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RESEARCH ARTICLE

Aspirin does not reduce the clinical benefits of the mineralocorticoid receptor antagonist eplerenone in patients with systolic heart failure and mild symptoms: an analysis of the EMPHASIS-HF study

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Aims It is not known whether concomitant use of aspirin might attenuate the beneficial effects of mineralocorticoid receptor antagonists (MRAs). The purpose of this subgroup analysis was to explore the interaction between baseline aspirin treatment and the effect of eplerenone on the primary efficacy outcomes (composite of hospitalization for heart failure or cardiovascular mortality), its components, and safety markers [estimated glomerular filtration rate (eGFR), systolic blood pressure (SBP), and serum potassium >5.5 mmol/L] in the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure trial (EMPHASIS-HF).

Methods and results Patients with chronic heart failure, reduced ejection fraction (HFREF), and mild symptoms were enrolled in EMPHASIS-HF. We evaluated baseline characteristics according to aspirin use. We explored the interaction between aspirin and eplerenone, using Cox proportional hazards models providing adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) and *P*-values for interaction. Of the 2737 patients randomized, 1605 patients (58.6%) were taking aspirin. The beneficial effects of eplerenone on the primary endpoint were similar in patients not treated (adjusted HR 0.59, 95% CI 0.46–0.75) or treated (adjusted HR 0.71, 95% CI 0.59–0.87) with aspirin at baseline (interaction *P*-value = 0.19). We did not observe any significant modification of the safety markers by aspirin that was clinically meaningful.

Conclusion Aspirin use in patients with chronic systolic heart failure and mild symptoms did not substantially reduce the overall beneficial effects of the MRA eplerenone contrary to what has been described in some studies with ACE inhibitors.

Keywords Heart failure • Aspirin • Eplerenone • Aldosterone • Bradykinin

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Introduction

The potential antagonistic effect between aspirin and ACE inhibitors has been an area of intense debate following publication of a pre-specified subgroup analysis of the Studies of Left Ventricular Dysfunction (SOLVD) trial.[1] Several studies provided conflicting data on the clinical significance of this potential detrimental interaction in heart failure (HF) patients.[2–7] Mechanistically, however, such an interaction is possible given the potential role of stimulation of vasodilator prostaglandins in the action of ACE inhibitors and the inhibitory action of aspirin on the production of these substances.

Mineralocorticoid receptor antagonists (MRAs) reduced morbidity and mortality in several landmark studies.[8–10] Pharmacological interactions between aspirin and the MRA spironolactone have been described previously.[11–13] Spironolactone was reported to increase reno-medullary prostaglandin synthesis.[11] Aspirin has been reported to decrease the natriuretic effect of spironolactone, possibly through active competition for the renal tubular secretion mechanism or mineralocorticoid receptor blockade.[11–13] Therefore, a clinically meaningful adverse interaction between aspirin and MRAs is theoretically plausible and could potentially lead to detrimental outcomes in HF patients. However, the potentially deleterious impact of aspirin–MRA counteraction on clinical outcomes (if any) is uncertain, especially with eplerenone, a selective MRA.

While there was no apparent effect of aspirin use at baseline on the beneficial effects of eplerenone in patients with early post-acute myocardial infarction (AMI) complicated by LV systolic dysfunction (LVSD) and HF (EPHESUS),[14] its effect on the risk/benefit of eplerenone in patients with chronic HF and a reduced ejection fraction (HFREF) with mild symptoms has not been investigated. It is therefore of both therapeutic and mechanistic interest to evaluate the impact of concomitant administration of aspirin to patients with HF who are receiving MRAs. To address this, we conducted a pre-specified subgroup analysis on the safety and efficacy of eplerenone according to baseline aspirin use in EMPHASIS-HF.

