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RESEARCH ARTICLE

Effect of eplerenone in patients with heart failure and reduced ejection fraction: potential effect modification by abdominal obesity. Insight from the EMPHASIS-HF trial

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Aims An excessive production of aldosterone influences outcome in patients with heart failure (HF) and in obese patients. Findings from laboratory studies suggest that chronic aldosterone blockade maybe more beneficial in abdominally obese HF-prone rats. In the current study, we investigated if the clinical response to a mineralocorticoid receptor antagonist in mildly symptomatic HF patients varied by abdominal obesity.

Methods and results A total of 2587 NYHA class II, reduced ejection fraction HF (HFrEF) patients enrolled in the EMPHASIS-HF trial were randomly assigned to eplerenone and placebo. In this *post hoc* analysis, patients were categorized according to waist circumference (WC) (normal if WC < 102 cm in men and < 88 cm in women; abdominal obesity if WC ≥ 102 cm in men and ≥ 88 cm women). The potential statistical interaction between the treatment and WC was assessed on the primary endpoint of death from cardiovascular causes or hospitalization for HF and other secondary endpoints. Over a median follow-up of 21 months, a significant benefit of eplerenone for the primary outcome was noted in both normal [hazard ratio (HR) 0.77, 95% confidence interval (CI) 0.61–0.98, $P = 0.03$] and increased (HR 0.48, 95% CI 0.37–0.63, $P < 0.0001$) WC subgroups, but the latter patients appeared to receive greater benefit than patients with normal WC (P for interaction = 0.01). This suggests a significant quantitative (treatment effect varies in magnitude by subgroup, but is always in same direction) rather than a qualitative interaction (direction of the treatment effect varies by subgroup) between eplerenone and WC in the adjusted analysis. Mean doses of eplerenone, blood pressure and serum potassium changes and adverse events were similar between WC subgroups.

Conclusion In EMPHASIS-HF, eplerenone improved outcomes in HFrEF patients with and without abdominal obesity, although the benefit appeared to be more pronounced among those with abdominal obesity. The findings are potentially hypothesis generating and need to be replicated in other HFrEF populations.

Keywords Abdominal obesity • Heart failure with reduced ejection fraction • Eplerenone

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Introduction

Obesity is recognized as a cardiovascular risk factor and the worldwide epidemic of obesity parallels the one observed for heart failure (HF).[1−3] It is associated with increased risk of cardiorenal disease, including hypertension, coronary artery disease and adverse cardiac remodelling (left ventricular hypertrophy and dilation), and progression towards HF.[4] In addition obese subjects have higher aldosterone levels, which may result in mineralocorticoid receptor (MR) over-activation. Reciprocally, higher aldosterone levels have been implicated in the development and maintenance of obesity.[5−7]

Mineralocorticoid receptor antagonist (MRA) therapy improves outcomes in patients with chronic systolic HF with mild symptoms (EMPHASIS-HF trial), acute symptomatic systolic HF in post-myocardial infarction (EPHESUS trial) and in severe NYHA class III−IV systolic HF (RALES trial).[8−11] However, to the best of our knowledge the influence of established overweight or obesity on the response to MRAs is unknown. Studies in obese non-HF patients with or without associated metabolic disorder[12] suggested that MRA therapy improved left ventricular function and myocardial abnormalities with concurrent decreases of circulating fibrotic markers. Knowing that visceral fat is a source of serum aldosterone and that several experimental studies[7,13−15] have implicated aldosterone as an important mediator of obesity-related cardiovascular risk, we have recently published the first experimental data suggesting that, as compared to leaner counterparts, viscerally obese HF-prone rats may further benefit from chronic MRA treatment.[16] Yet no study has specifically evaluated whether clinical response to a MRA over a long follow-up period might be better in HF patients with vs. without abdominal obesity.

In this context, we sought for the first time to evaluate the interaction between increased adiposity estimated by the waist circumference (WC) and body mass index (BMI, as reference obesity measurement parameter) and the clinical benefit from the MRA eplerenone in patients with congestive HF receiving recommended therapy for systolic HF (ejection fraction <35%) and enrolled in the EMPHASIS-HF trial.[11]

Methods

The design, patient eligibility criteria, study procedure and main results of the EMPHASIS-HF study have been previously reported.[11] In brief, in this randomized double-blind trial, patients with NYHA class II HF and an ejection fraction of no more than 35% (HFrEF) were randomly assigned to receive eplerenone (up to 50 mg daily) or placebo, in addition to recommended therapy.

Study outcomes

The same primary and secondary outcomes were used in the current analysis as in the main study.[11] Briefly, the primary outcome was the composite of death from cardiovascular causes or first hospitalization for HF. The pre-specified adjudicated secondary outcomes were, respectively, all-cause death, cardiovascular death and hospitalization for HF. For continuous variables, the baseline value was defined according to the EMPHASIS-HF statistical analysis plan as the measurement that was made on the closest date prior to the study medication starting date. If there were more than one measurement made on the same date, the average value of these data was calculated and used as the baseline measurement.

Because the following variables did not fulfil the assumption of log-linearity, WC and BMI were not analysed as continuous variables but as categorical variables.

Waist circumference

Baseline measurement of WC was performed by a tape measure placed around the subject's bare abdomen just above the subject's hipbone, at the level of the subject's navel, when the relaxed subject exhaled. The tape measure was positioned parallel to the floor without compressing the subject's skin. Values were considered aberrant and were excluded from the data analysis when WC < 60 cm.

Subjects were divided into two WC groups according to the American Heart Association (AHA) defined cut-offs.[17] Men and women with WC values <102 and <88 cm, respectively, were considered to have a normal WC (NWC group), whereas those with WC values ≥102 and ≥88 cm, respectively, were considered to have high WC (HWC group) and harbour an abdominal obesity. Subjects were further categorized according to WC quintiles taking into account sex differences.

Body mass index

Body mass index is defined as the weight in kilograms divided by the square of the height in metres (kg/m^2). BMI values were considered missing when height or weight measures were not reported. Obesity was defined according to the World Health Organization BMI classification (http://apps.who.int/bmi/index.jsp?introPage=intro_3.html): BMI values ≥ 30 kg/m^2 were classified as obese patients while BMI values <30 kg/m^2 characterized normal-weight and overweight patients.

Statistical analysis

Waist circumference and BMI were the key explanatory variables. Continuous variables are expressed as mean ± standard deviation (SD), categorical variables as frequencies (percentage). Comparisons of baseline characteristics between WC or BMI groups were performed using Student's *t*-test, Mann−Whitney, or χ^2 test as required. Risk probabilities were calculated using the Kaplan−Meier method and plotted as survival curves.

Hazard ratios (HRs) and respective 95% confidence intervals (CIs) were estimated using univariable and multivariable Cox proportional hazards regression models. Assumptions of log-linearity, absence of multicollinearity and hazards proportionality were thoroughly verified.

Interactions between BMI or WC and eplerenone effect on outcomes were assessed by introducing an interaction term (BMI or WC variable × eplerenone) in crude (i.e. BMI or WC, eplerenone, BMI or WC × eplerenone) and adjusted models. The following candidate covariates were considered for adjustment: age, gender, heart rate, systolic blood pressure, left ventricular ejection fraction, QRS duration, medical history (hospitalization for HF, hypertension, angina pectoris, myocardial infarction, coronary angioplasty, coronary artery bypass surgery, atrial fibrillation or flutter, diabetes mellitus, stroke), device therapy (implantable cardioverter-defibrillator, cardiac resynchronization therapy, implantable cardioverter-defibrillator with cardiac resynchronization), blood sodium, blood potassium, estimated glomerular filtration rate and use of diuretics, angiotensin-converting

enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), beta-blockers, and lipid-lowering agents. Among these candidate covariates, variables significantly associated with the outcome of interest with a *P*-value <0.15 on univariable Cox regression[18] were further selected using an interactive backward selection process. Only the covariates associated with the outcome of interest with a *P*-value <0.05 were retained in multivariable models.

In addition, we evaluated the functional form of the interaction between treatment and WC/BMI with regards to the risk of outcomes using WC/BMI as a non-linear continuous variable. To do so, we used restricted cubic splines and plotted the HRs of treatment effect according to WC/BMI calculated from the Cox model.

Adverse events and those leading to permanent study drug withdrawal were presented according to WC or BMI category groups.

