Effect of Obesity on Response to Spironolactone in Patients With Heart Failure With Preserved Ejection Fraction

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Obesity is common in heart failure with preserved ejection fraction (HFpEF). Whether obesity modifies the response to spironolactone in patients with HFpEF remains unclear. We aimed to investigate the effect of obesity, defined by body mass index (BMI) and waist circumference (WC), on response to spironolactone in patients with HFpEF enrolled in Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist trial. This was a post-hoc, exploratory analysis of the Americas cohort of Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist trial. BMI≥30 kg/m2 was used to define the obese group and WC≥102 cm in men and ≥88 cm in women were defined as high WC. In separate analyses, BMI and WC were treated as continuous variables. The effect of spironolactone versus placebo on outcomes was calculated by BMI and WC using Cox proportional hazard models. Obese patients were younger and had more co-morbidities. In multivariate analysis, spironolactone use was associated with a significant reduction in the primary end point, compared with placebo in obese [hazard ratio (HR = 0.618, 95% CI 0.460 to 0.831, p = 0.001), but not in nonobese subjects (HR = 0.946, 95% CI 0.623 to 1.437, p = 0.796; p for interaction = 0.056). There was a linear association between continuous BMI and the effect of spironolactone, with the effect becoming significant at 33kg/m^2. Similar results were obtained for the WC-based analysis. In conclusion, use of spironolactone in obese patients with HFpEF was associated with a decreased risk of the primary end point, cardiovascular death and HF hospitalizations, compared with placebo. Further prospective randomized studies in obese subjects are required. **(Am J Cardiol 2021;146:36−47)**

Heart failure (HF) with preserved ejection fraction (HFpEF) is one of the most prevalent cardiovascular conditions, is associated with significant morbidity and mortality, and unlike HFrEF there is no evidence-based treatment that improves clinical outcomes.[1,2] Obesity is a well−established risk factor for HFpEF, and is associated with a systemic pro-inflammatory state and activation of the renin −angiotensin-aldosterone system with established deleterious cardiovascular effects.[3,4] Drugs that antagonize aldosterone have been shown to decrease the systemic pro-inflammatory state and could be an attractive therapeutic option for patients with obesity-related HFpEF. Nonetheless, in the TOPCAT (Aldosterone Antagonist Therapy for Adults with Heart Failure and Preserved Systolic Function; NCT00094302) trial, spironolactone failed to show any beneficial effect compared with placebo on the primary composite end point of cardiovascular death, HF hospitalization, or aborted cardiac arrest patients with HFpEF.[5] However, a post-hoc analysis, which included patients enrolled in the Americas, demonstrated a significant reduction in the primary and several secondary end points with spironolactone treatment.[6] In light of the inflammatory phenotype associated with obesity and the anti-inflammatory effects of spironolactone, we hypothesized that spironolactone would result in a better outcome in obese compared with nonobese patients enrolled in TOPCAT.

Methods

TOPCAT was a multicenter, randomized, double−blind, placebo−controlled trial that evaluated the effects of spironolactone in patients with symptomatic HFpEF. The details of the study design and primary findings were previously reported.[5] Briefly, the trial included patients older than 50 years with signs and symptoms of heart failure, left ventricular ejection fraction >45%, who fulfilled at least 1 of the following inclusion criteria: (1) history of hospitalization for HF within the past 12 months; or (2) brain natriuretic peptide (BNP)≥100 pg/mL or an N−terminal−pro-BNP (NT−pro-BNP)≥360 pg/mL within 60 days of randomization. The study included 3445 participants from 233 sites across the Americas (United States, Canada, South America) (n = 1767 participants), and Europe (Russia and Republic of Georgia, n = 1,678 participants). The mean duration of follow-up was 3.4±1.7 years. The primary end point was time to cardiovascular death, HF hospitalization,

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or aborted cardiac arrest. All end points were adjudicated by a central adjudication committee blinded to treatment assignment. HF hospitalization was defined as an overnight stay for the acute management of HF with ≥1 symptom and ≥2 signs of HF with qualified treatment.[5] The data and study materials were made available through the National Institutes of Health and the Institutional Review Board of the University of Oklahoma Health Sciences Center approved the present analysis.

The primary end point for the present study was the composite of cardiovascular death, HF hospitalization, or aborted cardiac arrest. Secondary end points analyzed were cardiovascular death, HF hospitalization and all-cause death. Due to the very small number of aborted cardiac arrest (n=6), we did not include this individual end point in the analysis.

Because of the previously reported significant regional differences between the Americas and Russia and Georgia, and with very few events in Russia and Georgia,[6] the primary analysis was carried out on the 1751 patients from the Americas cohort (USA, Canada, Argentina, Brazil) with available data about waist circumference, weight and height.

Obesity was defined according to World Health Organization criteria: BMI≥30Kg/m^2 for obese group and <30Kg/m^2 for non-obese group. Subjects were divided into 2 groups according to waist circumference (WC) using the American Heart Association defined cut-offs.[7] Men and women with WC values <102 cm and <88 cm, respectively, were considered to have a normal WC (NWC), whereas those with WC values ≥102cm and ≥88 cm, respectively, were considered to have high WC (HWC).

Actual plasma volume (aPV) was calculated for participants with available hematocrit and weight data (n = 1,734). These values were generated from equations previously validated against both measured plasma volume and clinical outcomes in patients with HF,[8,9] as follows: aPV = (1−hematocrit) x [a + (b × weight in kg)], where hematocrit is a proportion. In this equation, a=1,530 or 864; and b=41 or 47.9, for men and women, respectively.

Echocardiographic data were available for 642 patients in our analysis and were not used in the multivariate analysis as the analysis would have been underpowered.

Of the 1,751 patients enrolled in the Americas cohort, 786 (44.9%) patients were enrolled in the natriuretic peptide (NP) stratum and 965 patients in the HF hospitalization stratum. The study-qualifying BNP or NT-pro BNP values were available in 1,047 patients. According to NP values, we divided patients into tertiles: NP tertile I (BNP<177pg/ml, NT-Pro-BNP<684pg/ml), NP tertile II (BNP 177-366pg/ml, NT-Pro-BNP 684-1496pg/ml) and NP tertile III (BNP>366pg/ml, NT-Pro-BNP>1496pg/ml).

Baseline characteristics between WC and BMI groups were compared using the chi-square test and Student's *t*-test test for categorical and continuous variables, respectively. Associations between BMI or WC (both as a continuous and categorical variable) and end points were determined using Cox proportional hazards models. The effect of spironolactone vs. placebo on end points was calculated for BMI and WC categories. Interactions between BMI or WC and spironolactone effect on end points were assessed by introducing an interaction term BMI or WC variable × spironolactone. Multivariate associations were adjusted for all patient characteristics that differed significantly between BMI and WC categories in frequency or magnitude with backwards elimination until a parsimonious model was achieved. Hazard ratios (HR) and 95% confidence intervals (CI) were calculated. p values <0.05 were considered statistically significant for the main effect. Due to the low power of interaction tests, a p value <0.1 was considered statistically for the interaction effect, as previously described.[10] All analyses were performed using SAS 9.4 (SAS Institute, Cary, North Carolina).

