Impact of obesity as a mortality predictor in high-risk patients with myocardial infarction or chronic heart failure: a pooled analysis of five registries

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Aims	To explore the influence of obesity on prognosis in high-risk patients with myocardial infarction (MI) or heart failure (HF).
Methods and results	Individual data of 21 570 consecutively hospitalized patients from five Danish registries were pooled together. After a follow-up of 10.4 years, all-cause mortality using multivariate model and adjusted hazard ratios (HR) with 95% confidence intervals were calculated. Compared with normal weight [body mass index (BMI) 18.5–24.9 kg/m^2], obesity class II (BMI $\geq$ 35 kg/m^2) was associated with increased risk of death in patients with MI but not HF [HR = 1.23 (1.06–1.44), P = 0.006 and HR = 1.13 (0.95–1.36), P = 0.95] (P-value for interaction = 0.004). Obesity class I (BMI 30–34.9 kg/m^2) was not associated with increased risk of death in MI or HF [HR = 0.99 (0.92–1.08) and 1.00 (0.90–1.11), P > 0.1]. Pre-obesity (BMI 25–29.9 kg/m^2) was associated with decreased death risk in MI but not HF [HR = 0.91 (0.87–0.96), P = 0.0006 and 1.04 (0.97–1.12), P = 0.34] (P-value for interaction = 0.007). Underweight (BMI < 18.5 kg/m^2) patients were in increased death risk regardless of MI or HF [HR = 1.54 (1.35–1.75) and 1.37 (1.18–1.59), P < 0.001].
Conclusion	In patients with MI but not HF, the relationship between BMI and mortality is U-shaped with highest mortality in underweight and obese class II, but lowest in the other BMI classes.
Keywords	Obesity • Body mass index • Myocardial infarction • Heart failure

Introduction

Obesity is associated with an increased risk of mortality and myocardial infarction (MI) in the general population,[1,2] but apparently not in high-risk patients with MI or chronic heart failure (HF), where obesity in several studies appears even to be associated with a favourable prognosis.[3–9] The current recommendation for overweight patients with MI or HF is to lose weight despite the observational studies[10,11] and is based provisionally on the logical implications of improved risk factors with weight loss. Most of the cited studies are based on selected populations participating in randomized controlled trials of patients with MI or HF. The studies' sizes limit their statistical power and most have included only a minority of patients who were severely obese. Recently, a meta-analysis based on summary data of several cohort studies including patients with MI showed an increased risk of cardiovascular, but not of total mortality in severely obese patients.[12] So, the prognosis of high-risk obese and pre-obese patients with MI or HF needs to be further clarified. We therefore pooled a series of registries that specifically included consecutively hospitalized patients with either MI or HF, and who were investigated and analysed in a single core laboratory. This enabled us to study a

large sample of unselected patients with a high risk of death and with sufficient power to study all weight classes. We aimed to examine whether the results were consistent with the previous studies or not and to explore the outcome in a large-scale study with patients characterized by high long-term mortality rates and distinguish between those with MI and HF.

Methods

We combined five registries where patients were included consecutively after an MI or after admission with HF in the same country, and where all participating centres have complete regional coverage for these patients. Each register was formed during screening for a clinical trial, and with a dedicated staff responsible for consecutive screening. These registries were: the Trandolapril in Cardiac Evaluation (TRACE) study, the Danish Investigations of Arrhythmia and Mortality HF (DIAMOND-HF) study, the DIAMOND-Acute Myocardial Infarction (DIAMOND-MI) study, the Bucindolol Evaluation in Acute Myocardial Infarction Trial (BEAT), and finally the Echo Cardiography and Heart Outcome Study (ECHOS). The designs of these studies have been published previously.[13–16] BMI data on TRACE and DIAMOND-HF studies have been published before.[7,17] The TRACE ($n = 6676$), BEAT ($n = 2978$), and DIAMOND-MI ($n = 7974$) registries included patients after MI, while DIAMOND-HF ($n = 5177$) and ECHOS ($n = 2904$) registries included patients with HF. Overall, these registries constituted 26 578 patients. After data combination, the total population of these five registries constituted 25 709 patients. The reason for the fall in the number was due to exclusion of duplicate patients who had participated in one and later in another study. BMI was not available in 4139 patients, i.e. 16% of the total population. The main reason for missing BMI data was the inappropriate recording by the investigators. Finally, a total of 21 570 patients characterized by MI and/or HF with available BMI were left for analyses (Table 1).

