

### Target Audience

This activity has been designed to meet the educational needs of cardiologists currently associated with The American Medical Association across the United States, as well as other health care professionals within those practices, including nurses, physician assistants, and nurse practitioners.

### Statement of Need/Program Overview

This educational program will review the cardiovascular benefits of weight loss, as well as the history of phentermine, focusing on the misperception that phentermine pharmacotherapy for obesity increases blood pressure and heart rate, exposing treated patients to increased cardiovascular risk. The program will also discuss recently approved treatments for overweight and obese patients.

### Educational Objectives

*After completing this activity, the participant should be better able to:*

- Describe the relationship between obesity and cardiovascular risk
- Identify cardiovascular imaging options for obese patients to improve cardiac risk assessment
- Describe a holistic approach to weight loss in the obese patient
- Review the important role of pharmacology in the treatment of obesity with a focus on recently FDA approved agents
- Explain the role of the cardiologist in the treatment of obesity

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Peter A. McCullough, MD, MPH, FACC, FACP, FCCP, FAHA, FNKF	Nothing to disclose

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# New Vistas for the Treatment of Obesity: Turning the Tide Against the Leading Cause of Morbidity and Cardiovascular Mortality in the Developed World

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Excess adiposity and obesity are the root cause of at least 27 diseases that cause considerable lifelong morbidity and, in many scenarios, eventual cardiovascular mortality. The human body has the ability to increase the number and size of its adipocytes by approximately 10-fold over the course of a lifetime. As fat mass increases, its blood supply, supporting cells, tissue structure, and local and systemic hormonal control also increase. This results in excess adiposity, leading to progressive obesity and the resistance to weight-loss attempts. There have been numerous trials of food diets combined with exercise that, in general, have a 50% dropout rate at 1 year and lead to very modest (~ 5%) reductions in body weight. Thus, many with obesity require interventions beyond casual diet and exercise advice. Meal replacement diets and bariatric surgery offer considerably greater degrees of weight loss, but both can be plagued by weight regain. Because the ability to control food urges has been shown to be a key psychological factor for success, medicinal approaches that work in this domain are attractive adjuncts to diet, exercise, and weight-loss surgery. This article reviews the emerging role of medical therapy in the treatment of excess adiposity with the goal of reducing comorbidities and possibly improving cardiovascular survival.

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## KEY WORDS

Obesity • Cardiovascular disease • Weight-loss management • Metabolic syndrome • Bariatric • Adiposity • Appetite suppressants

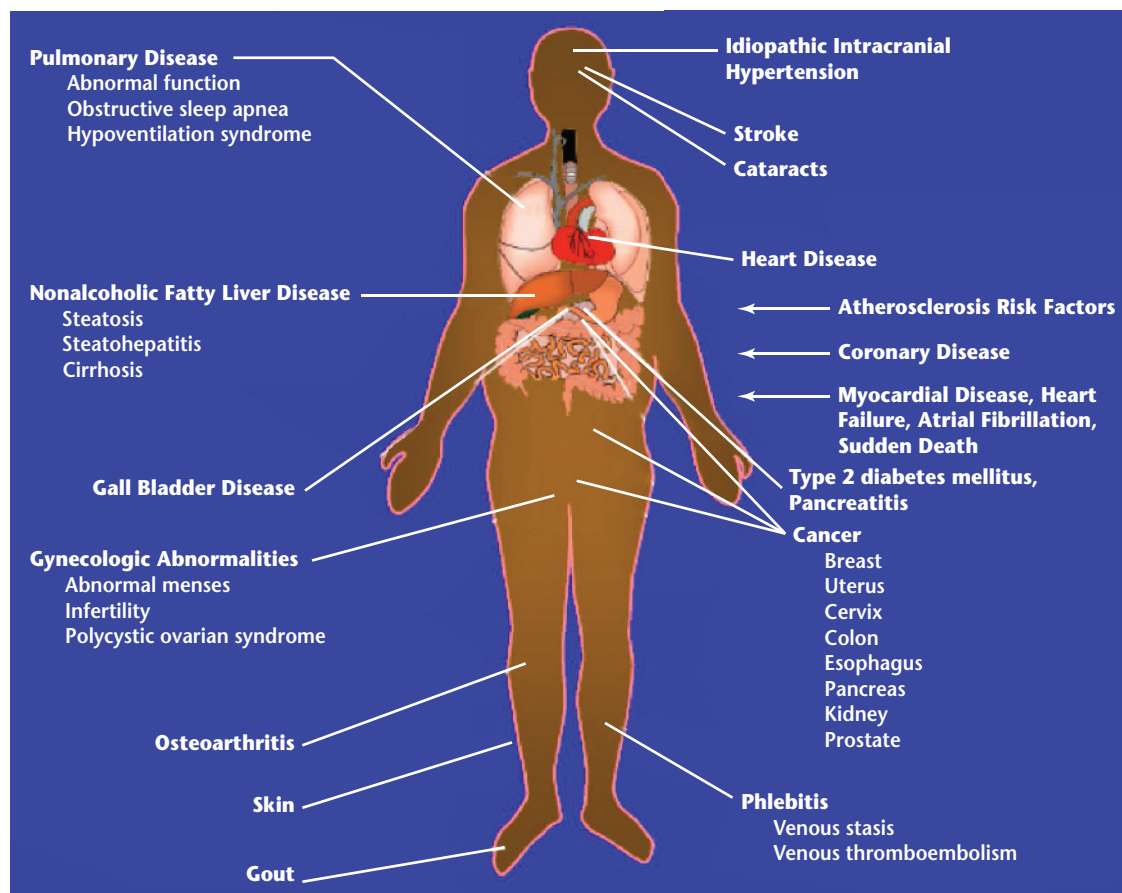
Excess adiposity and obesity have been cited as the root cause of at least 27 different diseases of the human body (Figure 1). In animals, weight is carefully regulated by many internal and environmental factors, most important of which is the availability of food. Since the domestication of plants and animals as much as 7000 years ago, human history has recorded adiposity in some form, most likely associated with greater availability of food. Of interest, it is with this change that evidence of coronary atherosclerosis has been found.<sup>1</sup> In the hunter-gatherer time periods, neither evidence of adiposity nor atherosclerosis has been found in human remains.

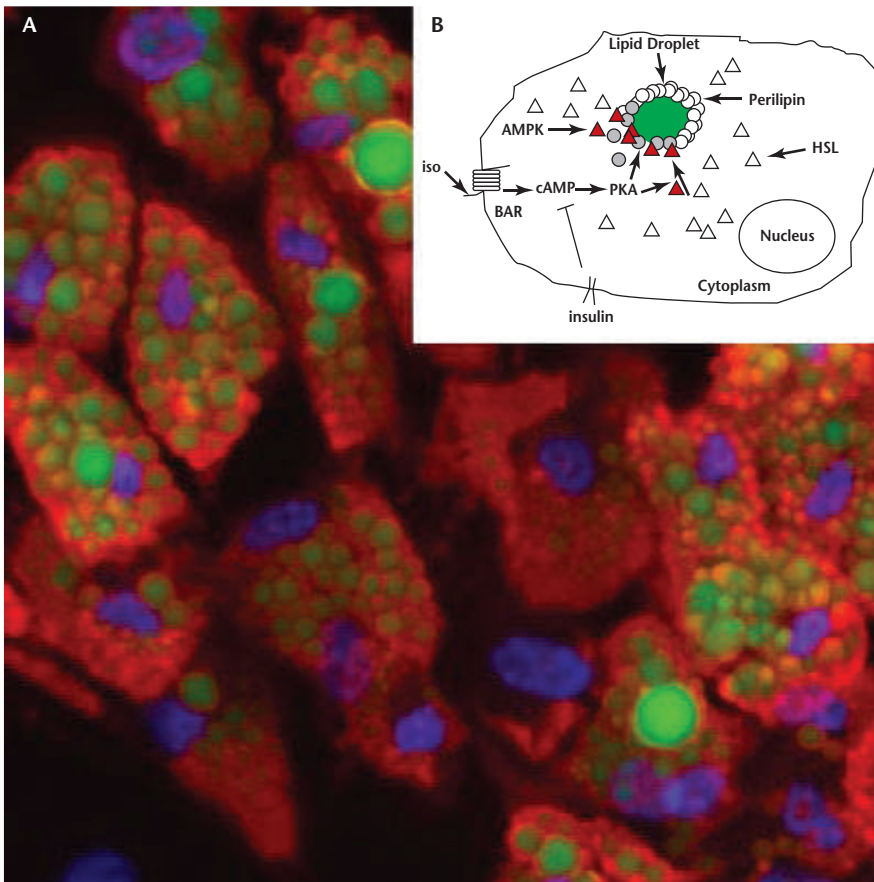
Each adipocyte has the ability to increase in number and individual size by approximately 10-fold over the course of an average human lifetime. This explains why body weight

can double or triple in those with morbid obesity, usually between the ages of 18 and 45 years (Figure 2).<sup>2</sup> This massive increase in adipose tissue, supporting cells, paracrine and central cell signaling systems, and metabolic demands outstrips the body's ability to manage weight and directly results in hyperinsulinemia, dyslipidemia, and structural and functional changes in the liver, resulting in increased production of inflammatory factors (high-sensitivity C-reactive protein [hs-CRP]), and directly leads to atherosclerosis.<sup>3</sup> Thus, unlike individual cardiovascular risk factors, which are epidemiologically independent, obesity can be viewed as the only central risk factor that directly causes or worsens traditional determinants of atherosclerosis (Figure 3).<sup>4</sup> For example, excess adiposity is responsible for > 90% of type 2 diabetes mellitus (DM),

which is not only an individual risk factor, but a coronary artery disease (CAD) risk equivalent.<sup>4</sup> Likewise, obesity is directly linked to low levels of high-density lipoprotein cholesterol (HDL-C), elevated triglycerides, and increased numbers of atherogenic small, low-density lipoprotein cholesterol (LDL-C) particles.<sup>5</sup> These changes have been closely related to the observation that obesity leads to progressively premature myocardial infarction (MI) in young and middle-aged individuals.<sup>6</sup> Similarly, obesity is related to activation of the sympathetic and renin-angiotensin systems, leading to sodium retention and hypertension. With increasing levels of adiposity, there is a reduction in levels of plasminogen activator inhibitor-1, and a prothrombotic state that contributes both to atherothrombosis and venous thromboembolism (Figure 4).

