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Adverse Renal Response to Decongestion in the Obese Phenotype of Heart Failure with Preserved Ejection Fraction

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Abstract

Background—Patients with heart failure (HF) with preserved ejection fraction (HFpEF) and obesity display a number of pathophysiologic features that may render them more or less vulnerable to negative effects of decongestion on renal function, including greater right ventricular remodeling, plasma volume expansion, and pericardial restraint. We aimed to contrast the renal response to decongestion in obese compared to non-obese HFpEF

Methods and Results—NIH heart failure network studies that enrolled patients with acute decompensated HFpEF (EF ≥ 50%) were included [DOSE, CARRESS, ROSE and ATHENA]. Obese HFpEF was defined as a body mass index (BMI) ≥ 30 kg/m². Compared to non-obese HFpEF (n=118), patients with obese HFpEF (n=214) were an average of 9 years younger (71 vs 80 years, <0.001), with more diabetes (64% vs 31%, p<0.001) but less atrial fibrillation (56% vs 75%, p<0.001). Renal dysfunction (GFR<60 mL/min/1.73m²) was present in 82% of patients, with no difference at baseline in obese and non-obese patients. Despite similar weight loss with decongestive therapies, obese HFpEF patients demonstrated a greater rise in creatinine (Cr) and decline in GFR, with a two-fold higher incidence of mild worsening renal function (rise in Cr ≥ 0.3

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TRIAL REGISTRATIONS

Aldosterone Targeted NeuroHormonal CombinEd with Natriuresis TherApy in Heart Failure (ATHENA-HF) [clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study?term=ATHENA-HF&rank=1) Identifier: ; Diuretic Optimization Strategies Evaluation (DOSE), [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study?term=DOSE&rank=1) number: ; Renal Optimization Strategies Evaluation (ROSE), [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study?term=ROSE&rank=1) Identifier: ; Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARRESS-HF), [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study?term=CARRESS-HF&rank=1) Identifier: .

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mg/dl) (28 vs 14%, $p=0.008$) and a substantially greater increase in severe worsening of renal function (rise in $Cr>0.5$ mg/dl) (9 vs 0%, $p=0.002$).

Conclusion—Despite being nearly a decade younger, obese HFpEF patients experience greater deterioration in renal function during decongestion compared to non-obese HFpEF. Further study to elucidate the complex relationships between volume distribution, cardiorenal hemodynamics and adiposity in HFpEF are needed.

Keywords

heart failure; HFpEF; obesity; hospitalization

Introduction

Obesity is associated with inflammation, neurohormonal activation and plasma volume expansion.(1,2) Patients with heart failure (HF) with preserved ejection fraction (HFpEF) and obesity display a number of pathophysiologic features that differentiate them from non-obese patients, including greater plasma volume expansion, right ventricular (RV) dysfunction, cardiomegaly, and pericardial restraint.(3) This milieu sets the stage for enhanced ventricular interaction, whereby RV overload (as with decompensation) interferes with left ventricular (LV) filling to impair cardiac output.

In patients with HF with reduced EF (HFrEF), acute reduction in RV volumes with maneuvers to reduce venous return improves LV filling and cardiac output by decreasing pericardial restraint and ventricular interdependence.(4,5) This would suggest that patients with the obese phenotype of HFpEF, who display this physiology, may respond more favorably to decongestion in the setting of decompensated heart failure. Conversely, patients with obesity often display reduction in systemic vascular resistance,(6) which may lead to arterial underfilling, enhanced sodium retention and greater plasma volume expansion to maintain adequate intravascular volume and cardiac preload.(1,2,7) Aggressive decongestion in such patients might destabilize cardiorenal function if the cardiovascular system is somehow reliant on maintenance of a hypervolemic state in obesity.

In order to determine if there is a differential response to decongestion in patients with the obese phenotype of HFpEF, we examined patients who were hospitalized for acute decompensated HF participating in the prospective inpatient studies that included HFpEF conducted within the NHLBI-sponsored HF clinical research network.(8–11)

Methods

Study subjects

The DOSE, CARRESS, ROSE and ATHENA trials were multicenter, randomized clinical trials conducted by the NHLBI-sponsored Heart Failure Clinical Research Network in hospitalized HF patients testing diuretic infusion strategies, ultrafiltration compared to conventional therapy, addition of dopamine/nesiritide to diuretic therapy, and high dose spironolactone in tandem with diuretic therapy.(8–11) Participants from these studies with unequivocal decompensated HF and an EF $\geq 50\%$ were included in this analysis.

