## STATE-OF-THE-ART PAPER

# Obesity and Cardiovascular Disease

## Risk Factor, Paradox, and Impact of Weight Loss

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Obesity has reached global epidemic proportions in both adults and children and is associated with numerous comorbidities, including hypertension (HTN), type II diabetes mellitus, dyslipidemia, obstructive sleep apnea and sleep-disordered breathing, certain cancers, and major cardiovascular (CV) diseases. Because of its maladaptive effects on various CV risk factors and its adverse effects on CV structure and function, obesity has a major impact on CV diseases, such as heart failure (HF), coronary heart disease (CHD), sudden cardiac death, and atrial fibrillation, and is associated with reduced overall survival. Despite this adverse association, numerous studies have documented an obesity paradox in which overweight and obese people with established CV disease, including HTN, HF, CHD, and peripheral arterial disease, have a better prognosis compared with nonoverweight/nonobese patients. This review summarizes the adverse effects of obesity on CV disease risk factors and its role in the pathogenesis of various CV diseases, reviews the obesity paradox and potential explanations for these puzzling data, and concludes with a discussion regarding the current state of weight reduction in the prevention and treatment of CV diseases. **(J Am Coll Cardiol 2009;53:1925–32) © 2009 by the American College of Cardiology Foundation**

Obesity has been increasing in epidemic proportions in both adults and children (1,2). In adults, overweight is defined as a body mass index (BMI) 25 to 29.9 kg/m² and obesity as BMI ≥30 kg/m². Other indexes that have been used less commonly but possibly with more predictive power include body fatness, waist circumference (WC), waist-to-hip ratio (WHR), and weight-to-height ratio (3). A recent study of nearly 360,000 participants from 9 European countries showed that both general obesity and abdominal adiposity are associated with risk of death and support the importance of WC or WHR in addition to BMI for assessing mortality risk (4).

Obesity has now become a critical problem in the U.S., with the prevalence among adults increasing by nearly 50% during the 1980s and 1990s (5); now, nearly 70% of adults are classified as overweight or obese compared with fewer than 25% 40 years ago (5–7). Additionally, the distribution of BMI in the U.S. has shifted in a skewed fashion such that the proportion of the population with morbid obesity has increased by a greater extent than overweight and mild obesity (1,2,5,7). Recent evidence indicates that obesity is associated with more morbidity than smoking, alcoholism, and poverty, and if current trends continue, obesity may soon overtake cigarette abuse as the leading cause of preventable death in the U.S. (6–8). Should we fail to stop the obesity epidemic, it has been predicted that we may soon witness an abrupt end, or even a reversal, of the steady increase in life expectancy (3,9).

There are numerous adverse effects of obesity on general, and especially, cardiovascular (CV) health (Table 1) (6). Although obesity has been implicated as one of the major risk factors for hypertension (HTN), heart failure (HF), and coronary heart disease (CHD), evidence from clinical cohorts of patients with established CV diseases indicates an obesity paradox because overweight and obese patients with HTN, HF, CHD, and peripheral arterial disease (PAD) tend to have a more favorable short- and long-term prognosis (Table 2).

This paper reviews the metabolic consequences of obesity as well as its pathological effects on blood pressure and CV structure and function contributing to its role in HTN and HF as well as to its role in increasing CHD and atrial fibrillation (AF). We also review the evidence for the obesity paradox in these disorders as well as PAD. Finally, we discuss the current evidence for the potential risks and benefits of purposeful weight loss.

## Pathophysiology

The adipocyte acts as an endocrine organ, and plays a substantial role in the pathogenesis and complications of obesity (1,10). Increased levels of leptin, an adipocyte-derived hormone that controls food intake and energy metabolism, may be particularly related with CV disease and has been reviewed in detail elsewhere (Fig. 1) (10,11). C-reactive protein (CRP) may play a role in the develop-

ment of leptin resistance, which is important because endogenous hyperleptinemia does not reduce appetite or increase energy expenditure (12).

