



Impact of eplerenone on major cardiovascular outcomes in patients with systolic heart failure according to baseline heart rate

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Abstract

Background Increased resting heart rate is a risk factor for cardiovascular mortality and morbidity. Mineralocorticoid receptor antagonists (MRAs) have been shown to improve cardiac sympathetic nerve activity, reduce heart rate and attenuate left ventricular remodelling. Whether or not the beneficial effects of MRA are affected by heart rate in heart failure patients with reduced ejection fraction (HFREF) is unclear.

Methods We undertook a secondary analysis of data from the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure study to assess if clinical outcomes, as well as the efficacy of eplerenone, varied according to heart rate at baseline.

Results High resting heart rate of 80 bpm and above predisposed patients to greater risk of all outcomes in the trial, regardless of treatment allocation. The beneficial effects of eplerenone were observed across all categories of heart rate. Eplerenone reduced the risk of primary endpoint, the composite of cardiovascular death and hospitalisation for heart failure, by 30% (aHR 0.70; 95% CI 0.54–0.91) in subjects with heart rate \geq 80 bpm, and by 48% (aHR 0.52; 95% CI 0.33–0.81) in subjects with heart rate \leq 60 bpm. Eplerenone also reduced the risks of hospitalisation for heart failure, cardiovascular deaths and all-cause deaths independently of baseline heart rate.

Conclusions Baseline heart rate appears to be an important predictor of major clinical outcome events in patients with HFREF, as has been previously reported. The benefits of eplerenone were preserved across all categories of baseline heart rate, without observed heterogeneity in the responses.

Keywords ClinicalTrials.gov identifier: NCT00232180 · Heart rate · Aldosterone antagonists · Aldosterone · Heart failure

In memory of Henry Krum.

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Introduction

Elevated resting heart rate is an established risk factor for cardiovascular mortality and morbidity in people with cardiovascular disease [1]. The magnitude of autonomic dysfunction is partly reflected by heart rate [2], and increased heart rate accelerates the progression of coronary atherosclerosis, as well as predisposes to myocardial ischaemia, ventricular arrhythmias and left ventricular dysfunction [3, 4].

Lower resting heart rate was associated with better prognosis for patients with heart failure with reduced ejection fraction (HFREF) in sinus rhythm, regardless of beta-blocker (BB) use in the Candesartan in Heart Failure: Assessment of Reduction in Mortality and morbidity (CHARM) program [5]. In a meta-analysis of randomised controlled trials comparing BB and placebo in patients with HFREF [6], higher heart rate was associated with a higher risk of

all-cause mortality for patients in sinus rhythm [adjusted hazards ratio (aHR), 1.11 per 10 beats per min (bpm); 95% confidence interval (CI) 1.07–1.15], but not atrial fibrillation (AF) (aHR 1.03 per 10 bpm; 95% CI 0.97–1.08). Furthermore, patients with the highest heart rates at baseline had the greatest reduction in outcomes after being treated with ivabradine in the Systolic Heart failure treatment with the *I*f inhibitor ivabradine Trial (SHIFT) [7].

Aldosterone is known to augment the sympathetic activity of catecholamines by attenuating their uptake by myocardial tissues, leading to autonomic dysfunction [8]. It also blunts the baroreceptor response by decreasing parasympathetic action via stimulation of $\text{Na}^+/\text{K}^+/\text{ATPase}$ [9]. It is for these reasons that the mineralocorticoid receptor antagonists (MRAs) improve cardiac autonomic function, reduce heart rate and attenuate left ventricular remodelling [10–12]. While the clinical benefits of MRAs are mainly driven by mineralocorticoid receptor antagonism, it is not known whether these effects vary according to heart rate. This is a relevant question in view of the interaction of MRAs with the sympathetic nervous system and because heart rate reflects sympathetic activity. Accordingly, we sought to determine the efficacy of the MRA eplerenone according to baseline heart rate in the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) study.

