Published in final edited form as:
Mayo Clin Proc. 2013 March ; 88(3): 251–258. doi:10.1016/j.mayocp.2012.11.020.

Impact of Cardiorespiratory Fitness on the Obesity Paradox in Patients With Heart Failure

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Data Previously Presented: These data were presented in part at the 2012 American Heart Association Annual Scientific Meeting in Los Angeles, CA.

Abstract

Objective—To determine the impact of cardiorespiratory fitness (FIT) on survival in relation to the obesity paradox in patients with systolic heart failure (HF).

Patients and Methods—We studied 2066 patients with systolic HF (body mass index [BMI] ≥18.5 kg/m^2) between April 1, 1993 and May 11, 2011 (with 1784 [86%] tested after January 31, 2000) from a multicenter cardiopulmonary exercise testing database who were followed for up to 5 years (mean ± SD, 25.0±17.5 months) to determine the impact of FIT (peak oxygen consumption <14 vs ≥14 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$) on the obesity paradox.

Results—There were 212 deaths during follow-up (annual mortality, 4.5%). In patients with low FIT, annual mortality was 8.2% compared with 2.8% in those with high FIT (*P*<.001). After adjusting for age and sex, BMI was a significant predictor of survival in the low FIT subgroup when expressed as a continuous (*P*=.03) and dichotomous (<25.0 vs ≥25.0 kg/m^2) (*P*=.01) variable. Continuous and dichotomous BMI expressions were not significant predictors of survival in the overall and high FIT groups after adjusting for age and sex. In patients with low FIT, progressively worse survival was noted with BMI of 30.0 or greater, 25.0 to 29.9, and 18.5 to 24.9 (log-rank, 11.7; *P*=.003), whereas there was no obesity paradox noted in those with high FIT (log-rank, 1.72; *P*=.42).

Conclusion—These results indicate that FIT modifies the relationship between BMI and survival. Thus, assessing the obesity paradox in systolic HF may be misleading unless FIT is considered.

Being classified as overweight or obese is known to adversely impact left ventricular (LV) geometry and hypertrophy and to have adverse effects on LV systolic and, especially, diastolic function.[1–3] Overweight and obesity increase the prevalence of heart failure (HF).[1,4] However, despite the adverse effects of obesity on risk factors for HF and prevalence of HF, many studies, and even large meta-analyses, have reported that once cardiovascular (CV) diseases, including HF, become established, overweight and obese individuals seem to have a better overall clinical prognosis, which has been termed the "obesity paradox."[1,5–11] Some investigators have suggested that the obesity paradox may be partly explained by confounding factors.12–14 Cardiorespiratory fitness (FIT) is strongly related to prognosis in healthy individuals and in cohorts withCVdiseases.[15–18] Many studies have reported the importance of FIT and other cardiopulmonary exercise testing (CPX) variables in predicting prognosis in HF.[19–22] In fact, the classic cutoff point for peak oxygen consumption ($\dot{V}O_2$) of 14 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$ proposed by Mancini et al[23] is still frequently used to classify patients with HF into low- and high-risk groups. In cohorts of patients with coronary heart disease (CHD), in which a strong obesity paradox has also been noted,[24–27] we and others have found that an obesity paradox was not present in cohorts with high levels of FIT.[28–30] To our knowledge, the impact of FIT on the obesity paradox has not been assessed in a cohort with systolic HF.

Using a multicenter CPX database, we assessed the impact of FIT, using the standard peak $\dot{V}O_2$ cutoff point of 14 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$, on survival in normal-weight, overweight, and obese patients with systolic HF to determine whether FIT affects the obesity paradox in HF.