In these registries, the baseline demographic values, weight and height of all patients were recorded to calculate BMI. Left ventricular systolic function was evaluated centrally from echocardiograms for all patients. Echocardiograms were recorded on videotape and wall motion index (WMI) was calculated in the same core laboratory by experienced investigators.[18] We used a reverse scoring system for WMI, where WMI multiplied by 30 corresponded roughly to ejection fraction.[19] Creatinine clearance was calculated from serum creatinine values using the Cockroft and Gault method.[20] Information on hypertension, previous ischaemic heart disease (IHD), diabetes, and previous MI was based on patient interview and chart review. The presence or absence of chronic obstructive pulmonary disease (COPD) was decided and reported by the investigator based on patient history and hospital records.

The primary endpoint was death from all causes and was reported by the Danish Central Personal Registry, where all deaths in Denmark were registered within 2 weeks. In May 2006, an interrogation of this register provided a mean follow-up of 10.4 years (range 2.9–16.4) for all surviving patients included in the current study. Of the total of 21 570 registered patients, survival data were unavailable for 51 patients who had emigrated and 20 who had disappeared.

Statistics
The individual patient data reported in the five registries were combined and analysed using the SAS (SAS Institute, Cary, NC, USA) version 9.1. Patients were divided into five pre-specified BMI groups using the World Health Organization (WHO) classification: BMI < 18.5 kg/m^2 denotes underweight, 18.5–24.9 kg/m^2 denotes normal

weight, 25–29.9 kg/m^2 denotes pre-obese, 30–34.9 kg/m^2 denotes obese class I, and ≥35 kg/m^2 denotes obese class II.[21] Continuous baseline variables in different BMI groups were presented as medians with 5% and 95% percentiles and were analysed using Kruskal–Wallis test, while the discrete variables were analysed by chi-squared test.

Univariable Cox analyses were performed to identify survival predictors. Multivariable model was constructed to assess all available covariates: age, gender, BMI, WMI, creatinine clearance, diabetes, history of hypertension, previous MI, history of IHD, HF, smoking, and COPD (Table 2), but use of medical treatment was not included in the model because of the potential risk of selection bias as patients were not randomized to their treatment regime. Each BMI group was entered as an independent variable using normal weight as reference. Relative risks with 95% confidence intervals were calculated as hazard ratios obtained from the Cox proportional hazard models. Thus, adjusted hazard ratios with 95% CI for all baseline variables except for use of medical treatment were generated from this model. The final model was checked for assumptions. The proportional hazard assumption was checked graphically [log survival vs. log(−log survival distribution function)] as well as studying a time dependent variable (lifetime × variable). No significant deviations from the proportional hazard assumption were identified. Linearity was studied by adding, to the model, quintiles of a variable along with the continuous variable. If the set of quintiles were without importance, linearity was accepted. Statistical significant deviations were found for creatinine clearance, but the importance of BMI in subgroups of creatinine clearance was nearly identical and creatinine clearance was therefore used as a continuous variable. Linearity of BMI was studied similarly using the predefined groups. The deviation from linearity was significant with $P < 0.0001$. Finally, interaction was tested with a likelihood ratio test in the final multivariable model using a P-value of 0.01 as significant. There was significant interaction with WMI driven by the important difference between WMI in patients with and without underweight.

The survival plots for the five BMI groups were constructed by the Kaplan–Meier method.

Since the BEAT registry provided creatinine clearance only in a minority of patients, the multivariable analyses were performed both with and without the inclusion of this registry. The five registries separately and the three MI registries (TRACE, DIAMOND-MI, and BEAT) vs. the two HF registries (DIAMOND-HF and ECHOS) were entered in the model as class variables. Interaction analyses were performed to explore heterogeneity. Furthermore, the groups of MI and HF registries were entered in the multivariable model also as 0-1 variables to test any change in the outcomes compared with the original model. All P-values are two-tailed and values below 0.05 were considered statistically significant.

Results

Baseline demography and characteristics of the five registries and that of the analysed 21 570 patients' individual data with available BMI groups are presented in Tables 1 and 2, respectively. Of the total population, 15 091 patients had MI and 6479 had HF. There were significant differences between the five BMI groups. Compared with the normal BMI group, the underweight BMI group included a significantly higher number of older patients, females, and smokers. These patients were generally characterized by lower WMI and lower creatinine clearance, and had more often HF, IHD, and COPD. Conversely, obese class I and II included significantly higher numbers of younger patients, who were more

