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Value of Weight Reduction in Patients with Cardiovascular Disease

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Opinion statement

Obesity is an independent risk factor for cardiovascular (CV) disease and contributes markedly to individual CV risk factors, including hypertension, diabetes mellitus, dyslipidemia, and other chronic conditions, such as osteoarthritis, obstructive sleep apnea, and physical deconditioning. Obesity, defined as a body mass index ≥30 kg/m^2, is associated with increased morbidity and mortality, particularly in severely obese patients with a body mass index ≥35 kg/m^2. Physical activity, healthy eating and behavioral modification are three pivotal approaches to treating obesity. Some individuals may benefit from pharmacologic agents to achieve meaningful weight loss. Unfortunately, there are few such agents at present with proven efficacy and safety profiles. In this review, we discuss the obesity epidemic and its detrimental effects on the CV system, and focus on exercise training and on established pharmacologic agents as well as those on the horizon. We conclude by summarizing the surgical therapeutic options available to treat obesity and the evidence supporting the CV benefits of surgery, and discuss the potential adverse effects of both pharmacologic and surgical options.

Introduction

Obesity independently increases the risk of cardiovascular (CV) risk factors, including hypertension (HTN), diabetes mellitus (DM), and dyslipidemia. Obesity also adversely affects other systems, thus contributing to osteoarthritis, cancer, functional disability, sleep-disordered breathing, and liver and gallbladder disease [1••,2–4].

Overweight is defined as a body mass index (BMI) of 25 to 29.9 kg/m^2 and *obesity* as a BMI≥30 kg/m^2 [1••]. Overweight and obesity both are associated with increased morbidity and mortality, with even greater risk noted in extremely obese individuals—that is, those with a BMI≥35 kg/m^2 [1••,3]. Although BMI is the most commonly used definition for expressing overweight and obesity in epidemiologic and clinical studies, it does not always accurately reflect the at-risk body fatness [1••]. Recently, many clinical trials using other obesity indices, including waist circumference (WC), waist-to-hip ratio, weight-to-height ratio, percentage of body fat, and total body fat, highlighted the better predictive power of these obesity measures [4].

During the past few decades, obesity rates have been increasing exponentially in the United States and worldwide [5]. From 1986 to 2000, the prevalence of BMI greater than 30 kg/m^2 doubled, that of BMI≥ 40 kg/m^2 quadrupled, and that of extreme or morbid obesity, with BMI≥50 kg/m^2, increased fivefold [6].

Obesity currently is the second leading cause of preventable death in the United States. It is predicted that obesity soon may overtake smoking addiction as the leading cause of preventable death. Moreover, if the rapidly growing obesity epidemic is not reversed in time, we likely will witness the reversal of the steady improvements in life expectancy [7].

This epidemic also is being witnessed in the developing world because of the consumption of high-calorie, inexpensive, unhealthy foods. A sedentary lifestyle resulting from industrialization is another contributor to the progressive increase in obesity rates [3].

Obesity imparts numerous deleterious effects on general and CV health (Table 1) [1••]. Obese patients typically have increased total blood volume to meet their increased body demands, which over time affects CV structure and function, eventually leading to systolic and diastolic left ventricular (LV) dysfunction [8••,9, 10]. Obesity, independent of age and arterial pressure, increases the risk of LV structural abnormalities, including concentric remodeling and both concentric and eccentric LV hypertrophy [10]. Obesity also leads to left atrial enlargement, which in turn increases the risk of atrial fibrillation and its associated complications [1••]. As a whole, obesity, through its impact on the CV system, is associated with numerous CV complications, including coronary heart disease (CHD), heart failure (HF), atrial fibrillation, and sudden cardiac death [7,8••].