PATIENTS AND METHODS

This study was a multicenter analysis of patients with HF from the CPX laboratories at San Paolo Hospital, Milan, Italy; LeBauer Cardiovascular Research Foundation, Greensboro, North Carolina; Stanford University, Palo Alto, California; VA Palo Alto Health Care System, Palo Alto, California; Brigham and Women's Hospital, Boston, Massachusetts; and Virginia Commonwealth University, Richmond. All the patients included in this analysis were clinically referred for CPX to determine heart transplantation/device implantation candidacy or functional capacity. A total of 2066 patients with systolic HF were included in the present analysis. Tests were conducted between April 1, 1993 and May 11, 2011, with 1784 (86%) of the tests conducted after January 31, 2000. The inclusion criteria consisted of a diagnosis of HF[31] and evidence of LV systolic dysfunction by 2-dimensional echocardiography (ie, LV ejection fraction <50%) obtained within 1 month of data collection. Underweight individuals with a body mass index (BMI) (calculated as the weight in kilograms divided by the height in meters squared) below the lower end of the normal-weight threshold according to BMI (ie, <18.5) were excluded from the analysis. All the participants completed a written informed consent form, and institutional review board approval was obtained from each institution.

CPX Procedures

Symptom-limited CPX was performed on all the participants, and pharmacologic therapy was maintained during CPX. Progressive CPX protocols were used at all the centers, and ventilatory expired gas analysis was performed using a metabolic cart (CPX-D and Ultima from Medgraphics; Vmax 29 from SensorMedics; or TrueOne 2400 from ParvoMedics). Before each test, the equipment was calibrated in standard fashion using reference gases. Minute ventilation (VE), $\dot{V}O_2$, and carbon dioxide output (VCO_2) were acquired breath-by-breath and were averaged over 10-second intervals. Peak $\dot{V}O_2$ and peak respiratory exchange ratio were expressed as the highest 10-second averaged sample obtained during the last 20 seconds of testing. The VE and VCO_2 values, acquired from the initiation of exercise to peak, were input into spreadsheet software (Microsoft Excel; Microsoft Corp) to calculate the VE/VCO_2 slope via least squares linear regression ($y = mx + b$, where m indicates slope). The BMI was calculated for each patient on the day of CPX. Weight was obtained on a calibrated scale after the removal of shoes, jewelry, etc. Height was determined from the medical record and was confirmed by the patient.

End Points

Patients were followed up for death from any cause via medical record review for up to 5 years after CPX. Patients were followed up by the HF programs at their respective institutions, providing a high likelihood that all events were captured. External means of tracking events, such as the Social Security Death Index, were not used in the present study. Transplantation and LV assist device implantation were considered censored events.

Statistical Analyses

A statistical software package (SPSS, version 19.0; SPSS Inc) was used to perform all the analyses. Continuous and categorical data are reported as mean ± SD and frequency as percentages. Independent *t* tests were used to assess differences in baseline and CPX variables according to low FIT vs high FIT, which was dichotomized according to a peak $\dot{V}O_2$ threshold of 14 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$ Oneway analysis of variance assessed differences among baseline and CPX variables according to a BMI classification of 18.5 to 24.9, 25.0 to 29.9, or 30.0 or greater in the low and high FIT subgroups. The Tukey honestly significant difference was used to determine differences in subgroups at one-way analysis of variance $P<.05$. Categorical data were assessed by the χ^2 test according to low vs high FIT and by BMI category within the FIT subgroups. Life tables were used to determine annual mortality rates. Cox regression analysis was used to assess the prognostic value of BMI, as a continuous and dichotomous variable, in the overall group and in low and high FIT subgroups after adjusting for age and sex. Cox regression analysis was also used to assess the prognostic value of peak $\dot{V}O_2$ according to the threshold of 14 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$ Kaplan-Meier analysis was used to calculate survival in patients according to a BMI classification of 18.5 to 24.9, 25.0 to 29.9, or 30.0 or greater. This analysis was performed in the overall group and in the low and high FIT subgroups. The log-rank test was used to assess differences in overall survival between BMI categories within the low and high FIT subgroups. $P<.05$ was considered statistically significant for all tests.

RESULTS

Table 1 lists differences in key baseline and CPX variables according to low vs high FIT. Except for angiotensin-converting enzyme inhibitor use, all the other variables of interest were statistically significantly different. Patients with high FIT were younger and were more likely to be male; to have a nonischemic HF diagnosis; to have a lower BMI, New York Heart Association class, and VE/VCO_2 slope; and to have a higher LV ejection fraction. Peak respiratory exchange ratio was also slightly, but statistically significantly, higher in the high FIT group. Table 2 lists differences in key baseline and CPX variables according to BMI classification in the low and high FIT subgroups.