Table 1 Baseline demography and characteristics of the included five registries

Characteristic	TRACE	DIAMOND-HF	DIAMOND-MI	BEAT	ECHOS
Total number	6676	5177	7974	2978	2904
Patients with available BMI	6169	4412	6936	1986	2067
Register period (year)	1990–1992	1993–1996	1993–1996	1998–1999	2001–2003
Follow-up period (year) median (range)	14.8 (13.9–16.4)	11.3 (10.4–12.5)	10.9 (9.9–12.5)	7.2 (6.4–8.3)	4.5 (2.9–5.5)
All-cause mortality (%)	4945 (74)	4349 (84)	4433 (56)	1267 (43)	1538 (53)
Age (year) median (range)	68.5 (47–84)	73.0 (53–86)	68.0 (46–83)	68.7 (46–86)	75.0 (53–89)
Gender (male) %	67.5	59.9	69.8	67.3	60.2
Body mass index (kg/m^2)	25.4 (20–33)	25.4 (19–35)	25.8 (20–33)	25.9 (20–34)	25.8 (19–36)
Wall motion index (median)	1.4 (0.7–2.0)	1.4 (0.6–2.0)	1.6 (0.9–2.0)	1.6 (0.8–2.0)	1.4 (0.5–2.0)
Creatinine clearance (mL/min)	66.2 (30–118)	52.4 (23–106)	66.5 (29–123)	NA	57.6 (24–126)
History of diabetes (%)	10.8	16.2	10.3	13.2	15.2
History of hypertension (%)	22.6	24.4	23.9	24.1	26.9
History of IHD (%)	43.7	54.3	40.6	34.6	40.8
History of COPD (%)	11.5	22.5	9.5	9.6	24.0
Previous MI (%)	23.4	33.3	20.4	22.3	26.8
HF (%)	53.6	100	40.9	44.5	100
Smokers (%)	51.5	34.0	49.7	45.2	29.1

TRACE, Trandolapril in Cardiac Evaluation study; DIAMOND-HF, the Danish Investigations of Arrhythmia and Mortality HF study; DIAMOND-MI, the DIAMOND-Acute Myocardial Infarction study; BEAT, the Bucindolol Evaluation in Acute Myocardial Infarction Trial; ECHOS, Echo Cardiography and Heart Outcome Study; BMI, body mass index; COPD, chronic obstructive pulmonary disease; IHD, ischaemic heart disease; HF, heart failure; MI, myocardial infarction; NA, not available; WMI, wall motion index. Age, BMI, WMI, and creatinine clearance are presented as medians with 5% and 95% percentiles. The other variables are presented as numbers with percentages.

Table 2 Baseline characteristics of all patients in the five registries according to weight classes

Variable	Under weight (*n* = 638)	Normal weight (*n* = 8600)	Pre-obese (*n* = 8854)	Obese class I (*n* = 2714)	Obese class II (*n* = 764)	*P*-value
Age (year)	75.5 (54–89)	71.4 (48–86)	68.3 (47–84)	66.6 (46–82)	63.4 (45–80)	<0.001
Gender (male)	175 (27.5)	5254 (61.1)	6665 (75.3)	1923 (70.9)	447 (58.6)	<0.001
Body mass index (kg/m^2)	17.4 (14.5–18.4)	22.9 (19.5–24.7)	27.0 (25.1–29.4)	31.5 (30.1–34.4)	37.2 (35.1–46.6)	<0.001
Wall motion index	1.3 (0.5–2.0)	1.4 (0.6–2.0)	1.5 (0.7–2.0)	1.6 (0.7–2.0)	1.6 (0.7–2.0)	<0.001
Creatinine clearance (mL/min)	36.4 (17.1–71.5)	53.2 (24.7–96.6)	68.1 (32.2–117.0)	80.6 (38.1–137.9)	98.1 (45.7–178.6)	<0.001
Diabetes	43 (6.8)	883 (10.3)	1041 (11.8)	502 (18.5)	184 (24.0)	<0.001
History of hypertension	117 (18.4)	1726 (20.1)	2185 (24.7)	835 (30.8)	295 (38.5)	<0.001
Previous MI	182 (28.5)	2148 (25.0)	2339 (26.4)	634 (23.4)	166 (21.7)	<0.001
HF	483 (75.9)	5426 (63.1)	5181 (58.5)	1751 (64.6)	543 (70.9)	<0.001
Smokers	332 (52.6)	4060 (47.8)	3836 (43.9)	1083 (40.2)	292 (38.6)	<0.001
COPD	174 (27.3)	1303 (15.2)	1076 (12.2)	404 (14.9)	143 (18.7)	<0.001
IHD	291 (45.7)	3762 (43.8)	4035 (45.6)	1152 (42.4)	312 (40.7)	0.004
ACE-I at discharge[a]	209 (44.1)	2481 (41.4)	2480 (39.7)	889 (43.3)	296 (47.4)	<0.001
Beta-blocker at discharge[a]	65 (28.6)	1042 (40.4)	1281 (50.1)	407 (47.1)	132 (44.6)	<0.001

Age, body mass index, wall motion index and creatinine clearance are presented as medians with 5% and 95% percentiles. The other variables are presented as numbers with percentages. ACE-I, angiotensin-converting enzyme-inhibitor; COPD, chronic obstructive pulmonary disease; CI, confidence interval; HF, heart failure; IHD, ischaemic heart disease; MI, myocardial infarction; *N*, number.
[a]Information on use of ACE-I and beta-blocker at discharge was available in 15 392 and 6523 patients, respectively.

often male, with higher prevalence of diabetes and hypertension and a significant number of them used life-prolonging agents like angiotensin-converting enzyme-inhibitors (ACE-I) and beta-blockers.