Statistical interaction has come into increasing use in trial analysis. Given the low power of interaction tests, selected a priori a 0.10 cut-off threshold for the interaction *P*-value has been used. As a consequence, a *P* -value of <0.05 was considered statistically significant for the main effects and <0.10 for the interaction terms.

All analyses were performed using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Clinical characteristics

Of the 2737 patients randomized in EMPHASIS-HF, 2579 were included in the WC analysis (158 patients had a missing or implausible WC value). Median WCs were 100 cm [interquartile range (IQR) 92–108] and 94 cm (IQR 85–104) in men and women, respectively, and 1295 patients (50.2%) had a HWC (abdominal obesity if WC ≥ 102 cm for men and ≥ 88 cm for women). The remaining 1284 individuals had a NWC (if WC < 102 cm for men and < 88 cm for women) (*Table 1*; Supplementary material online, *Table S1*). Patients with a HWC had more obesity-related disorders such as hypertension, atrial fibrillation, and diabetes mellitus, as compared to patients with NWC (*Table 1*). However, there were no clinically significant differences between patients allocated to eplerenone or placebo within the two WC subgroups (*Table S1*).

Of the 2737 patients randomized in EMPHASIS-HF, 2722 were included in the BMI analysis (15 patients had a missing or implausible BMI value). The median BMI was 27 kg/m^2 (IQR 24–30) and 739 patients (27.1%) had global obesity with BMI ≥ 30 kg/m^2 and 1983 (72.9%) a BMI < 30 kg/m^2. Similar to patients with HWC, those with a high BMI had more obesity-related disorders as compared to patients with BMI < 30 kg/m^2 (*Table 1*).

The median follow-up duration among all patients was 21 months (IQR 10–33 months).

Eplerenone safety profile across subgroups

Adverse events leading to eplerenone withdrawal occurred in 101 (15.7%) NWC patients as compared to 74 (11.5%) HWC patients ($P = 0.034$) leading to a *P*-value for the interaction of 0.01 (Supplementary material online, *Table S2*). Hyperkalaemia adverse events and hyperkalaemia leading to study-drug discontinuation occurred equally in WC and BMI eplerenone subgroups (*Table S2*).

Mean doses achieved across subgroups

The mean dose of eplerenone did not differ between WC subgroups ($P = 0.67$). Among patients assigned to eplerenone, 61.4% and 62.3% of the HWC and NWC groups, respectively, received the highest daily dose (50 mg daily, $P = 0.81$). Likewise, the mean dose of eplerenone did not differ between BMI subgroups ($P = 0.79$) and 60.8% of the BMI ≥ 30 kg/m^2 patients against 61.6% of the BMI < 30 kg/m^2 groups received the highest daily dose of eplerenone (50 mg daily, $P = 0.96$).

Effect of eplerenone on clinical outcomes

Overall, there were fewer primary endpoints in the eplerenone group in EMPHASIS-HF (multivariable HR 0.63, 95% CI 0.52–0.75). This was also the case for other outcomes, including all-cause mortality (HR 0.76, 95% CI 0.61–0.94), cardiovascular mortality (HR 0.73, 95% CI 0.58–0.93), and hospitalization for HF (HR 0.59, 95% CI 0.48–0.73) (*Figures 1* and *2*).

When analysing according to WC and BMI anthropomorphic subgroups, no differential effect of the treatment was observed on blood pressure, heart rate, body weight, and serum potassium levels, expressed as changes from baseline to month 1 and month 5 post-randomization (data not shown).

Interaction between abdominal obesity and the effects of eplerenone

The modifying effect of abdominal obesity on the impact of eplerenone for each outcome is shown in *Figures 1* and *2*. The effect of eplerenone on the primary outcome was significant in both patients with HWC (multivariable HR 0.48, 95% CI 0.37–0.63) and in patients with NWC (multivariable HR 0.77, 95% CI 0.61–0.98), but significantly stronger in the HWC group as demonstrated by a *P*-value for the interaction of 0.01 *(Figures 1A and 2A*).

Importantly, abdominal obesity, i.e. HWC, was not associated with the primary outcome in the placebo group (multivariable HR 0.96, 95% CI 0.76–1.20) whereas it was associated with lower rates for the primary events in the eplerenone group (multivariable HR 0.60, 95% CI 0.45–0.80), resulting in a significant interaction between eplerenone and HWC in the adjusted analysis ($P = 0.01$).

Overall, similar patterns were observed for the secondary outcomes but the interaction between eplerenone and HWC reached statistical significance only for the secondary outcomes of death from cardiovascular causes and hospitalization for HF (*P* for interaction 0.09 and 0.07, respectively) (*Figure 2* and *Table 2*). In addition, we identified a significant interaction in men between treatment and WC within the model using restricted cubic splines (*P*-value for the interaction is 0.025 in the adjusted model, *Figure 3A*). The shape of the association is difficult to assess in women given the wide CIs resulting from the small number of patients within the subset of female patients. In this subset, the interaction did not reach statistical significance ($P = 0.30$ in the adjusted model, *Figure 3B*). Likewise the interaction between treatment and BMI for both genders using restricted cubic splines did not reach significance ($P = 0.15$ in the adjusted model, *Figure 3C*).

Table 1 Baseline characteristics of the patients according to morphometric parameter subgroups

Characteristics	NWC $n = 1284$	HWC $n = 1295$	*P*-value	BMI < 30 kg/m^2 $n = 1983$	BMI ≥ 30 kg/m^2 $n = 739$	*P*-value
Age (years)	69.1 ± 7.9	68.2 ± 7.3	0.003	69.2 ± 7.7	67.0 ± 7.2	<0.0001
Male gender (%)	85.4	70.0	<0.0001	79.7	72.5	<0.0001
BMI (kg/m^2)	25 ± 3	31 ± 4	<0.0001	25 ± 3	34 ± 4	<0.0001
Weight (kg)	70 ± 12	89 ± 16	<0.0001	73 ± 12	97 ± 14	<0.0001
Height (cm)	169 ± 9	170 ± 10	<0.0001	169 ± 9	170 ± 10	0.22
WC (cm)	90 ± 8	109 ± 10	<0.0001	94 ± 10	112 ± 11	<0.0001
Heart rate (b.p.m.)	71.0 ± 12.2	72.4 ± 12.4	0.01	71.5 ± 12.4	72.4 ± 12.6	0.16
Systolic blood pressure (mmHg)	122 ± 17	126 ± 16	<0.0001	123 ± 17	127 ± 16	<0.0001
Systolic blood pressure ≥ 130 mmHg (%)	38.2	45.2	0.0004	38.8	48.7	<0.0001
Left ventricular ejection fraction (%)	26 ± 5	26 ± 4	0.006	26 ± 5	26 ± 4	0.03
Left ventricular ejection fraction < 35% (%)	98.7	97.7	0.07	98.2	98.1	0.83
QRS duration (ms)	121 ± 46	123 ± 44	0.23	121 ± 44	122 ± 46	0.90
Ischaemic heart disease (%)	69.9	69.3	0.74	69.9	66.7	0.10
Medical history (%)						
Hospitalization for heart failure	53.1	52.0	0.59	52.3	53.5	0.61
Hypertension	59.4	74.4	<0.0001	62.7	76.6	<0.0001
Angina pectoris	43.5	45.3	0.34	42.1	47.2	0.02
Myocardial infarction	51.9	50.7	0.56	51.3	48.3	0.16
PCI	21.3	21.8	0.76	22.2	20.7	0.41
CABG	20.7	17.0	0.02	19.7	16.8	0.09
Atrial fibrillation	28.0	34.1	0.0007	28.8	36.4	0.0001
Diabetes mellitus	27.0	36.2	<0.0001	28.7	38.6	<0.0001
Stroke	8.8	10.4	0.17	9.3	10.9	0.20
Biology						
Estimated GFR (ml/min/1.73 m^2)	71 ± 22	71 ± 22	0.92	70 ± 22	72 ± 22	0.07
Estimated GFR < 60 ml/min/1.73 m^2 (%)	34.5	32.2	0.21	34.2	31.0	0.11
Potassium (mmol/L)	4.3 ± 0.4	4.3 ± 0.4	0.05	4.3 ± 0.4	4.3 ± 0.4	0.52
Sodium (mmol/L)	139.8 ± 4.2	140.4 ± 3.8	<0.0001	139.9 ± 4.1	140.6 ± 3.5	<0.0001
Device therapy (%)						
Implantable cardioverter-defibrillator	12.9	14.4	0.27	13.4	13.1	0.86
Implantable cardioverter-defibrillator with cardiac resynchronization	6.0	7.6	0.13	6.2	7.4	0.28
Cardiac resynchronization therapy	2.1	2.5	0.45	2.4	1.8	0.35
Medications at randomization visit (%)						
Eplerenone	50.2	49.7	0.80	49.2	51.8	0.22
Diuretic	84.3	86.6	0.10	84.8	87.2	0.12
ACE inhibitor or ARB	92.1	94.4	0.02	93.3	93.8	0.65
Beta-blocker	87.4	87.4	1.00	86.7	88.7	0.17
Lipid-lowering agent	63.3	62.2	0.60	63.5	61.5	0.33

Values are ± SD or percentage.
ACE, angiotensin-converting enzyme; ARB, angiotensin receptor type II blocker; BMI, body mass index (characterizing global obesity when ≥30 kg/m^2); CABG, coronary artery bypass grafting; GFR, glomerular filtration rate; HWC, high waist circumference (≥102 cm for men and ≥88 cm for women characterizing abdominal obesity); NWC, normal waist circumference (<102 cm for men and <88 cm for women); PCI, percutaneous coronary intervention; WC, waist circumference.

