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ORIGINAL PAPER

Mean BMI, visit-to-visit BMI variability and BMI changes during follow-up in patients with acute myocardial infarction with systolic dysfunction and/or heart failure: insights from the High-Risk Myocardial Infarction Initiative

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Abstract

Background In patients with acute myocardial infarction (MI), BMI < 18.5 kg/m^2 and a decrease in BMI during follow-up have been associated with poor prognosis. For BMI ≥ 25 kg/m^2, an "obesity paradox" has been suggested. Recently, high visit-to-visit BMI variability has also been associated with poor prognosis in patients with coronary artery disease.

Aims To simultaneously evaluate several BMI measurements and study their association with cardiovascular (CV) outcomes in a large cohort of patients with acute myocardial infarction (MI) and left ventricular (LV) systolic dysfunction, heart failure (HF) or both.

Methods The high-risk MI dataset is pooled from four trials: CAPRICORN, EPHESUS, OPTIMAAL and VALIANT. Mean BMI, change from baseline, and variability were assessed during follow-up. The primary outcome was CV death. Cox-proportional hazard models were performed to study the association between the various BMI parameters and outcomes (median follow-up = 1.8 years).

Results A total of 12,719 patients were included (72% male, mean age 65 ± 11 years). Mean, change and visit-to-visit variability in BMI had a non-linear association with CV death ($P < 0.001$). Mean BMI < 26 kg/m^2 (vs. ≥ 26–35 kg/m^2) and BMI decrease during follow-up were independently associated with CV death (adjusted HR 1.32, 95% CI 1.16–1.51, $P < 0.001$ and adjusted HR 1.57, 95% CI 1.40–1.76, $P < 0.001$, respectively). Low and high BMI variability (< 2% and > 4%) were associated with increased event-rates, but lost statistical significance in sensitivity analysis including patients with ≥ 5 measurements or excluding patients with HF hospitalization, suggesting that BMI variability may be particularly associated with HF hospitalizations.

Conclusion Mean BMI < 26 kg/m^2 and a BMI decrease during follow-up were independently associated with CV death in patients with MI and LV systolic dysfunction, HF or both. These associations likely reflect poorer patient status and causality cannot be inferred.

Keywords Acute myocardial infarction · Systolic dysfunction · Body mass index · Prognosis · Variability

Introduction

In patients with acute myocardial infarction (MI), a low body mass index (BMI) (< 18.5 kg/m^2) is associated with poor outcomes [1, 2]. The association between high BMI (> 25 kg/m^2) and outcome is, however, less clear with either a similar [3, 4] or lower risk [5–8] compared to a normal BMI (18–25 kg/m^2). This phenomenon is also observed in heart failure (HF) patients [9, 10]. Based on these studies,

All authors are members of the High-Risk Myocardial Infarction Database Initiative.

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an "obesity paradox" has been suggested where obesity in patients with established cardiovascular (CV) disease may be protective in contrast to the general population [11–13]. An important concern here is reverse causality; i.e., it is not that a low BMI causes mortality, but rather that sicker patients have a lower BMI. In keeping with the above, weight loss in patients with acute MI and signs of HF has been associated with poor outcomes [14]. However, there may be a difference in prognosis between intentional and unintentional weight loss. For example, patients with coronary artery disease (CAD) who lost weight during cardiac rehabilitation (vs. those who did not) had better outcomes [15].

In a recent study, higher body weight visit-to-visit variability in patients with established coronary artery disease was associated with a higher rate of CV events [16]. However, the associations of visit-to-visit variability in BMI with outcomes have not been assessed in patients with acute MI complicated by systolic dysfunction, HF or both. To date, no studies have simultaneously evaluated mean BMI during follow-up and changes in BMI in acute MI patients complicated by HF.

The aim of the present study is to assess the association between mean BMI, change in BMI through follow-up and visit-to-visit variability in BMI and CV death in a large cohort of patients with acute MI complicated by left ventricular (LV) systolic dysfunction, HF or both.

Methods

Study population

The High-Risk MI initiative consists of a previously published cohort of pooled patient data derived from four randomized, controlled, double-blind clinical trials in high-risk survivors of MI [17]. The main objective of this initiative was to use this large database to perform analyses of long-term outcomes in MI patients with LV dysfunction and/or HF. The cohorts included in this high-risk MI database are: the effect of Carvedilol on Outcome after Myocardial Infarction in Patients with Left Ventricular Dysfunction trial (CAPRICORN) [18, 19], the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) [20, 21], the Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan (OPTIMAAL) [22, 23], and the Valsartan in Acute Myocardial Infarction trial (VALIANT) [24, 25]. Detailed characteristics of the cohorts included in this initiative have previously been published [17]. Each trial enrolled patients with LV systolic dysfunction, HF or both between 12 h and 21 days after MI. Baseline laboratory measurements and demographic data were obtained at the time of inclusion in the trials. All studies were approved by the ethical committees in their respective centers and all participants gave written informed consent to participate in the studies.

