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Timing of eplerenone initiation and outcomes in patients with heart failure after acute myocardial infarction complicated by left ventricular systolic dysfunction: insights from the EPHESUS trial†

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Aims To test the hypothesis that an earlier post-acute myocardial infarction (AMI) eplerenone initiation in patients with left ventricular systolic dysfunction (LVSD) and heart failure (HF) is associated with better long-term outcomes.

Methods and results The 6632 patients of the EPHESUS study were randomized from day 3 to 14 after the index AMI (median = 7 days), of these 3319 were assigned to eplerenone. We analysed the differential effects of time-to-eplerenone initiation vs. placebo, based on the median time to initiation of treatment (<7 days—'earlier', ≥7days—'later'). Effects on outcomes were evaluated over a mean 16-month follow-up, using Cox proportional hazards regression analysis. The earlier eplerenone initiation (<7 days) reduced the risk of all-cause mortality by 31% ($P = 0.001$) when compared with the 'earlier' placebo' and also reduced the risks of cardiovascular (CV) hospitalization/CV mortality by 24% ($P < 0.0001$) and sudden cardiac death (SCD) by 34% ($P < 0.0001$). In contrast, later eplerenone initiation (≥7 days) had no significant effect on outcomes. Interactions between time-to-randomization and treatment were significant. These associations remained substantially unchanged after risk adjustment in multivariable models.

Conclusion An earlier eplerenone administration (3–7days) post-AMI improved outcomes in patients with LVSD and HF. This benefit was not observed when eplerenone was initiated later (≥7days).

Keywords Aldosterone antagonists • Myocardial infarction • Heart failure • Mortality • Ventricular remodelling

Introduction

Recent evidence suggests that high plasma aldosterone levels from the first hours to the first days after the onset of acute myocardial infarction (AMI) and increased transcardiac extraction of aldosterone early after AMI are correlated with poor outcomes and adverse cardiac remodelling.[1–3] It has also been shown that early aldosterone blockade within 24 h after an AMI may prevent the post-infarct left ventricular remodelling.[4] However, the long-term effect of early aldosterone blockade in these patients is unknown. In the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS), eplerenone, a selective aldosterone receptor antagonist, improved outcomes when initiated 3–14 days after AMI complicated by left ventricular systolic dysfunction (LVSD) and heart failure (HF) or diabetes.[5] However, whether timing of initiation of eplerenone had associated with outcomes in EPHESUS has not been examined before. In a preliminary exploratory analysis of the EPHESUS data and

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before proceeding to further analyses, we identified a significant interaction between time-to-randomization (as a continuous variable) and treatment with respect to the primary endpoint of death from any cause ($P = 0.01$). The objective of this study was to test the hypothesis that an earlier initiation of eplerenone in patients with AMI complicated by HF and LVSD is associated with better long-term outcomes.

Methods

Patients and study design

This study is a *post hoc* analysis of EPHESUS, a multicentre, randomized double-blind clinical trial of eplerenone after AMI. The design and primary results of EPHESUS have been published.[5,6] Briefly, EPHESUS enrolled 6632 patients with AMI complicated by clinical HF and LVSD [left ventricular ejection fraction (LVEF) $\leq$40%]. Patients were randomized during a 12-day period (days 3–14) after AMI to eplerenone (25 mg/day, titrated to 50 mg/day after 4 weeks) or matching placebo. Patients were receiving background therapy with angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), beta-blockers, diuretics, and coronary reperfusion therapy as indicated.

For the purpose of this analysis, treatment status was categorized into four groups: (i) placebo 'earlier' ($<$7days); (ii) eplerenone 'earlier' ($<$7days), (iii) placebo 'later' ($\geq$7days), and (iv) eplerenone 'later' ($\geq$7days), based on the median time-to-randomization after AMI in EPHESUS which was 7 days. Of the 6632 enrolled patients, 1388 received placebo and 1369 received eplerenone $<$7 days after the AMI (from days 3 to 6) and 1925 received placebo and 1950 received eplerenone $\geq$7 days after the AMI (from days 7 to 14).

Co-primary endpoints of EPHESUS were all-cause mortality and the combined endpoint of cardiovascular (CV) hospitalization or CV death. Cause-specific CV mortalities including sudden cardiac death (SCD) were evaluated as secondary endpoints. For the present analysis, the co-primary endpoints as well as the secondary endpoint of SCD were assessed during a mean follow-up of 16 months. All endpoints were adjudicated by a blinded clinical events committee. All patients randomized in EPHESUS were included in this analysis.