Results

The baseline characteristics of obese and nonobese patients are summarized in Table 1. Compared with nonobese patients, obese patients were younger and had a higher frequency of hypertension, diabetes, dyslipidemia, asthma and atrial fibrillation. Use of diuretics, angiotensin converting enzyme inhibitors or angiotensin receptor blockers, calcium channel blockers and statins were more frequent in obese compared with nonobese patients. Furthermore, obese patients had higher blood pressure, aPV and higher incidence of edema, were enrolled more frequently through the HF hospitalization stratum and had lower NP values.

A total of 1,643 patients were included in the WC analysis (124 patients were excluded due to missing information about WC). Table 2 shows differences in baseline characteristics between NWC and HWC subgroups. Similar to patients with high BMI, those with HWC had more complications related to obesity, including diabetes, hypertension, dyslipidemia, and asthma.

There was no significant difference in the incidence of permanent hyperkalemia and abnormal renal function adverse events that led to drug discontinuation across BMI or WC subgroups (Tables 1 and 2, respectively).

After multivariate adjustment, there was no difference in the primary end point in the primary end point or any of the secondary end points between the 2 groups (Figure 1 and Table 3). Importantly, there was no interaction between NP tertiles and BMI (p for interaction = 0.210). When treated as a continuous variable in multivariate analysis, higher BMI was not associated with the primary end point or any of the secondary end points. Likewise, there was no difference in the primary end point or any of the secondary end points between the 2 groups (Figure 2 and Table 4). In addition, there was no interaction between NP tertiles and WC (p for interaction = 0.130). When treated as a continuous variable in multivariate analysis, higher WC was not associated with the primary end point or HF hospitalization, but was associated with increased risk of cardiovascular death (HR=1.019, 95% CI 1.001 to 1.037, p=0.036) and all-cause death (HR=1.013, 95% CI 1.000 to 1.026, p = 0.045).

Kaplan Meier curves for multivariate adjusted outcomes in obese vs. nonobese subjects stratified by treatment arm are shown in Figure 3. In the obese group there was a 39% significant decrease in the primary end point rates in the spironolactone arm compared with placebo (HR=0.618, 95% CI 0.460 to 0.831, p = 0.001), but not in the nonobese group (HR=0.946, 95% CI 0.623 to 1.437, p = 0.796; p for BMI

Table 1
Baseline characteristics according to BMI group for TOPCAT Americas population

Characteristic	BMI (Kg/m^2) < 30(n=616)	BMI (Kg/m^2) ≥ 30(n= 1135)	p value
Age (years)	75.3 ± 9	69.4±9.3	**<0.001**
Spironolactone	303 (49%)	580 (51%)	0.453
BMI (Kg/m^2)	25.9 ± 2.7	38 ± 6.7	**< 0.001**
Waist circumference (cm)	95.9 ±11	118±15.9	**< 0.001**
Women	297 (48%)	578 (51%)	0.293
Men	319 (52%)	557 (49%)	
White	508 (83%)	865 (76%)	**< 0.001**
Black	70 (11%)	229 (20%)	
Others	38 (6%)	41 (4%)	
Enrollment strata:			
HF hospital admission	274 (44%)	691 (61%)	**< 0.001**
Natriuretic Peptide	342 (56%)	444 (39%)	
BNP (pg/ml)	458 ± 538 (n=244)	339 ± 343 (n=447)	**0.002**
NT Pro-BNP (pg/ml)	1983 ± 2141 (n= 156)	1368 ± 1699 (n= 200)	**0.004**
Natriuretic Peptide tertiles:			**< 0.001**
I (n= 348)	106 (27%)	242 (37%)	
II (n= 349)	134 (33%)	215 (33%)	
III (n= 350)	160 (40%)	190 (29%)	
Actual plasma volume (aPV) (ml)	2702.4 ± 387.2	3603.4 ± 662.4	**<0.001**
Heart rate (beats/min)	67 ± 10.4	69 ± 11.5	**< 0.001**
Systolic Blood Pressure (mm Hg)	125.8 ± 15.4	128.7 ± 15.8	**< 0.001**
Diastolic Blood Pressure (mm Hg)	70.1 ± 11	72 ± 11.6	**0.001**
NYHA			**< 0.001**
I or II	446 (72%)	687 (61%)	
III or IV	170 (28%)	445 (39%)	
Edema over the past year	536 (90%)	1069 (96%)	**< 0.001**
Hypertension	529 (87%)	1047 (92%)	**< 0.001**
Diabetes mellitus	177 (29%)	608 (54%)	**< 0.001**
Dyslipidemia	407 (66%)	837 (74%)	**0.001**
Atrial fibrillation	279 (45%)	458 (40%)	**0.048**
Stroke	49 (8%)	109 (10%)	0.294
Myocardial Infarction	126 (21%)	231 (20%)	0.951
PCI	115 (19%)	229 (20%)	0.488
CABG	118 (19%)	216 (19%)	0.949
Angina	178 (29%)	306 (27%)	0.401
Peripheral arterial diseases	61 (10%)	142 (13%)	0.118
COPD	91 (15%)	197 (17%)	0.177
Asthma	48 (8%)	146 (13%)	**0.001**
Sodium	139.38 ± 3.4	139.86 ± 2.9	**0.004**
Potassium	4.2 ± 0.42	4.1 ± 0.43	0.063
Glomerular filtration rate (ml/min/1.73 m^2)	64.3 ± 22.2	64.5 ± 21	0.836
Hemoglobin	12.8 ± 1.6	12.8 ± 1.6	0.618
Hematocrit	38.6 ± 4.8	38.6 ± 4.7	0.889
Albumin	3.9 ± 0.47	3.9 ± 1.9	0.502
Ejection fraction	57 ± 7	58 ± 7	0.252
Left ventricular end diastolic volume	87.3 ± 31.3	100.4 ± 31.6	**< 0.001**
Left ventricular end systolic volume	36.6 ± 19.4	40.4 ± 17.3	**0.015**
Stroke volume	50.6 ± 15.5	60 ± 18.1	**< 0.001**
Left ventricular mass	199.2 ± 63.1	236.4 ± 71.9	**< 0.001**
Left atrial volume	60 ± 23.4	63.1 ± 28.2	0.151
Global longitudinal strain	-15.3 ± 3.4	-15.5 ± 3.4	0.598
E/e' lateral	11.2 ± 5.5	13.1 ± 6.2	**0.003**
E/e' medial	15.8 ± 7.1	16.6 ± 7.2	0.308
Diuretics	513 (83%)	1045 (92%)	**< 0.001**
ACEIs/ARBs	447 (73%)	936 (83%)	**< 0.001**
Beta blockers	484 (79%)	893 (79%)	0.951
Calcium channel blockers	211 (34%)	464 (41%)	**0.006**
Nitrates	100 (16%)	203 (18%)	0.391
Aspirin	343 (56%)	681 (60%)	0.084
Statin	372 (60%)	769 (68%)	0.002