BMI

BMI was defined as body mass (in kilograms) divided by the square of body height (in meters) and expressed in units of kg/m^2. Mean BMI levels were calculated from the BMI assessments at each follow-up visit. Change in BMI was calculated as the percentage change between the last available measurement and baseline measurement. BMI variability was calculated as the coefficient of variation, which is the ratio of the standard deviation (SD) to the mean [CV = (SD/mean) × 100] (Pearson's correlation coefficient between the coefficient of variation and the SD is 0.92, such that they can be used interchangeably). Importantly, only BMIs which were measured prior to a given event were used for the calculation of BMI variability to be used in the models focusing on this event. For instance, for CV hospitalization, BMI recorded after the occurrence of CV hospitalization was not used to create BMI variability. Conversely, all BMI measurements (i.e., the BMI measured prior to CV hospitalization and all subsequent BMI measurements) were used to generate the BMI variability variable used in models focusing on mortality.

Endpoints

The primary endpoint of the present study was CV mortality. Secondary endpoints were all-cause mortality, a composite of CV death or CV hospitalization, and CV hospitalization. Patients with at least two BMI measurements during follow-up were included in the analyses. Endpoints were independently adjudicated in the respective trials.

Statistical analysis

Categorical data are presented as frequencies and percentages and compared using Fisher's exact test. Continuous variables are reported as mean ± SD or median with interquartile range (IQR) and compared using Student's *t* tests (or ANOVA) or Mann–Whitney *U* (or Kruskal–Wallis) tests, as appropriate. Linearity between mean, percentage change and visit-to-visit variability and the hazard of outcome was assessed using restrictive cubic splines with 5 knots (5th, 25th, 50th, 75th, and 95th percentile), shown in the Supplemental Fig. 1. The splines were adjusted for the same variables as in the Cox regression analyses (see below). The association of the mean BMI with the studied outcomes was non-linear. Patients with a mean BMI < 26 kg/m^2 and those with a mean BMI > 35 kg/m^2 had higher event rates, compared with patients with a BMI between 26 and 35 kg/m^2.

There was a linear association between low (< 26 kg/m^2) and high BMI (> 35 kg/m^2) and outcome, i.e., patients with a mean BMI of 20 kg/m^2 had higher event rates compared to patients with a mean BMI of 25 kg/m^2. To account for the shape of the aforementioned associations, the mean BMI was further analyzed in categories (BMI < 26 vs. 26–35 vs. ≥ 35 kg/m^2). For percentage change in BMI, there was a linear association between the increase in BMI and improved outcome and a neutral effect for decreasing levels of BMI. Percentage change in BMI was, therefore, analyzed dichotomously (decrease vs. stable/increase). For BMI variability, there was an increase in risk of events for patients with a variability < 2% and > 4% compared with patients with BMI variability from 2 to 4%. Consequently, BMI variability was categorized as < 2%, 2–4% and > 4%.

Cox proportional hazard regression models were used to assess the associations between mean, change and visit-to-visit variability in BMI and long-term events in univariable and multivariable analysis. Proportional hazards assumptions for the dependent variables were verified with log[− log(survival)] plots for the aforementioned BMI categories. Proportional hazards assumptions were met. In the multivariable models, adjustments were made for variables previously found to be clinically relevant and associated with outcomes in this cohort: age, gender, Killip class, estimated glomerular filtration rate, glucose, hemoglobin, systolic blood pressure at baseline, smoking status, history of hypertension, diabetes, HF history, previous MI, previous stroke, peripheral arterial disease, atrial fibrillation, heart rate, beta-blockers and diuretics [26, 27]. Models were not adjusted for left ventricular ejection fraction, prescription of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers and a history of coronary artery bypass graft or percutaneous coronary interventions due to the high percentage of missing values (40%). No data imputation was performed.

Additional sensitivity analyses were performed in subsets of patients with (1) ≥ 3 BMI measurements, (2) ≥ 5 BMI measurements, and (3) without hospitalization for HF during follow-up.

Statistical analyses were performed using SPSS 24 (IBM inc., Armonk, NY) and R (The R Foundation for Statistical Computing, Vienna, Austria). A P value of < 0.05 was considered statistically significant.