Patient Assessment

All participants underwent history and physical examination by a cardiologist prior to receipt of study intervention, wherein functional class was determined using the NYHA classification. The evaluating cardiologist was blinded to individual treatment assignment. Serum NT-proBNP concentration was measured prospectively in all patients at study entry along with serum creatinine. Estimated glomerular filtration rate was determined by the Modification of Diet in Renal Disease equation. The baseline data reported from these studies was prior to receipt of study medications. Plasma volume was estimated by: $(1 - \text{hematocrit}) \times (a + [b \times \text{weight in kg}])$, where $a = 1,530$ in men and 864 in women, and $b = 41$ in men and 47.9 in women.⁽¹²⁾ This ancillary study was designed and approved by the Heart Failure Network (HFN) ancillary studies committee and all analyses were completed by the HFN Coordinating Center.

Group assignment

Obese HFpEF was defined as a body mass index (BMI) $\geq 30 \text{ kg/m}^2$ and non-obese HFpEF as a BMI $< 30 \text{ kg/m}^2$. To mirror previously-utilized definitions,⁽³⁾ sensitivity analyses defining obese HFpEF with grade 2 obesity as a BMI $\geq 35 \text{ kg/m}^2$, and stratified by World Health Organization BMI categories were also performed.

Outcome assessment

Worsening Renal Function (WRF) was defined as a 0.3 mg/dl or greater increase in serum creatinine during hospitalization. In addition, severe WRF was defined as a 0.5 mg/dl or greater increase in serum creatinine. Clinical characteristics, response to decongestion therapies, and death and rehospitalization rates at 30 days were compared.

Statistical Analysis

Categorical variables were summarized by frequencies with percentages, and compared using Chi square or Fisher's exact test. Continuous variables were summarized by the median, 25th and 75th percentiles, and compared using Kruskal-Wallis test. Thirty day outcomes were compared using Cox proportional Hazard models adjusted for trial, age, sex, heart rate and blood pressure. All statistical tests were two-sided, and a p value of < 0.05 was considered statistically significant. Given the exploratory nature of the analyses, adjustment for multiple comparisons was not performed. All the statistical analyses were performed using SAS statistical software (version 9.4, SAS Institute, Cary, NC).

Results

Study sample

A total of 332 patients hospitalized with decompensated HFpEF across the 4 trials (ROSE 107, DOSE 79, CARRESS 58, ATHENA 88) were included. The overall prevalence of obesity, defined by BMI $\geq 30 \text{ kg/m}^2$, was 64%. The proportion of obese HFpEF patients was similar across all 4 trials (ROSE 62%, DOSE 66%, CARRESS 69%, ATHENA 64%). There was no significant difference in prevalence of obesity between the placebo and treatment groups across each of the 4 study samples ($p > 0.1$ for all, data not shown).

Baseline demographics

Compared to non-obese HFpEF (n=118), patients with obese HFpEF (n=214) were an average of 9 years younger at the time of HF hospitalization and tended to be more likely to be female and of non-white ethnicity (Table 1, Figure 1). Obese HFpEF patients were more likely to have had a prior HF hospitalization in the past year (67 vs 56%, $p=0.043$) and had a two-fold greater prevalence of diabetes mellitus (64 vs 31%, $p<0.001$). In contrast, atrial fibrillation was less common in obese HFpEF as compared to non-obese HFpEF (56 vs 75%, $p<0.001$). Blood pressure was higher in obese HFpEF patients and prevalence of hypertension tended to be higher (Figure 1, Table 1).

