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The Relationship Between Obesity and Atherosclerotic Progression and Prognosis Among Patients With Coronary Artery Bypass Grafts

The Effect of Aggressive Statin Therapy

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- Objectives** This study examines whether obesity accelerates atherogenic progression or adverse outcomes after coronary artery bypass graft (CABG) surgery.
- Background** Obesity is a major risk factor for developing coronary heart disease. Whether obesity accelerates disease progression after CABG is unclear.
- Methods** We examined how body mass index (BMI) related to atherosclerotic graft progression and a clinical composite outcome of death, nonfatal myocardial infarction, stroke, CABG surgery, or angioplasty among 1,314 participants in the Post CABG trial. Participants who had undergone CABG surgery were randomly assigned in a 2 × 2 factorial design to warfarin versus placebo and aggressive low-density lipoprotein cholesterol (LDL-C) lowering with lovastatin 40 to 80 mg/day (to achieve LDL-C of 60 to 85 mg/dl) versus moderate LDL-C lowering with lovastatin 2.5 to 5 mg/day (to achieve LDL-C of 130 to 140 mg/dl). Angiographic progression was assessed by coronary angiography at 4 to 5 years.
- Results** Higher BMI was associated with a higher likelihood of angiographic progression (p trend = 0.003) after adjustment for demographic factors, treatment assignment, smoking status, and years since CABG surgery, but not with clinical events (p trend = 0.81). In stratified analyses, higher BMI was associated with angiographic progression in the low-dose lovastatin group (p trend <0.001) but not in the high-dose group (p = 0.03 for test for interaction of BMI and statin treatment). In the high-dose lovastatin group, higher BMI appeared to be protective against clinical events (p trend = 0.06, test of interaction: 0.02).
- Conclusions** Higher BMI is strongly associated with atherogenic progression after CABG surgery. Aggressive statin therapy may be protective against obesity-related acceleration of coronary heart disease. (J Am Coll Cardiol 2008;52: 620–5) © 2008 by the American College of Cardiology Foundation

Obesity is a leading cause of preventable death, a growing epidemic, and a major contributor to cardiovascular disease risk and mortality in the U.S. (1–6). Although obesity's adverse effect on cardiovascular disease risk is

well established, it is less clear whether obesity predicts adverse outcomes after coronary artery bypass graft (CABG) surgery (7,8).

In addition to its association with traditional cardiovascular factors such as diabetes, hypertension, and dyslipidemia, obesity leads to metabolic changes that precipitate an atherogenic milieu (9). Adipose tissue is a major producer of proinflammatory cytokines and hormones and is thought to induce low-grade systemic inflammation that has been implicated in the pathogenesis of cardiovascular disease (10). Few studies have been able to examine the impact of obesity on atherogenic outcomes after CABG surgery, however. Earlier studies that examined the impact of obesity after CABG surgery have primarily focused on post-operative complications and short-term mortality (7,8,11,12). Studies

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on obesity's effect on post-CABG mortality over the long term have produced conflicting results, with a few studies suggesting a protective relationship but others showing no effect or higher mortality risk (13-15). Moreover, interpretation of the previous literature has been complicated by the differences in study design and ways in which body mass index (BMI) has been categorized (7,8,11-15).

Over the past few decades, several medical therapies have been shown to improve cardiac disease outcomes, including improved graft patency after CABG surgery (16). In particular, growing evidence suggests that statins may improve coronary artery disease outcomes, including CABG graft patency, not only by improving lipid levels but also by lowering systemic inflammation (17,18). Given that obesity is believed to confer adverse cardiovascular risk by inducing low-grade inflammation in addition to its other adverse effects on traditional cardiovascular risk factors, statins may produce a larger benefit in patients who are obese than in those who are normal weight.

In this context, we examined the relationship between obesity and progression of graft atherosclerosis and risk of clinical cardiovascular events among participants enrolled in the Post CABG trial (16,19). This trial evaluated low-dose warfarin versus placebo and aggressive versus moderate-level treatment with lovastatin on graft progression in patients with patent coronary artery bypass grafts; the study's original results demonstrated that aggressive lowering of low-density lipoprotein cholesterol (LDL-C) reduced progression of graft atherosclerosis and the risk of subsequent clinical events, whereas low-dose warfarin did not. Our second aim was to examine whether aggressive lipid-lowering therapy could attenuate the potentially adverse impact of obesity.

