Surgical Management of Obesity and the Relationship to Cardiovascular Disease

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The World Health Organization estimates that by 2015 the number of adults who are overweight (body mass index [BMI], 25.0–29.9 kg/m²) or obese (BMI ≥30 kg/m²) will surpass 1.5 billion. Excess body weight is an independent risk factor for mortality. Among the constellation of weight-related comorbidities that bring the greatest burden for obese patients and their healthcare providers are diabetes mellitus and cardiovascular disease (CVD). Obesity, diabetes mellitus, and CVD cannot be successfully addressed in isolation; therefore, weight loss achieved by any means is a key component of comprehensive cardiovascular care.

Dietary, Lifestyle, and Pharmacological Management of Obesity

Obesity prevention is the ideal scenario. However, in the midst of an obesity pandemic, treatment options are essential. The initial approach must always address lifestyle and dietary choices, which contribute so greatly to the current obesogenic environment. A healthy lifestyle is easily prescribed but challenging to maintain. Stalonas et al demonstrated not only that patients who diet usually regain their lost weight within 5 years but also that the average subject was 1.5 lb heavier at follow-up than on entering the program. A recent systematic review of dietary and lifestyle options demonstrated no conclusive evidence for sustainable weight loss. However, it is possible for intensive lifestyle coaching to achieve moderate weight loss, as demonstrated by Appel et al. Of their 392 obese subjects, those receiving in-person support lost a mean of 5.1 kg (P<0.001 for comparison with control subjects) and those receiving only telephone/Internet support lost a mean of 4.6 kg (P<0.001 for comparison with control subjects) at 24 months. The superiority of bariatric surgery over pharmacological and lifestyle interventions in modulating weight, hyperglycemia, and hypertriglyceridemia has been demonstrated by meta-analysis. Few studies have directly compared medical and surgical management of obesity, but 2 head-to-head comparisons highlight the differential impacts. Morbidly obese subjects were assigned to gastric bypass surgery (n=80) or intensive lifestyle intervention (n=66), with the 76 surgical completers and 63 lifestyle completers achieving 1-year weight losses of 30±8% and 8±9%, respectively.

Diabetes mellitus and hypertension remission rates were significantly higher in the surgery group (70% versus 33% [P=0.027] and 49% versus 23% [P=0.016], respectively). Andersen et al randomized 57 patients to gastropasty or a very-low-calorie diet; at 5 years, 8 of 27 gastropasty patients (30%; 95% confidence interval [CI], 14–50) had maintained >10-kg weight loss compared with 5 of 30 diet-only patients (17%; 95% CI, 6–35).

Several pharmacological agents have been marketed for weight loss assistance, although the degree of weight loss in excess of placebo tends to be modest, generally lying in the −2- to −6-kg range. After the withdrawal of sibutramine from the American market, the sympathomimetic drugs with established and ongoing roles in the short-term treatment of obesity are phentermine, diethylpropion, benzphetamine, and phendimetrazine. Use is generally limited to 12 weeks, and potential side effects include hypertension. Two newer agents have recently gained Food and Drug Administration approval. Lorcaserin, a selective 5-HT₄ receptor agonist, was approved under the trade name Belviq in June 2012. It is intended to promote satiety in individuals with a BMI >30 kg/m² or >27 kg/m² plus at least 1 obesity-related comorbidity and is contraindicated in pregnancy. An extended-release preparation combining phentermine and topiramate (an antiepileptic) was subsequently approved in July 2012 as Qsymia. The standard dose contains 7.5 mg phentermine and 46 mg topiramate; there is also a high-dose 15-mg/92-mg option. Contraindications include pregnancy, glaucoma, hyperthyroidism, and unstable heart disease or stroke within the prior 6 months.

An alternate medication option is orlistat, which inhibits pancreatic lipases, thus increasing the proportion of dietary fat that is incompletely hydrolyzed and fecally excreted. It can be used for up to 2 years and achieved a 2.9-kg (95% CI, 2.5–3.2) mean weight reduction beyond placebo at 1 year in a meta-analysis of 15 studies. In obese individuals with diabetes, orlistat also decreases hemoglobin A₁c (HbA₁c) at 1 year compared with placebo. Other medications that may have a role in supporting weight loss include antidepressants such as venlafaxine, bupropion, and fluoxetine, as well as diabetes medications such as metformin and the glucagon-like peptide-1 (GLP-1) analogs exenatide, pramlintide, and liraglutide. At the time of writing, the Food and Drug

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Administration was reviewing a fixed-dose sustained-release combination of naltrexone and bupropion.15

Surgical Management of Obesity

Bariatric surgery is currently the most effective strategy for attaining significant and sustainable weight loss. Dr Richard Varco (Minnesota) performed the first jejunoileal bypass in 1953, specifically to induce weight loss from malabsorption. Although fraught with nutritional complications, this procedure achieved marked weight reduction and dramatically improved the lipid profiles of severely hyperlipidemic patients.16 The jejunoileal bypass was subsequently modified and refined to reduce malabsorptive complications while retaining the weight loss and lipid-lowering capabilities. Hence, procedures such as the biliopancreatic diversion (BPD; Dr Scopinaro) and duodenal switch (DS; Dr Marceau) emerged, followed by procedures with a “restrictive,” or gastric volume reduction, component, including the Roux-en-Y gastric bypass (RYGB) and vertical-banded gastroplasty. More recent developments are pure gastric volume reduction operations such as adjustable gastric banding (AGB) and sleeve gastrectomy (SG; see the Figure). RYGB, which combines gastric volume reduction and malabsorptive functions, was the most popular weight loss procedure in the United States and Canada as of 2008, being performed in 51% of 220,000 of surgical procedures.17 Conversely, gastric banding was more popular outside North America, with 43.2% AGBs versus 39% RYGBs in Europe and 82.5% AGBs versus 9.1% RYGBs in Asian and Pacific centers. Vertical-banded gastroplasty, the commonest surgery in the Swedish Obese Subjects (SOS) studies, is now rarely performed in the United States because it encourages maladaptive eating behavior.18

Candidacy for weight loss surgery is an evolving field, although the original 1991 National Institutes of Health guidelines recommending surgical intervention in patients with BMI >40 kg/m² or BMI ≥35 kg/m² plus significant obesity-related comorbidities continue to underline current practice (Table 1).19,20 The International Diabetes Federation proposed the newest additions to bariatric candidacy in 2011. They support consideration of surgery for patients with type 2 diabetes mellitus (T2DM) and obesity (BMI ≥30 kg/m²) who are failing to achieve International Diabetes Federation treatment targets with optimal medical therapy alone, especially in the presence of additional cardiovascular risk factors.20 The importance of incorporating bariatric surgery into a wider-reaching strategy including strict preoperative and postoperative dietary and physical activity modifications is comprehensively reviewed in the 2011 American Heart Association scientific statement on bariatric surgery and cardiovascular risk factors.21

Postoperative weight loss is typically expressed as a percentage of excess weight, referring to the difference between the actual and ideal weights for an individual. The primary goal of bariatric procedures is weight loss, and an excess weight lost (EWL) ≥50% is considered a surgical success. The 22,094-patient meta-analysis of Buchwald et al demonstrated a mean EWL of 61.2% (95% CI, 58.1–64.4) overall, 47.5% (95% CI, 40.7–54.2) for gastric band patients, 61.6% (95% CI, 56.7–66.5) for patients undergoing gastric bypass, 68.2% (95% CI, 61.5–74.8%) for those undergoing gastroplasty, and 70.1% (95% CI, 66.3–73.9) for BPD or DS patients, but mean follow-up periods were not stated. Sjöström et al reported a peak in weight loss at 1 to 2 years postoperatively followed by a small weight regain in all surgical procedure subgroups and subsequent weight stabilization after 8 to 10 years.

