analysis suggests that compared to standard therapy MRA regimens are associated with a reduction of death and death or resuscitated sudden death in STEMI.

What is already known about this subject?

Mineralocorticoid receptor antagonists reduce mortality in the setting of myocardial infarction complicated by heart failure.

What does this study add?

The study shows that regardless of heart failure, mineralocorticoid receptor antagonists reduce mortality in the setting of ST elevation myocardial infarction, in addition to optimal treatment.

How might this impact on clinical practice?

The use of very low cost mineralocorticoid receptor antagonists may be considered in ST elevation myocardial infarction patients irrespective of heart failure to reduce mortality

Introduction

Rationale

High aldosterone plasma levels early after myocardial infarction are associated with mortality, sudden cardiac death and heart failure. [1–5] Experimental studies have shown that early administration of MRA after myocardial infarction could improve myocardial healing and both electrical and structural remodeling.[6,7] Small-sized studies have also reported a benefit of MRAs, initiated early after myocardial infarction in the prevention of left ventricular remodeling [8,9] and life-threatening arrhythmia.[10,11]

Mineralocortoid receptor antagonists (MRA) spironolactone and eplerenone reduce mortality in the setting of congestive heart failure with reduced ejection fraction and myocardial infarction complicated by left ventricular dysfunction and heart failure.[12–14]

The Double-Blind, Randomized, Placebo-Controlled Trial Evaluating The Safety And Efficacy Of Early Treatment With Eplerenone In Patients With Acute Myocardial Infarction (REMINDER) [15] showed that eplerenone used within the first 24 hours of ST-segment elevation MI (STEMI) excluding patients with heart failure, was safe and effective on a composite outcome mainly driven by the biological outcome of a lower plasma level of B-type natriuretic peptide. More recently the Aldosterone Lethal effects Blockade in Acute myocardial infarction Treated with or without Reperfusion to improve Outcome and Survival at Six months follow-up (ALBATROSS) failed to demonstrate a benefit of a spironolactone-based MRA regimen in improving outcome in the general setting of STEMI or non-STEMI irrespective of heart failure, but suggested a potential significant reduction of rates of death by the MRA in the STEMI subgroup of patients (77% of the population).[16] Both ALBATROSS and REMINDER studies were undersized to detect a difference in rates of hard clinical outcomes. A pooled analysis of individual participant-level data was preplanned by the steering committees of the 2 trials prior to the end of the inclusion periods.

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Objectives

The aim of this pooled analysis of patient-level data was to investigate the effect of a MRA regimen initiated early after the onset of STEMI, irrespective or in absence of heart failure, on mortality and the composite of death or resuscitated sudden death.

Methods

Study design and population

Our study used pooled individual patient-level data of the STEMI subgroup of the ALBATROSS[16] and the total population of the REMINDER[15] randomized trials. Both trials studied the efficacy of an MRA regimen in addition to standard therapy in comparison with either standard therapy alone or associated with a placebo. The designs of the studies are briefly depicted in supplementary table 1. ALBATROSS- and REMINDER-eligible patients were men and non-pregnant women presenting with STEMI within 72 and 24 hours of symptom onset respectively. REMINDER included STEMI patients only while ALBATROSS included not only STEMI (n=1229) but also Non-STEMI patients (n=369) with a significant interaction between the presentation type and treatment with respect to mortality. Hence only STEMI patients of the ALBATROSS trial were included in the present analysis. Other differences between the ALBATROSS and REMINDER studies included the treatment (IV potassium canrenoate followed by oral spironolactone versus oral eplerenone), the timing of the randomization with respect to symptom onset (within 24 versus within 72 hours) and the duration of follow-up (182±40 versus 317±218 days). Furthermore, to be included in REMINDER no sign of heart failure was to be present at randomization while in ALBATROSS patients were included regardless of signs of heart failure. The comparison between the patients' characteristics of the 2 studies is reported in supplementary table 2.

