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RESEARCH ARTICLE

Renal function stratified dose comparisons of eplerenone versus placebo in the EMPHASIS-HF trial

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Background Current heart failure guidelines recommend target eplerenone dose of 50 mg/day. We have examined the effect of different eplerenone doses based on pre-specified renal function stratification in the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF).

Methods and results In EMPHASIS-HF, the target dose of eplerenone/placebo was stratified at randomization according to estimated glomerular filtration rate (eGFR): 50 mg/day if eGFR $\geq$ 50 mL/min/1.73 m^2 and $\leq$ 25 mg/day if eGFR 30–49 mL/min/1.73 m^2. Patients remained within these dose ranges during the trial (as per stratification). The primary outcome was a composite of heart failure hospitalization or cardiovascular mortality. Eplerenone was superior to placebo within each respective eGFR stratum [eplerenone vs. placebo in the eGFR $\geq$ 50 mL/min/1.73 m^2 stratum: hazard ratio (HR) 0.58, 95% confidence interval (CI) 0.45–0.74; and eplerenone vs. placebo in the eGFR 30–49 mL/min/1.73 m^2 stratum: HR 0.62, 95% CI 0.49–0.78; $P_{interaction} = 0.89$]. Despite receiving lower eplerenone doses, patients in the eGFR 30–49 mL/min/1.73 m^2 stratum more often had hyperkalaemia, renal failure events, and drug discontinuation.

Conclusion In EMPHASIS-HF the eplerenone dose was stratified according to renal function and the treatment effect was not influenced by renal function: 25 mg/day in patients with eGFR 30–49 mL/min/1.73 m^2 was as effective as 50 mg/day in patients with eGFR > =50 mL/min/1.73 m^2. However, patients with impaired renal function experienced more adverse events, despite reveiving lower eplerenone doses. Current guidelines do not recommend tailoring the dose of eplereone according to renal function but the current data suggest they should.

Keywords Eplerenone • Heart failure • Treatment dose • Renal function • Stratification

Introduction

Current heart failure (HF) guidelines recommend uptitration of angiotensin-converting enzyme inhibitor (ACEi), angiotensin receptor blocker (ARB), and beta-blocker doses to evidence-based targets based upon those used in pivotal clinical trials in HF 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 beta-blocker doses.[1–6]

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By contrast, there is no study comparing different doses of mineralocorticoid receptor antagonists.[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 Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF), eplerenone reduced the risk of death and the risk of hospitalization, compared to placebo, in patients with HFrEF 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 has been published.[8] In short, EMPHASIS-HF was a randomized, double-blind trial in which 2737 patients in NYHA functional class II and with left ventricular ejection fraction $\leq 35\%$ were randomized to eplerenone or placebo, added to other recommended therapies. The primary outcome was a composite of death from cardiovascular causes or hospitalization for HF (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 [hazard ratio (HR) 0.63, 95% confidence interval (CI) 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 pre-specified dose allocation was performed, patients with eGFR < 50 mL/min/1.73 m^2 had higher incidence of serious hyperkalaemia with eplerenone compared to placebo (10.1% vs. 5.9%; $P = 0.006$), whereas in patients with an eGFR ≥ 50 mL/min/1.73 m^2 the corresponding hyperkalaemia 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 pre-specification.

In concordance, placebo/eplerenone was started at a dose of ≤ 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 30–49 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 5.5–5.9 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 h after dose reduction or study drug withdrawal, and the study drug was to be restarted only if the level was < 5.0 mmol/L.

Statistical analysis

In descriptive analyses, continuous variables are expressed as mean ± standard deviation. 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 vs. 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 cardiovascular mortality. 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, eGFR,[11] diabetes, prior HFH, haemoglobin, prior myocardial infarction/coronary artery bypass grafting, and body mass index.