Methods

Study design and patient population

The patients involved in EMPHASIS-HF have been described in detail previously [13, 14]. In brief, patients were eligible for enrolment if they (1) had New York Heart Association (NYHA) class II symptoms; (2) were >55 years of age; (3) had an ejection fraction of no more than 30% (or 30–35% if QRS duration > 130 ms); (4) were receiving standard background heart failure therapy comprising angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB) (or both), and BB at recommended or maximal tolerated doses; and (5) had been hospitalised for cardiovascular reasons within the past 6 months, or had a plasma B-type natriuretic peptide (BNP) of at least 250 pg/mL or N terminal proBNP (NT-proBNP) \geq 500 pg/mL for males and \geq 750 pg/mL for females within 15 days prior to randomisation. Investigators were encouraged to up-titrate patients to the highest stable doses of these therapies before randomisation. Key exclusion criteria included an indication for MRA treatment according to current heart failure guidelines, need for adjunctive potassium-sparing diuretic therapy, serum potassium > 5.0 mmol/L within 24 h prior to randomisation, estimated glomerular filtration rate < 30 mL/

min/1.73 m² within 24 h prior to randomisation, and any other significant co-morbid condition.

Patients were randomised to receive either eplerenone (up to 50 mg daily) or placebo, in addition to recommended therapy. Patients were reviewed 4 weeks after randomisation and then every 4 months during follow-up. The primary outcome was the composite of death from cardiovascular causes or hospitalisation for heart failure. An independent Endpoint Events Committee adjudicated all the study endpoint events. The trial was stopped prematurely due to evidence of overwhelming benefit with eplerenone, after a median follow-up period of 21 months.

In the present analysis, we undertook a post hoc assessment of clinical outcomes according to heart rate at baseline, as well as of the efficacy of eplerenone according to baseline heart rate categories. Event rates for the primary composite outcome and its components were calculated according to study treatment assignment (eplerenone or placebo) and baseline heart rate was categorised a priori into the groups < 60, 60–69, 70–79 and 80 + bpm. The cut-points for these groups corresponded closely to those for quartiles of the heart rate distribution in the sample (62, 71, 82 bpm). The consequent event rates and 95% CI were based on the Poisson distribution, adjusted for age, sex, race, systolic blood pressure, body mass index, left ventricular ejection fraction, serum creatinine, cause of heart failure, duration of heart failure, diabetes mellitus, AF, hypertension, prior hospitalisation for heart failure, stroke, implantable cardioverter-defibrillator/cardiac-resynchronisation therapy and medications (ACE inhibitors/ARBs, BBs, BBs dose, non-dihydropyridine calcium channel blockers, digoxin and anti-arrhythmic agents). Efficacy analyses were performed using a multivariable Cox proportional hazards models, adjusted for the same list of covariates stated above. All *p* values were two sided. Analyses were performed using Stata Version 15 (StataCorp 2015).

Results

Baseline characteristics according to heart rate

Of the total of 2737 patients in the EMPHASIS-HF, data from 2736 patients were available for the analysis. Baseline characteristics of patients according to heart rate are summarised in Table 1. At baseline, a total of 844 (31%) had history of AF. Patients with higher baseline heart rate were younger, and more likely to have elevated diastolic blood pressure, non-ischaemic aetiology of heart failure, AF or flutter, diabetes, prior hospitalisation for heart failure, and be prescribed diuretics and digoxin. In contrast, patients with lower heart rate were more likely to be ex-smokers, have an ischaemic origin of heart failure, coronary artery disease, a

Table 1 Baseline patient characteristics in the EMPHASIS-HF study according to baseline heart rate categories