Renal function at the time of enrollment was similar in obese and non-obese patients, with 82% demonstrating an impaired glomerular filtration rate (GFR) <60 mL/min/1.73m² consistent with stage 3 chronic kidney disease or worse (Tables 1 and 2). Renal function was similar between groups even after adjusting for age, race, diabetes and hypertension ($p=0.45$). Estimated plasma volume was 40% higher in the obese HFpEF group as compared to non-obese HFpEF (Figure 1), with greater severity of peripheral edema, but similar prevalence of jugular vein distention and orthopnea, exceeding 90% in both groups. Most patients were functional class III or IV, with no difference between the obese and non-obese HFpEF groups. Despite greater plasma volume expansion and peripheral edema in the obese HFpEF group, NT proBNP levels were lower compared to non-obese patients with HFpEF (2577[1328–4613] vs 4006[2519–9271] pg/ml, $p<0.001$) (Table 2).

Response to decongestion

Median length of stay was 6 (4, 8) days, with no difference between groups ($p=0.37$, Table 3). Despite similar degrees of absolute weight loss, and less proportional weight loss, obese HFpEF patients demonstrated a greater rise in creatinine and greater decline in estimated GFR (Figure 2, Table 3). There was a two-fold higher incidence of worsening renal function during decongestion (28 vs 14%, $p=0.008$) and a substantially greater incidence of severe worsening renal function (rise in creatinine >0.5 mg/dl) in obese HFpEF (9 vs 0%, $p=0.002$). Although baseline blood pressure was higher in the obese HFpEF patients, the blood pressure decline during diuresis was similar in both groups.

Clinical Outcomes

At 30 days, the overall mortality rate was 5.2% and rehospitalization rate was 22% (Table 4). Despite the differences in worsening renal function, there was no difference in survival or rehospitalization in obese as compared to non-obese HFpEF patients.

Sensitivity analysis

In a sensitivity analysis evaluating patients with Grade 2 or higher obesity compared to non-obese HFpEF, results were similar, with a 2-fold greater incidence of worsening renal function during decongestion in obese HFpEF (Supplemental table 1). Stratification of results by diabetes showed results directionally similar to the primary analysis, with a greater decline in estimated GFR with diuresis in obesity, which tended to be somewhat greater in obese patients with diabetes (Supplemental table 2). Additional sensitivity analyses stratified by World Health Organization BMI categorization (Supplemental table 3)

and comparing normal weight HFpEF patients with severe (grade II) obesity (Supplemental table 4) produced similar results.

Discussion

The major findings of our study can be summarized as follows: 1) among decompensated patients with HFpEF admitted for volume overload, patients with the obese phenotype are, on average, nearly a decade younger than non-obese HFpEF patients, 2) despite younger age, nearly 80% of obese HFpEF patients have a glomerular filtration rate consistent with at least stage 3 chronic kidney disease, and most significantly 3) decongestion was less well tolerated from a renal filtration standpoint in obese HFpEF, with a greater proportion experiencing worsening renal function, despite similar to lesser magnitude of net decongestion reflected by weight loss.

This study demonstrates a potentially important difference in the response to decongestion in patients with HFpEF based upon the presence or absence of obesity. Because patients with the obese phenotype of HFpEF display greater plasma volume expansion, more profound cardiomegaly, and heightened extrinsic pericardial restraint on the heart,(3) one could posit that decongestion would enhance renal function by reducing RV volumes to mitigate external restraint more in this cohort, improving LV filling, cardiac performance and by extension, end-organ perfusion. This phenomenon is well-described in patients with advanced HFrEF, where reduction in cardiac venous return improves LV preload and stroke volume because of enhanced diastolic ventricular interaction.(4,5) Reduction in pericardial restraint with decongestion would be expected to lower central venous pressure and reduce renal congestion,(5) with secondary improvements in renal function, as has been observed in experimental preparations(13) and from clinical studies of HF with reduced ejection fraction.(14,15)

Instead, we observed that obese HFpEF patients were two-fold more likely to develop worsening renal function with decongestion and an even more substantially greater likelihood of developing more substantial worsening renal function, despite similar absolute weight loss and lower relative weight loss. This is particularly notable since obese HFpEF patients had greater estimated plasma volume expansion and peripheral edema. The mechanism for the differential response cannot be discerned from these data, but a number of possibilities merit consideration.