Recently, increased concentrations of both CRP and leptin were associated with an increased risk of major CV events, but leptin seems to be a more robust predictor (13). In a multivariate model, leptin was an independent predictor of CV events, whereas CRP was not. Clearly, the increase in inflammatory markers is associated with insulin resistance, obesity, and CV events (11).

## Effects of Obesity on Hemodynamics and CV Structure and Function

Obesity has many adverse effects on hemodynamics and CV structure and function (Fig. 2) (14). Obesity increases total blood volume and cardiac output, and cardiac workload is greater in obesity. Typically, obese patients have a higher cardiac output but a lower level of total peripheral resistance at any given level of arterial pressure (14,15). Most of the increase in cardiac output with obesity is caused by stroke volume, although because of increased sympathetic activation, heart rate is typically mildly increased as well (16). The Frank-Starling curve is often shifted to the left because of increases in filling pressure and volume, thus increasing CV work. Obese patients are more likely to be hypertensive than lean patients, and weight gain is typically associated with increases in arterial pressure (15,16).

With increased filling pressure and volume, overweight and obese individuals often develop left ventricular (LV) chamber dilation (14,16,17). Even independent of arterial pressure and age, obesity increases the risk of left ventricular hypertrophy (LVH), as well as other structural abnormalities, including concentric remodeling (CR) and concentric LVH (18). In addition to LV structural abnormalities, obesity also leads to left atrial (LA) enlargement, both from increased circulating blood volume as well as abnormal LV diastolic filling (14,19). These abnormalities not only increase the risk of HF, but LA enlargement may increase the risk of AF and its morbid complications discussed later (20). In addition to increasing LV structural abnormalities and the propensity for more frequent and complex ventricular arrhythmias (16), obesity also has adverse effects on diastolic and systolic function (14,19,21–23).

| Table 1 | Adverse Effects of Obesity |
|---|---|
| **A. Increases in insulin resistance** | |
|    1)   Glucose intolerance | |
|    2)   Metabolic syndrome | |
|    3)   Type 2 diabetes mellitus | |
| **B. Hypertension** | |
| **C. Dyslipidemia** | |
|    1)   Elevated total cholesterol | |
|    2)   Elevated triglycerides | |
|    3)   Elevated LDL cholesterol | |
|    4)   Elevated non-HDL cholesterol | |
|    5)   Elevated apolipoprotein-B | |
|    6)   Elevated small, dense LDL particles | |
|    7)   Decreased HDL cholesterol | |
|    8)   Decreased apolipoprotein-A1 | |
| **D. Abnormal left ventricular geometry** | |
|    1)   Concentric remodeling | |
|    2)   Left ventricular hypertrophy | |
| **E. Endothelial dysfunction** | |
| **F. Increased systemic inflammation and prothrombotic state** | |
| **G. Systolic and diastolic dysfunction** | |
| **H. Heart failure** | |
| **I. Coronary heart disease** | |
| **J. Atrial fibrillation** | |
| **K. Obstructive sleep apnea/sleep-disordered breathing** | |
| **L. Albuminuria** | |
| **M. Osteoarthritis** | |
| **N. Cancers** | |

