Eplerenone versus placebo renal function stratified dose comparisons in the EMPHASIS-HF trial

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Abstract

Background: Current heart failure (HF) guidelines recommend target eplerenone dose of 50mg/day. We have examined the effect of different eplerenone doses based on prespecified renal function stratification in the Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms (EMPHASIS-HF) trial.

Methods: In EMPHASIS-HF, the target dose of eplerenone/placebo was stratified at randomisation according to estimated glomerular filtration rate (eGFR): 50mg/day if eGFR ≥50ml/min/1.73m^2 and ≤25mg/day if eGFR30-49ml/min/1.73m^2. Patients remained within these dose ranges during the trial (*per* stratification). The primary outcome was a composite of heart failure hospitalization (HFH) or cardiovascular mortality (CVM).

Results: Eplerenone was superior to placebo within each respective eGFR stratum: hazard ratio (HR) eplerenone vs. placebo in the eGFR ≥50ml/min/1.73m^2 stratum=0.58 (0.45-0.74) and HR in the eGFR 30-49ml/min/1.73m^2 stratum=0.62 (0.49-0.78); p for interaction=0.89. Despite receiving lower eplerenone doses patients in the eGFR30-49ml/min/1.73m^2 stratum had more often hyperkalemia, renal failure events, and drug discontinuation.

Conclusion: In EMPHASIS-HF the eplerenone effect was not influenced by the eGFR. Patients with impaired renal function experienced more adverse events despite receiving lower eplerenone doses. The current guidelines do not specify eplerenone dose recommendation according to renal function and should thus be adapted in the light of these data.

Key-words: eplerenone, heart failure, treatment dose, renal function, stratification.

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Introduction

Current heart failure (HF) guidelines recommend up-titration of angiotensin converting enzyme inhibitor (ACEi), angiotensin receptor blocker (ARB), and beta-blocker (BB) doses to evidence-based targets based upon those used in pivotal clinical trials in heart failure with reduced ejection fraction (HFrEF). In ordinary practice, these doses are not attained in many patients despite the randomized evidence showing the benefit of higher ACEi/ARB and BB doses[1-6].

By contrast, there is no study comparing different doses of a mineralocorticoid receptor antagonists (MRA)[7]. For eplerenone, the current guidelines recommend a starting dose of 25 mg/day and a target dose of 50 mg/day regardless of renal function[1, 2].

In the Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms trial (EMPHASIS-HF), eplerenone reduced the risk of death and the risk of hospitalization, compared with placebo, in patients with heart failure and reduced left ventricular ejection fraction (LVEF) who were in New York Heart Association (NYHA) functional class II at the time of randomization[8]. Because of pharmacokinetic and safety considerations, patients were stratified at randomization to either a higher target dose (50 mg/day) of placebo/eplerenone or to a lower target dose (up to 25 mg/day), according to estimated glomerular filtration rate (eGFR) strata. We used this pre-specified dose-stratification to compare the efficacy and safety of low-dose eplerenone vs. low-dose placebo and high-dose eplerenone vs. high-dose placebo by renal function strata.

Methods

EMPHASIS-HF trial design

The design of EMPHASIS-HF is published[8]. In short, EMPHASIS-HF was a randomized, double-blind trial in which 2,737 patients in NYHA functional class II and with LVEF ≤35% were randomized to eplerenone or placebo, added to other recommended therapies. The primary outcome was a composite of death from cardiovascular causes (CVM) or hospitalization for heart failure (HFH). The median duration of follow-up was 21 months. The primary outcome occurred in 18.3% of patients in the eplerenone group, compared with 25.9% in the placebo group: HR (95%CI) =0.63 (0.54-0.74); p<0.001.

Eplerenone dose attribution and adjustment

Patients were stratified to receive “high-dose” or “low-dose” study treatment according to eGFR as *per* stratification protocol. The main reason why a lower target dose of eplerenone was chosen in patients with an eGFR between 30 and 49 ml/min/1.73 m^2 was because in the Eplerenone Post–Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS)[9], where no prespecified dose allocation was performed, patients with eGFR <50 ml/min/1.73m^2 had higher incidence of serious hyperkalemia with eplerenone compared to placebo (10.1% vs. 5.9%; p =0.006), whereas in patients with an eGFR ≥50 ml/min/1.73m^2 the corresponding hyperkalemia rates were much lower

(4.6 % vs. 3.5%; p =0.04). In order to avoid excessive side-effects in high-risk patients with impaired renal function, these received lower study drug doses by protocol prespecification.

