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Original Scientific Paper

Body mass index and outcome in patients with coronary, cerebrovascular, or peripheral artery disease: findings from the FRENA registry

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Background **The relationship between body mass index (BMI) and mortality in patients with established arterial disease remains controversial.**

Methods **FRENA is an ongoing, observational registry of consecutive outpatients with coronary artery disease (CAD), cerebrovascular disease, or peripheral artery disease (PAD). We examined the prognostic importance of accepted BMI categories on outcome among patients in the FRENA registry.**

Results **In April 2008, 2274 patients (mean age, 66 years) had been enrolled, of whom 14 (0.6%) were underweight; 533 (23%) normal; 1051 (46%) overweight; and 676 (30%) were obese. Over a mean follow-up of 14 months, the incidence of major cardiovascular events (myocardial infarction, ischemic stroke, or critical limb ischemia) per 100 patient-years was: 7.1 [95% confidence interval (CI): 0.4–35]; 11 (95% CI: 8.4–14); 6.9 (95% CI: 5.6–8.5); and 8.5 (95% CI: 6.6–11), respectively. Their cardiovascular mortality was: 7.1 (95% CI: 0.4–35); 4.1 (95% CI: 5.9–11); 1.3 (95% CI: 0.9–2.3); and 1.5 (95% CI: 1.4–3.5), respectively. On multivariate analysis, the hazard ratio for cardiovascular mortality was: 2.2 (95% CI: 0.3–17); 1.0 (reference); 0.37 (95% CI: 0.20–0.69); and 0.37 (95% CI: 0.18–0.73), respectively. Survival benefit was only found in patients with CAD or PAD. Weight loss had little influence on outcome.**

Conclusion **Patients with CAD or PAD (not those with cerebrovascular disease) have an inverse correlation between BMI and cardiovascular mortality, even after adjusting for confounding variables.** ***Eur J Cardiovasc Prev Rehabil*** **16:457–463 © 2009 The European Society of Cardiology**

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Introduction

The relationship between body mass index (BMI) and mortality remains controversial. In the general population, obesity is usually associated with an increased risk of coronary artery disease (CAD), heart failure, and death [1–6]. Hence, current guidelines for the secondary prevention of CAD from the American College of Cardiology/American Heart Association recommend weight loss for all overweight and obese patients [7]. However, studies of patients with heart failure [8,9], CAD [10–17], or pulmonary embolism [18], found an inverse correlation

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between BMI and mortality. Moreover, there is little information on the influence of BMI on outcome in patients with cerebrovascular disease (CVD) or peripheral artery disease (PAD).

The FRENA (Factores de Riesgo y ENfermedad Arterial) registry was initiated in March 2003 to prospectively record the current clinical management and outcome of outpatients with established artery disease in Spanish hospitals [19,20]. It is an ongoing, multicenter, observational registry designed to gather and analyze data on treatment patterns and outcomes in consecutive outpatients with symptomatic ischemic disease in the heart, brain, and/or major peripheral arteries. Given the uncertain role of BMI in the clinical management of these patients, we examined the prognostic importance of accepted BMI categories on outcome among patients in the FRENA registry.

Patients and methods

Inclusion criteria

Participating hospitals in the FRENA registry prospectively enroll consecutive outpatients with symptomatic artery disease meeting at least one recent (< 3 months before enrollment) episode of CAD (manifesting as angina or acute coronary syndrome); CVD (manifesting as transient ischemic attack or ischemic stroke); or PAD (either intermittent claudication with an ankle–brachial index < 0.9, or previous vascular intervention, or limb amputation for PAD). The Fontaine classification was used for categorization of PAD [21]. All patients provided oral consent to their participation in the registry, according to the requirements of the ethics committee within each hospital.

Study design

As recommended by the World Health Organization, patients were categorized as underweight (BMI < 18.5), normal weight (BMI 18.5–24.9), overweight (BMI 25.0–30), or obese (BMI > 30). Weight and height were measured at baseline. Patients with normal weight were used as reference, and their mortality rate was compared with that in the other three groups. The primary outcome was to compare the incidence of major cardiovascular events (i.e. acute myocardial infarction, ischemic stroke, or critical limb ischemia), cardiovascular death, or overall mortality among BMI subgroups. The secondary outcome was to compare the incidence of major cardiovascular events or death according to changes in body weight during follow-up.