HDL = high-density lipoprotein; LDL = low-density lipoprotein.
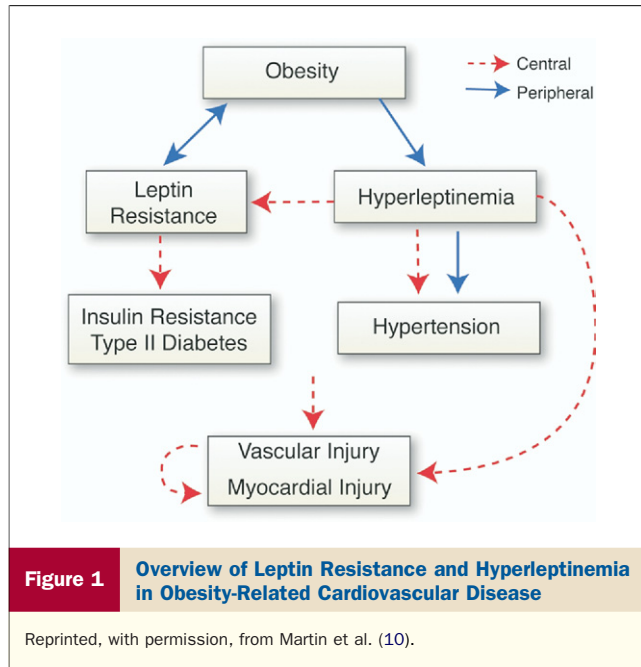
## Clinical Consequences of Obesity

_The art of simplicity is a puzzle of complexity._
—Doug Horton (1891–1968) (24)

**Obesity, HTN, and the obesity paradox.** Typically, HTN leads to thickening of ventricular walls without chamber dilation, a process referred to as CR when LV mass is not increased or concentric LVH when LV mass is increased, whereas obesity is characterized as increasing chamber

| Table 2 | Obesity Paradox* in Cardiovascular and Noncardiovascular Patients |
|---|---|
| **Cardiovascular** | |
|   A. Hypertension | |
|   B. Heart failure | |
|   C. Coronary heart disease | |
|     1)   Percutaneous revascularization | |
|     2)   Coronary artery bypass graft surgery | |
|     3)   Treadmill referrals | |
|   D. Peripheral arterial disease | |
|   E. Echocardiography referrals | |
| **Noncardiovascular** | |
|   A. Elderly | |
|   B. End-stage renal disease and dialysis | |
|   C. Advanced cancers | |
|   D. Chronic obstructive lung disease | |
|   E. Rheumatoid arthritis | |
|   F. Human immunodeficiency virus/acquired immune deficiency syndrome | |

*Conditions in which obesity has been associated with a more favorable prognosis compared with that in nonobese patients.

**Figure 1**   **Overview of Leptin Resistance and Hyperleptinemia in Obesity-Related Cardiovascular Disease**

Reprinted, with permission, from Martin et al. (10).

dilation without marked increases in wall thickness, a process that leads to eccentric LVH (6,18).

Despite having a higher prevalence of HTN in obesity, recent data have shown an obesity paradox. Uretsky et al. (25) investigated the effects of obesity on CV outcomes in 22,576 treated hypertensive patients with known CHD. During 2-year follow up, all-cause mortality was 30% lower in overweight and obese patients, despite less effective blood pressure control in these patients compared with the normal weight group. A previous study also showed decreased stroke risk and total mortality among overweight patients compared with lean patients (26). Similarly, another major HTN study showed a U-shaped relationship between all-cause, CV, and non-CV mortality and BMI, meaning excess mortality at both extremes of BMI (27). In another study of 800 elderly hypertensive patients, total mortality and CV and non-CV major events were highest in those with the leanest BMI quintile (28). The association between BMI and major CV events was U-shaped, whereas non-CV mortality decreased with increasing BMI. In aggregate, these studies suggest that although obesity may be a powerful risk factor for HTN and LVH, obese hypertensive patients may paradoxically have a better prognosis, possibly because of having lower systemic vascular resistance and plasma renin activity compared with more lean hypertensive patients (29).

**Obesity, HF, and the obesity paradox.** In a study of 5,881 Framingham Heart Study participants, Kenchaiah et al. (30) showed that during a 14-year follow-up, for every 1 $kg/m^2$ increment in BMI, the risk of HF increased 5% in men and 7% in women. In fact, a graded increase in the risk of HF was observed across all categories of BMI. In a study of 74 morbidly obese patients, nearly one-third had clinical evidence of HF, and the probability of HF

increased dramatically with increasing duration of morbid obesity (23).