Methods

Study design and patient population

The design and primary results of EMPHASIS-HF have been reported elsewhere.[10,15] Briefly, patients with NYHA class II symptoms, who were >55 years of age, with an EF of no more than 30% (or 30–35% if QRS duration >130 ms), as well as receiving standard background HF therapy, comprising ACE inhibitors, an ARB (or both), and a beta-blocker (BB) at recommended or maximal tolerated doses, and had been hospitalized for cardiovascular reasons within the past 6 months (or had a plasma BNP of at least 250 pg/mL or NT-proBNP ≥500 pg/mL for males and ≥750 pg/mL for females within 15 days prior to randomization) were eligible for enrolment. Investigators were encouraged to up-titrate patients to the highest stable doses of these therapies before randomization into the EMPHASIS-HF study. Key exclusion criteria included an indication for MRA treatment according to current HF guidelines, need for adjunctive potassium-sparing diuretic therapy, serum potassium >5.0 mmol/L within 24 h prior to randomization, estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 within 24 h prior to randomization, and any other pre-existing and ongoing significant co-morbid condition.

Patients were randomized to receive either eplerenone (up to 50 mg daily) or placebo, in addition to recommended therapy. Patients were seen 4 weeks after randomization and then every 4 months during trial follow-up. The primary outcome was the composite of death from cardiovascular causes or HF hospitalization. The trial was stopped prematurely for overwhelming benefit, after a median follow-up period of 21 months.

Patients analysed

The analysis included all randomized patients in EMPHASIS-HF. Aspirin use was determined from the screening and baseline concomitant drug treatment pages of the study case report form.

Statistical analysis

We compared the characteristics of patients according to aspirin use at baseline. *P*-values were calculated using a χ^2 test or two-sample *t*-test as appropriate. Event rates for the primary composite outcome and its components were calculated according to study treatment assignment (eplerenone or placebo) and baseline aspirin use. Efficacy analyses were performed using a multivariable Cox proportional hazards models, including treatment, baseline aspirin, and treatment by baseline aspirin interaction. Models were also adjusted for the EMPHASIS-HF risk score.[16] The effect of eplerenone (and any interaction with aspirin) on safety markers including eGFR, systolic blood pressure (SBP), and serum potassium >5.5 mmol/L were also investigated. Comparisons at each visit were made using linear regression models adjusting for baseline values. Overall comparisons were made using mixed models adjusting for baseline values.

All *P*-values were two sided, and $P < 0.05$ was considered statistically significant. Analyses were performed using Stata Version 13 (StataCorp 2013).

Results

Baseline characteristics according to aspirin use

The baseline characteristics of the patients, based on aspirin use, are presented in *Table 1*. Of the 2737 patients randomized, 1605 patients (58.6%) were taking aspirin. Patients not taking aspirin were more likely to have atrial fibrillation/flutter, as well as to be receiving treatment with digoxin and oral anticoagulants compared with aspirin users ($P < 0.0001$). Patients on aspirin therapy were more likely to be overweight and have a history of hypertension, diabetes, coronary heart disease, and coronary revascularization. Aspirin users were also more likely to be treated with an ACE inhibitor/ARB and BB. Of note, an ACE inhibitor/ARB and a BB were used in >85% of patients.

Study outcomes

The primary and secondary endpoints according to treatment and baseline aspirin use are summarized in *Figures 1* and *2*. Baseline treatment with aspirin did not significantly attenuate the effect of

Table 1 Association between baseline aspirin use and other baseline variables in EMPHASIS-HF