(*continued*)

Table 1 (***Continued***)

Characteristic	BMI (Kg/m^2) < 30(n=616)	BMI (Kg/m^2) ≥ 30(n= 1135)	p value
Warfarin	220 (36%)	367 (32%)	0.168
Study drug discontinuation	573 (93%)	1066 (93%)	0.475
Discontinuation due to permanent hyperkalemia	18 (3%)	33 (3%)	1.00
Discontinuation due to abnormal renal function	33 (5%)	70 (6%)	0.594

Table 2
Baseline characteristics according to WC group for TOPCAT Americas population

Characteristic	NWC (n=349)	HWC (n= 1294)	p value
Age (years)	75.9 ± 9	71±9.4	**<0.001**
Spironolactone	181 (52%)	647 (50%)	0.547
BMI (kg/m^2)	26.11 ± 4.4	35.7 ± 7.4	**< 0.001**
Waist circumference (cm)	89.7 ± 9.2	115 ± 15.6	**<0.001**
Women	107 (31%)	701 (54%)	**<0.001**
Men	242 (69%)	593 (46%)	
White	282 (81%)	1031 (80%)	**< 0.001**
Black	38 (11%)	215 (17%)	
Others	29 (8%)	48 (3%)	
Enrollment strata:			
HF hospital admission	158 (45%)	733 (57%)	**< 0.001**
Natriuretic peptide	191 (55%)	561 (43%)	
BNP (pg/ml)	481 ± 630 (n=127)	367 ± 363 (n=484)	0.052
NT Pro-BNP (pg/ml)	2158 ± 2276 (n= 106)	1428 ± 1714 (n=253)	0.003
Natriuretic Peptide Tertiles:			**< 0.006**
I (n= 320)	65 (28%)	255 (35%)	
II (n= 318)	68 (29%)	250 (34%)	
III (n= 332)	100 (43%)	232 (31%)	
Actual plasma volume (aPV) (ml)	2736.7 ± 477.2	3405.9 ± 692.2	**<0.001**
Heart rate (beats/min)	67.5 ± 10.7	69 ± 11.2	**0.027**
Systolic Blood Pressure (mm Hg)	124.2 ± 15.4	128.3 ± 15.8	**< 0.001**
Diastolic Blood Pressure (mm Hg)	69.6 ± 11.1	71.9 ± 11.5	**0.001**
NYHA			
I or II	262 (75%)	827 (64%)	**< 0.001**
III or IV	87 (25%)	467 (36%)	
Edema over the past year	304 (90%)	1202 (94%)	**< 0.008**
Hypertension	293 (84%)	1188 (92%)	**< 0.001**
Diabetes mellitus	96 (28%)	642 (50%)	**< 0.001**
Dyslipidemia	227 (65%)	951 (74%)	**0.003**
Atrial fibrillation	144 (41%)	559 (43%)	0.542
Stroke	25 (7%)	121 (9%)	0.243
Myocardial Infarction	78 (22%)	267 (21%)	0.505
PCI	73 (21%)	252 (20%)	0.545
CABG	76 (22%)	245 (19%)	0.254
Angina	107 (31%)	355 (27%)	0.254
Peripheral arterial diseases	41 (12%)	151 (12%)	1
COPD	49 (14%)	214 (17%)	0.285
Asthma	21 (6%)	155 (12%)	**0.001**
Sodium	139.1 ± 3.2	139.8 ± 3.1	**< 0.001**
Potassium	4.2 ± 0.42	4.1 ± 0.43	0.195
Glomerular filtration rate (ml/min/1.73 m^2)	67 ± 24	63.7 ± 20.6	**0.012**
Hemoglobin	12.9 ± 1.6	12.8 ± 1.6	0.288
Hematocrit	38.9 ± 4.9	38.7 ± 4.7	0.546
Albumin	3.9 ± 0.49	4 ± 1.8	0.618
Ejection fraction	57.1 ± 8	58.3 ± 7.6	**0.015**
Left ventricular end diastolic volume	93.7 ± 31.3	96.3 ± 32.5	0.425
Left ventricular end systolic volume	40.1 ± 19.9	39.3 ± 17.9	0.664
Stroke volume	53.5 ± 16	57 ± 18.1	0.056
Left ventricular mass	210.7 ± 65.1	227.14 ± 71.7	**0.018**

(*continued*)

Table 2 (***Continued***)

Characteristic	NWC (n=349)	HWC (n= 1294)	p value
Left atrial volume	58.7 ± 23	62.9 ± 28.4	0.093
Global longitudinal strain	-14.9 ± 3.5	-15.5 ± 3.4	0.191
E/e' lateral	11.2 ± 5.3	12.5 ± 6.1	0.09
E/e' medial	16.8 ± 7.5	16.1 ± 7.1	0.502
Diuretics	284 (81%)	1176 (91%)	**< 0.001**
ACEIs/ARBs	252 (72%)	1050 (81.2%)	**< 0.001**
Beta blockers	279 (80%)	1016 (79%)	0.606
Calcium channel blockers	114 (33%)	516 (40%)	**0.015**
Nitrates	57 (16%)	224 (17%)	0.69
Aspirin	208 (60%)	749 (58%)	0.583
Statin	210 (60%)	857 (66%)	**0.037**
Warfarin	115 (33%)	443 (34%)	0.656
Study drug discontinuation	320 (92%)	1216 (94%)	0.142
Discontinuation due to permanent hyperkalemia	11 (3%)	38 (3%)	0.724
Discontinuation due to abnormal renal function	15 (5%)	84 (7%)	0.161

category by treatment arm interaction=0.056). Cardiovascular death was significantly decreased by 52% in the spironolactone arm compared with placebo in obese (HR=0.483, 95% CI 0.281 to 0.833, p = 0.009), but not nonobese subjects (HR=0.742, 95% CI 0.415 to 1.326, p = 0.313; p for interaction = 0.412). All-cause death was not significantly different between spironolactone or placebo arms in obese (HR=0.759, 95% CI 0.518 to 1.112, p = 0.157) and