Despite the known adverse effects of obesity on both systolic and particularly diastolic CV function and the epidemiologic data showing a strong link between obesity, generally defined by BMI criteria, and HF, many studies have suggested that obese HF patients had a better prognosis (Fig. 3) (31). In fact, we previously showed in a small study of 209 patients with chronic systolic HF that both higher BMI and percent body fat were independent predictors of better event-free survival (Fig. 4) (32). Preliminary data in nearly 1,000 patients with systolic HF also showed the prognostic impact of body fat on total survival (33).

In a recent meta-analysis of 9 observational HF studies (n = 28,209) in which patients were followed up for an average of 2.7 years, Oreopoulos et al. (34) showed that compared with individuals without elevated BMI, overweight and obese HF patients had reductions in CV (−19% and −40%, respectively) and all-cause (−16% and −33%, respectively) mortality. Likewise, in an analysis of BMI and in-hospital mortality for 108,927 decompensated HF patients, higher BMI was associated with lower mortality (35). In fact, for every 5-unit increase in BMI, the risk of mortality was 10% lower (p < 0.001).

Although these investigators raised the possibility that selection bias and baseline characteristics may have affected these results, they also suggested that excess body weight may confer some protective effects on HF mortality
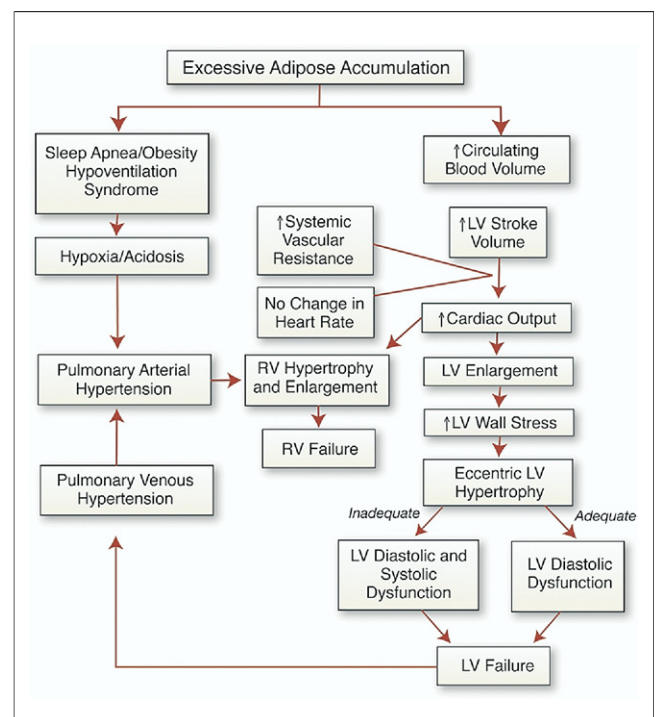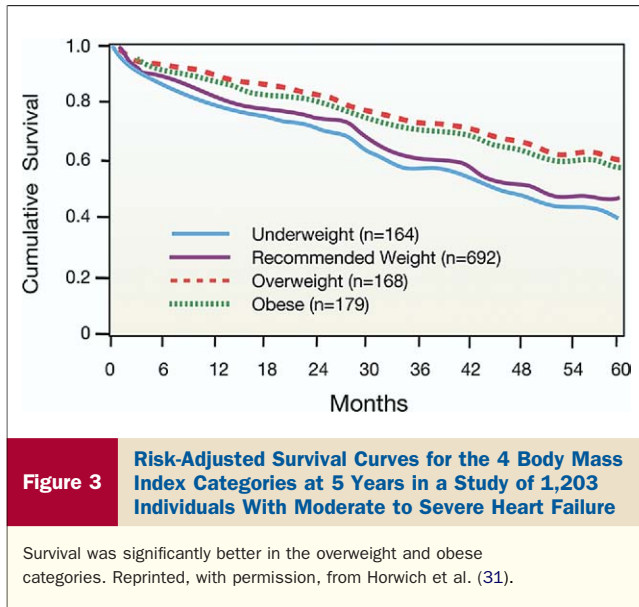