	Baseline aspirin use		*P*-value[a]
	Yes ($n = 1605$)	No ($n = 1132$)	
Treatment group, *n* (%)			
Placebo	821 (51.2)	552 (48.8)	
Eplerenone	784 (48.9)	580 (51.2)	0.22
Sex, *n* (%)			
Male	1261 (78.6)	866 (76.5)	
Female	344 (21.4)	266 (23.5)	0.20
Age, *n* (%)			
<75 years	1222 (76.1)	858 (75.8)	
75+ years	383 (23.9)	274 (24.2)	0.84
Mean (SD), years	68.7 (7.6)	68.6 (7.8)	0.81
Vital signs, mean (SD)			
SBP, mmHg	125.3 (16.5)	122.5 (17.3)	<0.0001
DBP, mmHg	75.0 (10.1)	74.2 (10.4)	0.055
Heart rate, b.p.m.	72.1 (14.9)	75.4 (16.2)	<0.0001
Race, *n* (%)			
White	1330 (82.9)	937 (82.8)	
Black	34 (2.1)	33 (2.9)	
Asian	190 (11.8)	127 (11.2)	
Other	51 (3.2)	35 (3.1)	0.58
Region, *n* (%)			
Asia/Middle East/Africa	228 (14.2)	152 (13.4)	
East Europe	595 (37.1)	316 (27.9)	
South/North America	219 (13.6)	127 (11.2)	
West Europe/Australia	563 (35.1)	537 (47.4)	<0.0001
Heart failure diagnosis, *n* (%)			
Ischaemic	1295 (80.7)	591 (52.2)	
Non-ischaemic	307 (19.1)	539 (47.6)	
Unknown	3 (0.2)	2 (0.2)	<0.0001
Days since index event, *n* (%)			
0–41	681 (48.5)	481 (51.6)	
42+	724 (51.5)	452 (48.5)	0.14
Co-morbidities, *n* (%) yes			
Previous HFH	819 (51.0)	620 (54.8)	0.051
Previous MI	992 (61.8)	389 (34.4)	<0.0001
Angina	848 (52.8)	341 (30.2)	<0.0001
Ischaemic stroke	116 (7.3)	79 (7.0)	0.83
Overweight (BMI 25+)	1147 (71.9)	759 (67.4)	0.012
Hypertension	1142 (71.2)	677 (59.9)	<0.0001
Diabetes	530 (33.0)	329 (29.1)	0.029
CABG	351 (21.9)	165 (14.6)	<0.0001
PCI	455 (28.4)	141(12.5)	<0.0001
Atrial fibrillation/flutter	322 (20.1)	522 (46.2)	<0.0001
Medications, *n* (%) yes			
Beta-blockers	1414 (88.1)	956 (84.5)	0.006
Diuretics	1340 (83.5)	972 (85.9)	0.091
ACE inhibitor	1331 (82.9)	870 (76.9)	<0.0001
ARB	283 (17.6)	238 (21.0)	0.026
ACE inhibitor or ARB	1533 (95.5)	1057 (93.4)	0.014
Digoxin	240 (15.0)	276 (24.4)	<0.0001
Oral anticoagulants	136 (8.5)	356 (31.5)	<0.0001

BMI, body mass index; DBP, diastolic blood pressure; HFH, heart failure hospitalization; MI, myocardial infarction; SBP, systolic blood pressure.
[a]*P*-value from χ^2 test for categorical variables or two-sample *t*-test for comparison of means.

eplerenone on the primary endpoint (either a first hospitalization for HF or a cardiovascular death). The adjusted hazard ratio (HR; eplerenone vs. placebo) was 0.59 [95% confidence interval (CI) 0.46–0.75] in those not treated with aspirin compared with 0.71 (95% CI 0.59–0.87) in patients treated with aspirin (*P* for interaction = 0.19).

Baseline treatment with aspirin did not significantly reduce the effect of eplerenone on cardiovascular death. The adjusted HR for cardiovascular death was 0.69 (95% CI 0.50–0.94) in those not treated with aspirin compared with 0.86 (95% CI 0.67–1.12) in patients treated with aspirin (*P* for interaction = 0.25).

There was borderline evidence that baseline treatment with aspirin did modify the effect of eplerenone on HF hospitalization. The adjusted HR for HF hospitalization was 0.48 (95% CI 0.35–0.65) in those not treated with aspirin compared with 0.69 (95% CI 0.54–0.87) in patients treated with aspirin (*P* for interaction = 0.05).

