JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
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PUBLISHED BY ELSEVIER

VOL. 70, NO. 22, 2017
ISSN 0735-1097/$36.00
https://doi.org/10.1016/j.jacc.2017.09.1111

ORIGINAL INVESTIGATIONS

Abdominal Obesity Is Associated With an Increased Risk of All-Cause Mortality in Patients With HFpEF

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ABSTRACT

BACKGROUND There is a lack of studies that evaluate the association between abdominal obesity and subsequent outcomes in patients with heart failure with preserved ejection fraction (HFpEF).

OBJECTIVES The present study aimed to assess the association between abdominal obesity and risk of all-cause mortality in patients with HFpEF.

METHODS The present study used data from the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist) trial. The primary outcome was all-cause mortality. We analyzed and compared the hazard ratios (HRs) in patients with abdominal obesity and those without abdominal obesity using multivariable Cox proportional hazard models. Abdominal obesity was defined as a waist circumference of ≥102 cm in men and ≥88 cm in women.

RESULTS The present study included 3,310 patients with HFpEF: 2,413 patients with abdominal obesity and 897 without abdominal obesity. The mean follow-up was 3.4 ± 1.7 years. During follow-up, 500 patients died. All-cause mortality rates in patients with and without abdominal obesity were 46.1 and 40.7 events per 1,000 person-years, respectively. After multivariable adjustment, the risk of all-cause mortality was significantly higher in patients with abdominal obesity than in those without abdominal obesity (adjusted HR: 1.52; 95% confidence interval [CI]: 1.16 to 1.99; p = 0.002). The risk of cardiovascular and noncardiovascular mortality was also significantly higher in patients with abdominal obesity than in those without abdominal obesity (adjusted HR: 1.50; 95% CI: 1.08 to 2.08; p = 0.01 and adjusted HR: 1.58; 95% CI: 1.00 to 2.51; p = 0.04, respectively).

CONCLUSIONS The risk of all-cause mortality was significantly higher in patients with HFpEF with abdominal obesity than in those without abdominal obesity. (J Am Coll Cardiol 2017;70:2739–49) © 2017 by the American College of Cardiology Foundation.

Heart failure with preserved ejection fraction (HFpEF) accounts for approximately one-half of all cases of heart failure, and this proportion has been increasing (1-3). Although rates of hospitalization and all-cause mortality in patients with HFpEF are similar to those in patients with heart failure with reduced ejection fraction (HFrEF), there is little evidence to support any specific treatment

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Manuscript received September 27, 2017; accepted September 28, 2017.

ABBREVIATIONS AND ACRONYMS

BMI = body mass index

eGFR = estimated glomerular filtration rate

HFpEF = heart failure with preserved ejection fraction

HFrEF = heart failure with reduced ejection fraction

NYHA = New York Heart Association

for HFpEF. Furthermore, clinical guidelines have offered no specific recommendations for the management of HFpEF (4,5).

The fundamental pathophysiology of HFpEF is complex and poorly understood. In the traditional pathophysiological model, pressure overload leads to left ventricular hypertrophic and fibrotic remodeling, as well as diastolic dysfunction (3,6). In addition, recent reports have suggested that the development of HFpEF is associated with a systemic proinflammatory state related to commonly coexisting conditions, such as obesity, metabolic syndrome, diabetes, hypertension, lung disease, anemia, and smoking (6–9). Systemic microvascular endothelial inflammation leads to myocardial inflammation, oxidative stress, and fibrosis. Moreover, alterations in cardiomyocyte signaling pathways promote cardiomyocyte remodeling and microvascular dysfunction, and result in left ventricular dysfunction (6). However, it remains unknown whether abdominal obesity, which is strongly associated with the proinflammatory state, is associated with the development and worsening of HFpEF. Furthermore, there is a lack of studies that have evaluated the association between abdominal obesity and subsequent outcomes in patients with HFpEF. Therefore, this study aimed to assess the association between abdominal obesity and risk of all-cause mortality in patients with HFpEF.

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METHODS

STUDY DESIGN AND PATIENTS. Using data from the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist) trial (10), we assessed the association between abdominal obesity and mortality in patients with HFpEF. The design, protocol, and patient characteristics of the TOPCAT study were previously reported (11,12). Briefly, TOPCAT was a phase 3, international, multicenter, randomized, double-blind, placebo-controlled trial. A total of 3,445 patients from 233 sites in 6 countries (1,151 in the United States, 1,066 in Russia, 612 in Georgia, 326 in Canada, 167 in Brazil, and 123 in Argentina) were randomly assigned to receive spironolactone or a placebo from August 10, 2006 to January 31, 2012. Patients aged 50 years or older were included if they had at least 1 symptom and 1 sign of heart failure on a pre-specified list of clinically defined symptoms and signs, controlled systolic blood pressure (defined as a blood pressure of <140 mm Hg or ≤160 mm Hg if the patient was taking ≥3 medications to control blood pressure), a left ventricular ejection fraction of ≥45% measured at the local site by echocardiography or radionuclide ventriculography, and a serum potassium level of <5.0 mmol/l. Eligible patients had a history of hospital admission for heart failure in the past 12 months or an elevated natriuretic peptide level in the 60 days before randomization (brain natriuretic peptide level ≥100 pg/ml or N-terminal pro–brain natriuretic peptide level ≥360 pg/ml). Patients were excluded if they had any of the following conditions: a severe systemic illness with a life expectancy judged to be <3 years; severe pulmonary disease, such as chronic pulmonary disease requiring home oxygen; known infiltrative or hypertrophic obstructive cardiomyopathy or known pericardial constriction; severe renal dysfunction (defined as an estimated glomerular filtration rate [eGFR] <30 ml/min or serum creatinine level ≥2.5 mg/dl); heart transplant; or known chronic hepatic disease (defined as aspartate aminotransferase and alanine aminotransferase levels >3.0 times the upper limit of the normal range as read at the local laboratory) (12). In the present study, patients with missing information regarding abdominal obesity and potential confounders were excluded (n = 135), which resulted in a final sample of 3,310. The present study was approved by the institutional review board of the National Center for Global Health and Medicine. The National Heart, Lung, and Blood Institute approved our use of TOPCAT data.