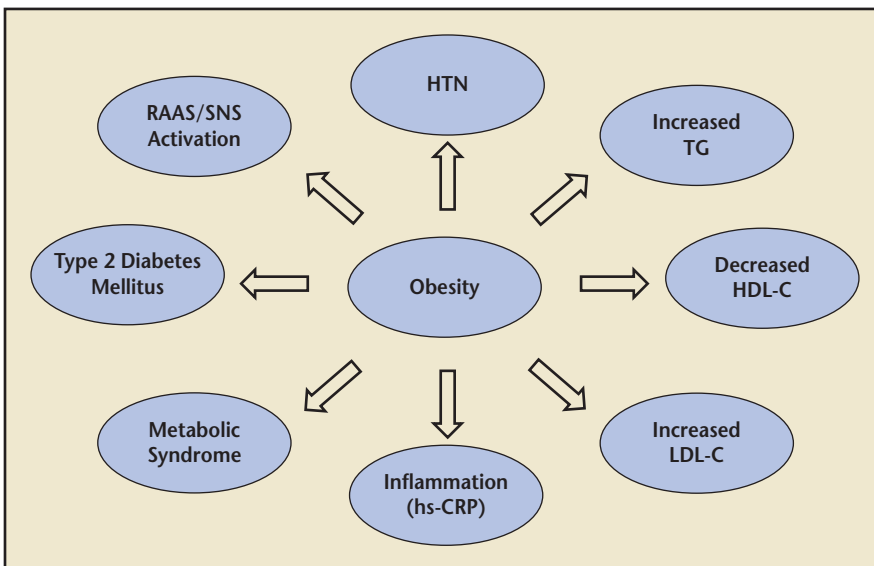
Figure 1. Obesity-related comorbidities.





**Figure 2.** (A) Human adipocytes visualized for nuclei (blue), lipid droplets (green), and perilipin (red). (B) Lipolysis in adipocytes is regulated by perilipin (circles), hormone sensitive lipase (HSL, triangles), and other regulatory proteins (eg, ATGL, not shown). A well-known pathway, depicted here, is activation of lipolysis by  $\beta$ -adrenergic stimulation. Interaction of isoproterenol (Iso) with  $\beta$ -adrenergic receptors (BAR) leads to increased cAMP, and activation of cAMP-dependent protein kinase (PKA). PKA phosphorylates both perilipin (filled circles) and HSL and phosphoHSL (filled triangles), leading to translocation of HSL to the lipid droplets. AMPK, 5' adenosine monophosphate-activated protein kinase; ATGL, adipose triglyceride lipase; cAMP, cyclic adenosine monophosphate. Reproduced with permission from Vala Sciences, Inc. (San Diego, CA).

**Figure 3.** Obesity positioned as the only central and reversible cardiovascular disease risk factor that favorably influences all the other associated factors. HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; HTN, hypertension; LDL-C, low-density lipoprotein cholesterol; RAAS, renin-angiotensin-aldosterone system; SNS, sympathetic nervous system; TG, triglycerides. Reproduced with permission from Zalesin KC et al.<sup>4</sup>



## Direct Contributions to Anatomic and Functional Cardiovascular Disease

Obesity is a well-established, direct determinant of a variety of cardiovascular diseases, including coronary atherosclerosis, stroke, sudden cardiac death, cardiomyopathy, and venous thromboembolic and peripheral vascular disease.<sup>7</sup> Obesity can also be associated with other risk conditions for heart disease, including gout and sleep apnea syndrome with pulmonary and systemic hypertension (Figure 4).<sup>8</sup> Depending on the degree of association with these comorbidities, as well as the type of obesity (eg, truncal vs central, subcutaneous vs visceral), there is a wide spectrum of relative risk connecting the obese patient to cardiovascular disease due to the complex interplay between the direct cardiovascular and systemic effects of obesity (Table 1).<sup>9</sup>

There may also be a predisposition in any obese individual to develop a particular type of cardiovascular complication due to the widely disparate variables that make up each individual's unique obesity physiology. In fact, there are situations in which an obese patient may be protected from some cardiovascular manifestations; this is termed *the obesity paradox*. This paradox may be related to the complex interplay of the adipocyte, through which its protective effects (such as being the source of endothelial progenitor cells that may protect vascular endothelium) are matched against their known source of inflammatory mediators. Intramyocardial fat can also play a role in causing cardiac dysfunction in obesity-related disorders. Pathologic lipid accumulation in the myocardium is evidenced by increased levels of toxic lipid intermediates (eg, diacylglycerol and

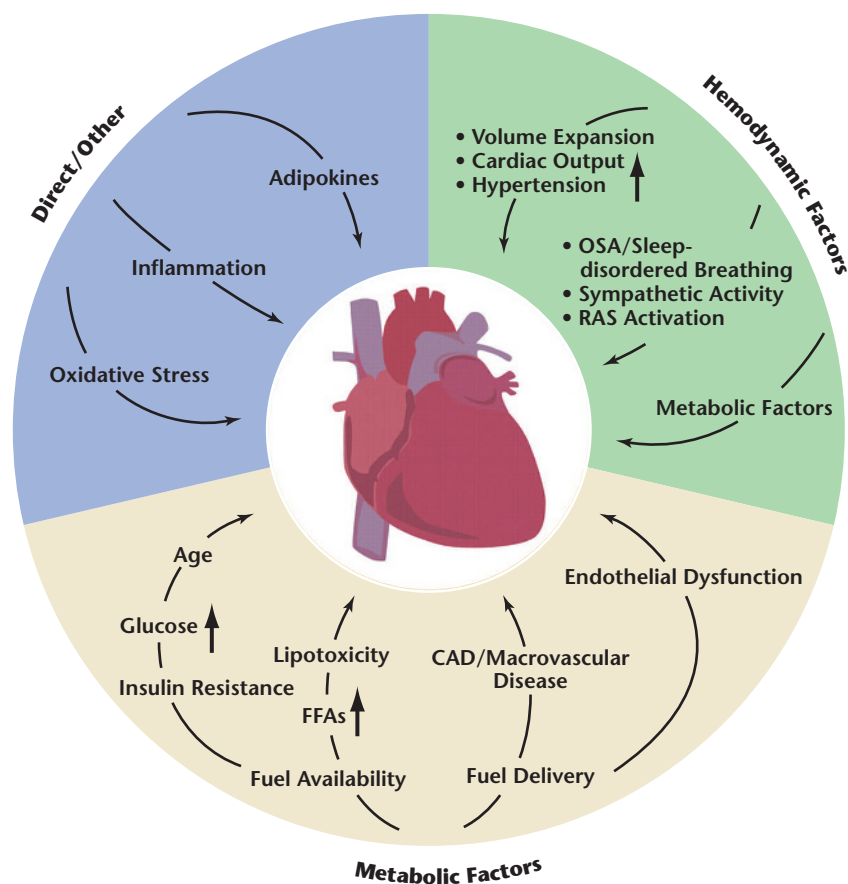


Figure 4. Potential mechanisms via which obesity can influence structure and function of the heart. CAD, coronary artery disease; FFAs, free fatty acids; OSA, obstructive sleep apnea; RAS, renin-angiotensin system. Reproduced with permission from Abel ED et al.<sup>8</sup>

**TABLE 1**

**Effects of Obesity on the Cardiovascular System**

Systemic	Cardiac
Insulin resistance	Altered cardiac geometry
Glucose intolerance	Left atrial enlargement
Metabolic syndrome	LV concentric and eccentric hypertrophy
Diabetes mellitus	LV remodeling
Dyslipidemia	LV dysfunction
Increases in total and LDL-C and triglycerides	Diastolic
Decrease in HDL-C	Systolic
Hypertension	Endothelial dysfunction
Increased inflammation	Coronary artery disease
Prothrombotic state	Heart failure
	Arrhythmias
	Atrial fibrillation
	Ventricular tachycardia and fibrillation

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LV, left ventricular. Reproduced with permission from Lavie CJ et al, "Obesity and cardiovascular disease: risk factor, paradox, and impact of weight loss," *J Am Coll Cardiol*. 2009;53:1925–1932.

ceramide), which are linked to mitochondrial dysfunction, insulin resistance, and apoptosis.<sup>10</sup> In addition, it has been shown that prolonged caloric restriction in obese patients with DM is associated with decreased myocardial triglyceride content and improved diastolic function, indicating that presumed lipotoxicity is reversible and amendable by metabolic intervention.<sup>11</sup>

Cardiovascular imaging plays an important role in the ability to accurately characterize the type of cardiovascular manifestations that occur in obese patients. This is critical to effective management because it enables physicians to assess for occult manifestations of cardiovascular disease, and it can motivate both patients and clinicians to treat the underlying obese condition.

Echocardiography remains the mainstay for assessing cardiac morphology in obese patients, despite the challenge of finding an adequate acoustic window, particularly in morbidly obese patients. Differentiation between subepicardial adipose tissue and pericardial effusion is often a challenge in obese patients.<sup>12</sup> Some of the changes in cardiac morphology and function that seem to predate the development of obesity-related heart failure are due to the increased circulating blood volume leading to an increase in venous return to both ventricles, and increases in right- and left-side chamber dimensions. The increase in wall stress and tension leads to ventricular hypertrophy, interstitial matrix deposition, tissue fibrosis, and diastolic dysfunction. Stress (treadmill or pharmacologic) echocardiography can also be a useful tool to evaluate for physiologically significant obstructive CAD in symptomatic patients. Because obese patients are often sedentary, with activity levels not reaching an ischemic threshold,

they are less likely to present with stress-induced symptoms that would indicate provocative testing. In general, when body mass index (BMI) exceeds 30 kg/m<sup>2</sup> there is a high rate of echocardiographic abnormality, and the diagnostic yield is considerable in the evaluation of effort intolerance or other cardiopulmonary symptoms.<sup>13</sup> Often, optimal acoustic windows are limited in the obese (particularly the morbidly obese) patient.

Cardiac magnetic resonance imaging (cMRI) for the evaluation of patients with obesity-related cardiac disease provides excellent diagnostic information. The strength of cMRI stems from its ability to provide information on anatomy, physiology, and function in a single noninvasive study without exposure to iodinated contrast or ionizing radiation. cMRI can be very useful in determining the pathologic abnormalities in cardiac architecture associated with obesity and changes that may occur with weight loss from lifestyle changes or pharmacologic or surgical interventions. Recently, there is renewed interest in using cMRI to assess for myocardial steatosis, or the accumulation of fatty acids and triglycerides within the myocardial cells, which is associated with increased reactive oxygen species and inflammation.<sup>14</sup> cMRI has an advantage over echocardiography in the detection and quantification of cardiac fibrosis. Late gadolinium enhancement (retention) occurs in fibrotic areas of the myocardium, which can be the substrate for myocardial dysfunction, re-entrant arrhythmias, and sudden cardiac death. Limitations of cMRI include the bore and gantry diameter and upper weight range limits between 158.76 and 204.12 kg (which also happens to be the weight limit for most computed tomography [CT] scanners).