Definitions

Death was classified as cardiovascular when appearing within 15 days after the onset of signs or symptoms of a major cardiovascular event, or because of progressive heart failure, fatal arrhythmias, ruptured aneurysm, pulmonary embolism, or sudden death. Major cardiovascular events were defined as the composite outcome of myocardial infarction, ischemic stroke, critical limb ischemia, or cardiovascular death. Myocardial infarction was defined as a transient increase of CK-MB or troponin in combination with ischemic symptoms and/or typical electrocardiogram signs (development of pathologic Q-waves or ST-segment elevation or depression). Ischemic stroke was diagnosed if the patient had an appropriate clinical event not resolving completely within 24 h, and had a brain computed tomography or magnetic nuclear resonance that showed a compatible low-density lesion or was normal, or had findings compatible with hemorrhagic conversion of a cerebral infarct. Critical limb ischemia was considered in patients with intermittent claudication when presenting symptoms at rest (Fontaine stages III or IV). In PAD patients with stage III or IV, critical limb ischemia was considered when amputation was needed.

Weight change was predefined as weight gain or weight loss from baseline of greater than 0.1 kg per baseline BMI-unit. Consequently, for a patient with a BMI of 25 kg/m^2, a change of greater than ± 2.5 kg was categorized as weight change [22]. This corresponds to 3–3.5% change in total body weight. Patients were accordingly divided into three groups with regard to weight change: weight loss, weight stability, and weight gain.

Follow-up

A detailed history was performed on all patients at study entry (< 3 months after an acute ischemic episode). Comorbid conditions were characterized, including a history of CAD, CVD or PAD, diabetes mellitus, hypertension, hyperlipidemia, chronic lung disease, chronic heart failure, cancer, and smoking status. Then, physical examination was performed comprising weight, height, heart rate, and blood pressure on standard conditions, after 5 min of rest. An electrocardiogram was also recorded. After the initial visit, all patients were followed-up at 3-month intervals for at least 12 months. At these visits, medical history and data from physical examination were recorded, with special attention to risk factors; laboratory tests; lifestyle habits; the type, dose, and duration of treatment received; and clinical outcome. Standard enzymatic methods were used for serum total cholesterol, high-density lipoprotein cholesterol and triglycerides, and plasma glucose concentrations. Low-density lipoprotein cholesterol concentration was calculated using the Friedewald formula [23]. Creatinine clearance (CrCl) levels were measured according to the Cockcroft and Gault formula [24]. Physicians are allowed to use any and all appropriate medications, as dictated by their usual clinical practice patterns.

Statistical analysis

For this analysis, BMI groups were compared with the normal BMI (control) group. Incidence rates were calculated as both cumulative incidence and as person-time (events/100 patient-years). Categorical variables were compared using the χ^2 test. Odds ratios and corresponding 95% confidence intervals were calculated. Associations between BMI and mortality were assessed using the multivariate Cox proportional hazards regression model, in which age, chronic heart failure, diabetes, smoking habit, earlier history of arterial disease, heart rhythm, CrCl levels, cancer, and drug therapy were adjusted as confounding factors. Statistical analyses were conducted with SPSS for Windows Release 12.5 (SPSS Inc., Chicago, Illinois, USA).

Results

As of April 2008, a total of 2274 patients had been enrolled in FRENA in 24 participating Spanish hospital centers, of whom 14 (0.6%) were underweight, 533 (23%) normal weight, 1051 (46%) overweight, and 676 (30%) were obese. Mean age was 66 ± 11 years, and 1887 patients (83%) were more than 55 years. Underweight patients were more frequently smokers, had cancer and intermittent claudication more often, but had diabetes less often than those with normal weight (Table 1). By contrast, overweight and obese patients had diabetes or hypertension more frequently, and higher levels of CrCl or serum triglycerides. Moreover, the obese were less often males and received diuretics, β-blockers, angiotensin II antagonists, calcium antagonists, statins, or antidiabetics more frequently than those with normal weight.

Over a mean follow-up of 14 months (range, 2–42 months), there were 220 major cardiovascular events in 208 patients (9.1%): 57 (2.5%) had an acute myocardial infarction, 64 (2.8%) an acute ischemic stroke, and 99 (4.4%) acute limb ischemia (39 underwent limb amputation). Patients with overweight or obesity had a lower incidence of critical limb ischemia, but the incidence of myocardial infarction

