

# The Role of Bariatric Surgery in Managing the Macrovascular Complications of Obesity-Related Type 2 Diabetes

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**Reducing the risk** of macrovascular events, including myocardial infarction and stroke, is a major goal when treating diabetes. Despite this focus, of the major randomized trials used to support current diabetes guidelines (ACCORD, ADVANCE, UKPDS 33, UKPDS 34, VADT), none showed reductions in macrovascular events when the trial results were first reported.<sup>1,2</sup> For example, UKPDS is still frequently cited in support of aggressive glucose lowering, yet when the primary outcome data were presented in 1998, the results showed no difference between groups in terms of reducing the risk of all-cause mortality (relative risk [RR], 0.94 [95% CI, 0.80-1.10]), myocardial infarction (RR, 0.84 [95% CI, 0.71-1.00]), heart failure (RR, 0.91 [95% CI, 0.54-1.52]), stroke (RR, 1.07 [95% CI, 0.68-1.69]), or kidney failure (RR, 0.73 [95% CI, 0.25-2.20]). Only 1 of 21 clinical end points showed a statistically significant difference attributable to intensive glucose control after 10 years of treatment.<sup>3</sup> Of the 21 end points, only the need for retinal photocoagulation was significantly reduced with intensive glucose lowering, although the effect size was small (RR, 0.71 [95% CI, 0.53-0.98]). An effect of aggressive glucose lowering was only seen 10 years after the trial was completed, when patients were no longer receiving the assigned interventions and had similar glycated hemoglobin levels.<sup>4</sup> This observational analysis of this randomized clinical trial eventually showed reduction in macrovascular disease, including for myocardial infarction (RR, 0.85 [95% CI, 0.74-0.97]) and all-cause mortality (RR, 0.80 [95% CI, 0.79-0.96]) but not for stroke (RR, 0.91 [95% CI, 0.73-1.13]).

In ACCORD, there was no reduction in macrovascular disease, including the primary outcome of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes (hazard ratio [HR], 0.90 [95% CI, 0.78-1.04]).<sup>5</sup> In VADT, there was also no reduction in the macrovascular disease primary outcome of myocardial infarction, stroke, death from cardiovascular causes, congestive heart failure, surgery for vascular disease, inoperable coronary disease, and amputation for ischemic gangrene (HR, 0.88 [95% CI, 0.74-1.05]).<sup>6</sup>

Even the newer agents for treatment of diabetes, touted because of their effect on cardiovascular disease, show only modest reductions in macrovascular events. A recent network meta-analysis that compared various classes of these new agents with placebo suggested that of the newer drugs, sodium-glucose cotransporter 2 agents were the most effective for controlling macrovascular disease.<sup>7</sup>

Glucose lowering with medication for treating diabetes is universally accepted. Bariatric surgery also effectively con-

trols diabetes but is not considered a first-line approach for treating diabetes in patients with obesity. Compared with the large amount of clinical trial information available for drug treatment of diabetes, much less exists for bariatric surgery. One gap is how improved glucose control following bariatric surgery might result in better cardiovascular outcomes. In October 2018 Fisher et al<sup>8</sup> reported in *JAMA* the results of an observational analysis from 4 integrated health systems that included 5301 obese patients with diabetes who underwent bariatric surgery and were compared with 14 934 patients who served as controls. At 7 years, although there was no significant reduction in incident coronary artery disease or cerebrovascular disease (HR, 0.56 [95% CI, 0.29-1.08] and 0.58 [95% CI, 0.25-1.36], respectively), all-cause mortality was significantly reduced among patients who had received bariatric surgery (HR, 0.34 [95% CI, 0.15-0.74]).

In this issue of *JAMA*, Aminian et al<sup>9</sup> report macrovascular outcomes, described as incident extended major adverse cardiac events (a composite of 6 outcomes as the primary end point, defined as first occurrence of all-cause mortality, coronary artery events, cerebrovascular events, heart failure, nephropathy, and atrial fibrillation) among 2287 obese patients (mean BMI, 45.1) with diabetes (mean glycated hemoglobin level, 7.1%) who underwent bariatric surgery between 1998 and 2017. These patients were compared with 11 435 similar patients who received usual care. After a median follow-up of 3.9 years, bariatric surgery was associated with statistically significant better outcomes for the primary outcome, with 8-year cumulative incidence of 30.8% in the surgical group vs 47.7% in the nonsurgical group (absolute risk difference, 16.9% [95% CI, 13.1%-20.4%]; adjusted hazard ratio, 0.61 [95% CI, 0.55-0.69]). Bariatric surgery was also associated with lower risk of all-cause mortality (10.0% vs 17.8%; absolute risk difference, 7.8% [95% CI, 5.1%-10.2%]; adjusted HR, 0.59 [95% CI, 0.48-0.72]) and reductions in each of the major cardiovascular outcomes and kidney failure.

The results of this study should be interpreted with caution, reflecting the observational design and, as reported by Aminian et al, imprecise matching of the study groups. The control group was slightly older (52.5 years v 54.8 years), had higher diastolic blood pressures, and had much more missing data. Patients who underwent bariatric surgery had higher body mass index and systolic blood pressure and more hypertension and dyslipidemia. Despite careful propensity matching, these sorts of imbalances always persist in observational studies, highlighting the limitations of interpreting comparisons made between groups in such studies. Although

patients are referred to as “matched” in observational studies, a more appropriate description is “similar.” Although similar, important differences exist that can influence how observational studies are interpreted. That patients had more severe comorbid disease in the bariatric surgery group suggests that because there were many fewer major cardiovascular events in this group, the intervention was even more effective than is apparent from the observed differences, considering that the bariatric surgery group started at a relative clinical disadvantage. That the control group was older suggests that these patients might have had diabetes longer and, because it takes time for macrovascular disease to develop, had more substantial vascular disease, biasing the results in favor of bariatric surgery.

The greater amount of missing data in the control group belies a major source of confounding that affects all bariatric surgery studies. Patients who undergo these operations are sufficiently motivated that they are willing to undergo a major, risky intervention to lose weight and improve their health outcomes. Within the control group will be a subset of patients motivated to neither lose weight nor take care of themselves. These patients may not have aggressively pursued health care

on a regular basis, manifested in part by having fewer laboratory test results available for review. The difference in health outcomes between highly motivated obese patients who pursue bariatric surgery and those who are not motivated will be manifested by a stark difference in health outcomes and might contribute to the apparent benefits of bariatric surgery found in observational studies.

In 2019, for obese patients with diabetes, what is the best treatment option? The results from drug studies, although of relatively high quality, suggest limited effect on long-term macrovascular outcomes. In contrast, bariatric surgery appears to improve long-term outcomes, including mortality, but the quality of evidence is not as high. However, by inducing substantial weight loss, bariatric surgery not only treats diabetes but also improves hypertension, lipid levels, and sleep apnea; reduces osteoarthritis; and improves many other weight-related problems.<sup>10-12</sup> When balancing the imperfections in the evidence for both medical and surgical treatment of diabetes, the many benefits associated with bariatric surgery-induced weight loss suggest that it should be the preferred treatment option for carefully selected, motivated patients who are obese and have diabetes and cannot lose weight by other means.

#### ARTICLE INFORMATION

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