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Evaluation of eplerenone in the subgroup of EPHESUS patients with baseline left ventricular ejection fraction ≤30%

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Abstract

Aims: Because of the prognostic importance of LV dysfunction following an AMI and the increasing use of electrical and/or mechanical interventions in patients with LV systolic dysfunction, this retrospective analysis of EPHESUS patients with LVEF ≤30% at baseline was conducted to determine the value of eplerenone in this setting.
Methods and results: In EPHESUS, 6632 patients with LVEF ≤40% and clinical heart failure (HF) post-AMI who were receiving standard therapy were randomized to eplerenone 25 mg/day titrated to 50 mg/day or placebo for a mean follow-up of 16 months. Treatment with eplerenone in the subgroup of patients with LVEF ≤30% (N=2106) resulted in relative risk reductions of 21% versus placebo in both all-cause mortality (P=0.012) and cardiovascular (CV) mortality/CV hospitalization (P=0.001), and 23% for CV mortality (P=0.008). The relative risk of sudden cardiac death (SCD) was reduced 33% (P=0.01) and HF mortality/HF hospitalization was reduced 25% (P=0.005) with eplerenone compared with placebo. Within 30 days of randomization, eplerenone resulted in relative risk reductions of 43% for all-cause mortality (P=0.002), 29% for CV mortality/CV hospitalization (P=0.006), and 58% for SCD (P=0.008).
Conclusions: Treatment with eplerenone plus standard therapy in patients with post-AMI HF and LVEF ≤30% provided significant incremental benefits in reducing both early and late mortality and morbidity.

Keywords: Aldosterone; Heart failure; Left ventricular systolic dysfunction; Eplerenone; EPHESUS

1. Introduction

The Eplerenone Post-acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) [1] demonstrated the efficacy of eplerenone in addition to standard therapy in reducing all-cause mortality, sudden cardiac death, cardiovascular (CV) mortality/CV hospitalization, the incidence of hospitalization for heart failure, and heart failure mortality/heart failure hospitalization in patients with left ventricular ejection fraction (LVEF) ≤40% and clinical evidence of heart failure post-acute

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myocardial infarction (AMI) when eplerenone or placebo treatment was initiated between 3 and 14 days (mean, 7.3 days) post-AMI.

There is increasing evidence of the prognostic importance of left ventricular dysfunction post-AMI. In particular, there is an increased risk for early as well as late sudden cardiac death, and death and hospitalization due to heart failure in those patients with LVEF $\leq$30% post-AMI [2]. For example, a recent analysis of 14,609 patients with left ventricular systolic dysfunction (LVEF $\leq$40%), heart failure, or both after AMI found that each 5% decrease in LVEF was associated with a 21% increase in the risk of sudden unexpected death or cardiac arrest with resuscitation in the first 30 days following an AMI [3]. In patients with LVEF $\leq$30%, there was a 2.3% incidence of sudden death or cardiac arrest with resuscitation during the first 30 days post-infarction, compared with a 1.4% incidence in all patients during this timeframe. Overall, 19% of all sudden death or cardiac arrest occurred within the first 30 days post-infarction, and 54% of these events occurred in patients with LVEF $\leq$30%. This increased early risk in patients with LVEF $\leq$30% persisted over the long term despite routine treatment with angiotensin-converting enzyme (ACE) inhibitors/angiotensin receptor blockers (ARBs) and β-blockers [3].

Patients with severely reduced LVEF following AMI have an increased need for implantation of electrical and/or mechanical devices, which has important health care cost implications [4,5]. Unfortunately, current evidence demonstrates that these devices are not beneficial in reducing mortality in the immediate post-infarction period, the time of highest risk in these patients [6]. Based on these considerations, we have performed a retrospective analysis of the subset of EPHESUS patients with a baseline LVEF of $\leq$30%, representing approximately one-third of the overall EPHESUS population, to provide insight into the potential importance of using selective aldosterone blockade with eplerenone for preventing early and late all-cause mortality, sudden cardiac death, and heart failure mortality/heart failure hospitalization in this high-risk population and, therefore, its potential to impact the need for electrical and/or mechanical interventions in these patients.

