

## AHA SCIENTIFIC STATEMENT

# Obesity and Cardiovascular Disease

## A Scientific Statement From the American Heart Association

**ABSTRACT:** The global obesity epidemic is well established, with increases in obesity prevalence for most countries since the 1980s. Obesity contributes directly to incident cardiovascular risk factors, including dyslipidemia, type 2 diabetes, hypertension, and sleep disorders. Obesity also leads to the development of cardiovascular disease and cardiovascular disease mortality independently of other cardiovascular risk factors. More recent data highlight abdominal obesity, as determined by waist circumference, as a cardiovascular disease risk marker that is independent of body mass index. There have also been significant advances in imaging modalities for characterizing body composition, including visceral adiposity. Studies that quantify fat depots, including ectopic fat, support excess visceral adiposity as an independent indicator of poor cardiovascular outcomes. Lifestyle modification and subsequent weight loss improve both metabolic syndrome and associated systemic inflammation and endothelial dysfunction. However, clinical trials of medical weight loss have not demonstrated a reduction in coronary artery disease rates. In contrast, prospective studies comparing patients undergoing bariatric surgery with nonsurgical patients with obesity have shown reduced coronary artery disease risk with surgery. In this statement, we summarize the impact of obesity on the diagnosis, clinical management, and outcomes of atherosclerotic cardiovascular disease, heart failure, and arrhythmias, especially sudden cardiac death and atrial fibrillation. In particular, we examine the influence of obesity on noninvasive and invasive diagnostic procedures for coronary artery disease. Moreover, we review the impact of obesity on cardiac function and outcomes related to heart failure with reduced and preserved ejection fraction. Finally, we describe the effects of lifestyle and surgical weight loss interventions on outcomes related to coronary artery disease, heart failure, and atrial fibrillation.

**Tiffany M. Powell-Wiley, MD, MPH, FAHA, Chair**  
**Paul Poirier, MD, PhD, FAHA, Vice Chair**  
**Lora E. Burke, PhD, MPH, FAHA**  
**Jean-Pierre Després, PhD, FAHA**  
**Penny Gordon-Larsen, PhD, FAHA**  
**Carl J. Lavie, MD**  
**Scott A. Lear, PhD, FAHA**  
**Chiadi E. Ndumele, MD, PhD, FAHA**  
**Ian J. Neeland, MD, FAHA**  
**Prashanthan Sanders, MBBS (Hons), PhD, FAHA**  
**Marie-Pierre St-Onge, PhD, FAHA**  
**On behalf of the American Heart Association Council on Lifestyle and Cardiometabolic Health; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; Council on Epidemiology and Prevention; and Stroke Council**

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Obesity is a multifactorial disease with a complex pathogenesis related to biological,<sup>1</sup> psychosocial,<sup>2</sup> socioeconomic,<sup>3</sup> and environmental<sup>4,5</sup> factors and heterogeneity in the pathways and mechanisms by which it leads to adverse health outcomes.<sup>6–8</sup> The “2013 AHA [American Heart Association]/ACC [American College of Cardiology]/TOS [The Obesity Society] Guideline for the Management of Overweight and Obesity in Adults”<sup>7</sup> uses the World Health Organization criteria<sup>9</sup> to define overweight as a body mass index (BMI)  $\geq 25$  and  $< 30$  kg/m<sup>2</sup> and obesity as a BMI  $\geq 30$  kg/m<sup>2</sup>.<sup>7</sup> Although BMI is strongly correlated with percent body fat across populations, there are limitations in its predictive ability to estimate body fat for any given individual,<sup>10–12</sup> with considerable variation by sex, age, and race/ethnicity.<sup>13,14</sup> Country-specific cut points have been developed for Asian subpopulations such as in China, for which cut points of 24 kg/m<sup>2</sup> for overweight and 28 kg/m<sup>2</sup> for obesity are recommended.<sup>15</sup> The GBD (Global Burden of Disease) Obesity Collaborators estimated that a total of 603.7 million adults had obesity, with obesity prevalence doubling between 1980 and 2015 in 73 countries and continuously increasing in most of the other countries.<sup>16</sup> It is estimated that 39% to 49% of the world’s population (2.8–3.5 billion people) have overweight or obesity.<sup>17</sup> In addition, the GBD investigators found an increase in the burden of elevated BMI, with high BMI accounting for 4.0 million deaths in 2015, more than two-thirds of which were caused by cardiovascular disease (CVD),<sup>16</sup> even after accounting for smoking and ill health.<sup>18</sup> Furthermore, a large proportion of both BMI-related deaths (41%) and BMI-related disability-adjusted life-years (34%) were caused by CVD among individuals with obesity.<sup>16</sup> The most recent nationally representative US estimates for obesity prevalence based on the National Health and Nutrition Examination Survey reported a crude prevalence of 39.8% in 2015 to 2016, which is an increase from the crude prevalence of 37.9% in 2013 to 2014.<sup>19</sup> The prevalence of class 3 obesity (BMI  $\geq 40$  kg/m<sup>2</sup>) is relatively high at an unadjusted prevalence of 7.7% in the total sample, with racial/ethnic and sex differences in class 3 obesity prevalence ranging from 5.5% in non-Hispanic White men to 16.9% in non-Hispanic Black women.<sup>19</sup> Important contributors to racial/ethnic differences in obesity prevalence in the United States include racial/ethnic discrimination,<sup>20,21</sup> weight stigmatization,<sup>22</sup> and disproportionate experience of psychosocial stressors,<sup>23</sup> as well as structural racism that promotes obesogenic environments and socioeconomic inequalities.<sup>24</sup> Disparate exposure to psychosocial and environmental factors that contribute to both obesity and other CVD risk factors directly relates to disparities in CVD outcomes across racial/ethnic groups in the United States.<sup>25</sup> Among pediatric populations, adolescent obesity is a global health epidemic; worldwide, marked increases