Methods

Study population and design. The Post CABG trial was a multicenter, double-blind, randomized, controlled trial of participants who had undergone CABG surgery recruited from the Montreal Heart Institute, Cedars-Sinai Medical Center, the Cleveland Clinic, the University of Minnesota, and Baylor College of Medicine. To be eligible, participants had to have undergone CABG surgery 1 to 11 years before entry and be 21 to 74 years of age. Other inclusion criteria included the presence of 2 completely independent, patent saphenous vein grafts in men or 1 in women; an LDL-C level between 130 and 175 mg/dl; plasma triglycerides below 300 mg/dl; and a left ventricular ejection fraction of at least 30%. Participants were excluded if there was a high likelihood of revascularization or death in 5 years, unstable angina or myocardial infarction within 6 months before the start of the trial, severe angina, heart failure, and absolute contraindications to treatment with any of the study medications. Patients who had a markedly positive exercise test, defined as the presence of ST-segment depression greater than 2.5 mm in at least 1 lead, were also re-evaluated for possible exclusion from the study. A total of 1,351 patients were

enrolled. All participants provided written informed consent.

Participants were randomly assigned in a 2 × 2 factorial design to 1 of 4 treatment groups: aggressive LDL-C lowering with lovastatin 40 to 80 mg/day to achieve an LDL-C of 60 to 85 mg/dl versus moderate LDL-C lowering with lovastatin 2.5 to 5 mg/day to achieve an LDL-C of 130 to 140 mg/dl and warfarin 1 to 4 mg/day to achieve an international normalized ratio of 1.8 to 2.0 versus placebo. Participants could receive cholestyramine 8 mg/day as necessary to achieve LDL-C goals. All participants also received instruction regarding a National Cholesterol Education Program Step I diet and were offered programs on exercise and smoking cessation.

Exposure assessment. Study staff measured the weight and height of all participants at baseline and recorded BMI as the ratio of the weight in kilograms to the square of the height in meters. We categorized participants into 4 BMI categories according to National Institutes of Health guidelines: normal weight (18.5 to 24.9 kg/m²), overweight (25.0 to 29.9 kg/m²), class I obesity (30.0 to 34.9 kg/m²), and class II to III (≥35 kg/m²) (20). To minimize the bias related to underweight, we excluded the 37 participants with a BMI <18.5 kg/m² or who had a history of cancer or severe pulmonary disease.

Outcome measurements. Participants were followed for up to 5 years. Angiography was performed at baseline and at 4 to 5 years after enrollment. The primary end point of the trial was atherosclerotic graft progression assessed by angiography 4 to 5 years after enrollment. The definition of graft worsening in the Post CABG trial was a decrease of ≥0.6 mm in lumen diameter at the site of greatest change at follow-up. As in previous Post CABG trial publications (21), all initially patent grafts were considered to have developed graft worsening in patients who died prior to repeat angiography.

In addition, participants were followed for clinical events through the end of the trial. The pre-defined principal clinical end point was a composite clinical outcome including death from cardiovascular or unknown causes, nonfatal myocardial infarction, stroke, CABG surgery, or angioplasty.

Other covariates. At baseline, participants were assessed for left ventricular function by angiography. Lipids were measured in all participants at the individual clinical centers using the Lipid Research Clinics Program protocol (22). Participants reported their smoking history, which we separated into 3 categories (never, former, and current). Enrolling centers recorded participants' medical histories, including cardiovascular risk factors and previous clinical diagnoses. Finally, limited physical activity information was also assessed. All participants reported 3 indicators of their

Abbreviations and Acronyms

BMI	= body mass index
CABG	= coronary artery bypass graft
CHD	= coronary heart disease
LDL-C	= low-density lipoprotein cholesterol

physical activity: how their activity level compared with that of others of the same age and sex at baseline in 5 categories (much more active to much less active), whether they engaged in strenuous exercise or labor, and whether they exercised for 20 min at least 3 times a week.

Statistical methods. We prospectively evaluated the relationship between BMI and 2 measures of prognosis: the risk of progression of graft atherosclerosis and the risk of recurrent coronary heart disease (CHD) events.

As in previous analyses from the Post CABG Trial Investigators, we analyzed graft progression on a per-graft basis, using generalized estimating equations to account for the clustering of grafts within participants (21). In these analyses, the primary outcome was a binary decrease of ≥ 0.6 mm in lumen diameter. We used a logit link to estimate odds ratios and an exchangeable correlation matrix.

In analyses of CHD events using the pre-defined clinical end point, we used Cox proportional hazards models, censored at the date of first clinical event, death, or the end of follow-up. Accordingly, we present hazard ratios with their 95% confidence intervals. Analysis of time-varying covariates demonstrated no violation of the proportional hazards assumption.