2. Methods

2.1. Study design and study population

EPHESUS was a multicenter, international, randomized, double-blind, placebo-controlled trial, which has been described previously [1]. Stable patients with left ventricular systolic dysfunction (LVSD), documented by LVEF $\leq$40%, and heart failure, diagnosed clinically by the presence of pulmonary rales, pulmonary vascular congestion on chest radiography, or the presence of a third heart sound, who were receiving standard optimal therapy were eligible for randomization 3 to 14 days after AMI (N=6632). LVEF was measured and analyzed at the study site by echocardiogram, radionuclide angiography, or left ventricular angiography. Patients were randomized to receive either eplerenone (25 mg/day) or placebo for 4 weeks. The eplerenone dose was increased in a single step to 50 mg/day at week 4 if tolerated; the final mean dose was 43 mg/day. Follow-up visits were scheduled at 1 and 4 weeks, 3 months, and every 3 months thereafter until the study ended. Patients were followed for up to 2.5 years, with a mean follow-up of 16 months.

Symptoms of heart failure were not necessary for study inclusion among patients with diabetes mellitus and LVSD post-AMI; diabetic patients with LVSD but without heart failure comprised about one-third of the diabetic patients and about 10% of the entire study population. Exclusion criteria for the entire study population included the use of potassium-sparing diuretics, a serum creatinine concentration greater than 2.5 mg/dl (220 μmol/l), or a serum potassium concentration greater than 5.0 mmol/l.

The mean age of the overall population in EPHESUS was 64±11.5 years; mean LVEF was 33%±6%. At baseline, 87% of EPHESUS patients were receiving ACE inhibitors or ARBs; 75%, β-blockers; 60%, diuretics; 88%, aspirin; 47%, statins; and 45% had received pre-randomization reperfusion therapy (thrombolysis, angioplasty, or coronary artery bypass grafts).

2.2. Study end points

The end points assessed in this subgroup analysis of the EPHESUS trial included the 2 primary study end points: time to all-cause mortality and time to first occurrence of the composite of CV mortality/CV hospitalization. CV hospitalization was defined as hospitalization for heart failure, recurrent AMI, stroke, or ventricular arrhythmia. Other efficacy variables assessed included sudden cardiac death, and the composite end point of death due to progressive heart failure or nonfatal hospitalization for heart failure. In addition to the findings at mean 16-month follow-up, results for each of these end points also were examined 30 days post-randomization.

2.3. Statistical analysis

This analysis evaluated the treatment effects in the subgroup of patients with LVEF $\leq$30%, based on the time to the first occurrence of an event. Results were based on a proportional hazards model stratified by region with treatment as factor. Ninety-five percent confidence intervals (CI) were based on the Wald test. The between-treatment comparisons were based on the log-rank test stratified by geographical region. The between-treatment comparison of the number of episodes of nonfatal heart failure hospitalizations was based on a Cochran–Mantel–Haenszel test stratified by region. All reported P values were 2-sided. The between-treatment

comparison of the incidence of adverse events was based on Fisher's Exact Test.

3. Results

3.1. Study patients

The subgroup of EPHESUS patients with LVEF ≤30% totaled 2106 (32% of the overall population). Of these, 1048 received eplerenone and 1058 received placebo. Baseline characteristics were comparable between the treatment groups (Table 1).

Similar to the overall EPHESUS population [1], the majority of patients in both treatment groups were receiving standard treatment with ACE inhibitors, β-blockers, aspirin, diuretics, and statins at baseline, and nearly half of each subgroup had undergone coronary reperfusion. More patients in the LVEF ≤30% group had a history of diabetes, heart failure, and MI than in the overall EPHESUS population [1].