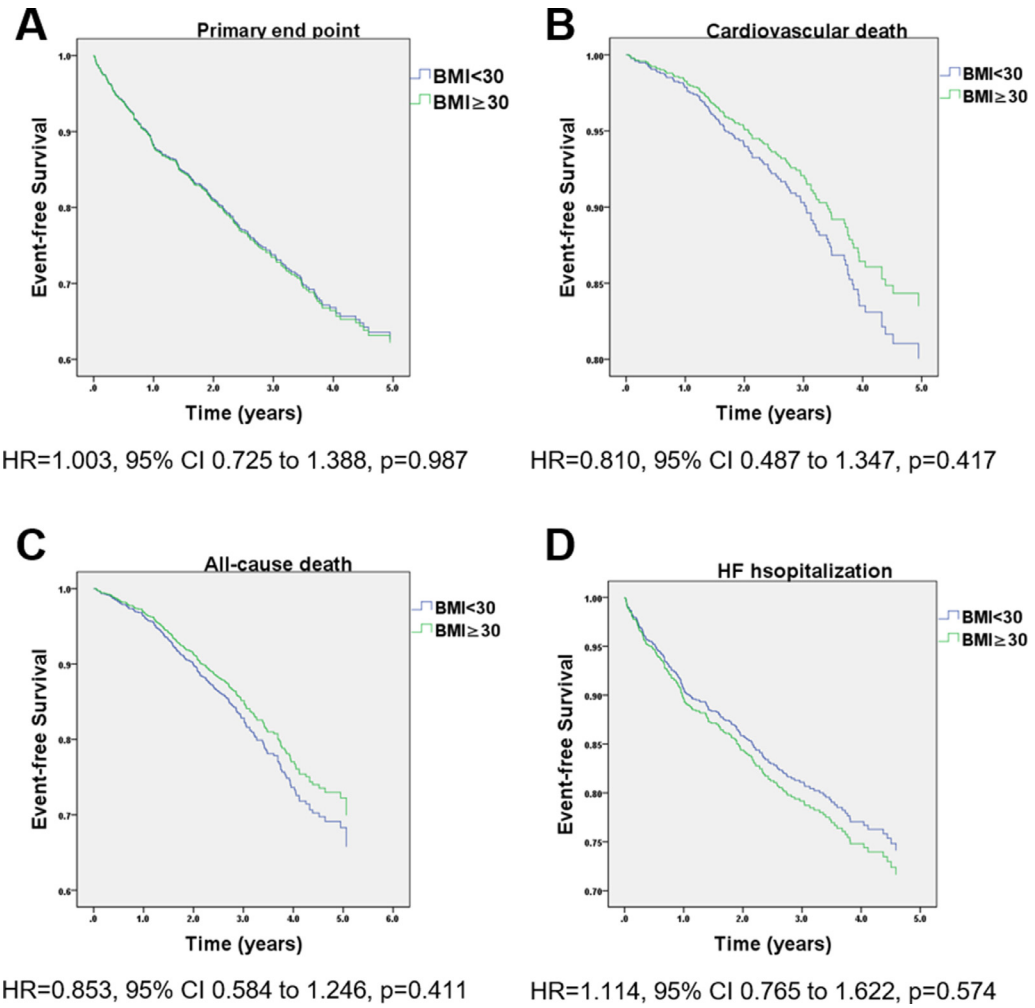

Figure 1. Kaplan-Meier survival curves for event-free survival stratified by BMI group in the Americas TOPCAT cohort. (A) primary outcome (cardiovascular death, aborted cardiac arrest, or hospitalization for heart failure), (B) cardiovascular death and (C) all-cause death. Adjustment was done for the following covariates: age, race, study enrollment status, actual plasma volume, NP tertiles, heat rate, systolic BP, edema over the past year, NYHA class, sodium, hypertension, diabetes, atrial fibrillation, dyslipidemia, asthma, diuretics, ACEIs/ARBS, CCB, statin.

Table 3
Adjusted outcomes according to BMI group

	TOPCAT Americas cohort			
	BMI (Kg/m^2)			
	< 30(n=616)	≥ 30(n=1,135)	Hazard ratio (95% CI)	pvalue
Primary end point	169 (27%)	346 (31%)	1.003 (0.981 - 1.441)	0.987
Cardiovascular death	94 (15%)	124 (11%)	0.810 (0.582 - 1.020)	0.417
All-cause death	159 (26%)	219 (19%)	0.853 (0.688 - 1.055)	0.411
HF hospitalizations	118 (19%)	277 (24%)	1.114 (0.765 - 1.622)	0.574