Table 1 Clinical characteristics of the patients, according to their BMI

	<18.5	18.5–24.9	25–30	>30
Patients (*N*)	14	533	1051	676
Number of visits (mean ± SD)	4.1 ± 2.0	4.2 ± 2.0	4.5 ± 2.4*	4.5 ± 2.3*
Clinical characteristics				
Mean age (years ± SD)	71 ± 16	67 ± 12	66 ± 11	66 ± 11
Sex (males) *n* (%)	10 (71)	400 (75)	812 (77)	445 (66)**
Mean BMI (± SD)	17 ± 1.0***	23 ± 1.6	27 ± 1.4***	33 ± 3.1***
Waist circumference (cm ± SD)	75 ± 16*	89 ± 8.1	98 ± 7.1***	108 ± 9.8***
Underlying diseases				
Cancer, *n* (%)	3 (21)*	38 (7.1)	60 (5.7)	24 (3.6)**
Hypertension, *n* (%)	5 (36)	308 (58)	711 (68)***	514 (76)***
Diabetes mellitus, *n* (%)	1 (7.1)*	170 (32)	411 (39)**	315 (47)***
Current smoking, *n* (%)	8 (57)**	114 (21)	198 (19)	86 (13)***
Clinical presentation				
Angina, *n* (%)	0	46 (8.6)	117 (11)	100 (15)**
Myocardial infarction, *n* (%)	4 (29)	134 (25)	292 (28)	172 (25)
Ischemic stroke, *n* (%)	0	115 (22)	267 (25)	158 (23)
Transient ischemic attack, *n* (%)	0	36 (6.8)	76 (7.2)	60 (8.9)
PAD Fontaine stage II, *n* (%)	9 (64)**	157 (28)	238 (23)*	154 (23)
PAD Fontaine stage III, *n* (%)	0	24 (4.5)	36 (3.4)	15 (2.2)*
PAD Fontaine stage IV, *n* (%)	1 (7.1)	29 (5.4)	39 (3.7)	22 (3.3)
Physical examination				
Sinus rhythm, *n* (%)	11 (79)	479 (90)	928 (88)	588 (87)
Mean SBP levels (mmHg)	128 ± 19	134 ± 18	137 ± 26*	139 ± 17***
Mean DBP levels (mmHg)	70 ± 9.7	73 ± 9.8	75 ± 9.1***	77 ± 9.4***
Mean laboratory levels				
CrCl (ml/min)	43 ± 26*	58 ± 22	71 ± 25***	82 ± 32***
Total cholesterol (mg/dl)	182 ± 23	184 ± 37	181 ± 37	183 ± 35
HDL-cholesterol (mg/dl)	51 ± 13	48 ± 14	46 ± 13**	46 ± 13**
LDL-cholesterol (mg/dl)	110 ± 21	111 ± 31	109 ± 30	109 ± 30
Glucose (mg/dl)	99 ± 19	116 ± 42	119 ± 39	123 ± 38**
Triglycerides	95 ± 34	124 ± 80	136 ± 88*	147 ± 77***
Drugs				
Diuretics, *n* (%)	2 (14)	184 (34)	380 (36)	320 (47)***
Beta-blockers, *n* (%)	2 (14)	187 (35)	407 (39)	282 (42)*
ACE-inhibitors, *n* (%)	2 (14)*	218 (41)	517 (49)**	312 (46)
Angiotensin-II antagonists, *n* (%)	1 (7.1)	127 (24)	295 (28)	278 (41)***
Calcium antagonists, *n* (%)	3 (21)	107 (20)	264 (25)*	219 (32)***
Antiplatelets, *n* (%)	13 (93)	484 (91)	942 (90)	620 (92)
Anticoagulants, *n* (%)	1 (7.1)	72 (14)	167 (16)	104 (15)
Statins, *n* (%)	5 (36)*	376 (71)	815 (76)**	532 (79)**
Insulin, *n* (%)	0	68 (13)	139 (13)	126 (19)**
Oral antidiabetics, *n* (%)	1 (7.1)	108 (20)	295 (28)**	220 (33)***

ACE, angiotensin-conversive enzyme; BMI, body mass index; CrCl, creatinine clearance; DBP, diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PAD, peripheral artery disease; SBP, systolic blood pressure; SD, standard deviation. Comparisons between patients: *$P<0.05$; **$P<0.01$; ***$P<0.001$.

Table 2 Clinical outcomes according to BMI[a]