Obesity is now considered an independent risk factor for the development of CAD and is associated with other coronary risk factors in a highly variable way.<sup>15</sup> The Framingham study reported subclinical atherosclerotic disease in up to 50% of obese individuals.<sup>16</sup> The presence of epicardial fat has been associated with local production of inflammatory and proatherosclerotic factors, abnormal lipid trafficking, and the presence of significant local coronary plaques.<sup>17</sup> Lubanski and colleagues<sup>18</sup> evaluated coronary CT imaging with both coronary calcium scoring (CCS) and CT coronary angiography (CTCA) and found a prevalence of asymptomatic CAD in morbidly obese patients of 61%. The vast majority (95%) of patients were also identified using CCS. This is consistent with the findings of our group, showing the ability of CCS (which exposes patients to much lower doses of radiation than CTCA) and nuclear stress testing to identify > 95% of asymptomatic patients with CAD.<sup>19</sup>

One should, therefore, consider performing CCS to better assess coronary risk in obese asymptomatic men between the ages of 45 and 75 years and women between 55 and 75 years of age as they enter menopause. Carotid intimal media thickness (cIMT) and the identification of plaque by direct visualization by carotid ultrasound is an alternative modality that enhances coronary risk assessment. With modern ultrasound techniques, in addition to measurement of cIMT, direct visualization of carotid plaques is possible and very helpful in the confirmation of the anatomic presence of atherosclerosis. Compared with CCS, cIMT and carotid duplex ultrasound as surrogate measures can only suggest the possibility of coronary atherosclerosis but do not expose the

patient to ionizing radiation. The cIMT and carotid duplex examination are favored for use in the younger patients at coronary risk. With either modality, direct anatomic confirmation of the presence of atherosclerosis is an important clinical reality for both the patient and the clinician. Not only is risk for MI, stroke, and cardiovascular death increased, but secondary prevention measures are called into play and increased attention and compliance are heralded with the understanding that disease is present and will progress unless there are interventions directed at the modifiable risk factors.

Myocardial perfusion imaging using single-photon emission computed tomography (SPECT MPI) uses radioactive isotopes such as technetium and thallium to assess myocardial blood flow. This technology is useful in determining if symptoms such as dyspnea on exertion or chest discomfort are due to obstructive coronary disease. In the obese patient, rubidium positron emission tomography examinations yield superior image quality over SPECT imaging due to their higher spatial resolution and attenuation correction.<sup>20</sup> In addition, in the setting of intermediate or undetermined plaque severity by CT angiography, MPI assessment is critical in the evaluation of hemodynamically significant coronary disease.

## Cardiologists and the Treatment of Obesity

Cardiologists should take a leadership role in the evaluation and management of obesity; the rationale is manifest and includes the following points:

1. Cardiologists have assumed a primary role in the intensive treatment of hypertension and lipids and have become more

active in the medical management of DM, including insulin management, given the increasing impact of primary and secondary prevention.

2. Obesity is looked upon by cardiologists as an important modifiable risk factor that contributes to the development of other coronary risk factors, myocardial disease, and arrhythmias.<sup>21</sup>
3. There is a greater appreciation among cardiovascular practitioners about the role of the adipocyte and profound cardiometabolic changes leading to a hypercoagulable and proinflammatory state.
4. Often by default, cardiologists are left treating obese patients who have cardiovascular symptoms including effort intolerance, chest discomfort, dyspnea, fatigue, and edema, and look at weight reduction as an integral part of the holistic approach to treating these patients.
5. Action-oriented cardiologists appreciate that, in many instances, they are closing a treatment gap for patients who have already received repetitive recommendations from their primary care providers to decrease caloric intake and increase activity without leading to substantive weight loss.
6. Cardiologists play a principal role in the determination of safety of diet, exercise, medical treatment, and bariatric surgery in those with morbid obesity.

## Brief Advice from the Cardiologist

Cardiologists have one of the lowest rates of obesity among all specialists in the United States.<sup>22</sup> Therefore, this group of physicians can set an excellent example for patients and members of the community. Every cardiologist should

be comfortable giving brief advice on diet, exercise, and weight loss in the office.<sup>23</sup> The principles for dietary advice include two components: healthy food choices and portion control. Healthy choices provide essential amino and fatty acids, micronutrients, and fiber; importantly, they significantly limit and reduce the major sources of calories and fat-promoting macronutrients known as *the three SSSs*: sugars, starches, and saturated fats (Figure 5). Brief advice

can be limited to a one-page sheet that each patient over his or her goal weight should receive (Figure 5). Exercise advice is best couched in a mild to moderate and cumulative approach that includes taking more steps per day, avoiding elevators and escalators, and building up to daily voluntary exercise sessions, in as few as 5 to 10 minutes, progressing to  $\geq 30$  minutes per day. It is beyond the scope of this article to review the voluminous data on exercise and weight;

Figure 5. One-page dietary advice for cardiology practice.

**Suggested Dietary Approach: Healthy Choices and Portion Control (Low Sugar, Starch, and Saturated Fat)**

**Healthy Food Choices**

High-Quality Sources of Protein

- Fish, seafood
- Beans
- Nuts
- Eggs
- Non- or lowfat dairy (yogurt, skim milk, lowfat cheese)
- Lean pork, chicken, beef

Fresh Fruits and Vegetables

- Unlimited

**Priority Foods**

**Sugars**

- Regular soda, juices, candy, sweets, treats

**Starches**

- Anything made with flour, bread, baked goods, cookies, crackers, chips, pretzels
- Pasta, potatoes, rice (high-fiber cereal, limited very low-carbohydrate flat bread OK)

**Saturated Fat**

- Fried foods
- Pizza
- Burgers, fries
- Regular ice cream (low-sugar, lowfat OK)
- Large amounts of cheese

**Portion Control**

- Try not to exceed 1500 kcal/d
- If lower calorie levels are desired, replace 1 meal with 1 protein shake or bar up to 2 meals per day
- No eating after 8 PM at night
- Consciously work to control food urges

**Foods to Avoid**

however, the important concept is that exercise facilitates weight loss and is essential to weight maintenance. Without it, weight regain is assured and even the best dietary habits will not be successful.

## Treatment Gap in Weight-Loss Management

There is no intervention more difficult and in many cases more important to make in the cardiologist's office than to achieve substantial weight loss in the obese and, in particular, the morbidly obese patient. These efforts need to be initiated early on in life because it is clear that the years of life lost due to obesity are greater among young adults 20 to 30 years of age than adults > 60 years of age. Among white men there was a 13-year reduction in lifespan observed.<sup>24</sup> Dietary modifications, including a reduction in calories in the form of sugars, starches, and saturated fats, in addition to sodium restriction, result in lower blood pressure, improved lipids, and better insulin tolerance; this, in turn, leads to a reduction in overall cardiovascular risk. Substantial losses in weight with intensive measures can lead to an approximately 50% reduction in cardiovascular risk, but

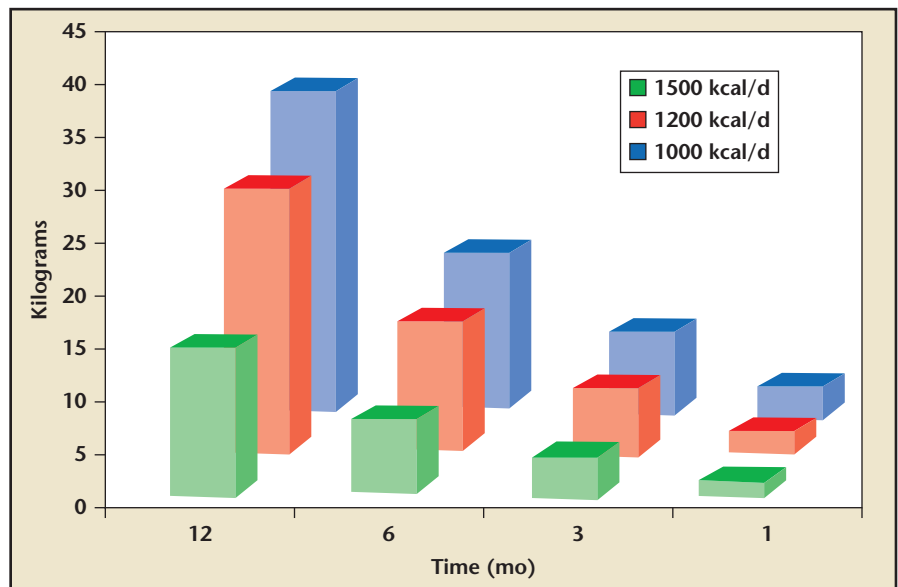


Figure 6. Mean projected weight loss of participants engaging in 150 min/wk of exercise on a restricted caloric intake diet. Reproduced with permission from Vanhecke TE et al.<sup>51</sup>

compared with those receiving less intense (“intense-only” or “irregular”) counseling.<sup>26</sup> For many obese patients, their ability to participate in intense lifestyle-modification programs is limited by associated disabling conditions such as degenerative arthritis and obstructive sleep apnea.<sup>27</sup> Furthermore, obesity results in reduced exercise capacity and increased discomfort with physical effort, leading to a progressively sedentary lifestyle and avoidance of activity.<sup>28</sup> Only forms of intensive caloric restriction with meal replacement diets have been