Baseline treatment with aspirin did not significantly attenuate the effect of eplerenone on all-cause mortality. The adjusted HR for all-cause mortality was 0.69 (95% CI 0.52–0.92) in those not treated with aspirin compared with 0.82 (95% CI 0.65–1.05) in patients treated with aspirin (*P* for interaction = 0.34).

Safety markers

The mean change in eGFR from baseline in patients randomized to eplerenone compared with placebo was −2.06 (95% CI −3.21 to −0.91; $P < 0.001$). eGFR in those not treated with aspirin was reduced by −1.89 mL/min/1.73 m^2 (95% CI −3.63 to −0.15) from baseline compared with −2.13 mL/min/1.73 m^2 (95% CI −3.66 to −0.60) in patients treated with aspirin (*P* for interaction = 0.83) (*Table 2*).

Figure 3 shows the mean change in SBP from baseline over the 37 months of follow-up. The mean change in SBP from baseline in patients randomized to eplerenone compared with placebo was −1.81 mmHg (95% CI −2.58 to −1.03; $P < 0.001$). SBP in those not treated with aspirin was reduced by −1.28 mmHg (95% CI −2.41 to 0.06) from baseline compared with −2.17 mmHg (95% CI −3.17 to −1.16) in patients treated with aspirin (*P* for interaction = 0.26).

Patients randomized to eplerenone were more likely to have potassium >5.5 mmol/L during the follow-up compared with those receiving placebo (11.0% vs. 6.7%, $P < 0.001$). There was no evidence of an interaction between aspirin and eplerenone in having potassium >5.5 mmol/L at any point during follow-up (*P* for interaction = 0.46) (*Table 3*).

Discussion

The present findings showed that concurrent use of aspirin did not attenuate the overall beneficial effects of eplerenone in patients with chronic HF and mild symptoms. Although our results showed that there was borderline evidence of concomitant use of aspirin modifying the effects of eplerenone on the risk of hospitalization for HF, the overall clinical benefits of eplerenone were preserved among aspirin users. The clinical benefits of eplerenone were