	Heart rate				<i>p</i> value ^a
	< 60 bpm (<i>N</i> =423)	60–69 bpm (<i>N</i> =792)	70–79 bpm (<i>N</i> =697)	80 + bpm (<i>N</i> =824)	
Eplerenone, <i>N</i> (%)	197 (46.6)	401 (50.6)	360 (51.6)	405 (49.2)	0.58
Age, years	69.3 (7.5)	68.8 (7.6)	68.9 (7.9)	68.0 (7.5)	0.006
Male, <i>N</i> (%)	344 (81.3)	616 (77.8)	533 (76.5)	633 (76.8)	0.10
Smoking, <i>N</i> (%)					<0.001
Never	173 (40.9)	334 (42.2)	324 (46.5)	391 (47.5)	
Current	38 (9.0)	83 (10.5)	74 (10.6)	98 (11.9)	
Ex	212 (50.1)	375 (47.3)	299 (42.9)	335 (40.7)	
Ethnicity, <i>N</i> (%)					<0.001
White	373 (88.2)	696 (87.9)	575 (82.5)	623 (75.6)	
Black	5 (1.2)	21 (2.7)	24 (3.4)	17 (2.1)	
Asian	30 (7.1)	53 (6.7)	72 (10.3)	161 (19.5)	
Other	15 (3.5)	22 (2.8)	26 (3.7)	23 (2.8)	
SBP, mmHg	125.8 (17.3)	124.4 (16.3)	123.9 (16.6)	123.2 (17.4)	0.009
DBP, mmHg	73.4 (10.5)	73.6 (9.8)	74.8 (10.1)	76.1 (10.4)	<0.001
LVEF, %	26.6 (4.2)	26.1 (4.7)	26.2 (4.7)	25.8 (4.7)	0.02
BMI, kg/m ²	27.6 (4.7)	27.4 (4.4)	27.6 (4.9)	27.6 (5.4)	0.81
Principal cause of heart failure, <i>N</i> (%)					<0.001
Ischaemic	309 (73.0)	578 (73.0)	469 (67.3)	530 (64.3)	
Non-ischaemic	113 (26.7)	214 (27.0)	227 (32.6)	292 (35.4)	
Unknown	1 (0.2)	0 (0.0)	1 (0.1)	2 (0.2)	
Duration of HF, years	4.9 (5.6)	5.3 (6.1)	4.7 (5.7)	4.0 (5.4)	<0.001
Medical history, <i>N</i> (%)					
Hospitalisation for heart failure	190 (44.9)	439 (55.4)	354 (50.8)	456 (55.3)	0.02
Hypertension	289 (68.3)	540 (68.2)	455 (65.3)	535 (64.9)	0.11
Angina	205 (48.5)	393 (49.6)	300 (43.0)	291 (35.3)	<0.001
Previous MI	246 (58.2)	450 (56.8)	340 (48.8)	345 (41.9)	<0.001
PCI	113 (26.7)	195 (24.6)	140 (20.1)	148 (18.0)	<0.001
CABG	84 (19.9)	185 (23.4)	122 (17.5)	125 (15.2)	<0.001
Atrial fibrillation or flutter	101 (23.9)	201 (25.4)	210 (30.1)	332 (40.3)	<0.001
Any pacemaker/CRT pacing	31 (7.3)	149 (18.8)	129 (18.5)	91 (11.1)	0.97
Left bundle branch block	101 (26.4)	169 (27.0)	158 (28.7)	180 (25.1)	0.65
Right bundle branch block	27 (7.0)	45 (7.2)	45 (8.2)	51 (7.1)	0.89
Diabetes	99 (23.4)	231 (29.2)	222 (31.9)	307 (37.3)	<0.001
Stroke	54 (12.8)	75 (9.5)	59 (8.5)	74 (9.0)	0.06
ICD	59 (13.9)	139 (17.6)	94 (13.5)	70 (8.5)	<0.001
Haemoglobin, g/dl	13.7 (1.5)	13.9 (1.5)	13.8 (1.6)	13.8 (1.7)	0.90
Creatinine, mg/dl	1.2 (0.3)	1.1 (0.3)	1.1 (0.3)	1.1 (0.3)	0.02
eGFR, ml/min/1.73 m ²	69.7 (20.5)	70.9 (21.8)	70.5 (22.9)	71.5 (21.6)	0.25
eGFR < 60, <i>N</i> (%)	146 (34.7)	265 (33.6)	247 (35.5)	248 (30.2)	0.13
Potassium, mmol/l	4.4 (0.4)	4.3 (0.4)	4.3 (0.4)	4.3 (0.5)	0.006
Medication at randomisation visit, <i>N</i> (%)					
Diuretic	344 (81.3)	649 (81.9)	576 (82.6)	732 (88.8)	<0.001
ACE inhibitor	323 (76.4)	610 (77.0)	543 (77.9)	626 (76.0)	0.84
ARB	82 (19.4)	150 (18.9)	136 (19.5)	152 (18.4)	0.74
ACE and/or ARB	393 (92.9)	732 (92.4)	652 (93.5)	755 (91.6)	0.51
Beta-blocker	383 (90.5)	706 (89.1)	604 (86.7)	659 (80.0)	<0.001
Calcium channel blocker	49 (11.6)	82 (10.4)	72 (10.3)	73 (8.9)	0.14
Antiarrhythmic drug	77 (18.2)	123 (15.5)	85 (12.2)	97 (11.8)	<0.001
Antithrombotic drug	378 (89.4)	703 (88.8)	608 (87.2)	703 (85.3)	0.02
Digitalis glycosides	73 (17.3)	154 (19.4)	197 (28.3)	310 (37.6)	<0.001
Lipid-lowering agent	297 (70.2)	517 (65.3)	418 (60.0)	457 (55.5)	<0.001

Table 1 (continued)

Numbers are mean (SD) unless otherwise specified

^a*p* value from test for trend

history of undergoing percutaneous coronary interventions and coronary artery bypass grafting, implantable cardiac defibrillator, and be prescribed BB, non-dihydropyridine calcium channel blockers, antiarrhythmic agents, antithrombotics and lipid-lowering drugs. More than 80% of the patients were prescribed ACE inhibitors/ARB and BB.