Statistical analysis

Data are reported as mean (SD) for continuous variables and percentages for categorical variables. Continuous variables were analysed by the Kruskal–Wallis test and categorical variables by the χ^2 test.

We used Cox proportional hazards models to study the relationship between the time of eplerenone initiation and all-cause mortality, CV hospitalization/CV death and SCD, using earlier and later eplerenone and placebo groups as dummy variables. By taking consecutively, placebo 'earlier', placebo 'later', and eplerenone 'later' groups as the reference category we obtained all the clinically relevant comparisons between the different treatment categories (i.e. placebo 'earlier' vs. eplerenone 'earlier', placebo 'later' vs. eplerenone 'later' and eplerenone 'later' vs. eplerenone 'earlier'). We then repeated our analysis using multivariable models to determine the adjusted hazard ratios (HR) for each treatment category including clinically relevant prognostic variables (age, gender, body mass index, systolic blood pressure, heart rate, LVEF, Killip class III–IV, atrial fibrillation, serum sodium, serum potassium, creatinine clearance, prior AMI, prior hospitalizations for HF, diabetes, history of hypertension, smoking, history of angina, ACE-inhibitor or ARB, beta-blockers, diuretics, aspirin, statins, digitalis, potassium supplements, reperfusion/revascularization). We determined that the assumption of proportional hazards was met in all Cox models. Time-to-event distributions were summarized using Kaplan–Meier survival curves. We report unadjusted and adjusted HR and corresponding 95% confidence intervals (CI) for the treatment variable. We do not present full models, because we did not aim to develop a risk stratification tool but rather to determine the extent to which the timing of treatment initiation altered outcomes and generate a hypothesis. The existence of an interaction between time-to-randomization and treatment was evaluated for each endpoint with use of a Cox model incorporating terms for treatment, time-to-randomization and interaction between treatment and time-to-randomization. For these analyses, time-to-randomization was initially considered as a continuous variable (in our preliminary explorative analysis) and then as a binary variable dichotomized at the median value. We then performed a subgroup sensitivity analysis in separate cohorts of propensity score-matched 'earlier' and 'later' patients. Among each group, we estimated propensity score for eplerenone use based on 65 baseline characteristics, and then assembled 1184 pairs of propensity-matched earlier eplerenone and placebo patients and 1739 pairs of propensity-matched later eplerenone and placebo patients. Matched Cox regression analyses were used to estimate the effect of eplerenone vs. placebo, separately within matched earlier and later patients.

Statistical tests were two-tailed and a *P*-value less than 0.05 was taken as the level of significance.

Results

Patient characteristics

Baseline characteristics of patients by treatment and time-to-randomization are displayed in *Table 1*. Patients had a mean age of 64 years, about three-quarters were men, a third had diabetes, and a quarter had a prior AMI. Most patients were receiving background therapy with ACE-inhibitor, ARB, and beta-blockers. In general, patients who were randomized 'later' were more likely to have worse renal function and were less likely to receive revascularization, ACE-inhibitors, beta-blockers, aspirin, and statins.

Event rates

Crude rates of death and hospitalization for placebo, eplerenone 'earlier' and eplerenone 'later' groups are displayed in *Table 2*. Patients assigned earlier to eplerenone had significantly lower event rates when compared with 'earlier' placebo patients for all-cause mortality (11.5 vs. 16.1%), CV hospitalization/CV mortality (24 vs. 30.3%), and SCD (3.7 vs. 6.9%). No significant differences were found between 'later' eplerenone patients and their placebo comparators regarding the crude rates of outcomes.

Timing of treatment initiation and risk

Unadjusted and adjusted HR according to the time of eplerenone initiation (vs. placebo) are reported in *Table 3*. Earlier eplerenone administration ($<$7 days) when compared with 'earlier' placebo was associated with significant unadjusted reduction of risk with respect to all endpoints (*Figure 1A–C*). Even after adjustment for other risk factors, earlier eplerenone initiation substantially reduced the risk of all-cause mortality (HR: 0.72; 95% CI: 0.58–0.89; $P = 0.002$), CV hospitalization/CV mortality (HR: 0.78; 95% CI: 0.67–0.90; $P = 0.001$), and SCD (HR: 0.54; 95%