All analyses were performed with SAS® software version 9.4 (SAS Institute Inc., Cary, NC, 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 estimated glomerular filtration rate strata

The mean eplerenone/placebo doses in the eGFR ≥ 50 mL/min/1.73 m^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 30–49 mL/min/1.73 m^2 stratum were < 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* & *Figure 2*).

Comparison of eplerenone with placebo by estimated glomerular filtration rate strata

The event rate reduction with eplerenone compared to placebo was similar within each eGFR stratum [eplerenone vs. placebo in the eGFR ≥ 50 mL/min/1.73 m^2 stratum: HR 0.58, 95% CI 0.45–0.74; and eplerenone vs. placebo in the eGFR

Table 1 Comparison of patients within each estimated glomerular filtration rate stratum at week 4

Patient characteristics	eGFR stratum					
	≥ 50 mL/min/1.73 m²		*P*-value	30–49 mL/min/1.73 m²		*P*-value
	High-dose eplerenone (*n* = 742)	High-dose placebo (*n* = 825)		Low-dose eplerenone (*n* = 618)	Low-dose placebo (*n* = 544)	
Demographics						
Age (years)	67.7 ± 7.3	67.7 ± 7.4	NS	69.8 ± 7.9	70.1 ± 7.0	NS
Male gender, *n* (%)	579 (78)	660 (80)	NS	474 (77)	409 (75)	NS
BMI (kg/m²)	27.6 ± 4.9	27.6 ± 4.7	NS	27.4 ± 5.0	27.4 ± 5.0	NS
SBP (mmHg)	125 ± 17	125 ± 16	NS	123 ± 18	122 ± 17	NS
Heart rate (b.p.m.)	74 ± 16	73 ± 15	NS	73 ± 15	74 ± 16	NS
Laboratory						
eGFR (mL/min/1.73 m²)	78 ± 20	76 ± 20	0.048	63 ± 20	62 ± 22	NS
Haemoglobin (g/dL)	13.9 ± 1.5	13.9 ± 1.6	NS	13.7 ± 1.6	13.6 ± 1.6	NS
Sodium (mmol/L)	140 ± 4	140 ± 4	NS	140 ± 4	139 ± 4	NS
Potassium (mmo/L)	4.2 ± 0.4	4.3 ± 0.4	<0.001	4.3 ± 0.5	4.3 ± 0.4	NS
Echocardiography						
LVEF (%)	26 ± 5	26 ± 5	NS	26 ± 5	26 ± 5	NS
Co-morbidities, *n* (%)						
Diabetes	235 (32)	225 (27)	NS	222 (36)	173 (32)	NS
AF	221 (30)	243 (30)	NS	188 (30)	189 (35)	NS
Prior HFH	365 (49)	409 (50)	NS	346 (56)	313 (58)	NS
Prior MI	378 (51)	414 (50)	NS	352 (57)	279 (51)	NS
ICD/CRT	133 (18)	160 (19)	NS	166 (27)	150 (28)	NS
Medications, *n* (%)						
ACEi/ARB	708 (95)	784 (95)	NS	589 (95)	507 (93)	NS
Beta-blocker	661 (89)	745 (90)	NS	540 (87)	468 (86)	NS

ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BMI, body mass index; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; HFH, hospitalization for heart failure; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; MI, myocardial infarction; SBP, systolic blood pressure.

Table 2 Mean eplerenone/placebo doses (in mg) within each estimated glomerular filtration rate stratum during the trial

	eGFR stratum			
	≥ 50 mL/min/1.73 m²		30–49 mL/min/1.73 m²	
	High-dose eplerenone	High-dose placebo	Low-dose eplerenone	Low-dose placebo
Study start	24.7 ± 2.6	24.8 ± 2.7	17.0 ± 6.4	16.1 ± 5.6
Week 4	38.9 ± 13.2	40.4 ± 12.7	23.4 ± 9.6	23.3 ± 9.8
Month 5	42.0 ± 12.3	43.6 ± 11.2	24.8 ± 10.8	27.3 ± 11.6
Month 12	42.3 ± 12.4	43.9 ± 11.1	26.8 ± 12.3	30.2 ± 12.6
Month 24	41.6 ± 12.5	43.7 ± 11.3	28.0 ± 11.2	30.8 ± 12.7
Study end	39.8 ± 13.3	41.8 ± 12.3	24.6 ± 11.6	26.3 ± 12.7

eGFR, estimated glomerular filtration rate.