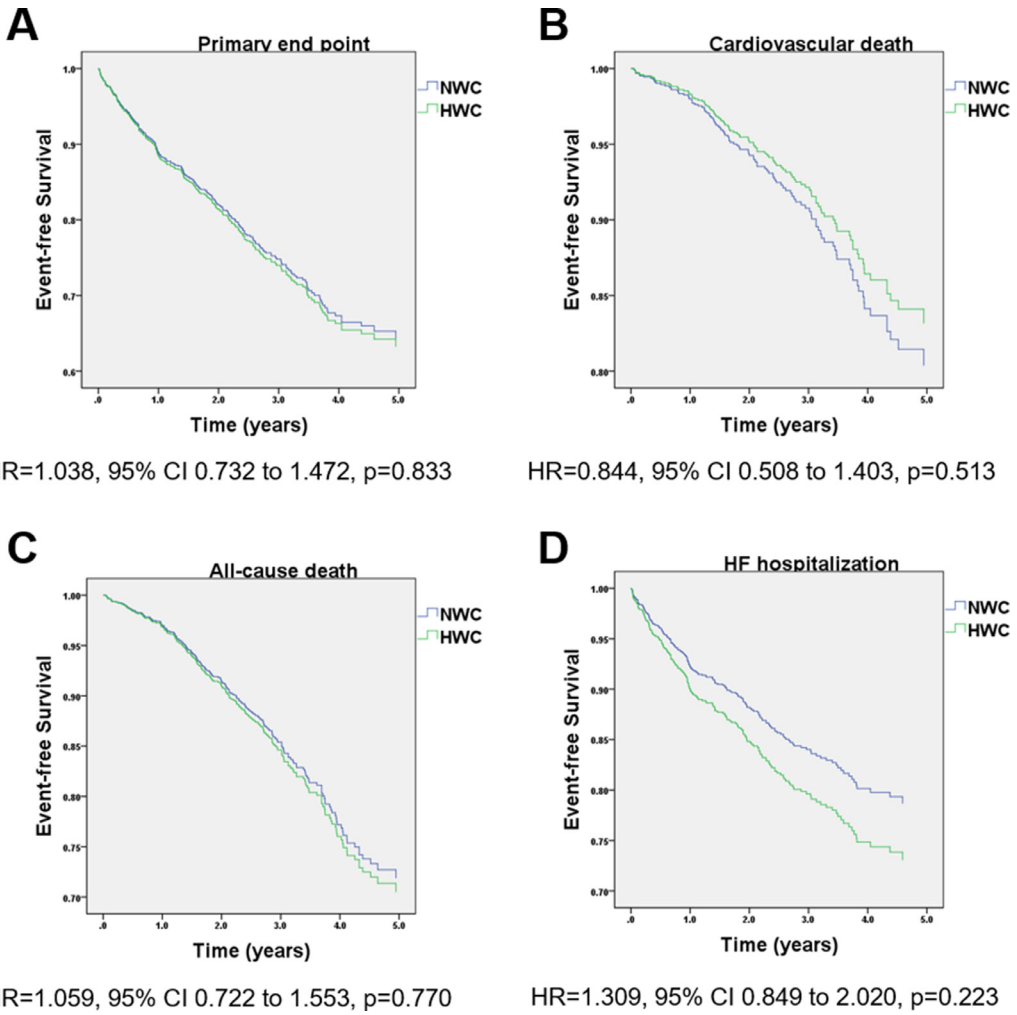

Figure 2. Kaplan-Meier survival curves for event-free survival stratified by WC group in the Americas TOPCAT cohort. (A) primary outcome (cardiovascular death, aborted cardiac arrest, or hospitalization for heart failure), (B) cardiovascular death and (C) all-cause death. Adjustment was done for the same covariates in Figure 1.

Table 4
Adjusted outcomes according to WC group

	TOPCAT Americas cohort			
	NWC (n=349)	HWC (n=1,294)	Hazard ratio (95% CI)	p value
Primary end point	102 (29%)	373 (29%)	1.030 (0.731 - 1.472)	0.834
Cardiovascular death	53 (15%)	156 (12%)	0.841 (0.501 - 1.403)	0.513
All-cause death	86 (25%)	274 (21%)	1.052 (0.722 - 1.553)	0.762
HF hospitalizations	70 (20%)	288 (22%)	1.301 (0.840 - 2.021)	0.221

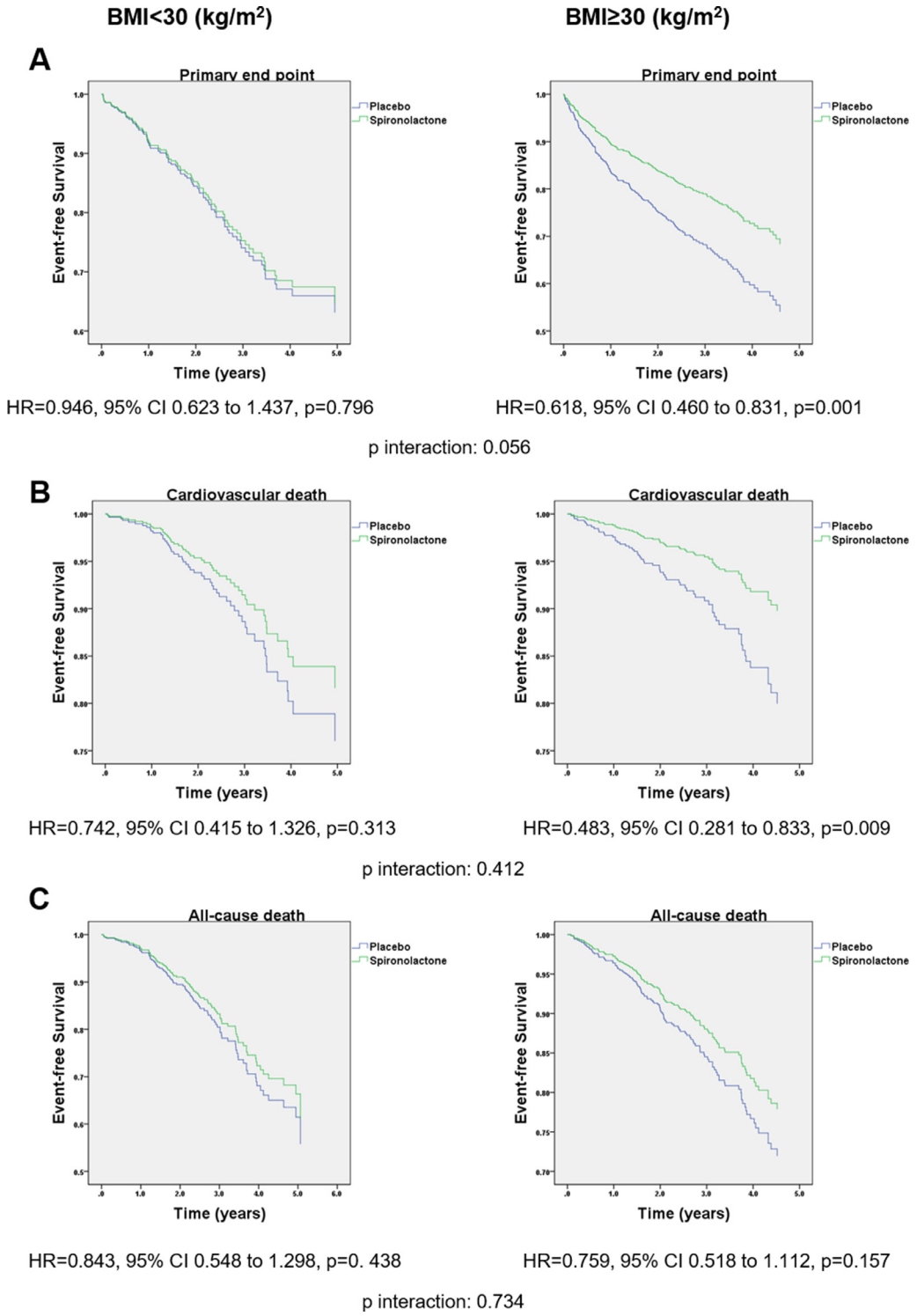

Figure 3. Kaplan-Meier survival curves for event-free survival stratified by BMI and treatment group in the Americas only cohort of TOPCAT. (A) primary outcome (cardiovascular death, aborted cardiac arrest, or hospitalization for heart failure), (B) cardiovascular death and (C) all-cause death. Adjustment was done for the same covariates in Figure 1.

nonobese groups (HR=0.843, 95% CI 0.548 to 1.298, p = 0.438; p for interaction = 0.734). The rate of HF hospitalization was significantly lower in the spironolactone arm compared with placebo in obese (HR=0.641, 95% CI 0.465 to 0.883, p = 0.007), but not in nonobese subjects (HR=1.029, 95% CI 0.613 to 1.728, p = 0.913; p for interaction = 0.130). When BMI was treated as a continuous variable, there was a linear association between BMI and the effect of spironolactone vs. placebo for the primary outcome and cardiovascular death, with the benefit becoming statistically significant at 33kg/m^2 and 30kg/m^2, respectively (Figure 4). A similar linear association between the