OUTCOME MEASUREMENTS. The primary outcome of the present study was all-cause mortality. To analyze mortality in detail, cardiovascular and noncardiovascular mortality were separately assessed as secondary outcomes. Cardiovascular mortality included death from myocardial infarction, stroke, sudden death, pump failure, pulmonary embolism, and cardiovascular procedure-related events. Noncardiovascular mortality included death from noncardiovascular events, such as infection and malignancy. All events were adjudicated according to pre-specified criteria by a clinical endpoint committee at the Brigham and Women's Hospital (11). Patients were assessed every 4 months during the first year of the study and every 6 months thereafter. More detailed information regarding outcome evaluation was previously reported (10).

POTENTIAL CONFOUNDERS. We extracted data on the following potential confounders at baseline: age; sex; race and ethnicity; smoking status; alcohol intake; New York Heart Association (NYHA)

functional class; body mass index (BMI; body weight in kilograms divided by the square of the height in meters); comorbidities of diabetes, hypertension, and dyslipidemia; history of cardiovascular events (myocardial infarction, angina pectoris, percutaneous coronary intervention, coronary artery bypass graft surgery, implanted cardioverter-defibrillator, implanted pacemaker, atrial fibrillation, hospitalization for heart failure, stroke, or peripheral arterial disease) or chronic obstructive pulmonary disease; medications (angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, calcium-channel blockers, diuretics, beta-blockers, aspirin, or statins); randomization arm (spironolactone or placebo); eGFR; systolic and diastolic blood pressures; and heart rate. Race and ethnicity were classified as white, black, or others. Smoking status was classified as never smoked, former smoker, or current smoker. Alcohol intake was categorized as 0, 1 to 5, 6 to 10, or ≥11 drinks per week. BMI was categorized as <18.5, 18.5 to 24.9, 25.0 to 29.9, and ≥ 30.0 kg/m^2. Obesity was defined as BMI ≥30.0 kg/m^2.

STATISTICAL ANALYSIS. Demographic data are presented as numbers, proportions (%), or mean ± SD. Patients in the present study were divided into 2 groups according to the presence of abdominal obesity, which was defined as a waist circumference of ≥102 cm in men and ≥88 cm in women (13). Continuous variables were compared using Student's *t*-test, and categorical variables were compared using chi-square tests. Kaplan-Meier survival curves were constructed for primary and secondary outcomes in patients with and without abdominal obesity. Using the Cox proportional hazard models, we analyzed and compared hazard ratios (HRs) for the primary and secondary outcomes with 95% confidence intervals (CIs) in patients with abdominal obesity and those without abdominal obesity. The proportional hazards assumption was tested and confirmed by graphical methods using the scaled Schoenfeld residuals (14). Abdominal obesity is associated with BMI and many obesity-related diseases such as diabetes, hypertension, and cardiovascular disease. Because multicollinearity in statistical analyses can yield biased estimates, we carefully performed various analyses using different models to reveal the association between abdominal obesity and mortality. In model 1, we included minimum parameters for multivariable adjustment: age, sex, race, and ethnicity; smoking status; and alcohol intake. In model 2, we included the parameters of model 1 along with the following conditions and diseases: NYHA functional class, BMI, diabetes, hypertension, dyslipidemia, myocardial infarction, atrial fibrillation, stroke, peripheral arterial disease, eGFR, and randomization arm (spironolactone or placebo). In model 3, we included the parameters of model 2 along with the following treatments and conditions: treatment by percutaneous coronary intervention or coronary artery bypass graft surgery; implanted cardioverter-defibrillator; implanted pacemaker; hospitalization for heart failure; chronic obstructive pulmonary disease; use of angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, calcium-channel blockers, diuretics, beta blockers, aspirin, or statins; systolic and blood pressures; and heart rate. As a sensitivity analysis, a further adjustment was made to add country or self-reported health state to the parameters of the multivariable adjustments of model 3. Self-reported health state was assessed using a visual analog scale (0 to 100, with the worst state marked 0 and the best state marked 100). In addition, we performed similar analyses using continuous data of waist circumference (centimeters) instead of abdominal obesity. Moreover, we performed sensitivity analyses that excluded patients with a BMI of <18.5 kg/m^2 because these patients might have had unknown or unmeasured comorbidities. We also performed a further sensitivity analysis limited to patients who were white or black because the "others" category might have included patients in whom definitions of obesity and abdominal obesity might be inaccurate.

Furthermore, we performed Cox proportional hazard analyses to assess primary and secondary outcomes in propensity score–matched patients with and without abdominal obesity (15). We used 1:1 nearest-neighbor matching without replacement to match all baseline characteristics. The propensity score was derived using a logistic regression model that included abdominal obesity as the outcome variable and all potential confounders listed in **Table 1** as explanatory variables. Standardized differences of <0.10 between propensity score–matched patients were considered negligible (15).

The primary outcome was further analyzed according to clinically relevant subgroups: age (<70 or ≥70 years), sex (male or female), obesity (nonobesity or obesity), diabetes (nondiabetes or diabetes), ischemic heart disease (no history of ischemic heart disease or history of ischemic heart disease), atrial fibrillation (no history of atrial fibrillation or history of atrial fibrillation), spironolactone (not taking spironolactone or taking spironolactone), and NYHA functional class (I and/or II or III and/or IV). To explore effect modification, we tested for interactions between abdominal obesity in patients at rest and

TABLE 1 Baseline Characteristics of Study Patients With and Without Abdominal Obesity

	Abdominal Obesity		
	(–) (n = 897)	(+) (n = 2,413)	p Value
Age, yrs	69.0 ± 9.9	68.3 ± 9.4	0.08
Female	33.9	57.8	<0.001
Race and ethnicity			
White	92.3	88.9	0.004
Black	4.1	8.9	<0.001
Others	3.6	2.2	0.02
Smoking status			
Never	49.5	54.5	0.01
Former	34.7	36.9	0.24
Current	15.8	8.6	<0.001
Alcohol drinks/week			
0	72.6	80.1	<0.001
1–5	20.5	15.4	<0.001
6–10	5.0	3.1	0.007
11+	1.9	1.4	0.31
NYHA functional class			
I/II	74.7	65.2	<0.001
III/IV	25.3	34.8	
Body mass index, kg/m^2			
<18.5	1.6	0.0	<0.001
18.5–24.9	36.2	3.4	<0.001
25.0–29.9	50.2	25.8	<0.001
≥30.0	12.0	70.8	<0.001
Diabetes	17.3	37.6	<0.001
Hypertension	88.2	92.8	<0.001
Dyslipidemia	54.5	62.3	<0.001
History of cardiovascular events			
Myocardial infarction	29.3	25.3	0.02
Angina pectoris	53.3	45.9	<0.001
Percutaneous coronary intervention	14.8	14.3	0.72
CABG surgery	13.0	12.7	0.80
Implanted cardioverter defibrillator	0.9	1.4	0.27
Implanted pacemaker	7.3	8.0	0.47
Atrial fibrillation	32.1	36.5	0.01
Hospitalization for heart failure	72.0	72.9	0.59
Stroke	6.5	8.0	0.12
Peripheral arterial disease	10.1	8.8	0.22
COPD	8.6	12.2	0.004

Continued on the next page

these subgroups in multivariable model 3. Ischemic heart disease was defined as myocardial infarction, angina pectoris, or previous treatment with percutaneous coronary intervention or coronary artery bypass graft surgery. To avoid bias of the Cox proportional hazards models, we performed competing risk regression models for cardiovascular and noncardiovascular mortality (16).