Hemodynamic changes at 1 year in the EPHESUS patients with LVEF ≤30% included a mean increase in systolic blood pressure (SBP) of 4.7 mm Hg with eplerenone versus an increase of 7.6 mm Hg ($P=0.004$) with placebo and a mean increase in diastolic blood pressure (DBP) of 3.0 mm Hg with eplerenone versus an increase of 3.6 mm Hg with placebo ($P>0.20$). The mean decrease in sitting pulse rate was 7.8 beats per minute with eplerenone versus 7.3 beats per minute with placebo ($P=0.162$). At 30 days, increases in blood pressure in eplerenone- and placebo-treated patients were 1.5 mm Hg and 3.2 mm Hg for SBP ($P=0.069$), and 1.6 mm Hg and 2.4 mm Hg for DBP ($P=0.080$), respectively.

Table 1
Baseline characteristics of EPHESUS patients with LVEF ≤30%

Characteristic	Eplerenone	Placebo
	$n=1048$	$n=1058$
Age (years)	65±11	65±12
Sex, *n* (%)		
Male	777 (74)	752 (71)
Female	271 (26)	306 (29)
Race, *n* (%)		
Caucasian	914 (87)	922 (87)
Black	14 (1)	18 (2)
Other	120 (11)	118 (11)
Blood pressure (mm Hg)	117/70±16/11	116/70±16/11
LVEF (%)	26±4	26±5
Serum creatinine (mg/dl)	1.2±0.4	1.2±0.4
Serum potassium (mmol/l)	4.3±0.5	4.2±0.5
Time from AMI to randomization (days)	7.4±3.0	7.3±3.0
Medical history (%)		
Diabetes	39	36
Hypertension	58	58
Heart failure	20	21
MI	35	34
Baseline medications (%)		
ACEI/ARB	92	92
β-Blocker	73	73
Diuretics	71	73
Digitalis	25	26
K^+ supplements	18	20
Aspirin	87	87
Statins	51	50
Revascularization	44	45

Plus–minus values represent mean±SD.
ACEI—angiotensin-converting enzyme inhibitor; AMI—acute myocardial infarction; ARB—angiotensin receptor blocker; LVEF—left ventricular ejection fraction.

3.2. End points

Compared with the overall placebo-treated EPHESUS population, placebo-treated patients with LVEF ≤30% had a higher incidence of all-cause death (24.0% versus 16.7%), CV mortality/CV hospitalization (40.9% versus 30.0%), and sudden cardiac death (9.7% versus 6.1%). Among all EPHESUS patients with LVEF ≤30%, a total of 254 patients (24.0%) in the placebo group versus 205 patients (19.6%) treated with eplerenone died (Fig. 1A), a relative risk reduction of 21% ($P=0.012$) with eplerenone (Table 2). (In the entire EPHESUS population, the relative risk reduction for all-cause mortality was 15% with eplerenone [$P=0.008$]). For the composite end point of CV mortality/CV hospitalization in patients with LVEF ≤30%, eplerenone reduced the relative risk by 21% versus placebo ($P=0.001$) (Fig. 1B). (The relative risk reduction for this end point was 13% in the entire EPHESUS population [$P=0.002$]). For the end point of CV mortality, eplerenone reduced the relative risk by 23% compared with placebo ($P=0.008$) in patients with LVEF ≤30%; this compares to a relative risk reduction of 17% with eplerenone in the entire EPHESUS population ($P=0.005$). The relative risk of sudden cardiac death in EPHESUS patients with LVEF ≤30% was reduced by 33% ($P=0.01$) among patients treated with eplerenone compared with those treated with placebo (Fig. 1C). (Among the entire EPHESUS population, relative risk reduction for sudden cardiac death was 21% with eplerenone compared with placebo [$P=0.03$]).

The relative risk for the composite end point of death due to progressive heart failure or nonfatal hospitalization for heart failure in EPHESUS patients with LVEF ≤30% was reduced with eplerenone by 25% ($P=0.005$) compared with placebo. The number of patients who experienced nonfatal hospitalization for heart failure was reduced by 20% with eplerenone ($P=0.037$) and death due to progressive heart failure was reduced by 19% with eplerenone ($P=0.277$) (Table 2). There were 216 episodes of nonfatal hospitalizations for heart failure in eplerenone-treated patients versus 296 episodes with placebo, a reduction of 27% ($P=0.015$). (In the overall EPHESUS population, the number of episodes of nonfatal hospitalizations for heart failure was reduced by 23%