In both westernized and nonwesternized societies, the obesity epidemic is compounded by an epidemic of physical inactivity, which reduces cardiorespiratory fitness (CRF), and thus increases the risk of CV diseases (CVDs) [11,12]. Improving the CRF of obese patients through active participation in rehabilitation, physical activity (PA), and fitness programs likely will lower the risk of CVDs substantially [13•,14••]. Recently, we confirmed this finding in a large cohort of women with impaired fasting glucose or undiagnosed DM. Interestingly, in this study, CRF, not BMI, was a strong predictor of CV and all-cause mortality [14••]. This study further emphasizes the point that CRF, independent of traditional CV risk factors, is a powerful predictor of all-cause morbidity and mortality [14••].

Table 1. Adverse effects of obesity

Increases in insulin resistance
Glucose intolerance
Metabolic syndrome
Type 2 diabetes mellitus
Hypertension
Dyslipidemia
Elevated total cholesterol
Elevated triglycerides
Elevated LDL cholesterol
Elevated non-HDL cholesterol
Elevated apolipoprotein B
Elevated small, dense LDL particles
Decreased HDL cholesterol
Decreased apolipoprotein A-I
Abnormal left ventricular geometry
Concentric remodeling
Left ventricular hypertrophy
Endothelial dysfunction
Increased systemic inflammation and prothrombotic state
Systolic and diastolic dysfunction
Heart failure
Coronary heart disease
Atrial fibrillation
Obstructive sleep apnea/sleep-disordered breathing
Albuminuria
Osteoarthritis
Cancers

HDL high-density lipoprotein; *LDL* low-density lipoprotein. (*Adapted from* Lavie et al. [1].)

Weight reduction

- Paradoxically, some long-term epidemiologic studies have shown that weight loss in overweight and obese subjects is associated with

increased mortality. This evidence, coupled with many other studies showing better prognosis associated with greater BMI in patients with HF, HTN, CHD, and peripheral arterial disease, led to the perception that purposeful weight loss may not be beneficial and, in fact, may be detrimental [15–17]. However, studies assessing mortality based on body fat and lean mass rather than BMI have suggested that losing body fat rather than lean body mass is associated with lower morbidity and mortality [15].

- Lifestyle modifications, including a healthy diet, behavioral therapy, and PA, are the prime components of effective weight management in overweight and obese individuals [18]. Subtle changes in caloric intake and participation in PA for at least 30 to 45 min/day at least 5 days/week likely would play a major role in curbing the obesity epidemic [18]. Nutritional research suggests that increasing the consumption of high-fiber foods, such as fruits, vegetables, nuts, and whole grains, may help patients lose weight by increasing satiety and lessening the intake of overall calories [18,19].
- Although there is insurmountable evidence linking cardiac rehabilitation and exercise training (CRET) to weight loss and proven CV benefits, it is highly underused. There are many reasons for poor referral for CRET, one of which is physicians' lack of awareness of its potential benefits [20•,21–24]. Therefore, many international and national CV societies have highlighted the importance of CRET for CV protection by publishing dedicated guidelines on CRET, making it reimbursable by Medicare and most insurance plans, and holding physicians accountable for referring appropriate patients to CRET after major CHD events. It is hoped this effort will lead to more routine adoption of CRET services in secondary CHD prevention.
- Numerous studies have documented the impact of formal CRET in obese patients with CHD. In a subgroup analysis from our center, CRET resulted in ≥5% weight loss (10% being the average weight loss) in a small cohort of 45 obese subjects; we also noted marked improvements in exercise capacity and lipid levels in patients with successful weight loss compared with 81 obese subjects who did not lose weight [24].
- In a recent study from our center, we assessed the safety and efficacy of purposeful weight loss through CRET programs in 529 CHD patients, including 393 overweight and obese patients. We observed marked improvements in CHD risk factors, including percentage of body fat (−8%; $P<0.0001$), C-reactive protein (−40%; $P<0.0001$), fasting blood glucose (−4%; $P=0.02$), peak oxygen consumption (+16%; $P<0.0001$), and lipid levels, among overweight and obese CHD patients, especially in the group with greater weight loss. We also observed significant improvements in quality-of-life (QoL) scores and behavioral factors [8••]. The other significant observation from this study was the trend for better survival in the baseline overweight/obese participants with greater weight loss, emphasizing the CV benefits of formal CRET programs [20•,21–24].