In concordance, placebo/eplerenone was started at a dose ≤25 mg/day and could be increased after 4 weeks up to 50 mg/day if the eGFR was ≥50 ml/min/1.73 m^2; or started at 25 mg on alternate days, and increased to 25 mg/day if the eGFR was 30 to 49 ml/min/1.73 m^2. By protocol, eplerenone/placebo doses were maintained in these dose ranges with drug-dose adjustments allowed according to potassium levels, as follows: if the serum potassium level was 5.5 to 5.9 mmol/L the study drug dose would be decreased and if the serum potassium level was ≥6.0 mmol/L the study drug would be temporarily stopped. Potassium was to be re-measured within 72 hours after the dose reduction or study-drug withdrawal, and the study drug was to be restarted only if the level was below 5.0 mmol/L.

Statistical analysis

In descriptive analyses, continuous variables are expressed as mean ± standard deviation (SD). Categorical variables are expressed as frequencies and proportions (%). Comparison of patients in the low-dose and high-dose strata and within each dose strata (placebo versus eplerenone) was performed using an independent samples t-test and a chi-square test for categorical variables. Normality assumptions were verified.

The primary outcome was a composite of HFH or CVM. Cox proportional hazard regression models were used to model long-term event rates both in univariable and multivariable analysis. Cox proportional-hazards assumptions were assessed and no violations were found. The variables used to adjust outcomes were those used in a published risk model developed in EMPHASIS-HF[10] *i.e.*, age, sex, systolic blood pressure (SBP), eGFR[11], diabetes, prior HFH, haemoglobin, prior myocardial infarction (MI)/coronary artery bypass grafting (CABG), body mass index (BMI).

All analyses were performed with SAS® software version 9.4 (SAS Institute Inc., Cary, N.C., USA).

Results

Characteristics of the study population

Within the respective eGFR stratum the randomization resulted in treatment groups that were well balanced in terms of their clinical characteristics, in accordance with the study overall. **Table 1**.

Comparison of eplerenone and placebo doses during the trial by eGFR strata

The mean eplerenone/placebo doses in the eGFR ≥50ml/min/1.73m^2 stratum were of 25 mg/day at the study start, increased to ≥40 mg/day at week 4 and were maintained stable at ≥40 mg/day during the trial. **Table 2**. The mean eplerenone/placebo doses in the eGFR 30-49ml/min/1.73m^2 stratum were inferior to 17 mg/day at the study start, increased up to 23 mg/day at week 4 and did not exceed 30 mg/day during the trial. **Table 2**.

Comparison of eplerenone with placebo by eGFR strata

The event rate reduction with eplerenone compared to placebo was similar within each eGFR stratum: HR eplerenone vs. placebo in the eGFR ≥50ml/min/1.73m^2 stratum =0.58 (0.45-0.74) and HR eplerenone vs. placebo in the eGFR 30-49ml/min/1.73m^2 stratum =0.62 (0.49-0.78); between strata p for interaction =0.89. **Table 3** & **Figure 1**.

Adverse events

Hyperkalemia (K^+ >5.5 mmol/L) was more frequent with eplerenone compared to placebo regardless of the eGFR stratum. However, hyperkalemia, renal failure and drug discontinuation were more frequent with low-dose eplerenone/placebo (*i.e.*, eGFR 30-49ml/min/1.73m^2 stratum) compared with high-dose (*i.e.*, eGFR ≥50ml/min/1.73m^2 stratum). For example, hyperkalemia was observed in 1% and 4% of patients randomized to placebo and eplerenone, respectively, in the eGFR ≥50ml/min/1.73m^2 stratum, whereas in the eGFR 30-49ml/min/1.73m^2 stratum these proportions increased to 7% with placebo and 13% with eplerenone (p <0.001). **Table 4.**

Discussion

In EMPHASIS-HF the eplerenone effect was not influenced by the eGFR *i.e*. the treatment effect was similar regardless of the eGFR stratum. However, as *per* stratification, eplerenone/placebo doses were much lower in patients with eGFR below 50ml/min/1.73m^2; and despite these lower doses, side effects were observed more often. Therefore, using high (up to 50 mg/day) eplerenone doses in patients with impaired renal function may greatly increase the rate of adverse events and drug discontinuation. The current guidelines do not specify eplerenone dose recommendation in HFrEF and should thus be adapted in order to reflect the protocol of the EMPHASIS-HF trial.