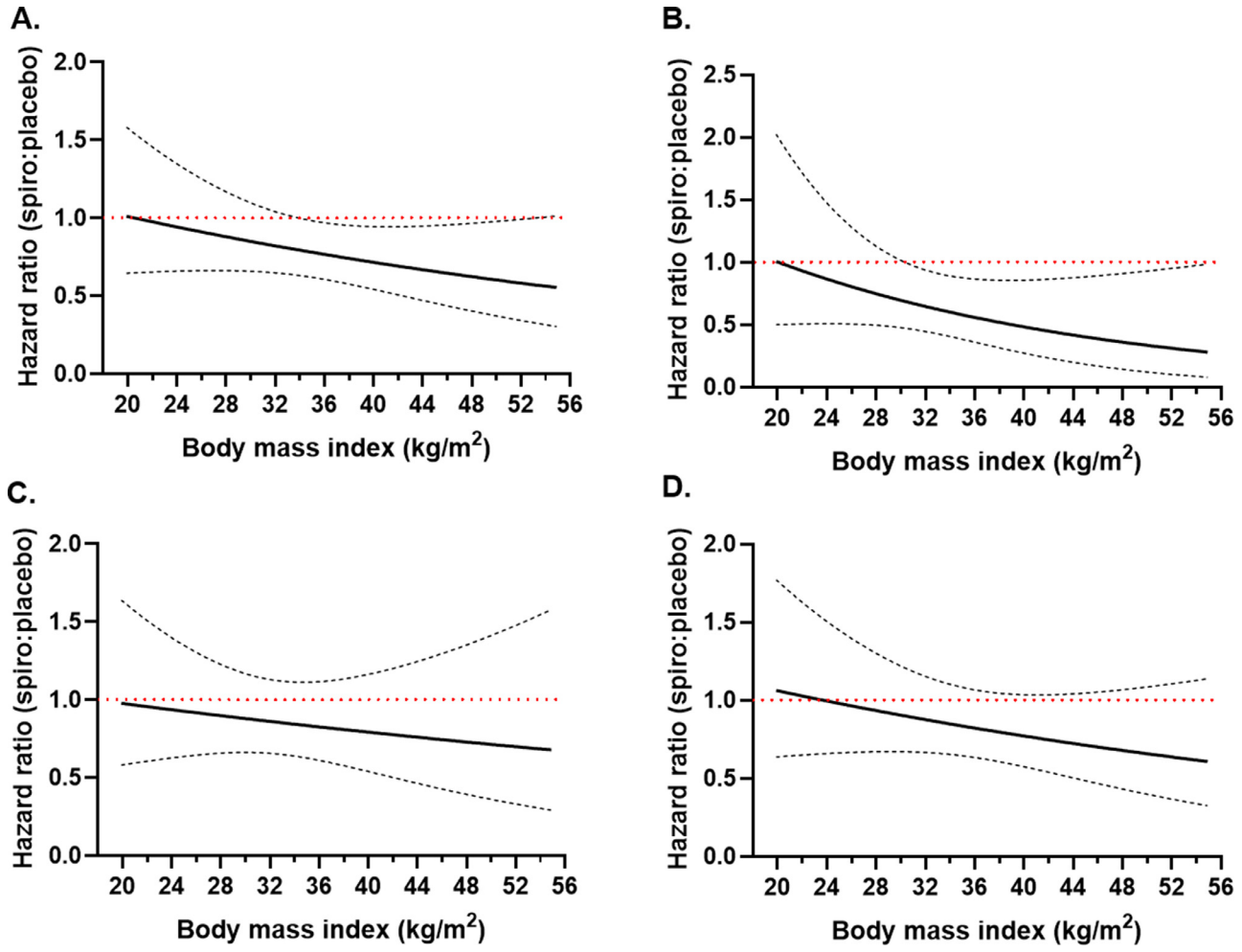

Figure 4. Plot of the spironolactone effect vs. placebo as a function of continuous BMI in the adjusted model for the primary outcome (A), cardiovascular death (B), all-cause death (C) and heart failure hospitalizations (D). Dashed lines represent 95% confidence intervals of the hazard ratio. The red horizontal line depicts where the upper limit of the confidence intervals crosses 1, indicating a statistically significant effect.

effect of spironolactone and BMI as a continuous variable was observed for all cause death and HF hospitalizations, but none of them reached statistical significance (Figure 4).

Kaplan Meier curves and HRs for multivariate adjusted outcomes in HWC versus NWC subjects stratified by treatment arm are shown in Figure 5. In HWC group, use of spironolactone was associated with a 26% significant reduction of primary end point compared with placebo (HR=0.740, 95% CI 0.559 to 0.980, p = 0.035) but not in the NWC group (adjusted HR=0.639, 95% CI 0.355 to 1.149, p = 0.134; p for WC category by treatment arm interaction = 0.930). Cardiovascular death was significantly decreased by 46% in the spironolactone arm compared with placebo in HWC group (HR= 0.541, 95% CI 0.335 to 0.873, p = 0.012), but not the NWC group (HR 0.650, 95% CI 0.288 to 1.466, p = 0.299; p for interaction = 0.887). All-cause mortality did not different between the 2 arms in HWC and NWC groups. Likewise, there was no significant difference in rate of HF hospitalization between the 2 arms in HWC (HR= 0.777, 95% CI 0.570 to 1.061, p = 0.112) and NWC group (HR=0.607, 95% CI 0.278 to 1.328, p = 0.211; p for interaction = 0.990). When waist circumference was treated as a continuous variable, there was a linear association between WC and the effect of spironolactone versus placebo for the primary outcome, cardiovascular death and HF hospitalizations, with the benefit becoming statistically significant at 109 cm, 103 cm and 123 cm, respectively (Figure 6). The association between the effect of spironolactone and waist circumference as a continuous variable for all-cause death did not reach statistical significance (Figure 6).

