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Is There an Obesity Paradox After Percutaneous Coronary Intervention in the Contemporary Era?

An Analysis From a Multicenter Australian Registry

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Objectives We sought to determine whether an obesity paradox exists in the contemporary era of percutaneous coronary intervention (PCI) and to explore potential clinical factors that might contribute.

Background Previous studies have suggested that overweight and obese patients might have better outcomes after PCI than patients with a normal or low body mass index (BMI); however this "obesity paradox" remains poorly understood.

Methods We evaluated 4,762 patients undergoing PCI between April 1, 2004 and September 30, 2007, enrolled in the MIG (Melbourne Intervention Group) registry. Patients were classified as underweight, normal, overweight, class I obese, and class II to III obese, BMI $<$20, 20 to 25, 25.1 to 30, 30.1 to 35, and $>$35 kg/m^2, respectively. We compared in-hospital, 30-day, and 12-month outcomes.

Results As BMI increased from $<$20 to $>$35 kg/m^2, there was a statistically significant, linear reduction in 12-month major adverse cardiac events (MACE) (21.4% to 11.9%, $p = 0.008$) and mortality (7.6% to 2.0%, $p < 0.001$). Obesity was, with multivariate analysis, an independent predictor of reduced 12-month MACE and showed a trend for reduced 12-month mortality. At 12 months, obese patients had higher use of aspirin, clopidogrel, beta-blockers, renin-angiotensin system blockers and statins.

Conclusions Compared with normal-weight individuals, overweight and obese patients had lower in-hospital and 12-month MACE and mortality rates after PCI. Moreover, obese patients had a higher rate of guideline-based medication use at 12 months, which might in part explain the obesity paradox seen after PCI. (J Am Coll Cardiol Intv 2010;3:660–8) © 2010 by the American College of Cardiology Foundation

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Obesity has been described as a worldwide epidemic, and its prevalence is increasing at an alarming rate. In 2005, 1.6 billion adults were classified as overweight and at least 400 million were obese (1). This is expected to rise to 2.3 billion overweight and 700 million obese adults by 2015. The adverse health consequences associated with obesity are well-documented, including coronary artery disease (CAD), stroke, heart failure, hypertension, and diabetes (2). Obesity has also been linked with higher rates of malignancy and overall mortality (3,4). Yet, increasingly, studies also suggest that obesity might also have a protective role in some chronic diseases once they are established, including CAD (5,6), heart failure (7), end-stage renal failure (8), and stroke (9).

Recent studies, including a meta-analysis, have demonstrated an "obesity paradox" after percutaneous coronary intervention (PCI), whereby overweight and obese patients seem to have better outcomes compared with normal weight individuals (10–15). Similar findings have also been demonstrated after coronary artery bypass graft (CABG) surgery (16). Few studies, however, have attempted to explain why this paradox exists. One observation is that obese patients are more likely to receive guideline-based medical therapy during hospital admission and at discharge (6,17). Alternatively, it is possible that "underweight" individuals, at the other extreme, might have increased adverse event rates. We sought to confirm that an obesity paradox exists in the modern era of PCI and to determine whether obese patients are more likely to remain on optimal medical therapy at 12 months after procedure.

Methods

Study population and data collection. We analyzed 4,762 patients undergoing PCI procedures between April 1, 2004 and September 30, 2007, enrolled in the MIG (Melbourne Intervention Group) registry. The MIG registry is a voluntary collaborative PCI registry comprising 7 major public and private hospitals in Victoria, Australia. Registry design and methods of data collection have been described previously (18). Data are prospectively collected at the time of PCI, with a case report form that includes standardized definitions for all fields. The study protocol has been approved by the ethics committee at each participating hospital, and "opt-out" informed consent was obtained from all patients.

The registry is coordinated by the Centre for Cardiovascular Research and Education in Therapeutics at Monash University in Melbourne, Australia. Case record forms for the collection of registry data have been developed with Teleform, version 9 (Cardiff, Vista, California). Completed forms are faxed to the data center, verified on receipt, and electronically uploaded into the central database. An independent audit of data collection was conducted at all sites by an investigator not affiliated with that institution. Fifteen verifiable fields from 5% of all patients enrolled from each site were randomly selected and audited. Overall data accuracy was determined to be 97%, which compares favorably with other large registries (19).

Body mass index (BMI) was calculated by dividing the weight in kilograms by the square of the height in meters. Patients were classified as underweight (BMI <20 kg/m^2, n = 131), normal weight (BMI 20 to 25 kg/m^2, n = 1,189), overweight (BMI 25.1 to 30 kg/m^2, n = 2,016), class I obese (BMI 30.1 to 35 kg/m^2, n = 1,021), and class II to III obese (BMI >35 kg/m^2, n = 405), in line with the World Health Organization classification system (1). Height and weight values were recorded at the time of PCI. In-hospital complications were recorded at the time of hospital discharge. Thirty-day and 12-month clinical outcomes and medication use were ascertained by telephone interview, and medical records were reviewed to substantiate adverse events.