Table 1 Baseline characteristics by time-to-randomization and treatment group

Characteristic [*n* (%) or mean ± SD]	Placebo 'earlier' (*n* = 1388)	Placebo 'later' (*n* = 1925)	Eplerenone 'earlier' (*n* = 1369)	Eplerenone 'later' (*n* = 1950)	*P*-value[a]
Age (years)	63.9 ± 11.9	64.3 ± 11.5	63.1 ± 11.5	64.2 ± 11.1	0.01
Male	73	68	75	70	<0.0001
Body mass index (kg/m^2)	27.3 ± 4.4	27.1 ± 4.4	27.5 ± 4.7	27.5 ± 4.4	NS
Systolic blood pressure (mmHg)	119 ± 16	118 ± 16	120 ± 17	119 ± 16	NS
Diastolic blood pressure (mmHg)	71 ± 10	72 ± 10	72 ± 11	72 ± 11	NS
Heart rate (b.p.m.)	75 ± 12	74 ± 11	76 ± 12	74 ± 12	<0.0001
LVEF (%)	33 ± 6	33 ± 6	33 ± 6	33 ± 6	NS
Heart failure symptoms (Killip >1)	84	85	85	85	NS
Killip class III–IV	17	22	18	21	0.05
Atrial fibrillation at entry	9	12	9	11	0.05
Serum potassium (mmol/L)	4.17 ± 0.42	4.32 ± 0.45	4.17 ± 0.42	4.35 ± 0.44	<0.0001
Serum sodium (mmol/L)	139 ± 4	139 ± 4	139 ± 4	139 ± 5	0.05
Serum creatinine (mmol/L)	98 ± 28	100 ± 30	99 ± 28	100 ± 29	0.02
Creatinine clearance (mL/min)[b]	80 ± 34	75 ± 31	81 ± 35	76 ± 31	<0.0001
Medical history					
Prior AMI	29	26	27	28	NS
Prior heart failure hospitalizations	8	8	7	7	NS
Diabetes mellitus	32	32	32	32	NS
Hypertension	60	62	58	61	NS
Smoking	61	60	65	59	0.01
Angina	39	42	39	44	0.02
Baseline treatment[c]					
ACE-I or ARB	90	86	90	84	<0.0001
Beta-blocker	79	72	80	72	<0.0001
Diuretics	61	60	60	59	NS
Potassium supplements	20	15	19	14	<0.0001
Digitalis	14	16	13	16	0.025
Aspirin	92	87	90	86	<0.0001
Statins	52	43	53	42	<0.0001
Reperfusion/revascularization	51	41	51	41	<0.0001

AMI, acute myocardial infarction; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; LVEF, left ventricular ejection fraction.
[a]*P*-values denote differences between groups.
[b]Creatinine clearance was calculated according to Cockroft–Gault formula.
[c]Data for treatment taken at randomization or up to 14 days after the index acute myocardial infarction (AMI).

Table 2 Crude rates of death and hospitalization according to treatment assignment

Endpoint	Placebo group <7 days ('earlier') (*n* = 1388)	Eplerenone group <7 days ('earlier') (*n* = 1369)	*P*-value*	Placebo group ≥7 days ('later') (*n* = 1925)	Eplerenone group ≥7 days ('later') (*n* = 1950)	*P*-value[a]
All-cause mortality, *n* (%)	224 (16.1%)	157 (11.5%)	<0.0001	330 (17.1%)	321 (16.5%)	NS
Death from CV causes or hospitalization for CV events, *n* (%)	420 (30.3%)	329 (24%)	<0.0001	573 (29.8%)	556 (28.5%)	NS
Sudden cardiac death, *n* (%)	96 (6.9%)	51 (3.7%)	<0.0001	105 (5.5%)	111 (5.7%)	NS

[a]*P*-values indicate differences between each eplerenone group vs. the corresponding placebo group.

CI: 0.38–0.77; $P = 0.001$). In contrast, later eplerenone initiation (≥7 days) was not associated with unadjusted or adjusted reduction of risk for any of the endpoints. In a head-to-head comparison between the two eplerenone groups, 'earlier' eplerenone administration was associated with significantly lower risk (unadjusted and adjusted) with respect to all endpoints (*Table 3*).