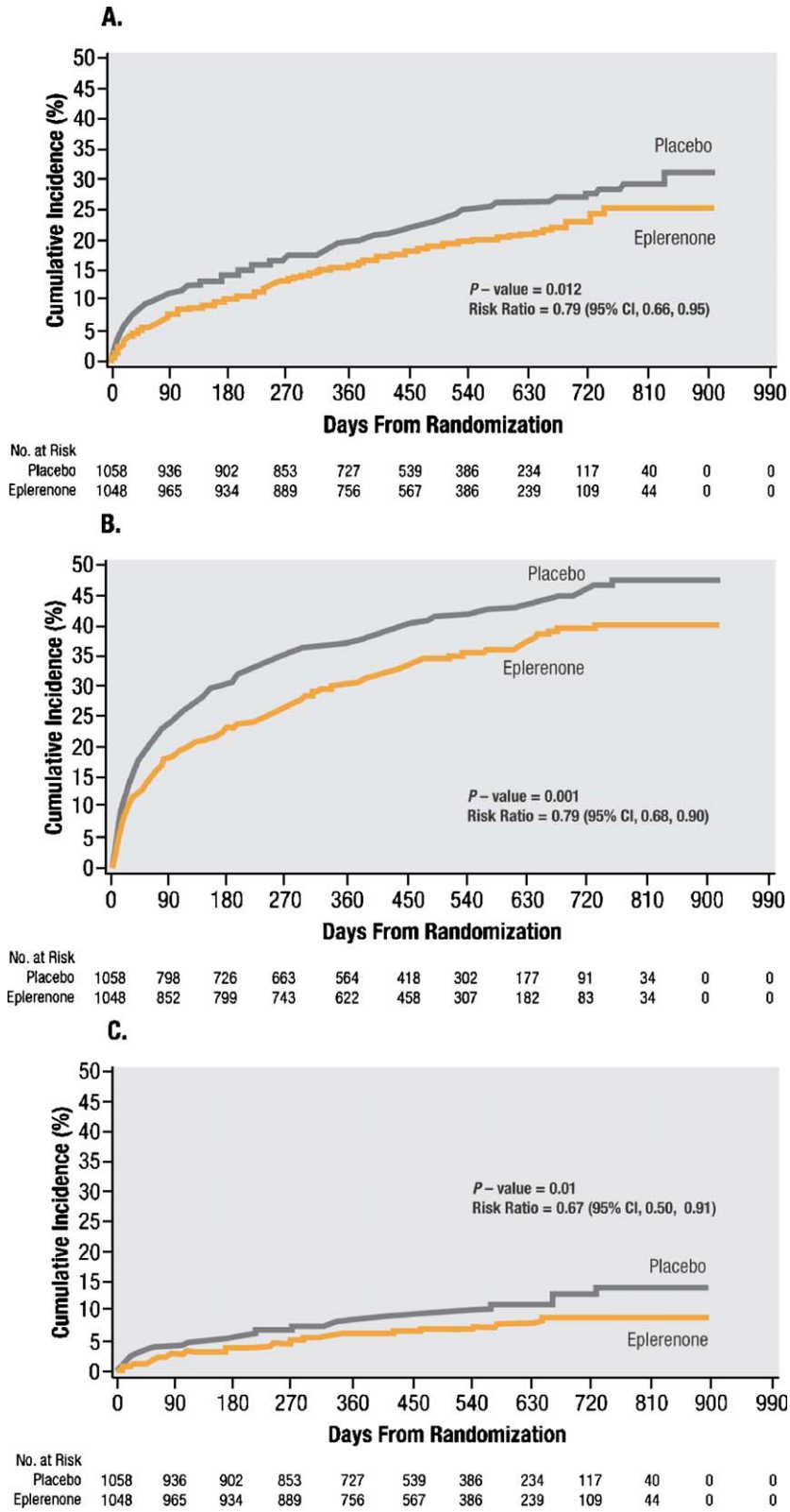

Fig. 1. Kaplan–Meier estimates of the cumulative incidence of (A) all-cause mortality, (B) CV mortality/CV hospitalization, and (C) sudden cardiac death in EPHESUS patients with LVEF $\leq$30%.