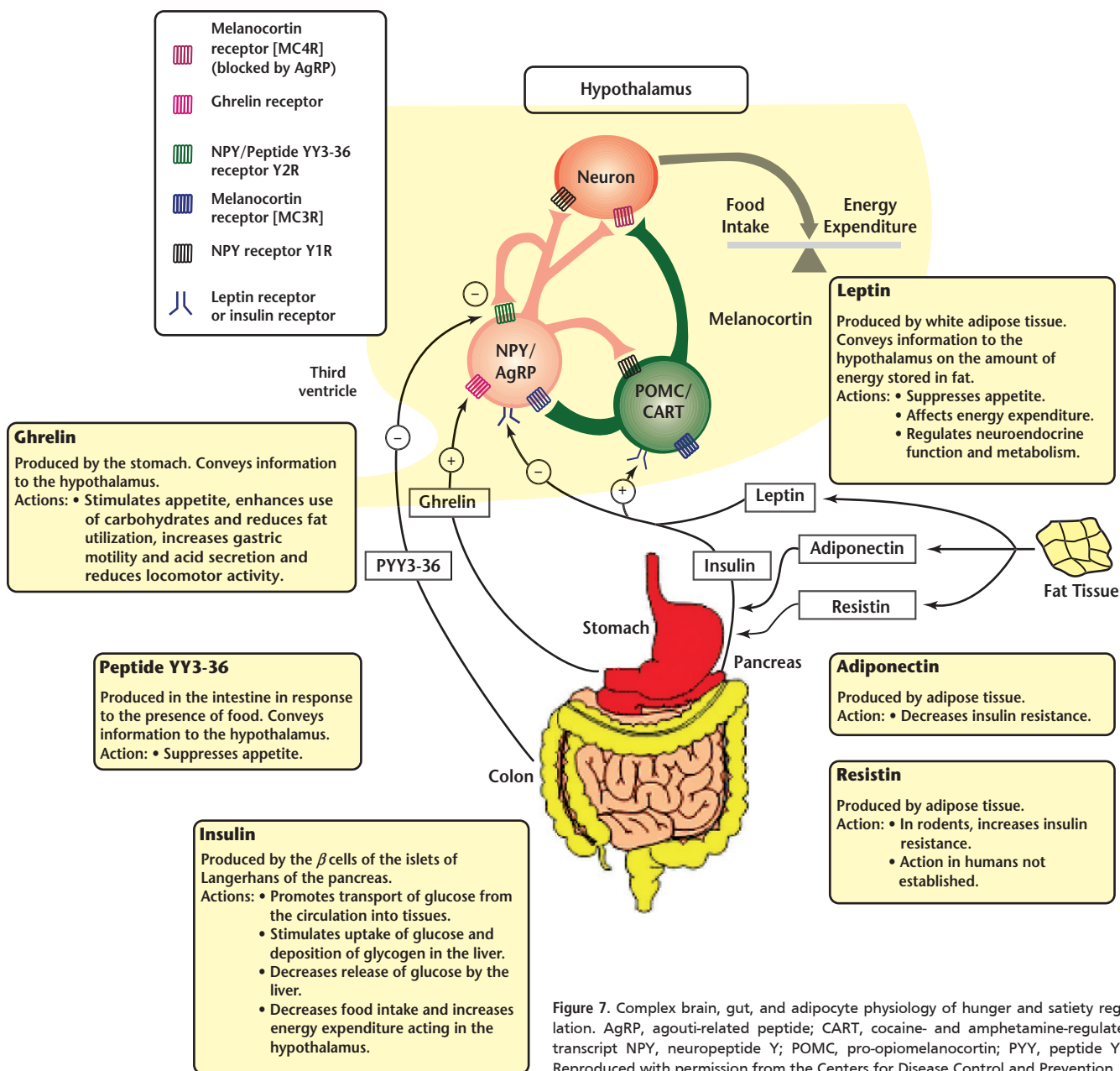
expenditure should result in considerable weight loss, as shown in Figure 6. Safe and effective pharmacologic or surgical options to help achieve weight loss are requisite as adjuvants to lifestyle-modification efforts.

Because hunger and satiety are regulated by a complex web of redundant brain, gut, and metabolic factors (Figure 7), there has been considerable interest in chronic oral drug therapy for control of food urges and as an aid to diet and exercise. The most frequently prescribed appetite suppressants in the past few years have been phentermine and diethylpropion.<sup>31</sup> A meta-analysis of 108 clinical trials performed by Haddock and colleagues<sup>32</sup> found that anti-obesity agents not only improve initial weight loss, but patients who were prescribed weight-loss agents typically sustained weight loss at follow-up more effectively compared with the placebo-treated groups. However, when the agents were stopped, predictable weight regain occurred. Prior to 2012, the only commercially available US Food and Drug Administration (FDA)-approved weight-loss

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often require aggressive measures such as bariatric surgery.<sup>25</sup> Obesity counseling remains a clinical challenge. A recent observational study of obesity-related counseling based on the Veterans Administration Hospital national database found no difference in BMI among patients who received intense and sustained counseling over 5 years

shown to have a significant impact in this patient population.<sup>29</sup> To be effective, these methods additionally require structured group counseling and exercise sessions.<sup>30</sup> In theory, if an individual has a genetic and hormonal profile that is permissive to weight loss, deep caloric restriction with substantial increase in exercise and caloric



agents included orlistat, phentermine, diethylpropion, and phendimetrazine. In a report from 2009 evaluating the use of pharmacology by obesity specialists, agents prescribed by at least 50% of those who responded to a survey included phentermine, diethylpropion, phendimetrazine, and topiramate (Table 2).<sup>33</sup>

Orlistat, 120 mg, was approved as a prescription product by the FDA in 1999 for obesity management

in conjunction with a reduced-calorie diet to reduce the risk of regaining weight after prior weight loss. In 2007, orlistat, 60 mg, was approved for over-the-counter use for weight loss in overweight adults 18 years and older, in conjunction with a reduced-calorie and low-fat diet. Orlistat is a lipase inhibitor that is minimally absorbed (< 2% bioavailable) and acts non-systemically in the intestinal tract. By binding to pancreatic lipase

in the small intestine, it partially prevents dietary triglycerides from being hydrolyzed and absorbed. It has few drug interactions and has a well-established safety profile; the principal adverse effect is steatorrhea. Because orlistat may reduce the absorption of fat-soluble vitamins, it is recommended that patients take a multivitamin daily. The long-term efficacy of orlistat (120 mg three times daily) for weight loss, with resultant

**TABLE 2****Oral Antiobesity Pharmacologic Agents Under Consideration as of 2013**

Drug	Mode of Action	Drug Type	United States	European Union
Orlistat	Lipase inhibitor	Branded	Marketed	Marketed
Phentermine	NA + DA-releasing agent	Generic	Marketed	Withdrawn 2001
Methamphetamine <sup>a</sup>	DA + NA-releasing agent	Generic	Marketed	Withdrawn 2000
Phendimetrazine	Sympathomimetic	Generic	Marketed	Withdrawn 2000
Diethylpropion	Sympathomimetic	Generic	Marketed	Withdrawn 2000
Benzphetamine	Sympathomimetic	Generic	Marketed	Withdrawn 2000
Sibutramine	NA + 5-HT reuptake inhibitor	Branded	Withdrawn 2010	Withdrawn 2010
Rimonabant	CB <sub>1</sub> antagonist	Branded	Not approved	Withdrawn 2008
Topiramate + phentermine	Unknown/NA + DA-releasing agent	Branded	Preregistration <sup>b</sup>	Preregistration
Bupropion + naltrexone	DA reuptake inhibitor/opioid antagonist	Branded	Preregistration	Phase 3
Lorcaserin	5-HT <sub>2C</sub> agonist	Branded	Preregistration	Phase 3
Zonisamine + bupropion	Unknown/DA reuptake inhibitor	Branded	Phase 2	Phase 2

<sup>a</sup>Approved only for the treatment of refractory obesity.

<sup>b</sup>US Food and Drug Administration Advisory Committee recommended approval as a treatment for adult obesity on February 22, 2012.

5-HT<sub>2C</sub>, 5-hydroxytryptamine receptor 2C; CB<sub>1</sub>, cannabinoid receptor type 1; DA, dopamine; NA, noradrenaline.

Adapted with permission from Heal DJ et al.<sup>31</sup>

improvements in blood pressure, insulin resistance, and serum lipid levels, has been demonstrated in several randomized, controlled trials (RCTs) of 2- to 4-year therapy when compared with placebo.<sup>34,35</sup>

Phentermine is approved as an appetite suppressant to help reduce weight in obese patients when used short-term and combined with exercise, diet, and behavioral modification. Phentermine works like an amphetamine on the sympathetic nervous system and the hypothalamic-pituitary axis to stimulate the adrenal glands to release nor-epinephrine. It is recommended that phentermine be used short-term, which is usually interpreted as  $\leq 12$  weeks. A 36-week RCT in 108 overweight women demonstrated a mean weight loss of 12.2 kg (13%) with phentermine (30 mg/d) compared with 4.8 kg (5.2%) with placebo ( $P < .001$ ).<sup>36</sup> The usual adult dose is one tablet (37.5 mg)

daily, as prescribed by a physician, administered before breakfast or 1 to 2 hours after breakfast. The dosage may be adjusted to the patient's need. For some patients, a half tablet (18.75 mg) daily may be adequate, whereas in some cases it may be desirable to give half tablets (18.75 mg) twice daily. Use of phentermine is contraindicated during or within 14 days following the administration of monoamine oxidase inhibitors because of the risk of hypertensive crisis.

Diethylpropion hydrochloride is a sympathomimetic amine with some pharmacologic activity similar to that of amphetamines, the prototype drugs of this class used to treat obesity. Actions include some central nervous system stimulation and elevation of blood pressure. It is indicated in the management of exogenous obesity as a short-term adjunct (a few weeks) in a regimen of weight reduction based on caloric

restriction in patients with an initial BMI  $\geq 30$  kg/m<sup>2</sup> and who have not responded to an appropriate weight-reducing regimen (diet and/or exercise) alone. It is contraindicated in patients with pulmonary hypertension, advanced arteriosclerosis, hyperthyroidism, known hypersensitivity or idiosyncrasy to the sympathomimetic amines, glaucoma, or severe hypertension. Prolonged use of diethylpropion hydrochloride may induce dependence with withdrawal syndrome on cessation of therapy. Hallucinations have occurred rarely following high doses of the drug. It is available in an immediate-release form of 25 mg taken three times daily or in a sustained-release (SR) formulation of 75 mg taken once in mid-morning. Diethylpropion (75 mg/d) demonstrated significantly greater weight loss in a small, 24-week study of 20 patients than did placebo (11.6 kg vs 2.5 kg;  $P < .01$ ).<sup>37</sup>

Phendimetrazine is also a sympathomimetic amine indicated for short-term weight loss. It has an efficacy and adverse-event profile similar to that observed with the other sympathomimetic amines mentioned above. Phendimetrazine is available in 35-mg tablets that are taken twice or three times daily, and in a longer-acting 105-mg slow-release capsule.<sup>38</sup>

Until recently, the medical community has been cautious to use pharmacology to treat obesity because of safety concerns and the limited efficacy of pharmacologic agents. Additionally, in 1997 fenfluramine and dexfenfluramine were withdrawn from the US market due to associations with cardiac valvulopathy and pulmonary hypertension. The development and demise of the cannabinoid receptor type 1 antagonist, rimonabant, received considerable attention in the lay and medical press. In clinical trials, rimonabant was efficacious in treating obesity with or without associated comorbidities; however, adverse psychiatric events ultimately overshadowed clinical benefits and drug development was halted after brief exposure on the European market from 2006 to 2008. Sibutramine, which inhibits reuptake of norepinephrine, serotonin, and dopamine, resulting in appetite suppression, was withdrawn from the US commercial market in October 2010 after the Sibutramine Cardiovascular and Diabetes Outcome Study (SCOUT) found that treatment with sibutramine (10-15 mg/d) exposed subjects with pre-existing cardiovascular disease to significantly increased risk of nonfatal MI and nonfatal stroke, but not cardiovascular death or all-cause mortality.<sup>39</sup> It has taken 13 years for the FDA to approve two new agents for the management of obesity, phentermine + extended-release topiramate and lorcaserin.