30–49 mL/min/1.73 m² stratum: HR 0.62, 95% CI 0.49–0.78; between strata $P_{interaction} = 0.89$] (*Table 3* and *Figure 1*).

Adverse events

Hyperkalaemia ($K^+ > 5.5$ mmol/L) was more frequent with eplerenone compared to placebo regardless of the eGFR stratum. However, hyperkalaemia, renal failure and drug discontinuation were more frequent with low-dose eplerenone/placebo (i.e. eGFR 30–49 mL/min/1.73 m² stratum) compared with high-dose (i.e. eGFR ≥ 50 mL/min/1.73 m² stratum). For example, hyperkalaemia was observed in 1% and 4% of patients randomized to placebo and eplerenone, respectively, in the eGFR ≥ 50 mL/min/1.73 m² stratum, whereas these proportions increased to 7% with placebo and 13% with eplerenone in the eGFR 30–49 mL/min/1.73 m² stratum ($P < 0.001$) (*Table 4*).

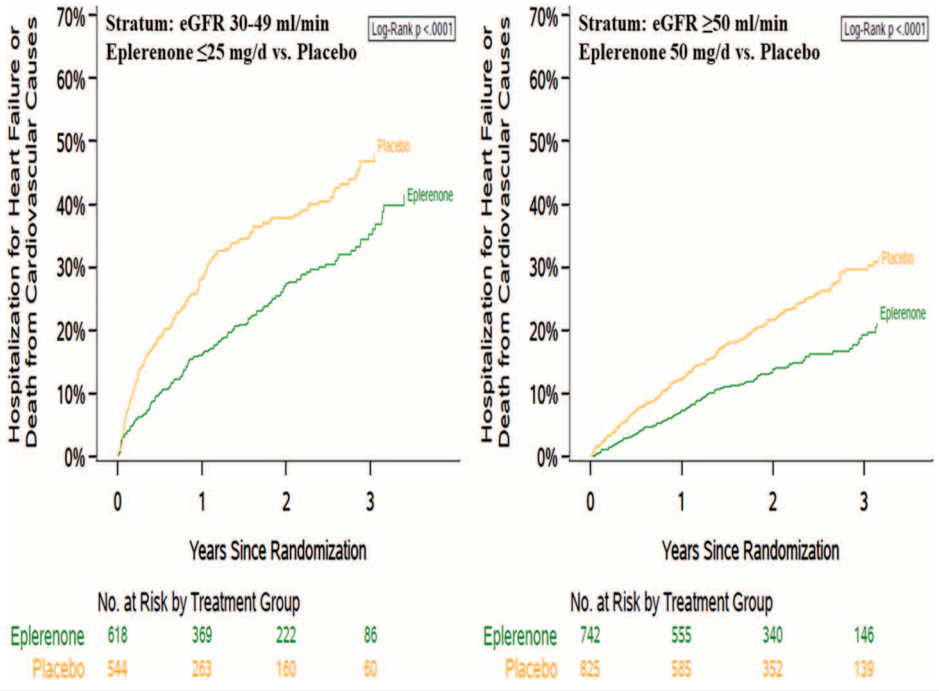

Figure 1 Kaplan–Meier curves for the primary outcome of hospitalization for heart failure or cardiovascular mortality of eplerenone vs. placebo within estimated glomerular filtration rate (eGFR) strata. Between eGFR strata. $P_{interaction} = 0.89$.