- Recent evidence from the Mayo Clinic in 377 consecutive CHD patients demonstrated a 38% relative risk reduction in the composite end point of all-cause mortality and CV events, including fatal and nonfatal myocardial infarction (MI), strokes, and HF hospitalizations, in patients who successfully lost weight compared with those who had no weight loss. There also was a trend for lower mortality in the weight loss group [25].
- The current cardiac rehabilitation (CR) exercise protocol used by most programs was developed in the 1970s, when patients were enrolled in the program after more prolonged hospitalizations, with associated deconditioning [26]. There have been debates and discussions regarding whether this protocol is effective for contemporary CR patients. Addressing this question, Ades et al. [27••] recently evaluated the impact of high calorie-expenditure (3000–3500 kcal/wk) exercise on weight loss and CV risk factors in 74 overweight and obese patients with CHD, comparing it with the standard CR exercise protocol (700–800 kcal/wk). At 5 months, the investigators noted significant fat mass loss (5.9±4 kg vs 2.8±3 kg; $P<0.001$) and weight loss (8.2±4 kg vs 3.7±5 kg; $P<0.001$) and greater waist reduction (−7±5 cm vs −5±5 cm; $P=0.02$) in the high calorie-expenditure exercise group compared with the group randomly assigned to the standard CR exercise protocol.

Pharmacologic agents

- Like DM and HTN, obesity is a chronic illness and requires a long-term commitment to promote and sustain weight loss [28]. Dietary and lifestyle modification is the initial mainstay therapy for obesity [29]. However, the resultant weight loss often is disappointingly small and long-term success is unattainable [29]. As a result, drug therapy often is considered in individuals with a BMI≥ 30 kg/m^2 or in those with a BMI of 25 to 30 kg/m^2 with associated CV comorbidities. In these groups, therapeutic agents may be of value in achieving and sustaining meaningful weight loss [30]. Table 2 summarizes the prescription medications used for weight loss [31].
- Sibutramine hydrochloride, available under the trade name Meridia (Abbott Laboratories, North Chicago, IL), is the first US Food and Drug Administration (FDA)-approved medication in its class for the treatment and maintenance of weight loss [32]. This agent acts by inhibiting the reuptake of serotonin and norepinephrine at the nerve endings of the hypothalamus, thus modulating the appetite and satiety centers in the brain [32].
- In many studies, sibutramine was shown to have a moderate effect in producing weight loss in obese subjects, with most losing 5% to 10% of their baseline body weight [33]. In addition to reducing body weight and WC, this drug reduces low-density lipoprotein (LDL) cholesterol and slightly increases high-density lipoprotein (HDL)