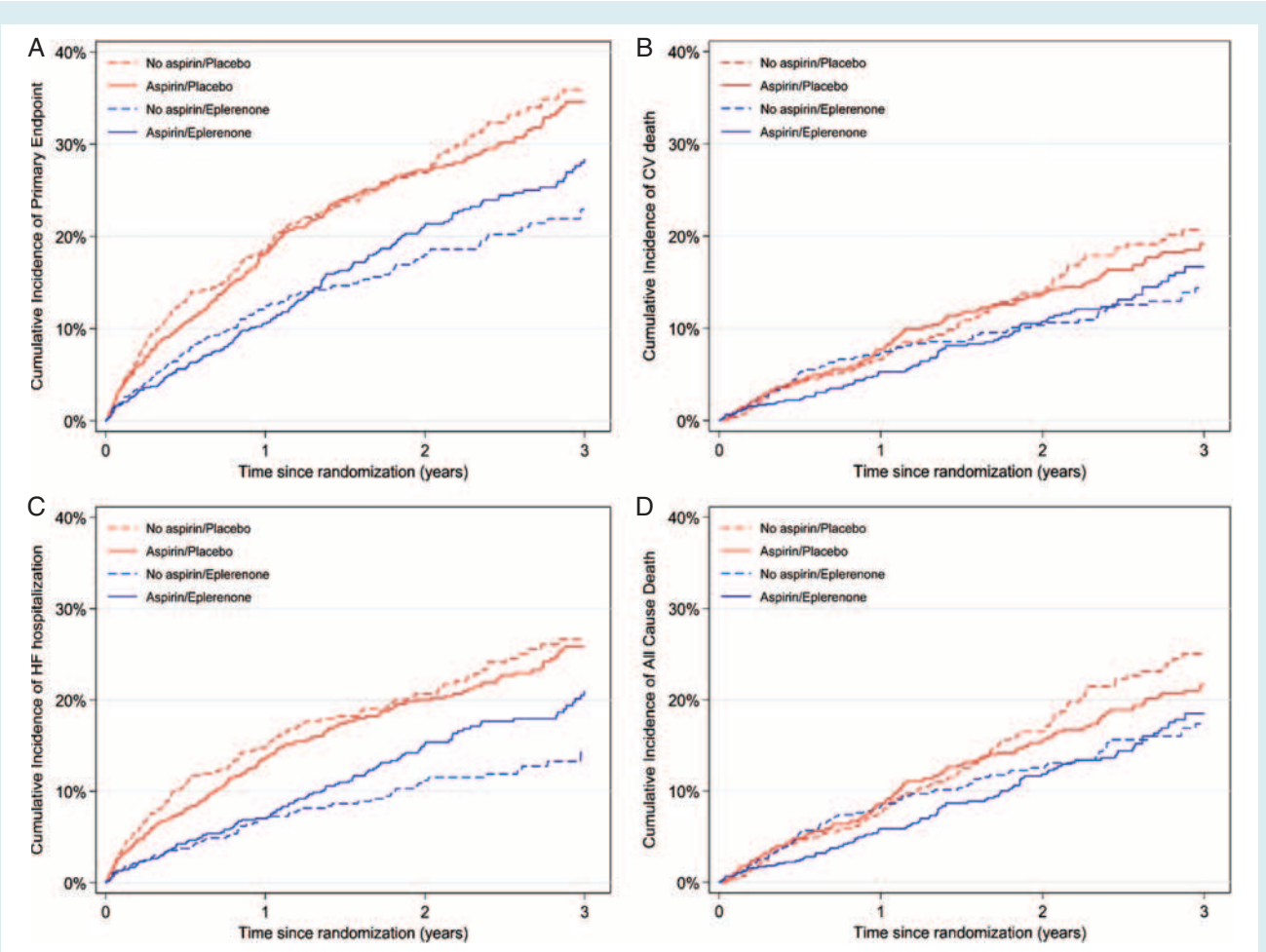

Figure 1 Kaplan–Meier cumulative incidence of the primary and secondary endpoints by baseline aspirin use and treatment. (*A*) Primary endpoint [cardiovascular (CV) death/heart failure (HF) hospitalization]. (*B*) CV death. (C) HF hospitalization. (D) All-cause death.

obtained even though nearly all patients were also treated with other effective pharmacological agents (i.e. ACE inhibitors/ARBs and a BB). Our data showed that while eplerenone use was associated with greater reductions in eGFR and SBP, and a higher risk of hyperkalaemia, these changes appeared to be no different in the presence of aspirin.

Prostaglandin I_2 and prostaglandin E_2 are potent vasodilators and may play an important role in counteracting excessive vasoconstrictive effects of other neurohormonal pathways in HF patients.[17,18] Mean circulating levels of these prostaglandins have been shown to be 3–10 times higher in patients with severe congestive HF with hyponatraemia, a marker of renin–angiotensin–aldosterone system (RAAS) activation, compared with healthy individuals.[18] While the inhibitory action of aspirin on prostaglandin synthesis is well documented, previous reports of aspirin decreasing the natriuretic effect and reno-medullary prostaglandin synthesis of spironolactone suggest that the impact of this interaction on the clinical outcomes in patients with HF is worth investigating.

Concomitant CAD is the leading cause of systolic HF. More than 60% of patients enrolled in major systolic HF trials such as Studies of Left Ventricular Dysfunction Treatment trial (SOLVD-T), Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity-Added (CHARM-Added), EMPHASIS HF, and Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM HF) were found to have an ischaemic aetiology.[19] There is a widely held belief that aspirin has a protective role in patients at increased risk of occlusive vascular events.[20,21] Because of these two factors, aspirin and MRAs are widely used together in patients with HF.