As bariatric surgery has become increasingly accepted among both physicians and patients as a mainstream strategy for weight loss over recent decades, the actual weight loss has almost been overshadowed by the impact on obesity-related comorbidities, as outlined in Table 2. However, these multisystem health benefits must be carefully weighed against the potential for surgical complications. Bariatric surgical risk has declined steadily with the widespread adoption of minimally invasive techniques and advanced medical device technology, with the majority of cases now being performed.
Table 1. Current Patient Criteria for Candidacy for Bariatric Surgery

Unsuccessful weight loss with dietary and exercise interventions, and one of the following:
- BMI ≥40 kg/m²
- BMI 35–39.9 kg/m² with ≥1 comorbidities such as type 2 diabetes mellitus, hypertension, or obstructive sleep apnea

Per International Diabetes Federation criteria, BMI 30–34.9 kg/m² with type 2 diabetes mellitus and failure to achieve glycemic treatment targets with an optimal medical regimen

Acceptable operative risk
- Psychosocially stable with no active depression, psychosis, or substance abuse
- Well-motivated patient, able to adhere to postoperative dietary restrictions
- BMI indicates body mass index.

Sources: National Institute of Health19 and International Diabetes Federation.20

Laparoscopically.42,43 Rates of conversion to open procedures are in the range of 0% to 5.7%, with the highest rates seen in the most complex malabsorptive procedures or revisional surgeries.44–46

Risks and Complications
In the first meta-analysis of published mortality data after bariatric surgery in 2004, Buchwald et al22 reported 30-day postoperative mortality of 0.1% for the gastric volume reduction procedures (2297 patients undergoing banding and 749 patients with gastroplasty), 0.5% in 5644 patients undergoing

Table 2. Rates of Comorbidity Reduction After Bariatric Surgery

<table>
<thead>
<tr>
<th>Disease or Symptom</th>
<th>Percent Improvement or Remission at ≤2 y If Specified</th>
<th>Percent Improvement or Remission at 5–7 y</th>
<th>Percent Improvement or Remission at 10 y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus</td>
<td>72% (Sjöström et al23)</td>
<td>54% (Sultan et al24)</td>
<td>36% (Sjöström et al25)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>24% (Sjöström et al23)</td>
<td>66% (Sugerman et al26)</td>
<td>41% (Sjöström et al25)</td>
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<tr>
<td>Hypertriglyceridemia</td>
<td>62% (Sjöström et al200427)</td>
<td>82% (Steffen 200928)</td>
<td>46% (Sjöström et al25)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>22% (Sjöström et al23)</td>
<td>53% (Bolen et al29)</td>
<td>21% (Sjöström et al25)</td>
</tr>
<tr>
<td>Sleep apnea</td>
<td>94% Clinical improvement, 25% apnea resolved at 1 y (Dixon et al30)</td>
<td>66% Clinically resolved, 92% resolved or improved, apnea index reduced 50% (Sugerman et al31)</td>
<td></td>
</tr>
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92% Daytime somnolence at 18 mo (Fritscher et al32) Apnea index reduced 61% in LAGB group but not statistically different from apnea reduction in conservative weight management group at 2 y (Dixon et al30)

Nonalcoholic fatty liver disease   | 84% Steatosis resolution, 75% fibrosis resolution (with rare reports of fulminant steatohepatitis after rapid weight loss; Furuya et al33) |

Migraine                           | Mean number of headache days reduced by ≈50% at 6 mo (Bond et al35) |

Pseudotumor cerebri                | 84% at 1 y (Sugerman et al36)                                |

Depression                         | ≈50% Improvement in Beck Depression Inventory at 1 y (Dixon et al,37 Hayden et al38) |

Polycystic ovarian syndrome        | ≈50% Resolution of hirsutism, 100% restoration of normal menstruation at 1 y (Escober-Morreale et al39) |

Degenerative joint disease         | ≈50% Improvement in pain score and osteoarthritis severity at 6 mo (Richette et al40) |

Stress urinary incontinence        | 64% Resolved, 92% resolved/improved at 1 y (Laungani et al41) |

LAGB indicates laparoscopic adjustable gastric banding.
lines or anastomotic sites; early identification and surgical management improve outcomes. Conservative management is indicated only for leaks controlled by a surgical drain in a hemodynamically stable patient. Early bleeding, including intraluminal and intraperitoneal bleeds, complicates 1% to 4% of bariatric operations, and rapid identification of hemodynamic instability necessitating surgical intervention is critical. Additional contributors to postoperative morbidity and mortality include sepsis resulting from anastomotic dehiscence, respiratory failure, and postoperative cardiac events, which are discussed separately below.

Other complications are unique to the specific procedure. The dumping syndrome is a constellation of gastrointestinal and vasomotor symptoms such as abdominal bloating, vomiting, diaphoresis, and dizziness associated with gastric volume reduction surgery. It is frequently attributed to rapid gastric emptying, although a hormonal component is likely. Dietary modifications such as reducing carbohydrates and avoiding liquids for 30 minutes after a meal or the use of octreotide can help. Restrictive operations are also susceptible to stenosis or stricture formation. Edema can cause acute partial or complete obstruction; in late obstruction, the cause is local fibrosis. Anastomotic strictures usually present in the first postoperative month after RYGB, and most can be managed endoscopically with balloon dilatations. Another delayed complication of bariatric surgery is ulceration near the gastrojejunal anastomosis of an RYGB or a BPD. These marginal ulcers are consequent to exposure of the unprotected jejunal mucosa to gastric acidity. Proton pump inhibition is sufficient for the majority of cases, with surgical intervention rarely required for refractory ulceration. Gastric band patients are inherently predisposed to band slippage, leakage, and erosion, resulting in reintervention rates as high as 20%. Incisional and internal herniation can complicate open and laparoscopic procedures, respectively. Given that presenting symptoms and clinical signs may be subtle, a high index of suspicion is critical for timely surgical exploration, reduction of the hernia, and resection of nonviable bowel.

Deficiency of essential vitamins and minerals is common after RYGB and BPD and on rare occasions may be life threatening (eg, thiamine deficiency encephalopathy). The multidisciplinary team should implement dietary supplementation immediately after the procedure, including the mostly commonly depleted micronutrients vitamins D and B12, folic acid, iron, and calcium. Rates of vitamin and mineral deficiencies are highly variable, but 1 study of 298 RYGB subjects receiving a variety of Roux limb lengths and anastomotic locations found the following deficiency prevalences at 2 to 3 years postoperatively: iron deficiency, 45% to 52%; vitamin B12 deficiency, 8% to 37%; calcium deficiency, 10%; and vitamin D deficiency 51%. A meta-analysis from Maggard et al concluded that =20% of bariatric surgery patients will experience a surgical complication or side effect, although the likelihood is much lower in laparoscopic than open procedures. Table 3 outlines the rates of RYGB complications that surgical candidates are counseled on at our institution.