Overall, both WC groups derived significant benefit from eplerenone for the primary outcome and hospitalization for HF with quantitatively greater benefits derived from the treatment in patients with abdominal obesity from the HWC subgroup. A lower dropout rate was observed in patients randomized to eplerenone when they had HWC, which could contribute to the higher treatment effect observed in this subgroup, and further suggests a net higher benefit to risk ratio in the HWC group. A sensitivity analysis censoring the follow-up up to the time of permanent drug discontinuation yielded interaction still suggesting a higher benefit to risk ratio in the HWC group.

While analysing the EMPHASIS-HF population using WC quintiles, we observed lower HR for the primary outcome in patients within the 3rd to 5th quintiles (i.e. ≥97 cm in men and ≥90 cm in women) than in patients within the first two quintiles (Supplementary material online, *Table S3*) with a significant *P*-value for interaction between eplerenone and WC ($P = 0.09$). Interestingly, multivariable HR in the 3rd to 5th quintiles ranged from 0.47 (95% CI 0.32–0.71) to 0.53 (95% CI 0.34–0.82)

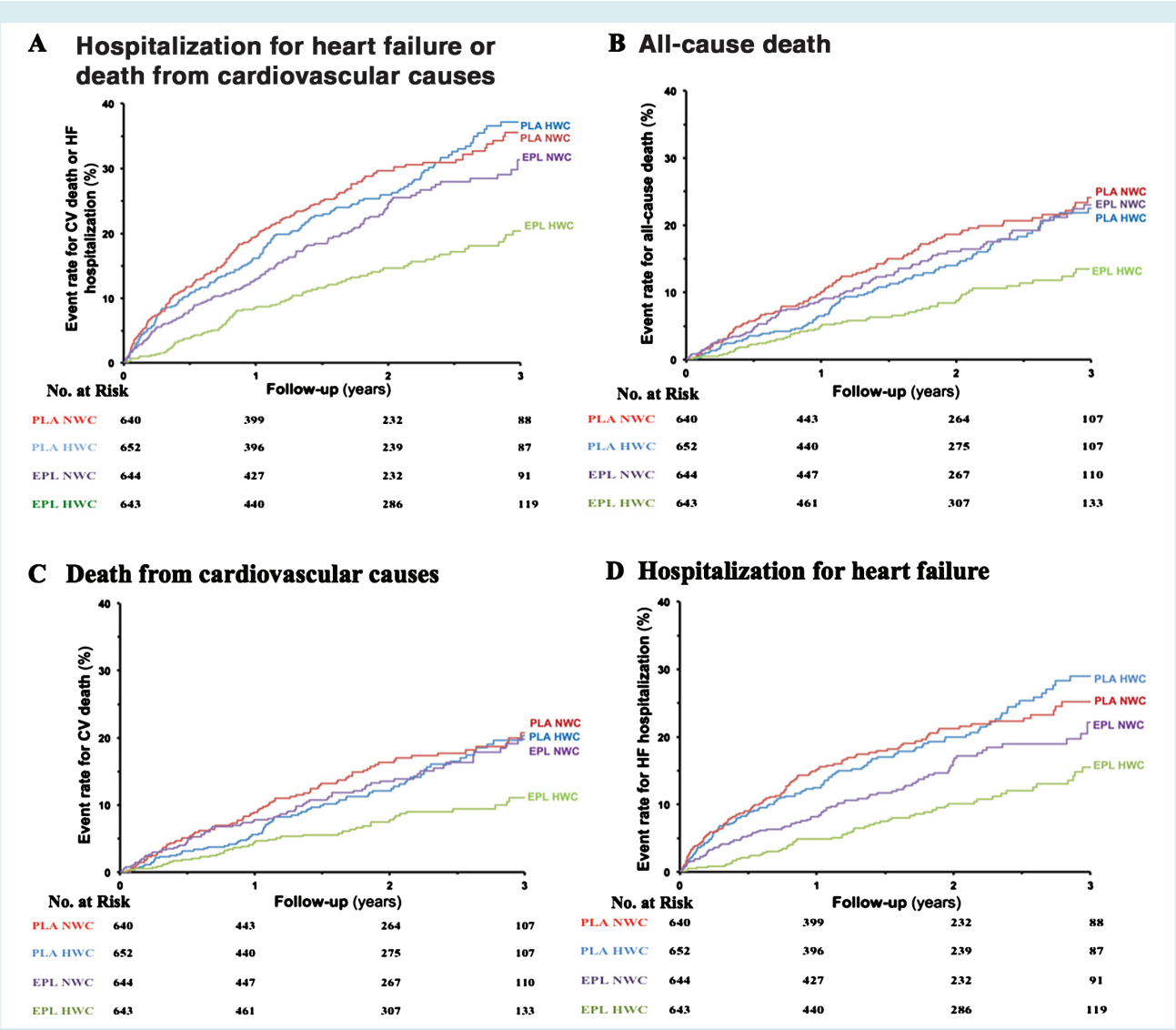

Figure 1 Cumulative Kaplan–Meier estimates of rates of the primary and secondary outcomes according to the four study groups. CV, cardiovascular; EPL, eplerenone; HF, heart failure; PLA, placebo; WC, waist circumference with NWC for normal waist circumference group (waist circumference < 102 cm for men and < 88 cm for women) and HWC for high waist circumference group characterized by the presence of abdominal obesity (waist circumference ≥ 102 cm for men and ≥ 88 cm for women).

whereas the HRs of the first two quintiles were 0.70 (95% CI 0.49–1.00) and 0.94 (95% CI 0.64–1.37), respectively. Of note, these cut-offs (i.e. ≥97 cm in men and ≥90 cm in women) within the EMPHASIS-HF population were below and above the cut-offs defining abdominal obesity in men and women, respectively.

Interaction between body mass index and the effects of eplerenone

The benefit of eplerenone on the rate of the primary outcome seemed to be greater in obese (BMI ≥ 30 kg/m^2) patients (multivariable HR 0.49, 95% CI 0.35–0.71) than in patients with BMI < 30 kg/m^2 (multivariable HR 0.69, 95% CI 0.57–0.83), but the difference was not as marked as for WC and the *P*-value for interaction between BMI and eplerenone was greater than 0.10 ($P = 0.11$, *Figure 2*; *Table 2*). Similar observations were done for secondary outcomes, with no significant interaction in the adjusted analyses between BMI and the effect of eplerenone (*Table 2*). When analysed according to the median BMI value of 27 kg/m^2, the benefit of eplerenone on the rate of the primary outcome was greater in patients with BMI ≥ 27 kg/m^2 (multivariable HR 0.50, 95% CI 0.38–0.65) than in patients with BMI < 27 kg/m^2 (multivariable HR 0.76, 95% CI 0.61–0.94; *P* for interaction = 0.018) (Supplementary material online, *Table S4*). These results of BMI analyses with a cut-off defined at 27 kg/m^2 and 30 kg/m^2 (*Table 2* and Supplementary material online *Table S4*, respectively) are confirmed by the shape of the

