Influence of body mass index on the efficacy of revascularization in patients with coronary artery disease

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Objective: We examined the effect of body mass index on the association between revascularization strategy and survival in patients with coronary artery disease.

Methods: Using the Duke Database for Cardiovascular Disease, we selected 22,877 patients who underwent cardiac catheterization from January 1986 to August 2004 and were found to have significant coronary artery disease. Patients were categorized into three coronary disease management groups: no revascularization, percutaneous coronary intervention, and coronary artery bypass surgery. Propensity scoring was used to control for coronary artery revascularization strategy. The relationship between body mass index, coronary disease treatment, and survival was assessed via Cox multivariable models adjusting for baseline demographic, clinical, and angiographic characteristics.

Results: The median body mass index was 27.2 kg/m² (24.4–30.4) in the overall cohort, 27.1 kg/m² (24.1–30.3) in the no revascularization group, 27.4 kg/m² (24.8–30.9) in the percutaneous intervention group, and 26.9 kg/m² (24.4–30.1) in the coronary bypass group. Body mass index was a significant, but weak, predictor of revascularization, with higher indexes predicting lower rates of coronary bypass. Thirty-day survival did not differ across body mass indexes among treatment groups, but survival curves appeared to separate over longer-term follow-up. An inverted U-shaped survival function was noted across all time points after 30 days, with the lowest risk of death at a body mass index of approximately 26 kg/m² (independent of revascularization strategy). Coronary bypass was associated with the highest survival at all later time points, whereas no revascularization was associated with the lowest.

Conclusions: Extremes of body mass index are associated with lower long-term survival in patients with significant coronary disease. Revascularization, particularly with coronary bypass, is consistently associated with the best survival across the spectrum of body mass indexes.

The incidence of obesity is increasing rapidly in the developed world, and especially in the United States, where recent estimates of prevalence are over 30% in adults.¹ These reports are of great concern from a public health standpoint, given the clear association between high body mass index (BMI) and the risk of death.^{2–6} Furthermore, this relationship does not appear to be linear; instead, the slope of the line increases at BMI over 25, signifying particularly high risk for obese and morbidly obese patients. This negative prognosis is especially true when evaluating cardiovascular mortality outcomes, where relative risks are doubled or even tripled.^{4,7}

There has been considerable interest in this problem, but studies to date have been limited by small sample sizes, short duration of follow-up, or methodologic problems, such as arbitrary BMI grouping and failure to account for different coronary artery disease (CAD) treatments. The published

data were reviewed in a recent overview that concluded that total and cardiovascular mortality was highest in obese and underweight patients with CAD, confirming the “obesity paradox.”⁸ However, the authors were unable to model BMI as a continuous variable because of considerable heterogeneity between cohorts and a lack of patient-level data. Furthermore, no conclusions could be drawn on the relative benefits of one method of CAD management over another for any given BMI. The major outstanding question in clinical practice is whether, given the clear relationship between BMI and outcome, patients and physicians should be altering their revascularization decisions on the basis of the patient’s BMI. We used the Duke Databank for Cardiovascular Disease (DDCD) to assess the impact of BMI on the effect of revascularization on survival in patients with significant CAD undergoing coronary angiography.

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PATIENTS AND METHODS

Patient Population

This study was approved by the Duke University Institutional Review Board. The population comprised patients undergoing left heart catheterization at Duke University Medical Center between January 1, 1986, and August 31, 2004. Only patients with significant or severe CAD were included in the analysis. Patients were excluded if they had moderate or severe valvular disease, pericardial or congenital heart disease, shock (defined as systolic blood pressure < 80 mm Hg or shock as an indication for

Abbreviations and Acronyms

BMI	= body mass index
CABG	= coronary artery bypass grafting
CAD	= coronary artery disease
DDCD	= Duke Databank for Cardiovascular Disease
MI	= myocardial infarction
PCI	= percutaneous coronary intervention

catheterization), or had previous coronary artery bypass grafting (CABG) surgery. In addition, patients were also excluded if their BMI was less than 18.5 (1 patient) or more than 70 kg/m² (12 patients).