Participants were tracked for a mean ± SD of 25.0±17.5 months. Of the 1854 patients who were classified as surviving, 46% (n=853), 40% (n=742), and 14% (n=259) were tracked for less than 24 months, 24 to 48 months, and 49 to 60 months, respectively. There were 212 deaths during the 5-year tracking period. Annual mortality for the overall group was 4.5%. There were 128 deaths in the low FIT group, equating to annual mortality of 8.2%. There were 84 deaths in the group with high peak $\dot{V}O_2$, equating to annual mortality of 2.8%. After adjusting age and sex, BMI was a significant predictor of survival in the low FIT subgroup when expressed as a continuous (hazard ratio, 0.97; 95% CI, 0.94–0.99; $P=.03$) and dichotomous (<25.0 vs ≥25.0) (hazard ratio, 0.61; 95% CI, 0.42–0.89; $P=.001$) variable. Dichotomous expression of BMI using a less than 30.0 vs 30.0 or greater threshold was not prognostically significant in the low FIT group ($P=.09$). Moreover, continuous and dichotomous BMI expressions were not significant predictors of survival in the overall group and in the high FIT subgroup after adjusting for age and sex (continuous: $P=.07$; </

≥25.0: *P*=.70; </≥25.0: *P*=.20). Peak $\dot{V}O_2$ was a significant prognostic marker in the less than 14 mL O_2 • kg^{-1} • min^{-1} subgroup (hazard ratio, 0.84; 95% CI, 0.78–0.90; *P*<.001) and in the 14 mL O_2 • kg^{-1} • min^{-1} or greater subgroup (hazard ratio, 0.90; 95% CI, 0.85–0.95; *P*<.001).

Figures 1 to 3 illustrate survival characteristics according to the traditional normal-weight, overweight, and obese BMI classifications. In the overall group, there was a slight trend toward better survival with higher BMI (log-rank, 4.8; *P*=.09). Differences in survival were significant in the low FIT group only, which had progressively worse survival with lower BMI (log-rank, 11.7; *P*=.003). However, the group with high FIT had excellent survival regardless of BMI.

DISCUSSION

This study has 3 important findings. First, these results provide support for an obesity paradox in patients with systolic HF referred for CPX. Second, these results demonstrate the important role of FIT to impact prognosis in patients with systolic HF. Third, to our knowledge and for the first time in this chronic CV population, we demonstrate that unlike patients with high-risk systolic HF with low levels of FIT(peak $\dot{V}O_2$ <14 mL O_2 • kg^{-1} • min^{-1}), those with high FIT (peak $\dot{V}O_2$ 14 mL O_2 • kg^{-1} • min^{-1}), albeit well below age- and sex-predicted normal values, have a good prognosis and do not demonstrate any evidence of an obesity paradox. The findings of the present study are consistent with those of previous investigations in CHD cohorts,[28–30] demonstrating that FIT also affects the obesity paradox.

Obesity has numerous adverse effects on hemodynamic and CV structure and function, which have been reviewed in detail elsewhere.[1,2] Obesity has adverse effects on systolic and diastolic LV function,[1–3] and overweight and obesity seem to predispose to the development of HF.[1,4,32] In a study of 5881 Framingham Heart Study participants, Kenchaiah et al[4] found that during 14-year follow-up, for every 1-U increase in BMI, the risk of HF increased by 5% in men and by 7% in women. In fact, in this large epidemiologic cohort, a greater increase in the risk of HF was observed across all the categories of BMI. Other studies also support the association of obesity, especially more severe obesity, with the development of HF.[1,32]

However, despite the known effects of obesity on systolic and diastolic LV function and the epidemiologic data demonstrating a strong link between obesity and HF, many studies have now found that overweight and obese patients with HF have a better prognosis.[1,5–10] In fact, we previously reported a favorable prognosis using high BMI and high percentage of body fat in patients with advanced systolic HF.[6] Recently, investigators have found that patients with HF with higher BMI and higher waist circumference had the best prognosis in advanced HF.[33,34] In a meta-analysis of 9 observational studies including nearly 30,000 patients with HF followed up, on average, for almost 3 years, Oreopoulos et al[7] found that compared with individuals without elevated BMI, overweight and obese patients with HF had reductions in CV mortality (−19% and −40%, respectively) and all-cause mortality (−16% and −33%, respectively). Likewise, in an analysis of BMI and in-hospital survival in

more than 100,000 decompensated patients with HF, high BMI was associated with lower mortality rates; for every 5-U increase in BMI, the risk of mortality was lowered by 10%.[8]