Clinical outcomes and definitions. In-hospital outcomes included all-cause mortality, cardiac death, periprocedural myocardial infarction (MI) (defined as new MI during or after PCI with at least 1 instance of elevation of creatine kinase/creatine kinase myocardial band >3× the upper limit of normal and/or evolutionary ST-segment elevation, development of new Q waves in 2 or more contiguous electrocardiography leads, or new left bundle branch block pattern); MACE (comprising death, MI, and urgent revascularization); congestive cardiac failure (CCF); arrhythmia (defined as a new or acute recurrence of an atrial or ventricular arrhythmia requiring treatment or a new high-level atrioventricular block); emergency PCI; emergency CABG; new renal impairment (defined as an increase of creatinine to >0.20 mmol/l and 2× the baseline creatinine level or a new requirement for dialysis); stroke; and bleeding (defined as requiring a transfusion and/or prolonged hospital stay and/or causing a drop in hemoglobin ≥3.0 g/dl). Thirty-day and 12-month clinical outcomes included all-cause mortality, cardiac death, MI, target lesion revascularization (TLR) (defined as revascularization within 5 mm of a previously treated lesion); target vessel revascularization (TVR) (defined as revascularization of a previously treated coronary artery), and MACE (comprising death, MI, and TVR). All patients included in this study had completed 12-month follow-up or had known MACE. This

Abbreviations and Acronyms

BMI = body mass index
CABG = coronary artery bypass graft
CAD = coronary artery disease
CCF = congestive cardiac failure
DES = drug-eluting stent(s)
MACE = major adverse cardiac events
MI = myocardial infarction
PCI = percutaneous coronary intervention
PVD = peripheral vascular disease
RAS = renin-angiotensin system
TLR = target lesion revascularization
TVR = target vessel revascularization

Table 1. Baseline Clinical Characteristics According to BMI

Variable	<20 kg/m² (n = 131)	20–25 kg/m² (n = 1,189)	25.1–30 kg/m² (n = 2,016)	30.1–35 kg/m² (n = 1,021)	>35 kg/m² (n = 405)	p Value
Age (yrs)	68.8 ± 12.6	67.4 ± 11.8	64.7 ± 11.7	63.0 ± 11.6	59.7 ± 10.7	0.036
Female	52 (39.7)	318 (26.8)	423 (21.0)	240 (23.5)	158 (39.0)	<0.001*
Diabetes	18 (13.7)	189 (15.9)	450 (22.3)	271 (26.5)	164 (40.6)	<0.001
Insulin-requiring diabetes	5 (3.8)	44 (3.7)	89 (4.4)	53 (5.2)	44 (10.9)	<0.001
Hypertension	76 (58.0)	696 (58.6)	1,245 (61.9)	699 (68.6)	322 (79.5)	<0.001
Dyslipidemia	76 (58.9)	808 (68.5)	1,435 (71.7)	749 (73.6)	311 (77.6)	<0.001
Family history of CAD	45 (34.9)	457 (39.7)	876 (44.5)	458 (46.4)	194 (49.1)	<0.001
Current smoker	35 (26.9)	275 (23.4)	395 (19.9)	219 (21.8)	99 (24.6)	0.714
Current or past smoking	87 (66.9)	733 (62.4)	1,329 (67.0)	688 (68.5)	280 (69.5)	0.003
Baseline creatinine (mmol/l)	0.105 ± 0.10	0.099 ± 0.12	0.097 ± 0.08	0.093 ± 0.04	0.089 ± 0.06	0.001
Renal failure†	9 (6.9)	51 (4.3)	58 (2.9)	29 (2.8)	13 (3.2)	0.024
Previous MI	45 (34.9)	348 (29.3)	568 (28.2)	315 (30.9)	111 (27.5)	0.669
Existing CCF‡	11 (8.4)	49 (4.1)	69 (3.4)	36 (3.5)	20 (5.0)	0.446
Cerebrovascular disease	8 (6.1)	88 (7.4)	87 (4.3)	52 (5.1)	30 (7.4)	0.384
Peripheral vascular disease	10 (7.6)	90 (7.6)	141 (7.0)	56 (5.5)	21 (5.2)	0.023
Chronic lung disease	29 (22.3)	129 (10.9)	184 (9.2)	113 (11.1)	55 (13.8)	0.841
Obstructive sleep apnea	1 (0.8)	23 (2.0)	63 (3.1)	59 (5.8)	50 (12.4)	<0.001
Previous PCI	40 (30.5)	289 (24.3)	494 (24.5)	263 (25.8)	101 (24.9)	0.967
Previous CABG	13 (9.9)	110 (9.3)	185 (9.2)	90 (8.8)	32 (7.9)	0.388
Clinical presentation/indication						
STEMI	33 (25.2)	299 (25.2)	440 (21.9)	200 (19.6)	84 (20.7)	0.003
NSTEMI	33 (25.2)	260 (21.9)	491 (24.4)	280 (27.5)	108 (26.7)	0.007
Unstable angina pectoris	17 (13.0)	181 (15.3)	290 (14.4)	132 (13.0)	52 (12.8)	0.154
Stable angina	34 (26.0)	369 (31.1)	650 (32.4)	345 (33.9)	141 (34.8)	0.031
Atypical angina	5 (3.8)	33 (2.8)	52 (2.6)	31 (3.0)	10 (2.5)	
No angina	9 (6.9)	43 (3.6)	86 (4.3)	31 (3.0)	10 (2.5)	
NYHA functional class I to II	87 (78.4)	766 (82.3)	1,283 (83.4)	641 (81.7)	264 (79.3)	0.478
NYHA functional class III to IV	24 (21.6)	165 (17.7)	256 (16.6)	144 (18.3)	69 (20.7)	0.478
New CCF§	13 (9.9)	71 (6.0)	78 (3.9)	43 (4.2)	17 (4.2)	0.006
Cardiogenic shock/IABP	4 (3.1)	35 (2.9)	45 (2.2)	21 (2.1)	5 (1.2)	0.035