Outcomes

The primary outcome of the ALBATROSS trial was the composite of death, resuscitated cardiac arrest, significant ventricular arrhythmia, class IA indication[17] for implantable defibrillator, new or worsening heart failure over the period of 6 months following randomization. The primary outcome of the REMINDER trial was the composite of cardiovascular mortality, re-hospitalization or extended initial hospital stay for heart failure or sustained ventricular tachycardia or ventricular fibrillation, left ventricular ejection fraction $\leq$ 40% $\geq$1 month post- randomization or high BNP or NT-proBNP levels.[15]

The primary efficacy outcome of the present study was mortality of any cause. As BNP was not measured in ALBATROSS and there were differences between definitions of events between the trials such as heart failure (requiring any treatment versus hospitalization or emergency room visit) or sustained/significant ventricular tachycardia (requiring any treatment versus hospitalization), any endpoint other than mortality was considered as a secondary endpoint. The key secondary efficacy outcome was the composite of death and resuscitated sudden death. Other secondary efficacy outcomes analyzed included cardiovascular death, resuscitated cardiac death, ventricular fibrillation, any ventricular arrhythmia (ventricular tachycardia or fibrillation), stroke, implanted cardiac defibrillator, class IA[17] indication for defibrillators-whether implanted or not- and recurrent myocardial infarction -study specific definitions-. An independent committee adjudicated all outcomes in both trials.

Safety outcomes included Hyperkalemia > 5.5 and > 6 mmol/L at any time after randomization and acute renal failure defined by an increase in estimated glomerular filtration rate (eGFR) of $\geq$25% in comparison with admission eGFR. For the present analysis, eGFR was calculated for all patients based on Cockroft-Gault method.

Statistical analysis

All analyses used individual patient-level data of the pooled STEMI subgroup of the

ALBATROSS and the total population of the REMINDER trials. The pooled analysis of the two patient populations was pre-planned by the steering committees of the two trials. The full raw datasets were provided by the studies' organizers and analyzed independently from the published data. All data were assessed within the 2 sets for completeness and coherence. No specific issue was observed.

A one stage approach was used for the analysis. Data were compared between treatment arms using the Cochran-Mantel-Haenszel test and a 2-way ANOVA both using the study identifier as the stratification variable. $\chi 2$ test and Student's t test were used for the comparison of the variables between the studies.

All efficacy endpoints were analyzed as time-to-event outcomes using Cox models systematically stratified on the study identifier with a follow-up time of 188 days equal to the median follow-up time of the pooled data. Kaplan-Meier cumulative hazards curves were drawn for the comparison of the primary and key secondary outcomes between treatment groups. Safety endpoints were analyzed as binary variables compared between treatment groups using a Cochran-Mantel-Haenszel test stratified on the study identifier.

Post hoc sensitivity analyses were performed for all efficacy endpoints using the Cox models stratified on the study identifier and adjusted on variables unequally distributed between the treatment arms with a p value threshold of <0.20.

Inter-study heterogeneity assessments were performed by the measurement of the interaction between the study identifier and the treatment arm using a cox model for efficacy endpoints and a logistic regression model for safety endpoints without stratification.

Interaction between subgroups pre-defined in the two trials and treatment was tested using the Cox models stratified on the study identifier when data were available for both trials.

All tests had a two-sided significance level of 5% and were performed using R software, version 3.2.3 for Mac (R foundation for statistical computation).

Results

A total of 2241 patients were randomly assigned to the MRA regimen (1118 patients) or control regimen (1123 patients).

Despite the differences between ALBATROSS and REMINDER trials (supplementary table 1), the active and control groups were well balanced with respect to most baseline characteristics and treatment strategies (Table 1) with the exception of significantly higher heart rate (p=0.02) and systolic blood pressure (p=0.02), as well as higher rates of Killip class ≥ II on admission in the control group (p=0.02). The standard of care for the index event included fibrinolysis in 189 (8.4%), primary percutaneous coronary intervention (PCI) in 1954 (87.2%), any PCI in 2060 (91.9%) and coronary artery bypass surgery in 41 (1.8%) patients.

Table 1. Patient characteristics according to treatment

Variable	Overall n= 2241	Active n=1118	Control n=1123	p
Age (years)	58±12	58±11	58±12	0.8
Gender (Female)	377(16.8%)	178(15.9)	199(17.7)	0.3
Admission characteristics				
Body mass index (Kg/m^2)	27±5	27±5	27±5	0.12
Heart rate (per minute)	73±15	73±15	74±15	0.02
Systolic blood pressure(mmHg)	124±21	123±21	125±21	0.02
Killip class	1.05±0.28	1.03±0.22	1.06±0.33	0.007
Killip class ≥ 2	82(3.7)	29(2.6)	53(4.7)	0.007
Plasma creatinine (µmol/L)	81.8±22.3	82±22	81±23	0.4
eGFR (mL/min)	104±36	102±35	105±37	0.14
Plasma potassium (mmol/L)	4.02±0.5	4.03±0.5	4.01±0.4	0.3
GRACE score	140±23	140±22	140±24	0.6
Medical history				
Systemic hypertension	964(43.0)	464(41.5)	500(44.5)	0.15
Diabetes mellitus	298(13.3)	145(13.0)	153(13.6)	0.7
Hypercholesterolemia	883(39.4)	450(40.3)	433(38.6)	0.4
Active smoking	772(34.5)	375(33.5)	397(35.4)	0.4
Prior myocardial infarction	136(6.1)	71(6.4)	65(5.8)	0.6
Prior stroke	44(2.0)	28(2.5)	16(1.4)	0.09