Analysis of mortality

In the univariable model, only the underweight class was associated with a clearly increased death risk [HR = 1.74 (1.57–1.92), $P <$ 0.0001], whereas other BMI groups appeared similar. In the multivariable model (*Table 3*), underweight class was again associated with increased mortality risk [HR = 1.46 (1.32–1.60), $P <$ 0.001], but now the obese class II was also associated with an independent increased mortality risk [HR = 1.15 (1.03–1.30), P = 0.013] (*Figure 1*). The relationship between BMI and mortality risk followed a U-shaped curve with the lowest mortality in normal weight, pre-obese, and obese class I patients and with the risk of death highest in the underweight and obese class II. The analysis of the subgroup of patients with MI showed a similar pattern (*Table 3*) and followed a U-shaped curve (*Figure 2A*) with a decreased death risk in pre-obese class [HR = 0.91 (0.87–0.96)] and increased death risk for underweight [HR = 1.54 (1.35–1.75), $P <$ 0.001] and for obese class II [HR = 1.23 (1.06–1.44), P = 0.0065] (*Table 3*). In contrast to MI, the analysis on HF patients showed an increased death risk only in underweight class [1.37 (1.18–1.59), $P <$ 0.001] without any increased death risk in obese class I [HR = 1.00 (0.90–1.11), P = 0.96] or obese class II [HR = 1.13 (0.95–1.36), P = 0.14] (*Table 3* and *Figure 2B*). Age, male gender, WMI, creatinine clearance, presence of diabetes, history of hypertension, IHD, previous MI, smoking, and COPD were all independent mortality predictors (*Table 3*).

Interaction analyses

In the multivariable model, the interaction analyses were insignificant between BMI groups and all included covariates except for WMI. Importantly, the interactions were not significant for age, gender, and admission year in any of the BMI groups. There was a significant interaction between underweight and WMI ($P <$ 0.001) indicating that with increasing WMI, the HR increased from 1.15 (0.92–1.44) in patients with WMI < 0.8 to 1.87 (1.60–2.20) in patients with WMI > 1.6.

There was a significant interaction between BMI groups and MI/HF registries as demonstrated in *Figure 2A* and *B*. The interactions were significant for pre-obese (P = 0.007) and obese class II patients (P = 0.004).

There was insignificant interaction between MI and HF registries (P = 0.207) and also between the five registries separately (P = 0.057).

Other analyses

Subgroup analysis in patients with normal creatinine clearance showed that underweight was associated with an HR of 1.79 (1.31–2.44), $P <$ 0.001 when compared with normal weight patients. The interaction between BMI and WMI only in the subgroup of HF patients showed that WMI > 1.2 (non-systolic left ventricle dysfunction) was associated with a significant increased mortality risk in underweight patients [HR = 1.85 (1.48–2.31), $P <$ 0.001], while WMI ≤ 1.2 (systolic left ventricle dysfunction)

was associated with increased mortality risk in obese class II patients [HR = 1.45(1.11–1.90), P = 0.0057]. Thus, the relationship between BMI and WMI in HF patients with WMI ≤ 1.2 was U-shaped as in the MI patients.

Because the BEAT registry did not provide serum creatinine levels in all patients, the results were repeated with and without inclusion of the BEAT registry. The results for BMI groups were unchanged. The results were also unchanged after inclusion of groups of MI or HF registries as 0–1 variables in the multivariable model.

Analyses for BMI linearity in the whole population showed a significant deviation with a chi-square value of 52 and $P <$ 0.001. The MI population showed a clear deviation from linearity with a chi-square value of 56 and $P <$ 0.001, which was in concordance with a U shape in the multivariable model results. The deviation from linearity was less clear in HF population with a chi-square value of 12 and P = 0.016.

Discussion

The important finding of this pooled analysis of unselected consecutive hospitalized patients is that both underweight and obese class II patients with MI do have increased death risk. This finding is consistent with some previous studies that have shown an increased risk of total mortality associated with high BMI,[22,23] but simultaneously inconsistent with other studies which have shown an inverse correlation.[7,24–26] This finding is also in disagreement with the result of the meta-analysis by Romero-Corral,[12] who found a decreased total mortality risk in mild and severe obese patients. However, Romero-Corral demonstrated that severe obese MI patients, but not mild obese or overweight ones, had still an increased cardiovascular mortality. The authors attributed their finding to a possible lack of the discriminatory power of BMI measurements to differentiate between body fat and lean mass. The different finding in our study may reflect the adequate statistical power provided by the systematic inclusion of unselected consecutive populations with a detailed record of risk factors and a long period of follow-up.