Data are n (%) or mean ± SD unless otherwise stated. *p value calculated with Pearson chi-square test. †Renal failure defined as baseline serum creatinine >0.20 mmol/l. ‡Existing congestive cardiac failure (CCF), at least 2 weeks before presentation. §New CCF, within 2 weeks of presentation.

BMI = body mass index; CABG = coronary artery bypass graft; CAD = coronary artery disease; IABP = intra-aortic balloon pump; MI = myocardial infarction; NSTEMI = non–ST-segment elevation myocardial infarction; NYHA = New York Heart Association functional class; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

represents 93.5% of the total cohort (n = 5,072), and rates of follow-up were similar in each BMI group.

Statistical analysis. Continuous variables were expressed as mean ± SD and compared with analysis of variance. Categorical variables were expressed as percentages and compared with linear association and Pearson chi-square tests as appropriate. Two-sided p values of <0.05 were considered statistically significant. Multivariate logistic regression analysis was used to determine independent predictors of 12-month MACE and mortality. Twenty-eight variables were considered, including age ≥75 years, BMI, sex, diabetes, hypertension, dyslipidemia, smoking, family history of CAD, renal failure, existing CCF, peripheral vascular disease (PVD), cerebrovascular disease, chronic lung disease, obstructive sleep apnea, previous MI, previous PCI, previous CABG, out-of-hospital cardiac arrest, cardiogenic shock/intra-aortic balloon pump, New York Heart Association functional class, ST-segment-elevation MI, American College of Cardiology and American Heart Association type B2 and C lesions, procedures involving the left anterior descending or left main coronary artery, bypass graft lesion, small stent size ≤2.5 mm, long stent length >20 mm, use of glycoprotein IIb/IIIa inhibitors, and use of drug-eluting stents (DES). All variables with a value of p ≤0.1 in the univariate model were included in the multivariate analysis.

Results

Study population. Baseline patient characteristics are listed (Table 1). Of 4,762 patients, 3,442 (72%) were overweight or obese. There were more men than women in all BMI groups; however, the percentage of female patients was higher at the