Initial/in-hospital management

Primary PCI	1954(87.2)	971(86.9)	983(87.5)	0.7
Any PCI	2060(91.9)	1028(91.9)	1032(91.9)	0.96
Coronary Bypass surgery	41(1.8)	23(2.1)	18(1.6)	0.5
Fibrinolysis	189(8.4)	96(8.6)	93(8.3)	0.8
Glycoprotein IIBIIIA inhibitors	833(37.2)	409(36.6)	424(37.8)	0.6
Aspirin	2201(98.2)	1096(98.0)	1105(98.4)	0.6
Clopidogrel	1445(64.5)	734(65.7)	711(63.3)	0.3
Prasugrel	1273(56.8)	619(55.4)	654(58.2)	0.2
Ticagrelor	28(1.3)	13(1.2)	15(1.3)	0.9
Any p2y12 inhibitor	2225(99.3)	1110(99.3)	1115(99.3)	1.0
ACEi or ARB	1964(87.6)	975(87.2)	989(88.1)	0.6
Beta-blockers	2077(92.7)	1037(92.8)	1040(92.6)	0.95
Diuretics	293(13.1)	135(12.1)	158(14.1)	0.2
Statins	2171(96.9)	1076(96.2)	1095(97.5)	0.11
LVEF*	53±9	53±9	53±9	0.2
Follow-up duration (days)	243±164	244±165	241±163	0.7

Data are n(%) or mean±SD. LVEF : left ventricular ejection fraction (*available in 2014 patients only) ; eGFR : estimated glomerular filtration rate (Cockroft-Gault method) ; PCI : percutaneous coronary intervention, ACEi : angiotensin converting enzyme inhibitor, ARB : angiotensin receptor antagonist

As reported in table 2, after a median follow-up of 188 days (interquartile range 52 days), the primary outcome (Figure 1) occurred in 5 (0.4 %) and 17 (1.5%) patients in the active and control groups, respectively (HR 0.30, 95% CI 0.11-0.81); p=0.01 and adjusted-HR 0.31, 95% CI 0.11-0.86; p=0.03). Two un-adjudicated deaths reported as security events 389 and 528 days after randomization in the control and the active groups of the REMINDER trial respectively were not included in the analysis. All resuscitated sudden deaths were reported within the analysis time. The key secondary outcome of death or resuscitated sudden death (Figure 2) occurred in 6 (0.5 %) and 22 (2%) patients in the active and control groups, respectively (HR 0.27, 95% CI 0.11-0.67; p= 0.002 and adjusted-HR 0.26, 95% CI 0.10-0.65; p=0.004). There were also trends toward lower rates of death from cardiovascular causes (p=0.06) and ventricular fibrillation (p=0.08 and adjusted-HR) in the active group. Other assessed efficacy endpoints did not differ between the two groups. The two trials were different with respect to the rates of the primary and secondary key outcomes as well as several other outcomes (supplementary table 3). However with the exception of a trend (p=0.06) towards a heterogeneity in rates of recurrent myocardial infarction, no significant inter-study heterogeneity was detected.