### Patient Selection and Optimization

In addition to the basic criteria for bariatric surgery candidacy (Table 1), patients presenting for multidisciplinary evaluation are also assessed for preexisting comorbidities (particularly thromboembolism, untreated obstructive sleep apnea, coronary artery disease [CAD], or heart failure), micronutrient deficiencies, psychiatric diagnoses that may affect the patient’s ability to follow the postsurgical dietary program, and active substance abuse. It should also be remembered that male patients and those ≥60 years of age are at particular risk for complications. Well-informed, motivated patients with a history of adherence to medical therapy and strong social support are ideal candidates. Selection of the optimal surgical procedure for each individual is a decision process that factors in patient preference, the degree of perioperative risk acceptable to the individual, the degree of weight loss targeted, the presence of prior gastrointestinal conditions or interventions, and existing comorbidities. In general, patients with a BMI <40 kg/m² may be more suited to SG or LAGB, whereas surgery with a malabsorptive component such as laparoscopic RYGB or BPD with or without DS is usually preferable in patient with a BMI >40 kg/m².

### Table 3. Published Perioperative Complication Rates For Roux-En-Y Gastric Bypass

<table>
<thead>
<tr>
<th></th>
<th>Immediate Complications (Postoperative Days 0–3)</th>
<th>Early Complications (Postoperative Days 3–30)</th>
<th>Late complications (Usually Beyond Postoperative Day 30)</th>
</tr>
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<tbody>
<tr>
<td>Mild</td>
<td>Nausea and vomiting without consequence, up to 100%; self-resolving impairment in renal function, 2%</td>
<td>Wound infection, 3%; pneumonia, 4%; nausea and vomiting requiring inpatient admission for intravenous volume repletion, 8%</td>
<td>Malnutrition of vitamins or minerals, up to 50%; dumping syndrome, up to 75% but clinically significant in &lt;5%; gallstones, 2%; anastomotic ulcer, 8%; anastomotic stricture, 7%; stomal stenosis, 5%</td>
</tr>
<tr>
<td>Moderate</td>
<td>Arrhythmia without hemodynamic instability, 2%; abdominal hemorrhage or anemia without a clear source, requiring blood transfusion, 5%</td>
<td>Pulmonary embolus, respiratory failure, or other potentially fatal medical complication, 0.5%</td>
<td>Herniation or small bowel obstruction, 4%</td>
</tr>
<tr>
<td>Severe</td>
<td>Reoperation for abdominal hemorrhage, 2%; anastomotic leak with/without sepsis, 2%; reoperation for any reason, 6%; myocardial infarction, 0.5%; unstable arrhythmia or cardiac arrest, &lt;1%</td>
<td></td>
<td>Generalized overall risk of mortality to postoperative day 30, =0.3%</td>
</tr>
</tbody>
</table>

**Generalized overall risk of mortality from postoperative day 30 to 2 y, =0.3%**

Sources: Podnos et al., Schauer et al., and Buchwald et al.
consideration, even for less obese patients, is the presence of metabolic consequences of obesity. T2DM is an indication to consider RYGB even in patients with a BMI in the 30- to 40-kg/m² range, and BPD/DS may offer superior effects on insulin homeostasis in the superobese (>50 kg/m²) with difficult-to-control diabetes mellitus.

Standard preoperative testing includes basic blood tests (particularly to identify occult anemia, hypothyroidism, or renal/hepatic dysfunction), baseline ECG, chest x-ray, pulmonary function testing, upper endoscopy if suspicion exists for a gastric pathology, and polysomnography if obstructive sleep apnea is suspected by history. If *Helicobacter pylori* infection is present, preoperative eradication is advisable. Abdominal ultrasound may be performed to detect cholecystitis and to allow the surgeon to consider concomitant cholecystectomy; if hepatic steatosis or cirrhosis is suspected, intraoperative liver biopsy may be indicated. Although identification of comorbidities preoperatively is crucial, most are not a contraindication to proceeding with surgery. The Utah Obesity Study excluded only 1% of eligible subjects because of medical conditions. Obstructive sleep apnea should be managed with aggressive use of peripheroperative continuous positive airway pressure, and asthma or other lung conditions must be optimized. Baseline micronutrient deficiencies, commonly of vitamin D and iron, should be corrected preoperatively. Patients are encouraged and supported to lose 5% to 10% of their initial weight preoperatively, which can significantly reduce operating room times and lengths of stay for patients with BMI ≥50 kg/m².

Screening for and optimization of CAD before bariatric surgery is an area of variable practice. The 2009 AHA guidelines on cardiovascular evaluation and management of severely obese patients undergoing surgery offer very useful guidance for preoperative cardiac screening. Essentially, in patients with 1 CVD risk factor or known stable CAD, further cardiac assessment is not indicated. In individuals with >1 risk factor who are unable to demonstrate good functional capacity or who have cardiovascular symptoms on exertion, stress testing should be considered. Difficulties arise because both single-photon emission computed tomography imaging and stress echocardiogram have reduced accuracy in the obese population, principally as a result of reduced specificity and sensitivity, respectively. Noninvasive stress testing must usually be performed pharmacologically in this deconditioned population, and a proportion of dobutamine echocardiograms will be nondiagnostic as a result of suboptimal stress. Coupled with the fact that attenuation correction and combined supine/prone protocols significantly reduce the rate of false-positive single-photon emission computed tomograms in obesity, single-photon emission computed tomography (or position emission tomography when available) is usually the preferred modality. Alternative strategies include stress transesophageal echocardiograms or proceeding directly to cardiac catheterization in high-risk individuals such as those with ≥3 risk factors or a history of cardiovascular events.

Coronary revascularization before noncardiac surgery has not been shown to enhance survival, so preoperative stress test testing is recommended only when it will change management. It remains unclear how an asymptomatic pre–bariatric surgery patient, albeit usually with poor functional capacity, with a positive stress test should be managed; hence, testing in the absence of risk factors should be discouraged. Perioperative β-blockade is commonly prescribed for patients with CAD or a positive stress, although the risk-to-benefit ratio in the obese population is unknown. As outlined below, limited data suggest that bariatric surgery can be performed safely in heart failure patients who are medically optimized preoperatively. Anesthesia for bariatric patients has become an area of subspecialty expertise, developing methods in airway, hemodynamic, glycemic, and analgesic management specific to the obese population. Brief hypotension is seen in 5% to 10% of patients on institution of the pneumoperitoneum and steep reverse-Trendelenburg positioning, which usually responds briskly to intravenous fluids.

**Metabolic Changes With Bariatric Surgery**

Two-year data from SOS, in which the majority of patients underwent vertical-banded gastroplasty, revealed that 72% of surgical patients achieved freedom from preexisting diabetes mellitus compared with 21% of control subjects (*P*<0.001). At 10 years, diabetes mellitus remained in remission in 36% of the surgical group and 13% of control subjects (*P*<0.001). These findings were mirrored in the 135 246-patient meta-analysis by Buchwald et al that demonstrated complete resolution of diabetes mellitus (defined as off diabetes medications with fasting blood glucose <100 mg/dL or HbA₁c <6%) for 80.3% of patients with <2 years’ follow-up and 74.6% of patients with ≥2 years’ follow-up. Adams et al recently described 75% diabetes remission at 2 years and 62% remission at 6 years among 418 RYGB patients with 92.6% follow-up; the remission odds ratio compared with 2 control groups was 16.5 (95% CI, 4.7-57.6; *P*<0.001). However, the definition of diabetes “remission” has been variable across studies. Hence, criteria have been formulated by which a diabetes “cure” can now be defined: Complete remission requires an HbA₁c or fasting glucose in the normal range without pharmacological therapy or ongoing procedures of at least a 1-year duration. A 2012 SOS publication reported on the potential for bariatric surgery to prevent diabetes mellitus, with a 78% reduction in T2DM incidence over a median of 10 years after bariatric surgery compared with a matched group of obese subjects receiving standard medical care.