	<18.5	18.5–24.9	25–30	>30
All patients (*N*)	14	533	1051	676
Follow-up (years)	14	565	1243	803
Myocardial infarction	0	2.9 (1.7–4.5)	1.9 (1.2–2.8)	2.3 (1.4–3.6)
Acute ischemic stroke	0	2.5 (1.4–4.1)	2.3 (1.5–3.2)	2.8 (1.8–4.1)
Critical limb ischemia	0	6.7 (4.8–9.2)	3.1 (2.2–4.2)***	3.0 (2.0–4.4)**
Major CV events	7.1 (0.4–35)	11 (8.4–14)	6.9 (5.6–8.5)**	8.5 (6.6–11)
Cardiovascular death	7.1 (0.4–35)	4.1 (2.6–6.0)	1.5 (0.9–2.3)***	1.5 (0.8–2.5)**
Overall death	14 (2.4–47)	8.0 (5.9–11)	3.1 (2.3–4.2)***	2.2 (1.4–3.5)***
CAD patients (*N*)	4	179	404	272
Follow-up (years)	2.6	187	501	347
Myocardial infarction	0	4.9 (2.4–9.0)	2.4 (1.3–4.1)	3.9 (2.2–6.5)
Acute ischemic stroke	0	1.1 (0.2–3.6)	0.8 (0.3–1.9)	0.6 (0.1–1.9)
Critical limb ischemia	0	2.2 (0.7–5.2)	0.2 (0.01–1.0)*	0.3 (0.01–1.4)*
Major CV events	38 (1.9–190)	8.2 (4.7–13)	4.0 (2.5–6.1)*	5.8 (3.6–8.9)
Cardiovascular death	38 (1.9–190)	4.8 (2.3–8.8)	1.6 (0.7–3.0)*	1.1 (0.4–2.8)**
Overall death	38 (1.9–190)	8.0 (4.7–13)	2.6 (1.4–4.3)**	1.4 (0.5–3.2)***
CVD patients (*N*)	0	149	333	209
Follow-up (years)	0	175	406	260
Myocardial infarction	0	0	0.8 (0.2–2.0)	0.4 (0.02–1.9)
Acute ischemic stroke	0	4.1 (1.8–8.1)	3.5 (2.0–5.8)	5.6 (3.2–9.1)
Critical limb ischemia	0	2.3 (0.7–5.6)	1.0 (0.3–2.4)	0.4 (0.02–1.9)*
Major CV events	0	6.5 (3.4–11)	5.4 (3.4–8.0)	6.7 (4.1–11)
Cardiovascular death	0	2.3 (0.7–5.5)	1.0 (0.3–2.4)	2.3 (0.9–4.8)
Overall death	0	2.9 (1.1–6.4)	3.0 (1.6–5.0)	3.1 (1.4–5.8)
PAD patients (*N*)	10	206	318	196
Follow-up (years)	11	204	339	202
Myocardial infarction	0	3.5 (1.5–6.9)	2.4 (1.1–4.6)	2.0 (0.6–4.9)
Acute ischemic stroke	0	2.5 (0.9–5.5)	3.0 (1.5–5.4)	3.0 (1.2–6.3)
Critical limb ischemia	0	15 (10–22)	10 (7.2–14)	12 (7.4–17)
Major CV events	0	18 (13–25)	13 (9.8–18)	16 (11–22)
Cardiovascular death	0	5.4 (2.8–9.4)	2.1 (0.9–4.1)*	1.0 (0.2–3.3)**
Overall death	8.8 (0.4–43)	13 (8.5–18)	4.1 (2.4–6.8)***	2.5 (0.9–5.5)***

BMI, body mass index; CAD, coronary artery disease; CV, cardiovascular; CVD, cerebrovascular disease; PAD, peripheral artery disease. [a]Incidence of events per 100 patient-years. Comparisons between patients: *$P<0.05$; **$P<0.01$; ***$P<0.001$.

Table 3 Causes of death according to BMI

	<18.5	18.5–24.9	25–30	>30
All patients (*N*)	14	533	1051	676
Cardiovascular death, *n* (%)	1 (7.1)	23 (4.3)	20 (1.9)	12 (1.8)
Fatal myocardial infarction, *n* (%)	0	8 (1.5)	3 (0.3)	0
Fatal ischemic stroke, *n* (%)	0	3 (0.6)	2 (0.2)	6 (0.9)
Fatal critical limb ischemia, *n* (%)	0	6 (1.1)	1 (0.1)	0
Heart failure, *n* (%)	1 (7.1)	0	6 (0.6)	4 (0.6)
Sudden death, *n* (%)	0	2 (0.4)	4 (0.4)	2 (0.3)
Ruptured aneurysm, *n* (%)	0	0	3 (0.3)	0
Arrhythmia, *n* (%)	0	3 (0.6)	0	0
Pulmonary embolism, *n* (%)	0	1 (0.2)	1 (0.1)	0
Noncardiovascular death, *n* (%)	1 (7.1)	22 (4.1)	19 (1.8)	6 (0.9)
Disseminated cancer, *n* (%)	1 (7.1)	9 (1.7)	6 (0.6)	3 (0.4)
Infection, *n* (%)	0	4 (0.8)	4 (0.4)	0
Bleeding, *n* (%)	0	1 (0.2)	1 (0.1)	1 (0.1)
Chronic lung disease, *n* (%)	0	2 (0.4)	1 (0.1)	0
Unknown, *n* (%)	0	4 (0.8)	5 (0.5)	2 (0.3)
Other, *n* (%)	0	2 (0.4)	2 (0.2)	0
Overall death, *n* (%)	2 (14)	45 (8.4)	39 (3.7)	18 (2.7)

BMI, body mass index.

or stroke was similar (Table 2). Overall, 104 (4.6%) patients died (56 had cardiovascular death). Those with overweight or obesity had a significantly lower mortality (either cardiovascular or overall death) than those with normal weight. Interestingly, any survival benefit was only found in patients with CAD or PAD, not in those with CVD. Most of the reported causes of death were less frequent as BMI raised (Table 3).