## New FDA-Approved Pharmacologic Agents

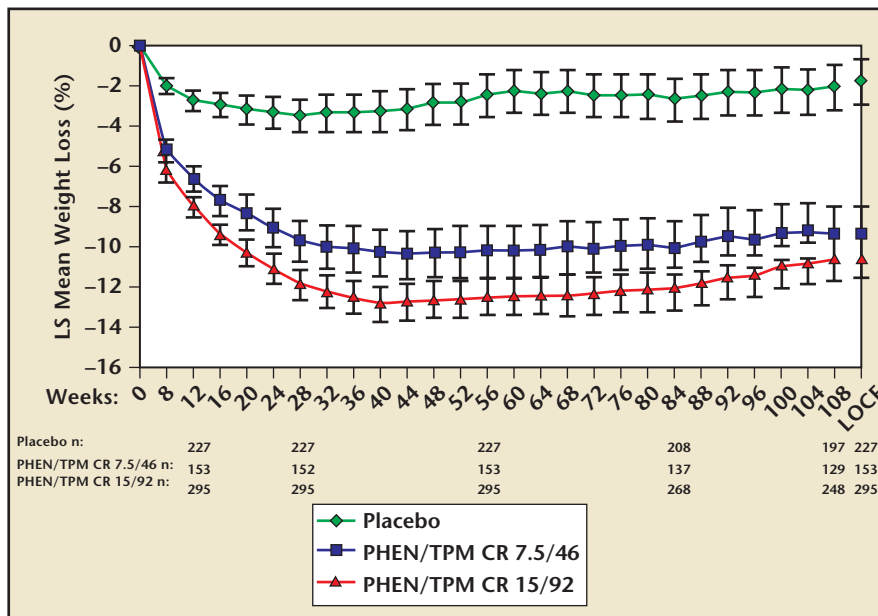
### *Phentermine + Extended-Release Topiramate*

The mechanisms of action and prior clinical results with phentermine have been reviewed above. Topiramate is an anticonvulsant used in the treatment of seizure disorders as well as in the prophylaxis of migraine headaches. It has been found to be effective and is a recommended treatment for control of food urges in those with binge-eating disorders.<sup>40</sup> The combination of low-dose phentermine + extended-release topiramate has received FDA approval as a weight-management agent as an addition to a reduced-calorie diet and exercise for chronic weight management. It is the only FDA-approved, once-daily prescription treatment indicated for chronic weight management. The drug is approved for use in adults with a BMI of  $\geq 30$  kg/m<sup>2</sup> (obese) or adults with a BMI of  $\geq 27$  kg/m<sup>2</sup> (overweight) who have at least one weight-related condition, such as hypertension, DM, or dyslipidemia.

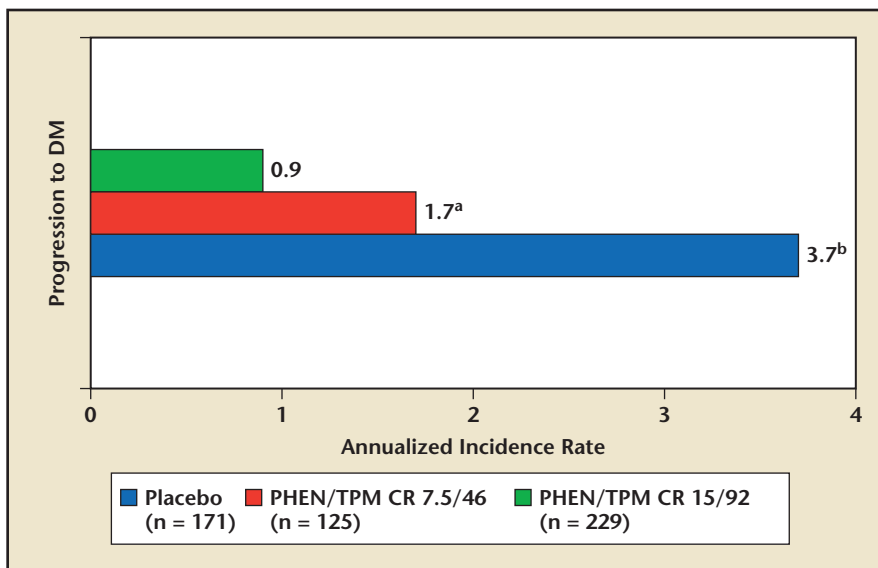
The safety and efficacy of this combination were evaluated in two RCTs that included approximately 3700 obese and overweight patients with and without significant weight-related conditions treated for 1 year, as well as open-label extension studies (Figure 8). All patients received lifestyle modification that consisted of a reduced-calorie diet and regular physical activity. Results from the two trials showed that after 1 year of treatment with the recommended and highest daily dose of phentermine + extended-release topiramate, patients had an average weight loss of 6.7% and 8.9%, respectively, over treatment with placebo (Figure 9). Approximately 62% and 69% of patients lost at least 5% of their body

weight with the recommended dose and highest dose of low-dose phentermine + extended-release topiramate, respectively, compared with only 20% of patients treated with placebo. The two pivotal trials of this combination were the Controlled-Release Phentermine/Topiramate in Severely Obese Adults: A Randomized Controlled Trial (EQUIP)<sup>41</sup> and Effects of Low-Dose, Controlled-Release, Phentermine Plus Topiramate Combination on Weight and Associated Comorbidities in Overweight and Obese Adults (CONQUER)<sup>42</sup> trials. A total of 1267 patients were evaluated in the EQUIP trial, comparing the effect of phentermine-extended release topiramate with placebo; the BMI of participants ranged from 35 to 79.<sup>41</sup> In the intention-to-treat last observed weight analysis, a 10.9% weight loss was observed for patients who took the highest dose (15 mg/92 mg); weight loss was 5.1% for patients whose last dose was 3.75 mg/23 mg, compared with 1.6% in those who took placebo. A second analysis, which compared patients who completed the 1-year study, showed a 14.4% weight loss in the high-dose group (12.3% placebo subtracted), 6.7% weight loss in the starting-dose group, and 2.1% weight loss in the placebo-treated group. Subjects in the high-dose group were found to have some reductions in systolic blood pressure (SBP), total cholesterol, LDL-C, fasting glucose, and waist circumference; increases in HDL-C and heart rate were noted.

In the CONQUER trial, 2487 overweight or obese patients with two or more weight-related comorbidities were evaluated.<sup>42</sup> Using the same intention-to-treat analysis there was a 9.8% weight loss in the high-dose group, a 7.8% weight loss in the starting-dose group, and a 1.2% weight loss recorded



**Figure 8.** Results from a long-term open-label extension study ( $n = 675$ ) in patients with a mean body mass index at baseline of  $36 \text{ kg/m}^2$ . Mean (95% confidence interval) percentage weight loss from baseline to week 108. Standardized lifestyle intervention was used across all treatment groups.  $P = .0001$  compared with placebo at all time points assessed. LOCF, last observation carried forward; LS, least-squares; PHEN/TPM CR 7.5/46, 7.5 mg phentermine/46 mg controlled-release topiramate; PHEN/TPM CR 15/92, 15 mg phentermine/92 mg controlled-release topiramate. Reproduced with permission from Garvey WT et al.<sup>43</sup>



**Figure 9.** Annualized incidence rate for progression to T2D. Data represent subjects without DM at baseline. Standardized lifestyle intervention was used across all treatment groups. <sup>a</sup> $P = .1514$  compared with placebo. <sup>b</sup> $P = .0078$  compared with placebo. PHEN/TPM CR 7.5/46, 7.5 mg phentermine/46 mg controlled-release topiramate; PHEN/TPM CR 15/92, 15 mg phentermine/92 mg controlled-release topiramate; DM, type 2 diabetes mellitus. Reproduced with permission from Garvey WT et al.<sup>43</sup>

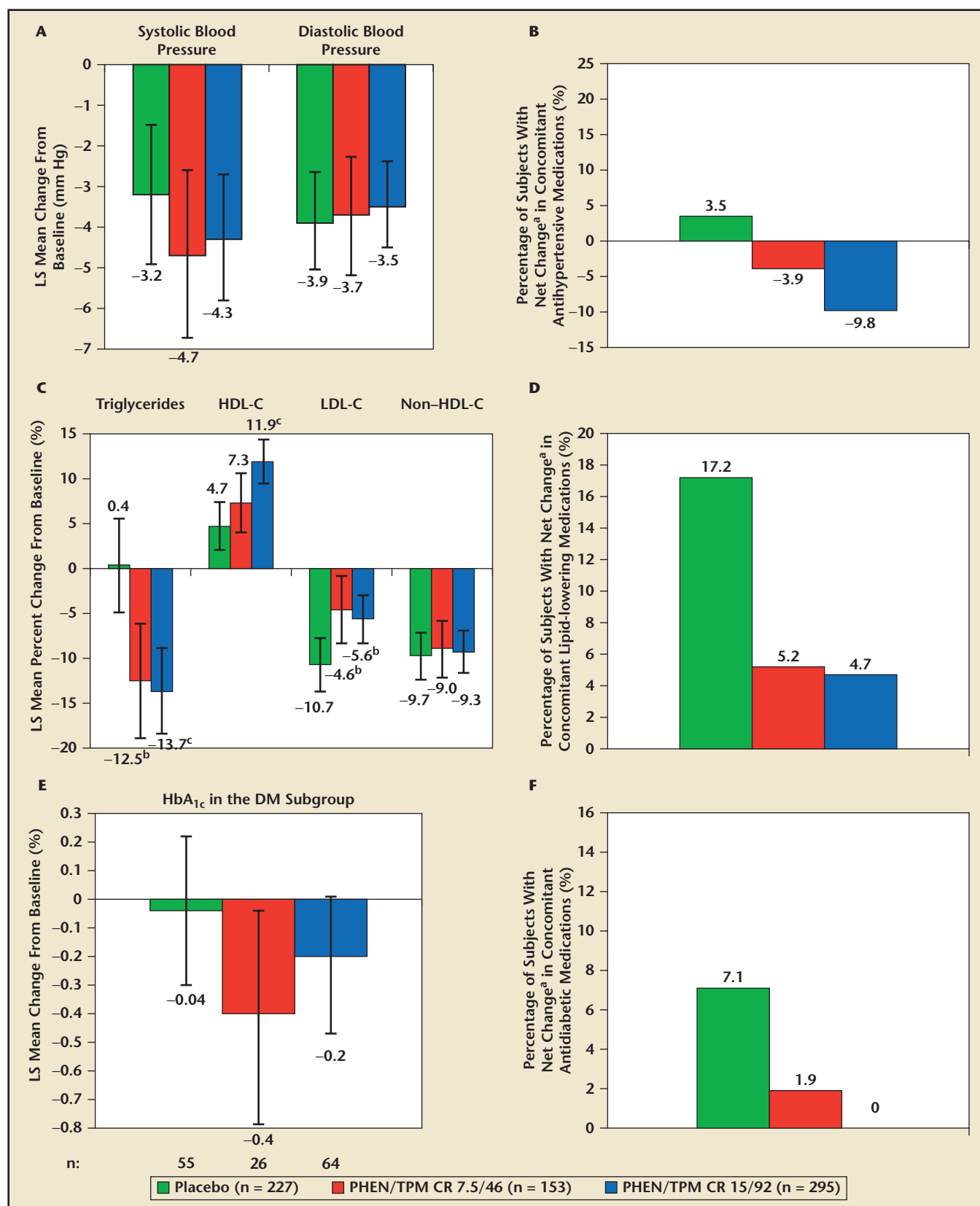
in the placebo-treated group. Among those who completed the study there was a 12.4%, 9.6%, and 1.6% weight loss, respectively, in the high-dose, starting-dose, and placebo-treated groups. In diabetic

patients, a reduction of hemoglobin  $A_{1c}$  ( $HbA_{1c}$ ) of 0.4% was observed (Figure 9). Cardiometabolic risk factors improved significantly in the drug combination groups, as compared with the placebo-treated

patients, with significant reductions in SBP, diastolic blood pressure (DBP; higher-dose group), triglyceride levels, hs-CRP, fasting glucose, and total cholesterol (Figure 10). HDL-C levels improved significantly in both groups, as did adiponectin levels. For almost all risk factors, greater improvement was observed with higher drug dosages. The most common adverse events were dry mouth, paresthesia, constipation, insomnia, dizziness, and dysgeusia, which all tended to be more common in the highest-dose group. Depression- and anxiety-related events were also reported by subjects in 7% and 8% of the highest-dose subjects, respectively. People with clinically significant depression were excluded from the trial.

