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Eplerenone improves prognosis in postmyocardial infarction diabetic patients with heart failure: results from EPHESUS

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Background: The Epleronone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) trial demonstrated that selective aldosterone blockade with eplerenone significantly reduced total mortality by 15%, combined cardiovascular (CV) mortality/CV hospitalization by 13%, CV mortality by 17% and sudden cardiac death by 21%, vs. placebo when added to standard care in patients with left ventricular systolic dysfunction (LVSD) and signs of congestive heart failure (CHF) following acute myocardial infarction (AMI). We retrospectively evaluated the effect of eplerenone vs. placebo in a subset of 1483 diabetic patients with LVSD and signs of CHF following AMI.

Methods: Diabetic status was determined from medical histories at screening. Analyses were based on time to first occurrence of an event. Results were based on a Cox's proportional hazards regression model stratified by region with treatment, subgroup and treatment-by-subgroup interaction as factors. The 95% confidence intervals for the risk ratios were based on the Wald's test.

Results: Treatment with eplerenone in diabetic patients with CHF following AMI reduced the risk of the primary endpoint, a composite of CV mortality or CV hospitalization, by 17% ($p = 0.031$). The absolute risk reduction of the primary endpoint was greater in the diabetic cohort (5.1%) than in the non-diabetic cohort (3%). Hyperkalaemia occurred more often with eplerenone than with placebo (5.6 vs. 3%, $p = 0.015$). Among the diabetic cohorts, the prespecified endpoint of 'any CV disorder' occurred in 28% of the eplerenone group and 35% of the placebo group ($p = 0.007$).

Conclusion: Eplerenone treatment may reduce adverse CV events in diabetic patients with LVSD and signs of CHF following AMI.

Keywords: congestive heart failure, diabetes, eplerenone, myocardial infarction
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Introduction

Approximately 2 to 3 million individuals with diabetes in USA have a history of cardiovascular (CV) events [1] including heart failure. Diabetes mellitus is also a common co-morbidity in patients with congestive heart failure (CHF). Patients with diabetes and CHF tend to have a worse prognosis than those patients with CHF alone and are at a greater risk of mortality and morbidity following a CV event [2–4]. Pharmacologic agents such as angiotensin-converting enzyme (ACE) inhibitors and beta-blockers have been shown to reduce morbidity and mortality in patients with diabetes and prior CV events including CHF [2,5–12]. The results of EPHESUS demonstrated that eplerenone, a selective aldosterone blocker, significantly reduced mortality and morbidity

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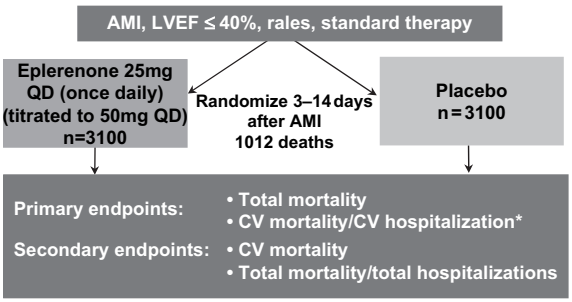

Fig. 1 Epleronone Post-Acute Myocardial Infarction Heart Failure Efficacy Study (EPHESUS) study design [13]. Asterisk indicates cardiovascular (CV) hospitalization for heart failure (HF), acute myocardial infarction (AMI), stroke or ventricular arrhythmia. LVEF, left ventricular ejection fraction.

when used with standard therapy that included ACE inhibitors and beta-blockers in patients with a left ventricular ejection fraction (LVEF) <40% and signs of CHF following acute myocardial infarction (AMI) [13]. Therefore, given the adverse influence of diabetes on CV prognosis, a *post hoc* analysis was conducted in the diabetic subgroup of the EPHESUS study to determine if eplerenone provides a survival benefit in this population.

Methods

Study Design and Study Population

The current study represents a *post hoc* analysis of the EPHESUS trial (figure 1), focusing on the subgroup of patients with diabetes. Diabetes status was determined from medical histories at screening. All patients were required to have had suffered an AMI within 3–14 days prior to enrolment. Additional inclusion criteria included an LVEF < 40% or signs of CHF including a third heart sound or pulmonary rales. Patients were started on eplerenone 25 mg daily initially and, after 1 month, the dose was titrated up to 50 mg daily. Mean chronic eplerenone dose during the study was 43 mg/day.