Table 2. Lesion Characteristics, Procedural Details, and Acute Medication Use

Variable	<20 kg/m^2 (n = 131)	20–25 kg/m^2 (n = 1,189)	25.1–30kg/m^2 (n = 2,016)	30.1–35 kg/m^2 (n = 1,021)	>35 kg/m^2 (n = 405)	p Value
Lesion characteristics						
Multivessel disease	69 (63.3)	591 (62.5)	969 (58.1)	519 (60.6)	211 (58.3)	0.210
Left main lesion	2 (1.2)	16 (1.1)	22 (0.9)	7 (0.6)	3 (0.6)	0.116
Proximal LAD lesion	29 (17.0)	211 (14.3)	361 (14.5)	174 (14.0)	75 (15.1)	0.829
Graft lesion	4 (2.3)	43 (2.9)	81 (3.2)	35 (2.8)	8 (1.6)	0.322
ACC/AHA type B2 or C lesion	89 (52.0)	681 (46.1)	1,227 (49.2)	578 (46.4)	240 (48.4)	0.966
Procedural details						
No stent	11 (8.4)	75 (6.3)	106 (5.3)	67 (6.6)	17 (4.2)	0.518
Bare-metal stent	66 (50.4)	565 (47.5)	960 (47.6)	475 (46.5)	207 (51.1)	0.518
Drug-eluting stent	54 (41.2)	549 (46.2)	950 (47.1)	479 (46.9)	181 (44.7)	0.518
Femoral access	129 (98.5)	1,135 (95.5)	1,914 (94.9)	964 (94.4)	384 (94.8)	0.182
Radial access	1 (0.8)	47 (4.0)	98 (4.9)	49 (4.8)	20 (4.9)	0.182
Brachial access	1 (0.8)	7 (0.6)	4 (0.2)	8 (0.8)	1 (0.2)	0.182
Closure device used	17 (13.2)	163 (14.0)	318 (16.3)	158 (16.0)	63 (16.0)	0.249
Pre-stenosis (%)	86.29 ± 11.3	86.2 ± 12.1	86.5 ± 11.8	86.7 ± 11.4	86.0 ± 12.3	0.815
Post-stenosis (%)	7.1 ± 20.3	4.8 ± 17.4	4.9 ± 18.2	5.2 ± 18.9	4.3 ± 15.4	0.450
Stent total length (mm)	17.76 ± 7.86	18.13 ± 9.18	18.23 ± 8.42	18.31 ± 7.99	18.41 ± 8.17	0.919
Stent diameter (mm)	2.88 ± 0.45	2.89 ± 0.46	2.93 ± 0.47	2.95 ± 0.49	2.99 ± 0.50	0.001
Maximum balloon size (mm)	2.93 ± 0.49	2.95 ± 0.50	2.98 ± 0.53	3.01 ± 0.55	3.06 ± 0.57	0.001
Unsuccessful procedure	6 (4.6)	54 (4.6)	90 (4.5)	45 (4.4)	11 (2.7)	0.249
In-hospital medication use						
Glycoprotein IIb/IIIa inhibitors	36 (27.5)	324 (27.2)	564 (28.0)	269 (26.3)	112 (27.7)	0.808
Unfractionated heparin	124 (94.7)	1,143 (96.1)	1,938 (96.1)	980 (96.1)	392 (96.8)	0.495
Low molecular weight heparin	27 (20.6)	251 (21.2)	490 (24.4)	266 (26.2)	116 (28.6)	<0.001
Clopidogrel	126 (96.2)	1,165 (98.2)	1,975 (98.2)	999 (98.1)	398 (98.5)	0.358
>72 h before PCI	41 (31.3)	390 (32.9)	652 (32.4)	325 (31.9)	140 (34.7)	
<72 h before PCI	27 (20.6)	184 (15.5)	355 (17.7)	199 (19.5)	72 (17.8)	
During/after PCI	58 (44.3)	591 (49.8)	968 (48.1)	475 (46.7)	186 (46.0)	

Data are n (%) or mean ± SD unless otherwise stated.
ACC/AHA = American College of Cardiology and American Heart Association; LAD = left anterior descending artery; other abbreviations as in Table 1.

extremes of BMI. Obese patients had a significantly higher prevalence of diabetes, hypertension, dyslipidemia, obstructive sleep apnea, current or past cigarette smoking, and family history of CAD. Notably, 40% of class II to III obese patients had diabetes. Underweight and normal weight patients were significantly older and more likely to have renal failure and PVD. Chronic lung disease, existing CCF, previous MI and previous PCI were numerically higher in underweight patients; however, there was no statistically significant linear trend across the BMI groups. In a separate analysis, BMI <20 kg/m^2 was compared with BMI >20 kg/m^2, with a statistically significant higher prevalence of chronic lung disease ($p < 0.001$) and CCF ($p = 0.018$) in underweight patients. Acute coronary syndromes (ACS) were the most common indication for PCI in all groups and comprised approximately two-thirds of all procedures. Compared with obese patients, underweight and normal weight patients were more likely to present with ST-segment-elevation myocardial infarction, new CCF, and cardiogenic shock/intra-aortic balloon pump. The prevalence of New York Heart Association functional class III to IV symptoms at presentation were similar.

Lesion characteristics and procedural details. High-risk coronary lesions, multivessel disease, the use of DES, final angiographic result, and procedural success were similar (Table 2). There was a statistically significant difference in stent diameter and maximum balloon size used in class II to III obese patients. Use of glycoprotein IIb/IIIa inhibitors, clopidogrel, and unfractionated heparin were similar; however, low molecular weight heparin use was higher in class II to III obese patients.