Numerous studies indicate the powerful impact of FIT in predicting prognosis in healthy cohorts and in those with CV diseases, including CHD and HF.[15–18,20,21] Clearly, many studies and meta-analyses have found that FIT is a potent predictor of prognosis in patients with advanced HF.[20,21,35] In fact, the traditional cutoff point for peak $\dot{V}O_2$ of 14 mL O_2 • kg^{-1} • min^{-1} proposed by Mancini et al[23] is still frequently used to divide patients with systolic HF into low- and high-risk subgroups. The present study found that FIT remains an important prognostic marker when the cohort was dichotomized according to a threshold of 14 mL O_2 • kg^{-1} • min^{-1}, further highlighting the importance of this measure in patients with systolic HF. Thus, irrespective of other characteristics, improvement of FIT should be considered a primary treatment goal in this chronic disease population.

Many investigators have suggested that the obesity paradox may at least partly be explained by confounding factors.[12–14] Certainly, we and others have suggested that in cohorts with CHD, patients with high levels of FIT did not seem to have an obesity paradox.[28–30] On the other hand, in higher-risk patients with CHD with low levels of FIT, a strong obesity paradox was present, with overweight and obese individuals having a better prognosis compared with their lean counterparts with low FIT. To our knowledge, the impact of FIT on the obesity paradox has not been assessed in patients with systolic HF. As previously found in patients with CHD, we found that FIT strongly mitigates the impact of overweight/obesity on prognosis in patients with systolic HF. In fact, in patients with HF with more preserved FIT (peak $\dot{V}O_2$ 14 mL O_2 • kg^{-1} • min^{-1}), the age- and sex-adjusted survival rate was equally good regardless of body composition. On the other hand, in patients with HF with low FIT (peak $\dot{V}O_2$ <14 mL O_2 • kg^{-1} • min^{-1}), overweight and obese patients had better age- and sex-adjusted survival rates than did their normal-weight counterparts, thus demonstrating an obesity paradox. Part of the explanation regarding the impact of FIT on survival and the obesity paradox in HF may simply be that patients with HF with high FIT have a good prognosis, regardless of body composition status. On the other hand, patients with HF with low FIT have a considerably worse prognosis, which is particularly noted in leaner patients, which likely represents a “lean paradox” as much as an “obesity paradox,” as we have discussed previously in CHD.[26] Although we did not assess body composition other than BMI in this HF cohort, in recent studies in CHD we found that the most lean patients, those with either low BMI and low percentage of body fat[26] or low body fat and low lean body mass,[27] especially combined with low FIT,[30] represent the group with particularly poor clinical prognoses. We recently reviewed the importance of muscular strength in predicting prognosis in patients with CV diseases.[36] Although we did not assess muscular strength in the present HF cohort, it seems plausible that the leanest patients with HF, especially those with low FIT, may also have poor overall muscular fitness and strength, thus adversely affecting their survival. In fact, we recently reported in a small study of patients with HF with impaired LV ejection fraction that adiposity correlates with greater strength, which may explain some of the protection that obesity has in patients with HF with low FIT.[37]