We performed additional analyses to assess the association between BMI and all-cause mortality based on 3 classifications of BMI: normal weight (BMI 18.5 to 24.9 kg/m^2), overweight (BMI 25 to 29.9 kg/m^2), and obese (BMI ≥30 kg/m^2). Because the number of patients with BMI of <18.5 kg/m^2 was small (n = 14), we did not evaluate outcomes in these patients.

All statistical analyses were conducted using Stata software version 14.1 (Stata Corp., College Station, Texas). Values of $p < 0.05$ indicated statistical significance.

RESULTS

CHARACTERISTICS OF STUDY PATIENTS. The present study included 2,413 patients with abdominal obesity and 897 without abdominal obesity. Baseline characteristics are shown in Table 1. Compared with patients without abdominal obesity, those with abdominal obesity were significantly associated with the following parameters: higher proportion of female sex; being black; never smoker; lower alcohol intake; higher proportion of NYHA functional class III and/or IV; higher BMI; higher prevalences of diabetes, hypertension, dyslipidemia, myocardial infarction, angina pectoris, atrial fibrillation, and chronic obstructive pulmonary disease; more use of angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, calcium-channel blockers, diuretics, and statins; lower eGFR; higher systolic blood pressure; and faster heart rate.

PRIMARY AND SECONDARY OUTCOMES. The mean follow-up was 3.4 ± 1.7 years. During follow-up, 500 patients died. Kaplan-Meier survival curves and cumulative event rates for all-cause, cardiovascular, and noncardiovascular mortality in patients with and without abdominal obesity are shown in Figure 1 and Table 2, respectively. All-cause mortality rates in patients with and without abdominal obesity were 46.1 and 40.7 events per 1,000 person-years, respectively. The unadjusted risk of all-cause, cardiovascular, and noncardiovascular mortality did not significantly differ between patients with and without abdominal obesity (all-cause mortality, unadjusted HR: 1.14; 95% CI: 0.93 to 1.39; $p = 0.21$ [Figure 1A]; cardiovascular mortality, unadjusted HR: 1.05; 95% CI: 0.82 to 1.34; $p = 0.71$ [Figure 1B]; and noncardiovascular mortality, unadjusted HR: 1.33; 95% CI: 0.94 to 1.89; $p = 0.11$ [Figure 1C]). After multivariable adjustment, the risk of all-cause mortality was significantly higher in patients with abdominal obesity than in those without abdominal obesity (model 1, adjusted HR: 1.34; 95% CI: 1.09 to 1.67; $p = 0.006$; model 2, adjusted HR: 1.54; 95% CI: 1.18 to 2.01; $p = 0.001$; and model 3, adjusted HR: 1.52; 95% CI: 1.16 to 1.99; $p = 0.002$) (Table 2). HRs for all-cause mortality remained similar after further

adjustment for country (adjusted HR: 1.48; 95% CI: 1.13 to 1.94; p = 0.004) and health status (adjusted HR: 1.53; 95% CI: 1.17 to 2.01; p = 0.002). In model 3, using waist circumference as a continuous variable, we showed that a higher waist circumference was significantly associated with an increased risk of all-cause mortality (adjusted HR: 1.01; 95% CI: 1.01 to 1.02; p < 0.001). In addition, in model 3, in which we excluded patients with a BMI of <18.5 kg/m^2, the analysis did not change the result (adjusted HR: 1.53; 95% CI: 1.17 to 2.00; p = 0.002). In model 3, with race and ethnicity limited to white or black, a similar result was observed (adjusted HR: 1.44; 95% CI: 1.10 to 1.89; p = 0.009). The risk of cardiovascular mortality was also higher in patients with abdominal obesity than in those without abdominal obesity (model 1, adjusted HR: 1.25; 95% CI: 0.97 to 1.62; p = 0.08; model 2, adjusted HR: 1.52; 95% CI: 1.09 to 2.11; p = 0.01; and model 3, adjusted HR: 1.50; 95% CI: 1.08 to 2.08; p = 0.01). Similarly, the risk of noncardiovascular mortality was significantly higher in patients with abdominal obesity than in those without abdominal obesity (model 1, adjusted HR: 1.55; 95% CI: 1.08 to 2.23; p = 0.01; model 2, adjusted HR: 1.58; 95% CI: 1.01 to 2.48; p = 0.04; and model 3, adjusted HR: 1.58; 95% CI: 1.00 to 2.51; p = 0.04). Competing risk regression analyses for cardiovascular and noncardiovascular mortality showed similar results (HR: 1.43; 95% CI: 1.04 to 1.96; p = 0.02 and HR: 1.51; 95% CI: 0.96 to 2.36; p = 0.07, respectively).

We performed additional sensitivity analyses using propensity score matching to verify the association between abdominal obesity and the risk of mortality in patients with HFpEF. In propensity score–matched patients (n = 1,058), baseline characteristics between those with and without abdominal obesity did not significantly differ (Online Table 1). The risk of all-cause mortality was significantly higher in propensity score–matched patients with abdominal obesity than in those without abdominal obesity (HR: 1.64; 95% CI: 1.18 to 2.28; p = 0.003) (**Central Illustration**, panel A). Similarly, the risk of cardiovascular mortality was significantly higher in those with abdominal obesity than in those without abdominal obesity (HR: 1.78; 95% CI: 1.17 to 2.72; p = 0.008) (**Central Illustration**, panel B), whereas that of noncardiovascular mortality was not significantly higher in those with abdominal obesity (HR: 1.44; 95% CI: 0.85 to 2.44; p = 0.17) (**Central Illustration**, panel C).