Results were recently reported from a prospective, randomized trial evaluating the efficacy of intensive medical therapy alone versus medical therapy plus RYGB or SG for patients with uncontrolled T2DM and BMIs ranging from 27 to 43 kg/m². The 150 subjects in Surgical Therapy and Medications Potentially Eradicate Diabetes Efficiently (STAMPEDE) had a mean age of 49±8 years and a mean baseline HbA₁c of 9.2±1.5%, and 66% were female. The primary end point was the proportion of patients with HbA₁c <6.0% at 12 months. Fifty subjects were randomized to each of the 3 study groups—medical therapy alone, RYGB, or SG—with a 93% follow-up rate. The primary end point was achieved by 12% of the medical therapy group compared with 42% of the RYGB group (*P*=0.002 compared with medical therapy alone) and 37% in the SG group (*P*=0.008 compared with...
medical therapy alone). There was improved glycemia in all 3 groups at 1 year, with a mean HbA1c of 7.5±1.8% in the medical therapy group, 6.4±0.9% in the RYGB group (P<0.001), and 6.6±1.0% in the SG group (P=0.003). The surgical subjects experienced greater mean weight loss (<29.4±9.0 kg for RYGB and ~25.1±8.5 kg for SG) compared with the medically treated subjects (~5.4±8.0 kg; P<0.001 for both comparisons). Medications for diabetes mellitus, hyperlipidemia, and hypertension were significantly reduced in both surgical groups but were increased in medically treated participants during the study. Specifically, insulin use remained high at 12 months (38%) in the medical therapy group but fell to 4% in the RYGB group and to 8% in the SG group (P<0.001 for both comparisons). Reoperation was required in 4 surgical subjects, but there were no mortalities or life-threatening complications. These biochemically defined outcomes, along with 2 similar randomized trials, add further weight to the potential for surgical interventions to significantly affect the metabolic consequences of obesity and to provide a mechanism for the modulation of future cardiovascular event rates.

The pathophysiology of metabolic responses to bariatric procedures is still incompletely understood. The rate of change of glucose homeostasis is quite remarkable, with many malabsorptive surgery patients showing a rapid decrease in their insulin requirement over the first postoperative week. There are interesting improvements in inflammatory and adipokine profiles postoperatively, which may have a role in the observed improvements in glucose and lipid homeostasis. Circulating C-reactive protein and interleukin-6 levels have been observed to fall by as much as 81% and 23%, respectively, paralleling the improvements in insulin sensitivity. Gastric bypass and SG lead to rapid reductions in leptin levels as early as 1 week postoperatively, with ongoing decreases until 12 months postoperatively; meanwhile, adiponectin increases progressively over this time. Although there is evidence supporting a key role for adipokines such as leptin, resistin, and adiponectin in the metabolic effects of bariatric surgery, some authorities place greater emphasis on the gut hormones that regulate appetite and satiety as the critical mediators of post-RYGB weight loss and improved insulin sensitivity. Ghrelin, peptide YY, glucose-dependent insulinotropic peptide (GIP), and GLP-1 are the gut hormones of particular interest. GLP-1 and GIP are incretins, a family of gastrointestinal hormones that stimulate postprandial β-cell insulin release, inhibit glucagon, slow gastric emptying, and promote weight loss. GLP-1 is cosecreted with peptide YY by enteroendocrine L cells of the ileum and colon in response to a carbohydrate load. Both GLP-1 analogs, and also the dipeptidyl peptidase-4 inhibitors (sitagliptin, saxagliptin, linagliptin, vildagliptin) that deter GLP-1 and GIP degradation, are new pharmacological agents for T2DM. RYGB patients demonstrate an immediate 3- to 5-fold increase in postprandial GLP-1 and peptide YY levels postoperatively, which precedes significant weight loss and is independent of caloric restriction. Restored GLP-1 levels may be a mechanism for the recovery of early-phase insulin secretion in response to oral carbohydrates. Ghrelin responses after RYGB are more heterogeneous and are therefore less likely to explain reduced appetite and improved glucose homeostasis. It is likely that both duodenal exclusion (the foregut hypothesis) and the rapid delivery of nutrients to the L cells of the small intestine owing to the accelerated transit through the proximal bypassed section of the gut (the hindgut hypothesis) are contributors to the restoration of gut hormone profiles, satiety, and euglycemia after RYGB.

Although the signaling mechanisms are still under investigation, it is now clear that β-cell glucose sensitivity increases in the early days and weeks after malabsorptive bariatric surgery independently of weight loss and without significant alterations in tissue insulin sensitivity. Fatty substrates are released into the circulation and promote lipid oxidation, which prompts weight loss. This is followed by a gradual improvement in peripheral and hepatic insulin sensitivity that is in proportion to the degree of weight lost. During the 12 months after RYGB, the likelihood and extent of diabetes remission is dependent on the degree of preoperative β-cell dysfunction. In large clinical studies, the eventual degree of weight loss generally correlated with the extent of metabolic benefit derived from surgery. EWL paralleled the magnitude of biochemical responses in studies by Schauer et al (RYGB), Sugerman et al (RYGB), and Dixon et al (LAGB). The meta-analysis by Buchwald et al also linked weight loss and diabetes resolution across a range of gastric volume reduction and malabsorptive procedures: Gastric banding resulted in a mean 46.2% EWL and 56.7% overall diabetes resolution compared with 55.5% EWL and 79.9% diabetes resolution for gastropasty, 59.7% EWL and 80.3% diabetes resolution for RYGB, and 63.6% EWL and 95.1% diabetes resolution for BPD/DS. Despite this relationship between fat mass loss and diabetes response, the SOS surgical cohort did not demonstrate a significant unadjusted (P=0.09) or adjusted (P=0.28) relationship between weight change and cardiovascular events, as discussed further below.