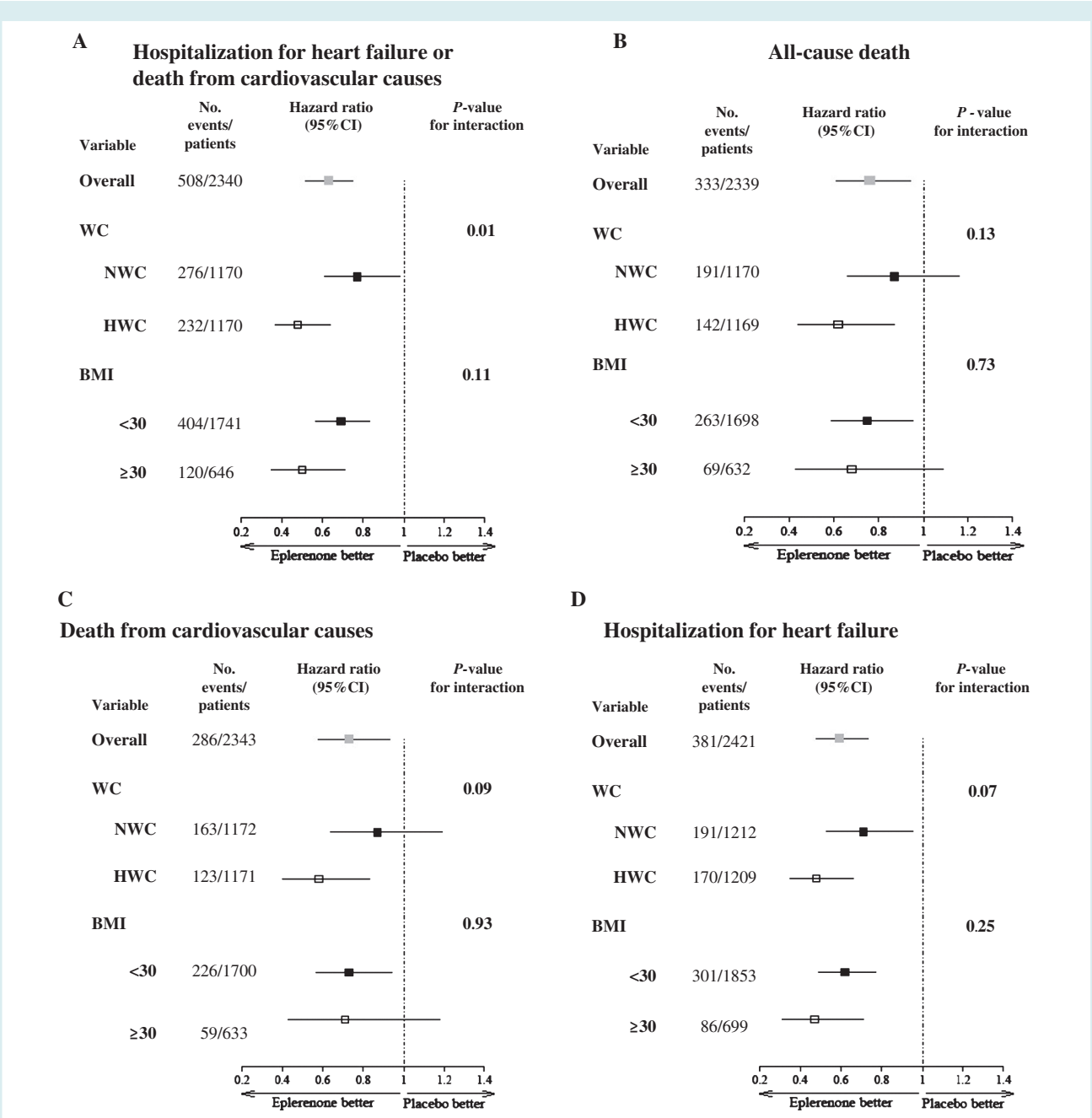

Figure 2 Hazard ratios for studied outcomes with eplerenone vs. placebo in the overall population and according to specified subgroups of waist circumference (WC) and body mass index (BMI). The subgroups are based on baseline demographic and clinical characteristics. Values within the entire population are presented in grey. Values within the normal ranges of WC (NWC, i.e. < 102 and < 88 cm for men and women, respectively) and BMI (<30 kg/m^2) are presented in black and increased values in white (HWC, i.e. ≥ 102 and ≥ 88 cm for men and women, respectively, and BMI ≥ 30 kg/m^2). Presented data are the results of multivariable model analysis adjusted for statistically significant covariates among those listed and tested in the statistical analysis section. Thus, the total number of patients (2340) is inferior in this figure to the number of 2579 in *Table 2* as the result of missing values in some patients.

association in adjusted model between eplerenone and the primary outcome according to the value of BMI when used as a continuous variable (*Figure 3C*). Risk of cardiovascular diseases or hospitalization for HF is higher for values around 25 kg/m^2, while it decreases until a value of 30 kg/m^2, and then remains steady (*Figure 3C*). Likewise, the benefit of eplerenone on the rates of hospitalization for HF was greater in patients with BMI ≥ 27 kg/m^2 (multivariable HR 0.44, 95% CI 0.33–0.62) than in patients with BMI < 27 kg/m^2 (multivariable HR 0.68, 95% CI 0.52–0.88; *P* for interaction = 0.051) (*Table S4*).

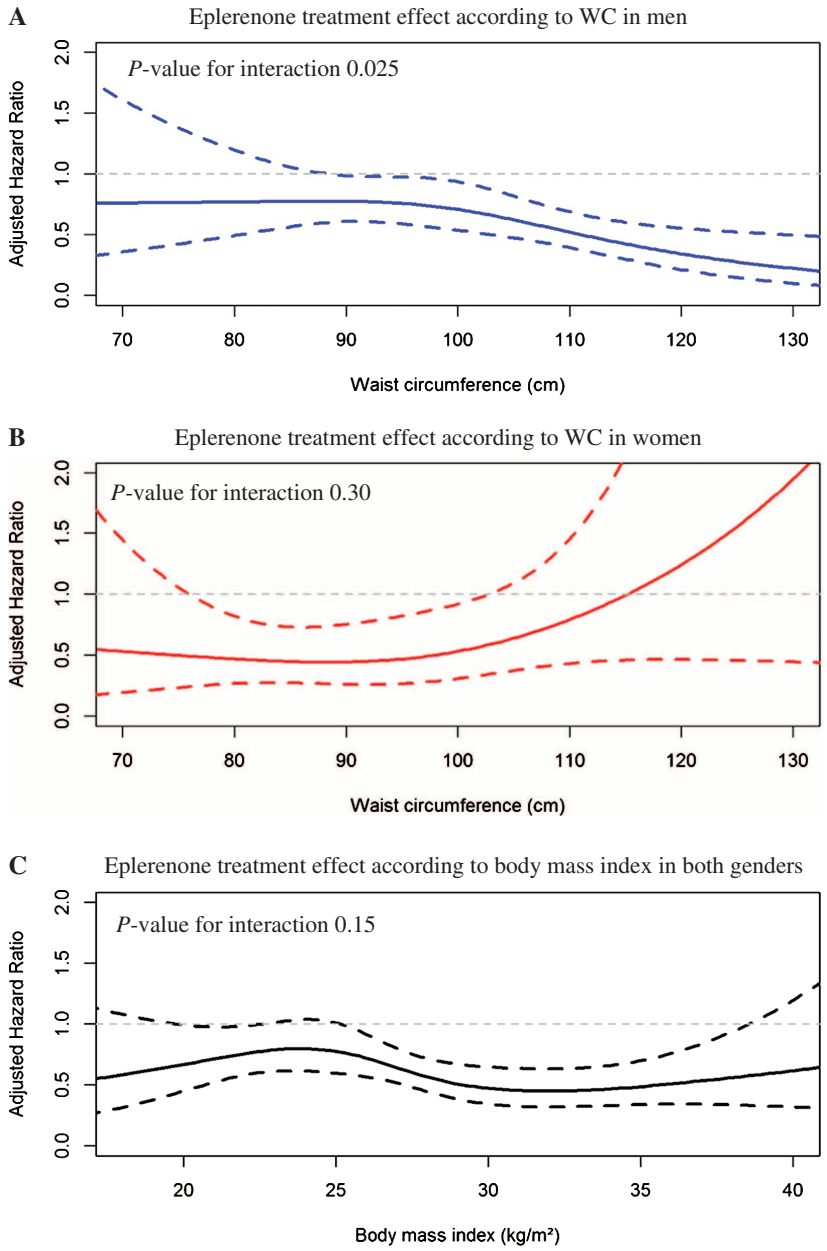

Figure 3 Eplerenone treatment effect according to morphometric parameters using restricted cubic spline. Restricted cubic splines were drawn for the composite primary outcome to model the interaction between treatment and waist circumference (WC) (*A* and *B*) or body mass index (*C*) when both morphometric parameters were used as a continuous variable. Interactions are presented for men (*A*), women (*B*) and both genders (*C*) in adjusted models. The continuous lines represent the hazard ratio and the dotted lines represent the confidence limits for the considered hazard ratio.