Table 2. Outcomes according to treatment arm

	n (%)		Active versus control				Inter-study heterogeneity
	Active	Control	HR (95% CI)	p	Adj-HR (95% CI)	p	p for interaction
	n=1118	n=1123					
Death	5 (0.4)	17 (1.5)	0.30 (0.11-0.81)	0.01	0.31 (0.11-0.86)	0.03	0.2
Death/resuscitated sudden death	6 (0.5)	22 (2)	0.27 (0.11-0.67)	0.002	0.26 (0.10-0.65)	0.004	0.6
Sudden cardiac death	3 (0.3)	3 (0.3)	1.15 (0.23-5.77)	0.9	0.84 (0.15-4.59)	0.8	1
Cardiovascular death	5 (0.4)	13 (1.2)	0.38 (0.14-1.07)	0.06	0.38 (0.13-1.12)	0.08	0.1
Resuscitated sudden death	1 (0.1)	5 (0.4)	0.20 (0.02-1.70)	0.1	0.21 (0.02-1.82)	0.2	1
Major ventricular arrhythmia	43 (3.8)	49 (4.4)	1.10 (0.73-1.66)	0.7	1.15 (0.76-1.74)	0.5	0.3
Ventricular fibrillation	1 (0.1)	6 (0.5)	0.18 (0.02-1.54)	0.08	0.18 (0.02-1.55)	0.1	1
Ventricular tachycardia	42 (3.8)	43 (3.8)	1.24 (0.81-1.91)	0.3	1.30 (0.84-2.00)	0.2	0.99
Heart failure	45 (4)	51 (4.5)	1.03 (0.69-1.55)	0.9	0.89 (0.59-1.35)	0.6	0.2

			HR (95% CI)	p	Adj-HR (95% CI)	p	
ALBATROSS primary outcome*	104 (9.3)	121 (10.8)	0.91 (0.70-1.19)	0.5	0.93 (0.71-1.21)	0.6	0.2
Implanted ICD	5 (0.5)	7 (0.6)	0.84 (0.27-2.65)	0.76	0.64 (0.19-2.12)	0.5	01
Indication for ICD	25 (2.2)	35 (3.1)	0.74 (0.44-1.24)	0.3	0.76 (0.45-1.28)	0.5	0.6
Recurrent myocardial infarction	12 (1.1)	11 (1)	1.17 (0.51-2.66)	0.7	1.24 (0.54-2.82)	0.6	0.1
Stroke	5 (0.4)	5 (0.4)	1.09 (0.31-3.81)	0.7	1.04 (0.30-3.63)	0.7	0.9
Death or heart failure	47 (4.2)	60 (5.3)	0.9 (0.61-1.32)	0.6	0.78 (0.53-1.16)	0.2	0.3
Safety outcomes			**OR (95% CI)**	**p**			
Acute renal failure	26 (2.3)	18 (1.6)	2.02 (0.91-4.53)	0.1	-	-	0.7
Hyperkalemia							
>5.5 mmol/L	37 (3.3)	20 (1.8)	1.89 (1.09-3.29)	0.03	-	-	0.09
>6 mmol/L	11 (1)	4 (0.4)	2.77 (0.88-8.74)	0.1	-	-	0.04

*The composite of death, resuscitated sudden death, ventricular arrhythmia, heart failure and indication for ICD. Adj-HR: HR adjusted on variable unequally distributed between treatment arms with a threshold p value <0.2 –i.e. baseline binary killip class, heart rate, systolic blood pressure, eGFR, body mass index and, history of systemic hypertension and stroke.

The results were consistent among all subgroups with respect to the primary and secondary key outcomes (supplemantry Figure). HR could not be calculated in the patient subgroups with a Killip class ≥2 in the active arms, as well as all patients with a grace score <109 because of absence of any primary or secondary key outcome. HR could also not be calculated for death in patients <65 because of absence of event in the active arm.

Hyperkalemia > 5·5 mmol/L occurred in 37 (3.3%) and 20 (1.8%) patients in the active and control groups, respectively (stratified OR 1.89; 95% CI, 1.09 to 3.29, p=0.03) while rates of Hyperkalemia > 6 mmol/L and acute renal failure were not significantly different between the two groups. A trend toward (p=0.09) and a significant inter-study heterogeneity (p=0.04) were detected with respect to the hyperkalemia >5.5 and 6 outcomes.

Discussion

Our analysis based on the pooled patient-level data of the two recent randomized trials addressing the question of early MRA blockade in low risk STEMI shows reduced rates of death compared to standard therapy. Although the subgroup analysis should be considered as only exploratory, it suggests a consistent effect of the treatment. MRA blockade appears to be associated with reduced risks of all-cause mortality and the composite of death *or* resuscitated sudden cardiac death. However the analysis failed to show a benefit with respect to other endpoints including heart failure or ventricular arrhythmia. Rates of hyperkalemia > 5.5 mmol/L were significantly higher among patients treated with MRA.