### Comparison Among Bariatric Procedures

Just as the efficacy of surgical weight loss favors procedures with a malabsorptive function, so too does the degree of metabolic adaptation, as outlined in Table 4.94-103 Head-to-head comparisons of metabolic impact confirm the superiority of malabsorptive over gastric volume reduction surgeries, albeit at the expense of a greater perioperative risk and higher likelihood of malnutrition. However, meta-analyses of the LAGB versus RYGB data highlight the excess of late (≥30 days) complications and the need for reoperation for LAGB patients. One study following up patients to a median of 16.2 months showed a 78% LAGB late complication rate compared with 28% in RYGB (P<0.05).103 Weight loss outcomes consistently favor RYGB by a margin of ~25% and show persistence to 5 years postoperatively (EWL, 47% versus 67%; P=0.001),100 with correspondingly superior rates of diabetes, hypertension, and hyperlipidemia remission for RYGB than LAGB patients at 3 years.105 SG is a gastric volume reduction procedure that is growing in popularity and is slightly more technically demanding. The weight loss offered by SG is superior to that of LAGB at 3 years (66% versus 48% EWL; P=0.0025), but the severity of early complications is greater.
than with LAGB.\textsuperscript{86} SG and RYGB appear to have nearly equivalent impacts on weight and glucose homeostasis at 3 months\textsuperscript{106} and 1 year.\textsuperscript{107}

In comparisons between the procedures with malabsorptive functions, the less commonly performed BPD and DS generally outperform RYGB in terms of weight loss and diabetes resolution.\textsuperscript{85} Among 350 patients with BMI $\geq$ 30 kg/m$^2$ (DS, n=198; RYGB, n=152), diabetes, hypertension, and dyslipidemia resolution was greater at 36 months for DS (diabetes mellitus, 100% versus 60%; hypertension, 68.0% versus 38.6%; dyslipidemia, 72% versus 26.3%), with the superior resolution of metabolic comorbidities being independent of weight loss.\textsuperscript{109} In a randomized trial comparing DS (n=29) with RYGB (n=31), DS achieved greater weight loss, greater cholesterol improvement, and more adverse events, although reductions in blood pressure and mean concentrations of glucose and insulin showed no difference between surgical groups.\textsuperscript{109} DS appears to achieve euglycemia without a rise in insulin levels and therefore may be a preferable procedure when the primary indication is diabetes management.\textsuperscript{68} There are limited head-to-head data comparing BPD with RYGB, but weight loss with BPD is superior to that with LAGB, although rates of diabetes and hypertension improvement at 5.4 years did not differ in 1 study.\textsuperscript{110} Scopinaro et al\textsuperscript{111} reported a more dramatic effect of BPD on diabetes mellitus among 443 severely obese patients compared with the data in the literature on gastric bypass. The proportion of patients with fasting serum glucose $\leq$ 110 mg/dL on free diet and with no therapy was 74% at 1 month, 97% at 1 and 10 years, and 91% at $\geq$20 years, with the 26% of patients not attaining remission at 1 month being those with the most severe preoperative T2DM. When performed as revisional surgery after a failed LAGB, BPD/DS offers slightly greater weight loss at 18 months but at a cost of greater complications and a longer operative time.\textsuperscript{112}

### Cardiovascular Outcomes of Bariatric Surgery

The overall impact of bariatric surgery on CVD risk factors is well documented. Among 23,543 surgical subjects (mean age, 42 years; 76% female) with a mean follow-up period of 57.8 months (range, 3–176 months), hypertension remitted or resolved in 63% of affected subjects, dyslipidemia in 65%, and diabetes mellitus in 73%.\textsuperscript{113} It must be emphasized that the majority of trials assessing the cardiovascular impact of bariatric surgery have thus far used only cardiovascular end points such as hypertension, diabetes mellitus, hyperlipidemia, and/or inflammatory markers, with far fewer reporting actual cardiovascular events or mortality postoperatively. There must now be a shift in the design of bariatric surgery trials toward the pursuit of longer-term data on actual cardiovascular events, cardiovascular mortality, and all-cause mortality. Additionally, such studies should ideally be randomized. At this point, it remains possible that features specific to obese patients who pursue a surgical intervention compared with those who do not opt for surgery are confounding the relationship between bariatric surgery and cardiovascular outcomes. Randomized, controlled trials examining cardiovascular or diabetes end points thus far have been very limited in sample size.\textsuperscript{57,84,85,109,114,115}

The existing studies reporting actual cardiovascular events or mortality outcomes after bariatric surgery merit further attention. A summary of the patient characteristics and major outcomes in these 14 studies is presented in Table 5.\textsuperscript{116–125} Despite the absence of randomized, controlled trials, the growing body of data on hard outcomes in obese patients who undergo weight loss surgery compared with matched

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Table 4. Comparison of the Bariatric Surgical Procedures: Their Risks, Outcomes, and Mechanisms

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Short-term (1 y) %EWL</th>
<th>Medium/Long-term (2.5–15 y) %EWL</th>
<th>Main Complications</th>
<th>Mortality at 30 d, %</th>
<th>Diabetes Remission &lt;2 and $\geq$2 y, %</th>
<th>Biochemical Mechanisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vertical-banded gastroplasty</td>
<td>68.2 (61.5 to 74.8) 56 at 30 mo</td>
<td>Weight regain, gastric outlet stenosis, gastrosaccic fistula</td>
<td>0.30 (0.15 to 0.46) for all open gastric volume reduction procedures, 0.07 (0.02 to 0.12) for all laparoscopic gastric volume reduction procedures</td>
<td>81.4 and 77.5</td>
<td>55.0 and 58.3</td>
<td>Limited data</td>
</tr>
<tr>
<td>Adjustable gastric band (77.5 min, 1.7 d)</td>
<td>47.5 (40.7 to 54.2) 42.8 (range, 24 to 143) at 12–15 y</td>
<td>Band-related complications (slip, prolapse, erosion)</td>
<td>Not included in this meta-analysis</td>
<td>Circulating leptin lower than expected for body weight, reduced total ghrelin, increased postprandial PYY, increased circulating GLP-1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleeve gastroplasty (100.4 min, 4.4 d)</td>
<td>57.7 (range, 0 to 125.3) 66 (range, –3.1 to 152.4) at 3 y</td>
<td>Staple line dehiscence/leak, bleeding</td>
<td>0.41 (0.24 to 0.58) open, 0.16 (0.09 to 0.23) laparoscopic</td>
<td>81.6 and 70.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Roux-en-Y gastric bypass (64.8 min, 4.2 d)</td>
<td>61.6 (56.7 to 66.5) 62 at 5 y</td>
<td>Anastomotic leak, bleeding, marginal ulcer, anastomotic stricture</td>
<td>Limited data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biliopancreatic diversion with/without duodenal switch (220 min, 10.1 d)</td>
<td>70.1 (66.3 to 73.9) 84.0±14.5 (mean±SD) at 3 y</td>
<td>Malabsorption, anastomotic leak, duodenal stump leak, bleeding</td>
<td>0.76 (0.29 to 1.23) open, 1.11 (0.00 to 2.70) laparoscopic</td>
<td>94.0 and 95.9</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

GLP-1 indicates glucagon-like peptide 1; PYY, peptide YY; and %ELW, percent excess weight lost. Numbers in parentheses are 95% confidence intervals unless otherwise stated.
Table 5. Major Studies of Bariatric Surgery With Cardiovascular Event or Mortality End Points