There are several potential limitations to this study. First, we used a CPX database obtained from major centers, so the study cannot evaluate the obesity paradox in patients with HF not referred for CPX, including those unable to undergo CPX owing to clinical considerations. We did not have data on the location from which patients were referred, although we assume that most lived in the region where CPX took place. In addition, we evaluated body composition by BMI only, and we did not assess other parameters of adiposity (percentage of body fat, waist circumference, etc). Therefore, we were not able to assess peak $\dot{V}O_2$ adjusted for lean body mass, which may be a better indicator of FIT and prognosis in patients with HF with higher body fat, including women and overweight/obese patients with HF; neither did we assess the impact of other CPX variables on prognosis.[22] We also assessed BMI at only one point in time (immediately before CPX), so similar to most studies assessing the obesity paradox, we cannot evaluate changes in weight and, especially, nonpurposeful weight loss, which is known to be associated with a poor prognosis.[38,39] The present patients were not all tracked for the full 5-year tracking period; the mean ± SD follow-up was 25.0±17.5 months. This study is not powered to assess the impact of FIT in patients with severe degrees of obesity. However, we did not evaluate “underweight” patients with HF (BMI <18.5), who are generally known to have a poor prognosis, which may be viewed as a positive attribute. Finally, we did not have data on smoking status, cancer, use of cardiac defibrillators, doses of medications, etc, all factors that could also affect survival in patients with HF.

CONCLUSION

We believe that these data indicate that FIT influences the importance of BMI on HF prognosis. Using BMI to assess risk in patients with systolic HF may be misleading unless FIT is considered. Patients with systolic HF and levels of FIT meeting or surpassing the established threshold of 14 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$ do not seem to have an obesity paradox. On the other hand, in patients with systolic HF and low levels of FIT, a strong obesity paradox is apparent, with overweight and obese patients having a better prognosis than their normal-weight counterparts.

Abbreviations and Acronyms

BMI	body mass index
CHD	coronary heart disease
CPX	cardiopulmonary exercise testing
CV	cardiovascular
FIT	cardiorespiratory fitness
HF	heart failure
LV	left ventricular
VCO_2	carbon dioxide output

VE	minute ventilation
$\dot{V}O_2$	oxygen consumption

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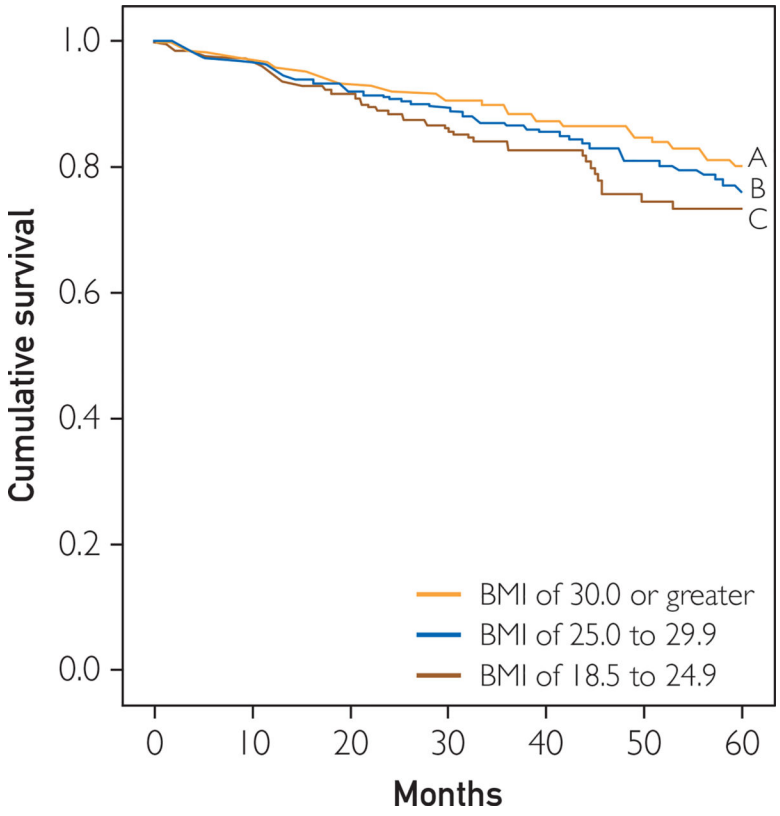

FIGURE 1.

Kaplan-Meier analysis according to body mass index (BMI) in the overall group. Log-rank, 4.8; *P*=.09. Line A shows patients with a BMI of 30.0 or greater. Of 728 patients, 546, 166, and 72 were still alive and tracked at 1, 3, and 5 years, respectively; 63 died. Line B shows patients with a BMI of 25.0 to 29.9. Of 768 patients, 577, 181, and 89 were still alive and tracked at 1, 3, and 5 years, respectively; 81 died. Line C shows patients with a BMI of 18.5 to 24.9. Of 570 patients, 395, 128, and 51 were still alive and tracked at 1, 3, and 5 years, respectively; 68 died.