Association between baseline heart rate and clinical outcomes

Results pertaining to the primary endpoint (composite of cardiovascular death or hospitalisation for heart failure), cardiovascular death alone, hospitalisation for heart failure alone and all-cause mortality according to baseline resting heart rate are summarised in Table 2 and Fig. 1. Compared to patients with a baseline heart rate of 60–69 bpm, those with baseline heart rate of 80+ bpm experienced a greater rate of the primary endpoint (17.2 per 100 patient-year versus 10.5 per 100 patient-year, adjusted hazard ratio (aHR)

1.61, 95% CI 1.31–1.99). The rates of cardiovascular death, hospitalisation for heart failure and all-cause mortality were also significantly higher.

Figure 2 depicts adjusted event rates for each outcome according to baseline heart rate categories and randomised group. Lower event rates were observed in eplerenone compared with placebo in each heart rate category, with similar absolute differences in event rates across the categories.

The beneficial effects of eplerenone were preserved across all heart rate categories (Fig. 3). The reduction in the primary endpoint and hospitalisation for heart failure were consistently above 30% across all heart rates, favouring eplerenone (Fig. 3). Eplerenone reduced the risk of primary endpoint by 30% (aHR 0.70; 95% CI 0.54–0.91) among patients with baseline heart rate ≥ 80 bpm and by 48% (aHR 0.52; 95% CI 0.33–0.81) among patients with baseline heart rate ≤ 60 bpm. Similar results were observed in hospitalisation for heart failure. Eplerenone also reduced the risks of cardiovascular and all-cause deaths risks in a similar fashion,

Table 2 Number of events, event rate and hazard ratios by baseline heart rate categories for the primary endpoint, its component events and all-cause death

Study endpoint	<i>N</i>	Events	Rate ^a	HR	95% CI	<i>p</i> value ^b	Adj HR ^c	95% CI	<i>p</i> value ^b
Primary endpoint									
< 60	423	96	11.4	1.09	0.85,1.41		1.15	0.89,1.49	
60–69	792	162	10.5	Reference			Reference		
70–79	697	163	12.0	1.15	0.93,1.43		1.16	0.93,1.44	
80 +	824	258	17.2	1.64	1.35,1.99	<0.001	1.61	1.31,1.99	<0.001
Cardiovascular death									
< 60	423	56	6.2	1.16	0.83,1.61		1.16	0.82,1.63	
60–69	792	90	5.4	Reference			Reference		
70–79	697	94	6.4	1.18	0.88,1.58		1.15	0.86,1.55	
80 +	824	152	9.0	1.66	1.28,2.16	<0.001	1.57	1.18,2.08	0.009
Hospitalisation for heart failure									
< 60	423	59	7.0	0.93	0.68,1.27		1.04	0.75,1.43	
60–69	792	117	7.5	Reference			Reference		
70–79	697	110	8.1	1.08	0.83,1.40		1.07	0.82,1.39	
80 +	824	177	11.8	1.55	1.23,1.96	<0.001	1.50	1.16,1.93	0.006
All-cause mortality									
< 60	423	63	7.0	1.05	0.77,1.43		1.06	0.77,1.46	
60–69	792	111	6.7	Reference			Reference		
70–79	697	107	7.2	1.09	0.83,1.42		1.08	0.82,1.42	
80 +	824	176	10.4	1.56	1.23,1.97	<0.001	1.53	1.18,1.98	0.003

^aRate per 100 patient years

^b*p* value from test for trend

^cHR was adjusted for randomised treatment, age, sex, race, SBP, BMI, LVEF, serum creatinine, cause of HF, duration of HF, DM, AF, hypertension, prior hospitalisation for HF, stroke, ICD/CRT, ACE inhibitors/ARBs, beta-blocker, CCB, digoxin, antiarrhythmic drugs