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year, Country</th>
<th>Surgical Subjects, n</th>
<th>Nonsurgical Control Subjects, n</th>
<th>Follow-up Period</th>
<th>Outcomes</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>MacDonald et al</td>
<td>1997, US</td>
<td>154 Obese patients with non–insulin-dependent diabetes mellitus who underwent RYGB (referred 1979–1994)</td>
<td>78 Obese patients with non–insulin-dependent diabetes mellitus who were referred for but did not receive surgery (patient choice/insurance)</td>
<td>9 y (mean)</td>
<td>9% Mortality in subjects (including perioperative) vs 28% in control subjects (P=0.0003); annualized mortality rate of 1.0% in subjects vs 4.5% in control subjects</td>
<td>Lower CV mortality in the surgical group was the primary driver of the overall survival benefit</td>
</tr>
<tr>
<td>Christou et al</td>
<td>2004, Canada</td>
<td>1035 Predominantly open RYGB patients</td>
<td>5746 Age/sex-matched control subjects extracted from a health insurance database, baseline BMIs unknown</td>
<td>5 y</td>
<td>0.68% Mortality in surgical group (including 0.4% perioperative mortality) vs 6.17% for control subjects (RR, 0.11; 95% CI, 0.04–0.27)</td>
<td>50% Fewer hospitalizations in surgical subjects and significantly fewer CV diagnoses in surgical group than controls (4.7% vs 26.8% incidence of CVD)</td>
</tr>
<tr>
<td>Flum and Delling</td>
<td>2004, US</td>
<td>3328 Gastric bypass patients</td>
<td>62781 Nonsurgical obese subjects matched for age, sex, comorbidities</td>
<td>Median, 4.4 y; maximum, 15.5 y</td>
<td>At 15 y, 11.8% mortality in subjects vs 16.3% in control subjects; after propensity matching, odds of survival at 5 y, 59% higher in surgical group (OR, 1.59; 95% CI, 1.49–1.72)</td>
<td>30-d surgical mortality, 1.9%; postoperative mortality associated with surgeon inexperience</td>
</tr>
<tr>
<td>Sampalis et al</td>
<td>2006, Canada</td>
<td>1035 Predominantly open RYGB patients; morbidity outcomes for the same cohort as Christou et al</td>
<td>5746 Age/sex-matched control subjects extracted from a health insurance database, baseline BMIs unknown</td>
<td>5 y</td>
<td>Decreased incidences of new pulmonary edema (RR, 0.42; 95% CI, 0.18–0.96), angina (RR, 0.53; 95% CI, 0.40–0.70), coronary artery bypass grafting (RR, 0.28; 95% CI, 0.14–0.61), and coronary angioplasty (RR, 0.36; 95% CI, 0.19–0.66)</td>
<td>Decrease in myocardial infarctions (RR, 0.71; 95% CI, 0.50–1.00) did not reach significance (P=0.05)</td>
</tr>
<tr>
<td>Livingston et al</td>
<td>2006, US</td>
<td>575 Veterans Affairs patients, 42% with BMI ≥50 kg/m²; 87% open bariatric procedures</td>
<td>None</td>
<td>Maximum, 2 y</td>
<td>30-d cardiac arrest rate, 1.6%; 30-d myocardial infarction rate, 0.5%; overall 30-d mortality, 1.4%; and 2-y mortality, 3.1%</td>
<td>Adverse postoperative event risk increased in patients &gt;350 lb and smokers</td>
</tr>
<tr>
<td>Adams et al</td>
<td>2007, US</td>
<td>7925 RYGB patients (1984–2002)</td>
<td>7925 Age/sex/BMI-matched obese control subjects drawn from driver’s license applicants</td>
<td>Mean, 7.1 y</td>
<td>All-cause mortality, 40% lower in surgical group (adjusted HR, 0.60; 95% CI, 0.45–0.67; P&lt;0.001); lower surgical mortality for all diseases combined (52%; P&lt;0.001), CAD (59%; P=0.006), diabetes mellitus (92%; P=0.005), and cancer (60%; P=0.001)</td>
<td>Rate of deaths not caused by disease such as accidents and suicide was 58% higher in the surgery group (P=0.04)</td>
</tr>
<tr>
<td>Torquati et al</td>
<td>2007, US</td>
<td>500 RYGB patients; mean age, 45 y; 81% female</td>
<td>None</td>
<td>5 y</td>
<td>1% for CV event rate at 5 y</td>
<td>Study primarily reported improvement in Framingham risk scores postoperatively</td>
</tr>
<tr>
<td>Sowemimo et al</td>
<td>2007, US</td>
<td>908, Majority open RYGB (mean age, 43.2 vs 47.9 y for control subjects; BMI, 54 vs 51 kg/m² in control subjects; both P&lt;0.0001)</td>
<td>112 Evaluated for surgery but did not proceed for a variety of reasons</td>
<td>9 y</td>
<td>2.9% Mortality in subjects vs 14.3% in control subjects; adjusted mortality, 82% lower in surgical subjects (HR, 0.18; 95% CI, 0.09–0.35; P&lt;0.0001)</td>
<td>Greatest surgical benefit seen in patients &lt;55 y of age and with a BMI &gt;50 kg/m²</td>
</tr>
<tr>
<td>Busetto et al</td>
<td>2007, Italy</td>
<td>821LAGB patients with BMI &gt;40 kg/m²</td>
<td>821 Sex/age/BMI-matched control subjects</td>
<td>5 y</td>
<td>Survival was 60% higher in surgical group (P=0.0004); on multivariate Cox analysis, adjusted mortality risk was 0.36 (95% CI, 0.16–0.80) in the surgical group</td>
<td>Other factors correlating with death on univariate analysis included male sex, older age, and higher BMI</td>
</tr>
</tbody>
</table>

(Continued)
nonsurgical control subjects broadly supports a cardiovascular event and all-cause mortality benefit conferred by bariatric surgery. The largest and most convincing outcome studies come from Flum and Dellinger, Adams et al., and Busetto et al., with follow-up periods ranging 4.4 to 14.7 years. Each of these studies used an obese nonsurgical control cohort matched on features such as age, sex, and baseline BMI whose outcomes were compared with those of the surgical study group. The modest short- to long-term survival benefit demonstrated by Flum and Dellinger persisted after propensity matching of the 2 groups; the odds of survival at 5 years = 0.76; 95% CI, 0.61–1.14). The 2007 study by Adams et al. demonstrated 40% lower all-cause mortality in the surgical group (adjusted hazard ratio, 0.47; 95% CI, 0.29–0.76; P < 0.001) despite the greater prevalence of smoking and higher baseline weights and blood pressures in subjects vs control subjects). The SOS study has formed the basis of much of our current understanding of medium- and long-term outcomes after bariatric surgery despite the fact that the majority of their surgical patients (2.2% vs 4.6% [P < 0.001] and 6.8% vs 15.3% [P < 0.001], respectively); significance of mortality benefit lost with propensity matching of 1694 patients (HR 0.83; 95% CI, 0.61–1.14). The 2007 study by Adams et al.118 demonstrated by Flum and Dellinger118 persisted after propensity matching of the 2 groups; the odds of survival at 5 years = 0.76; 95% CI, 0.61–1.14). The 2007 study by Adams et al. demonstrated 40% lower all-cause mortality in the surgical group (adjusted hazard ratio, 0.47; 95% CI, 0.29–0.76; P < 0.001) despite the greater prevalence of smoking and higher baseline weights and blood pressures in the surgical cohort vs control subjects (2.2% vs 4.6% [P < 0.001] and 6.8% vs 15.3% [P < 0.001], respectively); significance of mortality benefit lost with propensity matching of 1694 patients (HR 0.83; 95% CI, 0.61–1.14).