For both end points, we created initial models (model 1) that adjusted for age, gender, race, treatment assignment, smoking, and years since CABG surgery. We then developed additional models that further controlled for factors that might be in the causal pathway between obesity and end points of interest, including physical activity level (model 2) and clinical factors such as left ventricular ejection

fraction and prior history of hypertension, diabetes, myocardial infarction, and stroke. For tests of trend, we tested log (BMI) as a continuous measure after confirming the assumption of linearity within each BMI category; log (BMI) gave a better model fit than untransformed BMI with less sensitivity to outliers. To examine whether the effect of BMI varied with aggressive treatment of lipids with lovastatin, we tested for a potential interaction between randomized treatment assignment and log (BMI); we also tested for an interaction between baseline lipid level and log (BMI).

We used SAS System for Windows, release 9.1 (SAS Institute, Inc., Cary, North Carolina) for all analyses.

Results

Sample characteristics. A total of 1,314 Post CABG trial participants were included in our analysis, of whom 198 had a clinical event. A total of 870 of 2,603 grafts showed significant atherosclerotic progression during the course of follow-up. Table 1 shows the characteristics of study participants according to BMI category. Participants with higher BMI were generally younger and exhibited a more adverse cardiovascular risk factor profile.

BMI and prognosis. Table 2 shows the likelihood of clinical events and angiographic end points stratified by BMI among Post CABG trial participants. After adjustment for demographic factors, treatment assignment, smoking status, and years since CABG surgery, BMI was not

Table 1 Baseline Characteristics of Post-CABG Participants According to BMI

	BMI (kg/m ²)				p Value
	18.5 to 24.9 (n = 336)	25.0 to 29.9 (n = 656)	30.0 to 34.9 (n = 254)	35.0+ (n = 68)	
Median BMI (kg/m ²)	23.7	27.1	31.7	37.5	
Age (yrs), mean (SD)	61.9 (7.4)	61.7 (7.2)	60.3 (7.5)	60.2 (7.4)	0.02
Years since CABG	4.7 (2.5)	4.9 (2.6)	4.9 (2.5)	5.0 (2.4)	0.72
Male gender, n (%)	300 (89)	624 (95)	238 (94)	57 (84)	<0.001
White race, n (%)	304 (90)	632 (96)	239 (94)	64 (94)	0.003
Smoking status, n (%)					
Current smoker	42 (13)	72 (11)	21 (8)	8 (12)	0.41
Former smoker	191 (57)	413 (63)	180 (71)	49 (72)	0.002
Alcohol abstainer, n (%)	179 (53)	358 (55)	152 (60)	47 (69)	0.05
Baseline clinical status					
Diabetes, n (%)	14 (4)	48 (7)	23 (9)	9 (13)	0.02
Hypertension, n (%)	90 (27)	221 (34)	117 (46)	36 (53)	<0.001
Previous MI, n (%)	169 (50)	321 (49)	127 (50)	29 (43)	0.70
LVEF (%), mean (SD)	58.8 (11.9)	55.7 (12.2)	56.8 (11.9)	55.5 (10.1)	0.002
Baseline laboratory results, mean (SD)					
ALT, IU/l	20.8 (9.6)	22.4 (10.6)	25.6 (12.4)	28.3 (12.6)	<0.001
WBC, K/uI	6.3 (1.7)	6.5 (1.7)	6.8 (1.8)	7.6 (2.6)	<0.001
Triglycerides, mg/dl	140 (65)	163 (68)	182 (84)	200 (90)	<0.001
HDL-C, mg/dl	42.4 (10.9)	39.8 (9.7)	37.4 (8.2)	37.5 (7.8)	<0.001
LDL-C, mg/dl	158.3 (20.3)	158.3 (19.8)	158.7 (21.8)	163.2 (22.1)	0.31

The p values were derived from exact tests for categorical variables and analysis of variance for continuous variables.

ALT = alanine aminotransferase; BMI = body mass index; CABG = coronary artery bypass graft; HDL-C = high-density-lipoprotein cholesterol; LDL-C = low-density-lipoprotein cholesterol; LVEF = left ventricular ejection fraction; MI = myocardial infarction; WBC = white blood cell.