Recently, it has also been suggested that waist or waist-to-hip ratio (WHR) are stronger predictors of adverse cardiovascular events than BMI.[2] In our study, BMI and not WHRs were available in the majority of patients, but BMI was able to discriminate the impact of severe levels of obesity. It is, however, likely that the BMI value in the overweight or obese class I group in particular includes a wide range of patients with different proportions of body fat for their BMI and with very different degrees of abdominal obesity. The current results cannot therefore be used to reassure the moderately overweight about their risk, which seems more responsive to increases in body fat and its abdominal distribution.

The other finding of the current study was that obesity in HF in the same cohort was not associated with increased death risk, which was consistent with some previous studies.[3,4,8] Importantly, the previously described paradox that obese patients with HF have a lower mortality is not substantiated by our data. There was a strong tendency towards a U-shaped relation between BMI groups and hazard of death (*Figure 2B*). Secondly, we have in previously published data on the DIAMOND-HF study by

Table 3 Results of the multivariable analyses for the whole population and subgroups with myocardial infarction and heart failure according to weight classes and other predictors

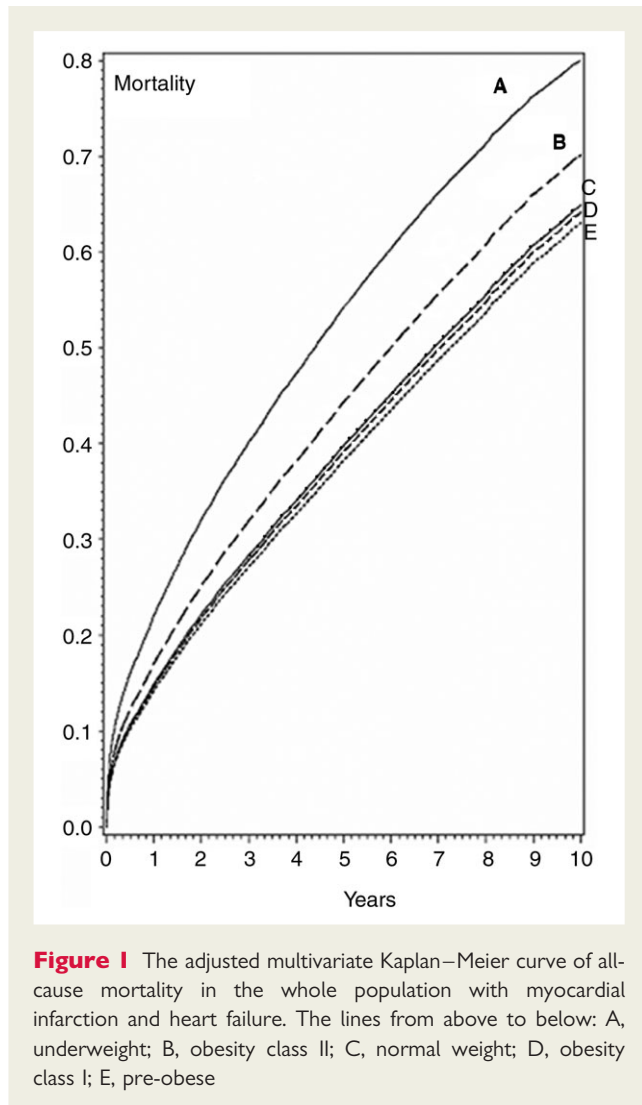| Variable	Hazard ratio (95% CI)	Parameter estimate	Standard error of estimate	P-value
Body mass index groups compared with normal weight				
Underweight—all	1.46 (1.32–1.60)	0.379	0.049	<0.001
Underweight—MI	1.54 (1.35–1.75)	0.434	0.065	<0.001
Underweight—HF	1.37 (1.18–1.59)	0.318	0.074	<0.001
Normal weight (all, MI, HF)	1.00	–	–	–
Pre-obese—all	0.95 (0.91–0.99)	−0.047	0.021	0.024
Pre-obese—MI	0.91 (0.87–0.96)	−0.088	0.025	0.0006
Pre-obese—HF	1.04 (0.97–1.12)	0.042	0.037	0.34
Obese class I—all	0.99 (0.93–1.06)	−0.006	0.033	0.84
Obese class I—MI	0.99 (0.92–1.08)	0.115	0.041	0.94
Obese class I—HF	1.00 (0.90–1.11)	0.002	0.054	0.96
Obese class II—all	1.15 (1.03–1.30)	0.147	0.059	0.013
Obese class II—MI	1.23 (1.06–1.44)	0.213	0.078	0.0065
Obese class II—HF	1.13 (0.95–1.36)	0.128	0.092	0.14
Other important predictors of mortality in the whole population				
Age	1.04 (1.04–1.05)	0.046	0.001	<0.001
Gender (male)	1.19 (1.15–1.24)	0.176	0.020	<0.001
Wall motion index	0.57 (0.55–0.60)	−0.558	0.021	<0.001
Creatinine clearance	0.99 (0.99–0.99)	−0.009	0.001	<0.001
Heart failure	1.73 (1.65–1.81)	0.547	0.023	<0.001
Diabetes mellitus	1.51 (1.43–1.59)	0.409	0.026	<0.001
History of hypertension	1.12 (1.08–1.17)	0.117	0.021	<0.001
Previous MI	1.14 (1.08–1.20)	0.132	0.025	<0.001
Smoking	1.148 (1.10–1.19)	0.138	0.019	<0.001
History of IHD	1.13 (1.08–1.19)	0.129	0.023	<0.001
History of chronic obstructive pulmonary disease	1.43 (1.36–1.49)	0.354	0.024	<0.001