Experimental studies have shown that the early use of MRA after MI reduces left ventricular expansion and extensive fibrosis by antagonizing activation of the mineralocorticoid receptor by aldosterone and cortisol.[18–20] The clinical benefit of MRA have been extensively demonstrated in heart failure irrespective of its ischemic or non-ischemic origin. [12,13] MRA use is also associated with a reduction of mortality in patients with heart failure and reduced systolic ventricular function

after myocardial infarction.[14] Thus, the addition of MRAs to beta-blockers and angiotensin converting enzyme inhibitors has been highly recommended [21–23] in patients with heart failure and reduced left ventricular function irrespective of the etiology of heart failure.

In the Eplerenone Post Acute MI Heart Failure Efficacy and Survival Study (EPHESUS) [15] eplerenone was initiated 3 to 14 days after the onset of MI complicated by heart failure and reduced left ventricular function. The benefit observed was apparently driven by the group of patients treated earlier (i.e. 3-7 days).[24] This finding is consistent with other studies reporting high aldosterone plasma levels early after MI[25,26] and the relationship of these levels with clinical outcomes.[1–3] The REMINDER study recruited low risk STEMI patients with no heart failure at admission and very low mortality rates. Although REMINDER showed a benefit of eplerenone over placebo, the benefit was driven by the B-type natriuretic peptide levels with only non-significant trends on clinical outcomes.[15] The ALBATROSS trial recruited a broader STEMI population at higher risk as compared with REMINDER. ALBATROSS STEMI population included all-comers presenting for primary PCI, few with heart failure (6.7%), with significantly higher admission GRACE scores but also more contemporary and optimal treatment as compared to REMINDER. Although the study failed to show the benefit of MRAs on the primary outcome it highlighted a significant signal in favor of a MRA effect on mortality in STEMI. The present pooled analysis includes a relatively young and low-to-intermediate risk STEMI population (mean grace score 140) treated optimally with very high rates of revascularization and optimal medical therapy. The mortality reduction with MRAs in addition to an optimal management in such a low risk population should not be neglected. The previously mentioned pre-clinical and clinical data, the reduction of mortality in the setting of chronic heart failure or post myocardial infarction heart failure as well as the strength of the association support the plausibility of a MRA effect on mortality in the setting of STEMI. The early blunting of biological effects of MR activation after acute coronary artery occlusion[7,6,19], may lead to a favorable effect in STEMI

through the un-triggering of the neurohormonal activation and the subsequent post-MI fibrosis and remodeling both leading to higher risk of death.

A recently published study-level meta-analysis of eleven randomized trials showed also the benefit of MRAs on mortality [27]. The study included STEMI and non-STEMI patients, with heart failure as an inclusion criteria or not. However the benefit of the MRAs was driven by studies that included patients with heart failure. Compared to the latter study, our patient-level analysis pooling only STEMI patients, without heart failure as an inclusion criteria and with a more adequate univariable and adjusted analysis of censored data may be considered as more sensitive in detecting differences between groups.

Interestingly, the MRA-related reduction of mortality found in our study was not associated with a concordant significant reduction of major ventricular arrhythmia or heart failure, although both events occurred numerically less in the active treatment group.

Sustained ventricular tachycardia or fibrillation have been reported to occur in 5.2% of patients after primary PCI essentially in the 48 first hours in the relatively recent analysis of the Harmonizing Outcomes with RevasculariZatiON and Stents in Acute Myocardial Infarction (Horizons-AMI) randomized trial.[28] In the latter study, such events did not portend decreased survival. The rates of ventricular tachycardia or fibrillation were approximately 4% in the pooled population of our analysis, with a difference between rates in the ALBATROSS (7.2%) and the REMINDER trials (0.4%). Such a difference is likely to be due to the difference of the definitions of ventricular tachycardia (requiring hospitalization) in REMINDER but also due to a more selected patient population without heart failure at admission, with preserved ejection fraction and with extremely low event rates – i.e death, heart failure, indication for ICD-. The absence of effect on rates of ventricular arrhythmia in our study is not in contradiction with a possible MRA effect on mortality. Concordant with our study, in both Randomized Aldosterone Evaluation Study (RALES)[12] and EPHESUS[14] trials mortality was reduced with MRA despite the absence of effect on the rates of ventricular arrhythmia. Moreover, in

concordance with the above-mentioned study[28] most ventricular tachycardia were reported within only 48hours after randomization and such events may not impact mortality. Finally ventricular arrhythmia suppression after myocardial infarction is known not to improve survival.[29] Considering the trend towards a reduction of rates of ventricular fibrillation but not ventricular tachycardia in our analysis, it is plausible that MRAs may reduce the rates of lethal arrhythmia, or prevent the fatal issue of arrhythmia without affecting the frequency of post-STEMI arrhythmia in general.

