

Clinical Benefit of Eplerenone in Patients With Mild Symptoms of Systolic Heart Failure Already Receiving Optimal Best Practice Background Drug Therapy

Analysis of the EMPHASIS-HF Study

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Background—In EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure), eplerenone significantly reduced major cardiovascular events versus placebo in 2737 patients with mild symptoms of heart failure and an ejection fraction of <35%, in addition to recommended therapy. However, it is not known whether such benefits were preserved in patients receiving optimal background drug therapy, that is, high doses of angiotensin-converting enzyme inhibitor (ACEi, or angiotensin receptor blocker), β -blocker, or both drug classes.

Methods and Results—We further analyzed EMPHASIS-HF according to the use and dose of these background drug classes. Patients receiving $\geq 50\%$ of target dose were considered to be receiving high doses; patients on <50% or no drug comprised the low-dose group. The primary end point of the study (cardiovascular death/heart failure hospitalization), as well as all-cause mortality, was evaluated in this way. The beneficial clinical effects of eplerenone (as observed in the main study) were preserved for the EMPHASIS-HF primary end point in patients receiving higher doses of ACEi or angiotensin receptor blocker, β -blocker, or both (hazard ratio for eplerenone versus placebo, ACEi/angiotensin receptor blocker: high dose, 0.67; low dose, 0.65; β -blockers: high dose, 0.55; low dose, 0.72; both ACEi/angiotensin receptor blocker and β -blocker: high dose, 0.59; low dose, 0.68; *P* value for interaction 0.80, 0.15, and 0.53, respectively), as well as for all-cause mortality. There were no major safety issues, except a borderline increased risk of hypotension with eplerenone in those on high-dose ACEi or ACEi/ β -blocker.

Conclusions—Eplerenone provides substantial benefit on major events (with an acceptable safety profile) in patients with mild symptoms of systolic heart failure, even in those already receiving high doses of standard background therapies.

Clinical Trial Registration—URL: <http://www.clinicaltrials.gov>. Unique identifier: NCT00232180.

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Key Words: ACE inhibitor ■ aldosterone ■ angiotensin receptor blocker ■ β -blocker ■ eplerenone ■ heart failure

Chronic heart failure (HF) is a major public health problem, associated with high mortality, frequent hospitalization, and large cost burden to the healthcare system.¹ Strategies to ameliorate this condition have focussed predominantly on blockade of key neurohormonal systems activated in this setting (eg, the renin-angiotensin-aldosterone^{1,2} and sympathetic nervous systems).¹ Mineralocorticoid receptor antagonists (MRAs) have been demonstrated to be beneficial in patients with HF and severe symptoms in RALES³ (Randomized Aldactone Evaluation Study) and more recently in mild (New York Heart Association class II) patients in the EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure) study.⁴ In EMPHASIS-HF, patients

were receiving standard HF therapies, that is, angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs), as well as β -blockers, as background therapy. Patients were considered well treated with these medications, at least in terms of the percent receiving these agents. However, for whatever reason, not all patients were receiving high doses of these therapies. It is of both therapeutic and mechanistic interest to evaluate the impact of eplerenone in patients who are receiving optimal (ie, high dose) background therapies to determine whether the beneficial effects observed in the overall study are preserved or diminished in this particular setting.

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Table 1. Dosage Equivalence of ACE Inhibitors, ARBs, and β -Blockers as Used in the Present Analysis

| | Total Daily Dose, mg |
|------------------------------|----------------------|
| ACE inhibitor | |
| Captopril | 150 |
| Enalapril | 20 |
| Lisinopril | 20 |
| Perindopril | 10 |
| Ramipril | 10 |
| Trandolapril | 4 |
| β -Blocker | |
| Bisoprolol | 10 |
| Carvedilol | 50 |
| Metoprolol succinate (CR/XL) | 200 |
| Nebivolol | 10 |
| ARB | |
| Candesartan | 32 |
| Valsartan | 320 |
| Losartan | 150 |

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CR, controlled release; and XL, extended release.

Accordingly, we conducted a subgroup analysis of EMPHASIS-HF to examine major clinical outcomes of EMPHASIS-HF according to background dose of ACEi (and ARB), β -blocker, and both classes of drug.