A third RCT, the Two-Year Sustained Weight Loss and Metabolic Benefits With Controlled-Release Phentermine/Topiramate in Obese and Overweight Adults (SEQUEL),<sup>43</sup> designed as a 1-year extension to the CONQUER trial, was performed to evaluate the long-term efficacy of phentermine + extended-release topiramate. Using the same intention-to-treat analysis there was a 10.5% weight loss in the high-dose group, a 9.3% weight loss in the starting-dose group, and a 1.8% weight loss in the placebo-treated group. Compared with the placebo-treated group, the drug combination groups showed significant reductions in SBP and DBP, triglyceride levels, LDL-C, fasting glucose, and fasting insulin levels, and increases in HDL-C. The adverse events that occurred during the SEQUEL trial were similar to those reported in the CONQUER sample, but the incidence of these events was lower.<sup>43</sup>

Patients who did not lose at least 3% of their body weight by week 12 of treatment with phentermine + extended-release topiramate



**Figure 10.** Effects of PHEN/TPM CR on cardiometabolic variables. LS mean changes (95% confidence interval) in (A) blood pressure, (B) antihypertensive medications, (C) lipid variables, (D) lipid-lowering medications, (E) HbA<sub>1c</sub>, and (F) antidiabetic medications from baseline (week 0) to week 108 (ITT-LOCF). Changes in HbA<sub>1c</sub> represent the DM subgroup. Changes in concomitant medications represent the safety study. Standardized lifestyle intervention was used across all treatment groups. <sup>a</sup>Percentage increase minus percentage decrease;  $P = .05$  for between-group differences. <sup>b</sup> $P = .01$  compared with placebo; <sup>c</sup> $P = .0001$  compared with placebo. HbA<sub>1c</sub>, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; ITT, intent-to-treat; LDL-C, low-density lipoprotein cholesterol; LOCF, last observation carried forward; LS, least-squares; PHEN/TPM CR 7.5/46, 7.5 mg phentermine/46 mg controlled-release topiramate; PHEN/TPM CR 15/92, 15 mg phentermine/92 mg controlled-release topiramate; DM, type 2 diabetes mellitus. Reproduced with permission from Garvey WT et al.<sup>43</sup>

were unlikely to achieve and sustain weight loss with continued treatment at this dose. Therefore, response to therapy with the recommended daily dose of phentermine + extended-release topiramate should be evaluated by 12 weeks to determine, based on the amount of weight loss, whether to discontinue the drugs or to increase to the higher dose. If, after 12 weeks on the higher dose, a patient has not lost at least 5% of his or her body weight, then the drug combination should be discontinued, as these patients are unlikely to achieve clinically meaningful weight loss with continued treatment. In all trials with this combination of drugs, there were expected blood pressure reductions that were concordant with the degree of weight loss.

Phentermine + extended-release topiramate is contraindicated in pregnancy, in patients with glaucoma or hyperthyroidism, in patients receiving treatment or within 14 days following treatment with monoamine oxidase inhibitors (MAOIs), and in patients with hypersensitivity to sympathomimetic amines or topiramate. Phentermine + extended-release topiramate can increase heart rate; the effect of this drug combination on heart rate in patients at high risk for MI, heart failure, or stroke is not known. Therefore, its use in patients with recent ( $\leq 6$  mo) or unstable heart disease or stroke is not recommended. Regular monitoring of heart rate is recommended for all patients at initiation and with dose escalation. Topiramate exposure in the first trimester of pregnancy has been associated with an increased risk of oral clefts (cleft lip with or without cleft palate). Women of reproductive potential should receive a negative pregnancy test result before treatment, be tested monthly thereafter, and use effective contraception consistently

during therapy. If a patient becomes pregnant while taking phentermine + extended-release topiramate, treatment should be discontinued immediately, and the patient should be informed of the potential hazard to the fetus.<sup>44</sup>

### *Lorcaserin*

Lorcaserin is a serotonin 2C receptor agonist indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial BMI of  $\geq 30$  kg/m<sup>2</sup> or  $\geq 27$  kg/m<sup>2</sup> in the presence of at least one weight-related comorbid condition (eg, hypertension, dyslipidemia, DM). It is administered twice daily in a 10-mg dose. Extreme caution should be used when coadministering lorcaserin with serotonergic drugs (selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, MAOIs, triptans, bupropion, dextromethorphan, St. John's wort) due to the risk of serotonin syndrome. Response to therapy should be evaluated by week 12. If a patient has not lost at least 5% of baseline body weight, administration should be discontinued, as it is unlikely that the patient will achieve and sustain clinically meaningful weight loss with continued treatment. Regurgitant cardiac valvular disease, primarily affecting the mitral and aortic valves, has been reported in patients who took serotonergic drugs with 5-hydroxytryptamine receptor 2B (5-HT<sub>2B</sub>) receptor agonist activity. The etiology of the regurgitant valvular disease is thought to be activation of 5-HT<sub>2B</sub> receptors on cardiac interstitial cells with prior administration of fenfluramine and dexfenfluramine. At therapeutic concentrations, lorcaserin is selective for 5-HT<sub>2C</sub> receptors as compared with 5-HT<sub>2B</sub> receptors. In clinical trials of 1 year

in duration, 2.4% of patients receiving lorcaserin and 2.0% of patients receiving placebo developed echocardiographic criteria for valvular regurgitation at 1 year. In clinical trials of at least 1 year in duration, impairments in attention and memory were reported adverse reactions associated with 1.9% of patients treated with lorcaserin and 0.5% of patients treated with placebo, and led to discontinuation in 0.3% and 0.1% of these patients, respectively. Other reported adverse reactions associated with lorcaserin in clinical trials included confusion, somnolence, and fatigue (Table 3). In clinical trials of at least 1 year in duration, 8.6% of patients treated with lorcaserin prematurely discontinued treatment due to adverse reactions, compared with 6.7% of placebo-treated patients. Caution should be used when administering lorcaserin together with drugs that are cytochrome P450 2D6 substrates, as lorcaserin can increase exposure of these drugs.<sup>45</sup>

The safety and efficacy of lorcaserin for chronic weight management in conjunction with reduced caloric intake and increased physical activity were evaluated in three double-blind, placebo-controlled RCTs with durations of 52 to 104 weeks. Two trials in adults without DM, Behavioral Modification and Lorcaserin for Overweight and Obesity Management (BLOOM)<sup>46</sup> and Behavioral Modification and Lorcaserin Second Study for Obesity Management (BLOSSOM),<sup>47</sup> and one study in adults with DM, Behavioral Modification and Lorcaserin for Overweight and Obesity Management in Diabetes Mellitus (BLOOM-DM)<sup>48</sup> evaluated the effect of administering lorcaserin, 10 mg twice daily. The primary efficacy parameter in these studies was weight loss at 1 year, which was assessed by percent of patients

**TABLE 3****Adverse Reactions in Patients Who Have Taken Lorcaserin**

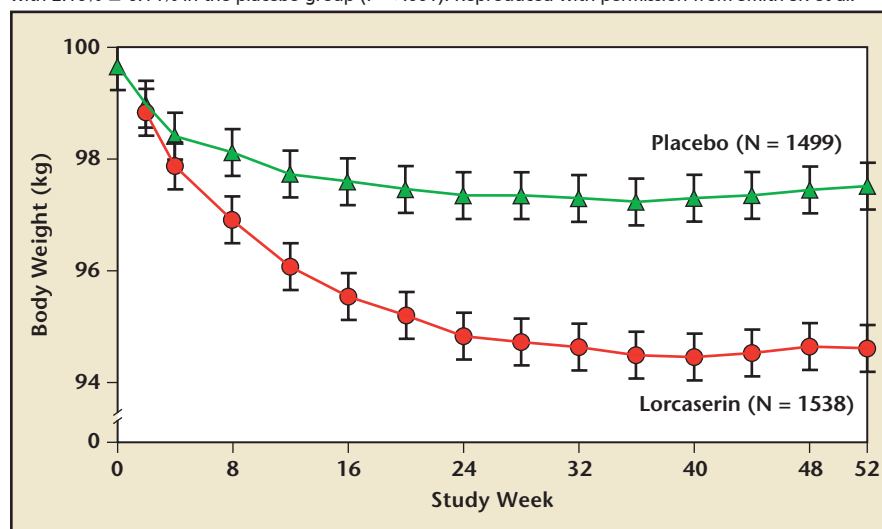
Adverse Reaction	Number of Patients (%)	
	Lorcaserin, 10 mg, BID (n = 3195)	Placebo (n = 3185)
Gastrointestinal Disorders		
Nausea	264 (8.3)	170 (5.3)
Diarrhea	207 (6.5)	179 (5.6)
Constipation	186 (5.8)	125 (3.9)
Dry mouth	169 (5.3)	74 (2.3)
Vomiting	122 (3.8)	83 (2.6)
General Disorders and Administration Site Conditions		
Fatigue	229 (7.2)	114 (3.6)
Infections and Infestations		
Upper respiratory tract infection	439 (13.7)	391 (12.3)
Nasopharyngitis	414 (13.0)	381 (12.0)
Urinary tract infection	207 (6.5)	171 (5.4)
Musculoskeletal and Connective Tissue Disorders		
Back pain	201 (6.3)	178 (5.6)
Musculoskeletal pain	65 (2.0)	43 (1.4)
Nervous System Disorders		
Headache	537 (16.8)	312 (10.1)
Dizziness	270 (8.5)	122 (3.8)
Respiratory, Thoracic, and Mediastinal Disorders		
Cough	136 (4.3)	109 (3.4)
Oropharyngeal pain	111 (3.5)	80 (2.5)
Sinus congestion	93 (2.9)	78 (2.4)
Skin and Subcutaneous Tissue Disorders		
Rash	67 (2.1)	58 (1.8)

BID, twice daily.