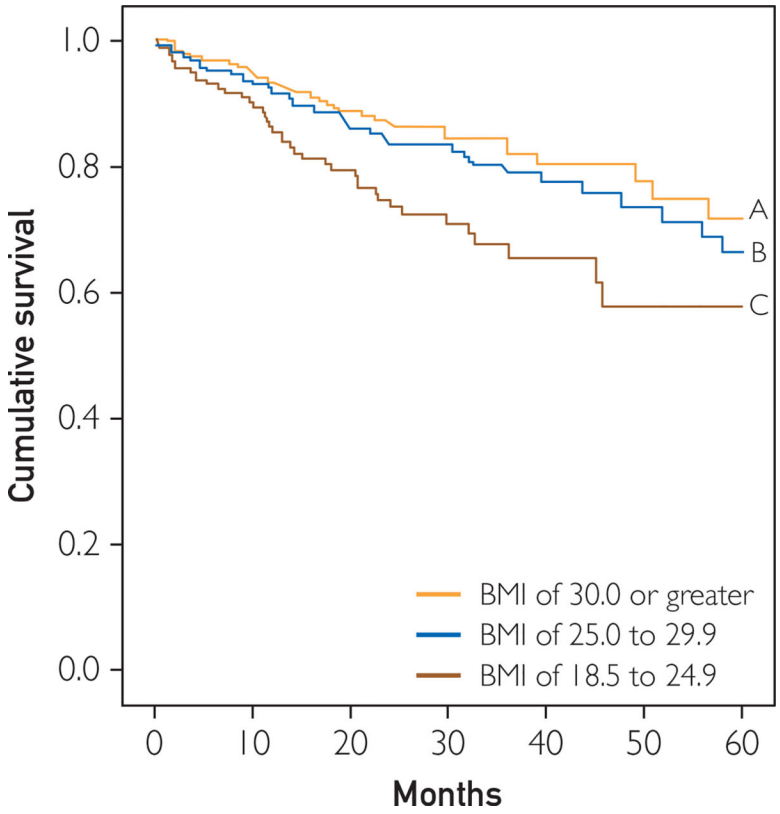

FIGURE 2.

Kaplan-Meier analysis according to body mass index (BMI) in the low cardiorespiratory fitness group (oxygen consumption <14 mL O_2 • kg^{-1} • min^{-1}). Log-rank, 11.7; *P*=.003. Line A shows patients with a BMI of 30.0 or greater. Of 334 patients, 223, 64, and 17 were still alive and tracked at 1, 3, and 5 years, respectively; 41 died. Line B shows patients with a BMI of 25.0 to 29.9. Of 275 patients, 195, 63, and 27 were still alive and tracked at 1, 3, and 5 years, respectively; 45 died. Line C shows patients with a BMI of 18.5 to 24.9. Of 192 patients, 106, 34, and 7 were still alive and tracked at 1, 3, and 5 years, respectively; 42 died.