Figure 2 shows the association between abdominal obesity and all-cause mortality in the different subgroups. There were no significant interactions between abdominal obesity and age, sex, obesity, diabetes, ischemic heart disease, atrial fibrillation, use of spironolactone, or NYHA functional class. Although not all subgroups showed a statistically significant association, the results indicated that the risk of all-cause mortality within these subgroups was higher in patients with abdominal obesity than in those without abdominal obesity.

TABLE 1 Continued

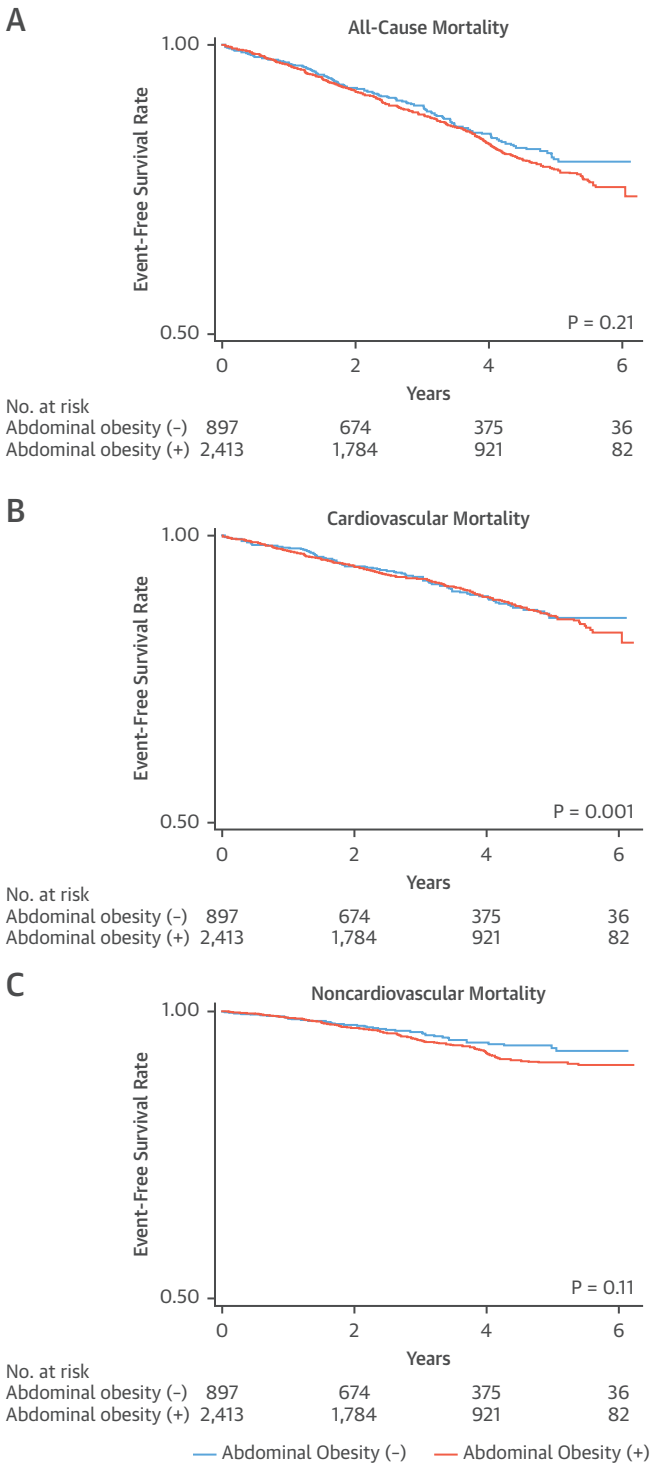
	Abdominal Obesity		
	(–) (n = 897)	(+) (n = 2,413)	p Value
Medications			
ACE-I/ARB	82.2	85.5	0.02
Calcium-channel blockers	32.7	39.3	0.001
Diuretics	71.8	85.0	<0.001
Beta blockers	78.5	77.6	0.59
Aspirin	67.3	65.1	0.22
Statin	47.1	53.6	0.001
Randomization arm			
Spironolactone	51.3	49.7	0.40
Estimated GFR, ml/min/1.73 m^2	71.4 ± 21.5	66.5 ± 19.3	<0.001
Systolic blood pressure, mm Hg	127.6 ± 13.1	129.9 ± 14.1	<0.001
Diastolic blood pressure, mm Hg	76.1 ± 10.2	76.0 ± 10.7	0.88
Heart rate, beats/min	68.0 ± 9.8	69.2 ± 10.5	0.002
Country			
United States	24.1	33.8	<0.001
Russia	37.9	30.1	<0.001
Republic of Georgia	23.5	16.6	<0.001
Canada	7.9	10.2	0.04
Brazil	4.1	5.1	0.22
Argentina	2.5	4.2	0.01

Values are mean ± SD or %.

ACE-I = angiotensin-converting enzyme inhibitors; ARB = angiotensin II receptor blockers; CABG = coronary artery bypass graft; COPD = chronic obstructive pulmonary disease; GFR = glomerular filtration rate; NYHA = New York Heart Association.

The association between BMI and waist circumference or abdominal obesity is presented in Online Figure 1. Waist circumference increased with BMI in both men and women. Kaplan-Meier survival curves and event rates for all-cause mortality in normal, overweight, and obese patients are shown in Online Figure 2 and Online Table 2. The cumulative event rates for all-cause mortality in patients with HFpEF were the highest in the normal BMI group. The overweight and obese group had significantly lower unadjusted HRs for all-cause mortality compared with the normal BMI group (overweight, unadjusted HR: 0.59; 95% CI: 0.45 to 0.78; p < 0.001 and obese, unadjusted HR: 0.73; 95% CI: 0.57 to 0.93; p < 0.01). Using the multivariable Cox proportional hazards model, and as shown in model 3, which included the parameter of abdominal obesity, we found that all-cause mortality was significantly lower in the overweight group (adjusted HR: 0.55; 95% CI: 0.41 to 0.74;

FIGURE 1 Kaplan-Meier Survival Curves for Primary and Secondary Outcomes



Rates of freedom from **(A)** all-cause mortality, **(B)** cardiovascular mortality, and **(C)** noncardiovascular mortality.

$p < 0.001$) and in the obese group (adjusted HR: 0.52; 95% CI: 0.38 to 0.72; $p < 0.001$) compared with the normal BMI group.

DISCUSSION

The results of the present study demonstrated that abdominal obesity in patients with HFpEF is significantly associated with an increased risk of all-cause mortality (**Central Illustration**). In addition, the risk of cardiovascular and noncardiovascular mortality was also significantly higher in patients with abdominal obesity than in those without abdominal obesity. The association between abdominal obesity and an increased risk of all-cause mortality was observed in all clinically relevant subgroups.