Methods

Study Patients

All randomized patients from the EMPHASIS-HF study contributed to this subgroup analysis. The characteristics of these patients have been well described previously, as have the inclusion and exclusion criteria of the study.⁵

Table 2. Baseline Patient Characteristics According to Background Drug Dose: ACEi/ARB

| | ACEi \geq 50% Dose (N=1530) | | ACEi<50% Dose (N=1207) | |
|---|-------------------------------|-----------------|------------------------|-----------------|
| | Eplerenone (n=776) | Placebo (n=754) | Eplerenone (n=588) | Placebo (n=619) |
| Age, y | 68.6 | 68.6 | 68.7 | 68.7 |
| Female, % | 22.4 | 21.1 | 23.0 | 22.9 |
| Ischemic HF, % | 67.4 | 65.1 | 72.8 | 71.7 |
| BMI, kg/m ² | 28.0 | 27.9 | 26.8 | 27.0 |
| Systolic BP, mm Hg | 127.0 | 126.3 | 120.8 | 121.0 |
| Heart rate, bpm | 72.5 | 72.7 | 75.1 | 73.7 |
| LVEF, % | 26.2 | 26.1 | 26.1 | 26.0 |
| eGFR, mL/min per 1.73 ² | 72.1 | 70.6 | 69.9 | 70.1 |
| Serum K ⁺ , meq/L | 4.3 | 4.3 | 4.3 | 4.3 |
| Device therapy, % | | | | |
| Implantable cardioverter-defibrillator | 12.6 | 12.2 | 13.6 | 14.9 |
| Cardiac resynchronization therapy | 2.7 | 1.3 | 2.9 | 1.9 |
| Implantable cardioverter-defibrillator with cardiac resynchronization | 4.9 | 6.4 | 6.1 | 8.2 |

ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; bpm, beats per minute; eGFR, estimated glomerular filtration rate; HF, heart failure; and LVEF, left ventricular ejection fraction.

Overall $P>0.05$ between groups.

Briefly, to qualify for randomization in EMPHASIS-HF, patients had to be >55 years of age, have New York Heart Association class II symptoms, and an ejection fraction of no more than 30% (or 30%–35% if QRS duration >130 ms), as well as receiving standard background HF therapy, comprising ACEi, ARB (or both), as well as β -blocker at recommended or maximal tolerated doses. Investigators were encouraged to uptitrate patients to highest stable doses of these therapies before randomization into the EMPHASIS-HF study.

Dosing Equivalent of Background Drugs

A target daily dose was established based on approved dose ranges and targets for individual ACEi, ARBs, and β -blockers (Table 1). The percentage daily dose of the individual patient was determined based on the total daily dose expressed as a percentage of the target daily dose of each agent being taken at baseline (before randomization). From this, outcomes according to patients receiving less or greater than 50% target dose were derived.

Study Outcomes

Assessment was made according to target dose, with patients receiving \leq 50% of target daily dose considered to be receiving low dose and >50% high dose. Patients not taking a particular drug class were considered to be in the low-dose group. Groups evaluated separately were as follows:

- ACEi (and ARB) \geq 50%, versus <50% target dose.
- β -blocker \geq 50%, versus <50% target dose.
- Both ACEi and β -blocker \geq 50%, versus at least one of ACEi or β -blocker <50% target dose.

Outcomes evaluated according to background drug dose were the EMPHASIS-HF primary end point (time to first event of cardiovascular [CV] death or HF hospitalization) and all-cause mortality.

In addition, relevant safety end points (frequency of hyperkalemia, estimated glomerular filtration rate [eGFR], clinical hypotension) were also evaluated according to background drug dose.

Statistical Analysis

The following analyses are performed on the background drug groups defined above. Descriptive statistics are summarized for the baseline data, including demographics and relevant baseline data. The efficacy analyses on the primary end point (HF hospitalization/CV death) and all-cause mortality are performed using a Cox proportional hazards

Table 3. Baseline Patient Characteristics According to Background Drug Dose: β -Blocker

| | BB \geq 50% Dose (N=1081) | | BB<50% Dose (N=1656) | |
|---|-----------------------------|-----------------|----------------------|-----------------|
| | Eplerenone (n=536) | Placebo (n=545) | Eplerenone (n=828) | Placebo (n=828) |
| Age, y | 68.2 | 68.1 | 69.0 | 68.9 |
| Female, % | 22.0 | 19.8 | 23.1 | 23.3 |
| Ischemic HF, % | 65.7 | 65.1 | 72.3 | 70.0 |
| BMI, kg/m ² | 28.5 | 28.3 | 26.9 | 27.0 |
| Systolic BP, mm Hg | 126.1 | 125.23 | 123.2 | 123.1 |
| Heart rate, bpm | 72.5 | 71.7 | 74.4 | 74.1 |
| LVEF, % | 26.0 | 26.2 | 26.2 | 26.0 |
| eGFR, mL/min per 1.73 ² | 72.1 | 70.5 | 70.6 | 70.3 |
| Serum K ⁺ , meq/L | 4.3 | 4.3 | 4.3 | 4.3 |
| Device therapy, % | | | | |
| Implantable cardioverter-defibrillator | 17.5 | 6.1 | 10.1 | 12.0 |
| Cardiac resynchronization therapy | 2.4 | 2.6 | 3.0 | 1.0 |
| Implantable cardioverter-defibrillator with cardiac resynchronization | 6.7 | 7.3 | 4.6 | 7.1 |

BMI indicates body mass index; BP, blood pressure; bpm, beats per minute; eGFR, estimated glomerular filtration rate; HF, heart failure; and LVEF, left ventricular ejection fraction.