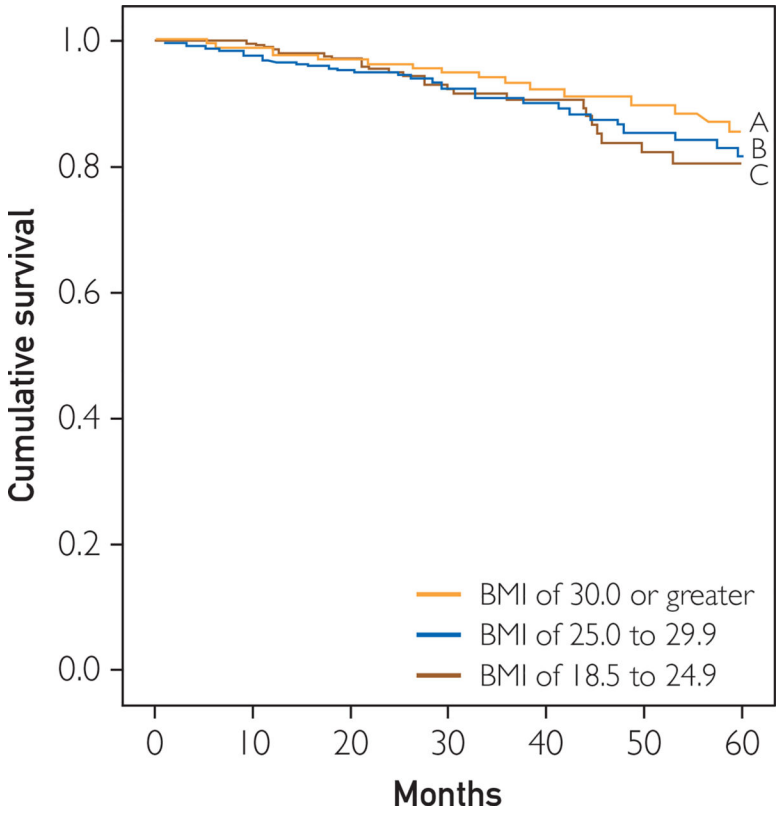

FIGURE 3.

Kaplan-Meier analysis according to body mass index (BMI) in the high cardiorespiratory fitness group (oxygen consumption ≥14 mL O_2 • kg^{-1} • min^{-1}). Log-rank, 1.72; *P*=.42. Line A shows patients with a BMI of 30.0 or greater. Of 394 patients, 322, 101, and 54 were still alive and tracked at 1, 3, and 5 years, respectively; 22 died. Line B shows patients with a BMI of 25.0 to 29.9. Of 493 patients, 381, 117, and 60 were still alive and tracked at 1, 3, and 5 years, respectively; 36 died. Line C shows patients with a BMI of 18.5 to 24.9. Of 378 patients, 288, 93, and 43 were still alive and tracked at 1, 3, and 5 years, respectively; 26 died.

TABLE 1.

Differences in Key Baseline and CPX Variables According to Aerobic Capacity

Variable	Low FIT (n=801)	High FIT (n= 1265)	*P* value
Age (y), mean ± SD	57.5±13.1	55.6±14.5	.003
Male sex, No. (%)	576 (72)	1050 (83)	<.001
BMI, mean ± SD	29.8±6.6	28.0±5.2	<.001
NYHA class, mean ± SD	2.8±0.74	2.2±0.80	<.001
HF ischemic etiology, No. (%)	352 (44)	455 (36)	<.001
LVEF (%), mean ± SD	26.0±9.8	30.1±10.1	<.001
Prescribed ACE inhibitor, No. (%)	505 (63)	759 (60)	.01
Prescribed β-blocker, No. (%)	609 (76)	834 (66)	<.001
Peak RER, mean ± SD	1.10±0.15	1.11±0.13	.02
VE/VCO_2 slope, mean ± SD	39.1±10.9	30.9±6.7	<.001

ACE = angiotensin-converting enzyme; BMI = body mass index; CPX = cardiopulmonary exercise testing; FIT = cardiorespiratory fitness (low: <14 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$; high: ≥14 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$); HF = heart failure; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; RER = respiratory exchange ratio; $\dot{V}O_2$ = oxygen consumption; VE/VCO_2 = minute ventilation/carbon dioxide production.

TABLE 2.

Differences in Key Baseline and CPX Variables According to BMI Classification in Aerobic Capacity Subgroups[a]