Table 2. Prescription medications used for weight loss

Agent	Description	Dosage, *mg/d*	AWP for 1-mo supply, *$*
Appetite suppressants			
Sibutramine	Combined norepinephrine and serotonin reuptake inhibitor. Its putative effect on weight loss is attributed to appetite suppression and increased thermogenesis secondary to stimulation of brown adipose tissue. Approved in 1998 for use in conjunction with a low-calorie diet as an aid to weight loss.	10	103.80
Fluoxetine	SSRI originally approved to treat depression. Original manufacturer submitted a New Drug Application for use as a weight loss drug in the early 1990s, but eventually it was withdrawn.[a]	20	79.94
Sertraline	Also an SSRI. Resulted in weight loss in laboratory animals in the early 1990s.	200	86.21
Phentermine	Sympathomimetic amine of the phenethylamine family. Approved by the FDA in 1959 as a short-term aid to weight loss in conjunction with a low-calorie diet and exercise. Unlike sibutramine, phentermine leads to the development of tolerance.	30	39.59
Diethylpropion	Sympathomimetic agent prescribed for short-term weight loss in conjunction with diet and exercise. Similar in chemical structure to bupropion, which is approved as an antidepressant and a smoking cessation aid and also has been tested as a weight loss aid.	75	40.73
Zonisamide	FDA approved in 2000 for treating partial (focal) seizures in adults with epilepsy, in conjunction with other anticonvulsant agents. Although the precise mechanism of action is unknown, it may act as a sodium or calcium channel blocker. Because one of its side effects is appetite suppression, its use as a weight loss drug has been tested.	600	414.05
Topiramate	Anticonvulsant agent approved in the mid-1990s for treating refractory seizures in conjunction with other anticonvulsant agents. In testing topiramate for treatment of mood disorders, it was discovered that it might mitigate the weight gain often observed with antidepressant treatment, and a dose-ranging study established that it does so in a dose-dependent manner.	200	159.84
Lipase inhibitors			
Orlistat	Approved in the late 1990s; currently the only lipase inhibitor approved for weight loss. Lipase inhibitors putatively aid weight loss by reversibly binding to the active center of the enzyme lipase, preventing digestion and absorption of some dietary fats. Orlistat inhibits ~30% of fat absorption, including absorption of fat-soluble vitamins.	360	170.64

[a]Croghan T, Personal communication.
AWP average wholesale price; *FDA* US Food and Drug Administration; *SSRI* selective serotonin reuptake inhibitor.
(*Adapted from* Li et al. [31].)

cholesterol. In patients with DM, it was shown to positively affect the glycosylated hemoglobin (HbA_{1c}) level [34].

- Unfortunately, weight lost through pharmacologic therapy often is quickly regained once the drug is discontinued, as was demonstrated in the Sibutramine Trial in Obesity Reduction and Maintenance (STORM) [35]. For the initial 6 months of this European study in 605 subjects, all patients received sibutramine, then were randomly assigned to receive sibutramine or placebo for the remainder of the

study. Follow-up showed maintenance of weight loss in the group that continued taking sibutramine, whereas the placebo group regained almost all weight lost [35].

- Previous appetite-suppressing agents included dexfenfluramine and "fen-phen," a combination of fenfluramine and phentermine [30]. These agents were taken off the US market in 1997 when they were shown to have serious adverse CV effects [36]. However, when used alone, phentermine was relatively safe, with no serious adverse effects.
- Orlistat (Xenical; Genentech, South San Francisco, CA), another popular pharmacologic agent, acts by inhibiting fat absorption in the gut. This pancreatic lipase inhibitor reduces fat absorption by partially blocking the hydrolytic breakdown of triglycerides. Alli (GlaxoSmithKline, Philadelphia, PA), a reduced-strength formulation of orlistat, is available over the counter in the United States [37,38].
- In a recent meta-analysis of 22 studies in obese subjects with a mean BMI of 36.7 kg/m^2, orlistat therapy, along with a low-calorie diet and behavior modification therapy, resulted in an average weight loss of 2.89 kg (95% CI, 2.27–3.51). The participant dropout rate ranged from 35% to 55%. Significant reductions in WC, blood pressure, and total and LDL cholesterol occurred, with no effect on HDL cholesterol or triglycerides [31].
- The major downside with Xenical is its side effect profile, specifically abdominal cramping and increased frequency of oily stools. Patients taking this medication should consume a low-fat diet, and most will have to consume multivitamin supplements to replace the minerals lost in the stool and to maintain a healthy micronutrient balance. This drug should not be prescribed to patients with cholestasis and malabsorption [37,39].
- Rimonabant, an endocannabinoid receptor antagonist, selectively inhibits the overactivation of the endocannabinoid system, producing anorectic stimuli in the higher centers of the brain. This agent also affects the other important metabolic pathways at the periphery, including adipose tissue, liver, endocrine organs, and skeletal muscles. Rimonabant was shown to be very effective in promoting significant weight loss, reduction in WC, and improvements in several metabolic risk factors [40]. Unfortunately, rimonabant had to be withdrawn from the world market because of safety issues, including risk of seizures and suicides.
- Although the pharmacologic treatment of obesity is associated with favorable short-term results, it often is associated with rebound weight gain once the agent is stopped. Another major disadvantage of many of these agents is their potential for substance abuse [38].
- Lorcaserin, a novel antiobesity drug with positive results from phase 2 and phase 3 clinical trials, is on the horizon of FDA approval. This compound acts by stimulating the 5-HT_{2C} serotonin receptors in the satiety and appetite centers of the hypothalamus in the brain, help-

