Cardiovascular Outcomes Improved by Bariatric Surgery Independent of Baseline BMI

Sjostrom L, Peltonen M, Jacobson P, et al. Bariatric surgery and long-term cardiovascular events. JAMA 2012;307:56–65.

Study Overview

Objective. To determine if bariatric surgery decreases risk of subsequent cardiovascular events in obese patients.

Design. Nonrandomized prospective trial of surgery versus traditional therapy for obese patients.

Setting and participants. The Swedish Obese Subjects (SOS) trial is one of the largest and longest-running prospective trials of bariatric surgery in the world. Participants were enrolled between 1987 and 2001 from 480 Swedish primary health care centers. Individuals were eligible to participate if they were between 37 and 60 years of age and obese (minimum BMI of 34 for men and 38 for women) but had not had previous bariatric or gastric/duodenal ulcer surgery, recent gastric ulcer, ongoing or recent (within 5 years) malignancy, recent (within 6 months) myocardial infarction (MI), drug or alcohol abuse, or other behavioral and psychological problems. Of 5335 eligible patients, 2010 elected to undergo surgery. They were matched with 2037 control participants based on 18 baseline variables. Intervention patients underwent 1 of 3 surgeries: 376 (18.7%) had gastric banding, 1369 (68.1%) had vertical banded gastroplasty (VBG, or "stomach stapling"), and 265 (13.2%) underwent gastric bypass. The decision about type of surgical procedure was presumably made by providers at the clinical site of the patient's surgery, though this is not made explicitly clear in the article. Patients in the control group received "the customary treatments for obesity at their centers of registration." The investigators describe that in some cases this meant lifestyle advice, while in others it meant no treatment whatsoever. Patients were followed for up to 20 years after enrollment.

Main outcome measures. The primary endpoint of the overall SOS trial was mortality; however, this publication focused on the secondary endpoints of MI and stroke, both separately and combined. These endpoints were determined both through data collection by the primary health center of the patient (the SOS registry), and through cross-checking of the Swedish National Patient Register, the Cause of Death Registry, and the Registry of the Total Population. ICD-9 classification

was used to identify diagnoses of MI, intracerebral bleeding, cerebral artery occlusion, and acute stroke. Episodes of angina pectoris, claudication, TIAs and subarachnoid hemorrhage were not included.

Results. At baseline, the surgical and control groups were well-matched on most characteristics. All patients in the trial were white and 71% were female. Patients in the surgical group had overall slightly higher levels of comorbid disease, and were more likely to be daily smokers (28% vs 20%; $P < 0.001$) at enrollment. Additionally, the mean BMI of the surgical group was slightly higher than that of the nonsurgical group (42 vs 40 kg/m^2, $P < 0.001$). The mean age in the surgical group was 46.4 years and 47.1 years in the control group ($P < 0.001$). Patients were followed up for a median of 14.7 years, with the analysis period terminating on 31 Dec 2009, at which point the authors report a follow-up rate of 99% for both groups with respect to time until first event (MI, stroke).

During the follow-up period, weight loss differed substantially between the surgical and control groups. Mean changes in body weight at 2, 10, and 20 years in the surgical group were –23%, –17%, and –18%, whereas in the control group the mean changes were only 0%, –1% and –1%. Of the surgical types, gastric bypass was associated with the highest degree of weight loss, and gastric banding the lowest. Cox proportional hazards regression models were used to evaluate the difference between the 2 groups with respect several endpoints. The endpoint of cardiovascular death (from MI or stroke) was less likely in the surgical group, with an unadjusted hazard ratio of 0.56 (95% CI, 0.35–0.88), and multivariable adjusted ratio of 0.47 (95% CI, 0.29–0.76). The surgical group also fared better when looking at all (fatal and nonfatal) cardiovascular events. Though the crude hazard ratio was not significantly improved compared with controls (HR, 0.83; 95% CI, 0.69–1.00), it became so after adjusting for other baseline covariates (HR, 0.67; 95% CI, 0.54–0.83). This pattern of reduced risk among surgical patients held when examining the endpoints of all myocardial infarctions (adjusted HR, 0.71; 95% CI, 0.54–0.94), and total stroke events (adjusted HR, 0.66; 95% CI, 0.49–0.90).