Discussion

The main finding of our *post hoc* analysis of the EMPHASIS-HF data suggests that patients with HFrEF and with mild symptoms and abdominal obesity derive greater benefit from eplerenone than those who are not obese or overweight. All HFrEF patients derived benefits from eplerenone in the EMPHASIS-HF trial, but the greater benefits afforded by eplerenone in HWC patients were substantiated by the significant interaction between WC and eplerenone for three out of the four studied outcomes. This characterized for the first time a quantitative rather than a qualitative interaction between adiposity and the response to MRA therapy. Importantly, this greater benefit occurred with the use of similar doses of eplerenone and overall the benefit/risk ratio was more favourable since the rate of adverse events was not different among WC subgroups. Altogether this

Table 2 Association between eplerenone and outcomes depending on morphometric parameters

Characteristics	Events/ patients (%)	Crude HR (95% CI)	*P*-value	Multivariable HR (95% CI)	*P*-value
Primary outcome: death from cardiovascular causes or hospitalization for heart failure					
Overall					
Placebo	335/1292 (25.9)				
Eplerenone	229/1287 (17.8)	0.64 (0.54–0.76)	<0.0001	0.63 (0.52–0.75)	<0.0001
NWC					
Placebo	169/640 (26.4)				
Eplerenone	137/644 (21.3)	0.79 (0.63–0.99)	0.04	0.77 (0.61–0.98)	0.03
HWC					
Placebo	166/652 (25.5)				
Eplerenone	92/643 (14.3)	0.50 (0.39–0.65)	<0.0001	0.48 (0.37–0.63)	<0.0001
Interaction EPL∝WC			**0.01**		**0.01**
Secondary outcome: all-cause mortality					
Overall					
Placebo	201/1292 (15.6)				
Eplerenone	160/1287 (12.4)	0.77 (0.63– 0.95)	0.01	0.76 (0.61–0.94)	0.01
NWC					
Placebo	107/640 (16.7)				
Eplerenone	97/644 (15.1)	0.91 (0.69–1.19)	0.48	0.87 (0.66–1.16)	0.35
HWC					
Placebo	94/652 (14.4)				
Eplerenone	63/643 (9.8)	0.63 (0.46–0.87)	0.004	0.62 (0.44–0.87)	0.005
Interaction EPL∝WC			**0.09**		**0.13**
Cardiovascular death					
Overall					
Placebo	175/1292 (13.5)				
Eplerenone	136/1287 (10.6)	0.75 (0.60–0.94)	0.01	0.73 (0.58–0.93)	0.009
NWC					
Placebo	91/640 (14.2)				
Eplerenone	83/644 (12.9)	0.91 (0.68–1.23)	0.54	0.87 (0.64–1.18)	0.38
HWC					
Placebo	84/652 (12.9)				
Eplerenone	53/643 (8.2)	0.59 (0.42–0.84)	0.003	0.58 (0.40–0.83)	0.003
Interaction EPL∝WC			**0.06**		**0.09**
Hospitalization for HF					
Overall					
Placebo	238/1292 (18.4)				
Eplerenone	151/1287 (11.7)	0.60 (0.49–0.73)	<0.0001	0.59 (0.48–0.73)	<0.0001
NWC					
Placebo	118/640 (18.4)				
Eplerenone	89/644 (13.8)	0.74 (0.56–0.97)	0.03	0.71 (0.53–0.95)	0.02
HWC					
Placebo	120/652 (18.4)				
Eplerenone	62/643 (9.6)	0.47 (0.35–0.64)	<0.0001	0.48 (0.35–0.66)	<0.0001
Interaction EPL∝WC			**0.03**		**0.07**

Characteristics	Events/ patients (%)	Crude HR (95% CI)	*P*-value	Multivariable HR (95% CI)	*P*-value
BMI < 30					
Placebo	271/1008 (26.9)				
Eplerenone	193/975 (19.8)	0.71 (0.59–0.85)	0.0003	0.69 (0.57–0.83)	0.0001
BMI ≥ 30					
Placebo	85/356 (23.9)				
Eplerenone	54/383 (14.1)	0.51 (0.37–0.72)	0.0001	0.49 (0.35–0.71)	0.0001
Interaction EPL∝BMI			**0.10**		**0.11**
BMI < 30					
Placebo	170/1008 (16.9)				
Eplerenone	135/975 (13.9)	0.81 (0.65–1.02)	0.07	0.75 (0.59–0.95)	0.02
BMI ≥ 30					
Placebo	43/356 (12.1)				
Eplerenone	35/383 (9.1)	0.67 (0.43–1.05)	0.08	0.68 (0.43–1.08)	0.11
Interaction EPL∝BMI			**0.46**		**0.73**
BMI < 30					
Placebo	149/1008 (14.8)				
Eplerenone	116/975 (11.9)	0.80 (0.63–1.02)	0.07	0.73 (0.57–0.94)	0.02
BMI ≥ 30					
Placebo	36/356 (10.1)				
Eplerenone	30/383 (7.8)	0.69 (0.42–1.12)	0.13	0.71 (0.43–1.18)	0.19
Interaction EPL∝BMI			**0.60**		**0.93**
BMI < 30					
Placebo	194/1008 (19.3)				
Eplerenone	129/975 (13.2)	0.66 (0.53–0.83)	0.0003	0.62 (0.49–0.77)	<0.0001
BMI ≥ 30					
Placebo	59/356 (16.6)				
Eplerenone	34/383 (8.9)	0.47 (0.31–0.71)	0.0004	0.47 (0.30–0.71)	0.0004
Interaction EPL∝BMI			**0.15**		**0.25**

BMI, body mass index expressed in kg/m^2; CI, confidence interval; EPL, eplerenone; HF, heart failure; HR, hazard ratio; NWC, normal waist circumference < 102 cm and < 88 cm for men and women, respectively; HWC, high waist circumference ≥ 102 cm and ≥ 88 cm for men and women, respectively.
Events/patients are given in unadjusted models.

post hoc analysis of EMPHASIS-HF suggests that abdominal obesity estimated by WC measurement could be a simple and straightforward classifier identifying a subset of patients with HFrEF that might derive greater benefit from MRA therapy. Despite the known adverse impact of obesity on most of the HF risk factors, our results suggest a better prognosis for patients with abdominal obesity, i.e. an obesity paradox. Thus, our results suggest for the first time that part of the known obesity paradox observed in HF trials might be explained by the greater benefits derived by obese patients from their HF MRA treatment.

The deleterious impact of excessive aldosterone/MR activation in the heart has been extensively documented during this past decade. Both cortisol and aldosterone adversely affect the cardiovascular events via the activation of the MRs in the heart, blood vessels, kidney, and other sites.[19] Notably, high levels of aldosterone promote the development of interstitial cardiac fibrosis, promote platelet aggregation, and contribute to endothelial dysfunction, in part by reducing nitric oxide bioavailability, and favour hypertension, chronic kidney disease, and concentric left ventricular hypertrophy in the general community.[20] Furthermore, MR activation in macrophages has been demonstrated to promote coronary and systemic inflammation, particularly in the initial response to reperfusion injury after ischaemic injury.[21,22] Collectively, these studies have justified the targeting of MR as a new approach for the treatment of HF patients.[8,11,23] The mechanism of action of MRAs in HF is multiple, including anti-inflammatory, anti-fibrotic and anti-remodelling properties, with a decrease in sympathetic drive and improvement in heart rate variability.[24–26] It could be in part attributed to the increased MR activation and more pronounced production of its ligands in the failing human heart.[4,27,28]