ing regulate the metabolic rate. Results of lorcaserin from a phase 2 trial showed significant, progressive, and dose-dependent weight loss over a 12-week period [41].

- The phase 3 program evaluating the investigational agent lorcaserin consisted of three trials, BLOOM (Behavioral Modification and Lorcaserin for Overweight and Obesity Management), BLOSSOM (Behavioral Modification and Lorcaserin Second Study for Obesity Management), and BLOOM-DM (BLOOM in Diabetes Mellitus), with approximately 7800 patients enrolled [42,43].
- BLOOM, the first of the three pivotal trials, evaluated the efficacy and safety of lorcaserin in weight loss at the end of 1 year and assessed the ability of lorcaserin to maintain weight loss at the end of the second year of treatment. This trial included obese subjects with a BMI of 30 to 45 kg/m^2 and overweight subjects with a BMI of 27 to 29.9 kg/m^2 and at least one of the cardiometabolic risk factors, including HTN, dyslipidemia, glucose intolerance, and sleep apnea. The trial enrolled 3182 subjects, who, for the first year, were randomly assigned in a 1:1 fashion to receive lorcaserin or placebo. At 1 year, 856 patients taking lorcaserin were re-randomized in a 2:1 ratio to continue lorcaserin or to switch to placebo [42–44].
- The proportion (%) of patients achieving ≥5% weight reduction at the end of the first and second years of treatment was the primary end point of the study. Forty-seven percent of patients in the lorcaserin group and 20% of those in the placebo group lost ≥5% of their baseline body weight. At the end of 1 year, patients in the treatment arm lost an average of 17.9 lb (8.1 kg), compared with 7.3 lb (3.3 kg) in the placebo arm ($P<0.0001$). The echocardiographic assessment both during and at the end of the study did not show any valve-related abnormalities or pulmonary hypertension [42,43].
- Treatment with lorcaserin also was associated with significant improvements in various secondary end points, such as total cholesterol, LDL cholesterol, triglycerides, and blood pressure. However, there were no differences in HDL cholesterol levels in either group. At the end of the study, patients who continued on lorcaserin for the entire 2 years were better able to maintain more weight loss compared with the group re-randomized to placebo during the second year.
- Qnexa (Vivus, Mountain View, CA) and Contrave (Orexigen Therapeutics, La Jolla, CA) are two other promising experimental agents with the potential for FDA approval. The initial evidence from late-stage clinical trials with these two agents appears to be very encouraging. Qnexa is a combination of phentermine, an appetite suppressant, and topiramate, an anticonvulsant. Contrave is a combination of two antidepressants, bupropion and naltrexone [42].
- In all the clinical trials with Qnexa and Contrave, the proportion of patients losing ≥5% of their body weight was three times higher in the treatment arms than in the placebo groups. In addition to weight

loss, these agents also were associated with significant improvement in cardiometabolic and inflammatory risk factors.