**Figure 2**   **Pathophysiology of Obesity and Cardiomyopathy**

LV = left ventricular; RV = right ventricular.
Reprinted, with permission, from Alpert (14).

| **Figure 3** | **Risk-Adjusted Survival Curves for the 4 Body Mass Index Categories at 5 Years in a Study of 1,203 Individuals With Moderate to Severe Heart Failure** |

Survival was significantly better in the overweight and obese categories. Reprinted, with permission, from Horwich et al. (31).
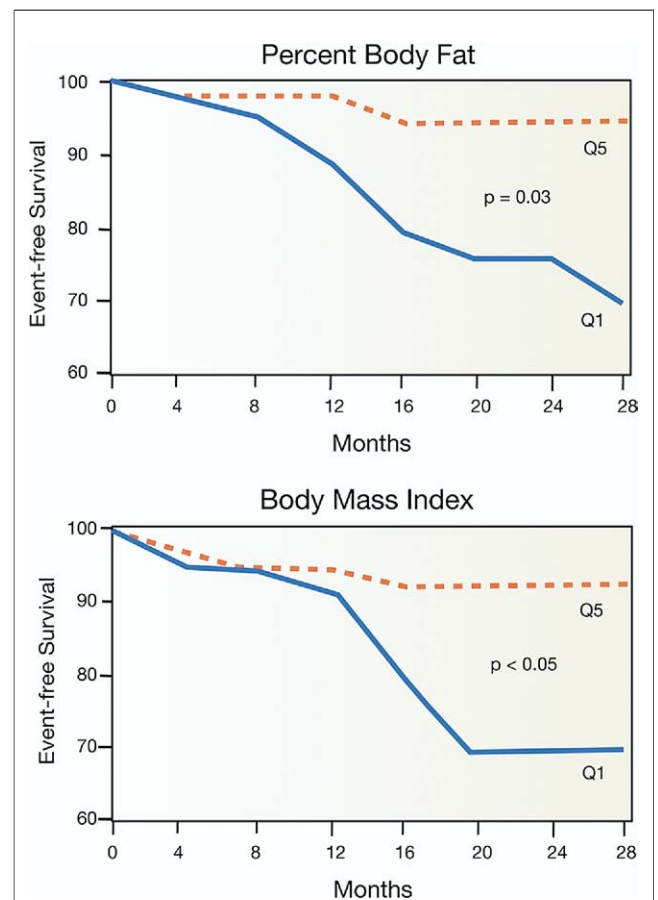
(32–35). Because advanced HF is a catabolic state, obese patients with HF may have more metabolic reserve (36–38). Cytokines and neuroendocrine profiles of obese patients also may be protective (34). Adipose tissue produces soluble tumor necrosis factor-alpha receptors and could play a protective role in obese patients with acute or chronic HF by neutralizing the adverse biological effects of tumor necrosis factor-alpha (39). Additionally, overweight and obese patients with acute and chronic HF have lower levels of circulating atrial natriuretic peptides (40). Obese patients with HF may have attenuated sympathetic nervous system and renin-angiotensin responses (34). Because obese patients typically have high levels of arterial pressure, they may have a better prognosis in advanced HF and may tolerate higher levels of cardioprotective medications (34). Higher circulating lipoproteins in obese patients may bind and detoxify lipopolysaccharides that play a role in stimulating the release of inflammatory cytokines, all of which may serve to protect the obese patient with HF (36,41). Unfortunately, these studies do not typically adjust BMI for other measures of adiposity (e.g., WC and WHR).