Patients were categorized into one of the following three initial revascularization strategy groups on the basis of therapy within 30 days of baseline cardiac catheterization: (1) percutaneous coronary intervention (PCI), if they had PCI; (2) CABG, if they had CABG not preceded by PCI; or (3) no revascularization (NONE), if they did not have revascularization. To minimize potential misclassification of patients who had received prior PCI to the NONE group, we also excluded patients if they had PCI before their baseline catheterization at our center. Patients who died within 5 days of initial catheterization (the median interval between catheterization and CABG at Duke University Medical Center during the study) without receiving PCI or CABG were excluded from NONE. For patients undergoing revascularization, the follow-up was started at the time of the procedure. Once patients were assigned to a revascularization group, all outcome events remained associated with that group, regardless of whether the patient subsequently had revascularization.

Data Collection

Baseline patient characteristics, medical histories, and physical examinations were collected prospectively before cardiac catheterization and entered into the DDCCD.⁹ Angiographic information was summarized to categorize patients into CAD severity groups. Catheterization data were used to define significant CAD as at least one luminal stenosis of 75% or more and severe CAD to be either significant 3-vessel disease or a left main stenosis of 75% or more.

Patients were contacted at 6 months and 1 year and annually thereafter as part of the DDCCD follow-up protocol for collection of vital status, rehospitalization information, subsequent cardiac procedures, and myocardial infarction (MI). Nonresponders to these questionnaires and/or telephone contacts were followed up through the National Death Index for vital status. Deaths were confirmed by an independent mortality committee. As of July 6, 2005, more than 99% of patients had follow-up. Alive patients were censored at the time of last follow-up.

Statistical Analysis

Baseline characteristics are categorized into the three revascularization strategy groups and are reported as percentages for discrete variables and as medians with 25th and 75th percentiles for continuous variables. Unadjusted survival results were examined using Kaplan–Meier methods. Survival estimates were generated using Cox proportional hazards regression models.

Baseline variables that were clinically relevant or statistically significant univariable predictors of outcome were selected as candidates for the propensity and final multivariable model. Candidate variables included age, sex, white race, BMI, year of catheterization, systolic and diastolic blood pressure, heart rate, ejection fraction, CAD severity (number of diseased vessels), hypertension, hyperlipidemia, history of heart failure, diabetes mellitus, history of chronic obstructive pulmonary disease, history of cerebrovascular disease, history of MI, history of peripheral vascular disease,

TABLE 1. Baseline characteristics by revascularization strategy

Variable	Overall (n = 22,877)	NONE (n = 7882)	PCI (n = 7737)	CABG (n = 7258)
Median age, y (IQR)	62 (53–70)	63 (54–70)	59 (50–67)	64 (56–71)
Male sex, %	68.9	66.4	67.9	72.8
White race, %	82.4	79.2	81.7	86.5
BMI, kg/m ² , median (IQR)	27.2 (24.4–30.4)	27.1 (24.1–30.3)	27.4 (24.8–30.9)	26.9(24.4–30.1)
History of MI, %	55.5	52.9	63.0	50.3
Hypertension, %	57.5	60.7	53.3	58.4
Diabetes, %	26.1	29.4	21.6	27.2
Hyperlipidemia, %	45.2	41.9	45.7	48.3
History of smoking, %	64.1	64.1	65.4	62.8
History of cerebrovascular disease, %	9.5	11.9	6.3	10.2
History of peripheral vascular disease, %	10.7	13.5	6.4	12.2
History of moderate or severe renal disease, %	2.4	3.2	1.9	2.0
Congestive heart failure, %	17.2	25.5	9.7	16.2
Cath for acute MI, %	27.4	17.5	43.4	21.0
Recent MI (6 wk), %	42.9	35.1	57.1	36.2
Ejection fraction, %, median (IQR)	54 (43–62)	51 (39–61)	56 (47–63)	53 (43–62)
No. of diseased vessels, %				
1	39.2	48.2	59.4	8.0
2	29.3	27.4	31.3	29.1
3	31.5	24.4	9.4	62.9
Extent of CAD, %				
Significant (not severe)	67.0	75.0	90.2	33.7
Severe	33.0	25.0	9.8	66.3

BMI, Body mass index; CABG, coronary artery bypass grafting; CAD, coronary artery disease; IQR, interquartile range; MI, myocardial infarction; NONE, no revascularization; PCI, percutaneous coronary intervention. All $P < .001$, except for smoking ($P = .003$).

FIGURE 1. BMI distribution of the study population. *BMI*, Body mass index.

family history of CAD, history of liver disease, history of moderate or severe kidney disease, connective tissue disease, history of dementia, history of metastatic cancer, history of any tumor, history of peptic ulcer, mitral insufficiency, New York Heart Association Class, MI within prior 6 weeks, third heart sound, carotid bruits, acute MI, mild valvular disease, history of smoking, left main disease of 50% or more, elective catheterization, and urgent catheterization.