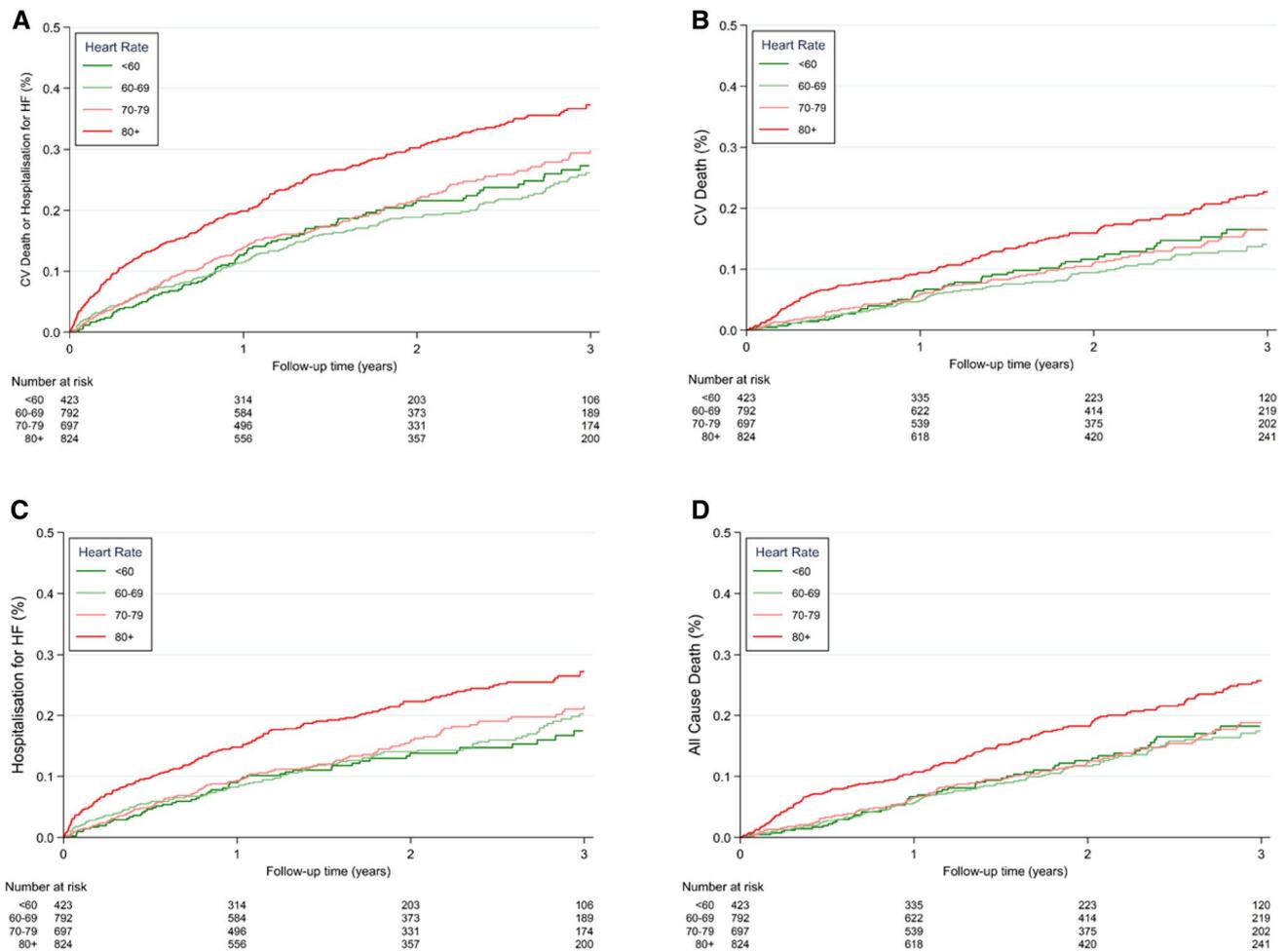


Fig. 1 Kaplan–Meier plots of major cardiovascular outcomes according to heart rate

but with broad confidence interval bands that crossed the null value in subgroups with heart rate 70 bpm and above. However, there was no evidence of interaction between eplerenone and heart rate (trend p value = 0.08–0.73). Also, AF was not found to modify the effect of eplerenone (trend p value = 0.59).

A total of 61 (2%) patients were excluded from the fully adjusted models due to missing data on risk factors. Subsequent sensitivity analyses using multiple imputation with chained equations did not change the conclusions. Further exploratory analysis treating heart rate as a continuous variable was carried out but did not add to or alter any conclusions.