On univariate analysis, age more than 70 years, BMI, diabetes, atrial fibrillation, renal insufficiency, and the use of some drugs, were significantly associated with an increased cardiovascular mortality (Table 4). On multivariate analysis, only BMI, diabetes, renal insufficiency, and the use of anticoagulants (instead of antiplatelets) were independently associated with an increased incidence of cardiovascular death (Table 5). In contrast, the use of β-blockers was associated with a lower incidence.

During follow-up, 124 patients (5.5%) gained weight, 2055 (90%) remained stable, and 95 (4.2%) lost weight. Neither the incidence of major cardiovascular events nor the mortality was significantly different between patients who gained or lost weight, as shown in Table 6.

Discussion

Our data, obtained from a prospective series of consecutive outpatients with CAD, CVD, or PAD in the FRENA registry, reveal that those with overweight or obesity had a similar incidence of major cardiovascular events but a less than half cardiovascular mortality compared with patients with normal weight. This

Table 4 Univariate analysis on the risk of cardiovascular death

	CV death, *n* (%)	No CV death, *n* (%)	Odds ratio (95% CI)	*P* value
Patients (*N*)	55	2219		
Clinical characteristics				
Age >70 years	38 (69)	869 (39)	3.5 (1.9–6.2)	<0.001
Sex (males)	37 (67)	1630 (74)	0.7 (0.4–1.3)	NS
BMI, 18.5–24.9 (reference)	23 (42)	510 (23)	–	
<18.5	1 (1.8)	13 (0.6)	1.7 (0.2–10)	NS
25–30	19 (35)	1032 (47)	0.4 (0.2–0.8)	0.003
>30	12 (22)	664 (30)	0.4 (0.2–0.8)	0.009
Underlying diseases				
Cancer	5 (9.1)	120 (5.4)	1.7 (0.7–4.5)	NS
Diabetes	32 (58)	865 (39)	2.2 (1.3–3.7)	0.004
Currently smoking	4 (7.3)	402 (18)	0.4 (0.1–0.98)	0.038
Initial clinical presentation				
Coronary artery disease	22 (40)	837 (38)	1.1 (0.6–1.9)	NS
Cerebrovascular disease	14 (26)	677 (31)	0.8 (0.4–1.4)	NS
Peripheral artery disease	20 (36)	710 (32)	1.2 (0.7–2.1)	NS
Physical examination				
Sinus rhythm	43 (78)	1963 (91)	0.4 (0.2–0.7)	0.002
Mean SBP levels >140 mmHg	17 (31)	878 (40)	0.7 (0.4–1.2)	NS
Mean DBP levels >90 mmHg	4 (7.3)	131 (5.5)	1.4 (0.5–3.8)	NS
Mean laboratory levels,				
Creatinine clearance <60 ml/min	41 (77)	767 (36)	6.1 (3.2–12)	<0.001
Total cholesterol >190 mg/dl	18 (35)	840 (39)	0.8 (0.5–1.4)	NS
LDL-cholesterol >100 mg/dl	28 (61)	1219 (60)	1.0 (0.6–1.9)	NS
Drugs				
Diuretics	32 (58)	854 (38)	2.2 (1.3–3.8)	0.003
Beta-blockers	12 (22)	866 (39)	0.4 (0.2–0.8)	0.010
ACE-inhibitors	24 (44)	1025 (46)	0.9 (0.5–1.5)	NS
Angiotensin-II antagonists	18 (33)	683 (31)	1.1 (0.6–1.9)	NS
Calcium antagonists	17 (31)	576 (26)	1.3 (0.7–2.3)	NS
Antiplatelets	45 (82)	2014 (91)	0.5 (0.2–0.9)	0.025
Anticoagulants	20 (36)	324 (15)	3.3 (1.9–5.9)	<0.001
Statins	37 (67)	1691 (76)	0.6 (0.4–1.1)	NS
Insulin	12 (22)	321 (15)	1.7 (0.9–3.2)	NS
Oral antidiabetics	15 (27)	609 (27)	1.0 (0.5–1.8)	NS

ACE, angiotensin-conversive enzyme; BMI, body mass index; CI, confidence intervals; CrCl, creatinine clearance; CV, cardiovascular; DBP, diastolic blood pressure; LDL, low-density lipoprotein; NS, non significant; SBP, systolic blood pressure.