Data from BELVIQ® package insert.<sup>45</sup>

achieving  $\geq 5\%$  weight loss, percent of patients achieving  $\geq 10\%$  weight loss, and mean weight change. At 1 year in the BLOOM trial, 47.5% of patients in the lorcaserin group and 20.3% in the placebo group had lost  $\geq 5\%$  of their body weight, corresponding to an average loss of  $5.8 \pm 0.2$  kg with lorcaserin and  $2.2 \pm 0.1$  kg with placebo during the first year (Figure 11). Expected reductions in blood pressure, LDL-C, triglyceride levels, hs-CRP, and waist circumference, and elevations in HDL-C were also noted.<sup>46</sup> In a recent abstract presentation at the ACC Scientific Sessions by Panchal

**Figure 11.** Results from a 52-week clinical trial for the serotonin 2c receptor agonist, lorcaserin. Patients in the lorcaserin group lost an average ( $\pm$  SE) of  $5.81\% \pm 0.16\%$  of the baseline body weight, as compared with  $2.16\% \pm 0.14\%$  in the placebo group ( $P < .001$ ). Reproduced with permission from Smith SR et al.<sup>46</sup>



and colleagues,<sup>49</sup> a meta-analysis suggested a dose-dependent worsening of preexisting aortic valve insufficiency; however, there was no effect on the development of new valvular insufficiency.

Similar results were found in the BLOSSOM trial. In BLOSSOM, patients were assigned to receive lorcaserin, 10 mg twice daily, 10 mg once daily, or placebo. Using the same intention-to-treat analysis, it was found that significantly more patients of the lorcaserin-treated groups (47.2% twice daily, 40.2% once daily) lost at least 5% body weight as compared with those in

the placebo-treated groups (25.0%). Small elevations in HDL-C and reductions in LDL-C and triglycerides were observed, but they were not statistically significant (Figure 12).<sup>47</sup>

BLOOM-DM was the third trial performed to evaluate the efficacy and safety of lorcaserin in patients with DM. Using the same intention-to-treat analysis, it was found that significantly more patients in the lorcaserin-treated groups (37.5% twice daily, 44.7% once daily) lost at least 5% body weight as compared with those in the placebo groups (16.1%). HbA<sub>1c</sub> decreased

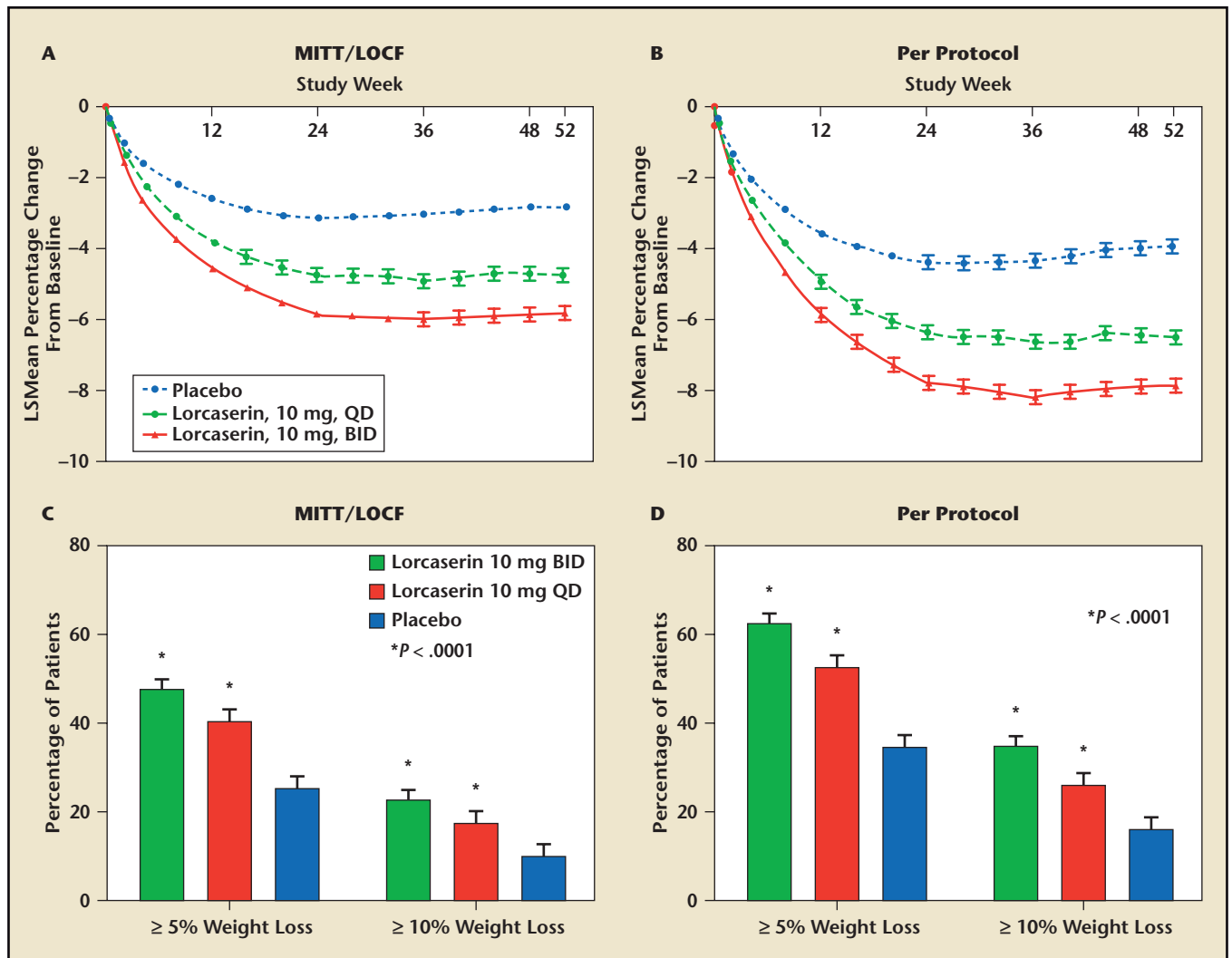
$0.9 \pm 0.06$  with lorcaserin twice daily,  $1.0 \pm 0.09$  with lorcaserin once daily, and  $0.4 \pm 0.06$  with placebo. Fasting glucose decreased  $27.4 \pm 2.5$  mg/dL with lorcaserin twice daily,  $28.4 \pm 3.8$  mg/dL with lorcaserin once daily, and  $11.9 \pm 2.5$  mg/dL with placebo.<sup>48</sup>

## A New Investigational Pharmacologic Agent

### Bupropion + Naltrexone

An investigational fixed-dose combination of SR bupropion and an SR version of naltrexone designed to improve drug tolerability is

Figure 12. Results from a clinical trial of lorcaserin, a serotonin 2c receptor agonist in patients with a baseline body mass index of 36 kg/m<sup>2</sup>. Body weight change from baseline to week 52. Weight change by study visit: (A) MITT/ LOCF analysis; (B) per-protocol analysis, lorcaserin, 10 mg twice daily (triangles), lorcaserin, 10 mg once daily (circles), placebo (diamonds). Categorical weight loss: (C) MITT/LOCF analysis; (D) per-protocol analysis lorcaserin, 10 mg twice daily (black bars), lorcaserin, 10 mg once daily (hatched bars), placebo (white bars) BID, twice daily; LOCF, last observation carried forward; MITT, modified intent-to-treat; QD, every day.



being investigated.<sup>31</sup> Bupropion is a weak, selective dopamine reuptake inhibitor and is dopaminergic, which appears to lead to a reduction in appetite and increase in energy expenditure by increasing activity of pro-opiomelanocortin (POMC) neurons. Bupropion is used as a treatment for depression and to aid smoking cessation. Naltrexone works by blocking opioid receptors on the POMC neurons, preventing feedback inhibition of these neurons and further increasing POMC activity. Naltrexone is a well-known opioid receptor antagonist that is used clinically to treat opiate and alcohol-dependence syndromes. The combination of bupropion + naltrexone may regulate activity in the dopamine reward system of the brain that helps control food cravings and overeating behaviors. The efficacy and safety of bupropion + naltrexone have been determined in four pivotal, 56-week, multicenter, double-blind, placebo-controlled RCTs: NB-301 (n = 1742 subjects, two dose levels), NB-302 (n = 793 subjects, high dose level), NB-303 (n = 1496 subjects, high dose level) and NB-304 (n = 505 subjects with DM).<sup>31</sup> These trials included subjects with uncomplicated obesity, or overweight/obesity with controlled hypertension and/or dyslipidemia. Bupropion + naltrexone was tested at two doses: naltrexone, 16 mg, + bupropion, 360 mg, and naltrexone, 32 mg, + bupropion, 360 mg. At week 56, the placebo-subtracted weight reductions produced by the higher dose of bupropion + naltrexone were 4.8 kg in NB-301, 4.2 kg in NB-302, 5.2 kg in NB-303, and 3.4 kg in NB-304. A categorical analysis of efficacy revealed that after correction for placebo, the proportion of subjects treated with the higher

dose of bupropion + naltrexone who achieved  $\geq 5\%$  and  $\geq 10\%$  reductions of body weight from baseline were 24% to 37% and 18% to 22%, respectively. When results for all subjects receiving the high-dose combination (naltrexone, 32 mg + bupropion, 360 mg) were pooled, SBP was unchanged from baseline and DBP was decreased by 0.7 mm Hg, compared with average decreases of 1.5 and 1.3 mm Hg in the placebo-treated subjects. In another analysis, 77 subjects treated with bupropion + naltrexone who had  $\geq 10\%$  weight loss reduced both SBP and DBP by approximately 2 mm Hg, whereas the small number of subjects who had  $\geq 10\%$  weight loss on placebo experienced decreases of 6.1 mm Hg in SBP and 4.0 mm Hg in DBP.

Although the FDA expert advisory committee voted to recommend approval of bupropion + naltrexone, the FDA declined the application in January 2011 because of the safety risk to patients from relative increases in blood pressure. The agency suggested the need for a long-term cardiovascular outcome trial before it would grant it approval as an antiobesity treatment. The manufacturer recently announced that it has reached a tentative agreement with the FDA over the design of the cardiovascular outcome trial and will conduct it with a view to resubmitting the new drug application in 2013 or 2014. A related drug in an earlier stage of development is bupropion + zonisamide (an anticonvulsant).

### A Multidisciplinary Approach to Obesity in the Clinic

Obesity is a chronic condition that affects the quality and quantity of life, and predisposes patients to a

host of other conditions that have their own health implications. All available data suggest that substantial and sustained weight loss calls for a multidisciplinary approach. Physicians, mid-level providers, psychologists, dietitians, exercise physiologists, and other health professionals can all play important roles in the success of a clinic or hospital-based program.