CI, confidence interval; IHD, ischaemic heart disease; MI, myocardial infarction; HF, heart failure.

Gustafsson[17] highlighted the importance of the interaction between obesity and systolic dysfunction that may increase death risk. This finding was reaffirmed in the current study even after combining the ECHOS study with the DIAMOND-HF study. The increased mortality risk in underweight HF patients with WMI > 1.2, as well as in obese class II with WMI < 1.2 is important. As HF, in contrast to MI, is a complex syndrome encompassing patients with both systolic and non-systolic dysfunction, it may be important to differentiate these categories concerning risk factors, though the prognosis is generally poor. Patients with HF and systolic dysfunction (WMI ≤ 1.2) overlap many characteristics with those having MI and systolic dysfunction and the management of both is similar. Interestingly, the hazard of death for HF patients with systolic dysfunction followed a U-shaped curve, which was similar to that one for MI patients in this study. This may indicate a possible common mechanism behind the increased death risk for both categories. Our finding is in contrast to that described by authors of the Candesartan in Heart Failure: Assessment of Reduction in Mortality and morbidity (CHARM) study.[27]

In the current study, obese patients were more often younger males, had better left systolic ventricular function, better renal function, and had fewer episodes of previous MI, HF, and IHD. The obese patients did have more cases of diabetes and hypertension, but it is likely that these risks were ameliorated by the coexisting use of the well-documented medications including ACE-I and beta-blockers that improve survival. The adjusted multivariable models highlight the importance of other risk factors in determining mortality. This was re-emphasized by our reaffirmation, from this large data set, of the importance of age as a strong predictor of mortality as in both the general population and in those with MI or HF. Furthermore, a history of hypertension, diabetes, left ventricular dysfunction, COPD, smoking, previous MI, and low creatinine clearance were all predictors of mortality.

These analyses imply that obesity needs to be considered an important risk factor in patients with MI or HF with systolic dysfunction, and we find no evidence of any protective effect of obesity. This analysis may also emphasize the importance of studying a large, high-risk population over a prolonged period of time (10.4 years) and having well-documented left ventricular systolic function by analysing all the data in a single core laboratory. The current study was also statistically powerful, given a mortality rate of more than 50%. Nevertheless, prospective interventional

Figure 1 The adjusted multivariate Kaplan–Meier curve of all-cause mortality in the whole population with myocardial infarction and heart failure. The lines from above to below: A, underweight; B, obesity class II; C, normal weight; D, obesity class I; E, pre-obese

Figure 2 The results of the adjusted multivariate all-cause mortality showed U-shaped form of curve in myocardial infraction (*A*) but not in heart failure patients (*B*)

trials are necessary to investigate whether weight reduction in high-risk obese patients does indeed reduce the risk of death.