The authors performed several subgroup analyses to determine which groups benefited most from bariatric surgery with respect to cardiovascular risk reduction. As expected, they found that people with risk factors for CVD at baseline (eg, men, previous MI, smokers) had higher rates of MI and stroke in the follow-up period, and that they seemed to have higher relative treatment effects of the surgery. Surprisingly, however, they found that baseline BMI was not related to the surgical treatment benefit. Specifically, the number needed to treat (NNT) for participants at or below the median BMI (41) was 52 (95% CI, 20–∞), and in participants above the median BMI it was 81 (95% CI, 24–∞). In contrast to this finding, participants with higher levels of baseline plasma insulin (> 17 mU/L) saw a greater relative benefit of surgical treatment (NNT, 21; 95% CI, 12–66) than those with lower plasma insulin levels (NNT, 173; 95% CI, 32–∞) (P for interaction < 0.001).

Conclusion. In this large, prospective trial of bariatric surgery, participants who received surgery were less likely to have cardiovascular events during the 20-year follow-up period than matched controls. Surprisingly, cardiovascular risk reduction was independent of baseline BMI, but was linked to baseline plasma insulin level, with a stronger effect of surgery in patients with higher insulin levels at baseline.

Commentary

Bariatric surgery produces dramatic weight loss in obese patients, but some of its major health effects may be mediated through other pathways. There are now numerous studies demonstrating diabetes resolution after bariatric surgery [1], in many cases independent of weight loss [2]. As published previously by the authors of this study, bariatric surgical patients also have decreased mortality [3] and cancer incidence relative to matched controls [4]. One question that has not been definitively answered is whether or not bariatric surgery reduces the risk of CVD in recipients. This question is particularly important in light of mixed epidemiological data surrounding weight loss and CVD risk. Some studies have shown an increased risk of cardiovascular events and death in obese adults who lose weight, although, as the authors of this study point out, this pattern may be confounded by the inclusion of people with unintentional weight loss. One recent prospective study did show a decrease in risk factors for future cardiovascular events (by Framingham score) after gastric bypass surgery, but follow-up was limited

to 1 year [5].

In this large, nonrandomized trial of bariatric surgery, the authors found that participants who underwent surgery had lower risk of subsequent MI and/or stroke relative to matched controls. Perhaps even more interesting, they discovered that this protective effect was independent of baseline BMI but highly related to baseline insulin levels of participants.

The study is quite unique in terms of the length of follow-up (up to 20 years) and retention rates (99% follow-up) of bariatric surgical patients. In part, this is likely due to the robust national medical record keeping systems in Sweden. Other strengths of the study are its large size and careful matching of control patients on 18 baseline variables. One novel aspect of this study is the notion that CVD reduction from weight-loss surgery has more to do with baseline insulin levels than it does baseline weight/BMI. Given that most guidelines on the use of bariatric surgery focus almost exclusively on BMI cutoffs, this data adds to the growing argument to consider comorbidities such as diabetes before using weight alone to justify performing these procedures.

Despite careful matching, the fact that the study is nonrandomized could have resulted in residual confounding. Namely, it is possible that patients who self-selected to have surgery differed from those in the control group with respect to unmeasured factors such as motivation, adherence, and follow-up with medical care—factors that could also confer reduced risk of subsequent CVD. Also, although the long duration of follow-up is a real strength for the study, it does pose a problem with respect to changing technologies. Approximately 70% of patients in the intervention arm had a procedure called vertical banded gastroplasty (commonly known as "stomach stapling"). This procedure is now largely obsolete due to safety and efficacy concerns, and it is hard to know whether the results of those patients would be directly comparable to the lap-band and gastric bypass patient population of today's world. Additionally, the findings of this trial (which had only white participants) may also have limited generalizability in a multiethnic population such as that of the United States.

In touting the benefits of surgical intervention, the authors make several comparisons to previous studies of lifestyle interventions. The control group in this study, however, did not appear to have any such structured intervention ("advanced lifestyle advice in many sites to no treatment in other sites"). While the effect of bariatric surgery may be impressive compared to no intervention, it is worth considering how strong that effect would have been compared to a structured 20-year lifestyle intervention. Also, as pointed out by Dr. Edward Livingston in an editorial accompanying this publication, although the relative risk of cardiovascular events was impressive in surgical patients relative to controls, the absolute risk reduction was relatively small [6].

Applications for Clinical Practice

The authors of this study report a decrease in cardiovascular events up to 20 years following bariatric surgery, an effect that was independent of baseline BMI but related to elevated plasma insulin levels. Physicians are increasingly faced with the challenges of caring for an obese patient population, many of whom have diabetes and CVD in addition to their excess weight. When considering referral for bariatric surgery, physicians should know the existing guidelines, but also be cognizant of a patient's overall risk factor profile, and remain up to date on changing recommendations around comorbidity-driven indications for surgery.

—Review by Kristina Lewis, MD, MPH

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