Table 5 Multivariate analysis (Cox-regression model) on the risk of cardiovascular death

	Hazard ratio (95% CI)	*P* value
Patients (*N*)		
Clinical characteristics		
BMI		0.036
18.5–24.9	Reference	–
<18.5	2.2 (0.3–17)	0.468
25–30	0.4 (0.2–0.8)	0.008
>30	0.5 (0.2–1.1)	0.078
Underlying diseases		
Diabetes	2.0 (1.1–3.6)	0.020
Mean laboratory levels		
Creatinine clearance <60 ml/min	3.1 (1.6–6.3)	0.001
Drugs		
Beta-blockers	0.4 (0.2–0.8)	0.008
Anticoagulants	2.1 (1.1–3.7)	0.018

BMI, body mass index; CI, confidence intervals.

reduction was only found in patients with CAD or PAD, and persisted after multivariate adjustment. The improved outcome of the obese observed in our study cannot be explained by an excess mortality in underweight patients, as they were considered separately. Current guidelines for the management of CAD, CVD, or PAD recommend weight loss for all overweight and obese patients [7,25–27]. Given the higher survival rates observed among CAD or PAD patients with higher BMI in our cohort, recommendations for weight management may not apply for such patients.

Obesity is a known risk factor for hypertension, diabetes mellitus, and high serum cholesterol levels, and an important component of the metabolic syndrome [28–30]. All these factors are associated with an increased risk for stroke or myocardial infarction. However, a number of cohort studies consistently found that overweight and obese patients with CAD have a better survival [10–17]. This inverse correlation between BMI and death has been coined as the 'obesity paradox', and up to now it has been reported only in patients with CAD [10]. Unfortunately, there is scarce information on the association between BMI and outcome in patients with CVD or PAD [31,32].

The underlying pathophysiology of the obesity paradox is not known. We found these patients to have hypertension or diabetes more often than those with normal weight, thus suggesting that they were more likely to be a target of aggressive control of diabetes or hypertension because of their obesity itself. In fact, they received β-blockers,

Table 6 Clinical outcome according to baseline BMI and changes in body weight during follow-up

	All patients	<18.5	18.5–24.9	25–30	>30
All patients (*N*)	2274	14	533	1051	676
Weight gain	124	4	67	37	16
Stable	2055	10	455	968	622
Weight loss	95	0	11	46	38
Weight gain and major CV events, *n* (%)	9 (7.3)	0	3 (4.5)	4 (11)	2 (12)
Stable and major CV events, *n* (%)	187 (9.1)	1 (10)	54 (12)	71 (7.3)	61 (9.8)
Weight loss and major CV events, *n* (%)	12 (13)	0	2 (18)	8 (17)	2 (5.3)
Weight gain and CV death, *n* (%)	1 (0.8)	0	0	1 (2.7)	0
Stable and CV death, *n* (%)	54 (2.6)	1 (10)	23 (5.1)	18 (1.9)	12 (1.9)
Weight loss and CV death, *n* (%)	1 (1.1)	0	0	1 (12)	0
Weight gain and overall death, *n* (%)	1 (0.8)	0	0	1 (2.7)	0
Stable and overall death, *n* (%)	97 (4.7)	1 (10)	44 (9.7)	33 (3.4)	18 (2.9)
Weight loss and overall death, *n* (%)	6 (6.3)	0	1 (9.1)	5 (11)	0

BMI, body mass index; CV, cardiovascular.

angiotensin-II antagonists, or statins more frequently. They also had cancer less often, and were more frequently nonsmokers, and their renal function levels were better. Differences in their coronary anatomy [33], or the high cardiac output, expanded blood volume, and lower systemic vascular resistance often found in the obese may also influence their outcome [17]. However, from the clinical standpoint, the main question is not whether BMI is associated with higher mortality but whether weight loss (or maintaining a normal weight) can decrease cardiovascular mortality in patients with established arterial disease.

Although no prospective studies to date show that intentional weight loss increases survival, strong evidence indicates that weight loss in overweight and obese individuals reduces risk factors for diabetes and cardiovascular disease [25]. However, some recent studies suggest that weight loss may be associated with an increased noncancer-related mortality, both in healthy but overweight men [34] and in patients with acute myocardial infarction or stable CAD [22]. Unfortunately, given the small percentage of patients who experienced weight changes, our study was not adequately powered to detect significant differences in the incidence of major cardiovascular events or mortality between subgroups during a 14-month follow-up.