Results

Baseline characteristics and outcomes

A total number of 12,719 patients were included in the present analyses (72% male, age 65 ± 11 years, baseline BMI range 13–103 kg/m^2), 1195 (9%) of whom died from cardiovascular causes during follow-up. Mean follow-up duration was 2.0 ± 0.9 years for survivors at the end of follow-up vs. 0.9 ± 0.8 years for patients with CV death. Patients who died during follow-up, compared to those who did not, had a lower BMI at baseline (27.0 ± 5.4 kg/m^2 vs. 27.3 ± 5.0 kg/m^2, P = 0.03), lower mean BMI during follow-up (26.7 ± 5.5 kg/m^2 vs. 27.4 ± 5.1 kg/m^2, P < 0.001), lower last BMI measurement (26.5 ± 5.6 kg/m^2 vs. 27.5 ± 5.4 kg/m^2, P < 0.001), a significantly greater reduction in BMI from baseline during follow-up (− 1.4% ± 7.2 vs. 0.8% ± 9.2, P < 0.001), and lower visit-to-visit BMI variability during follow-up (3.0 ± 2.6 vs. 3.2 ± 2.3, P = 0.001).

Mean BMI

Patients with a mean BMI < 26 vs. 26–35 or > 35 kg/m^2 were older, more often male and current smokers, had lower LVEF, had less frequently a history of HF, hypertension and diabetes mellitus, but had more often atrial fibrillation and past stroke. At baseline, they had a lower systolic blood pressure, worse renal function, lower hemoglobin and glucose. They also received less ACEi or ARBs, diuretics and beta-blockers (Table 1). Crude and adjusted hazard ratios (HRs) for the association between mean BMI and endpoints are depicted in Table 2 (and Supplemental Fig. 2C). A BMI < 26 compared to 26–35 kg/m^2 was significantly associated with higher rates of CV death, all-cause mortality and the composite of CV mortality or CV hospitalizations. There was a trend towards a significant association for CV hospitalizations. We observed a numerically (but not statistically significant) higher HR for CV death for patients with BMI < 20 compared to 20–25 kg/m^2, likely due the low number of patients with a BMI < 20 kg/m^2 (N = 298; Supplemental table 1). A BMI > 35 kg/m^2 (compared to 26–35 kg/m^2) was not associated with adverse outcomes in the adjusted multivariate analyses.

Change in BMI

In 5683 (45%) patients, BMI decreased during follow-up. Baseline characteristics of the study groups according to BMI change are depicted in Supplemental Table 2. Patients with a decrease in BMI were significantly older, more often female and current smokers. These patients had a worse renal function, higher systolic blood pressure and heart rate at baseline, and more often a history of HF, hypertension, atrial fibrillation, and stroke.

After adjustment for several clinical variables (including baseline BMI), a decrease in BMI during follow-up was independently associated with CV death and all-cause death (Table 2 and Supplemental Fig. 2C). There was no significant association between a decrease in BMI and the composite of CV death or CV hospitalization or CV hospitalizations alone. Patients with a decrease in BMI during

Table 1 Baseline characteristics according to mean BMI levels

	Overall, ($N=12,719$)	BMI < 26 kg/m^2, ($N=5426$)	BMI 26–35 kg/m^2, ($N=6699$)	BMI > 35 kg/m2, ($N=594$)	*P* value
Age (years), mean ± SD	64.7 ± 11.0	66.7 ± 11.1	63.5 ± 10.6	59.7 ± 10.5	< 0.001
Female, *n* (%)	3551 (27.9%)	1470 (27.1%)	1839 (27.5%)	242 (40.7%)	< 0.001
Smoking status, *n* (%)					
Current	4628 (36.4%)	2042 (37.7%)	2377 (35.5%)	209 (35.2%)	0.032
Never	4148 (32.6%)	1779 (32.8%)	2173 (32.5%)	196 (33.0%)	
Former	3936 (31.0%)	1601 (29.5%)	2146 (32.0%)	189 (31.8%)	
Killip class, *n* (%)					
1	3761 (29.7%)	1606 (29.7%)	1935 (29.0%)	220 (37.2%)	0.001
2	7204 (56.8%)	3052 (56.4%)	3855 (57.8%)	297 (50.2%)	
3	1451 (11.4%)	627 (11.6%)	758 (11.4%)	66 (11.1%)	
4	259 (2.0%)	125 (2.3%)	125 (1.9%)	9 (1.5%)	
LVEF, mean ± SD	33.2 ± 6.0	32.8 ± 6.3	33.5 ± 5.8	32.9 ± 6.2	< 0.001
ACEi/ARB, *n* (%)	6744 (84.6%)	2700 (82.8%)	3658 (85.5%)	386 (88.7%)	< 0.001
Diuretic, *n* (%)	4734 (37.2%)	1977 (36.4%)	2480 (37.0%)	277 (46.6%)	< 0.001
Beta blocker, *n* (%)	6849 (62.6%)	2824 (60.1%)	3730 (64.3%)	295 (65.6%)	< 0.001
Previous MI, *n* (%)	3007 (23.6%)	1290 (23.8%)	1576 (23.5%)	141 (23.7%)	0.95
Afib, *n* (%)	1398 (11.0%)	655 (12.1%)	690 (10.3%)	53 (8.9%)	0.002
HF history, *n* (%)	1931 (15.2%)	800 (14.7%)	995 (14.9%)	136 (22.9%)	< 0.001
PAD, *n* (%)	1008 (7.9%)	456 (8.4%)	513 (7.7%)	39 (6.6%)	0.14
Hypertension history, *n* (%)	6396 (50.3%)	2374 (43.8%)	3636 (54.3%)	386 (65.0%)	< 0.001
Diabetes, *n* (%)	3135 (24.6%)	999 (18.4%)	1866 (27.9%)	270 (45.5%)	< 0.001
History of stroke, *n* (%)	919 (7.2%)	443 (8.2%)	433 (6.5%)	43 (7.2%)	0.002
Hemoglobin (g/dL), mean ± SD	13.4 ± 1.6	13.2 ± 1.6	13.5 ± 1.6	13.4 ± 1.6	< 0.001
Potassium (mmol/L), mean ± SD	4.3 ± 0.5	4.3 ± 0.5	4.3 ± 0.5	4.3 ± 0.5	1
Sodium (mmol/L), mean ± SD	139.6 ± 3.9	139.5 ± 4.2	139.7 ± 3.7	139.5 ± 3.8	0.034
Glucose (mmol/L), mean ± SD	7.3 ± 3.4	7.0 ± 3.3	7.4 ± 3.3	8.1 ± 3.6	< 0.001
SBP (mmHg), mean ± SD	120.9 ± 16.7	119.1 ± 16.6	122.0 ± 16.6	125.2 ± 17.8	< 0.001
Heart rate (bpm), mean ± SD	74.8 ± 12.5	74.8 ± 12.7	74.7 ± 12.3	76.4 ± 12.4	0.007
eGFR (mL/min/1.73 m^2), mean ± SD	67.2 ± 20.1	66.3 ± 20.2	67.9 ± 20.0	68.8 ± 19.6	< 0.001