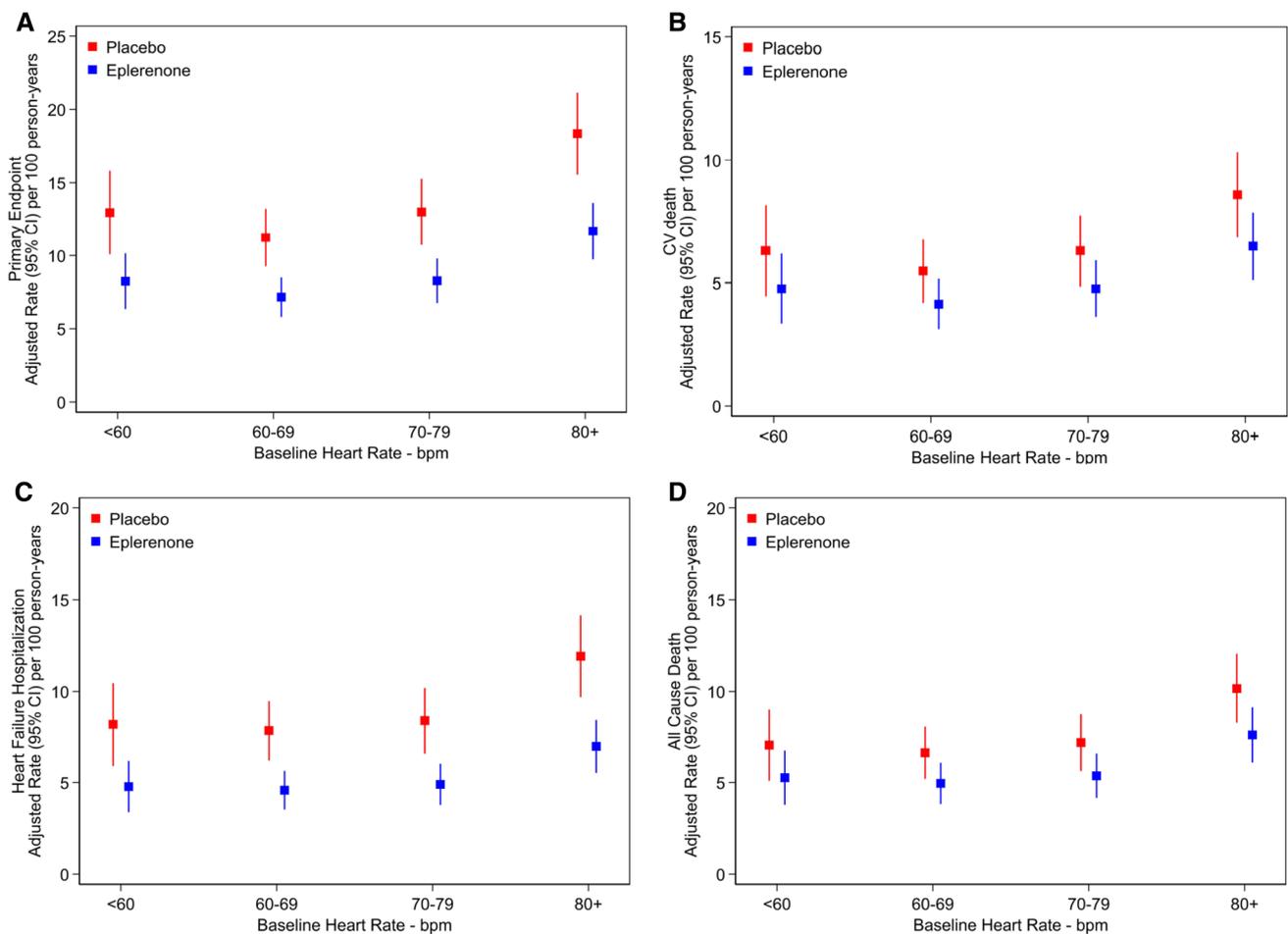
Discussion

To the best of our knowledge, this is the first study to examine the influence of heart rate on subsequent cardiovascular events in a trial using a MRA in patients with heart failure.

We found that a high resting heart rate of 80 + bpm predisposed patients with HFREF to a greater risk of primary endpoint, cardiovascular deaths, hospitalisation for heart failure and all-cause death, regardless of treatment allocation. The beneficial effects of eplerenone were preserved across all categories of baseline heart rate.