Experimental and clinical studies suggest that MR over-activation in hyperphagic conditions[29] and high fat diet-induced obesity may precipitate cardiac remodelling and HF development.[14,30,31] In fact, all components of the renin–angiotensin–aldosterone system (RAAS) are expressed in adipose tissue and their gene expression has been found increased in adipose tissues of both obese animal models and obese humans.[7,32,33] The increments in body weight and overall obesity are known to result from chronic positive energy balance, a condition which is known to increase MR expression and further favour the development of adipose tissue inflammation and fibrosis.[30] We recently demonstrated that chronic eplerenone treatment delayed cardiac remodelling and HF onset in both lean and obese spontaneously hypertensive HF rats but that obese rats presenting a higher aldosterone level further benefited from MRA treatment through improvement of their obesity, dyslipidaemia and myocardial fibrosis.[16] Further experimental studies have demonstrated that the benefits of MR blockade included reduced obesity-related cardiac fibrosis, coronary microvascular disorders, cardiac oxidative stress, and systemic inflammation.[14,31] Small exploratory clinical studies further suggested beneficial effects of spironolactone on left ventricular dysfunction in obese individuals without other co-morbidities and in patients with metabolic syndrome, which supports our observation of a more pronounced clinical benefit of MRA therapy in overweight to obese individuals.[12,24] It also suggests that overweight to obese HF patients may derive great benefit from MRA at least in part because of their high inflammatory and fibrotic clinical status.[34–36]

This is of strong interest when considering that in the USA approximately one-half to two-thirds of HF patients are overweight or obese.[37] Interestingly, aldosterone was proposed to promote adipogenesis by inducing peroxisome proliferator-activated receptor γ expression, while increased adiposity is known to have adverse effects on left ventricular structure and function, and other risk factors of HF, including hypertension and coronary artery disease.[14,38] Thus, although speculative in clinic but based on strong experimental evidence, one tentative explanation of the better response to eplerenone of HF patients with abdominal obesity might be that these patients have higher aldosterone levels associated with hyper-secretion of trophic factors from the visceral adipose tissue.[5,39] The observed better discriminative power of the WC parameters in defining the best responder group of HFrEF to eplerenone as compared to BMI might be explained in part by the fact that the RAAS has been described to have variable activity depending on the adipose tissue location. A high RAAS activity has been reported in abdominal adipocytes, which are more closely associated with aldosterone biosynthesis and where angiotensinogen and angiotensin II receptor gene expression levels are high. A lower RAAS activity was reported in gluteofemoral adipose tissue, which may explain why the fat from this latter location is less metabolically active.[40]

Adipose tissue is considered as an endocrine organ influencing the maintenance of the body metabolic and inflammatory homeostasis, especially when located in close vicinity to the heart, kidney, liver and the skeletal muscle. The development of visceral fat tissue results in crucial endocrine interactions with those vital organs that may lead to their structural and functional alterations.[41,42]

While largely used to classify obesity, a clear limitation of BMI is that it is unable to distinguish between increased body fat content and increased lean body mass (breakdown of body composition) and cannot indicate where adiposity preferentially develops as it is accountable for the characterization of global obesity. Our results highlight the different relevance of these two anthropometric parameters, and confirm that BMI and WC are not characterizing the same type of adiposity. Altogether, a total of 668 EMPHASIS-HF patients were 'misclassified' when using BMI: 626 of them were non-obese (BMI $< 30\,kg/m^2$) but harboured abdominal obesity (HWC) and 42 of them were classified obese (BMI $\geq 30\,kg/m^2$) but had NWC. These are the patients causing a difference in the results between BMI and WC parameters, leading to the statistically significant results for the interaction in WC but not in BMI subgroups. Not all types of adipose fat depot are alike and can differ by their location (gynoid, android, visceral, subcutaneous, overall) and degree (from overweight up to morbid obesity). Numerous imaging tools such as dual-energy X-ray absorptiometry, bioelectrical impedance analysis, and magnetic resonance imaging, and anthropometric measures such as BMI and WC can discriminate between them. Whether imaging data would better define fat deposition and, thus, better refine the subsequent risk is beyond the scope of our study, but WC is such an easy low-cost biomarker to access that its use in general clinic should be warranted.

Moreover, weight variation in HF patients is very much dependent on fluid retention, and the resulting congestion may mostly impact BMI and, to a lesser extent, WC. This suggests that the latter parameter might be more reliable in the context of HF. Our results suggest for the first time that the specific location of the excess of adiposity represents an important matter when treating HF patients.

While still requiring replication, the differential findings reported for WC and BMI with regards to patient response to eplerenone are consistent with the large body of literature suggesting that, depending on their location, adipose tissue deposits present distinct metabolic and inflammatory properties. While both subcutaneous and visceral adipose tissues are considered as endocrine organs, visceral adipose tissue has especially been shown to secrete adipocytokines and other vasoactive substances, including aldosterone,[25,26] and has been associated with higher mortality than overall obesity defined by BMI.[43,44] The increase in either or both types of fat deposit (subcutaneous and visceral) participates in the development of abdominal obesity, which is readily and easily measurable with WC. Interestingly, our data show no differential effect of the treatment on blood pressure, heart rate, body weight and serum potassium levels, according to WC anthropomorphic subgroups (not shown), and hyperkalaemia adverse events, including those leading to study drug discontinuation, occurred equally in WC eplerenone subgroups. In addition, adverse events leading to eplerenone withdrawal occurred significantly less frequently in patients with increased abdominal adiposity. Taken together, our results suggest that the benefit/risk ratio of eplerenone therapy is higher in patients with abdominal obesity.

Even though not verified here (the absence of available biosamples precluded us from reconciling the levels of MR ligands and the degree of abdominal adiposity in the EMPHASIS-HF patients), in clinic plasma aldosterone concentration correlated with increased adiposity measured by BMI and was associated with the development of metabolic syndrome with increased WC in the Framingham and African-American populations.[27,28] It was thus expected that EMPHASIS-HF obese patients presented worse clinical characteristics as compared to their lean counterparts. While overweight and obesity have been shown to increase the risk for cardiovascular disease in the general population, reduced mortality in the HF population with higher BMI values has been demonstrated and referred to as the obesity paradox.[45,46] Clark *et al.* demonstrated such paradox in an advanced HF cohort (left ventricular ejection fraction < 25%) and increased WC was mostly associated with improved outcomes in advanced HF.[37,43]

Our results suggest an improved response to MRA treatment of EMPHASIS-HF patients as one out of many other possible contributors to the obesity paradox. Indeed, such paradox, also described in other pathophysiological conditions, varies according to (i) aetiology of the wide range of clinical phenotypes observed in different HF cohorts restricting the protective effect of obesity to patients with non-ischaemic HF; (ii) patient gender; (iii) patient age; (iv) left ventricular ejection fraction; (v) cumulative exposure to excess adiposity and resulting metabolic reserve; and (vi) presence of diabetes.[36,38,46–50]

One could extrapolate that what is called the HF obesity paradox[38,43,45,47–49] described in other HF trials might also be a consequence of HF therapy being more effective in obese patients. This is at least suggested by the results of our study where abdominally obese patients are better responders to MR antagonism than leaner participants. Interestingly, this potentially better response to RAAS inhibitors-based therapy is also suggested in the placebo group where more than 90% of enrolled patients are already treated with ACE inhibitors or ARBs and where increased adiposity was not significantly associated with worsening outcomes. In other reports mentioning this HF obesity paradox phenomenon, the association of BMI with outcomes was studied while adjusting for the background medical therapy, but the interactions of BMI with therapy are yet to be reported. Thus, in-depth evaluation of the proposed paradoxical effect of obesity in HF patients as compared to the general population taking into account exposure to therapy is now required to validate our hypothesis. Future studies should explore the potential relationship between RAAS inhibition and the obesity paradox taking into account that our study was based on the cut-offs for WC and BMI that have been defined for their predictive value of health risks only, and not for their capacity to predict the response to a given drug. Further analysis in larger populations should be considered to challenge and potentially redefine these cut-offs in order to use WC and BMI as stratifying biomarkers when prescribing MRA therapy.