- EQUIP, a double-blind, placebo-controlled, randomized study, included 1267 obese subjects with an average BMI of 42.1 kg/m^2 and weight of 116 kg (256 lb) from 93 centers across the United States. The patients underwent 4 weeks of dose titration followed by 52 weeks of treatment with the investigational agents phentermine and topiramate or placebo. The patients were instructed to reduce their daily calorie intake by 500 calories. At 56 weeks' follow-up, 605 of the patients in the active treatment group lost 10% of their starting body weight and 43% lost 15% of their body weight. The average weight loss in the group taking the active compound was 16.8 kg (37 lb), compared with 2.7 kg (6 lb) in the placebo group. Preliminary results also suggested significant improvements in total cholesterol, LDL cholesterol, triglycerides, and blood pressure [42].
- CONQUER, a phase 3 study similar to EQUIP, evaluated the efficacy and safety of Qnexa in 2487 overweight and obese subjects with dyslipidemia, DM, and elevated blood pressure and with an average BMI of 36.6 kg/m^2 and weight of 103.0 kg (227 lb). The patients underwent 4 weeks of dose titration followed by 52 weeks of treatment and were instructed to decrease their daily caloric intake by 500 calories, with some minor modifications to their daily lifestyle. At study completion, patients taking the full dose of the drug lost 13.6 kg (30 lb) of their baseline body weight, compared with 2.7 kg (6 lb) in the placebo group. Forty percent of the patients taking the active compound lost 15% and 65% lost 10% of their baseline body weight. Marked improvements in cardiometabolic risk factors also were noted in this study, including reductions in blood pressure (20 mm Hg vs 14 mm Hg), triglycerides (98 mg/dL vs 42 mg/dL), and HbA_{1C} (0.6% vs 0.1%) with the active agent compared with placebo [42,43].
- Contrave (bupropion and naltrexone) was studied in three phase 3 clinical trials, each lasting 56 weeks. Contrave Obesity Trials I and II (COR-I and COR-II), enrolling 1742 and 1496 obese patients, respectively, showed a mean weight loss of 8.1% (17.6 lb) and 8.2% (17.5 lb), respectively, compared with 1.8% and 1.5% in the placebo groups. In the third trial, in patients with DM, the mean weight loss was 5.9% (13.5 lb), compared with 2.2% (5.1 lb) in the placebo group. The investigators also noted reductions in WC and other CV risk factors, including lipid levels and HbA_{1c}. The most frequent side effects in this trial were headache, nausea, and constipation. All these pharmacologic agents will need to be extensively evaluated in cohorts of CHD [43,45].
- Another recently reported phase 2 trial testing different doses of combination pramlintide and metreleptin, analogues of amylin and leptin involved in satiety and adiposity signaling, showed 7% weight loss compared with 2% with placebo at 24 weeks of follow-up.

However, the study was plagued by high dropout rates from injection site adverse reactions [46].

Bariatric surgery

- Conventional therapeutic options for weight loss include a healthy diet, behavioral therapy, and PA. When used individually, these three options often are very effective in treating obesity and associated CV risk factors. However, when used in combination, they have a positive impact on the individual CV risk factors [47]. Unfortunately, these therapeutic interventions have not been shown to be effective in treating morbid obesity with BMI greater than 40 kg/m^2. Bariatric surgery is a well-established surgical weight loss therapy with strong evidence from multiple prospective clinical studies and is endorsed by National Institutes of Health (NIH; United States) and National Institute of Clinical Excellence (United Kingdom) guidelines [48••]. This approach is reserved for patients who have failed to achieve or maintain a healthy weight through exercise and diet; those with a BMI between 35 and 39.9 kg/m^2 and associated comorbidities, such as HTN, type 2 DM, severe sleep apnea, life-threatening cardiopulmonary problems, and severe osteoarthritis in major joints; and extremely obese patients with a BMI exceeding 40 kg/m^2. The success of the procedure depends on one's commitment to a healthy diet and regular PA. The NIH consensus panel, however, did not make any recommendations for surgery in children and adolescents because of the lack of evidence supporting its use in young people [49].
- Epidemiologic evidence from long-term studies indicates that obesity is associated with increased mortality [50]. Morbidly obese subjects have a 5- to 20-year reduction in life expectancy compared with healthy individuals [51]. In recent years, substantial evidence has demonstrated that bariatric surgical procedures are associated with short- and long-term improvements in morbidity and all-cause mortality [52••]. As a result, there has been a rapid increase in the use of these procedures as a mainstream weight loss therapeutic strategy. The annual number of surgical interventions for obesity increased from 16,000 in the 1990s to approximately 103,000 in 2003 [53].
- The three most common surgical procedures for treating severe obesity are the Roux-en-Y gastric bypass (RYGB), vertical banded gastroplasty, and laparoscopic gastric banding [53].
- In RYGB, a small proximal gastric pouch is connected to a Y-shaped loop of the small bowel. The proximal stomach is separated from the remaining part of the stomach with staples. In the gastric banding procedure, a saline adjustable band is placed around the upper part of the stomach, creating a small pouch that opens into the remaining, larger part of the stomach through a narrowed passage. The major advantages with laparoscopic gastric banding are that it is technically less challenging, less invasive, and less expensive. In