Unfortunately, clinical trials in HFpEF failed to demonstrate that effective treatments for HFrEF improve outcomes in patients with HFpEF (10,17). Therefore, appropriate strategies for HFpEF treatment remain poorly defined, possibly due to the complex pathophysiological mechanisms underlying HFpEF. Patients with HFpEF frequently have several comorbidities, such as obesity, metabolic syndrome, diabetes, hypertension, lung disease, anemia, and smoking. Based on these coexisting conditions, a systemic proinflammatory state has been proposed as a fundamental mechanism that leads to myocardial inflammation and fibrosis, oxidative stress, and alterations in cardiomyocyte signaling pathways (6-9). These alterations promote microvascular dysfunction and cardiomyocyte remodeling, and result in left ventricular dysfunction (6-9). Obesity is a prominent comorbidity among patients with HFpEF. A previous study reported the prevalence of being overweight or obese as >80% among older patients with HFpEF (1,18-20). A study recently suggested that compared with patients with HFpEF but without obesity, those with obesity displayed unique pathophysiological features, including greater volume overload, more biventricular remodeling, greater right ventricular dysfunction, worse exercise capacity, more profound hemodynamic derangements, and impaired pulmonary vasodilation (21). Obesity has direct and indirect effects on the heart, including increased myocardial load associated with plasma volume expansion, worsening of arterial hypertension, left ventricular hypertrophy, and increased aortic stiffness (22). Furthermore, aortic stiffness is worse in patients with abdominal obesity (23,24). These effects are very important mechanisms that may contribute to HFpEF pathophysiology (7). Adipose tissue is an active endocrine organ and produces proinflammatory

cytokines, such as interleukin-1beta, tumor necrosis factor-alpha, and interleukin-18, which may be associated with diastolic dysfunction (25,26). However, although obesity, particularly abdominal obesity, is related to systemic inflammation (7), the association between abdominal obesity and the development or worsening of HFpEF is poorly understood (27–29). Moreover, there is a lack of studies that has evaluated the association between abdominal obesity and all-cause mortality in patients with HFpEF. Obesity is an independent predictor of heart failure, whereas once heart failure is diagnosed, patients with heart failure, including those with obesity, have a better prognosis than those who are normal weight (30). This phenomenon has been termed the "obesity paradox," which is observed in both patients with HFrEF and HFpEF (30,31). The obesity paradox was also observed in the present study. There continues to be considerable discussion regarding the obesity paradox, and whether it is a true phenomenon (22,32). Several explanations include that it is the result of residual confounding, unrecognized or unmeasured systemic illness, unintentional weight loss, or selection bias (32–35). In addition, the inability of BMI to accurately characterize the severity of obesity may be associated with the obesity paradox, which may not be present in sarcopenic obese patients (33,36,37). Because BMI does not distinguish between fat mass and lean mass, it is reasonable to assume that higher amounts of lean mass, particularly skeletal muscle, exert protective effects (37). Furthermore, parameters such as waist circumference, waist-to-hip ratio, and waist-to-height ratio more accurately measure body composition than BMI (38). Abdominal obesity is a major risk factor for cardiovascular disease, whereas peripheral fat appears to confer protective effects (39). A recent study reported that abdominal obesity is associated with several measures of adverse cardiac functions, which are independent of BMI; this effect could be observed even in nonobese individuals (40). These data concurred with our observations regarding the association between abdominal obesity and adverse cardiovascular outcomes. Not only the amount of fat, but also the location of adipose tissue, might be important in patients with HFpEF. In the present study, abdominal obesity was also associated with an increased risk of noncardiovascular mortality. Although the exact reasons remain unknown, a large-scale study with a long follow-up, which used data from the Nurses' Health Study, indicated that abdominal obesity was positively associated with cancer mortality and was independent of BMI (41). Because death from noncardiovascular causes is more common in patients with HFpEF than in those with HFrEF (42,43), further studies are warranted to reveal the association between abdominal obesity and noncardiovascular mortality.

TABLE 2 All-Cause, Cardiovascular, and Noncardiovascular Mortality in HFpEF Patients With and Without Abdominal Obesity