**Obesity, CHD, and the obesity paradox.** Obesity plays a major role in adversely affecting major CHD risk factors, including HTN, dyslipidemia, and diabetes mellitus (DM), is the major component of metabolic syndrome, and is probably an independent risk factor for atherosclerosis and CHD events (6,29,42,43). Although recent studies indicate that the various measures to define obesity are not all created equally regarding overall CV disease risk, the consensus is that compared with the traditional BMI assessments, the more refined modalities (e.g., WC, WHR, waist-to-height ratio, and so on) do not add significantly to the BMI assessment from a clinical standpoint (3,44,45), although this has not been assessed for the obesity paradox. Therefore, however measured, increasing obesity typically confers an increased risk of CV diseases and CHD. Additionally, excess adipos-

ity has been strongly related to first non–ST-segment myocardial infarction (MI) occurring at a younger age (46).

Nevertheless, as with HTN and HF, many studies have also reported an obesity paradox in CHD, including in patients treated with revascularization (6,47). In a recent systematic review of over 250,000 patients in 40 cohort studies followed up for 3.8 years, Romero-Corral et al. (47) reported that overweight and obese CHD patients have a lower risk for total and CV mortality compared with underweight and normal-weight CHD patients. However, in patients with a BMI $\geq 35$ kg/m$^2$, there was an excess risk for CV mortality without any increase in total mortality. These investigators explained the better outcomes for CV and total mortality in overweight and mildly obese CHD groups, which could not be explained by confounding factors, by implicating the lack of discriminatory power of BMI to differentiate between body fat and lean mass. However, data from our institution have shown the same obesity paradox when comparing patients with high and low percent body fat as with high and low BMI, although this study did not assess WC, WHR, and other body composi-



| **Figure 4** | **Body Composition and Heart Failure Prognosis** |

Freedom from cardiovascular death or urgent transplantation in patients in quintiles (Q) 1 and 5 for percent body fat **(upper panel)** and body mass index **(lower panel)**. Reprinted, with permission, from Lavie et al. (32).

tion parameters (48). Importantly, the obesity paradox has also been shown in patients after MI and revascularization, and more recently has been shown in patients referred for exercise stress testing (47,49). Although the mechanism for this effect is uncertain, in aggregate, these studies suggest that despite the fact that obesity increases the risk for developing CHD, at least overweight and mild obesity do not seem to adversely affect prognosis in patients with established CHD.

**Obesity paradox in other CV populations.** Galal et al. (50) have recently assessed 4.4-year mortality in 2,392 patients with PAD who had undergone major vascular surgery and had high mortality risk during follow-up. This study also showed a powerful obesity paradox, with progressive reductions in mortality in normal BMI, overweight, and obese groups compared with underweight patients. Although BMI was an independent predictor of greater mortality in the entire cohort, a higher prevalence of moderate-severe chronic obstructive pulmonary disease almost completely explained the increased risk statistically in the underweight patients. Nevertheless, adjusting for lung disease did not abolish the relationship between higher BMI and lower mortality in the overweight and obese PAD groups (50,51). Although many of the HTN, HF, and CHD studies discussed previously also attempted to correct for smoking as a risk factor, lower BMI remained an independent predictor of higher risk (51).

We have also documented the inverse relationship between BMI and all-cause mortality in over 30,000 patients with preserved LV systolic function referred for echocardiography (18). Like many studies, we found the highest mortality in underweight patients, yet overweight, mildly obese, and obese patients with BMI $\geq 35$ kg/m$^2$ had significantly lower mortality than those with ideal BMI (18.5 to 25 kg/m$^2$). Although overweight and obese patients in our cohort had a higher prevalence of LV structural abnormalities, including CR as well as both eccentric and concentric LVH, which were associated with increased mortality, still higher BMI was independently associated with lower mortality. Nevertheless, when only examining the obese patients with BMI $\geq 30$ kg/m$^2$, higher BMI was independently associated with higher mortality, supporting the idea that more marked obesity may still be associated with a worse prognosis.