[P=0.002] with eplerenone and the number of patients hospitalized for heart failure was reduced by 15% [P=0.03]).

Within 30 days of randomization, eplerenone demonstrated significant risk reductions in EPHESUS patients with LVEF $\leq$30%, including relative risk reductions of 43% for

Table 2
Summary of primary and secondary end points in EPHESUS patients with LVEF ≤30%

Event, *n* (%)	Eplerenone *n*=1048 *n* (%)	Placebo *n*=1058 *n* (%)	Risk ratio	*P* Value
All-cause mortality	205 (19.6)	254 (24.0)	0.79	0.012
CV mortality/CV hospitalization	359 (34.3)	433 (40.9)	0.79	0.001
CV mortality	177 (16.9%)	226 (21.4%)	0.77	0.008
Sudden cardiac death	71 (6.8)	103 (9.7)	0.67	0.01
Death due to progressive heart failure/ nonfatal hospitalization for heart failure	176 (16.8)	221 (20.9)	0.75	0.005
Nonfatal hospitalization for heart failure	152 (14.5)	181 (17.1)	0.80	0.037
Death due to progressive heart failure	49 (4.7)	59 (5.6)	0.81	0.277

CV—cardiovascular.

all-cause mortality, 29% for CV mortality/CV hospitalization, and 58% for sudden cardiac death (Fig. 2).

3.3. Safety

Treatment with eplerenone was safe and well tolerated. The incidence of adverse events was similar in eplerenone-treated and placebo-treated patients with LVEF ≤30%, except as noted below for changes in serum potassium, and did not differ from those reported in each respective treatment group for the overall population [1].

Among patients with LVEF ≤30%, serious hyperkalemia, defined as serum potassium (K^+) ≥6.0 mmol/l, occurred in 3.5% of placebo-treated patients and 5.9% of eplerenone-treated patients, an absolute increase of 2.4% ($P=0.01$) with eplerenone; this compares with a 1.6% increase in serious hyperkalemia observed in the main EPHESUS findings. Hypokalemia ($K^+ \leq 3.5$ mmol/l) occurred in 14.8% of placebo-treated patients versus 7.5% of eplerenone-treated patients, an absolute decrease of 7.3% ($P<0.001$) with eplerenone treatment. Among all patients in EPHESUS, there were no deaths adjudicated to hyperkalemia in eplerenone-treated patients, and 1 death attributed to hyperkalemia among placebo-treated patients (all deaths in EPHESUS were adjudicated by a blinded, independent panel).

4. Discussion

The results of this analysis suggest an important role for eplerenone both in the early (30 days) as well as late prevention of all-cause mortality, sudden cardiac death, and heart failure mortality/heart failure hospitalizations in patients with heart failure post-AMI and baseline LVEF ≤30% (Table 2, Figs. 1 and 2). These findings are of particular importance because patients with severely reduced ejection fraction have a high incidence of sudden death, death due to progressive heart failure, and all-cause mortality [3]. These results are especially important in view of the recent findings from the Defibrillator in Acute Myocardial Infarction Trial (DINAMIT) [6], which indicate that automatic implantable cardioverter/defibrillator (ICD)