BMI body mass index, *SBP* systolic blood pressure, *LVEF* left ventricular ejection fraction, *eGFR* estimated glomerular filtration rate, *MI* myocardial infarction, *Afib* atrial fibrillation, *HF* heart failure, *PAD* peripheral arterial disease, *ACE/ARB* angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, *SD* standard deviation

follow-up had higher baseline BMI levels (Table 3), without significant interaction or correlation between baseline BMI and decrease in BMI during follow-up (*P* for interaction = 0.31; Pearson $r = 0.1$).

BMI variability

Baseline characteristics of patients according to categories of visit-to-visit BMI variability are depicted in Supplemental Table 3. Patients with a BMI variability < 2% compared to 2–4% were older, more likely to be male and current smokers and more often had a history of MI, HF and hypertension. They had a slightly better LVEF, higher systolic blood pressure, higher levels of potassium, lower glucose, and worse renal function. Patients with a high variability (> 4%) (compared to 2–4%) were more often diabetics and had peripheral artery disease, had the lowest systolic blood pressure and most often a poor Killip class (3/4).

After adjustment for several clinical variables (including baseline BMI), low variability in BMI (< 2%) during follow-up was significantly associated with higher rates of CV death, all-cause death, the composite of CV death or CV hospitalization, and CV hospitalization alone (Table 2 and Supplemental Fig. 2C). High BMI variability (> 4%) during follow-up was significantly associated with higher rates of CV death, all-cause death but not with the composite endpoint of CV death or CV hospitalization or CV hospitalization alone. There was no interaction with baseline BMI levels (*P* for interaction = 0.67). Baseline and mean BMI did not differ between patients with a variability < 2% vs. 2–4% vs. > 4% (Table 3).

Table 2 Crude and adjusted hazard ratios for mean BMI, change in BMI, and BMI variability