Definition of Study Endpoints

We utilized the same endpoints used in the original analysis: the two primary endpoints were time to death from any cause and time to death from CV causes or first hospitalization for a CV event, including heart failure, recurrent AMI, stroke, or ventricular dysrhythmias. The major secondary endpoints were death from CV causes and death from any cause or any hospitalization. All endpoints were adjudicated by a blinded critical-events committee.

Statistical Analysis

This subgroup analysis of diabetic patients for the two primary endpoints was performed with a Cox's model stratified according to region, with terms for treatment, subgroup and interaction between treatment and subgroup. Measured variables were treated as binary variables, dichotomized at the median value, and also considered as continuous variables. The patients were followed for a mean of 16 months, beginning with their index hospitalization for AMI.

Results

Study Patients

Of 6642 patients enrolled in the EHPESUS trial, 1483 (22.3%) were found to be diabetic. Of these, 749 were in the eplerenone group and 734 in the placebo group. There

Table 1 Baseline characteristics in EPHESUS patients with diabetes and documented heart failure at baseline

Characteristic	EPL (eplerenone) (N = 749)	PBO (placebo) (N = 734)	p value
Age (years)	66 ± 10	66 ± 10	0.961
Males (%)	63	64	0.754
Race (%)			
White	90	90	0.929
Black	2	2	
Asian	2	1	
Hispanic	5	5	
Others	2	2	
Systolic blood pressure (mmHg)	122 ± 17	121 ± 18	0.178
LVEF (%)	32 ± 6	32 ± 6	0.667
Serum creatinine (mg/dl)	1.2 ± 0.4	1.2 ± 0.4	0.647
Serum potassium (mEq/l)	4.3 ± 0.5	4.3 ± 0.5	0.492
Days from MI to randomization	7.2 ± 2.9	7.2 ± 3.0	0.860
Reperfusion (%)	38	37	0.701
Medical history (%)			
History of hypertension (%)	71	69	0.335
History of HF (%)	21	23	0.367
History of acute MI (%)	13	14	0.397
Medications (%)			
ACE inhibitors	87	86	0.774
ARB	4	3	0.206
Beta-blockers	72	73	0.426
CCB	18	18	0.864
Diuretics	71	73	0.398
Digoxin	19	21	0.374
K^+ supplements	15	20	0.018
Aspirin	88	90	0.323
Statins	48	47	0.807

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; LVEF, left ventricular ejection fraction; MI, myocardial infarction.

were no significant differences between the two groups at baseline (table 1). Medical therapy was also not different at baseline between the two groups: the majority of patients were receiving standard therapies for AMI complicated by left ventricular (LV) dysfunction and heart failure, including ACE inhibitors (in 87% of patients), angiotensin receptor blockers (ARBs) (in 4% of patients), beta-blockers (in 72%), aspirin (in 88%) and diuretics (in 71%).

Endpoints

The endpoint of death from CV causes or hospitalization for CV events was reached by 268 (35.8%) in the eplerenone group and 300 (40.9%) in the placebo group (relative risk 0.83, $p = 0.031$). A total of 153 patients in the eplerenone group (20.4%) and 175 (23.8%) patients in the placebo group died (relative risk 0.85, $p = 0.131$). A total of 131 deaths in the eplerenone group (17.5%) and 152 deaths in the placebo group (20.7%) were attributed to CV causes (relative risk 0.83, $p = 0.128$). The rate of death from sudden cardiac death was reduced by 8.1% in the eplerenone group (relative risk 0.89, $p = 0.533$) (table 2) (figure 2). Therefore, only the endpoint of death from CV causes or hospitalization for CV events reached statistical significance. Of note, there was an absolute risk reduction of 5.1% in the prespecified combined endpoint of CV mortality and hospitalization for CV causes in this diabetic subgroup, which favourably compares with the 3.5% absolute reduction in events noted in the cohort of patients without diabetes at baseline.

Hyperkalaemia (defined as serum potassium of $\geq$5.5 mmol/l) developed in 5.6% of patients in the eplerenone group and in 3% of those in the placebo group ($p = 0.015$). There were no deaths attributable to hyperkalaemia in the eplerenone group. The placebo group compared with the eplerenone group had a higher incidence of hypokalaemia (1.9 vs. 0.4%, $p = 0.007$), hyperuricaemia (4.2 vs. 2.1%, $p = 0.026$) and CV adverse events (34.7 vs. 28.2%, $p = 0.007$).