Clinical outcomes. In-hospital, 30-day, and 12-month outcomes are shown (Tables 3 and 4, Figs. 1 and 2). Compared with normal weight patients, class II to III obese patients had significantly fewer in-hospital cardiac complications, including periprocedural MI, arrhythmias, CCF, and MACE. In-hospital mortality was lowest in class II to III obese patients and there was a trend to lower cardiac death. The in-hospital incidence of stent thrombosis, stroke,

Table 3. In-Hospital Complications

Complication	<20 kg/m² (n = 131)	20–25 kg/m² (n = 1,189)	25.1–30 g/m² (n = 2,016)	30.1–35 kg/m² (n = 1,021)	>35 kg/m² (n = 405)	p Value
Arrhythmia	8 (6.1)	58 (4.9)	89 (4.4)	29 (2.8)	8 (2.0)	0.001
CCF	4 (3.1)	35 (2.9)	39 (1.9)	11 (1.1)	7 (1.7)	0.005
Periprocedural MI	2 (1.6)	26 (2.2)	37 (1.9)	12 (1.2)	3 (0.8)	0.030
New renal impairment	2 (1.5)	14 (1.2)	20 (1.0)	9 (0.9)	1 (0.2)	0.097
Stroke	0 (0)	3 (0.3)	4 (0.2)	1 (0.1)	0 (0)	0.327
Stent thrombosis*	0 (0)	1 (0.7)	5 (2.0)	3 (2.8)	1 (2.2)	0.220
Coronary dissection	0 (0)	4 (0.3)	7 (0.3)	1 (0.1)	0 (0)	0.229
Perforation	0 (0)	4 (0.3)	10 (0.5)	2 (0.2)	0 (0)	0.388
Tamponade	1 (0.8)	1 (0.1)	4 (0.2)	1 (0.1)	0 (0)	0.309
Emergency PCI	0 (0)	10 (0.9)	18 (0.9)	8 (0.8)	4 (1.0)	0.638
Unplanned CABG	1 (0.8)	8 (0.7)	12 (0.6)	9 (0.9)	2 (0.5)	0.932
Bleeding	5 (3.8)	27 (2.3)	41 (2.0)	22 (2.2)	8 (2.0)	0.447
Pseudoaneurysm	1 (0.8)	3 (0.3)	5 (0.2)	6 (0.6)	1 (0.2)	0.653

Data are n (%). *Total cohort 565 patients.
Abbreviations as in Table 1.

bleeding, and vascular complications were not significantly different between groups. There was no significant difference in MI, TLR, TVR, MACE, or mortality at 30 days. As BMI increased from <20 to >35 kg/m², there was a statistically significant, linear reduction in 12-month MACE (21.4% to 11.9%, p = 0.008) and mortality (7.6% to 2.0%, p < 0.001). Twelve-month cardiac mortality demonstrated a similar trend but did not reach statistical significance. Rates of 12-month MI, TLR, and TVR were not significantly different.

Predictors of outcome. Independent predictors of 12-month MACE and mortality are listed (Tables 5 and 6). With multivariate analysis, where BMI was entered as a continuous variable, BMI was an independent predictor of

Table 4. Mortality and Cardiac Complications

Complication	<20.0 kg/m² (n = 131)	20–25 kg/m² (n = 1,189)	25.1–30 kg/m² (n = 2,016)	30.1–35 kg/m² (n = 1,021)	>35.0 kg/m² (n = 405)	p Value
In-hospital						
MACE	6 (4.6)	53 (4.5)	80 (4.0)	28 (2.7)	8 (2.0)	0.005
Mortality						
All-cause	3 (2.3)	14 (1.2)	19 (0.9)	6 (0.6)	1 (0.2)	0.013
Cardiac	3 (2.3)	10 (0.8)	18 (0.9)	6 (0.6)	1 (0.2)	0.059
30 Days						
MI	2 (1.5)	37 (3.1)	58 (2.9)	20 (2.0)	6 (1.5)	0.071
TLR	1 (0.8)	23 (1.9)	45 (2.2)	22 (2.2)	8 (2.0)	0.587
TVR	1 (0.8)	30 (2.5)	49 (2.4)	27 (2.6)	10 (2.5)	0.578
MACE	6 (4.6)	72 (6.1)	112 (5.6)	47 (4.6)	15 (3.7)	0.066
Mortality						
All-cause	3 (2.3)	19 (1.6)	23 (1.1)	11 (1.1)	4 (1.0)	0.141
Cardiac	3 (2.3)	13 (1.1)	21 (1.0)	9 (0.9)	3 (0.7)	0.233
12 Months						
MI	16 (12.2)	58 (4.9)	112 (5.6)	40 (3.9)	21 (5.2)	0.057
TLR	6 (4.6)	61 (5.1)	96 (4.8)	46 (4.5)	25 (6.2)	0.761
TVR	13 (9.9)	91 (7.7)	138 (6.8)	75 (7.3)	35 (8.6)	0.996
MACE	28 (21.4)	165 (13.9)	252 (12.5)	115 (11.3)	48 (11.9)	0.008
Mortality						
All-cause	10 (7.6)	48 (4.0)	58 (2.9)	22 (2.2)	8 (2.0)	<0.001
Cardiac	4 (3.1)	23 (1.9)	35 (1.7)	15 (1.5)	5 (1.2)	0.143

Data are n (%).
MACE = major adverse cardiac events, including target vessel revascularization (TVR), myocardial infarction (MI), and death; TLR = target lesion revascularization.