	CV death				All-cause death				CV death/CV hospitalization				CV hospitalization			
	Crude HR (95% CI)	*P* value	Adj. HR (95% CI)	*P* value	Crude HR (95% CI)[a]	*P* value	Adj. HR (95% CI)[a]	*P* value	Crude HR (95% CI)	*P* value	Adj. HR (95% CI)[a]	*P* value	Crude HR (95% CI)	*P* value	Adj. HR (95% CI)[a]	*P* value
Mean BMI[a]																
< 26 kg/m^2	1.45 (1.29–1.63)	< 0.001	1.33 (1.17–1.53)	< 0.001	1.47 (1.32–1.64)	< 0.001	1.34 (1.18–1.51)	< 0.001	1.22 (1.12–1.32)	< 0.001	1.14 (1.04–1.26)	0.007	1.18 (1.07–1.30)	< 0.001	1.10 (0.99–1.23)	0.083
26–35 kg/m^2	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
> 35 kg/m^2	1.40 (1.07–1.82)	0.013	1.21 (0.86–1.70)	0.28	1.34 (1.05–1.72)	0.02	1.24 (0.91–1.70)	0.17	1.37 (1.14–1.65)	< 0.001	1.18 (0.93–1.49)	0.17	1.32 (1.08–1.63)	0.008	1.11 (0.85–1.44)	0.46
BMI change[b]																
Decrease vs. stable/increase in BMI	1.57 (1.40–1.76)	< 0.001	1.39 (1.22–1.59)	< 0.001	1.69 (1.52–1.87)	< 0.001	1.52 (1.36–1.72)	< 0.001	1.20 (1.11–1.31)	< 0.001	1.08 (0.99–1.19)	0.097	1.14 (1.04–1.25)	0.006	1.03 (0.93–1.14)	0.61
Variability[b]																
< 2%	1.99 (1.74–2.28)	< 0.001	1.85 (1.59–2.15)	< 0.001	1.92 (1.70–2.17)	< 0.001	1.78 (1.55–2.04)	< 0.001	2.20 (2.00-2.41)	< 0.001	2.00 (1.80–2.22)	< 0.001	2.22 (1.20–2.46)	< 0.001	2.04 (1.81–2.29)	< 0.001
2–4%	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
> 4%	1.40 (1.20–1.63)	< 0.001	1.23 (1.04–1.45)	0.013	1.48 (1.29–1.69)	< 0.001	1.35 (1.17–1.56)	< 0.001	1.04 (0.92–1.17)	0.53	0.99 (0.87–1.14)	0.95	1.01 (0.88–1.16)	0.88	0.97 (0.83–1.13)	0.68

[a]Multivariable models adjusted for age, gender, Killip class, baseline estimated glomerular filtration rate, glucose, hemoglobin, systolic blood pressure at baseline, smoking status, history of hypertension, diabetes, heart failure history, previous myocardial infarction, previous stroke, peripheral arterial disease, atrial fibrillation, heart rate, beta-blockers, and diuretics (not adjusted for left ventricular ejection fraction and use of ACE inhibitor or ARB due to ~40% missing values)

[b]In addition to [a] multivariable models adjusted for baseline BMI levels

Table 3 Body mass index descriptives for mean, change, and BMI variability

	Baseline BMI (mean ± SD)	Mean BMI (mean ± SD)	Last BMI (mean ± SD)	Percentage BMI change (mean ± SD)	Percentage patients a decrease in BMI [%, (*N*)]	Number of BMI measurements (mean ± SD)
Complete cohort	27.3 ± 5.1	27.3 ± 5.2	27.5 ± 5.4	0.6 ± 9.0	41% (5232)	7.4 ± 2.2
Mean BMI						
< 26 kg/m^2	23.7 ± 2.2$^{*,\#}$	23.5 ± 1.9$^{*,\#}$	23.5 ± 2.2$^{*,\#}$	− 0.5 ± 7.9$^{*,\#}$	46% (2473)$^{*,\#}$	7.3 ± 2.3$^{*,\#}$
26–35 kg/m^2	29.0 ± 2.7$^{*,¥}$	29.1 ± 2.3$^{*,¥}$	29.3 ± 2.6$^{*,¥}$	1.1 ± 7.9$^{*,¥}$	38% (2558)$^{*,¥}$	7.5 ± 2.2*
> 35 kg/m^2	40.4 ± 9.9$^{\#,¥}$	41.6 ± 10.2$^{\#,¥}$	41.9 ± 10.8$^{\#,¥}$	4.9 ± 20.7$^{\#,¥}$	34% (201)$^{\#,¥}$	7.5 ± 2.4$^{\#}$
Change in BMI						
Decrease	27.9 ± 5.0*	26.8 ± 4.8*	26.4 ± 4.8*	− 6.4 ± 5.2*	100%	7.2 ± 2.3*
Increase	26.8 ± 5.1*	27.7 ± 5.4*	28.2 ± 5.6*	5.5 ± 7.8*	0%	7.5 ± 2.2*
BMI variability						
< 2%	27.3 ± 5.0	27.3 ± 5.0	27.3 ± 5.1	− 0.1 ± 4.1$^{*,\#}$	39% (1627)$^{\#}$	6.8 ± 2.4$^{*,\#}$
2–4%	27.4 ± 5.1	27.4 ± 5.1	27.5 ± 5.3	0.8 ± 7.1*	40% (2123)$^{¥}$	7.7 ± 2.0*
> 4%	27.1 ± 5.1	27.2 ± 5.4	27.3 ± 6.0	1.2 ± 14.5$^{\#}$	45% (1482)$^{\#,¥}$	7.7 ± 2.2$^{\#}$

$^{*,\#,¥}$Significant differences (with $P < 0.05$) between studied BMI categories