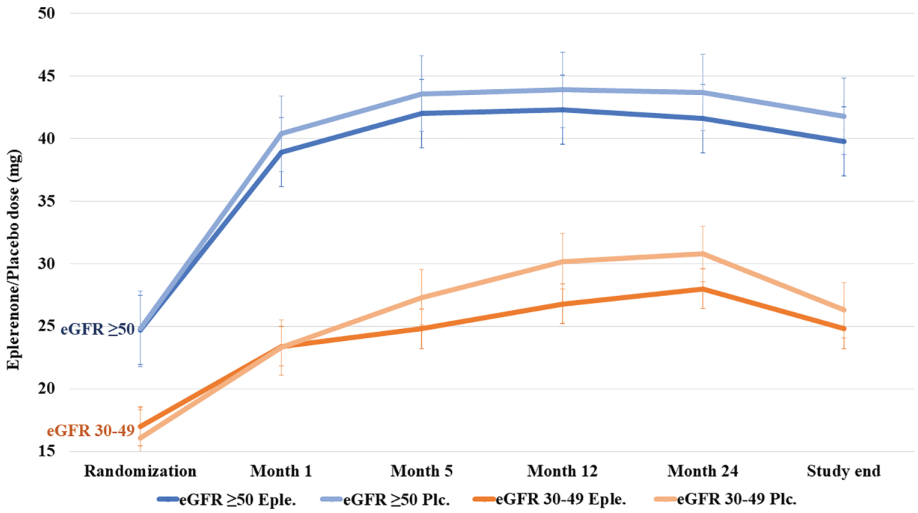

Figure 2 Eplerenone doses by renal function strata. eGFR, estimated glomerular filtration rate in mL/min/1.73 m^2; Eple., eplerenone; Plc., placebo.

Discussion

In EMPHASIS-HF, the efficacy of eplerenone was not influenced by 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 < 50 mL/min/1.73 m^2, and despite these lower doses, adverse 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 rates of adverse events and drug discontinuation. Current HFrEF treatment guidelines do not specify that the initial dose of eplerenone should be adjusted according to renal function. However, we believe that these data show that they should, in keeping with the EMPHASIS-HF protocol.

Table 3 Adjusted hazard ratio within each estimated glomerular filtration rate strata

Study outcomes	eGFR stratum									$P_{interaction}$
	≥ 50 mL/min/1.73 m²: high-dose eplerenone vs. placebo					30–49 mL/min/1.73 m²: low-dose eplerenone vs. placebo				
	Events, *n* (%)		ARD (%)	HR (95% CI)[a]	*P*-value	Events, *n* (%)		ARD (%)	HR (95% CI)[a]	*P*-value	
	Eplerenone	Placebo				Eplerenone	Placebo				
HFH/CVM	100 (13.5)	178 (21.6)	−8.1	0.58 (0.45–0.74)	<0.001	149 (24.1)	177 (32.5)	−8.4	0.62 (0.49–0.78)	<0.001	0.89
CVM	51 (6.9)	89 (10.8)	−3.9	0.61 (0.43–0.86)	0.004	96 (15.5)	95 (17.5)	−1.9	0.77 (0.58–1.04)	0.084	
HFH[b]	69 (9.3)	126 (15.3)	−6.0	0.56 (0.42–0.76)	<0.001	95 (15.4)	127 (23.3)	−8.0	0.55 (0.41–0.72)	<0.001	

ARD, absolute risk difference; CI, confidence interval; CVM, cardiovascular mortality; eGFR, estimated glomerular filtration rate; HFH, hospitalization for heart failure; HR, hazard ratio.
[a]Model adjusted on age (≥ 75 vs. < 75 year), gender (male vs. female), systolic blood pressure (< 130 vs. ≥ 130 mmHg), heart rate (< 80 vs. ≥ 80 b.p.m.), diabetes (yes vs. no), haemoglobin (< 11 vs. 11–12.9 vs. ≥ 13 g/dL), prior HFH (yes vs. no), eGFR (< 60 vs. ≥ 60 mL/min/1.73 m²), prior myocardial infarction/coronary artery bypass graft (yes vs. no), body mass index (< 25 vs. ≥ 25 kg/m²). Note: unadjusted models provide similar results.
[b]Rate ratio including repeated events.