Overall $P>0.05$ between groups.

model, including treatment, subgroup, and treatment by subgroup interaction. In addition, the frequency of serum potassium ≥ 5.5 mmol/L and hypotension adverse event were analyzed using Fisher exact test, and eGFR and blood pressure data at end of study are also summarized.

Results

Main Study Results

The EMPHASIS-HF primary outcome (time to first event of CV death or HF hospitalization) occurred in 18.3% of patients in the eplerenone group compared with 25.9% in the placebo group (hazard ratio [HR], 0.63; 95% confidence interval, 0.54–0.74; $P<0.001$). Death (all-cause) occurred in 12.5% of patients

receiving eplerenone and in 15.5% of those receiving placebo (HR, 0.76; 95% confidence interval, 0.62–0.93; $P=0.008$). Eplerenone was overall well tolerated; however, there were increases compared with placebo (as expected) in rates of worsened renal function, hyperkalemia, and hypotension. However, there were no differences between groups in rate of adverse events, leading to permanent withdrawal of study drug.

Baseline Patient Characteristics According to Background Drug Dose

Key patient characteristics, when subdivided according to background drug and dose, are summarized in Tables 2–4.

Table 4. Baseline Patient Characteristics According to Background Drug Dose: ACEi/ARB and β -Blocker

| | ACEi and BB \geq 50% Dose (N=736) | | At Least One of ACEi or BB<50% Dose (N=2001) | |
|---|-------------------------------------|-----------------|--|------------------|
| | Eplerenone (n=371) | Placebo (n=365) | Eplerenone (n=993) | Placebo (n=1008) |
| Age, y | 68.1 | 67.9 | 68.9 | 68.9 |
| Female, % | 22.9 | 19.5 | 22.6 | 22.8 |
| Ischemic HF, % | 64.4 | 63.3 | 71.7 | 69.8 |
| BMI, kg/m ² | 28.7 | 28.4 | 27.1 | 27.2 |
| Systolic BP, mm Hg | 127.9 | 126.5 | 123.0 | 123.0 |
| Heart rate, bpm | 71.9 | 71.9 | 74.3 | 73.7 |
| LVEF, % | 26.0 | 26.2 | 26.2 | 26.0 |
| eGFR, mL/min per 1.73 ² | 72.7 | 70.8 | 70.6 | 70.2 |
| Serum K ⁺ , meq/L | 4.3 | 4.3 | 4.3 | 4.3 |
| Device therapy, % | | | | |
| Implantable cardioverter-defibrillator | 15.9 | 15.6 | 12.0 | 12.6 |
| Cardiac resynchronization therapy | 2.4 | 2.5 | 2.9 | 1.3 |
| Implantable cardioverter-defibrillator with cardiac resynchronization | 5.7 | 6.3 | 5.3 | 7.5 |

ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; bpm, beats per minute; eGFR, estimated glomerular filtration rate; HF, heart failure; and LVEF, left ventricular ejection fraction.

Overall $P>0.05$ between groups.

Table 5. EMPHASIS-HF Primary End Point (CV Death/HF Hospitalization) According to Background Dose of Key Neurohormonal Agents

| | Eplerenone, % | Placebo, % | Hazard Ratio | <i>P</i> Value for Dose×Treatment Interaction |
|--|---------------|------------|--------------|---|
| ACEi≥50% dose (n=1530) | 131 (16.9) | 181 (24.0) | 0.67 | |
| ACEi<50% dose (n=1207) | 118 (20.1) | 175 (28.3) | 0.65 | 0.80 |
| BB≥50% dose (n=1081) | 73 (13.6) | 121 (22.2) | 0.55 | |
| BB<50% dose (n=1656) | 176 (21.3) | 235 (28.4) | 0.72 | 0.15 |
| ACEi and BB≥50% dose (n=736) | 51 (13.7) | 78 (21.4) | 0.59 | |
| At least one of ACEi or BB<50% dose (n=2001) | 198 (19.9) | 278 (27.6) | 0.68 | 0.53 |

ACEi indicates angiotensin-converting enzyme inhibitor; BB, β -blocker; CV, cardiovascular; and HF, heart failure.