The goal of weight management is to prevent further weight gain (a minimum goal), reduce body weight, and to maintain that loss over the long term. A target for weight reduction needs to be realistic and lead to incremental health improvement. Metabolic parameters such as blood pressure, glucose, triglycerides, and HbA<sub>1c</sub> can improve with as little as 5% reduction in weight. A short-term, realistic goal could be a 10% weight loss at a rate of .45 to 1.36 kg/wk for most individuals. If weight loss is > 1.36 kg/wk, then gallstone prophylaxis is advised with oral ursodiol. A multidisciplinary approach to weight loss includes dietary approaches discussed in this article, physical activity, behavior therapy, pharmacotherapy, and weight loss surgery (Figure 13). For overweight patients with BMIs in the typical range of 27 to 35 kg/m<sup>2</sup>, caloric deficits of 300 to 500 kcal/d will result in weight losses of .45 to 1.36 kg/wk and a 10% weight loss in 6 months. For more severely obese patients with BMIs > 35 kg/m<sup>2</sup>, deficits of up to 500 to 1000 kcal/d will lead to weight losses of > 1.36 kg/wk and a 10% weight loss in 6 months. Theoretically, this caloric deficit should result in a loss of 11.79 to 23.59 kg/y. For the most compliant patients with all measures, the degree of weight loss is often governed by “genetic permissiveness,” meaning that some individuals more readily allow contraction of adipocyte size and mass whereas others are more resistant.

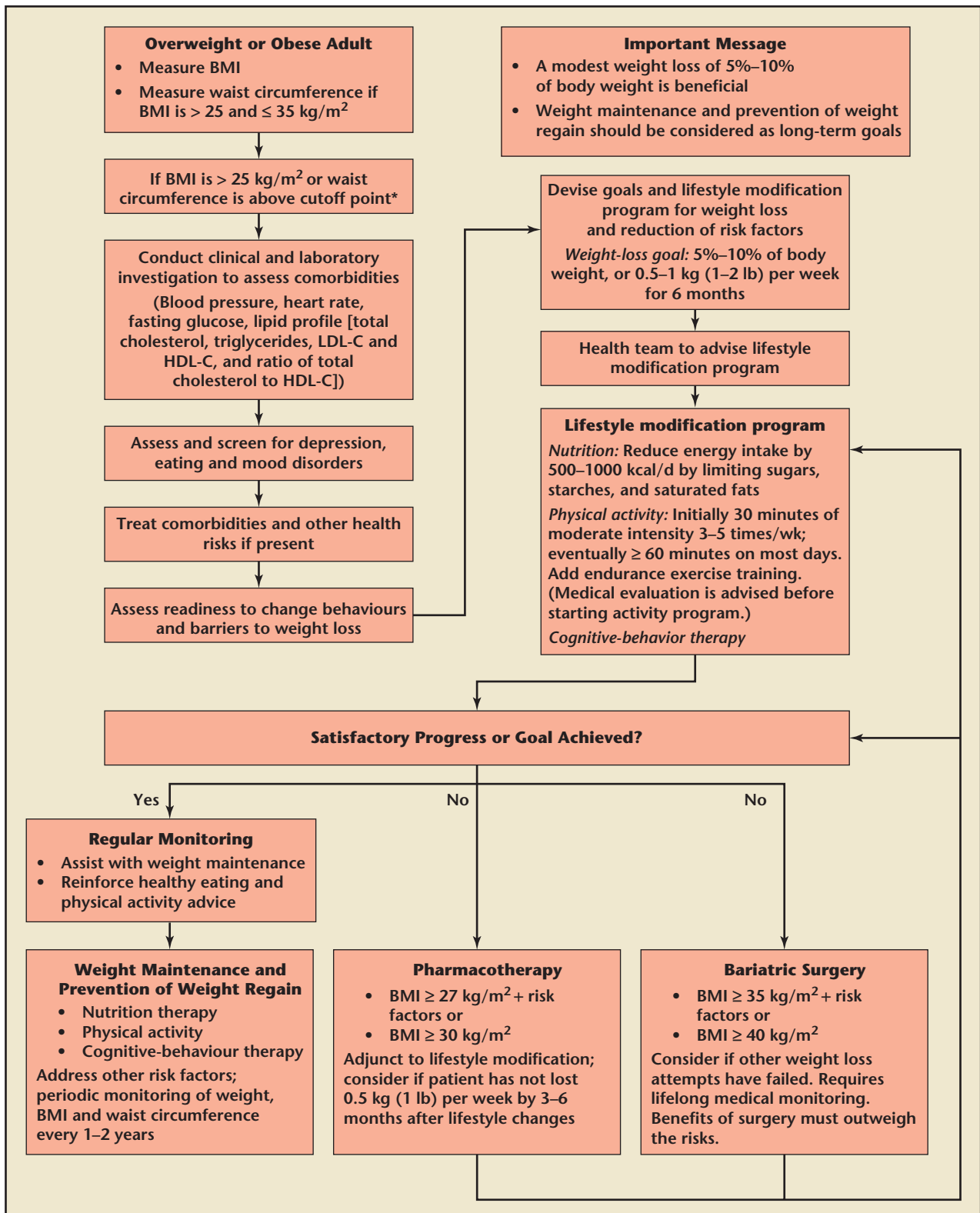


Figure 13. Algorithm for treatment of obesity. BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

The American College of Sports Medicine recommends that people who are overweight or obese get at least 150 min/wk

of moderate-intensity physical activity to prevent further weight gain or to lose a modest amount of weight. As much as 250 to

300 min/wk of exercise may be necessary to achieve weight loss and, more importantly, maintain that loss over time.

A behavior modification program that identifies current habits to determine what factors, stresses, or situations contribute to obesity can help expedite lifestyle changes leading to sustained weight loss. The underpinning of most obesity counseling is cognitive behavioral therapy. Self-monitoring, stimulus control, and self-talk are key competencies that every successful patient must acquire.

Pharmacotherapy is often required to achieve weight-loss goals, not as a substitute for the above approaches, but as an adjunct in patients with a BMI  $\geq 30$  or in those with BMI  $> 27$  kg/m<sup>2</sup> who have comorbidities including CAD, DM, hypertension, dyslipidemia, or sleep apnea. In some cases, bariatric surgery is an option. Bariatric surgery offers the best chance of losing the most weight (up to one-third of initial body weight), but it can pose serious risks. It can be used in patients with extreme obesity with a BMI  $\geq 40$  or a BMI of 35 to 40 kg/m<sup>2</sup>, associated with weight-related comorbidities. In summary, a multidisciplinary approach that

is tailored to the severity of obesity is essential for the success of the patient and for effective health-care delivery.

## The Future

Many have pointed out that primordial prevention of obesity in children is very realistic and achievable with dietary and counseling methods.<sup>50</sup> Although these efforts need to be increased quickly, the burgeoning adult population that is already obese needs and deserves the attention of the medical community. Obesity is now recognized as a disease state and not simply a cosmetic problem. In this new paradigm, there are new treatment vistas and considerable hope for those with excess adiposity. Through new pharmacologic adjuncts to healthy dietary choices and portion control, there can be better control over food urges and continued and sustained reductions in fat mass. These fundamental changes in the human condition reverse or ameliorate disease, and lead to improved cardiovascular survival ■

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## MAIN POINTS

- Excess adiposity and obesity are the root cause of at least 27 diseases that cause considerable lifelong morbidity and, in many scenarios, eventual cardiovascular mortality.
- Many obese individuals require interventions beyond casual diet and exercise advice. A multidisciplinary approach, including dietary modification, exercise, behavior therapy, pharmacotherapy, and possibly bariatric surgery, is essential for long-term success and maintenance of weight loss.
- Cardiologists consider obesity an important modifiable risk factor that contributes to the development of other coronary risk factors; therefore, cardiologists must take a leadership role in the evaluation and management of obesity. Cardiologists often treat obese patients who have cardiovascular symptoms such as effort intolerance, chest discomfort, dyspnea, fatigue, and edema, and look at weight reduction as an integral part of the holistic approach to treating these patients.
- Pharmacologic treatment of obesity has been restrained until recently, because of safety concerns and the limited efficacy of available agents. However, recently approved treatments (phentermine + extended-release topiramate and lorcaserin) will aid physicians in the management of overweight and obese patients.

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## SELF-ASSESSMENT POST-TEST

### New Vistas for the Treatment of Obesity: Turning the Tide Against the Leading Cause of Morbidity and Cardiovascular Mortality in the Developed World

1. It is recommended that phentermine be used for short periods of time, which is usually interpreted as up to \_\_\_\_\_ weeks.
  - a. 6
  - b. 12
  - c. 36
2. The combination of low-dose phentermine + extended-release topiramate is the only US Food and Drug Administration-approved, once-daily prescription treatment indicated for chronic weight management.
  - a. True
  - b. False
3. Excess adiposity is responsible for \_\_\_\_\_ of type 2 diabetes mellitus, which is both an individual risk factor and a coronary artery disease risk equivalent.
  - a. > 75%
  - b. < 85%
  - c. > 90%
4. The long-term efficacy of orlistat for weight loss, with resultant improvements in blood pressure, insulin resistance, and serum lipid levels, has been demonstrated at what dosage?
  - a. 120 mg, three times daily
  - b. 60 mg/d
  - c. 120 mg, twice daily
5. In the SEQUEL trial, the drug combination groups showed significant reductions in systolic and diastolic blood pressure, triglyceride levels, low-density lipoprotein cholesterol, fasting glucose, and fasting insulin levels, and increases in high-density lipoprotein cholesterol.
  - a. True
  - b. False
6. Phentermine works like an amphetamine on the sympathetic nervous system and the hypothalamic-pituitary axis to stimulate the adrenal glands to release \_\_\_\_\_.
  - a. adrenaline
  - b. norepinephrine
  - c. androgens
7. Extreme caution should be used when co-administering lorcaserin with what other drug(s)?
  - a. selective serotonin reuptake inhibitors
  - b. bupropion
  - c. dextromethorphan
  - d. all of the above
8. At therapeutic concentrations, lorcaserin is selective for \_\_\_\_\_ receptors.
  - a. 5-HT<sub>2B</sub>
  - b. 5-HT<sub>2C</sub>
  - c. neither
  - d. both
9. GH is a 47-year-old white man who has suffered from obesity for years. You have counseled him on caloric reduction and exercise in an effort to help him lose weight. The patient has shown very little progress so you have decided to take a pharmacologic approach. Which of the following is *not* FDA approved for the treatment of obesity?
  - a. Phentermine + extended release topiramate
  - b. Lorcaserin hydrochloride
  - c. Bupropion hydrochloride
  - d. There are no drugs approved by the FDA to treat obesity