in obesity prevalence among adolescents over the past 35 years ultimately contribute to CVD risk into adulthood.<sup>26</sup> Moreover, the trends in obesity prevalence in the United States and around the world highlight the significant impact that obesity will continue to have on CVD incidence and prevalence globally. Therefore, the purpose of this scientific statement is to provide an update to the 2006 American Heart Association scientific statement “Obesity and Cardiovascular Disease: Pathophysiology, Evaluation, and Effect of Weight Loss.”<sup>27</sup> Although obesity is linked to numerous diseases of the cardiovascular system, including stroke, venous thromboembolic disease, and pulmonary hypertension,<sup>28,29</sup> this statement focuses on the impact of obesity on the pathophysiology, diagnosis, treatment, and clinical outcomes of atherosclerotic CVD, heart failure (HF), and arrhythmias, especially sudden cardiac death (SCD) and atrial fibrillation (AF). Before focusing on the relationship between obesity and these CVD outcomes, we review recent data linking abdominal obesity and visceral adiposity to CVD risk.

## VISCERAL ADIPOSITY, LIVER FAT, AND CVD RISK



There is a strong correlation between overall obesity and abdominal obesity; however, some individuals may be classified as having overall obesity but not abdominal obesity. The converse may occur as well with abdominal obesity in the absence of overall obesity based on the BMI definition of obesity. The presence of cardiometabolic disease and CVD in those with “normal-weight obesity” leads to misclassification and underdiagnosis of CVD risk in clinical practice, particularly among patients who have excess fat but not obesity as classified by BMI.<sup>30–32</sup> Thus, high waist circumference (WC) even in individuals with normal weight may unmask higher CVD risk because WC is an indicator of abdominal body fat, which is associated with cardiometabolic disease and CVD and is predictive of mortality.<sup>33,34</sup> WC as a measure of abdominal obesity provides an indicator of body composition and adds critical information along with BMI.<sup>33</sup> Several organizations and expert panels have recommended that WC measures be assessed along with BMI in clinical evaluations<sup>7,14,35,36</sup> because increasing evidence supports visceral adiposity as a marker of cardiovascular risk.<sup>37–39</sup>

The development of imaging techniques such as computed tomography (CT) and magnetic resonance imaging (MRI) has been a remarkable advance in the study of human body composition and of its relationship with CVD risk.<sup>40,41</sup> With these methods, cross-sectional images of the body at any level allow the quantification of areas or volumes of various adipose tissue and ectopic fat depots. An ectopic fat depot is