The beneficial clinical effects of MRAs have been clearly demonstrated in patients with moderate to severe HF (RALES), chronic HF with mild symptoms (EMPHASIS-HF), and post-acute myocardial infarction patients with LVSD and HF (EPHESUS). In these trials, a large number of the patients had concomitant CAD and were taking aspirin. Specifically, aspirin use rates in our study were 58.6% compared with 88.5% in EPHESUS; and 36.5% in RALES.[8,14] Prior findings from EPHESUS subgroup analyses suggested that the concomitant use of aspirin at baseline did not significantly influence the beneficial effects of eplerenone in that

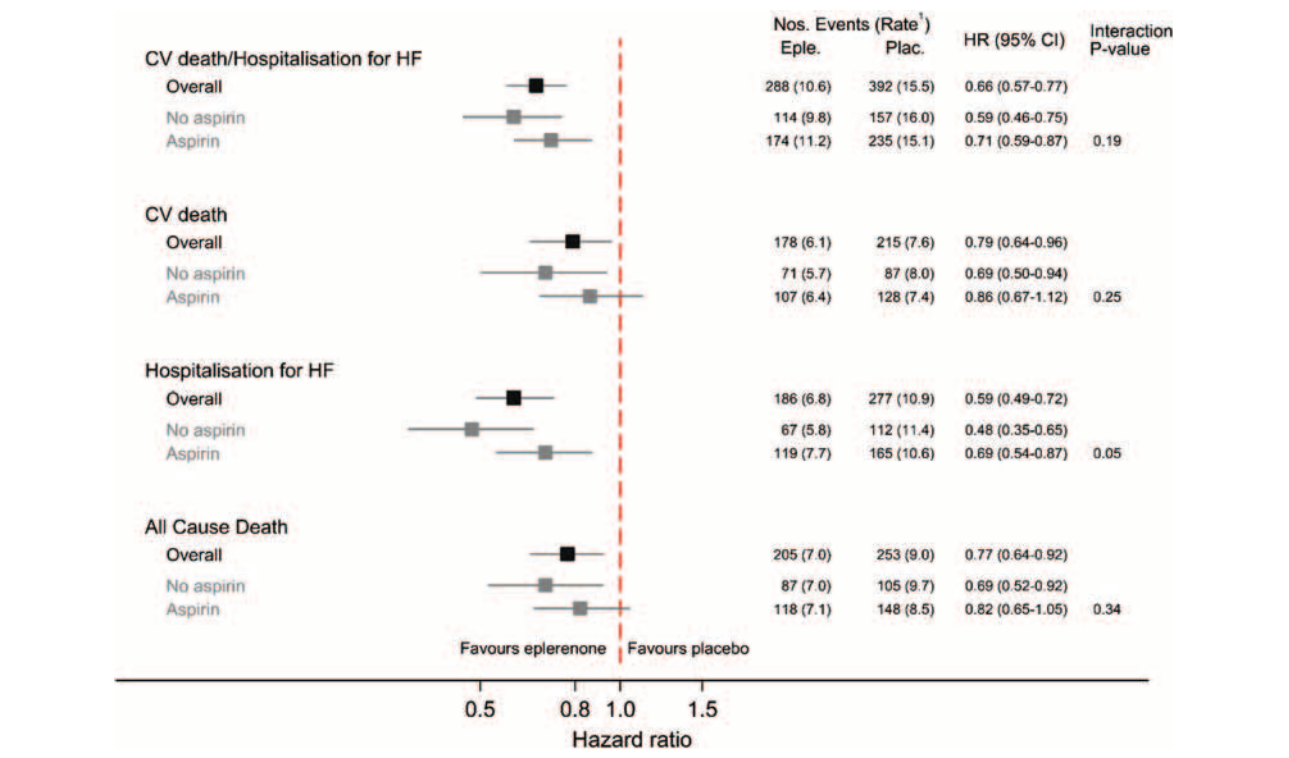

Figure 2 Primary and secondary endpoints according to baseline aspirin use. CI, confidence interval; CV, cardiovascular; Eple, eplerenone; HF, heart failure; HR, hazard ratio; Nos events (rate[1]), number of events (event rate per 100 person-years); Plac, placebo.