In general, patients were well matched with regard to these key demographic characteristics, despite the number of patients in specific subgroups being relatively small in some circumstances.

Efficacy End Points According to Background Drug Dose

Table 5 summarizes the effect of eplerenone versus placebo on the study's primary end point (CV death/HF hospitalization) according to dose of background neurohormonal antagonist drug therapy. Specifically, there was no significant difference in this outcome according to high (>50%) versus low dose of ACEi (or ARB), β -blocker, or both ACEi (or ARB) and β -blocker. *P* values for interaction between high and low doses for the EMPHASIS-HF primary end point were not significant. The HRs for eplerenone versus placebo for the EMPHASIS-HF primary end point were as follows: ACEi/ARB: high dose, 0.67; low dose, 0.65; β -blockers: high dose, 0.55; low dose, 0.72; both ACEi/ARB and β -blocker: high dose, 0.59; low dose, 0.68. Kaplan–Meier plots for this outcome in patients receiving high- and low-dose background therapy are shown in Figures 1 to 3.

Table 6 summarizes the effect of eplerenone versus placebo on all-cause mortality according to dose of background neurohormonal antagonist drug therapy. Similar to the study's primary end point, there was no significant difference in this outcome according to high (>50%) versus low dose of ACEi (or ARB), β -blocker, or both ACEi (or ARB) and β -blocker. *P* values for interaction between high and low doses for all-cause mortality were not significant. The HRs for eplerenone versus placebo for all-cause mortality were as follows: ACEi/

ARB: high dose, 0.77; low dose, 0.79; β -blockers: high dose, 0.71; low dose, 0.81; both ACEi/ARB and β -blocker: high dose, 0.83; low dose, 0.76.

Safety End Points According to Background Drug Dose

Table 7 summarizes the effect of eplerenone versus placebo on incident hyperkalemia according to dose of background neurohormonal antagonist drug therapy. As expected, there was a greater incidence of hyperkalemia in the eplerenone group compared with placebo. However, there was little evidence of greater absolute rate of hyperkalemia events in patients receiving high doses versus low doses of background agents. Furthermore, there was no significant interaction observed for HRs between high- and low-dose background therapy for ACEi (or ARB), β -blocker, or both agents.

Table 8 summarizes the effect of eplerenone versus placebo on eGFR at end of study according to dose of background neurohormonal antagonist drug therapy. Overall, there was little difference in eGFR at end of study in the eplerenone group compared with placebo. Furthermore, there was little to no evidence of an increase in eGFR in patients receiving high doses versus low doses of background agents. Specifically, there was no significant interaction observed for HRs between high- and low-dose background therapy for ACEi (or ARB), β -blocker, or both agents.

Table 9 summarizes the effect of eplerenone versus placebo on the clinical adverse events of hypotension or postural hypotension at end of study according to dose of background neurohormonal antagonist drug therapy. There was overall no significant increased risk of this adverse event with

Table 6. All-Cause Mortality According to Background Dose of Key Neurohormonal Agents

| | Eplerenone, % | Placebo, % | Hazard Ratio | <i>P</i> Value for Dose×Treatment Interaction |
|--|---------------|------------|--------------|---|
| ACEi≥50% dose (n=1530) | 88 (11.3) | 110 (14.6) | 0.77 | |
| ACEi<50% dose (n=1207) | 83 (14.1) | 103 (16.6) | 0.79 | 0.90 |
| BB≥50% dose (n=1081) | 56 (10.4) | 74 (13.6) | 0.71 | |
| BB<50% dose (n=1656) | 115 (13.9) | 139 (16.8) | 0.81 | 0.58 |
| ACEi and BB≥50% dose (n=736) | 41 (11.1) | 46 (12.6) | 0.83 | |
| At least one of ACEi or BB<50% dose (n=2001) | 130 (13.1) | 167 (16.6) | 0.76 | 0.70 |

ACEi indicates angiotensin-converting enzyme inhibitor; and BB, β -blocker.