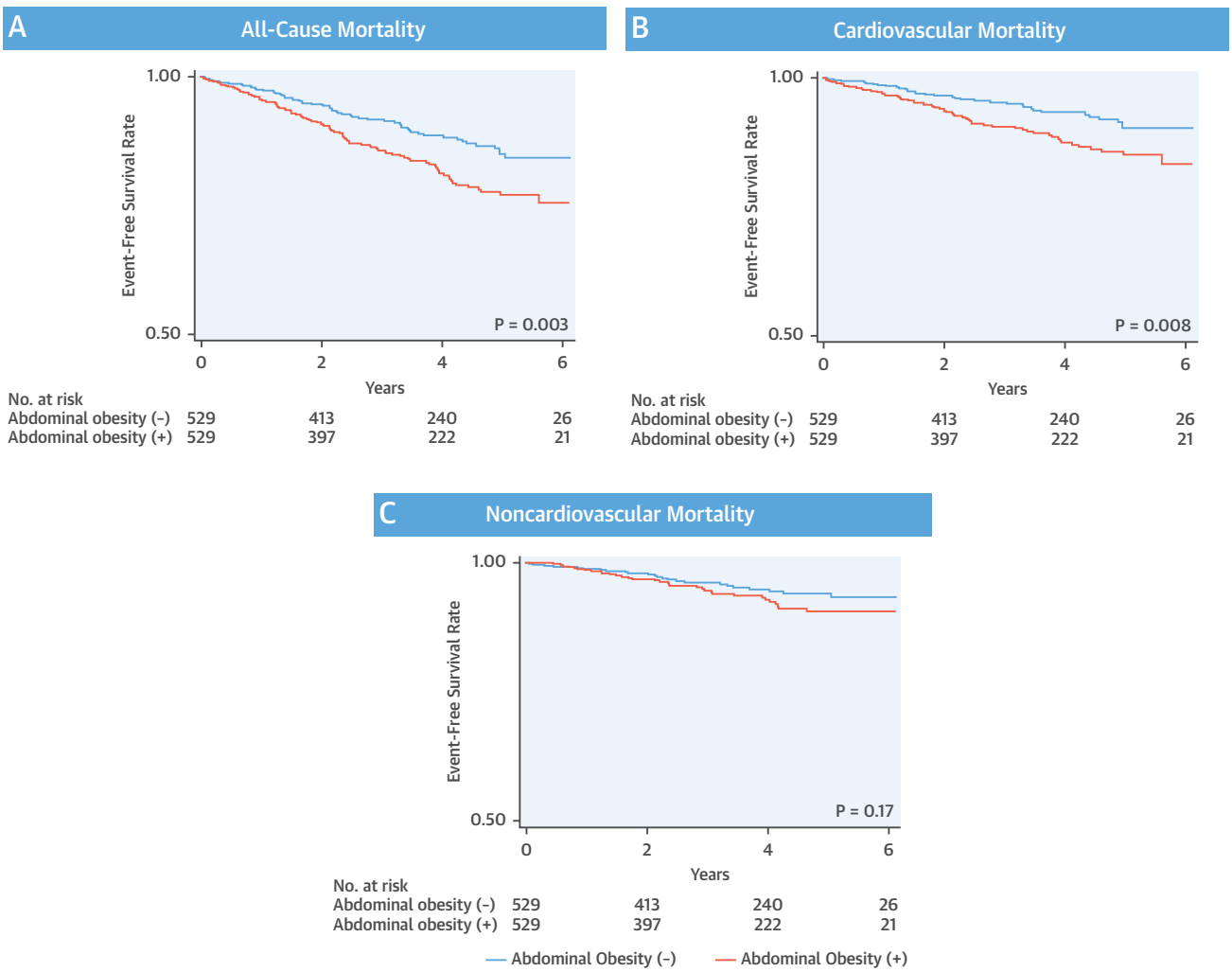
	Abdominal Obesity		
	(−) (n = 897)	(+) (n = 2,413)	p Value
All-cause mortality			
n	126	374	
Event rate (per 1,000 person-yrs)	40.7	46.1	
Unadjusted HR (95% CI)	1.00 (ref)	1.14 (0.93–1.39)	0.21
Model 1: adjusted HR (95% CI)	1.00 (ref)	1.34 (1.09–1.67)	0.006
Model 2: adjusted HR (95% CI)	1.00 (ref)	1.54 (1.18–2.01)	0.001
Model 3: adjusted HR (95% CI)	1.00 (ref)	1.52 (1.16–1.99)	0.002
Cardiovascular mortality			
n	86	235	
Event rate (per 1,000 person-yrs)	27.8	29.0	
Unadjusted HR (95% CI)	1.00 (ref)	1.05 (0.82–1.34)	0.71
Model 1: adjusted HR (95% CI)	1.00 (ref)	1.25 (0.97–1.62)	0.08
Model 2: adjusted HR (95% CI)	1.00 (ref)	1.52 (1.09–2.11)	0.01
Model 3: adjusted HR (95% CI)	1.00 (ref)	1.50 (1.08–2.08)	0.01
Noncardiovascular mortality			
n	40	139	
Event rate (per 1,000 person-yrs)	12.9	17.1	
Unadjusted HR (95% CI)	1.00 (ref)	1.33 (0.94–1.89)	0.11
Model 1: adjusted HR (95% CI)	1.00 (ref)	1.55 (1.08–2.23)	0.01
Model 2: adjusted HR (95% CI)	1.00 (ref)	1.58 (1.01–2.48)	0.04
Model 3: adjusted HR (95% CI)	1.00 (ref)	1.58 (1.00–2.51)	0.04

In model 1, the following parameters were adjusted: age, sex, race and ethnicity, smoking status, and alcohol intake. In model 2, the following parameters were adjusted: age, sex, race and ethnicity, smoking status, alcohol intake, NYHA functional class, body mass index (BMI), diabetes, hypertension, dyslipidemia, myocardial infarction, atrial fibrillation, stroke, peripheral arterial disease, estimated GFR, and randomization arm (spironolactone or placebo). In model 3, the following parameters were adjusted: age, sex, race and ethnicity, smoking status, alcohol intake, NYHA functional class, BMI, diabetes, hypertension, dyslipidemia, myocardial infarction, atrial fibrillation, stroke, peripheral arterial disease, estimated GFR, randomization arm (spironolactone or placebo), treatment by percutaneous coronary intervention, treatment by coronary artery bypass graft surgery, implanted cardioverter defibrillator, implanted pacemaker, hospitalization for heart failure, chronic obstructive pulmonary disease, use of ACE-I or ARBs, use of calcium-channel blockers, use of diuretics, use of beta blockers, use of aspirin, use of statins, estimated GFR, systolic blood pressure, diastolic blood pressure, and heart rate.

CI = confidence interval; HFpEF = heart failure with preserved left ventricular ejection fraction; HR = hazard ratio; other abbreviations as in Table 1.

CLINICAL IMPLICATIONS. After several adjustments, data from the present study showed that the risk of all-cause mortality was significantly higher in patients with abdominal obesity than those without abdominal obesity, whereas BMI was inversely associated with all-cause mortality. Because central body fat is strongly associated with systemic inflammation (44), our findings might support the recently proposed hypothesis that the presence of a systemic proinflammatory state is associated with the pathophysiological mechanisms that underlie HFpEF (6,7). Thus, improving abdominal obesity through diet, exercise, or both, might represent the most basic and important treatment in patients with HFpEF (45). Because the long-term outcome of weight reduction

CENTRAL ILLUSTRATION **Abdominal Obesity in Patients With HFpEF: All-Cause, Cardiovascular, and Noncardiovascular Mortality**