To date, no randomized trials exist directly comparing different doses of eplerenone (or any other aldosterone antagonist). There are, however, two large trials in which patients were prospectively randomized to a high or low dose of ACE inhibitor or ARB: The Assessment of Treatment with Lisinopril and Survival trial (ATLAS) and the Heart failure Endpoint evaluation with the Angiotensin II Antagonist Losartan trial (HEAAL). In ATLAS, 3,164 HF patients with an ejection fraction ≤30% were randomized to double-blind treatment with either low doses (2.5 to 5.0 mg daily, n =1596) or high doses (32.5 to 35 mg daily, n =1568) of the ACE inhibitor lisinopril. Compared with the low-dose group, patients in the high-dose group had a significant 12% lower relative risk of death or hospitalization for any reason (p =0.002) and 24% fewer hospitalizations for HF (p =0.002). Drug discontinuation due to side-effects was similar between groups. In HEAAL, 3,846 HF patients with an ejection fraction ≤40% and intolerance to ACE inhibitors were randomly assigned to low-dose (50 mg daily, n =1919) or high-dose (150 mg daily, n =1927) of the ARB losartan. Compared with the low-dose group, patients in the high-dose group had a significant 10% lower relative risk of death or hospitalization for HF (p =0.027) and 13% fewer hospitalizations for HF (p =0.025). Drug discontinuation due to side-effects was also similar between groups. These findings indicate that HF patients should not be maintained on low doses of an ACE inhibitor or ARB (unless these are the only

doses that can be tolerated). In contrast, MRA dose comparisons have not been perform to date. The design of EMPHASIS-HF was different: by stratification two dose-levels were compared with placebo rather than directly low vs. high treatment dose. It should be pointed out, that unlike ATLAS and HEAAL, EMPHASIS-HF patients were randomized within two strata which were determined by renal function, hence high-dose vs. low-dose treatment cannot be compared. In EMPHASIS-HF low-dose was as effective as high-dose eplerenone when used in appropriate patients (*i.e.*, low-dose for patients with eGFR 30-49ml/min/1.73m^2 and high-dose for patients with eGFR ≥50ml/min/1.73m^2), supporting the of eplerenone at doses around 25 mg/day in patients with eGFR 30-49ml/min/1.73m^2 and around 50 mg/day in patients with eGFR ≥50ml/min/1.73m^2, adapting for potassium levels when required.

Stratification is usually performed to ensure that strong outcome or treatment response predictors are balanced between randomization groups, but stratification is also the only situation in which balanced randomization is maintained in subgroups, since the randomization is performed within each stratum[12]. Therefore, strata analyses are less permeable to bias caused by imbalances in treatment allocation and patients` characteristics, which inevitably hamper all analyses made on subgroups defined from non-randomized baseline characteristics. In the absence of a statistical interaction (*i.e.* similar between-strata hazard ratios, as observed herein) the treatment effect can be considered similar between both strata provided that the same strata-treatment doses are used in clinical practice. These findings, should thus change the current guidelines where no eGFR-specific eplerenone dose recommendation is provided[1, 2]; and many patients may be receiving inappropriate doses of eplerenone contributing to higher hyperkalemia rates and drug discontinuation[13].

In summary, the present analysis of stratified randomized data from EMPHASIS-HF provides robust evidence that eplerenone is equally beneficial and should be used in clinical practice at the respective target doses of 50 mg/day in patients with eGFR ≥50 ml/min/1.73m^2 and 25 mg/day in patients with eGFR between 30 and 49 ml/min/1.73m^2.

Limitations

This is an analysis of prespecified strata. Hence, our findings are as robust as the main randomized clinical trial because no statistical interaction (*i.e.* treatment effect differences) was observed between strata.

Conclusion

In EMPHASIS-HF the eplerenone effect was not influenced by the eGFR. Patients with impaired renal function experienced more adverse events despite receiving lower eplerenone doses. The current guidelines do not specify eplerenone dose recommendation according to renal function and should thus be adapted in the light of these data.

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J.J.V.M., D.J.vV., K.S., S.J.P., B.P., and F.Z. are members of the EMPHASIS-HF Writing Committee and report having received fees and travel support in the past from the study sponsor, Pfizer Inc., for participation in and travelling to meetings of the committee. P.A., J.V. and K.L. are currently employed by Pfizer and own stock in Pfizer Inc., the makers of eplerenone. K.S. has received research support from Pfizer, Amgen, Novartis, and Servier. S.J.P. reports receiving consulting fees from Servier, Amgen, AstraZeneca, and Novartis, and that his institution receives grants from Servier and AstraZeneca on his behalf. B.P. 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, that his institution receives grant support from Forest Laboratories on his behalf and he and his institution receive grant support from Bayer. F.Z. 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. J.P.F. has reported that he has no relationships relevant to the contents of this paper to disclose.

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