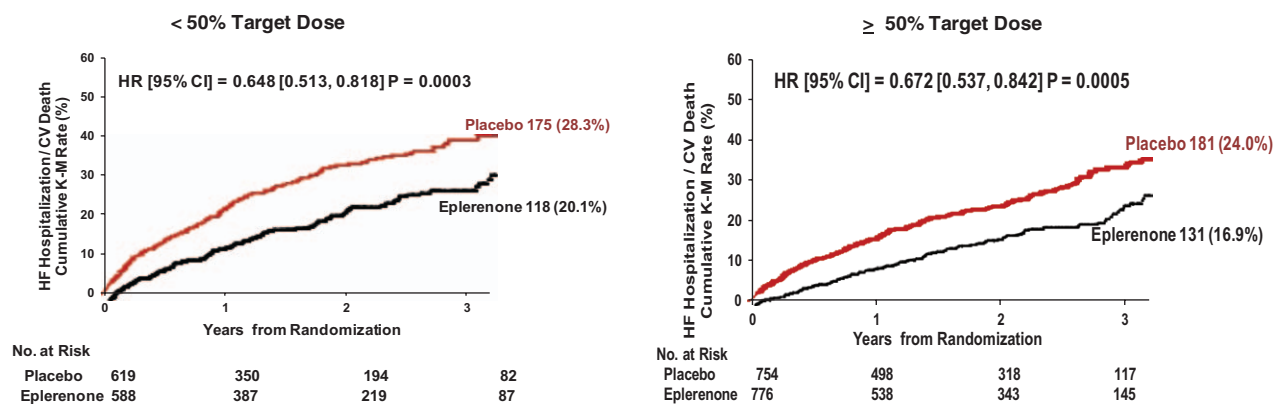


Figure 1. Effect of eplerenone versus placebo on the EMPHASIS-HF study primary end point (cardiovascular [CV] death/heart failure [HF] hospitalization) according to background angiotensin-converting enzyme inhibitor (or angiotensin receptor blocker) dose (above or below 50% of target dose). CI indicates confidence interval; and HR, hazard ratio.

eplerenone versus placebo, irrespective of receiving high- and low-dose background therapy for ACEi (or ARB), β -blocker, or both agents.

Discussion

The present analysis examined whether the beneficial effects of eplerenone observed in the overall EMPHASIS-HF study were maintained in the subgroup of patients receiving optimal best practice background drug therapy comprising use of high-dose ACEi (or ARB) or β -blocker or both.

This analysis is of relevance to the drug management of systolic HF patients with New York Heart Association class II symptoms as well as being of considerable mechanistic interest. ACEi and β -blockers are well established as mandatory life-saving background therapy in such patients.¹ However, it is well established that not all patients are able to tolerate these medications, and those that do often cannot reach target doses of these therapies for reasons of intolerance and adverse events. In the EMPHASIS-HF study,⁴ 77% of patients were receiving an ACEi, 19% ARB, and 94% either agent or both. Similarly, 87% of patients were receiving β -blockers.

Predefined subgroup analysis has determined that patients receiving these background therapies derived similar benefit

with eplerenone as regards the primary study end point (CV death or HF hospitalization) versus those who were not receiving these agents.⁴ However, analysis according to dosing of these agents has not been previously performed within the EMPHASIS-HF cohort. This is of importance as the question arises as to whether the benefits of eplerenone are maintained in the setting of higher doses of these agents. Alternatively, it may be argued that the same outcome benefit may be achieved by simply increasing the dose of background medication. When use of ivabradine additional to β -blockers was examined in this way in SHIFT (Systolic Heart failure treatment with I_f inhibitor ivabradine Trial),⁶ the magnitude of benefit of ivabradine in patients receiving >50% of dose of β -blocker was substantially reduced in comparison with the overall population. In contrast, the present analysis of EMPHASIS-HF demonstrates that the HRs generated for CV death/HF hospitalization or for all-cause mortality with the MRA eplerenone were of similar magnitude above and below 50% target dose for ACEi (or ARB) or β -blocker. Furthermore, this benefit was maintained in patients who had >50% of dosing for both background agents. These findings support the concept that addition of an MRA to background high-dose ACEi and β -blockers provides substantial additional clinical outcome benefit. Although a head-to-head