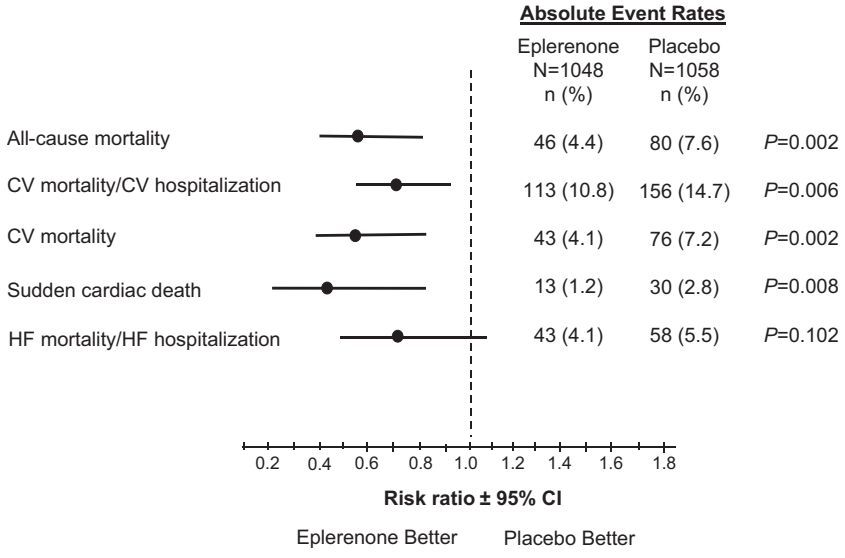

Fig. 2. Relative risks of mortality and morbidity at 30 days post-randomization in EPHESUS patients with LVEF ≤30%. Data represent hazard ratios and 95% confidence intervals.

implantation relatively early post-infarction might not be beneficial in reducing all-cause mortality.

The importance of eplerenone in decreasing all-cause mortality in patients early post-infarction with evidence of LVSD and signs of clinical heart failure is further emphasized by the failure of the ARB valsartan to reduce mortality or morbidity when added to conventional therapy including an ACE-inhibitor and a β-blocker under similar circumstances [7]. Thus, eplerenone in addition to standard therapy including reperfusion, aspirin, a statin, an ACE inhibitor or ARB, and a β-blocker could provide an important component of therapy to prevent both early and late all-cause mortality post-AMI in patients with decreased LVEF.

Studies in animal models of heart failure post-infarction have shown aldosterone blockade to be effective in attenuating ventricular remodeling and myocardial collagen formation, and have suggested that the combination of an ACE inhibitor or an ARB with an aldosterone blocker may be more effective than either alone in improving LVEF post-infarction [8]. The effectiveness of aldosterone blockade in attenuating ventricular remodeling also has been demonstrated in several studies in patients with chronic heart failure and LVSD due to nonischemic cardiomyopathy [9]. Of particular interest is the study by Rodriguez et al. [10], which demonstrated that in patients with AMI randomized to placebo, ramipril, or spironolactone, those assigned to either an ACE inhibitor or an aldosterone blocker did not develop left ventricular dilatation at 6 months compared with placebo patients, in whom increases in LV end-systolic and end-diastolic volumes occurred. Similar findings have been reported by Hayashi et al. [11], in patients with a first anterior myocardial infarction who were randomized to an aldosterone-blocking strategy with intravenous canrenoate on the day of admission and oral spironolactone thereafter, or to no aldosterone-blocking therapy. Starting on day 1 post-infarction following primary percutaneous transluminal coronary angioplasty (PTCA), all patients received an ACE inhibitor and aspirin, while β-blockers, diuretics, and other common cardiac medications were given as needed. Patients in that study had a mean baseline LVEF of approximately 47%. Those randomized to the aldosterone-blocking strategy had a significant increase in their LVEF at 1 month post-infarction compared with those randomized to placebo. Therefore, it appears that early administration of an aldosterone-blocking agent post-infarction to patients with an LVEF of $\leq 30\%$ could improve LVEF and attenuate adverse left ventricular remodeling.

The exact incidence of persistent LVSD and the incidence of cardiac death in those with persistent LVSD (LVEF $\leq 30\%$ for longer than 1 month) in EPHESUS cannot be determined because LVEF was consistently measured only prior to randomization, which occurred at a mean of 7.3 days post-infarction. However, it is likely that LVEF had improved to greater than 30% at 1 month in many patients due to the effects of reperfusion, recovery from myocardial stunning and hibernation, as well as the effects of ACE inhibition, β-blockade, and eplerenone on ventricular remodeling.