Limitations of the study

Despite the pooling of five registries' data, this analysis was not a systematic review of all available studies in the literature. We also recognized the possibility of heterogeneity but the multi-variate analyses showed no statistically significant heterogeneity either between the five studies individually or between the MI and HF populations. By including patients without discounting the first few years of observation, we may also have confounded the analyses of all-cause mortality particularly in underweight and some normal weight patients who might have had conditions such as cancer which could have both induced significantly recent falls in BMI and amplified the observed mortality rate of the groups. This is likely to be more important than BMI changes during the follow-up period, which in practice are most likely then to induce an underestimation of the prognostic importance of BMI. The exclusion of a significant number of patients (16% of the total) with unavailable BMI from the analyses has probably
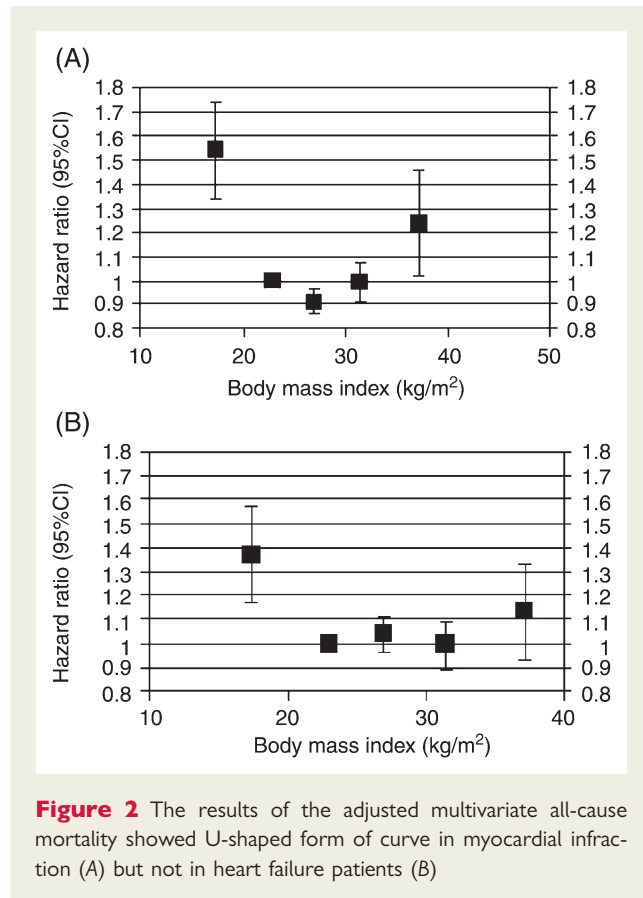
caused some selection bias. The five registries had also different inclusion periods ranging from 1990 to 2001, which may with respect to the changes in the demography and treatment strategies by time have confounded the results. Finally, fasting lipids was not included as a variable in the study.

Conflict of interests: C.T.-P. and W.P.T.J. are on the steering committee of a trial with the weight-reducing compound Sibutra-mine sponsored by Abbott Pharmaceutical Company. W.P.T.J. has also received honoraria or other support for his organization from Abbott, Roche Laboratories, and Sanofi-aventis. Lars Kober has received honoraria and is the advisory board member in Novartis. Other authors reported no relevant potential interests of conflict.

References

1. Calle EE, Thun MJ, Petrelli JM, Rodriguez C, Heath CW. Body-mass index and mortality in a prospective cohort of U.S. adults. *N Engl J Med* 1999;**341**:1097–1105.
2. Yusuf S, Hawken S, Ounpuu S, Bautista L, Franzosi L, Commerford MG, Lang P, Rumboldt CC, Onen Z, Lisheng CL, Tanomsup SL, Wangai P, Razak F, Sharma AM, Anand SS; on behalf of the INTERHEART Study investigators. Obesity and the risk of myocardial infarction in 27,000 participants from 52 countries: a case-control study. *Lancet* 2005;**366**:1640–1649.
3. Horwich TB, Fonarow GC, Hamilton MA, MacLellan WR, Woo MA, Tillisch JH. The relationship between obesity and mortality in patients with heart failure. *J Am Coll Cardiol* 2001;**38**:789–795.

4. Davos CH, Doehner W, Rauchhaus M, Cicoira M, Francis DP, Coats AJ, Clark AL, Anker SD. Body mass and survival in patients with chronic heart failure without cachexia: the importance of obesity. *J Card Fail* 2003;**9**:29–35.

5. Mosterd A, Cost B, Hoes AW, de Bruijne MC, Deckers JW, Hofman A, Grobbee DE. The prognosis of heart failure in the general population: The Rotterdam Study. *Eur Heart J* 2001;**22**: 1318–1327.

6. Lissin LW, Gauri AJ, Froelicher VF, Ghayoumi A, Myers J, Giacommini J. The prognostic value of body mass index and standard exercise testing in male veterans with congestive heart failure. *J Card Fail* 2002;**8**:206–215.

7. Kragelund C, Hassager C, Hildebrandt P, Torp-Pedersen C, Kober L. Impact of obesity on long-term prognosis following acute myocardial infarction. *Int J Cardiol* 2005;**98**:123–131.

8. Bozkurt B, Deswal A, Housten TX. Obesity as a prognostic factor in chronic symptomatic heart failure. *Am Heart J* 2005;**150**: 1233–1239.

9. Cicoria M, Maggioni AP, Latini R, Barlera S, Carreta E, Janosi A, Soler JS, Anand I, Cohn JN. Body mass index, prognosis and mode of death in chronic heart failure: results from the Valsartan Heart Failure Trial. *Eur Heart J* 2007;**9**:397–402.