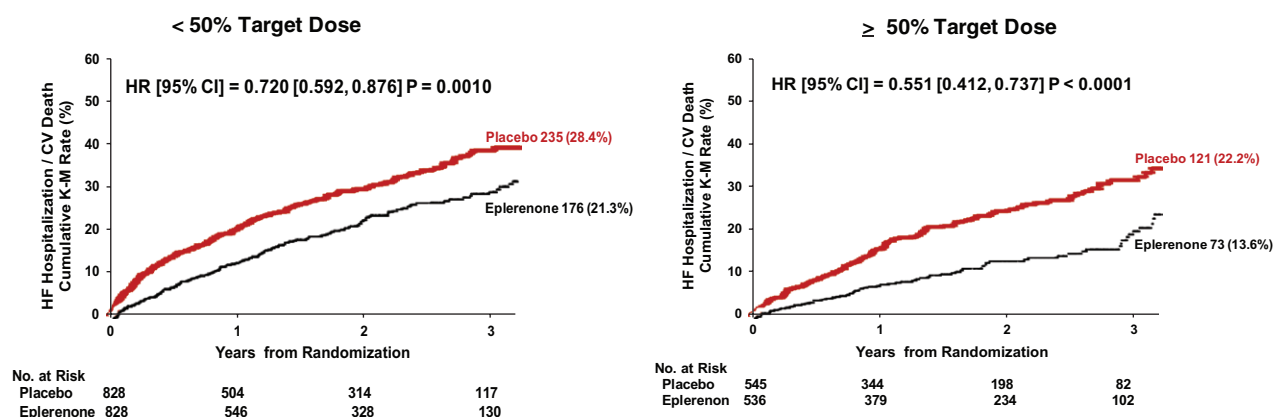


Figure 2. Effect of eplerenone versus placebo on the EMPHASIS-HF study primary end point (cardiovascular [CV] death/heart failure [HF] hospitalization) according to background β -blocker dose (above or below 50% of target dose). CI indicates confidence interval; and HR, hazard ratio.

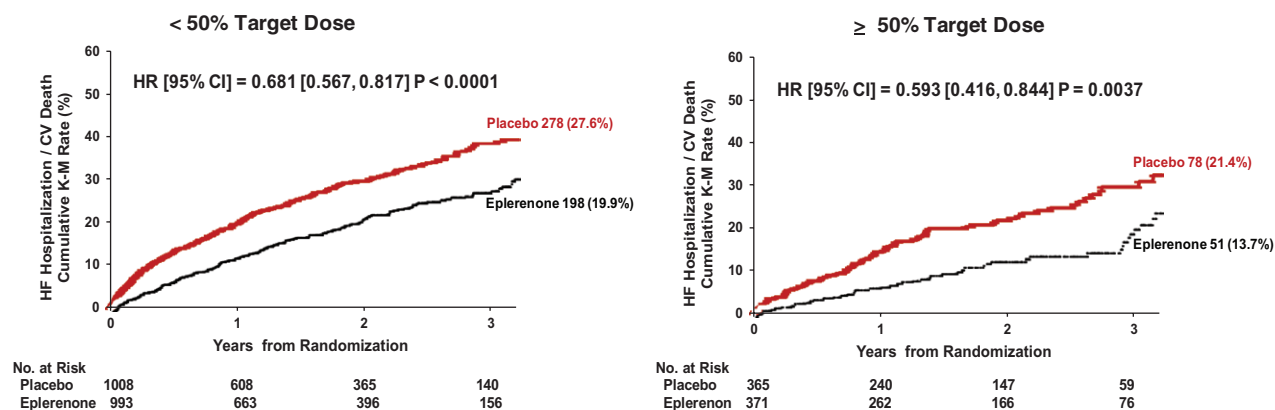


Figure 3. Effect of eplerenone versus placebo on the EMPHASIS-HF study primary end point (cardiovascular [CV] death/heart failure [HF] hospitalization) according to background angiotensin-converting enzyme inhibitor (or angiotensin receptor blocker) and β -blocker dose (above or below 50% of target dose). CI indicates confidence interval; and HR, hazard ratio.

study of increasing dose of these background agents versus the addition of eplerenone has not yet been performed, these findings would suggest that eplerenone may be the preferred strategy in this regard. However, this was not formally tested in the EMPHASIS-HF study nor has it been studied in other trials of MRAs in HF.

As mentioned, this analysis is also of considerable mechanistic interest and importance. As mentioned, there was maintenance of the overall benefit observed with eplerenone in the subgroup receiving high-dose ACEi and β -blocker. These findings suggest that the aldosterone inhibitory effect of a conventional strategy is either suboptimal or associated with clinically relevant aldosterone escape.⁷ These findings support the need for direct mineralocorticoid receptor blockade to maximize renin-angiotensin-aldosterone blockade and associated clinical benefits. However, serum aldosterone levels were not analyzed in the present analysis, so this remains a hypothesis still to be formally tested.