**Obesity and AF.** As with obesity and the obesity-related disorders, the prevalence of AF is increasing, and is expected to increase 2.5-fold by 2050 (52). Although the increase in AF may be attributable to the aging of our population combined with the improved prognosis of HTN, CHD, and HF, conditions that increase the risk of AF, the epidemic of obesity, with its attendant hemodynamic effects and impact on LV and LA structure and function, may also contribute to the higher prevalence of AF (20). Recently, Wanahita et al. (52) reviewed 16 studies enrolling 123,000 patients to assess the impact of obesity on AF. In the subgroup of 5 population-based studies enrolling 78,602

patients, obese patients had a nearly 50% increased risk of developing AF that escalated with increasing BMI. On the other hand, post-cardiac surgery studies enrolling 44,647 patients failed to show an increased risk of AF in obesity.

**Obesity and stroke.** Numerous studies have reported an association between BMI and stroke (1). In fact, for each 1-U increase in BMI, there was an increase of 4% in the risk of ischemic stroke and 6% for hemorrhagic stroke (1,53). This increased risk of stroke may be attributable to a higher prevalence of HTN, a prothrombotic/proinflammatory state that accompanies excess adipose tissue accumulation, as well as increased AF.

> *Sudden death is more common in those who are naturally fat than in the lean.*
>
> —Hippocrates (54)

**Obesity and ventricular arrhythmias.** Although progressive HF may be the most common cause of death in patients with obesity cardiomyopathy, sudden cardiac death (SCD) has been reported to be increased in apparently healthy obese patients (1). Substantial evidence supports an increased electrical irritability in obesity that may lead to more frequent and complex ventricular dysrhythmias (16), even in the absence of LV dysfunction or clinical HF. In the Framingham Heart Study (55), the annual SCD rate was nearly 40 times higher than in a matched nonobese population (16).

A positive association between corrected QT (QTc) interval and BMI has been noted, and prolonged QTc has predicted increased mortality even in apparently healthy populations (56,57). Although a relationship between QTc and increased obesity has been noted in many studies, this is most evident in the severely obese (56,58). Likewise, increased late potentials have also been linked to increased risk of SCD, and the prevalence and number of abnormal late potentials has increased with more marked obesity (59). The presence of late potentials may be related to some of the pathological changes noted with cardiomyopathy of obesity (adipositas cordis), including myocyte hypertrophy, fibrosis, and fat and mononuclear cell infiltration (1,14). Finally, obesity is associated with abnormalities in sympathovagal balance, leading to higher heart rate and reduced heart rate variability, known factors related with increased risk of SCD (2,11).

**Obesity and sleep apnea.** Obesity is a classic cause of alveolar hypoventilation and the obstructive sleep apnea (OSA) syndrome (60). In fact, OSA may contribute to the pathogenesis of HTN and increased inflammation and CRP (61). Clearly, patients with OSA have increased risk of HTN, dysrhythmias, pulmonary HTN (present in 15% to 20% with OSA), HF, MI, stroke, and overall mortality (62).

**Obesity and venous disease.** The combination of increased intravascular volume and high-volume lymphatic overload, as well as reduced physical activity, often lead to venous insufficiency and edema with increasing obesity (63).

Additionally, obesity is associated with an increased risk for venous thromboembolism and pulmonary embolism, especially in women (64,65).

## Status of Weight Reduction

Considering that some long-term studies have shown that weight loss in overweight and obesity is associated with increased mortality coupled with many CV studies showing a better prognosis with a higher BMI, it has been suggested that purposeful weight loss may not be beneficial and may even be detrimental in patients with CV diseases (31,66–68). In contrast, however, other studies assessing mortality based on body fat and lean mass rather than BMI or weight alone have suggested that subjects losing body fat rather than lean mass have a lower mortality (67,69). Nevertheless, there are potential adverse effects of weight loss. Certainly, starvation, very-low-calorie diets, liquid protein diets, and obesity surgeries have been associated with prolongation of the QTc interval and increased risk of malignant dysrhythmias (1), and various pharmacologic agents have either limited efficacy or considerable toxicity (70–72).