Table 3 Risk of death and hospitalization according to time of eplerenone initiation

Treatment[a]	All-cause mortality	*P*-value	Death from CV causes or hospitalization for CV events	*P*-value	Sudden cardiac death	*P*-value
Unadjusted hazard ratio (95% CI)						
Placebo 'earlier' vs. eplerenone 'earlier'	0.69 (0.57–0.85)	0.001	0.76 (0.66–0.88)	<0.0001	0.66 (0.55–0.80)	<0.0001
Placebo 'later' vs. eplerenone 'later'	0.94 (0.80–1.10)	0.45	0.94 (0.84–1.05)	0.30	1.02 (0.78–1.33)	0.85
Eplerenone 'later' vs. eplerenone 'earlier'	0.66 (0.55–0.80)	<0.0001	0.81 (0.70–0.92)	0.002	0.62 (0.44–0.87)	0.006
Adjusted hazard ratio (95% CI)						
Placebo 'earlier' vs. eplerenone 'earlier'	0.72 (0.58–0.89)	0.002	0.78 (0.67–0.90)	0.001	0.54 (0.38–0.77)	0.001
Placebo 'later' vs. eplerenone 'later'	0.93 (0.79–1.09)	0.37	0.94 (0.83–1.06)	0.32	1.01 (0.77–1.33)	0.91
Eplerenone 'later' vs. eplerenone 'earlier'	0.74 (0.60–0.90)	0.003	0.82 (0.71–0.94)	0.006	0.71 (0.51–0.99)	0.04
Interaction between Time-to-randomization and treatment		0.02		0.03		0.003

CV, cardiovascular; CI, confidence interval.
[a]The first group in each comparison indicates the reference group (hazard ratio = 1).

Finally, no significant difference was found in a direct comparison between 'earlier' and 'later' placebo groups (data not shown in the tables).

Interaction between time-to-randomization and treatment

In our preliminary explorative analysis, interaction between time-to-randomization (as continuous variable) and treatment was significant ($P = 0.01$) with respect to the primary endpoint of mortality due to any cause. Subsequent interaction tests between time-to-randomization (as binary variable) and treatment were significant for the three endpoints of this analysis and are summarized in *Table 3*.

Propensity-matched analysis

In the earlier randomized subgroup (<7 days), among the 1184 pairs of propensity-matched patients, death from any cause occurred in 11.1 and 15.4% of eplerenone and placebo patients, respectively (matched HR: 0.65; 95% CI: 0.51–0.83; $P < 0.0001$). However, in the later randomized subgroup (≥7 days), among the 1739 pairs of matched patients, death from any cause occurred in 16.3 and 16.7% of eplerenone and placebo patients, respectively (matched HR: 1.04; 95% CI: 0.87–1.25; $P = 0.65$).

Safety of earlier eplerenone therapy

Earlier eplerenone initiation was not associated with an excess of serious adverse events. The incidence of hypotension (systolic blood pressure <90 mmHg) in the eplerenone 'earlier' group was low (2.6%), and there was no significant difference in the incidence of hypotension between the eplerenone 'earlier', eplerenone 'later', and placebo groups. The incidence of serious hyperkalaemia (serum potassium increase above 6 mmol/L) was low (~1% in all groups) and did not differ between groups. Finally, the incidence of serum creatinine increase above 133 and 220 μmol/L was 3.1 and 0.6%, respectively, for the eplerenone 'earlier' patients and did not differ significantly between the treatment groups. Study adverse events have been reported at any visit from baseline to week 4.

Discussion

This *post hoc* analysis of the EPHESUS trial suggests that earlier eplerenone initiation, <7 days post-AMI complicated by LVSD and HF, was safe and associated with a significant reduction in the primary endpoint of all-cause mortality and the co-primary endpoint of CV hospitalization or CV mortality. Further, the benefit was extended to a profound reduction in SCD, an important cause of mortality in these patients. In contrast, these benefits were not observed when eplerenone therapy was initiated later (7 days or more) in the post-AMI period. Patients in this study were already receiving 'optimal' therapy including ACE-inhibitors or ARB, beta-blockers, aspirin, and coronary reperfusion. The subgroup propensity-matched analysis confirmed the results of our global analysis.