Logistic regression analysis was used to determine the probability of the physician's and patient's propensity to choose a specific revascularization strategy. Three propensity scores—(1) CABG versus NONE, (2) CABG versus PCI, and (3) PCI versus NONE—were created for each patient, which, taken as a whole, represent that patient's probability of selection for each strategy relative to another. Propensity scores were included in the final models.

For the final multivariable models, variables were chosen using stepwise selection with a *P* value of .05 as the level of statistical significance. Interactions of revascularization strategy with CAD severity, BMI with CAD severity, and BMI with revascularization strategy were tested for significance.¹⁰ Splines were used to generate curves comparing survival across BMI.¹¹ All analyses were performed with SAS software version 8.2 (SAS Institute Inc, Cary, NC).

RESULTS

The analysis included 22,877 patients with significant or severe CAD. The median duration of follow-up was 7 years (interquartile range 3.1–11.9 years). Approximately 65% of the patients in the cohort were either followed up for over 10 years or had died within 10 years of follow-up.

The baseline characteristics stratified by revascularization strategy are shown in Table 1. The median BMI was 27.2 kg/m² (24.4–30.4 kg/m²) in the overall cohort, 27.1 kg/m² (24.1–30.3 kg/m²) in the NONE group, 27.4 kg/m² (24.8–30.9 kg/m²) in the PCI group, and 26.9 kg/m² (24.4–30.1 kg/m²) in the CABG group. The BMI distribution of the entire study population is shown in Figure 1. When examined by revascularization strategy, there were no major differences in the distribution of BMIs.

Table 2 shows unadjusted survivals. The adjusted survivals of the study population stratified by revascularization strategy are shown in Figure 2. CABG was associated with higher adjusted survival than the other treatment modalities

TABLE 2. Unadjusted survivals by revascularization strategy

Time	NONE	PCI	CABG
30 d	97%	98%	97%
6 mo	93%	97%	95%
1 y	90%	96%	94%
5 y	70%	87%	82%
10 y	51%	73%	62%
15 y	36%	53%	42%

CABG, Coronary artery bypass grafting; NONE, no revascularization; PCI, percutaneous coronary intervention.

FIGURE 2. Adjusted survival for all patients stratified by revascularization strategy. CAD, Coronary artery disease; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention.

after 12 months, and this benefit appeared to be consistent over the duration of follow-up. Table 3 shows the predictors of revascularization strategy based on the results of the logistic regression propensity models. BMI was a significant variable in each of the propensity scores, although its relative contribution to the overall probability of undergoing a particular procedure was small compared with other clinical variables. The majority of patients were treated with a single revascularization strategy. Crossover rates were 11.9% for NONE to PCI, 13.8% for CABG to PCI, 21% for NONE to CABG, and 21% for PCI to CABG. The median time to crossover from NONE to CABG was 3 years and from PCI to CABG, 1.5 years.

Survival estimates for the different revascularization strategy groups at 30 days, 1 year, and 10 years are provided in Figure 3. There was no significant difference in survival at 30 days among revascularization strategy groups or across BMI. At longer follow-up, the survival curves continued to diverge, with CABG being associated with the highest survival across the entire spectrum of BMI. NONE was consistently associated with the lowest long-term survival. This relationship was similar when analyzed for procedures performed in the early balloon angioplasty (1986–1990), late balloon angioplasty (1991–1995), and stent (1996–2004) eras (data not shown). The BMI inflection point of these survival curves was at a BMI of approximately 26 kg/m² and was independent of revascularization strategy (interaction *P* value = .12).

Among the entire cohort, there were 711 (3.1%) patients with morbid obesity (BMI ≥ 40). Of these, 32.3% were treated with NONE, 43.2% with PCI, and 24.5% received CABG. The revascularization rate was not different in pa-

tients with BMIs of 40 or more compared with those with BMIs less than 40 (67.7 vs 65.5%; *P* = .245); however, there was less use of CABG (24.5 vs 32.0%; *P* < .0001). Among patients with severe (ie, left main or 3-vessel) CAD, there was a trend toward a lower rate of CABG in morbidly obese patients compared with those not morbidly obese (55.3 vs 61.5%; *P* = .072).