Variable	Low FIT (n=801)			High FIT (n=1265)		
	BMI 18.5–24.9 (n=192)	BMI 25.0–29.9 (n=275)	BMI ≥30.0 (n=334)	BMI 18.5–24.9 (n=378)	BMI 25.0–29.9 (n=493)	BMI ≥30.0 (n=394)
Age (y), mean ± SD	60.4±13.6	58.6±12.8	54.8±12.5[b]	55.3±16.5	56.9±14.0	54.3±13.1[c]
Male sex (%)	65	78[d]	70	72[e]	88	86
BMI, mean ± SD	22.6±1.7[f]	27.5±1.5[f]	35.8±5.6[f]	22.5±1.7[f]	27.4±1.4[f]	34.1±4.1[f]
NYHA class, mean ± SD	2.7±0.80	2.8±0.68	2.7±0.75	2.3±0.71	2.2±0.83	2.2±0.84
HF ischemic etiology, No. (%)	90 (47)	135 (49)	127 (38)[g]	132 (35)	207 (42)[h]	118 (30)
LVEF (%), mean ± SD	25.7±10.8	26.2±9.3	26.0±9.7	30.3±10.8	30.7±9.7	29.2±9.8
Prescribed ACE inhibitor, No. (%)	125 (65)	176 (64)	203 (61)	234 (62)	276 (56)[i]	244 (62)
Prescribed β-blocker, No. (%)	134 (70)	206 (75)	271 (81)[j]	241 (64)	315 (64)	272 (69)
Peak RER, mean ± SD	1.10±0.15	1.10±0.16	1.10±0.15	1.12±0.14	1.12±0.13	1.11±0.13
Peak $\dot{V}O_2$ (mL $O_2 \cdot kg^{-1} \cdot min^{-1}$), mean ± SD	10.9±2.3	11.5±2.1[k]	10.8±2.3	22.3±8.2[l]	21.1±6.4[m]	19.5±5.1
VE/VCO_2 slope, mean ± SD	43.7±12.3[n]	38.6±9.7	36.9±10.2	32.5±7.7[o]	30.9±6.6[p]	29.5±5.6

[a] ACE = angiotensin-converting enzyme; BMI = body mass index; CPX = cardiopulmonary exercise testing; FIT = cardiorespiratory fitness (low: <14 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$; high: ≥14 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$); HF = heart failure; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; RER = respiratory exchange ratio; VE/VCO_2 = minute ventilation/carbon dioxide production; $\dot{V}O_2$ = oxygen consumption.

[b] The BMI ≥30.0 group significantly less than the BMI 25.0 to 29.9 (*P*<.001) and BMI 18.5 to 24.9 (*P*<.001) groups.

[c] The BMI ≥30.0 group significantly less than the BMI 25.0 to 29.9 (*P*=.02) group.

[d] The BMI 25.0 to 29.9 group significantly greater than the BMI 18.5 to 24.9 (*P*<.001) and BMI ≥30.0 (*P*<.001) groups.

[e] The BMI 18.5 to 24.9 group significantly less than the BMI 25.0 to 29.9 (*P*<.001) and BMI ≥30.0 (*P*<.001) groups.

[f] All the BMI groups are significantly different in the low and high FIT groups (*P*<.001).

[g] The BMI ≥30.0 group significantly less than the BMI 25.0 to 29.9 (*P*<.001) and BMI 18.5 to 24.9 (*P*=.01) groups.

[h] The BMI 25.0 to 29.9 group significantly greater than the BMI 18.5 to 24.9 (*P*=.008) and BMI ≥30.0 (*P*<.001) groups.

Mayo Clin Proc. Author manuscript; available in PMC 2020 May 22.

[i] The BMI 25.0 to 29.9 group significantly less than the BMI 18.5 to 24.9 (P=.009) and BMI ≥30.0 (P=.02) groups.

[j] The BMI ≥30.0 group significantly greater than the BMI 25.0 to 29.9 (P=.02) and BMI 18.5 to 24.9 (P<.001) groups.

[k] The BMI 25.0 to 29.9 group significantly greater than the BMI 18.5 to 24.9 (P=.03) and BMI ≥30.0 (P=.001) groups.

[l] The BMI 18.5 to 24.9 group significantly greater than the BMI 25.0 to 29.9 (P=.02) and BMI ≥30.0 (P<.001) groups.

[m] The BMI 25.0 to 29.9 group significantly greater than the BMI ≥30.0 group (P=.002).

[n] The BMI 18.5 to 24.9 group significantly greater than the BMI 25.0 to 29.9 (P<.001) and BMI ≥30 (P<.001) groups.

[o] The BMI 18.5 to 24.9 group significantly greater than the BMI 25.0 to 29.9 (P=.002) and BMI ≥30 (P<.001) groups.

[p] The BMI 25.0 to 29.9 group significantly greater than the BMI ≥30.0 group (P=.004).