The FRENA registry provides insights into the natural history of artery disease with an unselected patient population, in contrast to the rigorously controlled conditions of randomized clinical studies. It can, therefore, help to identify factors associated with better or worse patient outcomes, and provide feedback from real-world clinical situations which may be valuable when designing new randomized clinical studies. Despite our efforts to control any bias from underlying diseases, it is likely that we were unable to eliminate such bias completely. Thus, the increased mortality associated with underweight in this study may reflect preexisting, unrecognized, disease processes, even after making careful exclusions. Another limitation of this study lies on the likely underestimated incidence of cardiovascular death. Certainly, the death at home of some patients reported to be of 'unknown cause' may have been because of unrecognized cardiovascular death. However, as the incidence of most causes of death decreased as BMI increased, it is unlikely that this could have influenced our conclusions. Finally, as most patients in our series were men, older than 55 years, we do not know whether our conclusions may apply to other subgroups of patients.

This study also has several strengths. To the best of our knowledge, this is the first time the prognostic importance of BMI has been assessed in a large study of patients with CAD, CVD, or PAD. The measurement of body weight at regular intervals during follow-up may have better reflected changes in BMI after a cardiovascular event. Moreover, we did not exclude patients with underlying diseases, recent weight loss, or smoking history. In summary, our findings reveal that overweight and obese patients with CAD or PAD (but not those with CVD) have less than half the mortality when compared with normal BMI patients. This reduction in mortality rates was consistent and persisted after multivariate adjustment.

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References

1 Seidell JC, Verschuren M, Van Leer E, Kromhout D. Overweight, underweight, and mortality. A prospective study of 48 287 men and women. *Arch Intern Med* 1996; **156**:958–963.

2 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.

3 Peeters A, Barendregt JJ, Willekens F, Mackenbach JP, Al Mamun A, Bonneux L. Obesity in adulthood and its consequences for life-expectancy: a life-table analysis. *Ann Intern Med* 2003; **138**:24–32.

4 Adams KF, Schatzkin A, Harris TB, Kipnis V, Mouw T, Ballard-Barbash R, *et al*. Overweight, obesity, and mortality in a large prospective cohort of persons 50–71 years old. *N Engl J Med* 2006; **355**:763–778.

5 Bogers RP, Bemelmans WJ, Hoogenveen RT, Boshuizen HC, Woodward M, Knekt P, *et al*.; for the BMI-CHD collaboration investigators. Association of overweight with increased risk of coronary heart disease partly independent of blood pressure and cholesterol levels: a meta-analysis of 21 cohort studies including more than 300 000 persons. *Arch Intern Med* 2007; **167**:1720–1728.

6 Hu G, Tuomilehto J, Silventoinen K, Sarti C, Männistö S, Jousilahti P. Body mass index, waist circumference, and waist-hip ratio on the risk of total and type-specific stroke. *Arch Intern Med* 2007; **167**:1420–1427.

7 Antman EM, Hand M, Armstrong PW, Bates ER, Green LA, Halasyamani LK, *et al*. 2007 Focused Update of the ACC/AHA 2004 Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines: developed in collaboration With the Canadian Cardiovascular Society endorsed by the American Academy of Family Physicians: 2007 Writing Group to Review New Evidence and Update the ACC/AHA 2004 Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction, Writing on Behalf of the 2004 Writing Committee. *Circulation* 2008; **117**:296–329.

8 Lavie CJ, Osman AF, Milani RV, Mehra MR. Body composition and prognosis in chronic systolic heart failure: the obesity paradox. *Am J Cardiol* 2003; **91**:891–894.

9 Curtis JP, Selter JG, Wang Y, Rathore SS, Jovin IS, Jadbabaie F, *et al*. The obesity paradox. Body mass index and outcomes in patients with heart failure. *Arch Intern Med* 2005; **165**:55–61.

10 Gruberg L, Weissman NJ, Waksman R, Fuchs S, Deible R, Pinnow EE, *et al*. The impact of obesity on the short-term and long-term outcomes after percutaneous coronary intervention: the obesity paradox? *J Am Coll Cardiol* 2002; **39**:578–584.

11 Lopez-Jimenez F, Jacobsen SJ, Reeder GS, Weston SA, Meverden RA, Roger VL. Prevalence and secular trends of excess body weight and impact on outcomes after myocardial infarction in the community. *Chest* 2004; **125**:1205–1212.

12 Kennedy LMA, Dickstein K, Anker SD, Kristianson K, Willenheimer R, for the OPTIMAAL study group. The prognostic importance of body mass index after complicated myocardial infarction. *J Am Coll Cardiol* 2005; **45**:156–158.