10. Swedberg K, Cleland J, Dargie H, Drexler H, Follath F, Komajda M, Tavazzi L, Smiseth OA, Gavazzi A, Haverich A, Hoes A, Jaarsma T, Korewicki J, Levy S, Linde C, Lopez-Sendon JL, Nieminen MS, Pierard L, Remme WTask force for the diagnosis treatment of chronic heart failure of the European Society of Cardiology. [Guidelines for the Diagnosis and Treatment of Chronic Heart Failure: executive summary (update 2005)]. *Eur Heart J* 2005;**26**: 1115–1140.

11. Hunt SA. ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to update the 2001 Guidelines for the Evaluation and Management of Heart Failure). *J Am Coll Cardiol* 2005;**46**:e1–e82.

12. Romero-Corral A, Montori VM, Somers VK, Korinek J, Thomas RJ, Allison TG, Mookadam F, Lopez-Jimenez F. Association of bodyweight with total mortality and with cardiovascular events in coronary artery disease: a systematic review of cohort studies. *Lancet* 2006;**368**:666–678.

13. Kober L, Torp-Pedersen C, Carlsen JE, Bagger H, Eliasen P, Lyngborg K, Videbaek J, Cole DS, Auclert L, Pauly NC. A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. Trandolapril Cardiac Evaluation (TRACE) Study Group. *N Engl J Med* 1995;**333**:1670–1676.

14. Danish Investigations of Arrhythmia and Mortality ON Dofetilide. Dofetilide in patients with left ventricular dysfunction and either heart failure or acute myocardial infarction: rationale, design, and patient characteristics of the DIAMOND studies. *Clin Cardiol* 1997;**20**:704–710.

15. Torp-Pedersen C, Kober L, Ball S, Hall A, Brendorp B, Ottesen M, Berning J, Jensen G, Hampton J, Zilles P, Eberle S, Carlsen J. The incomplete bucindolol evaluation in acute myocardial infarction Trial (BEAT). *Eur J Heart Fail* 2002;**4**:495–499.

16. Cleland JG, Coletta AP, Clark AL, Velavan P, Ingle L. Clinical trials update from the European Society of Cardiology Heart Failure meeting and the American College of Cardiology: DARBEPOETIN ALFA study, ECHOS, and ASCOT-BPLA. *Eur J Heart Fail* 2005;**7**: 937–939.

17. Gustafsson F, Kragelund CB, Torp-Pedersen C, Seibaek M, Buechardt H, Akkan D, Thune JJ, Kober LDIAMOND study group. Effect of obesity and being overweight on long-term mortality in congestive heart failure: influence of left ventricular systolic function. *Eur Heart J* 2005;**26**:58–64.

18. Kober L, Torp-Pedersen C, Carlsen J, Videbaek R, Egeblad H. An echocardiographic method for selecting high risk patients shortly after acute myocardial infarction, for inclusion in multi-centre studies (as used in the TRACE study). TRAndolapril Cardiac Evaluation. *Eur Heart J* 1994;**15**:1616–1620.

19. Schiller NB, Shah PM, Crawford M, De Marie A, Devereux R, Feigenbaum H, Gutgessel H, Reichek N, Sahn D, Schnittger I. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on quantitation of two-dimensional echocardiograms. *J Am Soc Echocardiogr* 1989;**2**:358–367.

20. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976;**16**:31–41.

21. Global database on body mass index. Body mass index classification of WHO. http://www.who.int/bmi/index.jsp?introPage= intro_3.html (April 2007).

22. Kaplan RC, Heckbert S, Furberg CD, Psaty BM. Predictors of subsequent coronary events, stroke, and death among survivors of first hospitalized myocardial infarction. *J Clin Epidemiol* 2002;**55**: 654–664.

23. Rana JS, Mukamal KJ, Morgan JP, Muller JE, Mittleman MA. Obesity and the risk of death after acute myocardial infarction. *Am Heart J* 2004;**147**:841–846.

24. Widlansky ME, Sesso HD, Rexrode KM, Manson JE, Gaziano JM. Body mass index and total and cardiovascular mortality in men with a history of cardiovascular disease. *Arch Intern Med* 2004; **164**:2326–2332.

25. Kennedy LM, Dickstein K, Anker SD, Kristianson K, Willenheimer R. The prognostic importance of body mass index after complicated myocardial infarction. *J Am Coll Cardiol* 2005; **45**:156–158.

26. Krumholz HM, Chen J, Chen YT, Radford MJ. Predicting one-year mortality among elderly survivors for an acute myocardial infarction: results of the Cooperative Cardiovascular Project. *J Am Coll Cardiol* 2001;**38**:453–459.

27. Satish Kenchaiah, Pocock S, Wang D, Finn PV, Zornoff LAM, Skali H, Pfeffer MA, Yusuf S, Swedberg K, Michelson EL, Granger CB, McMurray JJV, Solomon SDfor the CHARM study. Body mass index and prognosis in patients with chronic heart failure. *Circulation* 2007;**116**:627–636.