There were no other significant differences between the treatment groups in the number of patients with changes in laboratory variables that met prespecified criteria for abnormally low or high values. Adverse events are described in table 3. Importantly, there was no evidence of hypotension when eplerenone was added to standard therapy including ACE inhibitors, ARBs and beta-blockers.

Table 2 Summary of endpoints

Variable	EPL (eplerenone) (N = 749)	PBO (placebo) (N = 734)	Relative risk (95% CI or ratio)	p value
Death from any cause	153	175	0.85 (0.68–1.05)	0.131
Death from CV causes or any hospitalization	268	300	0.83 (0.71–0.98)	0.031
Death from CV causes	131	152	0.83 (0.60–1.05)	0.128
Sudden cardiac death	51	54	0.89 (0.60–1.30)	0.533

CI, confidence interval; CV, cardiovascular.

Discussion

The use of eplerenone (mean dose 43 mg/day) in diabetic patients 3–14 days (mean 7) after AMI (complicated by LV dysfunction and heart failure) resulted in reduction in the rate of death from CV causes or hospitalization for CV events. Our study, which is a *post hoc* analysis from the EPHESUS trial published earlier, demonstrated a trend for a reduction in overall mortality, CV mortality and sudden cardiac death in the eplerenone group. However, these did not reach statistical significance. These findings demonstrate that the beneficial effects of eplerenone found in the original EPHESUS study also apply to the subgroup of patients with diabetes, who are known to have more co-morbidities and a higher rate of CV events [2–4]. Interestingly, eplerenone achieved a higher rate of absolute risk reduction in this subgroup as compared with the cohort of patients without diabetes in the combined endpoint of death from CV causes or hospitalization for CV events (5.1 vs. 3.5%).

Angiotensin II and aldosterone, in addition to stimulating fibrosis and hypertrophy, predispose to oxidative stress, inflammation, thrombosis and sudden cardiac death [14–16]. Because of this central role, it is difficult to normalize the prognosis of postmyocardial infarction (post-MI) patients without addressing the overactivity of the renin angiotensin aldosterone system (RAAS). In the milieu of insulin resistance, which is one of the core underlying pathophysiologic defects in patients with type 2 diabetes, the CV system is sensitized to the adverse trophic effects of the RAAS [17,18]. This is manifested by the frequent occurrence of diffuse arterial disease and LV hypertrophy in diabetic patients, even when the lipid and blood pressure levels are relatively normal. Indeed, diabetic patients have been shown to benefit greatly from blockade of the RAAS, with reduction of CV mortality up to 40% in major randomized, controlled trials of ACE inhibitors and ARBs [6,12]. However, ACE inhibitors and ARBs do not reliably suppress aldosterone production over the long term [19]. This 'aldosterone escape' occurs in up to 40% of patients, providing the rationale for aldosterone blockade as an additive therapy beyond the standard ACE inhibition (or ARB use) and beta-blockade to improve survival in these post-MI patients with CHF and/or LV dysfunction. In patients with hypertension, eplerenone

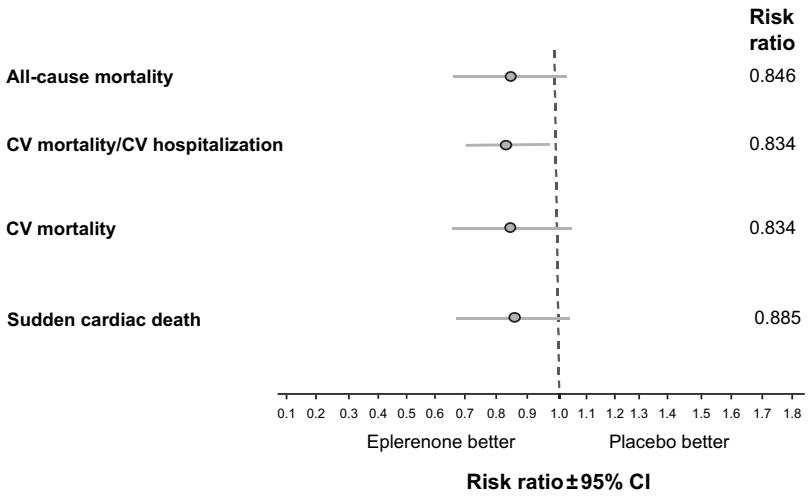

Fig. 2 Relative risk of endpoints in patients with diabetes and documented congestive heart failure at baseline. CI, confidence interval; CV = cardiovascular.