Table 2 Difference in mean change from baseline estimated glomerular filtration rate by treatment and aspirin use

	All patients			No aspirin		Aspirin		
Visit	Mean	95% CI	*P*-value	Mean	95% CI	Mean	95% CI	Interaction *P*-value
Month 5	−2.46	(−3.79 to −1.12)	<0.001	−2.47	(−4.50 to −0.44)	−2.36	(−4.15 to −0.58)	0.95
Month 13	−1.57	(−3.10 to −0.03)	0.046	−1.92	(−4.29 to 0.45)	−1.28	(−3.31 to 0.75)	0.68
Month 21	−2.36	(−4.28 to −0.44)	0.016	−2.41	(−5.42 to 0.59)	−2.36	(−4.88 to 0.16)	0.98
Month 29	0.43	(−1.88 to 2.750)	0.71	−0.68	(−4.38 to 3.02)	1.30	(−1.68 to 4.29)	0.40
Month 37	0.41	(−2.87 to 3.69)	0.80	−1.23	(−6.40 to 3.93)	1.21	(−3.11 to 5.52)	0.54
Month 42	0.66	(−5.24 to 6.55)	0.83	5.10	(−4.98 to 15.17)	−2.05	(−9.64 to 5.53)	0.34
Month 48	−0.85	(−8.25 to 6.55)	0.82	2.28	(−6.73 to 11.30)	−4.90	(−17.31 to 7.51)	0.30
Overall	−2.06	(−3.21 to −0.91)	<0.001	−1.89	(−3.63 to −0.15)	−2.13	(−3.66 to −0.60)	0.83

CI, confidence interval.

study (death from any cause, *P* for interaction = 0.63; death from cardiovascular causes or hospitalization for cardiovascular events, *P* for interaction = 0.33).[14]

The data presented here confirm such findings, i.e. the addition of eplerenone in patients already receiving standard HF therapy as well as aspirin was well tolerated along with preserving the substantial clinical benefits of eplerenone, albeit with borderline evidence of a modified effect on hospitalization for HF. The inhibitory effect of aspirin on prostaglandin synthesis does not offset the overall benefit observed in the eplerenone group. However, haemodynamic and remodelling changes were not evaluated in this analysis; hence, we could not evaluate the presence (or absence) of an interaction between prostaglandins and aldosterone in cardiac remodelling processes in HF. In addition, our analysis could not confirm whether aspirin attenuated the beneficial effect of eplerenone on HF deaths.

Importantly, we did not observe any significant modification of the safety markers by aspirin that was clinically meaningful. The incidence of mild hyperkalaemia (serum potassium >5.5 mmol/L) and mean change of SBP and renal function from baseline among