Aldosterone plasma levels and transcardiac extraction of aldosterone may be increased from the first hours to the first days after an AMI and are associated with adverse cardiac remodelling and poor prognosis.[1–3] Furthermore, early aldosterone blockade within 24 h post-AMI may prevent post-infarct left ventricular remodelling and fibrosis.[4] These findings provide a plausible explanation for the improved outcomes of the earlier eplerenone administration in our study. Data from animal studies suggest

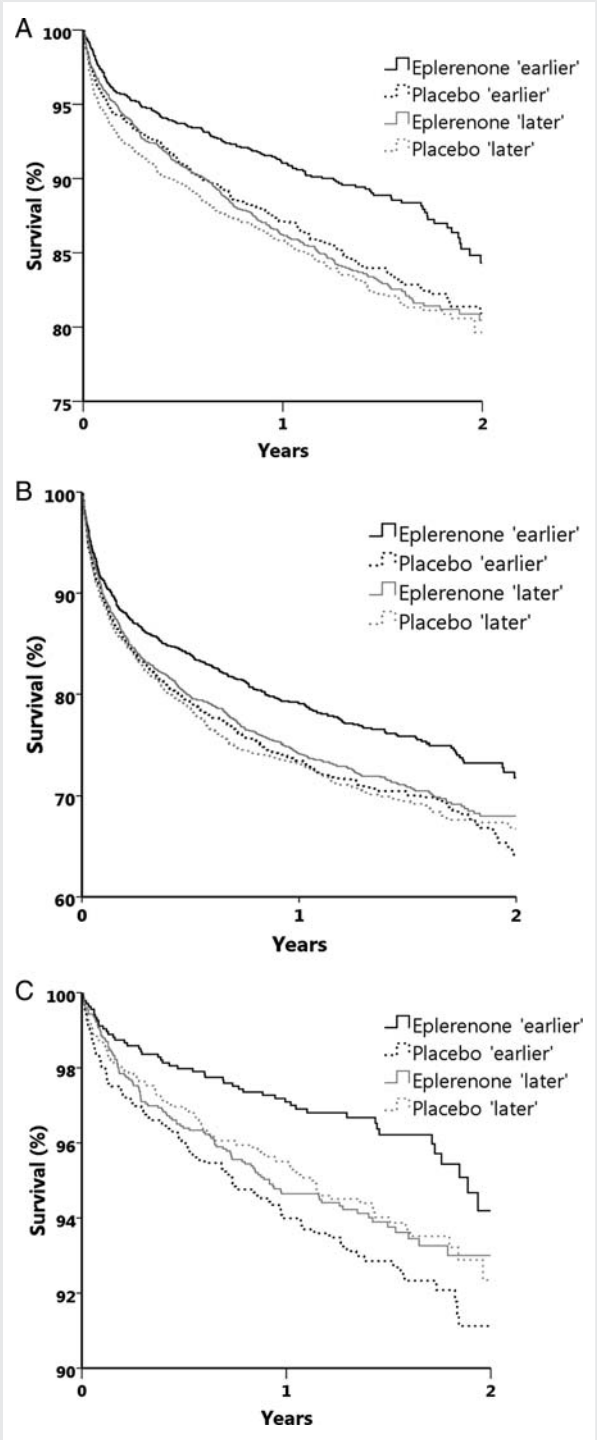

Figure 1 Kaplan–Meier estimates of the rate of all-cause mortality (*A*), the rate of death from cardiovascular causes or cardiovascular hospitalization for cardiovascular events (*B*), and the rate of sudden cardiac death (*C*).

that aldosterone antagonism may prevent early electrical remodelling that precedes cellular hypertrophy, arrhythmias, and sudden death post-AMI. The same data also showed that these early changes can be prevented by blockade of mineralocorticoid receptors.[7] Thus, the protective effect of eplerenone against SCD may be due to its effects on acute electrical remodelling rather than to chronic ventricular remodelling. In addition, it has been shown that eplerenone may prevent restenosis in laboratory animals when administered early at the time of the angioplasty,[8] and that aldosterone-blocking agents also have anti-thrombotic properties.[9–11] Finally, it has been recently reported that aldosterone blockade when administered early post-experimental AMI, results in enhanced infarct neovascularization, improved infarct healing and reduced ventricular dilation and dysfunction.[12]