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

14 Romero-Corral A, Montori VM, Somers VK, Korinek J, Thomas RJ, Allison TG, *et al*. 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.

15 Buettner HJ, Mueller C, Gick M, Ferenc M, Allgeier J, Comberg T, *et al*. The impact of obesity on mortality in UA/non-ST-segment elevation myocardial infraction. *Eur Heart J* 2007; **28**:1694–1701.

16 Galal W, van Domburg RT, Feringa HH, Schouten O, Elhendy A, Bax JJ, *et al*. Relation of body mass index to outcome in patients with known or suspected coronary artery disease. *Am J Cardiol* 2007; **99**:1485–1490.

17 Uretsky S, Messerli FH, Bangalore S, Champion A, Cooper-DeHoff RM, Zhou Q, Pepine CJ. Obesity paradox in patients with hypertension and coronary artery disease. *Am J Med* 2007; **120**:863–870.

18 Barba R, Zapatero A, Losa JE, Valdés V, Todolí JA, Di Micco P, Monreal M, and the RIETE Investigators. Body mass index and mortality in patients with acute venous thromboembolism. Findings from the RIETE Registry. *J Thromb Haemost* 2008; **6**:595–600.

19 Lopez-Jimenez L, Camafort M, Tiberio G, Carmona JA, Guijarro C, Martínez-Peñalver F, Monreal M. Secondary prevention of arterial disease in very elderly people: results from a prospective registry (FRENA). *Angiology* 2008; **59**:427–434.

20 Monreal M, Alvarez L, Vilaseca B, Coll R, Suárez C, Toril J, Sanclemente C, and the FRENA investigators. Clinical outcome in patients with peripheral artery disease. Results from a prospective registry (FRENA). *Eur J Intern Med* 2008; **19**:192–197.

21 Dormandy JA, Rutherford B, Management of peripheral arterial disease (PAD) TASC Working Group. Trans Atlantic Inter-Society Consensus (TASC). *J Vasc Surg* 2000; **31**:S1–S96.

22 Kennedy LMA, Dickstein K, Anker SD, James M, Cook TJ, Kristianson K, Willenheimer R. Weight-change as a prognostic marker in 12 550 patients following acute myocardial infarction or with stable coronary artery disease. *Eur Heart J* 2006; **27**:2755–2762.

23 Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem* 1972; **18**:499–502.

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

25 Adams RJ, Albers G, Alberts MJ, Benavente O, Furie K, Goldstein LB, *et al*.; American Heart Association, American Stroke Association. Update to the AHA/ASA recommendations for the prevention of stroke in patients with stroke and transient ischemic attack. *Stroke* 2008; **39**:1647–1652.

26 The European Stroke Organisation (ESO) Executive Committee and the ESO Writing Committee. Guidelines for management of ischaemic stroke and transient ischaemic attack 2008. *Cerebrovasc Dis* 2008; **25**:457–507.

27 Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FGR, on behalf of the TASC II Working Group. Inter-Society consensus for the management of peripheral arterial disease (TASC II). *J Vasc Surg* 2007; **45**:S5A–S67A.

28 Poirier P, Giles TD, Bray GA, Hong Y, Stern JS, Pi-Sunyer FX, Eckel RH. Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss. An update of the 1997 American Heart Association scientific statement on obesity and heart disease from the Obesity Committee of the Council on nutrition, physical activity, and metabolism. *Circulation* 2006; **113**:898–918.

29 Balkau B, Deanfield JE, Després JP, Bassand JP, Fox KA, Smith SC, *et al*. International day for the evaluation of abdominal obesity (IDEA): a study of waist circumference, cardiovascular disease, and diabetes mellitus in 168 000 primary care patients in 63 countries. *Circulation* 2007; **116**:1942–1951.

30 Shuger SL, Sui X, Church TS, Meriwether RA, Blair SN. Body mass index as a predictor of hypertension among initially healthy normotensive women. *Am J Hypertens* 2008; **21**:613–619.

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

32 Dagenais GR, Yi Q, Mann JFE, Bosch J, Pogue J, Yusuf S, on behalf of the HOPE Investigators. Prognostic impact of body weight and abdominal obesity in women and men with cardiovascular disease. *Am Heart J* 2005; **149**:54–60.

33 Rubinshtein R, Halon DA, Jaffe R, Shahla J, Lewis BS. Relation between obesity and severity of coronary artery disease in patients undergoing coronary angiography. *Am J Cardiol* 2006; **97**:1277–1280.

34 Nilsson PM, Nilsson JA, Hedblad B, Berglund G, Lindgärde F. The enigma of increased non-cancer mortality after weight loss in healthy men who are overweight or obese. *J Intern Med* 2002; **252**:70–78.

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