While the effects of eplerenone in preventing ventricular remodeling and myocardial collagen formation are likely important in preventing the development of progressive heart failure, it is likely that other mechanisms are of importance in explaining its effectiveness in reducing sudden cardiac death. Aldosterone blockade has important effects on the production of reactive oxygen species (ROS) by reducing NAD(P)H oxidase in the vascular wall and myocardium, and oxidized low-density lipoprotein cholesterol in circulating macrophages [12,13]. The production of ROS and the consequent destruction of nitric oxide have been shown to increase the release of norepinephrine from sympathetic nerve terminals and decrease heart rate variability [14]. Restoration of nitric oxide reduces norepinephrine release, improves heart rate variability, and baroreceptor function [15]. Aldosterone blockade has been shown to improve the availability of nitric oxide [16], improve myocardial norepinephrine uptake and hence decrease circulating catecholamine levels [17], shorten QT_C intervals [18], improve heart rate variability [19], and decrease ventricular arrhythmias in patients with chronic heart failure [17]. As mentioned above, aldosterone blockade also attenuates ventricular remodeling post-AMI, and, therefore, could be expected to reduce the activation of neurohormones such as angiotensin II and endothelin in the circulation and myocardial tissue. This should result in a further reduction in growth factors, cytokines, and inflammatory markers that also play an important role in ROS production and sudden cardiac death.

Aldosterone blockade also has been shown to have an effect on serum electrolytes, and more importantly, tissue electrolytes, including potassium, magnesium, and calcium. Recent data suggest that mineralocorticoid receptors in the endothelium could play an important role in electrolyte balance in that aldosterone results in sodium retention, endothelial swelling, and loss of potassium, whereas aldosterone blockade prevents endothelial sodium accumulation and cell swelling and increases intramyocardial potassium levels [20]. AMI has recently been shown to cause electrical remodeling of the myocardium, with an increase in intramyocardial calcium current (I_{Ca}), a decrease in potassium outward current (I_{to}), and a prolongation of action potential duration prior to the development of myocyte hypertrophy [21]. The early changes in electrical remodeling can be prevented by blockade of the mineralocorticoid receptor [21]. It is likely that the early reduction of sudden cardiac death associated with the use of eplerenone in this study was due to its effects on electrical remodeling rather than its effects on ventricular remodeling. Regardless of the exact mechanism, there is increasing evidence for the effectiveness of aldosterone blockade in preventing sudden cardiac death as well as death due to progressive heart failure and, hence, overall mortality in patients with LVSD both post-AMI [1] and with chronic heart failure [22].

As in the overall trial, there was no increase in the incidence of breast pain, gynecomastia, or impotence in

males or abnormal vaginal bleeding in females, attesting to the selectivity of eplerenone for the mineralocorticoid receptor in comparison to spironolactone. There was, however, a 2.4% increase in the risk of serious hyperkalemia ($K^+ \geq 6.0$ mmol/l) in patients randomized to eplerenone compared to those randomized to placebo in this subset with an LVEF $\leq 30\%$ at baseline, compared with a 1.6% increase in the eplerenone group in the overall study. However, as emphasized in the original report of EPHESUS, the effect of eplerenone on total mortality was favorable and there were no deaths attributed to hyperkalemia in eplerenone-treated patients; the single death in EPHESUS that was attributable to hyperkalemia occurred in a patient randomized to placebo. It is however important to emphasize that in EPHESUS efforts were made to avoid serious hyperkalemia by excluding patients with a baseline serum potassium ≥ 5.0 mmol/l and/or serum creatinine >2.5 mg/dl, routine monitoring of serum potassium, reducing the dose of eplerenone in any patient in whom serum potassium rose above 5.5 mmol/l, and discontinuing therapy in any patient whose serum potassium reached 6.0 mmol/l in the absence of any precipitating factor (such as the use of a nonsteroidal anti-inflammatory drug; potassium supplement; or intercurrent illness affecting volume, such as diarrhea or vomiting). Thus, it appears from this analysis, as well as that from the overall EPHESUS trial, that the beneficial effects of eplerenone, if used with the inclusion criteria and potassium-monitoring strategy outlined above, outweigh any potential risk of serious hyperkalemia and that, unless contraindicated because of hyperkalemia or severe renal dysfunction, eplerenone should be considered for use in all patients with baseline LVSD and signs of heart failure post-AMI, especially those with baseline LVEF $\leq 30\%$.

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