The results of this analysis are also of relevance to the ongoing debate regarding how best to maximize the benefits of neurohormonal blockade in various CV settings, but specifically in systolic chronic HF. It is, however, uncertain whether 2 or 3 (or more) neurohormonal blocking agents are the optimal approach when added to standard background treatment.⁸ The data have been mixed in this regard. For example, the benefits of adding the ARB candesartan seemed to be preserved, irrespective of dose of ACEi background therapy in CHARM (Conduction in Heart Failure: Assessment of Reduction in Mortality and Morbidity)-Added.⁹ In contrast,

in Val-HeFT (Valsartan Heart Failure Trial), the beneficial effects of valsartan were progressively attenuated with increasing dose of background ACEi.¹⁰ The data seem more clear-cut with MRA therapy; in both EPHEsus (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study)¹¹ and now EMPHASIS-HF, the efficacy benefits of this strategy seem to be preserved in the setting of maximized background therapy.

With regard to safety, the present subgroup analysis evaluated hyperkalemia and renal function according to use of eplerenone versus placebo and background ACEi (or ARB) or β -blocker dose (as well as for both background agents combined). The findings of this subgroup analysis would suggest that 2 of the most feared adverse events of MRAs (hyperkalemia, worsened renal function) do not occur with significantly greater frequency when added to high-dose (versus low-dose) background neurohormonal drug therapy. Analysis of the impact of background neurohormonal drug dose on incidence of hypotension or postural hypotension does however suggest a borderline increase in risk of this adverse event in patients receiving high-dose (>50% dose) ACEi or ACEi combined with β -blocker at high dose.

Given that HF guidelines worldwide recommend highest tolerated dose of ACEi and β -blockers, the findings of the present subgroup analysis suggest that efficacy of eplerenone is maintained additional to these recommended drugs and doses and that safety is not unduly compromised in this setting (ie, patients with systolic HF and mild symptoms).

Table 7. Incident Hyperkalemia (Any Occurrence of Serum Potassium>5.5 mmol/L) According to Background Dose of Key Neurohormonal Agents

| | Eplerenone, % | Placebo, % | P Value by Fisher Exact Test |
|--|---------------|------------|------------------------------|
| ACEi≥50% dose (n=1530) | 12.6 | 7.0 | 0.0003 |
| ACEi<50% dose (n=1207) | 10.8 | 7.4 | 0.043 |
| BB≥50% dose (n=1081) | 10.8 | 7.9 | 0.14 |
| BB<50% dose (n=1656) | 12.5 | 6.7 | <0.0001 |
| ACEi and BB≥50% dose (n=736) | 11.2 | 6.5 | 0.027 |
| At least one of ACEi or BB<50% dose (n=2001) | 12.1 | 7.4 | 0.0006 |

ACEi indicates angiotensin-converting enzyme inhibitor; and BB, β -blocker.

Table 8. eGFR at End Study According to Background Dose of Key Neurohormonal Agents

| | Eplerenone, % Mean | SD | Placebo, % Mean | SD |
|--|-----------------------|------|--------------------|------|
| ACEi≥50% dose (n=1530) | 68.6 | 22.3 | 68.9 | 20.9 |
| ACEi<50% dose (n=1207) | 68.3 | 24.2 | 69.8 | 25.0 |
| BB≥50% dose (n=1081) | 69.0 | 22.2 | 69.1 | 22.2 |
| BB<50% dose (n=1656) | 68.1 | 23.8 | 69.4 | 23.2 |
| ACEi and BB≥50% dose (n=736) | 68.4 | 22.2 | 69.1 | 20.1 |
| At least one of ACEi or BB<50% dose (n=2001) | 68.5 | 23.6 | 69.4 | 23.7 |

ACEi indicates angiotensin-converting enzyme inhibitor; BB, β -blocker; and eGFR, estimated glomerular filtration rate.
All *P* values by Fisher exact test >0.05 for eplerenone vs placebo.

In summary, the present subgroup analysis of EMPHASIS-HF has found that MRA eplerenone provided substantial clinical benefit and acceptable safety, even in the setting of high-dose background ACEi (or ARB) or β -blocker or both. Thus, use of eplerenone should be strongly considered, irrespective of dose of background neurohormonal antagonist therapy in systolic HF patients with mild (New York Heart Association class II) symptoms.

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Disclosures

Drs Krum, Pitt, McMurray, Swedberg, van Veldhuisen, Pocock, and Zannad are members of the EMPHASIS-HF Writing Committee and report receiving support from the study sponsor, Pfizer Inc, for participation in and traveling to meetings of the committee. H. Shi and Dr Vincent are currently employed by Pfizer and own stock in Pfizer Inc, the makers of eplerenone. Dr Krum reports receiving