Table 2 HR for Cardiovascular Events and OR for Angiographic Findings According to Baseline BMI After CABG

	BMI (kg/m ²)				p for Trend
	18.5 to 24.9	25.0 to 29.9	30.0 to 34.9	35.0+	
Clinical events					
Participants (n)	336	656	254	68	
Death or MI (n)	33 (10)	59 (9)	27 (11)	6 (9)	
Composite events (n)	52 (15)	104 (16)	33 (13)	9 (13)	
HR*	1.00	0.97	0.81	0.79	0.81
95% CI		0.69-1.36	0.52-1.27	0.39-1.62	
Angiographic significant worsening					
Grafts (n)	652	1,333	487	131	
Significant worsening (n)	205 (31)	433 (32)	186 (38)	46 (35)	
OR*	1.00	1.01	1.36	1.29	0.003
95% CI		0.79-1.29	1.00-1.84	0.81-2.07	

*Model adjusts for age, gender, race, treatment assignment, smoking, and years since CABG surgery. A BMI <18.5 kg/m², history of cancer, or severe chronic obstructive pulmonary disease excluded. Test for trend uses BMI as a continuous variable.

CI = confidence interval; HR = hazard ratio; OR = odds ratio; other abbreviations as in Table 1.

associated with incident clinical events but was associated with angiographic progression.

Modifying effects of aggressive lipid lowering. Table 3 shows the relationships between BMI and angiographic end points and clinical events stratified by randomized treatment assignment. In the low-dose lovastatin group, higher BMI was associated with a higher odds ratio of angiographic progression and a higher hazard ratio of clinical events. In the high-dose lovastatin group, BMI was not clearly associated with adverse outcome and appeared to be protective against adverse clinical events. Tests for the interaction between BMI and lovastatin treatment groups on both angiographic and clinical end points were statistically significant in our primary models (model 1) ($p = 0.03$ and 0.02 , respectively). We did not detect a significant interaction between baseline lipid level and BMI. Additional adjustment for measures of physical activity and clinical factors had little effect on the point estimates.

Discussion

Summary of findings. In this population of patients who underwent CABG surgery and who were randomized to either high- or low-dose lovastatin, higher BMI was associated with a higher likelihood of atherosclerotic progression of CABG grafts but not with a higher likelihood of clinical cardiac events. However, even though higher BMI was associated with the likelihood of angiographic progression and clinical events among those randomized to the low-dose lovastatin group, BMI was not clearly associated with adverse outcomes among those in the high-dose lovastatin group and may be protective against clinical cardiovascular events.

Obesity and outcomes in established coronary disease. Although there is strong evidence to suggest that obesity is a major risk factor for developing CHD, it is less clear whether obesity accelerates progression of disease among those with existing coronary disease (7-15). An obesity

paradox has been observed in several clinical populations with cardiovascular and other diseases, in which greater BMI has been linked to better subsequent prognosis (23-28). It seems likely that this paradox is related, at least in part, to difficulty in fully accounting for weight loss related to clinical comorbidity or severity of illness (29), particularly during short-term follow-up. Previous studies of adiposity and BMI and longer-term outcomes after CABG surgery have shown mixed results (7,13-15). Gurm et al. (15) used data collected as part of the BARI (Bypass Angioplasty Revascularization Investigation) study and found that obesity was associated with a much higher 5-year risk of cardiac mortality. In contrast, Kim et al. (7) did not find differences in mortality across BMI at 30 days, 1 year, or 5 years after CABG.

Our study is unique in being able to examine the relationship between obesity and the more immediate end point of atherogenic graft progression, highlighting the clear risk of obesity with greater progression of atherosclerosis over time. As in many previous studies, we found no strong relationship between BMI and coronary events in the overall study sample. However, given the established relationship of atherosclerotic progression with long-term clinical events (30), obesity may well have led to a demonstrably greater risk of clinical events with longer follow-up.

Statin treatment on obesity's effect on cardiovascular end points. Our study also found important interactions between BMI and lovastatin treatment assignment for both atherogenic progression and clinical events. Among participants randomized to the low-dose lovastatin group, higher BMI was strongly associated with atherogenic progression and a trend toward a higher risk of clinical events. In contrast, higher BMI was not associated with atherogenic graft progression among those assigned to high-dose lovastatin; moreover, high-dose lovastatin appeared to have a greater protective effect on clinical end points. These findings suggest that the adverse atherogenic effects conferred

Table 3 HR for Cardiovascular Events and OR for Angiographic Progression (and 95% CI) Among Post-CABG Participants According to BMI and Statin Treatment