Our findings should be regarded as hypothesis generating for future studies that should be designed to confirm whether HF patients with increased adiposity, i.e. patients characterized by elevated MR ligand secretion, are potentially the best responders to MRA therapy. Because EMPHASIS-HF patients presenting an abdominal obesity derive greater benefit from eplerenone, future investigation should evaluate how the greater response to MRA therapy could contribute to and partly explain the so-called 'obesity paradox' observed in HF populations.[38,42,51] Our results call upon further investigations of obesity-associated measurements as potential straightforward classifiers predicting the therapeutic response to MRAs in HF patients and in other cardiovascular diseases and their respective risk factors for which MR activation has been implicated. More specifically, it is tempting to explore whether increased adiposity may also help identify responders to MRA therapy among HF patients with preserved ejection fraction, an important category of HF patients in much need of novel effective therapies. Indeed, recently reported neutral results of clinical trials using MRA in HF patients with preserved ejection fraction have been so far explained by international geographic variation.[52] Regarding our results, event rates should be analysed according to differences in anthropomorphic parameters of the Russian, Georgian and American patients enrolled in the TOPCAT trial.[23]

Supplementary Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Baseline characteristics of patients according to waist circumference and to treatment per subgroup of waist circumference.

Table S2. Selected investigator-reported adverse events and those leading to permanent withdrawal of the study drug, according to study groups.

Table S3. Association between eplerenone and outcomes depending on waist circumference.

Table S4. Association between eplerenone and outcomes depending on body mass index.

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References

1. De Pergola G, Nardecchia A, Giagulli VA, Triggiani V, Guastamacchia E, Minischetti MC, Silvestris F. Obesity and heart failure. *Endocr Metab Immune Disord Drug Targets* 2013;**13**:51–57.
2. Kenchaiah S, Pocock SJ, Wang D, Finn PV, Zornoff LA, Skali H, Pfeffer MA, Yusuf S, Swedberg K, Michelson EL, Granger CB, McMurray JJ, Solomon SD; CHARM Investigators. Body mass index and prognosis in patients with chronic heart failure: insights from the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) program. *Circulation* 2007;**116**:627–636.
3. Schocken DD, Benjamin EJ, Fonarow GC, Krumholz HM, Levy D, Mensah GA, Narula J, Shor ES, Young JB, Hong Y, American Heart Association Council on Epidemiology and Prevention; American Heart Association Council on Clinical Cardiology; American Heart Association Council on Cardiovascular Nursing; American Heart Association Council on High Blood Pressure Research; Quality of Care and Outcomes Research Interdisciplinary Working Group; Functional Genomics and Translational Biology Interdisciplinary Working Group. Prevention of heart failure: a scientific statement from the American Heart Association Councils on Epidemiology and Prevention, Clinical Cardiology, Cardiovascular Nursing, and High Blood Pressure Research; Quality of Care and Outcomes Research Interdisciplinary Working Group; and Functional Genomics and Translational Biology Interdisciplinary Working Group. *Circulation* 2008;**117**:2544–2565.
4. Mizuno Y, Yoshimura M, Yasue H, Sakamoto T, Ogawa H, Kugiyama K, Harada E, Nakayama M, Nakamura S, Ito T, Shimasaki Y, Saito Y, Nakao K. Aldosterone production is activated in failing ventricle in humans. *Circulation* 2001;**103**:72–77.
5. Caprio M, Feve B, Claes A, Viengchareun S, Lombes M, Zennaro MC. Pivotal role of the mineralocorticoid receptor in corticosteroid-induced adipogenesis. *FASEB J* 2007;**21**:2185–2194.
6. Funder JW, Reincke M. Aldosterone: a cardiovascular risk factor? *Biochim Biophys Acta* **2010**;1802:1188–1192.
7. Lastra G, Sowers JR. Obesity and cardiovascular disease: role of adipose tissue, inflammation, and the renin-angiotensin-aldosterone system. *Horm Mol Biol Clin Investig* 2013;**15**:49–57.
8. Pitt B, Williams G, Remme W, Martinez F, Lopez-Sendon J, Zannad F, Neaton J, Roniker B, Hurley S, Burns D, Bittman R, Kleiman J. The EPHESUS trial: eplerenone in patients with heart failure due to systolic dysfunction complicating acute myocardial infarction. Eplerenone Post-AMI Heart Failure Efficacy and Survival Study. *Cardiovasc Drugs Ther* 2001;**15**:79–87.
9. Pitt D. ACE inhibitor co-therapy in patients with heart failure: rationale for the Randomized Aldactone Evaluation Study (RALES). *Eur Heart J* 1995;**16** (Suppl N):107–110.
10. Pitt B. Effect of aldosterone blockade in patients with systolic left ventricular dysfunction: implications of the RALES and EPHESUS studies. *Mol Cell Endocrinol* 2004;**217**:53–8.
11. Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, Vincent J, Pocock SJ, Pitt B; EMPHASIS-HF Study Group. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med* 2011;**364**:11–21.
12. Kosmala W, Przewlocka-Kosmala M, Szczepanik-Osadnik H, Mysiak A, Marwick TH. Fibrosis and cardiac function in obesity: a randomised controlled trial of aldosterone blockade. *Heart* 2013;**99**:320–326.
13. Caprio M, Antelmi A, Chetrite G, Muscat A, Mammi C, Marzolla V, Fabbri A, Zennaro MC, Feve B. Antiadipogenic effects of the mineralocorticoid receptor antagonist drospirenone: potential implications for the treatment of metabolic syndrome. *Endocrinology* 2011;**152**:113–125.
14. Guo C, Ricchiuti V, Lian BQ, Yao TM, Coutinho P, Romero JR, Li J, Williams GH, Adler GK. Mineralocorticoid receptor blockade reverses obesity-related changes in expression of adiponectin, peroxisome proliferator-activated receptor-gamma, and proinflammatory adipokines. *Circulation* 2008;**117**:2253–2261.
15. Hirata A, Maeda N, Hiuge A, Hibuse T, Fujita K, Okada T, Kihara S, Funahashi T, Shimomura I. Blockade of mineralocorticoid receptor reverses adipocyte dysfunction and insulin resistance in obese mice. *Cardiovasc Res* 2009;**84**:164–172.
16. Youcef G, Olivier A, Nicot N, Muller A, Deng C, Labat C, Fay R, Rodriguez-Guéant R-M, Leroy C, Jaisser F, Zannad F, Lacolley P, Vallar L, Pizard A. Preventive and chronic mineralocorticoid receptor antagonism is highly beneficial in obese SHHF rats. *Br J Pharmacol* 2016;**173**:1805–1819.
17. Jensen MD, Ryan DH, Apovian CM, Ard JD, Comuzzie AG, Donato KA, Hu FB, Hubbard VS, Jakicic JM, Kushner RF, Loria CM, Millen BE, Nonas CA, Pi-Sunyer FX, Stevens J, Stevens VJ, Wadden TA, Wolfe BM, Yanovski SZ; American College of Cardiology/American Heart Association Task Force on Practice Guidelines; Obesity Society. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. *J Am Coll Cardiol* 2014;**63**:2985–3023.
18. Derksen S, Keselman HJ. Backward, forward and stepwise automated subset selection algorithms: Frequency of obtaining authentic and noise variables. *Br J Math Stat Psychol* 1992;**45**:265–282.
19. Weber KT. Aldosterone in congestive heart failure. *N Engl J Med* 2001;**345**:1689–1697.
20. Buglioni A, Cannone V, Cataliotti A, Sangaralingham SJ, Heublein DM, Scott CG, Bailey KR, Rodeheffer RJ, Dessi-Fulgheri P, Sarzani R, Burnett JC Jr. Circulating aldosterone and natriuretic peptides in the general community: relationship to cardiorenal and metabolic disease. *Hypertension* 2015;**65**:45–53.
21. Young MJ, Rickard AJ. Mineralocorticoid receptors in the heart: lessons from cell-selective transgenic animals. *J Endocrinol* 2015;**224**:R1–13.
22. Gilbert KC, Brown NJ. Aldosterone and inflammation. *Curr Opin Endocrinol Diabetes Obes* 2010;**17**:199–204.
23. Pfeffer MA, Claggett B, Assmann SF, Boineau R, Anand IS, Clausell N, Desai AS, Diaz R, Fleg JL, Gordeev I, Heitner JF, Lewis EF, O'Meara E, Rouleau JL, Probstfield JL, Shaburishvili T, Shah SJ, Solomon SD, Sweitzer NK, McKinlay SM, Pitt B. Regional variation in patients and outcomes in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) trial. *Circulation* 2015;**131**:34–42.
24. Kosmala W, Jedrzejuk D, Derzhko R, Przewlocka-Kosmala M, Mysiak A, Bednarek-Tupikowska G. Left ventricular function impairment in patients with normal-weight obesity: contribution of abdominal fat deposition, profibrotic state, reduced insulin sensitivity, and proinflammatory activation. *Circ Cardiovasc Imaging* 2012;**5**:349–356.
25. Marzolla V, Armani A, Zennaro MC, Cinti F, Mammi C, Fabbri A, Rosano GM, Caprio M. The role of the mineralocorticoid receptor in adipocyte biology and fat metabolism. *Mol Cell Endocrinol* 2012;**350**:281–288.
26. Whaley-Connell A, Sowers JR. Oxidative stress in the cardiorenal metabolic syndrome. *Curr Hypertens Rep* 2012;**14**:360–365.
27. Ingelsson E, Pencina MJ, Tofler GH, Benjamin EJ, Lanier KJ, Jacques PF, Fox CS, Meigs JB, Levy D, Larson MG, Selhub J, D'Agostino RB Sr, Wang TJ, Vasan RS. Multimarker approach to evaluate the incidence of the metabolic syndrome and longitudinal changes in metabolic risk factors: the Framingham Offspring Study. *Circulation* 2007;**116**:984–992.
28. Rossi GP, Belfiore A, Bernini G, Fabris B, Caridi G, Ferri C, Giacchetti G, Letizia C, Maccario M, Mannelli M, Palumbo G, Patalano A, Rizzoni D, Rossi E, Pessina AC, Mantero F; Primary Aldosteronism Prevalence in hYpertension Study Investigators. Body mass index predicts plasma aldosterone concentrations in overweight-obese primary hypertensive patients. *J Clin Endocrinol Metab* 2008;**93**:2566–2571.
29. Youcef G, Olivier A, L'Huillier CP, Labat C, Fay R, Tabcheh L, Toupance S, Rodriguez-Gueant RM, Bergerot D, Jaisser F, Lacolley P, Zannad F, Laurent V, Pizard A. Simultaneous characterization of metabolic, cardiac, vascular and renal phenotypes of lean and obese SHHF rats. *PLoS One* 2014;**9**:e96452.
30. Armani A, Cinti F, Marzolla V, Morgan J, Cranston GA, Antelmi A, Carpinelli G, Canese R, Pagotto U, Quarta C, Malorni W, Matarrese P, Marconi M,