DISCUSSION

Although there is a clear and previously described excess risk associated with extremes of BMI, the association between revascularization strategy and better outcome appears to be independent of BMI in this large cohort of patients with CAD undergoing coronary angiography. Importantly, revascularization (especially with CABG) is associated with a higher rate of survival even at the extremes of BMI.

Prior work has described a similar U-shaped relationship between BMI and the risk of overall and cardiovascular death.^{4,8} Our data support these findings of an “obesity paradox”; however, this is the first analysis to include the impact of treatment strategy in such a way as to allow a direct comparison of outcomes between patients treated with revascularization strategies for any given BMI.

At one extreme, very low BMI has been associated with overall mortality, possibly through a confounding effect by unrecognized or unmeasured comorbidities.^{4,8} At the other extreme, obesity continues to attract attention as its prevalence increases. It is clearly linked to several major cardiovascular risk factors but is also increasingly recognized as an independent contributor both to the development of CAD and to cardiovascular death.^{8,12–14} The results of this analysis show that BMI influences the risk of death even

TABLE 3. Major predictors of each revascularization strategy from the propensity model

Variable	Wald χ^2	OR	95% CI	
A. PCI vs NONE: Probability of undergoing PCI				
Year of catheterization*	679.9			
1986–1993		1.201	1.181	1.222
1997–2004		1.097	1.070	1.125
Ejection fraction (per 1% increase)	256.9	1.037	1.032	1.041
Acute MI	165.8	2.226	1.970	2.514
Left main disease $\geq 50\%$	140.4	0.384	0.328	0.450
MI within prior 6 wk	103.3	2.097	1.818	2.418
No. of diseased vessels	102.8	0.769	0.731	0.809
NYHA class (classes I–III vs class IV)	94.1	0.645	0.591	0.705
Elective catheterization	70.8	0.677	0.618	0.741
History of MI	48.6	0.635	0.559	0.721
White race	32.3	1.317	1.198	1.448
Age (per 10-y increase)	31.8	0.908	0.878	0.939
History of peripheral vascular disease	27.9	0.707	0.622	0.804
History of cerebrovascular disease	20.6	0.737	0.646	0.841
Mild valvular disease	14.3	0.522	0.373	0.731
BMI (below 26, <i>or</i> per 1 kg/m ² increase)	11.4	1.038	1.016	1.061
Hyperlipidemia	10.4	1.131	1.050	1.219
Diabetes mellitus	10.3	0.868	0.796	0.946
B. CABG vs NONE: Probability of undergoing CABG				
No. of diseased vessels	2643.7	4.126	3.909	4.355
Left main disease $\geq 50\%$	245.7	2.282	2.059	2.530
Ejection fraction	222.2	1.047	1.041	1.054
Age (OR per 10 y)	164.4			
Below 67 y		1.115	1.055	1.178
Above 67 y		0.513	0.462	0.568
Elective catheterization	113.3	0.624	0.572	0.680
White race	98.7	1.721	1.546	1.915
Year of catheterization*	76.5	1.039	1.030	1.048
NYHA class	72.6	0.841	0.808	0.875
History of cerebrovascular disease	30.2	0.704	0.621	0.798
Diabetes mellitus	29.2	0.779	0.712	0.853
History of MI	27.6	0.734	0.654	0.824
Mild valvular disease	23.7	0.469	0.346	0.636
Hyperlipidemia	23.1	1.215	1.122	1.315
History of peripheral vascular disease	21.7	0.757	0.673	0.851
Hypertension	14.8	0.851	0.784	0.924
History of moderate or severe renal disease	14.1	0.622	0.486	0.797
BMI	13.9			
Below 26		1.030	1.006	1.056
Above 26		0.982	0.972	0.992
History of connective tissue disease	10.1	0.389	0.217	0.697
C. CABG vs PCI: Probability of undergoing CABG				
No. of diseased vessels	3264.0	6.330	5.941	6.743
Left main disease $\geq 50\%$	525.9	6.283	5.370	7.352
Year of catheterization*	164.3			
1986–1993		0.890	0.871	0.909
1997–2004		0.960	0.933	0.989
Acute MI	101.8	0.450	0.386	0.526
MI within 6 wk before catheterization	41.1	0.648	0.568	0.740
Ejection fraction (below 60, <i>or</i> per 1% increase)	32.4	0.987	0.983	0.992