Notably, patients with higher baseline heart rates displayed distinct clinical characteristics compared to those with lower heart rates, with a trend towards lower use of BBs and higher prevalence of AF or flutter, diabetes and previous hospitalisation for heart failure. Such discrepancies may explain the increased heart rate and possible decrease in the effect of eplerenone on mortality.

Higher heart rate may reflect a compensatory mechanism for the loss of atrial contribution to cardiac output [15, 16]. Autonomic dysfunction in heart failure, characterised by decreased tonic and reflex vagal heart rate modulation and increased heart rate, venous plasma norepinephrine and cardiac norepinephrine stores, has been associated with greater mortality [17]. Higher heart rate is also associated with



Note: Rates are estimated from a Poisson model and adjusted for: age, sex, race, SBP, BMI, LVEF, serum creatinine, cause of HF, duration of HF, DM, AF, hypertension, prior hospitalization for HF, stroke, ICD/CRT, ACE inhibitors/ARBs, beta-blocker, beta-blocker dose, CCB, digoxin, antiarrhythmic drugs.

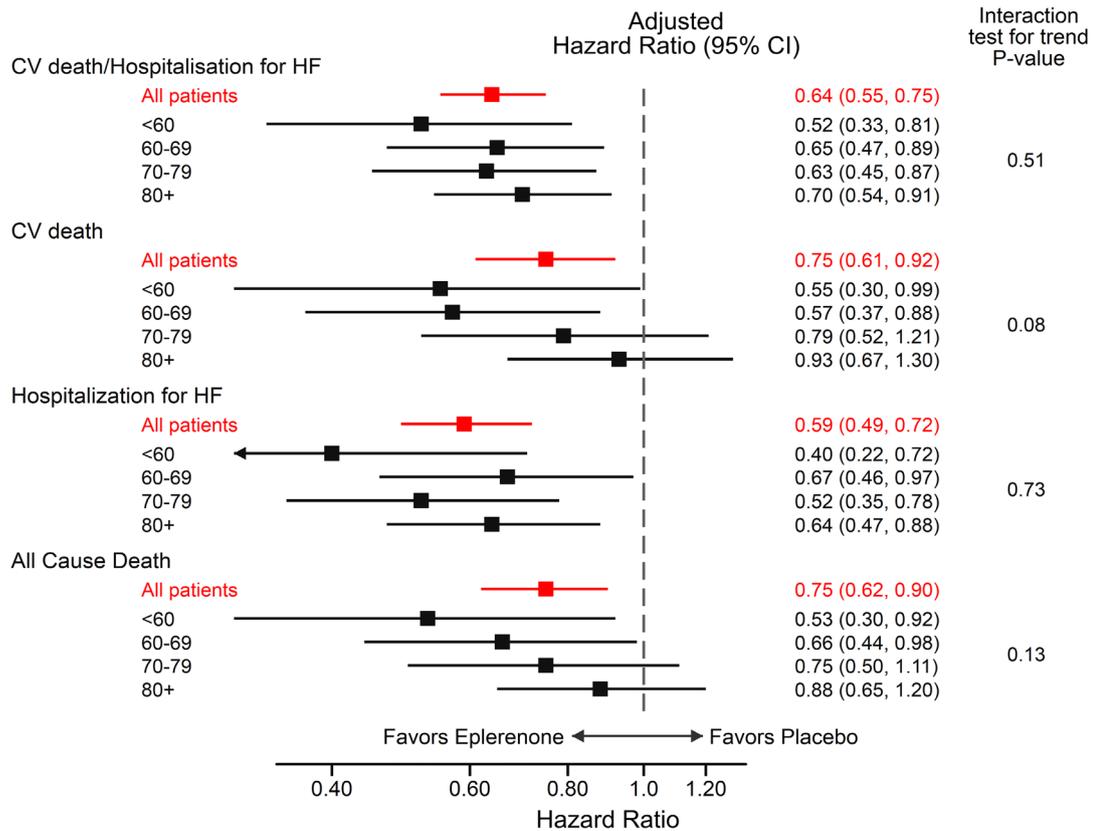
Fig. 2 Adjusted event rates and 95% CI by baseline heart rate categories on major cardiovascular outcomes

increased energy expenditure, reduced myocardial oxygen delivery because of shorter diastole, and loss of the positive force–frequency relationship (Bowditch effect) [18]. Over-activity of the sympathetic nervous system in heart failure, which is reflected by heart rate, has direct toxic effects on the cardiac myocytes, and facilitates the development of ventricular arrhythmias and alteration of the beta-adrenoceptor function [19].