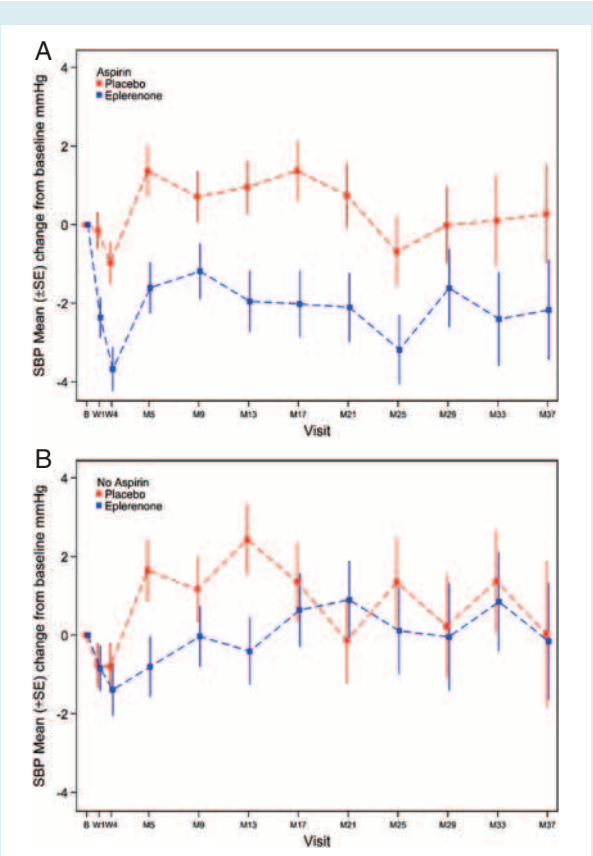

Figure 3 Mean change of systolic blood pressure (SBP) from baseline over the follow-up by treatment and aspirin use. (*A*) Patients with baseline aspirin use. (*B*) Patients without baseline aspirin use.

Table 3 Patients with potassium >5.5 mmol/L at any point during the follow-up period

	Total ($n = 2678$)	Eplerenone ($n = 1337$)	Placebo ($n = 1341$)	
All	237 (8.9%)	147 (11.0%)	90 (6.7%)	$P < 0.001$
No aspirin	82 (7.4%)	50 (8.7%)	32 (6.0%)	
Aspirin	155 (9.9%)	97 (12.7%)	58 (7.2%)	$P = 0.46$[a]

[a]Interaction *P*-value.

aspirin users in the eplerenone group is similar to that of the overall eplerenone group in our study and in EPHESUS.[10,14,22]

The EMPHASIS-HF trial was mainly conducted outside the USA. While low-dose aspirin is likely to be preferred at sites located outside the USA, high-dose aspirin (≥300 mg/day) is commonly prescribed in the USA.[23] The use of aspirin therapy during the conduct of our study was not analysed. Moreover, we did not determine the dosage of aspirin in this analysis, which may influence the outcomes of our analysis, as observed by Guazzi *et al.* and Meune *et al.*[24,25] In both studies, aspirin effects on vascular tone and survival rate in patients with HF who were taking ACE inhibitors were suggested to be dose related. Combinations of a high dose of aspirin (≥325 mg) with ACE inhibitors were observed to have significantly altered arterial functional properties and led to higher risk of death by 3% compared with patients who received a lower dose of aspirin (≤160 mg). Hence, our findings of an increased HF hospitalization rate with concomitant use of aspirin can be seen as hypothesis-generating, and future studies may be needed to evaluate whether the use of high-dose aspirin reduces the clinical benefits of MRAs.

Our study had several potential limitations. This is a subgroup analysis and therefore inadequately powered to evaluate subgroup–treatment effect interaction. Unmeasured variations could have confounded the findings. Since multiple comparisons were performed, the findings could be by chance. In addition, we only considered aspirin treatment at baseline for this analysis. Finally, our results may not be applicable to all patients with mild symptoms of HF, because, in order to be eligible for the study, patients had to have additional factors known to increase cardiovascular risk, including age >55 years, in most cases an EF of no greater than 30%, and a recent hospitalization for a cardiovascular reason.

In conclusion, background aspirin use in patients with mild symptoms of systolic HF does not offset the overall beneficial effect of eplerenone. The adverse interaction previously reported between aspirin and ACE inhibitors in patients with systolic HF in some but not all studies does not appear to occur with eplerenone in EMPHASIS-HF.

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Conflict of interest: H.K., B.P., J.J.V.M., K.S., D.J.vV., S.J.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. J.V. and E.T. are currently employed by Pfizer and own stock in Pfizer Inc., the makers of eplerenone. 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. 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. 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. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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