The global rate of hospitalization for heart failure (4.4%) in a recent multicenter real-life cohort of STEMI patients undergoing primary PCI [30] was higher than in REMINDER (1.4%) but lower than in ALBATROSS (6.3%). The differences in study definitions, the low-risk populations and the short durations of follow-up could explain the absence of detectable MRA effect on heart failure in the current analysis.

Our analysis also highlights the relative safety of the MRA regimens used in the studies. Although the rates of hyperkalemia >5.5 mmol/L were higher in the MRA group than in the control group, they remained lower than what has been previously reported[14,15] and the rates of hyperkalemia >6 mmol/L and acute renal failure were not different between treatment groups. However the results on hyperkalemia should be considered with great precaution because of a significant inter-study heterogeneity.

Our analysis has limitations inherent to its design pooling data from different studies with different designs and different active treatments. However a class effect is very likely between the drugs and the stratified and adjusted analyses as well as absence of detected inter-study heterogeneity may minimize the risk of bias. Furthermore event rates remained low and event definitions were different for ventricular tachycardia and heart failure. Nevertheless with respect to the primary and the key secondary outcomes of our study -death and death or resuscitated sudden death- the analysis may be considered as robust. The adjusted analysis should be interpreted with the consideration of low event rates, especially with respect to mortality. However the similar magnitude of effects and their

confidence intervals between the un-adjusted and adjusted analyses supports the robustness of the findings. The subgroup analysis should be considered with great precaution because of the risk of multiple testing with low event rates. Whether the benefit of MRA may interact with the infarct location or the culprit vessel could not be assessed by our study because of lack of data.

Although the present report is the largest experience in STEMI outside of the scope of heart failure, it may lack power to detect differences between several studied outcomes. Larger and specifically designed studies are needed to assess such outcomes.

Conclusions

Our analysis based on pooled patient-level data from two randomized trials suggests a significant reduction of death and death or resuscitated sudden death associated with MRA regimens given early after low risk STEMI. Despite strong recommendations based on robust clinical evidence in the setting of heart failure, MRAs are still underused in routine clinical practice. Our data on both efficacy and safety of MRAs may contribute to extend the use of these life-saving and low-cost drugs. Although our study seems robust with respect to its primary outcome, the low event rates highlight the need for more studies adequately sized and specifically designed to confirm the potentially major clinical benefit associated with low-cost treatments.

Glossary

ALBATROSS : Aldosterone Lethal effects Blockade in Acute myocardial infarction Treated with or without Reperfusion to improve Outcome and Survival at Six months follow-up. Clinical trial registration: NCT01176968

REMINDER : A Double-Blind, Randomized, Placebo-Controlled Trial Evaluating The Safety And Efficacy Of Early Treatment With Eplerenone In Patients With Acute Myocardial Infarction. Clinical trial registration:NCT01176968

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Study concept and design: FB, EV, GM. Analysis and interpretation of data: FB, EV. Drafting of the

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BP.

The first and last author had full access to all the data, prepared the first draft of the manuscript. The

manuscript was approved by all co-authors, who made the decision to submit the manuscript for

publication and assumed responsibility for data accuracy.

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F Beygui has received institutional grants and/or lecture or consultancy honoraria from AstraZeneca,

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C Hamm has received speaker fees from Pfizer

G Montalescot declares his competing interests on http://action-coeur.org/declarations-dinterets/

Ethics approval

The REMINDER trial was approved by each participating centre's ethics committee; the

ALBATROSS trial was approved by the French National Institutional Ethical Review Board.

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Figure Legends

Figure 1.· Kaplan-Meier cumulative hazard curves for death

Figure 2. Kaplan-Meier cumulative hazard curves for death or resuscitated sudden death

Supplementary Figure. Subgroup analysis

     A. Death

     B. Death or Resuscitated Sudden Death

ACEi: angiotensin conversion enzyme inhibitor; ARB: angiotensin receptor ablockers, PCI: percutaneous coronary intervention, LVEF: left ventricular ejection fraction; eGFR: estimated glomerular filtration rate; BMI: body mass index