Sensitivity analyses

A sensitivity analysis was performed including only patients with ≥ 3 BMI measurements during follow-up ($N = 12{,}218$) providing similar associations to those described in the main analysis (Supplemental Table 4). In another sensitivity analysis comprising only patients with ≥ 5 BMI measurements ($N = 11{,}255$), a mean BMI < 26 kg/m^2 and decrease in BMI remained independently associated with CV death. The association between low variability (< 2%) and CV death lost its statistical significance in this sensitivity analysis (Table 4). An additional sensitivity analysis was performed excluding patients with hospitalization for HF during follow-up ($N = 11{,}226$), providing similar associations as those observed in the main analyses except for the association between BMI variability > 4% and CV death which lost its significance (Supplemental Table 5).

Discussion

The present study simultaneously assessed the association between several BMI measurements in a large population of acute MI patients with LV systolic dysfunction, HF or both. Three key findings were identified: (1) a mean BMI < 26 kg/m^2; (2) a decrease in BMI during follow-up; and (3) a low (< 2%) and high (> 4%) BMI variability was associated with higher CV death rates.

Mean BMI

Patients with a mean BMI < 26 kg/m^2 were older, more often male, had lower systolic blood pressure, worse renal function, lower glucose at baseline and more often had atrial fibrillation. These are variables previously found to independently predict poor prognosis in patients with acute coronary syndromes and HF [28–31]. After adjustment for potential confounders, mean BMI < 26 kg/m^2 (vs. a BMI between 26 and 35 kg/m^2) remained an independent predictor of CV mortality.

Previous studies investigating the association between baseline BMI levels and outcome in patients with established heart disease demonstrated an "obesity paradox" in which obesity was associated with a better prognosis when compared to a normal BMI [5–7]. However, based on the assessment of the shape of the associations using spline-transformed variables, we found that patients with a mean BMI < 26 or > 35 kg/m^2 were at increased risk for adverse outcomes compared to patients with a mean BMI between 26 and 35 kg/m^2 in univariate analyses. However, after adjustment for potential confounders, the association between BMI > 35 kg/m^2 and the studied outcomes lost statistical significance, suggesting that other patient-related factors (e.g., age, blood pressure, and comorbid conditions) may play a more important prognostic role in obese patients, blunting the prognostic associations for high BMI. This is in line with a recent meta-analysis that evaluated associations between BMI and all-cause mortality in HFrEF patients that demonstrated comparable risks for patients with BMI exceeding 24 kg/m^2 [32]. Disease-related BMI changes may, therefore, represent an important confounder (i.e., an indication of reverse causation). However, a "low" mean BMI remained independently associated with CV death, after multiple adjustment and in sensitivity analyses, suggesting that patients with a MI and systolic dysfunction and/or HF plus "low" (< 26 kg/m^2 in the present study) BMI may

Table 4 Crude and adjusted hazard ratios for mean BMI, change in BMI, and BMI variability in selected patients with ≥ 5 BMI measurements (sensitivity analysis)

	CV death				All-cause death				CV death/CV hospitalization				CV hospitalization			
	Crude HR (95% CI)	*P* value	Adj. HR (95% CI)	*P* value	Crude HR (95% CI)[a]	*P* value	Adj. HR (95% CI)[a]	*P* value	Crude HR (95% CI)	*P* value	Adj. HR (95% CI)[a]	*P* value	Crude HR (95% CI)	*P* value	Adj. HR (95% CI)[a]	*P* value
Mean BMI[a]																
< 26 kg/m^2	1.39 (1.16–1.66)	< 0.001	1.28 (1.04–1.59)	0.022	1.42 (1.21–1.66)	< 0.001	1.28 (1.06–1.54)	0.010	1.09 (0.94–1.25)	0.25	1.02 (0.86–1.20)	0.85	1.05 (0.90–1.24)	0.52	0.97 (0.80–1.17)	0.75
26–35 kg/m^2	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
> 35 kg/m^2	1.35 (0.88–2.05)	0.17	1.24 (0.70–2.19)	0.47	1.31 (0.89–1.92)	0.17	1.29 (0.78–2.13)	0.32	1.42 (1.04–1.93)	0.025	1.32 (0.86–2.01)	0.20	1.33 (0.93–1.90)	0.12	1.15 (0.70–1.89)	0.59
BMI change[b]																
Decrease vs. stable/increase in BMI	1.75 (1.47–2.09)	< 0.001	1.58 (1.28–1.95)	< 0.001	1.86 (1.59–2.18)	< 0.001	1.71 (1.43–2.06)	< 0.001	1.17 (1.02–1.35)	0.025	0.94 (0.80–1.11)	0.48	1.03 (0.88–1.21)	0.69	0.82 (0.68–0.99)	0.041
Variability[b]																
< 2%	1.17 (0.94–1.45)	0.17	0.97 (0.74–1.26)	0.81	1.10 (0.90–1.35)	0.33	0.91 (0.72–1.15)	0.42	1.30 (1.11–1.52)	0.001	1.10 (0.92–1.33)	0.30	1.35 (1.13–1.62)	0.001	1.15 (0.94–1.42)	0.18
2–4%	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
> 4%	1.52 (1.24–1.86)	< 0.001	1.36 (1.08–1.72)	0.009	1.61 (1.34–1.93)	< 0.001	1.53 (1.25–1.87)	< 0.001	1.04 (0.87–1.25)	0.64	0.97 (0.79–1.20)	0.79	1.05 (0.86–1.29)	0.63	0.98 (0.78–1.24)	0.90