Table 3 Comparison of adverse events in patients with diabetes and documented heart failure at baseline

Body system adverse event	EPL (eplerenone) (N = 749), no. (%)	PBO (placebo) (N = 734), no. (%)	p value
Any event	625 (83.4)	613 (83.5)	NS
Cardiovascular disorders	211 (28.2)	255 (34.7)	0.007
Nervous system disorders			
Central and peripheral	117 (15.6)	105 (14.3)	NS
Autonomic	65 (8.7)	63 (8.6)	NS
Disorders in women	5 (6.0)	3 (4.7)	NS
Breast pain	1 (1.6)	0 (0.0)	
Menstrual disorder	1 (1.2)	0 (0.0)	
Disorders in men	12 (7.1)	13 (8.2)	NS
Gynaecomastia	1 (0.6)	2 (1.3)	
Impotence	4 (2.4)	4 (2.5)	
Endocrine disorders	5 (0.7)	6 (0.8)	NS
Gastrointestinal disorders	161 (21.5)	129 (17.6)	0.058
Metabolic/nutritional disorders	151 (20.2)	187 (25.5)	0.016
Hyperkalaemia	42 (5.6)	22 (3.0)	0.015
Hyperuricaemia	16 (2.1)	31 (4.2)	0.026
Hypoglycaemia	11 (1.5)	11 (2.6)	0.142
Hypokalaemia	3 (0.4)	14 (1.9)	0.00
Musculoskeletal disorders	38 (5.1)	45 (6.1)	NS
Psychiatric disorders	46 (6.1)	57 (7.8)	NS
Respiratory disorders	165 (22.0)	186 (25.3)	0.143
Coughing	37 (4.9)	41 (5.6)	NS
Dyspnoea	54 (7.2)	75 (10.2)	0.043
Pneumonia	26 (3.5)	32 (4.4)	NS
Disorders of skin or appendages	46 (6.1)	61 (8.3)	0.109
Urinary tract disorders	124 (16.6)	128 (17.4)	NS

NS, not significant; $p > 0.2$.

has been shown to be additive to ACE inhibitor therapy with respect to regressing proteinuria and LV hypertrophy and normalizing systolic blood pressure [20]. These are commonly encountered co-morbidities in diabetic patients that worsen prognosis. Thus, eplerenone may be of particular benefit for individuals with diabetes.

The most serious adverse effect of the aldosterone receptor blockers, (spironolactone and eplerenone) is the development of hyperkalaemia, especially in patients who are also on ACE inhibitors and/or ARBs or have chronic kidney disease [21]. The Randomized Aldosterone Evaluation Study (RALES) [22] found that spironolactone significantly improved outcomes in patients with severe CHF. Another study [23] examined the trends in spironolactone prescriptions and the rates of hospitalization for hyperkalaemia in ambulatory patients before and after the publication of RALES trial. This study found that the publication of RALES was associated with abrupt increases in the rate of prescriptions for spironolactone and subsequently in hyperkalaemia-associated morbidity and mortality. This is especially relevant for the diabetic population, as diabetes is an independent risk factor for hyperkalaemia [24]. This was evidenced by the higher incidence of hyperkalaemia in the EPHESUS diabetic vs. non-diabetic subgroups (5.6 vs. 3%). The combination of eplerenone and ACE inhibitors or ARBs increases the risk of hyperkalaemia, as does pre-existing renal dysfunction.

An important limitation of our study is the fact that it is a *post hoc* analysis, and it was not specifically powered to assess the effects of eplerenone on outcomes in the

EPHESUS diabetic subgroup. However, as mentioned previously, the combined endpoint of death from CV causes or hospitalization for CV events was lower in those treated with eplerenone and did reach statistical significance.

Conclusion

The study suggests that diabetic patients with LV dysfunction and/or CHF following acute MI benefit from chronic eplerenone therapy. The relative risk reduction is similar to that noted in the non-diabetic cohort of the EPHESUS trial, although the absolute risk reduction with eplerenone is superior (owing to the higher CV event rates in diabetic patients). However, close monitoring for hyperkalaemia is necessary when using eplerenone in diabetic patients who are also on ACE inhibitors or ARBs.

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