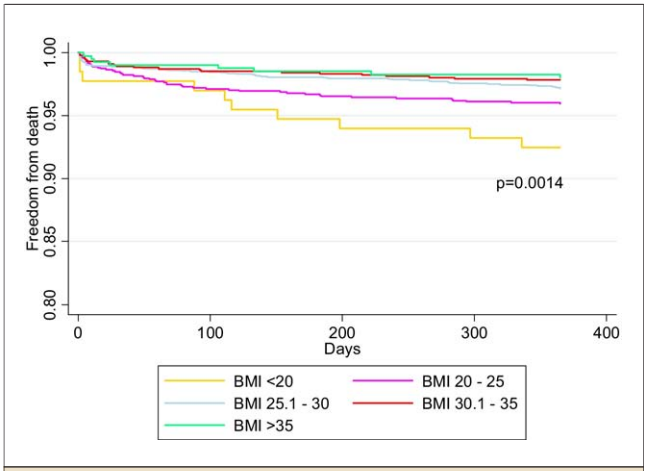

Figure 1. Kaplan-Meier Graph Illustrating Survival Curves for BMI Cohort at 12 Months

Overweight and obese patients had a lower death rate up to 12 months after percutaneous coronary intervention. BMI = body mass index (kg/m^2).

12-month MACE (odds ratio: 0.980 per unit increase kg/m^2 of BMI, 95% confidence interval: 0.961 to 0.999, p = 0.035) with a trend for reduced 12-month mortality (odds ratio: 0.961 per unit increase kg/m^2 of BMI, confidence interval: 0.922 to 1.001, p = 0.056).

30-day and 12-month medication use. Medication use at 30 days and 12 months are shown (Table 7). At 30-day follow-up, the use of renin-angiotensin system (RAS) blockers was lowest in underweight patients and highest in class II to III obese patients (69.7% vs. 83.6%, p < 0.001), and there was a trend to higher beta-blocker use in obese patients. At 12-month follow-up, there was a statistically significant difference in the use of all guideline-recommended medications. Compared with normal weight patients, class II to III obese patients were more likely to be taking aspirin (92.7% vs. 90.1%, p = 0.035), clopidogrel (66.1% vs. 59.5%, p = 0.037), beta-blockers (65.8% vs. 56.0%, p = 0.001), RAS-blockers (81.1% vs. 72.7%, p <0.001), and statins (90.7% vs. 89.8%, p = 0.044).

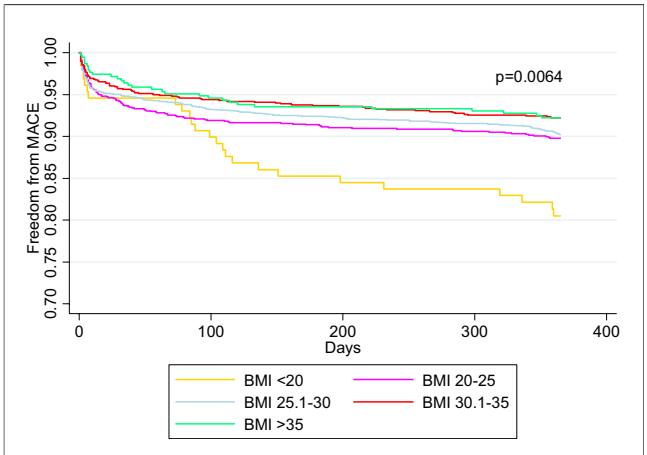

Figure 2. Kaplan-Meier Graph Illustrating MACE-Free Survival at 12 Months

Underweight patients had a higher major adverse cardiac event (MACE) rate up to 12 months after percutaneous coronary intervention, and obese patients had the lowest event rate. BMI = body mass index (kg/m^2).