[a]Multivariate models adjusted for age, gender, Killip class, baseline estimated glomerular filtration rate, glucose, hemoglobin, systolic blood pressure at baseline, smoking status, history of hypertension, diabetes, heart failure history, previous myocardial infarction, previous stroke, peripheral artery disease, atrial fibrillation, heart rate, beta-blockers, and diuretics (not adjusted for left ventricular ejection fraction and use of ACE inhibitor or ARB due to ~ 40% missing values)

[b]In addition to [a] multivariable models adjusted for baseline BMI levels

benefit from a closer follow-up. Additionally, for patients with a mean BMI below 26 kg/m^2 it is important to realize that there is a linear increase in risk for lower BMIs, i.e., a BMI of 20 kg/m^2 is associated with a higher event rate compared to a BMI of 25 kg/m^2.

Decrease in BMI

Similar to previous studies in CAD and HF, a decrease in BMI was also associated with poorer outcomes in our study [14, 33]. Baseline characteristics of patients with a decrease in BMI vs. a stable/increase in BMI demonstrated poor prognostic variables such as older age, a history of HF as well as several comorbidities including renal insufficiency, hypertension and stroke. In contrast to a smaller study in obese HF patients, we did not observe an interaction between obesity status, BMI decrease and outcomes [34]. In the present series, a BMI decrease was associated with worse outcomes, regardless of baseline BMI.

Despite the epidemiological uncertainties regarding survival of obese patients with CAD and/or HF, there are several potentially beneficial effects of weight loss such as greater functional capacity and improved quality of life, improved glycemia or even remission from diabetes, reductions in coronary and cerebrovascular events, and increased freedom from atrial fibrillation [35, 36]. A differential effect on outcome for intentional (improved outcome) and unintentional (decreased outcome) weight loss has been alluded to in a previous meta-analysis in 35,335 CAD patients [37]. In HF patients, an observational study showed an association between bariatric surgery and fewer HF exacerbations [38]. However, prospective randomized clinical trials on (intentional) weight loss in MI patients with systolic dysfunction are lacking.

Some of the patients in the present study might have presented with unintentional weight loss, which (itself) can be associated with worse outcomes. Weight loss remained independently associated with CV death, after multiple adjustment and sensitivity analyses. Thus, the finding of an unintentional weight loss should raise awareness of clinicians and lead to a thorough investigation of the potential weight loss causes.

BMI variability

It was recently demonstrated that fluctuations in BMI in patients with CAD (without HF) were associated with a poor prognosis [16]. Variability in BMI in HF patients may potentially reflect changes in body-fluid status and our subsequent hypothesis was that higher variability in BMI would be associated with a poor prognosis. Interestingly, we observed that patients with low (< 2%) and high (> 4%) BMI variability (compared to patients with BMI variability between 2 and 4%) had an increased risk of CV death, independently of conventional risk factors.

In a sensitivity analysis including only patients with ≥ 5 available BMI measurements, a high BMI variability remained associated with worse outcomes, but not low BMI variability. However, this may reflect loss of statistical power: patients with low variability had significantly fewer BMI measurements compared to the other patients with higher percentages of variability (Table 3), possibly resulting in lower BMI variability. Low variability in our study may, therefore, reflect an older and sicker population of patients who died shortly after baseline, and hence were not included in the sensitivity analysis including 5 or more measurements. When excluding patients with HF hospitalizations from the analyses, the outcome associations of high BMI variability also lost statistical significance, suggesting that patients with high weight variations were those more likely to be hospitalized for HF (although we also cannot exclude loss of statistical power). In either case, the finding of a patient with extreme BMI fluctuations should lead to an investigation of the potential underlying causes.

Implications for clinicians and further research

Current ESC guidelines for MI and HF have differing recommendations for weight management. For MI patients, weight loss is recommended when BMI levels exceed 25 kg/m^2 [39]. However, HF guidelines only recommend weight loss in severely obese patients (BMI ≥ 35 kg/m^2) with the reasoning that there is no evidence for a beneficial prognostic effect of weight control (given the lack of randomized controlled trials), in combination with a potential "protective" effect of obesity as suggested from observational studies [40].