Clinical implications

Patients with AMI who develop systolic HF are a high-risk population with increased risk of in-hospital and post-discharge mortality.[13–16] Early eplerenone initiation was associated with an additional mortality benefit above that provided by other established therapies for AMI. Other established therapies for AMI such as aspirin, ACE-inhibitors, coronary reperfusion, beta-blockers, and statins also seem to be most effective when initiated early after AMI.[17–21] Therefore, our data suggest that aldosterone blockade should not be delayed after AMI and that eplerenone may be initiated as early as 3 days after an AMI along with these other drugs. This is important, as risk reduction with eplerenone seemed to occur as early as 10 days after randomization[22] and also because patients receiving these drugs are more likely to benefit from eplerenone.[5] It is possible that initiation of eplerenone during the first 2 days after AMI might result in further mortality reduction and possibly before 10 days after initiation of therapy. Whether eplerenone can be initiated sooner than 3 days is currently unknown and will need to be prospectively determined in future randomized clinical trials. The risk of SCD is the highest in the first 30 days after myocardial infarction.[23] In contrast to eplerenone's effects on reducing SCD and all-cause death when administered during the early post-AMI period, implantable cardioverter defibrillators have not been shown to reduce all-cause mortality when placed early post-MI. Although with implantable cardioverter defibrillators a significant decrease in arrhythmic death was observed, the rate of non-arrhythmic death was significantly increased.[24]

Finally, an early initiation of eplerenone in the hospital setting will also ensure that patients are discharged on this drug. This is important as the mean length of stay for AMI is decreasing[25] and patients often do not receive new medications after hospital discharge.[26,27]

In this analysis, the lack of a statistically significant improvement in outcomes in the 'later' eplerenone group is seemingly contradictory with the results of the previously published RALES trial[28] which showed an important reduction in mortality in patients with chronic severe HF who received anti-aldosterone therapy. However, whereas the RALES trial enrolled patients with long-standing HF prior to initiation of the anti-aldosterone treatment, our EPHESUS 'later' group represents a late stage of a rapidly progressive acute event (AMI). Consequently, the major differences in the enrolled population in these two trials may explain the differential effect of the anti-aldosterone treatment. Another plausible explanation is that the mortality benefit in our analysis is largely driven by a striking reduction in SCD. This observation suggests that the protective effect of the anti-aldosterone therapy early in

the setting of an AMI may be predominantly due to its actions on early electrical remodelling rather than to its actions on chronic ventricular remodelling as may be the case in chronic HF.

Safety of early eplerenone therapy

Eplerenone was well tolerated in the early as well as the late subgroup. There were no major haemodynamic or biochemical adverse effects. Although aldosterone blockade early after AMI may potentially affect collagen formation and thus interfere with the healing of the infarct zone and increase the risk for aneurysm formation and/or cardiac rupture, Delyani *et al.*[29] have shown in an experimental model that aldosterone receptor antagonism does not retard infarct healing. In our analysis, the eplerenone-associated significant reduction in sudden and death from any cause suggests that the overall effect of eplerenone was beneficial.

Limitations

This study is a *post hoc*, hypothesis-generating analysis and the results should be interpreted with caution; patients were not randomized to 'earlier' or 'later' eplerenone treatment and the broad time window for entry into EPHESUS (3–14 days from the index AMI) may have resulted in a heterogeneous enrolled population; patients in these two groups represented the two spectrums of an acutely evolving process where insults or interventions in the early stage may affect prognosis later in the course. Despite adjustment for the confounding factors, causality cannot be definitively established based on these data.

Patients were randomized in EPHESUS between 3 and 14 days after AMI. Thus, we cannot evaluate whether these findings also apply to earlier timepoints (i.e. prior to 3 days).

Notwithstanding the lack of a statistically significant improvement in outcomes in the 'later' eplerenone group, a benefit of a later initiation of eplerenone cannot be completely excluded on the basis of this analysis alone. It remains possible that clinical benefits from later eplerenone initiation, though present, are inconsequential in magnitude and do not favourably impact on the overall prognosis of this patient population. However, the present data suggest that the effect of eplerenone is most robust when initiated early in the post-MI period.

Conclusion

Early eplerenone initiation (<7 days) in post-AMI patients with systolic HF and receiving baseline optimal therapy was safe and was associated with a statistically significant lower rate of all-cause mortality, CV hospitalization or CV death, and SCD when compared with placebo. In contrast, no significant differences in outcomes were observed for later initiation. These findings provide important insight with regard to the optimal timing for eplerenone initiation to ensure maximum clinical benefits are achieved. Prospective randomized clinical trials are needed to determine whether eplerenone initiated even earlier in the AMI setting (<3 days) would be effective at further improving patient outcomes.

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