Fabbri A, Rosano G, Cinti S, Young MJ, Caprio M. Mineralocorticoid receptor antagonism induces browning of white adipose tissue through impairment of autophagy and prevents adipocyte dysfunction in high-fat-diet-fed mice. *FASEB J* 2014;**28**:3745–3757.
31. Bender SB, DeMarco VG, Padilla J, Jenkins NT, Habibi J, Garro M, Pulakat L, Aroor AR, Jaffe IZ, Sowers JR. Mineralocorticoid receptor antagonism treats obesity-associated cardiac diastolic dysfunction. *Hypertension* 2015;**65**: 1082–1088.
32. Massiera F, Bloch-Faure M, Ceiler D, Murakami K, Fukamizu A, Gasc JM, Quignard-Boulange A, Negrel R, Ailhaud G, Seydoux J, Meneton P, Teboul M. Adipose angiotensinogen is involved in adipose tissue growth and blood pressure regulation. *FASEB J* 2001;**15**:2727–2729.
33. Whaley-Connell A, Johnson MS, Sowers JR. Aldosterone: role in the cardiometabolic syndrome and resistant hypertension. *Prog Cardiovasc Dis* 2010;**52**: 401–409.
34. Hu G, Jousilahti P, Antikainen R, Katzmarzyk PT, Tuomilehto J. Joint effects of physical activity, body mass index, waist circumference, and waist-to-hip ratio on the risk of heart failure. *Circulation* 2010;**121**:237–244.
35. Kenchaiah S, Evans JC, Levy D, Wilson PW, Benjamin EJ, Larson MG, Kannel WB, Vasan RS. Obesity and the risk of heart failure. *N Engl J Med* 2002;**347**: 305–313.
36. Levitan EB, Yang AZ, Wolk A, Mittleman MA. Adiposity and incidence of heart failure hospitalization and mortality: a population-based prospective study. *Circ Heart Fail* 2009;**2**:202–208.
37. Clark AL, Fonarow GC, Horwich TB. Waist circumference, body mass index, and survival in systolic heart failure: the obesity paradox revisited. *J Card Fail* 2011;**17**:374–80.
38. Lavie CJ, McAuley PA, Church TS, Milani RV, Blair SN. Obesity and cardiovascular diseases: implications regarding fitness, fatness, and severity in the obesity paradox. *J Am Coll Cardiol* 2014;**63**:1345–1354.
39. Mathieu P, Boulanger MC, Despres JP. Ectopic visceral fat: a clinical and molecular perspective on the cardiometabolic risk. *Rev Endocr Metab Disord* 2014;**15**:289–298.
40. Feliciano Pereira P, Eloiza Priore S, Bressan J. Aldosterone: a cardiometabolic risk hormone? *Nutr Hosp* 2014;**30**:1191–1202.
41. Bastien M, Poirier P, Lemieux I, Despres JP. Overview of epidemiology and contribution of obesity to cardiovascular disease. *Prog Cardiovasc Dis* 2014;**56**:369–381.
42. Lavie CJ, Sharma A, Alpert MA, De Schutter A, Lopez-Jimenez F, Milani RV, Ventura HO. Update on obesity and obesity paradox in heart failure. *Prog Cardiovasc Dis* 2016;**58**:393–400.
43. Gupta PP, Fonarow GC, Horwich TB. Obesity and the obesity paradox in heart failure. *Can J Cardiol* 2015;**31**:195–202.
44. Sahakyan KR, Somers VK, Rodriguez-Escudero JP, Hodge DO, Carter RE, Sochor O, Coutinho T, Jensen MD, Roger VL, Singh P, Lopez-Jimenez F. Normal-weight central obesity: implications for total and cardiovascular mortality. *Ann Intern Med* 2015;**163**:827–835.
45. Lavie CJ, Milani RV, Artham SM, Patel DA, Ventura HO. The obesity paradox, weight loss, and coronary disease. *Am J Med* 2009;**122**:1106–1114.
46. Zamora E, Lupon J, Enjuanes C, Pascual-Figal D, de Antonio M, Domingo M, Comin-Colet J, Vila J, Penafiel J, Farre N, Alonso N, Santesmases J, Troya M, Bayes-Genis A. No benefit from the obesity paradox for diabetic patients with heart failure. *Eur J Heart Fail* 2016;**18**:851–858.
47. Nasir K, Campbell CY, Santos RD, Roguin A, Braunstein JB, Carvalho JA, Blumenthal RS. The association of subclinical coronary atherosclerosis with abdominal and total obesity in asymptomatic men. *Prev Cardiol* 2005;**8**:143–148.
48. Reis JP, Allen N, Gunderson EP, Lee JM, Lewis CE, Loria CM, Powell-Wiley TM, Rana JS, Sidney S, Wei G, Yano Y, Liu K. Excess body mass index- and waist circumference-years and incident cardiovascular disease: the CARDIA study. *Obesity (Silver Spring)* 2015;**23**:879–885.
49. Shah R, Gayat E, Januzzi JL Jr, Sato N, Cohen-Solal A, diSomma S, Fairman E, Harjola VP, Ishihara S, Lassus J, Maggioni A, Metra M, Mueller C, Mueller T, Parenica J, Pascual-Figal D, Peacock WF, Spinar J, van Kimmenade R, Mebazaa A; GREAT (Global Research on Acute Conditions Team) Network. Body mass index and mortality in acutely decompensated heart failure across the world: a global obesity paradox. *J Am Coll Cardiol* 2014;**63**:778–785.
50. Zamora E, Lupon J, de Antonio M, Urrutia A, Coll R, Diez C, Altimir S, Bayes-Genis A. The obesity paradox in heart failure: is etiology a key factor? *Int J Cardiol* 2013;**166**:601–605.
51. Lavie CJ, Alpert MA, Arena R, Mehra MR, Milani RV, Ventura HO. Impact of obesity and the obesity paradox on prevalence and prognosis in heart failure. *JACC Heart Fail* 2013;**1**:93–102.
52. Kristensen SL, Kober L, Jhund PS, Solomon SD, Kjekshus J, McKelvie RS, Zile MR, Granger CB, Wikstrand J, Komajda M, Carson PE, Pfeffer MA, Swedberg K, Wedel H, Yusuf S, McMurray JJ. International geographic variation in event rates in trials of heart failure with preserved and reduced ejection fraction. *Circulation* 2015;**131**:43–53.