Obese HFpEF patients displayed a 2-fold greater burden of diabetes, and it is notable that despite being a decade younger, their baseline GFR was impaired to a similar degree as older non-obese HFpEF patients. Since GFR is known to decrease with aging, this implies an earlier onset of kidney disease in obese HFpEF. There is increasing recognition that obesity causes clinical HFpEF at a younger age, where a greater burden of chronic kidney disease has been described.(16,17) The current data further validates the potential impact of obesity on presentation with decompensated volume overload HFpEF at a younger age, in contrast to non-obese HFpEF patients where aging and atrial fibrillation may be important contributors to decompensation.

Glomerular filtration in HF is determined by the combination of intrinsic renal dysfunction, as well as reversible renal hypoperfusion caused by the combination of poor renal arterial perfusion and renal venous congestion.(18) In addition to potential intrinsic diabetic nephropathy, obesity has itself been directly implicated in causing renal dysfunction and glomerular pathology which may occur through a number of mechanisms including glomerular hyperfiltration, adipose mediated inflammation, oxidative stress and adipokine release, renin-angiotensin system activation and ectopic adipose accumulation.(19,20) Increased perinephric fat(21) in addition to heightened abdominal pressure related to increased visceral fat(22) could have a negative effect on renal function in obesity, and children and adults with obesity demonstrate improvements in renal function with weight loss.(23,24) While the blood pressure decline with diuresis was similar in obese and non-obese HFpEF, the former group displayed higher baseline pressure, and it is possible that obese patients may be more reliant on maintaining a higher renal perfusion pressure, and that this could contribute to the observed differences in renal response to decongestion.

In addition to potential differences in intrinsic renal reserve, obese HFpEF patients may be more reliant on volume expansion than non-obese patients. Total blood volume increases monotonically with body weight, but the ratio of volume to body weight decreases with obesity.(7) A recent study including a number of patients with obese HFpEF suggested that the vast majority of volume lost during diuresis originated from the interstitium rather than the vascular space.(25) If there is insufficient capillary refill to reconstitute vascular volume from the interstitium, this could destabilize cardiorenal homeostasis. This is supported by a recent trial in hospitalized patients with HFpEF (mean BMI 40.8), where continuous furosemide infusion caused a greater rise in creatinine when compared to intermittent bolus diuretic.(26) In HFrEF, diuresis and vasodilation do not necessarily compromise cardiac output,(27) but this may not hold in patients with HFpEF, who display marked diastolic LV chamber stiffening and are more likely to display reduction in stroke volume as LV preload is reduced. This preload sensitivity in combination with frequently observed decreased systemic vascular resistance in obesity(6) may predispose to renal hemodynamic compromise during diuresis. (28)

In this study as well as others, the creatinine elevation was prognostically benign, with no difference in 30 day event rates in the obese and non-obese HFpEF patients. Emerging evidence suggests that such transient elevations in creatinine during diuresis reflect changes in intraglomerular hemodynamics rather than true tubular injury, and the benefits of greater decongestion may outweigh any potentially negative effect on the kidneys.(29,30) While this small elevation in creatinine should not necessarily deter further diuresis for patients that remain clinically congested, these data suggest that closer monitoring may be warranted among patients with obese HFpEF. This may include use of invasive hemodynamic assessment when volume status is uncertain with rising creatinine, or use of implantable pressure monitoring,(31) particularly given the difficulties of physical examination estimates of hemodynamics in obesity. It also is reflective of the worse renal hemodynamic tolerance to diuresis in obese HFpEF which is particularly notable given their younger age, and emphasize our incomplete understanding of the complexity of cardiorenal interactions in obesity-related HFpEF. Further study of the role of novel renal protective agents such as

sodium glucose cotransporter 2 inhibitors(32) require investigation and clinical trials in HFpEF are ongoing () ()

Limitations

This was a secondary analysis of prior randomized trials and therefore the results are prone to type 1 error. More sophisticated measures of adiposity were not collected, and how these findings relate to the relatively crude estimate of adiposity using BMI in terms of renal response to diuresis requires additional investigation. Plasma volume was not directly measured but rather estimated using a previously validated equation, though this is less accurate compared to direct assessments.(12) Assessment of proteinuria or changes in hemoglobin during therapy were not available. Mineralocorticoid antagonist use was rather low (17%) and the current data cannot address how decongestion might relate to obesity in patients with more aggressive use of these drugs. Given the exploratory nature of analyses performed, correction for multiple hypothesis testing was not performed.