### Table 5. (Continued)

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year, Country</th>
<th>Surgical Subjects, n</th>
<th>Nonsurgical Control Subjects, n</th>
<th>Follow-up Period</th>
<th>Outcomes</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peeters et al123</td>
<td>2007, Australia</td>
<td>966 LAGB patients; mean age, 47 y; mean BMI, 45 kg/m²</td>
<td>2119 Matched community control subjects; mean age, 55 y; mean BMI, 38 kg/m²</td>
<td>Median, 4 y for surgical subjects; mean, 12 mo for control subjects</td>
<td>Surgical patients had a 72% lower risk of mortality, adjusted for sex/age/BMI, than control subjects (HR, 0.28; 95% CI, 0.10–0.85)</td>
<td>No perioperative deaths; sex, age, and degree of obesity did not significantly affect mortality risk</td>
</tr>
<tr>
<td>Maciejewski et al14</td>
<td>2011, US</td>
<td>850 Veterans who underwent bariatric surgery; mean age, 49.5 y; mean BMI, 47.4 kg/m²</td>
<td>41 244 Matched control subjects (mean age, 54.7 y; mean BMI, 42.0 kg/m²) from the same 12 Veteran Integrated Service Networks who were not treated for obesity</td>
<td>Mean, 6.7 y</td>
<td>2- and 6-y crude mortality significantly lower for surgical patients (2.2% vs 4.6% [P &lt; 0.001] and 6.8% vs 15.3% [P &lt; 0.001], respectively); significance of mortality benefit lost with propensity matching of 1694 patients (HR 0.83; 95% CI, 0.61–1.14).</td>
<td>Comprehensive claims data permitted adjustment for factors such as ethnicity, BMI, comorbidity burden, and marital status</td>
</tr>
<tr>
<td>Adams et al3</td>
<td>2012, US</td>
<td>418 RYGB (2000–2011)</td>
<td>418 Obese patients who sought but did not undergo surgery (group 1) and 321 control subjects from a population sample (group 2)</td>
<td>6 y</td>
<td>2.9% Mortality (12 of 418) in the surgical cohort vs 3.3% and 0.9% mortality in control groups 1 and 2, respectively</td>
<td>All 4 suicides occurred in the surgical cohort (4 of 12 mortalities)</td>
</tr>
<tr>
<td>Sjöström et al3</td>
<td>2012, Sweden</td>
<td>2010 SOS patients, 68% with vertical-banded gastropasty (significantly greater prevalence of smoking and higher baseline weights and blood pressures in subjects vs control subjects)</td>
<td>2037 Matched control subjects</td>
<td>Median, 14.7 y</td>
<td>Lower CV mortality rate in surgery group (adjusted HR, 0.47; 95% CI, 0.29–0.76; P = 0.002); first-time CV events also lower in surgical group (adjusted HR, 0.67; 95% CI, 0.54–0.83; P &lt; 0.001)</td>
<td>Baseline degree of insulin resistance rather than initial BMI was the most predictive of CV benefit</td>
</tr>
<tr>
<td>Romeo et al25</td>
<td>2012, Sweden</td>
<td>345 SOS surgical subjects with diabetes mellitus</td>
<td>262 Control subjects with diabetes mellitus</td>
<td>Mean, 13.3 y</td>
<td>Adjusted HR for myocardial infarction, 0.56 (95% CI, 0.34–0.93; P = 0.025); adjusted HR for first-time CV event, 0.53 (95% CI, 0.35–0.78; P = 0.002)</td>
<td>Benefit of bariatric surgery was unrelated to baseline age, sex, or BMI; number of obese diabetics needed to treat with bariatric surgery to prevent 1 myocardial infarction over 15 y = 16</td>
</tr>
</tbody>
</table>

BMI indicates body mass ratio; CAD, coronary artery disease; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; LAGB, laparoscopic adjustable gastric banding; OR, odds ratio; RR, relative risk; RYGB, Roux-en-Y gastric bypass; and SOS, Swedish Obese Subjects.

The authors of this study have considered and mitigated potential sources of bias in their research. They have also included sensitivity analyses to assess the robustness of their findings. The results of their study provide strong evidence for the efficacy of bariatric surgery in improving long-term survival outcomes compared to nonsurgical treatment options.
et al\textsuperscript{122} study. Conversely, the mortality benefit offered by bariatric surgery was unrelated to age, sex, or BMI in the studies of Peeters et al\textsuperscript{122} and Romeo et al.\textsuperscript{125} There are also contradictions between the outcome studies in their implications as to which obese individuals hold the potential for the greater mortality benefit after surgical intervention. Sowemimo et al\textsuperscript{121} saw the greatest surgical benefit in patients <55 years of age and those whose initial BMI exceeded 50 kg/m\textsuperscript{2}. However, it was the degree of baseline insulin resistance rather than the initial BMI that was most predictive of cardiovascular benefit in the study by Sjöström et al.\textsuperscript{1}

Among the 14 outcome studies listed, 2 studies suggested an absence of benefit on all-cause mortality. The 2012 study of Adams et al\textsuperscript{81} observed 2.9% mortality among the 418 RYGB subjects compared with 3.3% mortality for the 418 obese patients who sought but did not undergo surgery and 0.9% in the 321 population sample control subjects. None of the deaths in the RYGB group occurred within 30 days of surgery, but there was an excess of deaths resulting from suicide in this surgical cohort. The degree of propensity score adjustment was judged to have adequately corrected for the baseline intergroup differences, but the relative risk of cardiovascular death between subjects and control subjects was not further analyzed. Detailed matching of subjects and control subjects was performed by Maciejewski et al,\textsuperscript{124} who retrospectively reviewed survival data of veterans who had undergone bariatric surgery compared with control subjects who were untreated for obesity. The 2- and 6-year crude mortality rates were significantly lower for the operative cohort (2.2% versus 4.6% [\textit{P}<0.001] and 6.8% versus 15.3% [\textit{P}<0.001], respectively), but when propensity-score matching and Cox regression analyses were performed, the significance of the surgical mortality benefit was lost. The possibility remains that these adjustment strategies were more accurate than those used by other studies that reached the opposite conclusion and supported a surgical survival benefit. However, this cohort of obese veterans is quite dissimilar to the typical bariatric surgery candidate, with a predominantly male, older demographic (mean age, 49.5±8.3 years) and a relatively high 30-day postoperative mortality rate (1.29%). The implications of this study remain unclear in the context of the positive outcome studies described in Table 5, but the Maciejewski et al\textsuperscript{124} data carry an important message concerning optimal patient selection for operative intervention and the potential pitfalls of generalizing between dissimilar surgical cohorts.

**Left Ventricular Dysfunction, Heart Failure, and Bariatric Surgery**

A range of cardiac imaging techniques are providing insights into the potential for surgical weight loss to improve myocardial structure, diastolic function, and possibly systolic function. Obesity is a key risk factor for left ventricular (LV) hypertrophy and diastolic dysfunction.\textsuperscript{126–128} As demonstrated in cohorts of 16 to 60 obese patients, there can be improvements in ventricular mass and diastolic function in the 3 months to 3.6 years after bariatric surgery in patients without baseline clinical cardiac disease.\textsuperscript{1,10,129–132} The most convincing improvements are seen in LV mass and mass index, E/A ratio, and isovolumic relaxation time. Importantly, the LV mass regression appears to be independent of postoperative systolic blood pressure changes.\textsuperscript{133,134} There is also a growing role for cardiac magnetic resonance imaging in defining the structural and functional cardiac changes with weight loss. Thirty obese subjects without cardiac risk factors underwent magnetic resonance imaging at baseline and 1 year after weight loss (surgical or dietary).\textsuperscript{133} The LV absolute mass fell by 10%; right ventricular mass fell by 40%; and 3-dimensional calculations of LV end-systolic volume, stroke volume, and cardiac output showed significant reductions after weight loss. It is yet to be determined whether other cardiac structural changes associated with obesity such as increased epicardial fat, fatty infiltration of myocardium, or increased interstitial fibrosis associated with obesity also regress after successful bariatric surgery.