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 ACEi or ARB: the Assessment of Treatment with Lisinopril and Survival (ATLAS) trial[12] and the Heart failure Endpoint evaluation with the Angiotensin II Antagonist Losartan (HEAAL) trial.[13] In ATLAS, 3164 HF patients with an ejection fraction ≤ 30% were randomized to double-blind treatment with either low doses (2.5–5.0 mg/day, $n = 1596$) or high doses (32.5–35 mg/day, $n = 1568$) of the ACEi 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 HFH ($P = 0.002$). Drug discontinuation due to side effects was similar between groups.[12] In HEAAL, 3846 HF patients with an ejection fraction ≤ 40% and intolerance to ACEi were randomly assigned to low dose (50 mg/day, $n = 1919$) or high dose (150 mg/day, $n = 1927$) 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 HFH ($P = 0.027$) and 13% fewer HFH ($P = 0.025$). Drug discontinuation due to side effects was also similar between groups.[13] These findings indicate that HF patients should not be maintained on low doses of an ACEi or ARB (unless these are the only doses that can be tolerated). In contrast, mineralocorticoid receptor antagonist dose comparisons have not been performed 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 30–49 mL/min/1.73 m² and high dose for patients with eGFR ≥ 50 mL/min/1.73 m²), supporting the use of eplerenone at doses around 25 mg/day in patients with eGFR 30–49 mL/min/1.73 m² and around 50 mg/day in patients with eGFR ≥ 50 mL/min/1.73 m², adapting for potassium levels if required.

Stratification is usually performed to ensure that powerful predictors of outcome or response to treatment 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.[14] Therefore, stratified analyses are less susceptible to bias caused by imbalances in treatment allocation and patient characteristics, which inevitably hamper all analyses made on subgroups based on non-randomized baseline characteristics. In the absence of a statistical interaction (i.e. similar between-strata HRs, 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 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 rates of hyperkalaemia and drug discontinuation.[15]

Table 4 Investigator-reported adverse events by allocation dose

Adverse event	eGFR stratum						*P*-value high vs. low-dose eplerenone	*P*-value high vs. low-dose placebo
	≥ 50 mL/min/1.73 m^2		*P*-value	30–49 mL/min/1.73 m^2		*P*-value		
	High-dose eplerenone	High-dose placebo		Low-dose eplerenone	Low-dose placebo			
Hyperkalaemia	27 (3.6%)	11 (1.3%)	0.005	82 (13.3%)	39 (7.2%)	< 0.001	< 0.001	< 0.001
Hypokalaemia	5 (0.7%)	18 (2.2%)	0.018	11 (1.8%)	12 (2.2%)	0.68	0.064	1
Renal failure	9 (1.2%)	14 (1.7%)	0.53	29 (4.7%)	27 (5.0%)	0.89	< 0.001	0.001
Drug discontinuation	74 (10.0%)	108 (13.1%)	0.058	114 (18.4%)	114 (21.0%)	0.30	< 0.001	< 0.001

eGFR, estimated glomerular filtration rate.

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/1.73 m^2 and 25 mg/day in patients with eGFR between 30 and 49 mL/min/1.73 m^2.

Limitations

This is an analysis of pre-specified 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 dose was stratified according to renal function and the treatment effect was not influenced by renal function: 25 mg/day in patients with eGFR 30–49 mL/min/1.73 m^2 were as effective as 50 mg/day in patients with eGFR > =50 mL/min/1.73 m^2. However, patients with impaired renal function experienced more adverse events despite reveiving lower eplerenone doses. Current guidelines do not recommend tailoring the dose of eplereone according to renal function but the current data suggest they should.

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Conflict of interest: 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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