Table 5. Independent Predictors of 12-Month MACE

Variable	OR	95% CI	p Value
Age (per yr)	1.012	1.004–1.021	0.004
BMI* (per 1 kg/m^2)	0.980	0.961–0.999	0.035
Shock/IABP	3.689	2.391–5.692	<0.001
Renal failure	2.138	1.456–3.140	<0.001
LAD lesion	1.553	1.253–1.925	<0.001
Small vessels (≤2.5 mm)†	1.527	1.255–1.858	<0.001
Diabetes	1.459	1.184–1.799	<0.001
Glycoprotein IIb/IIIa	1.495	1.204–1.857	<0.001
ACC/AHA B2/C lesions	1.383	1.149–1.666	0.001
Previous MI	1.281	1.052–1.559	0.014
Hypertension	1.236	1.005–1.520	0.045
DES	0.549	0.452–0.667	<0.001

*BMI calculated as a continuous variable. †Mean stent diameter.
CI = confidence interval; DES = drug-eluting stent; OR = odds ratio; other abbreviations as in Tables 1, 2, and 4.

Discussion

In this study of PCI outcomes and medication use according to BMI, obese patients had a higher prevalence of traditional cardiovascular risk factors compared with nonobese patients, yet the latter group were older and more likely to have renal failure and PVD. Class II to III obese patients had significantly lower in-hospital cardiac complications and mortality and significantly lower 12-month MACE and mortality. After multivariate analysis, increasing BMI conferred a protective effect for both 12-month MACE and mortality. This finding is counterintuitive, and yet it has been consistently reported in several earlier studies (10–15). An important new finding of our study is that obese patients

Table 6. Independent Predictors of 12-Month Mortality

Variable	OR	95% CI	p Value
Age (per yr)	1.056	1.036–1.077	<0.001
BMI* (per 1 kg/m^2)	0.961	0.922–1.001	0.056
Shock/IABP	11.155	6.439–19.326	<0.001
Renal failure	5.269	3.127–8.881	<0.001
Chronic lung disease	2.212	1.424–3.437	<0.001
STEMI	2.198	1.378–3.505	0.001
CCF†	1.907	1.049–3.465	0.034
PVD	1.860	1.105–3.133	0.020
Diabetes	1.620	1.082–2.424	0.019

*BMI calculated as a continuous variable. †Existing CCF, at least 2 weeks before presentation.
PVD = peripheral vascular disease; other abbreviations as in Tables 1 and 5.

Table 7. Medication Use at Follow-Up

Medication	<20.0 kg/m² (n = 131)	20–25 kg/m² (n = 1,189)	25.1–30 kg/m² (n = 2,016)	30.1–35 kg/m² (n = 1,021)	>35.0 kg/m² (n = 405)	p Value
30 days						
Aspirin	116 (95.9)	1,078 (97.5)	1,841 (97.0)	922 (96.8)	371 (97.4)	0.901
Clopidogrel	116 (95.9)	1,030 (93.5)	1,779 (94.3)	894 (94.0)	357 (93.7)	0.948
Beta-blocker	76 (65.0)	716 (65.5)	1,265 (67.6)	656 (70.6)	253 (66.8)	0.086
RAS-blocker	83 (69.7)	792 (72.5)	1,427 (76.3)	725 (77.8)	317 (83.6)	<0.001
Statin	102 (85.0)	1,009 (92.1)	1,726 (91.8)	868 (92.5)	352 (92.6)	0.127
Warfarin	8 (6.6)	53 (4.8)	81 (4.3)	52 (5.5)	16 (4.2)	0.597
12 months						
Aspirin	95 (84.8)	943 (90.1)	1,662 (92.0)	831 (91.2)	341 (92.7)	0.035
Clopidogrel	71 (63.4)	618 (59.5)	1,118 (62.4)	570 (63.1)	242 (66.1)	0.037
Beta-blocker	61 (57.0)	580 (56.0)	1,075 (60.7)	551 (61.5)	240 (65.8)	0.001
RAS-blocker	78 (72.2)	751 (72.7)	1,332 (75.2)	720 (80.0)	296 (81.1)	<0.001
Statin	89 (81.7)	933 (89.8)	1,637 (91.6)	825 (91.5)	333 (90.7)	0.044
Warfarin	2 (1.9)	51 (4.9)	84 (4.7)	47 (5.2)	14 (3.8)	0.879

Data are n (%).
RAS = renin-angiotensin system.

were more likely to be receiving guideline-recommended medical therapy at 12 months after PCI.

Medical therapy. Optimal medical therapy improves morbidity and mortality in CAD and remains the cornerstone of treatment (20–22). The COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial (20) was a timely reminder, that advances in technology have not supplanted the need for careful attention to proven drug-therapies and risk factor modification. Jaber et al. (21) examined the effect of using multiple evidence-based classes of cardiovascular medications (antiplatelet agents, beta-blockers, RAS-blockers, and lipid-lowering therapy) on long-term outcomes after PCI. Despite having a higher risk profile at the time of PCI, patients treated with 3 or 4 of the aforementioned medications had a lower mortality rate at 36 months. A Canadian registry (22) demonstrated similar findings in ACS patients.