An echocardiographic study evaluating systolic and diastolic function in 41 SOS gastroplasty subjects reported favorable effects of bariatric surgery on the LV ejection fraction (LVEF).\textsuperscript{135} Despite a significant difference between LVEFs in the surgical and obese control patients at 1 year, the mean baseline and follow-up LVEFs in both groups were >50%, so the positive effect of surgery on LVEF was not clinically meaningful. More sensitive echocardiographic techniques than LVEF are now available for detecting changes in systolic function; 2-dimensional speckle tracking–derived strain and strain rate imaging have highlighted the subclinical systolic dysfunction that can be associated with obesity.\textsuperscript{135,136} Thirteen obese patients with LVEFs >40% demonstrated regression of myocardial deformability abnormalities at 6 to 24 months after bariatric surgery.\textsuperscript{137}

Several cross-sectional and prospective studies have demonstrated a strong and independent association between increased BMI and risk of heart failure.\textsuperscript{138,139} A prospective Framingham study of 5881 participants stratified by BMI at enrollment found that the risk of clinically symptomatic heart failure increased by 5% for men and 7% for women per 1-unit BMI increase despite adjustments for demographics and known CAD risk factors.\textsuperscript{140} The “obesity paradox,” whereby heart failure patients with higher BMIs have shown better survival rates than their leaner counterparts, has frequently been reported, raising questions as to whether surgical weight loss will prove beneficial in heart failure patients.\textsuperscript{141–143} Chronic heart failure subjects who lost >6% of their body weight during the Studies of Left Ventricular Dysfunction (SOLVD) and Vasodilator-Heart Failure Trial II (V-HeFT II) trials showed excess mortality, although weight loss may reflect cardiac cachexia and disease progression in this advanced cohort.\textsuperscript{144}

The published experience of bariatric surgery in patients with preexisting heart failure is very limited, but some emerging data suggest that it is safe and effective.\textsuperscript{145,146} Obese individuals with predominantly systolic heart failure can experience dramatic improvements in symptoms and systolic function with weight loss.\textsuperscript{147,148} Available evidence supporting a role for bariatric surgery in reversing myocardial dysfunction in heart failure patients is currently limited to 2 small cohorts. One early study of vertical-band gastroplasty that included 13 patients with preoperative LV dysfunction demonstrated...
modest postoperative improvements in fractional shortening (22±2% to 31±2% [P<0.01] at 4.3 months).149 A subsequent 14-patient study of heart failure subjects with mildly reduced fractional shortening did not replicate these results.150 Two additional studies reported on an overlapping cohort.146,151 Ramani et al160 described 12 patients with a mean age of 41 years, BMI of 53 kg/m², and LVEF of 22±7% and 10 matched control subjects who received diet and exercise counseling only. After 1 year, surgical patients showed improved LVEF (22±7% to 35±15%; P=0.005) and improved New York Heart Association functional class (2±0.7 to 2.3±0.5; P=0.02), with no improvement in control subjects.

Bariatric Surgery and Established CVD
In patients with established CAD, weight loss is associated with improved endothelial function and reduced risk of future cardiac events.152–154 Plecka Östlund et al155 showed a marked reduction in the hazard ratio for angina pectoris after gastric bypass but not with gastric volume reduction procedures (hazard ratio, from 3.8 to 2.04 in men and from 3.9 to 0.98 in women). Preliminary data from the Utah Obesity Study suggested that of 136 consecutive subjects returning for 5-year follow-up after gastric bypass, coronary artery calcium scores were markedly lower in postsurgical subjects than in a nonsurgical obese control group independently of traditional CVD risk factors.156 Carotid intima-media thickness measured at baseline and after a 3- to 4-year interval demonstrated a rate of progression in a postgastropasty group that was more in line with lean control subjects than with the 3-fold higher progression of patients who continued to be obese.157 The findings from these 2 subclinical atherosclerosis assessment modalities raise the possibility that bariatric surgery may slow the progression of CAD.

Lopez-Jimenez et al158 demonstrated the safety of RYGB in patients with preexisting CAD. There were no in-hospital deaths among the 52 clinical CAD patients (prior coronary revascularization, >30% angiographic stenosis, prior myocardial infarction, positive stress test) or 507 surgical patients without CAD. Three patients with CAD (5.8%; 95% CI, 0–12.2) and 7 patients without CAD (1.4%; 95% CI, 0.4–2.4) had cardiovascular complications (P=0.06). Of 6 patients with positive preoperative and postoperative stress tests, 1 patient received percutaneous coronary intervention and 4 patients showed decreased extension or severity of ischemia after bariatric surgery.

In addition, it has been observed that the risk of atrial and ventricular arrhythmias and of sudden cardiac death is elevated in obese individuals, possibly as a result of abnormal myocardial repolarization. Weight loss surgery appears to be associated with a decrease in the heterogeneity of ventricular repolarization159 and may improve the QT interval and QT dispersion.160,161 Such electrophysiological modulation may reduce the substrate for ventricular arrhythmias in this high-risk patient population. P-wave dispersion, a marker of atrial refractoriness heterogeneity, was also shown to regress significantly after bariatric surgery, which has the potential to reduce atrial fibrillation burden in obese patients.162

Conclusions
Obesity is one of the greatest public health challenges of modern times, with the potential to negatively affect almost every organ system. The interactions between dysfunctional adipose tissue and metabolic disturbances such as diabetes mellitus, hypertension, hyperlipidemia, and inflammation are the probable mediators between obesity and CAD. Bariatric surgery can reverse many obesity-related disease processes, and there is now evidence supporting decreases in short- and medium-term cardiovascular outcomes. Data also suggest improved biventricular hypertrophy and diastolic dysfunction after bariatric surgery. Limited data suggest that surgical weight loss is safe and effective in carefully selected and medically optimized obese heart failure patients. The next step is ascertaining the long-term cardiovascular outcomes for obese patients who undergo bariatric surgery, particularly those with preexisting cardiac disease. Large randomized, controlled trials would be the ideal approach, although the sample size required given the relatively low cardiovascular and mortality event rates in the middle-aged and predominantly female obese population seeking bariatric surgery may be challenging to accommodate. Refinement of patient selection criteria to optimally identify patients who derive the most benefit from surgical weight loss is a prime challenge in the obesity field and requires ongoing scientific input from the cardiology community. However, the available literature already provides a solid platform from which cardiologists can initiate discussions with their obese patients about the role of bariatric surgery in cardiovascular event prevention.

Disclosures
Dr Schauer has served as a consultant to and scientific advisory board member for and has received research support from Ethicon Endo-Surgery; has served on the Board of Directors for Remedy MD and SurgicalExcellence LLC; has served on the scientific advisory board for and has received an educational grant from Bard/Bard-Barbash R, Hollenbeck A, Leitzmann MF, Overweight, obesity, and mortality in a large prospective cohort of persons 50 to 71 years old. N Engl J Med. 2006;355:763–778.

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Bariatric Surgery for the Treatment of Obesity


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