TABLE 3. Continued

Variable	Wald χ^2	OR	95% CI	
Age (or per 10 y)	29.3			
Below 70 y		1.143	1.083	1.206
Above 70 y		0.699	0.591	0.826
BMI	14.3	0.984	0.975	0.992
White race	13.4	1.260	1.113	1.427

BMI, Body mass index; CABG, coronary artery bypass grafting; CI, confidence interval; MI, myocardial infarction; NYHA, New York Heart Association; NONE, no revascularization; OR, odds ratio; PCI, percutaneous coronary intervention. *Odds ratio for year of catheterization refers to the yearly increase in odds of receiving one treatment over another; for PCI vs. NONE and CABG vs. PCI, the OR from 1994–1996 did not increase and was the same as 1993. Only Wald χ^2 values over 10 are shown.

after revascularization and medical therapy for CAD, and, furthermore, that it affects prognosis independently of revascularization strategy.

The precise reason for the excess risk associated with obesity is unclear, but a number of biological mechanisms have been postulated, including effects on vascular remodeling¹⁵ and endothelial function,¹⁶ associated low-level chronic inflammation,¹⁷ impaired ventricular function,¹⁸ left ventricular hypertrophy,¹⁹ and QT prolongation.²⁰ Confounding from low cardiorespiratory fitness, itself probably a significant predictor of adverse cardiovascular outcomes, may also, in part, explain the influence of BMI on prognosis.^{21–23}

Finally, biases and barriers may exist in access to medical care for the obese and especially the morbidly obese patient, which may contribute negatively to outcomes.²⁴ The results of propensity modeling suggest that BMI does influence the likelihood of coronary revascularization and, perhaps more important, the mode of revascularization selected. This idea of a potential treatment bias is further supported by the finding that, even among patients with traditionally “surgical” disease (namely, left main or 3-vessel disease), rates of CABG were lower in those patients who were morbidly obese.

It is commonly believed that obese patients may not be appropriate surgical candidates because of an increased risk of complications^{25–36} and higher mortality after CABG. There are data, including from this analysis, to support the finding that obese patients undergoing CABG have worse outcomes than nonobese patients,^{8,31,35–39} although a number of previous studies conversely have not found higher mortality with CABG in obese^{25–30,32–34,40–45} and severely obese patients.^{25,28,32,40,41,44,46} All of these studies, however, have failed to account for the outcomes of similar patients treated with PCI or without revascularization. Although obese patients treated with CABG may have worse outcomes than lighter-weight patients, their outcomes are better with CABG than with alternative revascularization strategies or medical therapy.

Several limitations of our study must be acknowledged. First, this is a single-center study and may not reflect the experiences of other institutions. For example, the high

FIGURE 3. Survival across the spectrum of BMI by treatment group at short-, intermediate-, and long-term follow-up. CABG, Coronary artery bypass grafting; PCI, percutaneous coronary intervention.

rate of smoking in our population may reflect local social factors. Second, the DDCD includes patients enrolled over approximately 20 years. Although this provides for a large population and a long duration of follow-up, there have been therapeutic advancements in the treatment of CAD from both a medical and revascularization standpoint, and findings from the past may be less relevant to the future. The DDCD does not contain longitudinal information on medication use, so we cannot account for the adequacy of medical therapy with any revascularization strategy. As with any observational analysis, there may be measured or unmeasured confounders that are associated with either revascularization strategy or outcome. Patients with acute MI were more likely to have PCI and those with multivessel disease were more likely to receive CABG. We performed propensity analysis to adjust for the likelihood of receiving a particular treatment and to mitigate the effects of measurable confounders. There may also be unmeasured confounders, such as socioeconomic and psychological factors, which are not collected and thus cannot be adjusted for. Although observational databases have limitations, because patients of extremes of BMI are often excluded from randomized clinical trials, large observational datasets have an important role to play in understanding the influence of BMI on outcome in real world clinical practice. Finally, we did not assess the impact of revascularization beyond 30 days—such as repeat revascularization, crossover from medical to revascularization, or weight loss. Only a minority of the population crossed over, and there are considerable analytic challenges in accounting for crossover, in modeling time-

to-crossover, and introducing bias from patients dying before crossover.

In conclusion, although extremes of BMI are associated with worse survival in patients with CAD undergoing angiography, revascularization (particularly with CABG) is associated with better outcomes across all BMIs. Obese patients with significant CAD amenable to surgical revascularization should be considered for CABG.

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