Discussion

The results of this post hoc analysis for the Americas cohort from the TOPCAT study demonstrated that there are significant differences between obese and nonobese groups in terms of both clinical characteristics and outcomes related to spironolactone use. Obese patients with HFpEF were younger, had lower NP values and had higher prevalence of co-morbidities. After adjusting for these differences, use of spironolactone in obese patients with HFpEF was associated with a significantly decreased risk of the primary end point, cardiovascular death and HF hospitalizations. In addition, our analysis indicated that the benefit of spironolactone over placebo was more pronounced at

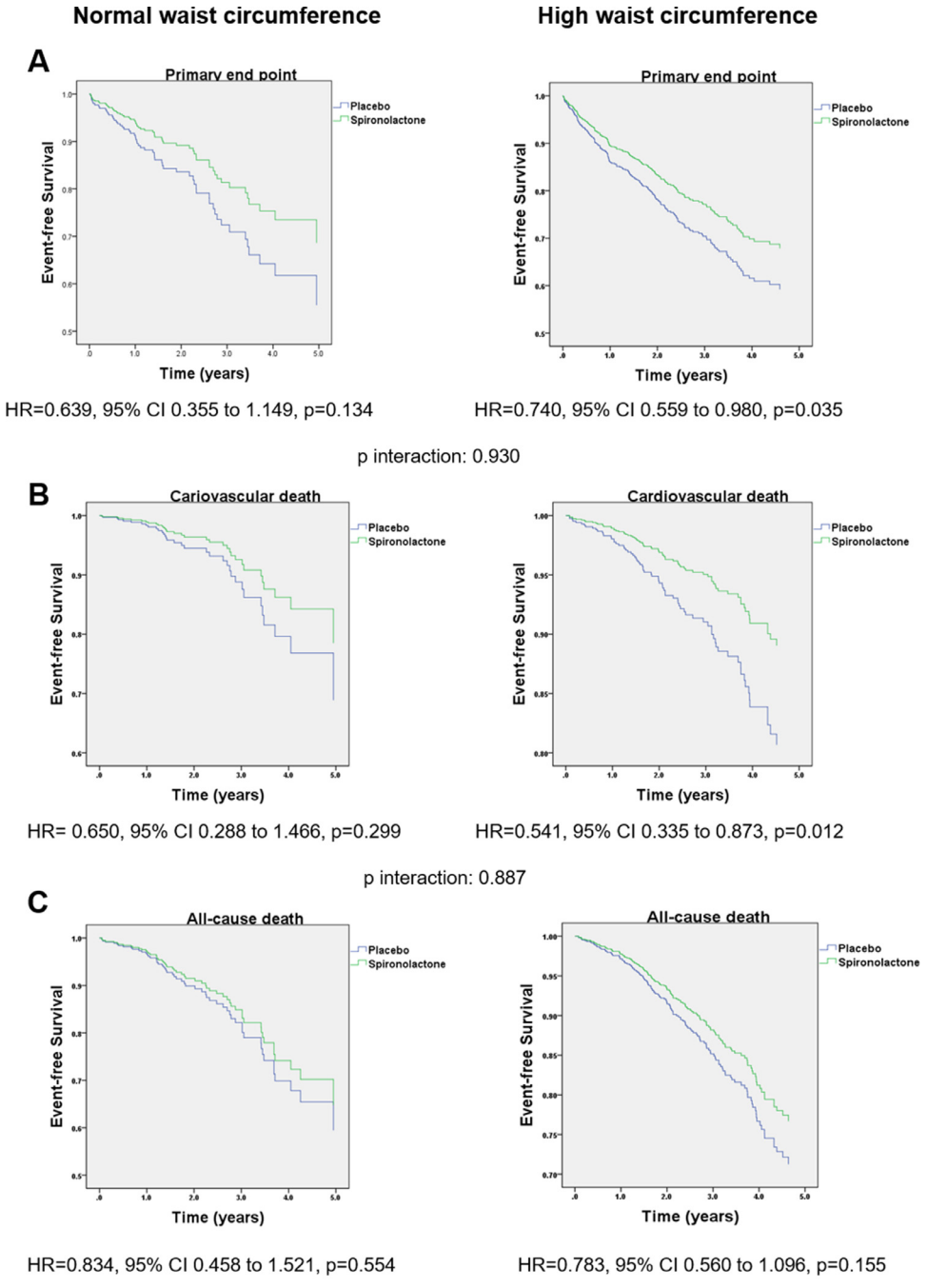

Figure 5. Kaplan-Meier survival curves for event-free survival stratified by WC and treatment group in the Americas only cohort of TOPCAT. (A) primary outcome (cardiovascular death, aborted cardiac arrest, or hospitalization for heart failure), (B) cardiovascular death and (C) all-cause death. Adjustment was done for the same covariates in Figure 1.

higher BMI (and WC) values, suggesting a possible causal association between obesity and aldosterone blockade in this patient population. However, in light of the fact that formal interaction testing was significant only for the primary end point, but not the other end points analyzed, the results of our analyses would suggest that a larger dedicated trial may be able to detect a smaller treatment effect interaction by obesity for spironolactone. The significance of these results is based on the fact that evidence-based treatments that improve morbidity or mortality in HFpEF are lacking.[1] Nonetheless, this analysis represents a post-hoc, secondary analysis and should only be regarded as hypothesis-generating. Further prospective randomized studies in obese subjects are required to confirm the validity of this finding prior to clinical application. It is also worth noting that some nonobese patients with high WC also benefitted from spironolactone. A future study may randomize obese and nonobese patients according to WC, which provides