Although certain studies have attributed the obesity paradox to a higher metabolic reserve presumably present in obese patients [41, 42], the observed associations are more likely due to reverse causation, i.e., BMI reflects the state of disease. Several findings in the present study accordingly suggest reverse causation. First, patients in our study who died vs. those who survived had a lower BMI at baseline and at the last follow-up measurement. Second, patients with a BMI < 26 kg/m^2 (vs. ≥ 25) and a BMI decrease (vs. stable/increase) during follow-up already had a "worse" risk profile at baseline. Moreover, the associations between mean BMI < 26 kg/m^2 and a decrease in BMI with poor prognosis were mostly driven by death, and not hospitalizations. This suggests that low mean BMI and change in BMI are characteristics of sick patients who are more likely to die.

Notwithstanding, it is clear from the present and previous studies that patients with a mean BMI < 26 kg/m^2 and/or a decrease in BMI during follow-up are sick patients at high risk of dying. A low BMI and/or decrease in BMI likely reflect poorer patient status and cachexia. Physicians should,

therefore, be alert for a mean BMI < 26 kg/m^2 (and not a BMI of 18.5, which is often the cut-off threshold used in clinical practice [43]) and a decrease in BMI during follow-up. Until randomized controlled trial trials on the prognostic effect of intentional weight loss in patients with established heart disease are available, whether there is a "true" protective effect of obesity will remain unknown. In addition, there is also a need to prospectively assess programs targeting an increase in weight in patients with lower BMIs and/or decrease in BMI during follow-up.

Limitations

Several limitations to this study should be mentioned. First, the present is a post hoc analysis conducted in a specific population of high-risk acute MI patients with LV systolic dysfunction, HF or both and the results may, therefore, not be generalizable to other patient populations.

Secondly, although BMI is most frequently used for classification of obesity, BMI may not accurately distinguish between percentage body fat and lean mass. It has been shown that these measurements, when combined with BMI, were superior to only BMI in predicting mortality risk in CAD patients [44]. Unfortunately, we did not have information on other adiposity measurements such as waist circumference and waist-to-hip ratio. Our aim was, however, not to improve risk stratification in these patients but rather to study serial BMI measurements to compare our results to other studies that have previously showed an "obesity paradox".

Thirdly, our high-risk MI database consists of four patient cohorts and there is a possibility that some of the weight and height measurements were self-reported by patients which may introduce a reporting-bias. However, systematic errors are unlikely given the large number of patients and measurements. As mentioned earlier, we were not able to compare patients based on intentional or unintentional weight changes since these data were not collected in the initial studies.

Fourthly, although extensive adjustments were performed to correct for potential confounding, there remains the possibility of residual confounding by unmeasured variables. For example, we did not have any information regarding biomarkers (i.e., natriuretic peptides, troponin T and CK-MB), severity of CAD, infarct size and medication dosages or changes during this study. Moreover, there was no available information on signs of congestion (such as peripheral edema) during follow-up, which may influence the association between the assessed BMI measurements and outcome. In addition, more than 40% of patients had missing data on their LVEF, the use of ACEi/ARBs and a history of coronary artery bypass grafting or percutaneous coronary interventions and we were, therefore, not able to adjust for these variables. This may have influenced the results. Additionally, we did not have any information on treatment during follow-up and it may be that patients with low (or high) BMIs received less appropriate treatments. Hospitalizations for HF may confound the association between the studied BMI measurements and outcome. A strength of our study is that HF hospitalization was added as a time-varying covariate to the models and a sensitivity analysis was performed excluding patients with an HF hospitalization. This did not change any of the observed associations for mean BMI or change in BMI. Furthermore, frailty and nutrition status were previously associated with poor outcome [45] but unfortunately we did not have any information on these variables. However, it has been shown in a previous study that after adjustment for several measures of frailty, comorbidities and laboratory markers of nutritional status, being underweight still remained predictive of poor prognosis [2].

Lastly, unfortunately we did not have information on the dates of BMI measurements which precluded a landmark analysis including patients with BMI measurements during comparable time frames.

Conclusion

Mean BMI < 26 kg/m^2 (compared to > 26 kg/m2) and a decrease in BMI during follow-up (compared to a stable/increase in BMI) were independently associated with poor outcome in a large cohort of patients with MI complicated by LV systolic dysfunction, HF or both. Despite the lack of causal inference, from a clinical perspective, a BMI < 26 kg/m^2 and decreasing BMI identified in routine practice in patients following complicated MI should raise a potential concern since they were independently associated with worse outcomes. Ultimately, only randomized controlled trials evaluating intentional weight loss in this population may provide therapeutic guidance.

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