2001, the FDA approved the Lap-Band adjustable gastric band (Allergan, Irvine, CA). Although there are slightly more perioperative complications with RYGB compared with gastric banding, the long-term results with RYGB are excellent, making it the gold-standard surgical therapeutic strategy for obesity [53,54].

- In the Swedish Obesity Study (SOS), CV risk factor improvement and weight loss were significantly greater with gastric bypass surgery compared with vertical banded gastroplasty [55]. The SOS investigators ascertained the impact of intentional weight loss on mortality, examining whether bariatric surgery (n=2010) is associated with lower mortality compared with conventional treatment (n=2037) during a mean follow-up of 10.9 years. After 1 to 2 years of randomization, 32%, 25%, and 20% reductions in weight loss were noted with gastric bypass, vertical banded gastroplasty, and gastric banding, respectively. There were 101 deaths in the surgery group and 129 in the control group (hazard ratio, 0.76; P=0.04). Results were even more impressive after adjustment for major confounding factors, with a 29% reduction in total mortality (hazard ratio, 0.71; P=0.01; Fig. 1) [56].
- A recent substudy of the SOS prospective clinical trial showed no benefit of bariatric surgery on fatal and nonfatal MI at 12 years of follow-up. However, patients with higher baseline glucose levels were shown to have lower MI rates with gastric bypass surgery [57].
- Obesity negatively affects CV structure and function, which over time may result in the development of cardiomyopathy and severe systolic

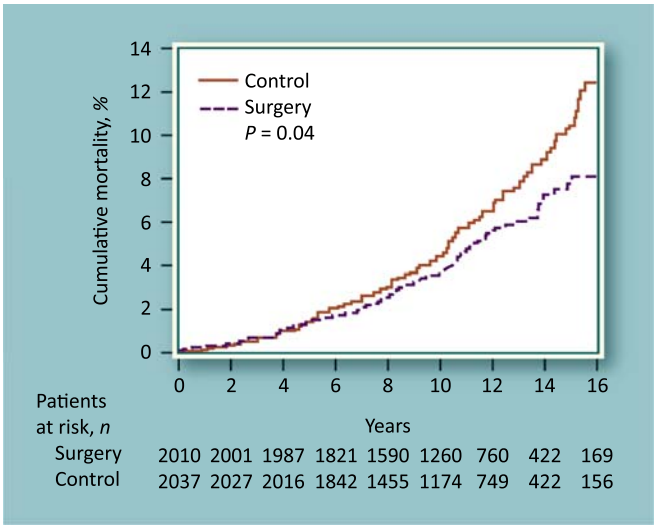

Figure 1. Unadjusted cumulative mortality in subjects who underwent bariatric surgery compared with control subjects with no intervention (129 deaths in the control group vs 101 deaths in the surgery group). (*Adapted from* Sjöström et al. [56].)

HF. Unfortunately, obese HF patients are subjected to functional impairment from these two comorbidities, limiting their QoL and survival. With excellent long-term outcomes from heart transplantation, more HF patients are undergoing this procedure. Morbidly obese patients have increased perioperative complications from cardiac transplantation, often leading to their exclusion from the transplant list. Recent evidence has shown positive results from bariatric surgery in obese HF patients with respect to functional status, QoL, and cardiac function. Therefore, surgical weight loss in obese HF subjects is safe and effective and may serve as a bridge to cardiac transplantation [58•].