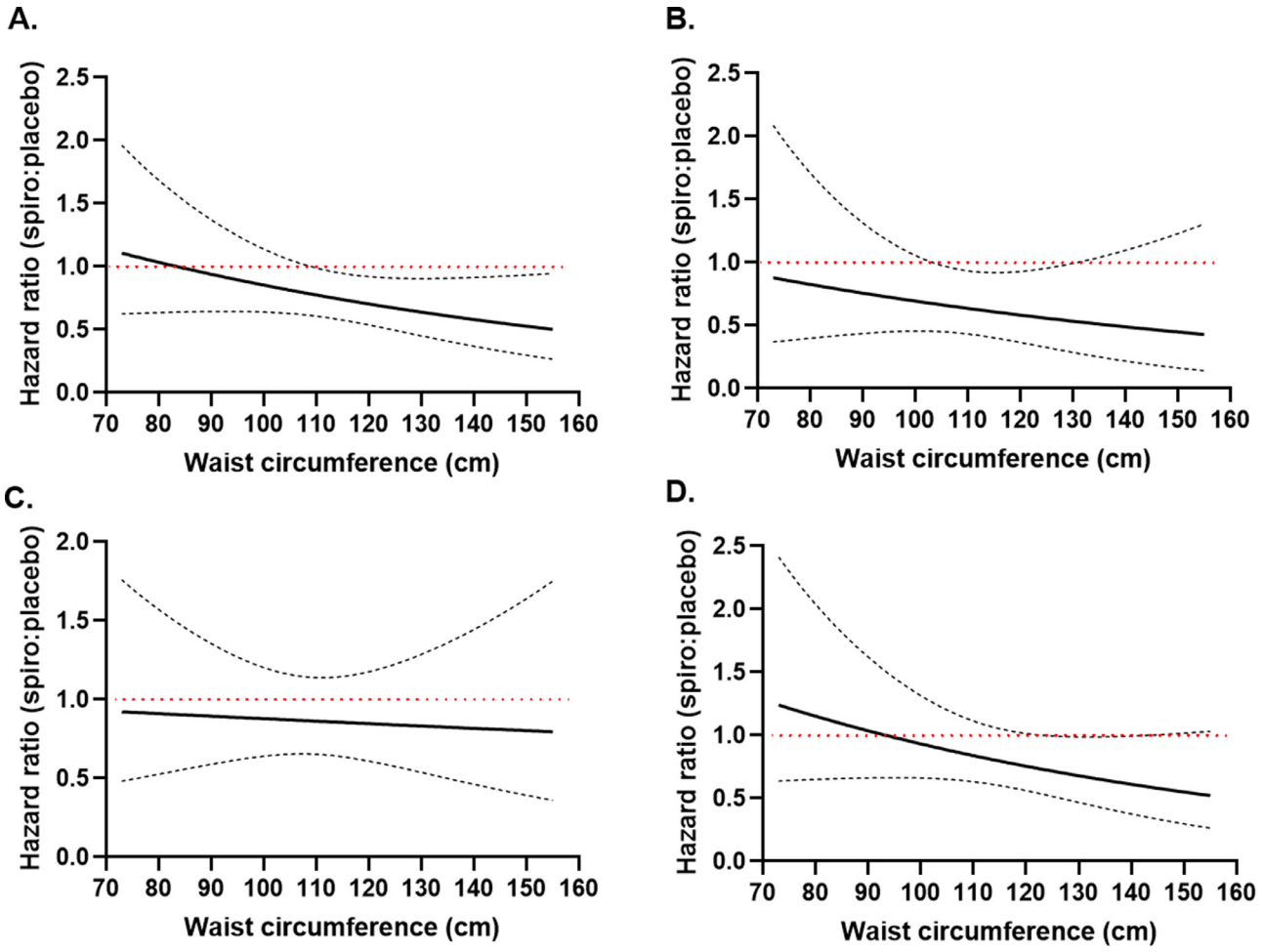

Figure 6. Plot of the spironolactone effect vs. placebo as a function of continuous waist circumference in the adjusted model for the primary outcome (A), cardiovascular death (B), all-cause death (C) and heart failure hospitalizations (D). Dashed lines represent 95% confidence intervals of the hazard ratio. The red horizontal line depicts where the upper limit of the confidence intervals crosses 1, indicating a statistically significant effect.

information on body fat distribution, in contrast to BMI, which does not distinguish between adipose mass and muscle mass.[11]

Obesity has reached epidemic proportions worldwide and is a common comorbidity in patients with HFpEF.[12] Obesity has many deleterious effects on the cardiovascular system, mediated by changes in volume status, cardiac loading, tissue metabolism, and systemic inflammation, which are believed to promote disease progression.[13,14] Consequently, obesity-related HFpEF may represent a clinically relevant phenotype within the broader spectrum of HFpEF that may require specific treatments.[15] Consistent with the notion that aldosterone blockade exerts anti-inflammatory and anti-fibrotic effects in experimental models of obesity,[16,17] and based on our results, we propose that spironolactone may reverse the U-shaped relationship between BMI and the risk of adverse clinical outcomes at the higher end of the BMI spectrum,[18] as suggested by the linear relationship between BMI and the effect of spironolactone, with the benefit for the primary outcome becoming statistically significant at 33kg/m^2. In a recent post-hoc analysis of the TOPCAT trial, obese phenotype HFpEF was associated with increased levels of renin, impaired natriuresis and fluid retention.[19] In our analysis, obese patients had higher aPV, end diastolic volume, stroke volume and LV mass index, which lends credence to this theory.

It has been previously shown that low NP levels possibly predicted response to therapy in TOPCAT[20] but also in I-PRESERVE[21] with spironolactone and irbesartan, respectively. Notably, obese patients with HF have lower NP levels compared with nonobese patients.[22] Consistent with a secondary analysis of the same trial, which showed that there was a U-shaped association between BMI and NP levels, with elevated NP levels noted at the extremes of BMI distribution,[18] in our analysis, more patients in the obese group were in the lower NP tertiles compared with the nonobese group (Table 1). Based on the finding that the interaction between BMI and NP levels was not significant, our analysis suggests that the lower NP levels in obese patients do not fully explain the beneficial effect of spironolactone in this group of patients. In addition, elevation of NP levels potentially reflects an advanced stage in the pathophysiological process of HFpEF in this patient population, when decompensation has occurred,[23] rendering therapies targeting the renin angiotensin aldosterone system less effective. This notion is supported by a secondary analysis of TOPCAT, which showed that patients in the high BMI/high NP category had the worse outcome.[18]

Several theories have been proposed to explain the "obesity paradox," but the possibility that it may be due to residual confounding, unintentional weight loss, or selection bias, cannot be excluded.[24,25] Our results suggested that there was no obesity paradox, after controlling for various co-morbidities in multivariate analysis. These data are consistent with a recent analysis from the same trial, which showed that obese patients with high NP levels experienced the worst outcomes.[18] Furthermore, detailed phenomapping of HFpEF patients in TOPCAT identified a group of obese, diabetic patients with higher inflammation and renal impairment, who had a higher risk of adverse outcomes, but also responded better to spironolactone.[19]

This is a post-hoc exploratory analysis, that stratified patients according to BMI and WC, and should thus be regarded as hypothesis-generating only. In such an analysis, randomization is breached and even though we adjusted for differences between the 2 groups, there may be unknown confounders which may have biased the results. Because of the significantly smaller sample size of the analysis when the subjects enrolled from Russia and Georgia were excluded, the results of the analysis in the Americas only cohort may have been underpowered, illustrated by the absence of a statistically significant interaction, even though the spironolactone effect was numerically better in the obese group. These issues highlight the importance of conducting an appropriately powered, prospective trial examining the role of spironolactone in obese patients with HFpEF prior to making firm recommendations regarding the use of spironolactone in this patient population. In our primary analysis, we treated BMI as a dichotomous variable in order to have the maximum power to detect small differences. However, the association between BMI and spironolactone effect appears to be rather linear, with the benefit being more pronounced at higher BMI levels.

In conclusion, use of spironolactone in obese patients with HFpEF was associated with a decreased risk of the primary end point, cardiovascular death and HF hospitalizations, compared with placebo. Further prospective randomized studies in obese subjects are required to confirm the validity of this finding prior to clinical application.

Authors contribution

Khaled Elkholey: Conceptualization; Formal analysis; Writing – Original Drafta. **Lampros Papadimitriou:** Conceptualization; Writing – Review & Editingb. **Javed Butler:** Conceptualization; Writing – Review & Editingb. **Udho Thadani:** Writing – Review & Editinga, and **Stavros Stavrakis:** Conceptualization; Formal analysis; Writing – Review & Editinga.

Disclosures

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this study.

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