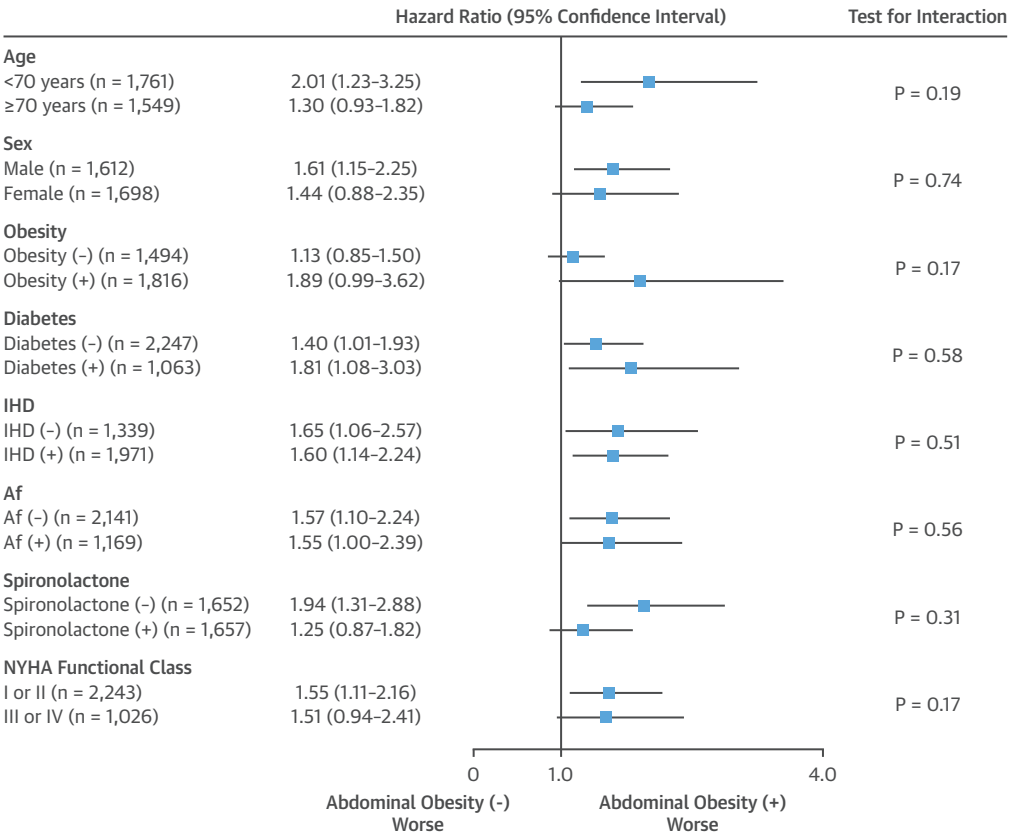
Tsujimoto, T. et al. J Am Coll Cardiol. 2017;70(22):2739–49.

Kaplan-Meier survival curves for all-cause, cardiovascular, and noncardiovascular mortality for in propensity score–matched patients with and without abdominal obesity. Rates of freedom from **(A)** all-cause mortality, **(B)** cardiovascular mortality, and **(C)** noncardiovascular mortality. HFpEF, heart failure with preserved ejection fraction.

in patients with HFpEF remains unknown, randomized controlled trials are required to assess whether an intervention to reduce visceral fat is effective in patients with HFpEF.

STUDY LIMITATIONS. First, because this was a post hoc analysis of the TOPCAT trial, the association between abdominal obesity and adverse outcomes might not be found in other patients with HFpEF. Second, because this was an observational study, residual and uncontrolled confounding might still be present. Specifically, the present study did not include data regarding obstructive sleep apnea. Many patients with HFpEF were obese, and the prevalence of obstructive sleep apnea might be high (46). Obstructive sleep apnea can contribute to HFpEF pathogenesis through multiple mechanisms, for example, sympathetic activation increases left ventricular afterload, hypoxic pulmonary vasoconstriction reduces left ventricular preload, and oxidative

FIGURE 2 Association Between Abdominal Obesity and All-Cause Mortality in the Subgroups



Af = atrial fibrillation; IHD = ischemic heart disease; NYHA = New York Heart Association.

stress stimulates inflammation. In addition, it might be difficult to completely eliminate reverse causality. However, the present study was evidence-based, and various sensitivity analyses, including propensity score matching, consistently showed that abdominal obesity was associated with an increased risk of mortality in patients with HFpEF. Further large-scale studies are required to evaluate whether abdominal obesity is associated with all-cause, cardiovascular, and noncardiovascular mortality in patients with HFpEF.

CONCLUSIONS

The findings of the present study demonstrated that abdominal obesity in patients with HFpEF is significantly associated with higher risks of all-cause, cardiovascular, and noncardiovascular mortality. The association between abdominal obesity and increased mortality was also observed in various clinically important subgroups. Further studies are required to elucidate the detailed mechanisms underlying the association between abdominal obesity and adverse outcomes in patients with HFpEF.

ACKNOWLEDGMENTS This paper was prepared using TOPCAT Research Materials obtained from the National Heart, Lung, and Blood Institute (NHLBI) Biologic Specimen and Data Repository Information Coordinating Center and does not necessarily reflect the opinions or views of the TOPCAT or the NHLBI.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: HFpEF patients with abdominal obesity face a higher risk of all-cause mortality than those without abdominal obesity.

TRANSLATIONAL OUTLOOK: Prospective studies are needed to assess the safety and efficacy of interventions that prevent or reduce abdominal obesity in patients with HFpEF.

REFERENCES

1. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. N Engl J Med 2006;355:251–9.

2. Steinberg BA, Zhao X, Heidenreich PA, et al. Trends in patients hospitalized with heart failure and preserved left ventricular ejection fraction: prevalence, therapies, and outcomes. Circulation 2012;126:65–75.

3. Gladden JD, Linke WA, Redfield MM. Heart failure with preserved ejection fraction. Pflugers Arch 2014;466:1037–53.

4. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016;37:2129–200.

5. Writing Committee M, Yancy CW, Jessup M, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. J Am Coll Cardiol 2013;62:e147–239.

6. Redfield MM. Heart failure with preserved ejection fraction. N Engl J Med 2016;375:1868–77.

7. Paulus WJ, Tschope C. A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. J Am Coll Cardiol 2013;62:263–71.

8. Shah SJ, Kitzman DW, Borlaug BA, et al. Phenotype-specific treatment of heart failure with preserved ejection fraction: a multiorgan roadmap. Circulation 2016;134:73–90.

9. Mohammed SF, Majure DT, Redfield MM. Zooming in on the microvasculature in heart failure with preserved ejection fraction. Circ Heart Fail 2016;9. pii: e003272.

10. Pitt B, Pfeffer MA, Assmann SF, et al. Spironolactone for heart failure with preserved ejection fraction. N Engl J Med 2014;370:1383–92.

11. Desai AS, Lewis EF, Li R, et al. Rationale and design of the treatment of preserved cardiac function heart failure with an aldosterone antagonist trial: a randomized, controlled study of spironolactone in patients with symptomatic heart failure and preserved ejection fraction. Am Heart J 2011;162:966–972.e10.

12. Shah SJ, Heitner JF, Sweitzer NK, et al. Baseline characteristics of patients in the treatment of preserved cardiac function heart failure with an aldosterone antagonist trial. Circ Heart Fail 2013;6:184–92.

13. Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation 2005;112:2735–52.

14. Schoenfeld D. Partial residuals for the proportional hazards regression model. Biometrika 1982;69:239–41.

15. Haukoos JS, Lewis RJ. The propensity score. JAMA 2015;314:1637–8.

16. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc 1999;94:496–509.