- In a recent meta-analysis of 22,094 patients with a mean BMI of 46.9, the average excess weight loss was 61% in all patients [59]. Weight loss was significantly greater with gastric bypass (62%) compared with gastric banding (48%). The other notable finding of this meta-analysis was the resolution and improvement of type 2 DM in 77% and 86% of patients, respectively. HTN resolved or improved in 79%, dyslipidemia improved in 70%, and obstructive sleep apnea resolved or improved in 84% of the patients [59].
- RYGB is accepted as the current standard of care, with strong positive evidence for its safety and efficacy. Another recent meta-analysis including 14 studies comparing laparoscopic gastric banding with RYGB showed greater weight loss at 1 year with RYGB than with gastric banding (76% vs 48%). In addition, resolution of CV risk factors, including DM (78% vs 50%), was better with bypass surgery. Although the perioperative complication rate was higher with gastric bypass compared with gastric banding (9% vs 5%), long-term recurrent surgical interventions were required more often in patients receiving gastric banding [54].
- Obesity is a major predisposing factor in the development of metabolic syndrome (MetS), a major public health problem that independently increases the risk of DM and CVD. Investigators from the Mayo Clinic examined the impact of weight loss from bariatric surgery on MetS prevalence in the Olmsted County population with a BMI≥35 kg/m^2, showing reversibility of MetS secondary to weight loss. The reversibility of MetS largely depended on the percentage of excess weight loss. Weight loss from bariatric surgery is known to reduce ghrelin and leptin levels, stimulate an increase in adiponectin levels, and improve insulin sensitivity and is associated with improved endothelial function [60].
- Obesity also is an independent risk factor for DM [1••], and the combination of these two disorders leads to premature morbidity and mortality. With increasing obesity incidence and prevalence, it is not surprising that 50% of patients with DM are obese, with a BMI greater than 30 kg/m^2, and 9% are morbidly obese, with a BMI greater than 40 kg/m^2 [60]. We have strong evidence showing the benefits of gastric bypass in patients with DM and a BMI greater than 35 kg/m^2.

- In a recent study by Rider et al. [61], investigators compared the relative benefits of surgical versus dietary weight loss on CV structure and function in obese patients with no identifiable CV risk factors. This study included 37 obese (BMI 40±8 kg/m^2) and 20 normal-weight subjects (BMI 21±2 kg/m^2) without known CV risk factors. Baseline and repeat cardiac MRI at the end of 1 year was performed in a weight loss group and a control group with no weight loss. Diet and bariatric surgery resulted in almost similar reduction/regression in both right ventricular and LV masses and end-diastolic volume, and reversal of both diastolic dysfunction and aortic distensibility impairment. No improvements were noted in the control group with continued obesity. This study highlights the fact that the beneficial effects of weight loss are independent of the weight loss modality [61].

Risks from weight loss

- Different weight loss modalities, including starvation, low-calorie diets, low-protein diets, and pharmacologic and surgical weight loss, are associated with arrhythmias related to QT prolongation [39].
- Dexfenfluramine and fenfluramine, appetite-suppressing agents, were once very popular as weight-losing agents. These agents act by enhancing the serotonin release in the hypothalamic nerve terminals. Subsequently, these two drugs were removed from the market, as they were shown to cause CV disorders and increased pulmonary hypertension [35].
- Sibutramine hydrochloride, a centrally acting agent, is another FDA-approved drug for long-term use. Sibutramine hydrochloride and phentermine are associated with increases in blood pressure and heart rate. In view of these adverse effects, these agents should not be used in patients with uncontrolled HTN, HF, or CHD, or in those with stroke or significant arrhythmias [34,37].

Disclosure

No potential conflicts of interest relevant to this article were reported.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:
- • Of importance,
- •• Of major importance

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