	BMI (kg/m ²)				p for Trend
	18.5 to 24.9	25.0 to 29.9	30.0 to 34.9	35.0+	
Composite clinical events					
Low-dose lovastatin, HR (95% CI)					
Model 1	1.00	1.45 (0.89–2.35)	1.09 (0.59–2.02)	1.89 (0.75–4.77)	0.14
Model 2	1.00	1.46 (0.89–2.39)	1.11 (0.59–2.07)	1.55 (0.59–4.05)	0.23
Model 3	1.00	1.43 (0.87–2.35)	1.14 (0.61–2.14)	1.63 (0.61–4.33)	0.20
High-dose lovastatin, HR (95% CI)					
Model 1	1.00	0.60 (0.37–0.98)	0.58 (0.30–1.10)	0.30 (0.09–1.00)	0.06
Model 2	1.00	0.58 (0.35–0.94)	0.52 (0.27–1.01)	0.26 (0.08–0.88)	0.03
Model 3	1.00	0.54 (0.32–0.90)	0.47 (0.24–0.92)	0.25 (0.07–0.86)	0.02
Angiographic significant worsening					
Low-dose lovastatin, OR (95% CI)					
Model 1	1.00	1.07 (0.75–1.51)	1.40 (0.93–2.10)	3.55 (1.79–7.06)	<0.001
Model 2	1.00	1.04 (0.73–1.49)	1.32 (0.87–2.00)	2.81 (1.42–5.53)	<0.001
Model 3	1.00	1.01 (0.70–1.46)	1.34 (0.88–2.05)	2.97 (1.50–5.88)	<0.001
High-dose lovastatin, OR (95% CI)					
Model 1	1.00	0.95 (0.66–1.36)	1.31 (0.84–2.05)	0.56 (0.27–1.15)	0.75
Model 2	1.00	0.95 (0.66–1.37)	1.30 (0.83–2.03)	0.56 (0.27–1.18)	0.71
Model 3	1.00	0.91 (0.62–1.32)	1.22 (0.77–1.93)	0.53 (0.25–1.14)	0.85

Model 1 adjusts for age, gender, race, treatment assignment, smoking, and years since CABG surgery. Model 2 includes variables from model 1 and additionally adjusts for activity relative to others and frequency of strenuous exercise. Model 3 includes variables from model 2 and additionally adjusts for LVEF and past history of hypertension, diabetes, MI, and stroke. A BMI <18.5 kg/m², history of cancer, or severe chronic obstructive pulmonary disease excluded. Test for trend uses BMI as a continuous variable.

Abbreviations as in Tables 1 and 2.

by obesity may be ameliorated by aggressive treatment with lovastatin. Whether this is a class effect of statins is not clear; however, statins have been shown to not only improve dyslipidemia but also reduce systemic inflammation that might lead to atherosclerosis (16).

Current guidelines already recommend statin treatment in patients with pre-existing coronary disease. Our findings reinforce its aggressive use in such patients who are also obese. Whether this added benefit in obesity is directly related to lipid-lowering or anti-inflammatory effects of statins warrants further study. Future research should also examine whether the stronger effect of statins in obese patients generalizes to patients without pre-existing coronary disease, as these findings could have important implications on whether thresholds for statin treatment should be lowered for patients with obesity.

Finally, our study suggests that once lipids are lowered, obesity may actually be protective against cardiovascular disease. Future studies will need to confirm our findings and explore potential underlying mechanisms.

Study strengths and limitations. The Post CABG trial was large and based in multiple centers, and the assessment of graft progression was uniform and systematic, an important strength. The trial included both angiographic and clinical end points, and objective measurements of BMI. Lipid-lowering treatment was randomly assigned, allowing us to evaluate the interaction of BMI with statin treatment free of confounding. However, clinical trial participants may practice healthier behaviors than other patients, and the trial predominately enrolled white men, both potentially limiting the generalizability of our study. Even though BMI was measured in the trial, it was measured only at baseline and is only one surrogate measure of adiposity; we were not able to measure changes in weight over time, which may have had an impact on our outcome, although weight change would be systematically different between those randomized to one treatment group compared with those in another group. Finally, there are few clinical events during the follow-up period, especially for more obese participants;

hence, our conclusions related to clinical events must be interpreted with caution.

Conclusions

In summary, among individuals with known CHD who had undergone previous CABG surgery, BMI was most strongly associated with significant angiographic progression in graft atherosclerosis in patients who were treated with low-dose lovastatin. Higher BMI was not associated with adverse atherogenic or clinical coronary end points in patients treated with high-dose lovastatin, suggesting that aggressive treatment with this and potentially with other statins may reverse the adverse effect of obesity on coronary artery disease progression. Future studies should examine whether the larger benefits of statins in obese persons generalize to those without pre-existing coronary disease.

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