Conclusions

Hospitalized patients with the obese phenotype of HFpEF experience greater acute decline in renal function with decongestion, despite similar weight loss and greater degree of volume overload as compared to non-obese HFpEF patients. These data suggests that closer monitoring may be warranted in this population during treatment for volume overload, and call for further study to elucidate the complex relationships between volume distribution, cardiorenal hemodynamics and adiposity in HFpEF.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations list

ATHENA-HF	Aldosterone Targeted NeuroHormonal CombinEd with Natriuresis TherApy in Heart Failure
DOSE	Diuretic Optimization Strategies Evaluation
ROSEL	Renal Optimization Strategies Evaluation
CARRESS-HF	Cardiorenal Rescue Study in Acute Decompensated Heart Failure
HFpEF	Heart failure with preserved ejection fraction
HFrfEF	Heart failure with reduced ejection fraction

RV	right ventricular
LV	left ventricular
WRF	Worsening renal function
GFR	Glomerular filtration rate

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Highlights

- In this pooled analysis from 4 clinical trials, patients with obese HFpEF were nearly a decade younger than non-obese HFpEF when presenting with decompensated HF requiring hospitalization.
- Despite the younger age, obese HFpEF patients experienced greater deterioration in renal function during decongestion.
- Given the high prevalence of impaired renal function in hospitalized HFpEF patients, future research into the complex relationships between adiposity, hemodynamics and renal hemodynamics in obese HFpEF is urgently needed.

Figure 1: Clinical characteristics of obese decompensated HFpEF

Obese HFpEF patients were younger with higher systolic blood pressure which would be expected to protect against renal hypoperfusion. In addition, they had greater estimated plasma volume despite lower NT-proBNP levels.

Figure 2: Renal response to decongestion in obese HFpEF

Despite similar weight loss with diuresis in HFpEF patients with increasing body mass index, there was greater reduction in glomerular filtration rate with decongestion as compared to non-obese patients.

Table 1:**Baseline Characteristics**

	Non-Obese HFpEF (BMI<30) (N=118)	Obese HFpEF (BMI ≥30) (N=214)	p-value
Age, years	80 (68 – 85)	71 (62 – 78)	<0.001
Female, n (%)	41 (35)	97 (45)	0.061
White race, n (%)	100 (85)	163 (76)	0.065
<u>Anthropometries and Vital Signs</u>			
Weight, lbs	167 (149–185)	243 (215–286)	<0.001
Body Mass Index, kg/m ²	26.8 (24.4 –28.0)	38.0 (34.1–45.4)	<0.001
Heart rate, bpm	75 (66 –81)	72 (64–82)	0.44
Systolic Blood Pressure, mmHg	118 (106 –132)	124 (112–140)	0.023
<u>Disease Severity and Ventricular Function</u>			
Hospitalization for HF in past year, n (%)	65 (56)	141 (67)	0.043
Ejection Fraction, %	58 (55–63)	55 (55–63)	0.68
<u>Comorbidities</u>			
Hypertension, n (%)	100 (85)	194 (91)	0.11
Atrial fibrillation/flutter, n (%)	88 (75)	119 (56)	<.001
Diabetes, n (%)	37 (31)	137 (64)	<.001
<u>Estimated Glomerular Filtration Rate</u>			
<30 mL/min/1.73 m ²	22 (19)	46 (22)	0.81
30–59 mL/min/1.73m ²	74 (63)	128 (60)	
>60 mL/min/1.73m ²	22 (19)	39 (18)	
<u>Medications on admission</u>			
ACE inhibitor/ARB, n (%)	45 (28)	100 (47)	0.13
Beta blocker, n (%)	91 (77)	154 (72)	0.31
Aldosterone antagonist, n (%)	20 (17)	35 (17)	0.92
Diuretic, n (%)	113 (96)	206 (96)	0.78
Calcium channel blocker, n (%)	37 (31)	67 (32)	0.99

Values represent Median (25th–75th) or % unless otherwise specified

Table 2:

Severity of Congestion and Laboratories

	Non-Obese HFpEF (BMI<30) (N=118)	Obese HFpEF (BMI ≥30) (N=214)	p-value
<u>Indicators of Congestion</u>			
Estimated plasma volume, ml	3685 (2954–4765)	5147 (4053–6450)	<0.001
Edema 2+, n (%)	86 (73)	177 (84)	0.022
Jugular vein distention ≥8 cm, n (%)	110 (93)	198 (93)	0.95
Orthopnea, n (%)	107 (92)	196 (93)	0.64
<u>NYHA Functional Class at Assessment</u>			
II, n (%)	9 (8)	11 (6)	0.54
III, n (%)	76 (67)	124 (65)	
IV, n (%)	28 (25)	57 (30)	
<u>Laboratory values</u>			
Sodium, mEq/L	139 (136 – 141)	140 (137 – 142)	0.009
Hemoglobin, g/dl	10.8 (9.9 – 11.9)	10.6 (9.7 – 12.2)	0.73
Blood urea nitrogen, mg/dl	38 (25 – 50)	33 (23 – 53)	0.39
GFR, mL/min/1.73m ²	44 (33 – 54)	42 (32 – 56)	0.62
Serum Creatinine, mg/dl	1.5 (1.2 – 1.9)	1.6 (1.2 – 2.1)	0.70
NT-pro BNP, pg/ml	4006 (2519 – 9271)	2577 (1328 – 4613)	<.001

Values represent Median (25th–75th) or % unless otherwise specified

Table 3:**Renal Response to Decongestion**

	Non-Obese HFpEF (BMI<30) (N=118)	Obese HFpEF (BMI ≥ 30) (N=214)	p-value
Diuretic dose at Randomization, mg/day ^a	80 (40, 160)	80 (40, 160)	0.39
Length of Stay, Days	5 (3, 8)	6 (4, 8)	0.37
<u>Changes in Renal Function</u>			
Change in Creatinine, mg/dl	-0.02 (-0.20, 0.12)	+0.10 (-0.10, 0.30)	<0.001
% Change in Creatinine	-2 (-12, 11)	+6 (-6, 20)	<0.001
Worsening renal function (rise in Cr ≥ 0.3 mg/dl), n (%)	16 (14)	56 (28)	0.008
Worsening renal function (rise in Cr ≥ 0.5 mg/dl), n (%)	0 (0)	17 (9)	0.002
Change in eGFR, mL/min/1.73m ²	0.7 (-5.1, 5.4)	-2.6 (-8.6, 2.8)	0.002
% Change in eGFR	2 (-11, 16)	-7 (-19, 7)	<0.001
<u>Estimates of Decongestion</u>			
Change in Weight, lb	-6 (-11, -3)	-7 (-14, -2)	0.23
% Change in Weight	-4 (-7, -2)	-3 (-5, -1)	0.04
Change in NT proBNP, pg/ml	-1046 (-2153, -83)	-583 (-1561, -106)	0.16
% Change in NT proBNP	-24 (-43, -6)	-35 (-57, -6)	0.058
<u>Hemodynamic Changes</u>			
Change in systolic blood pressure, mmHg	-6 (-20, 6)	-2 (-18, 7)	0.39
Change in mean blood pressure, mmHg	-5 (-15, 3)	-3 (-13, 8)	0.29

Values represent Median (25th–75th) or % unless otherwise specified

^aDose in intravenous furosemide equivalents

Table 4:

Clinical Outcomes at 30 Days

	Non-Obese HFpEF (BMI<30) (N=118)	Obese HFpEF (BMI ≥ 30) (N=214)	p-value
Mortality event rate, % (95% CI) ^a	6.5 (3.2, 13.2)	4.5 (2.4, 8.6)	0.49
Rehospitalization event rate, % (95% CI) ^a	25 (17, 34)	21 (16, 28)	0.54
Death or rehospitalization event rate, % (95% CI) ^a	27 (19, 36)	24 (18, 31)	0.62

Values represent Median (25th–75th) or % unless otherwise specified

^a Comparisons adjusted for trial, age, sex, heart rate and blood pressure