travel reimbursements from Pfizer. H. Shi and Dr Vincent report being employees of Pfizer and receiving stock options and travel reimbursements from Pfizer. Dr Pitt reports receiving fees for serving on the board of Novartis, consulting fees from Takeda, AstraZeneca, Boehringer Ingelheim, GE Healthcare, Relypsa, BG Medicine, Nile Therapeutics, Merck, Forest Laboratories, and Novartis, grant support from Forest Laboratories and Novartis, and stock options from Relypsa, BG Medicine, Nile Therapeutics, and Aurasenc and that his institution receives grant support from Forest Laboratories on his behalf and he and his institution receive grant support from Bayer. Dr McMurray reports receiving grant support from the Eugene Braunwald Endowment for the Advancement of Cardiovascular Discovery and Care. Dr Swedberg has received research support from Pfizer, Amgen, Novartis, and Servier. Dr Pocock reports receiving consulting fees from Servier, Amgen, AstraZeneca, and Novartis and that his institution receives grants from Servier and AstraZeneca on his behalf. Dr Zannad reports receiving fees for serving on the board of Boston Scientific, consulting fees from Novartis, Takeda, AstraZeneca, Boehringer Ingelheim, GE Healthcare, Relypsa, Servier, Boston Scientific, Bayer, Johnson & Johnson, and Resmed, and speaker's fees from Pfizer and AstraZeneca and that his institution receives grant support from BG Medicine and Roche Diagnostics on his behalf.

Table 9. Incident Hypotension or Postural Hypotension According to Background Dose of Key Neurohormonal Agents

| Subgroup | Adverse Event | Eplerenone n/N (%) | Placebo n/N (%) | <i>P</i> Value Fisher Exact Test |
|---|-------------------------|--------------------|-----------------|----------------------------------|
| ACE inhibitors >50% target dose | Hypotension | 30/772 (3.9) | 17/752 (2.3) | 0.076 |
| | Orthostatic hypotension | 6/772 (0.8) | 3/752 (0.4) | 0.507 |
| | Overall | 35/772 (4.5) | 20/752 (2.7) | 0.055 |
| ACE inhibitors <50% target dose | Hypotension | 16/588 (2.7) | 20/617 (3.2) | 0.616 |
| | Orthostatic hypotension | 1/588 (0.2) | 7/617 (1.1) | 0.070 |
| | Overall | 17/588 (2.9) | 25/617 (4.1) | 0.346 |
| β -Blockers >50% target dose | Hypotension | 16/533 (3.0) | 12/543 (2.2) | 0.449 |
| | Orthostatic hypotension | 5/533 (0.9) | 6/543 (1.1) | 0.999 |
| | Overall | 20/533 (3.8) | 17/543 (3.1) | 0.618 |
| β -Blockers <50% target dose | Hypotension | 30/827 (3.6) | 25/826 (3.0) | 0.584 |
| | Orthostatic hypotension | 2/827 (0.2) | 4/826 (0.5) | 0.452 |
| | Overall | 32/827 (3.9) | 28/826 (3.4) | 0.694 |
| ACE inhibitors \geq 50% target dose and β -blockers \geq 50% target dose | Hypotension | 13/369 (3.5) | 5/363 (1.4) | 0.092 |
| | Orthostatic hypotension | 5/369 (1.4) | 2/363 (0.6) | 0.451 |
| | Overall | 17/369 (4.6) | 7/363 (1.9) | 0.060 |
| ACE inhibitors <50% target dose and β -blockers <50% target dose | Hypotension | 33/991 (3.3) | 32/1006 (3.2) | 0.900 |
| | Orthostatic hypotension | 2/991 (0.2) | 8/1006 (0.8) | 0.107 |
| | Overall | 35/991 (3.5) | 38/1006 (3.8) | 0.812 |

ACE indicates angiotensin-converting enzyme.

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CLINICAL PERSPECTIVE

Eplerenone has been shown to be of benefit in patients with mild symptoms of systolic heart failure in the EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure) study. However, it is uncertain whether those clinical benefits remain significant when the agent is added to best practice background therapy, that is, high doses of angiotensin-converting enzyme inhibitor (or angiotensin receptor blocker), β -blocker, or both. We therefore analyzed major outcomes in EMPHASIS-HF according to dose of these key background heart failure therapies. The findings were that major clinical benefits were generally preserved with eplerenone even when added to higher doses of these background therapies. These findings should also be considered in the context of the safety profile of addition of eplerenone to high-dose background therapy. In general, safety was found to be acceptable. The clinical implication of these findings is that, even in patients in whom high doses of background therapies are used, a mineralocorticoid receptor antagonist is of benefit in this patient population.

Clinical Benefit of Eplerenone in Patients With Mild Symptoms of Systolic Heart Failure Already Receiving Optimal Best Practice Background Drug Therapy: Analysis of the EMPHASIS-HF Study

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