Studies to date have reported on short-term differences in cardiac medications after PCI according to BMI. Steinberg et al. (17) found that increased BMI was associated with an increased use of guideline-based medical therapy both in-hospital and at discharge in 130,139 patients hospitalized for CAD. Likewise, Diercks et al. (6) demonstrated that obese patients with ACS were more likely to undergo appropriate invasive procedures and to be discharged on lipid-lowing therapy and clopidogrel. Importantly, we demonstrated that this increased use of optimal medical therapy is most dramatic at 12 months, coinciding with the improvement in MACE and mortality.

Differences in baseline characteristics, such as diabetes mellitus, hypertension, and dyslipidemia might partly account for this finding. It could be argued, however, that all patients with CAD should be treated with long-term beta-blockers, RAS-blockers, and statins (23). Furthermore, increased use of antiplatelet therapy is not explained by either differences in baseline characteristics or the use of DES. The importance of neurohormonal blockade in obese patients with CAD was supported by Kennedy et al. (24) who found that BMI was associated with an increased mortality risk among obese patients who were not receiving beta- or RAS-blockade. Nonpharmacological measures such as smoking cessation, cardiac rehabilitation, and dietary counseling have also been shown to be higher in overweight and obese patients (6).

Obesity and cardiovascular risk. The use of BMI to estimate cardiovascular risk has been challenged in recent years (25). Because BMI does not discriminate adipose tissue content, higher BMI values might in some cases simply reflect greater lean body mass composition. Recently, a large study by Gelber et al. (26) comparing BMI, waist/hip ratio, waist/height ratio, and waist circumference found waist/height ratio showed the strongest association with incident cardiovascular disease. The differences were small, however, and the authors concluded they were unlikely to be clinically meaningful. Body mass index has been extensively studied, provides the "most useful population-level measure" of obesity because it is the same for both sexes (1), and the World Health Organization endorses its use as a measure of obesity by using BMI to define and classify obesity.

Whether obesity is a predictor of cardiac events independent of other risk factors remains controversial. The INTERHEART study (Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries) (27) found that BMI was not an independent predictor of first MI after multivariate adjustment. Perhaps

current obesity measures are largely surrogate markers of risk factors that are found more commonly in untreated obese patients, such as an adverse lipid profile. Therefore, targeted treatment of these risk factors after PCI might help explain why the reverse effect is seen, where obesity is seen as "protective."

Novel mechanisms. Novel theories to explain the obesity paradox after PCI have included the suggestion that obese patients have "larger vessels" (28). We found that coronary stent diameter (used as a surrogate for vessel size) progressively increased with BMI. In addition, after multivariate analysis, small vessel size was an independent predictor of 12-month MACE. An English study (29) also found that mid–left anterior descending coronary artery diameter positively correlated with BMI in cardiac surgical patients and that patients with larger vessel size had lower in-hospital mortality. Underweight patients in our study had the smallest vessel size and the highest in-hospital and 12-month MACE and mortality.

Adipose tissue is increasingly being recognized as an active endocrine organ; however, the effects of "adipokines" on coronary arteries and atherosclerosis are incompletely understood. Uretsky et al. (5) postulated that increased production of soluble tumor necrosis factor receptors by adipose cells in obese subjects might have a cardioprotective effect in patients with heart failure. Leptin, an adipokine that is increased in obesity, has previously been implicated as an independent risk factor for CAD (30). However, a recent study has shown that low serum leptin levels correlate with angiographically determined CAD (31). Furthermore, Momin et al. (32) demonstrated that leptin is an endothelial-independent vasodilator. Clearly, additional study is warranted to elucidate whether these adipokines can help explain the obesity paradox.

Study limitations. This study is a retrospective observational analysis; however, all the data were collected prospectively in a previously described multicenter registry. Although the overall number of patients included in this study was substantial, we excluded patients with missing height and/or weight data—which is a potential source of selection bias. The BMI was assessed at the time of PCI, which does not necessarily reflect BMI at 12 months. Our follow-up was 12 months; however, a longer period is warranted to assess the impact of obesity on long-term mortality after PCI and to further evaluate the effect of medication differences on subsequent morbidity and mortality.

Conclusions

This study suggests that overweight and obese individuals are at lowest risk of in-hospital complications and 12-month MACE and mortality after PCI. Although many theories have been proposed to explain this paradox, differences in medication use is certainly an important, potentially modifiable factor. To improve our understanding of the obesity paradox and its mechanisms, a prospective study is required, including additional measures of obesity and biomarkers, measured both at baseline and during follow-up. Furthermore, we should investigate why patients with a low or normal BMI are at higher risk of morbidity and mortality after PCI and whether this risk can be ameliorated through targeted medical therapy.

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Key Words: body mass index ■ obesity paradox ■ percutaneous coronary intervention.