17. Massie BM, Carson PE, McMurray JJ, et al. Irbesartan in patients with heart failure and preserved ejection fraction. N Engl J Med 2008;359:2456–67.

18. Redfield MM, Chen HH, Borlaug BA, et al. Effect of phosphodiesterase-5 inhibition on exercise capacity and clinical status in heart failure with preserved ejection fraction: a randomized clinical trial. JAMA 2013;309:1268–77.

19. Haass M, Kitzman DW, Anand IS, et al. Body mass index and adverse cardiovascular outcomes in heart failure patients with preserved ejection fraction: results from the Irbesartan in Heart Failure with Preserved Ejection Fraction (I-PRESERVE) trial. Circ Heart Fail 2011;4:324–31.

20. Alpert MA, Lavie CJ, Agrawal H, Aggarwal KB, Kumar SA. Obesity and heart failure: epidemiology, pathophysiology, clinical manifestations, and management. Transl Res 2014;164:345–56.

21. Obokata M, Reddy YNV, Pislaru SV, Melenovsky V, Borlaug BA. Evidence supporting the existence of a distinct obese phenotype of heart failure with preserved ejection fraction. Circulation 2017;136:6–19.

22. 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. J Am Coll Cardiol HF 2013;1:93–102.

23. Sutton-Tyrrell K, Newman A, Simonsick EM, et al. Aortic stiffness is associated with visceral adiposity in older adults enrolled in the study of health, aging, and body composition. Hypertension 2001;38:429–33.

24. Wildman RP, Mackey RH, Bostom A, Thompson T, Sutton-Tyrrell K. Measures of obesity are associated with vascular stiffness in young and older adults. Hypertension 2003;42:468–73.

25. Frayn KN, Karpe F, Fielding BA, Macdonald IA, Coppack SW. Integrative physiology of human adipose tissue. Int J Obes Relat Metab Disord 2003;27:875–88.

26. Ballak DB, Stienstra R, Tack CJ, Dinarello CA, van Diepen JA. IL-1 family members in the pathogenesis and treatment of metabolic disease: focus on adipose tissue inflammation and insulin resistance. Cytokine 2015;75:280–90.

27. Norton GR, Majane OH, Libhaber E, et al. The relationship between blood pressure and left ventricular mass index depends on an excess adiposity. J Hypertens 2009;27:1873–83.

28. Ammar KA, Redfield MM, Mahoney DW, Johnson M, Jacobsen SJ, Rodeheffer RJ. Central obesity: association with left ventricular dysfunction and mortality in the community. Am Heart J 2008;156:975–81.

29. Wohlfahrt P, Redfield MM, Lopez-Jimenez F, et al. Impact of general and central adiposity on ventricular-arterial aging in women and men. J Am Coll Cardiol HF 2014;2:489–99.

30. Padwal R, McAlister FA, McMurray JJ, et al. The obesity paradox in heart failure patients with preserved versus reduced ejection fraction: a meta-analysis of individual patient data. Int J Obes (2005) 2014;38:1110–4.

31. Kapoor JR, Heidenreich PA. Obesity and survival in patients with heart failure and preserved systolic function: a U-shaped relationship. Am Heart J 2010;159:75–80.

32. Carbone S, Lavie CJ, Arena R. Obesity and heart failure: focus on the obesity paradox. Mayo Clin Proc 2017;92:266–79.

33. Tsujimoto T, Kajio H, Sugiyama T. Risks for cardiovascular and cardiac deaths in nonobese patients with diabetes and coronary heart disease. Mayo Clin Proc 2016;91:1545–54.

34. Greenberg JA. The obesity paradox in the US population. Am J Clin Nutr 2013;97:1195–200.

35. Ferreira I, Stehouwer CD. Obesity paradox or inappropriate study designs? Time for life-course epidemiology. J Hypertens 2012;30:2271–5.

36. Upadhya B, Haykowsky MJ, Eggebeen J, Kitzman DW. Sarcopenic obesity and the pathogenesis of exercise intolerance in heart failure with preserved ejection fraction. Curr Heart Fail Rep 2015;12:205–14.

37. De Schutter A, Lavie CJ, Kachur S, Patel DA, Milani RV. Body composition and mortality in a large cohort with preserved ejection fraction: untangling the obesity paradox. Mayo Clin Proc 2014;89:1072–9.

38. Cornier MA, Despres JP, Davis N, et al. Assessing adiposity: a scientific statement from the American Heart Association. Circulation 2011;124:1996–2019.

39. Ferreira I, Snijder MB, Twisk JW, et al. Central fat mass versus peripheral fat and lean mass: opposite (adverse versus favorable) associations with arterial stiffness? The Amsterdam Growth and Health Longitudinal Study. J Clin Endocrinol Metab 2004;89:2632–9.

40. Selvaraj S, Martinez EE, Aguilar FG, et al. Association of central adiposity with adverse cardiac mechanics: findings from the Hypertension Genetic Epidemiology Network Study. Circ Cardiovasc Imaging 2016;9. pii: e004396.

41. Zhang C, Rexrode KM, van Dam RM, Li TY, Hu FB. Abdominal obesity and the risk of all-cause, cardiovascular, and cancer mortality: sixteen years of follow-up in US women. Circulation 2008;117:1658–67.

42. Lee DS, Gona P, Albano I, et al. A systematic assessment of causes of death after heart failure onset in the community: impact of age at death, time period, and left ventricular systolic dysfunction. Circ Heart Fail 2011;4:36–43.

43. Chan MM, Lam CS. How do patients with heart failure with preserved ejection fraction die? Eur J Heart Fail 2013;15:604–13.

44. Taube A, Schlich R, Sell H, Eckardt K, Eckel J. Inflammation and metabolic dysfunction: links to cardiovascular diseases. Am J Physiol Heart Circ Physiol 2012;302:H2148–65.

45. Kitzman DW, Brubaker P, Morgan T, et al. Effect of caloric restriction or aerobic exercise training on peak oxygen consumption and quality of life in obese older patients with heart failure with preserved ejection fraction: a randomized clinical trial. JAMA 2016;315:36–46.

46. Young T, Skatrud J, Peppard PE. Risk factors for obstructive sleep apnea in adults. JAMA 2004;291:2013–6.

KEY WORDS abdominal obesity, all-cause mortality, heart failure with preserved ejection fraction, inflammation, TOPCAT trial

APPENDIX For supplemental tables and figures, please see the online version of this paper.