Clearly lifestyle interventions, including exercise training and at least mild weight reduction with caloric restriction, showed a nearly 60% reduction in the risk of developing DM, which was considerably better than that noted in patients treated with metformin (73,74). The most studied nonpharmacologic therapy in CV disease for weight reduction has been cardiac rehabilitation and exercise training, which resulted in a 37% reduction in the prevalence of metabolic syndrome (75). In a small subgroup of 45 obese patients with 5% or more weight loss (average 10%) after cardiac rehabilitation, we noted more significant improvements in exercise capacity and plasma lipids than in 81 obese patients who did not lose weight (76). Recently, we noted marked reductions after cardiac rehabilitation in CRP levels in obese CHD patients, whereas lean patients had only slight and nonsignificant declines in CRP (77). In a study of 530 patients, we noted marked improvements in CHD risk factors among overweight and obese CHD patients who lost weight, including CRP, lipids, and glucose, and this group had a trend of lower mortality (48). Likewise, in a study of over 1,500 CHD patients, intentional weight loss from a 6-month dietary program also produced a lower incidence of CHD events over 4 years (78). A recent study from the Mayo Clinic of 377 consecutive patients showed a benefit of weight loss on a composite outcome (mortality plus major CV events), including benefits noted in those with a BMI $<25$ kg/m$^2$ as well as in overweight and obese CHD patients (68). These studies support purposeful weight reduction in overweight and obese CHD patients, despite the obesity paradox.

In HTN, weight reduction has resulted in significant decreases in arterial pressure (6,19). MacMahon et al. (79) showed that even an 8-kg weight loss resulted in small but statistically greater reductions in LV wall thickness in mildly obese hypertensive patients compared with standard pharmacologic intervention. In HF, despite the obesity paradox, trials have suggested that weight loss can induce improvements in LV mass as well as in systolic and diastolic ventricular function (14). In a study of 14 morbidly obese patients who achieved marked weight loss ($>30\%$ of body weight) after gastroplasty, New York Heart Association functional class improved in 12 patients by an average of $>1$ functional class (23). Weight loss also was associated with marked improvements in LV chamber size, LV end-systolic wall stress, and systolic and diastolic LV function.

Currently, many severely obese patients are being considered for various obesity surgical procedures, and specialists in CV diseases are increasingly being asked to evaluate and clear these patients for anesthesia and surgery. Although 30-day mortality after gastric bypass has recently been reported to be higher than expected, closely linked to surgeon inexperience (80), more studies are now showing that these surgical procedures are associated with short- and long-term improvements in major morbidity and all-cause mortality, particularly related with cancers, DM, and CV diseases, and also predict long-term decreases in CV risk in obese patients (81–85). Obesity surgery may reduce arterial pressure over the short term (2 to 3 years), but may not have a long-term (e.g., 6 to 8 years) effect to reduce HTN (82,86). Large-scale studies are needed on the risks and benefits of obesity surgeries in patients with advanced CV diseases, including HTN, CHD, HF, and AF; a recent small study suggests that bariatric surgery is safe and effective in patients with severe systolic HF (87).

## Conclusions

Overwhelming evidence supports the importance of obesity in the pathogenesis and progression of CV disease. Although an obesity paradox exists, in that overweight and obese patients with established CV diseases seem to have a more favorable prognosis than leaner patients, the constellation of data still support purposeful weight reduction in the prevention and treatment of CV diseases. Further research is needed in all of these areas, and if the current obesity epidemic continues, we may soon witness an unfortunate end to the steady increase in life expectancy.

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**Key Words:** obesity ■ cardiovascular disease ■ weight loss.