Accumulated evidence from the SHIFT, CHARM, and Efficacy of Vasopressin Antagonism in Heart Failure: Outcome Study with Tolvaptan (EVEREST) trials supports heart rate being an independent predictor of mortality and cardiovascular outcomes, and also highlights the importance of a heart rate reduction strategy for the improvement of clinical outcomes in patients with HFREF [5, 20, 21]. A resting heart rate of > 76 bpm at any time during follow-up

was associated with increased risk of cardiovascular death or hospitalisation for HF in the SHIFT and CHARM studies [7, 22]. However, these findings do not apply to all patients with HFREF, as some studies have showed paradoxical findings of lower heart rate being associated with higher mortality in heart failure patients with concomitant AF, and to date, the mechanistic explanation for this interaction is less well established [5, 23, 24]. Although ivabradine does not reduce heart rate and BBs do not improve outcomes in patients with HFREF and AF, treatment with MRAs has been demonstrated to reduce both heart rate and major cardiovascular outcomes in this subgroup of patients [12, 25].

Despite this, recent data from prospective observational studies suggest that MRAs remained under-prescribed and frequently discontinued among eligible patients with HFREF [26–28]. Only 40–60% of the patients in the BIOlogy Study



Note: Hazard ratio is adjusted for: age, sex, race, SBP, BMI, LVEF, serum creatinine, cause of HF, duration of HF, DM, AF, hypertension, prior hospitalization for HF, stroke, ICD/CRT, ACE inhibitors/ARBs, beta-blocker, beta-blocker dose, CCB, digoxin, antiarrhythmic drugs.

Fig. 3 Adjusted hazard ratio (eplerenone versus placebo) for all patients and by baseline heart rate categories for the primary endpoint, its components and all-cause death. Hazard ratio is adjusted for age, sex, race, SBP, BMI, LVEF, serum creatinine, cause of HF,

duration of HF, DM, AF, hypertension, prior hospitalisation for HF, stroke, ICD/CRT, ACE inhibitors/ARBs, beta-blocker, beta-blocker dose, CCB, digoxin, antiarrhythmic drugs

to Tailored Treatment in Chronic Heart Failure (BIOSTAT-CHF) and Swedish Heart Failure Registry were prescribed a MRA [26, 28]. In these studies, higher heart rate, lower use of BBs, history of diabetes, AF, hypertension, stroke/transient ischaemic attack, smoking, previous percutaneous coronary revascularisation, anaemia and the use of loop diuretics were associated with non-prescribing and underdosing of MRAs among patients with HFREF. The observed association between heart rate and use of MRAs in these studies is likely to be confounded.

The use of MRAs in HFREF has been shown to be cost-effective and has a significant impact on mortality and hospitalisation rates [29–32]. What is clear from our analysis is that the beneficial effects of eplerenone are preserved regardless of heart rate and higher heart rate is detrimental to patients with HFREF. These findings highlight the importance of optimising use of MRAs in eligible patients with HFREF.

Limitations

There are a number of limitations to our post hoc analysis. First, analysis was confined to that of heart rate at baseline only; post-randomisation heart rates were not measured. In addition, we relied on investigator-reported baseline heart rate, which may not have been measured in a standardised manner, and estimation of the ventricular rate in patients with AF may also have been less reliable than in patients in sinus rhythm. However, previous analyses examining the relationship between heart rate and pharmacological intervention in HFREF trials were also limited to baseline heart rate measured by investigators [5, 6, 33]. As with all subgroup analyses, there was less precision in the results for groups defined by baseline heart rate, reflected by wide 95% CIs. Furthermore, we acknowledge that our post hoc analyses were not pre-specified. Nonetheless, a

dose–response effect was clear, the findings are of clinical relevance and they accord with those of other studies.

Conclusions

Baseline heart rate is a predictor of major clinical outcome events in patients with HFREF, as has been previously reported. The cardiovascular benefits of eplerenone in this patient population are preserved across all ranges of baseline heart rate.

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Compliance with ethical standards

Conflict of interest Drs Pitt, McMurray, Swedberg, van Veldhuisen, Pocock, and Zannad were 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 traveling to meetings of the committee. Dr Vincent is currently employed by Pfizer and owns stock in Pfizer Inc, the makers of eplerenone. 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 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. Dr Liew reports receiving grants and honoraria from Abbvie, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Novartis, Pfizer, Sanofi and Shire. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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