generally considered a lipid deposit that is not physiologically stored in adipose tissues such as in the liver, the pancreas, the heart, and skeletal muscle.<sup>42</sup> Cohort imaging studies have shown that all adipose and ectopic fat depots are correlated with one another.<sup>43,44</sup> However, at any BMI or total adiposity level, there is considerable individual variation in the amount of subcutaneous versus intra-abdominal or visceral adipose tissue (VAT) in the abdominal cavity.<sup>42,45,46</sup> There may be a 2- to 3-fold variation in the amount of VAT at any level of total or subcutaneous adiposity.<sup>42,43,47</sup> Within overweight and obese categories, individuals with low levels of VAT are characterized by a more favorable CVD risk profile, sometimes referred to as metabolically healthy obesity.<sup>48,49</sup> Recent data suggest that metabolically healthy obesity may be a transient phenotype for the majority of the population, with the duration of metabolically healthy obesity differing by race/ethnicity and sex.<sup>49</sup> When those with metabolically healthy obesity are compared with patients with excess VAT, those with excess VAT represent a subgroup of individuals at highest CVD risk, regardless of BMI.<sup>42,46,50</sup> Studies that have examined the relationships between VAT and cardiovascular outcomes have also confirmed that VAT serves as a clear health hazard.<sup>51–53</sup> Imaging studies have shown that a frequent partner of visceral obesity is higher liver fat accumulation,<sup>54,55</sup> for which nonalcoholic fatty liver disease is a clinical manifestation.<sup>56</sup> Overall, excess liver fat has generally been associated with the same alterations in cardiovascular risk factors as visceral obesity.<sup>56,57</sup> However, the question remains as to whether excess liver fat in isolation is associated with higher cardiovascular risk. Mendelian randomization studies that have measured genetic variants predisposing to higher liver fat have not been able to show associations with CVD.<sup>58</sup> Excess liver fat is likely to play a major role in the pathogenesis of the dysmetabolic state that can be found in individuals with overweight/obesity.<sup>59</sup> From a clinical standpoint, health care practitioners should be aware of the fact that the most prevalent form of nonalcoholic fatty liver disease is found among individuals with excess VAT.<sup>60,61</sup> Thus, from a prevention standpoint, reducing visceral obesity by promoting improved lifestyle habits is key to addressing the current epidemic of nonalcoholic fatty liver disease.

## ECTOPIC FAT DEPOTS AND CVD RISK

Other ectopic fat depots of interest are pericardial and epicardial adipose tissues. In the literature, the two are often used interchangeably but have distinct anatomic locations and functions that should be clearly defined.<sup>62</sup> Pericardial fat can be imaged with CT and consists of the total fat content within the pericardial sac<sup>63</sup> below the superior extent of the left<sup>64,65</sup> or right<sup>66</sup> main

coronary artery. This depot has been associated with higher BMI, traditional cardiovascular risk factors, and more atherogenic lipoprotein particles.<sup>64</sup> Pericardial fat correlates with CVD after adjustment for age, sex, BMI, and WC but not after adjustment for cardiovascular risk factors.<sup>63</sup> In the Multi-Ethnic Study of Atherosclerosis, pericardial fat was associated with a higher risk of all-cause CVD, hard atherosclerotic CVD, and HF.<sup>65</sup> Adding pericardial fat to clinical parameters and coronary artery calcium (CAC) scores improved risk discrimination for these outcomes. In the Rancho Bernardo Study, all-cause mortality risk was higher by 34% per 1-SD increment in pericardial fat after adjustment for age, sex, lifestyle variables, lipids, glucose, and adipocytokines.<sup>66</sup> However, this study did not show that pericardial fat was predictive of incident CVD beyond traditional risk factors; additional studies must be done to assess this relationship. Epicardial adipose tissue represents visceral fat between the outer wall of the myocardium and the visceral layer of the pericardium. This adipose tissue originates from embryonic brown adipose tissue and releases cytokines and chemokines into the vasculature.<sup>67</sup> It has been associated with overall cardiovascular health score<sup>68</sup> and arterial stiffness in patients with CVD and type 2 diabetes.<sup>69</sup> Studies have shown that epicardial adipose tissue thickness is significantly correlated with WC, blood pressure, markers of insulin resistance, and dyslipidemia,<sup>68,70</sup> suggesting that this adipose tissue depot could be considered highly insulin resistant and may be an indicator of cardiovascular risk. In addition, epicardial fat thickness has been shown to be associated with sleep apnea severity in women independently of BMI,<sup>71</sup> and sleep apnea is associated with higher CVD risk.<sup>72</sup> This fat depot can be mobilized, with reductions observed after continuous positive airway pressure treatment.<sup>71</sup> However, short-term (8–12 weeks) continuous positive airway pressure use in patients with sleep apnea does not appear to affect VAT.<sup>73,74</sup> One must question, then, whether thicker epicardial fat is a predictor or a consequence of sleep-disordered breathing.

## IMPACT OF LIFESTYLE INTERVENTIONS ON ECTOPIC/PERICARDIAL FAT

Given the associations of ectopic fat with CVD risk, numerous interventions to reduce these adipose tissue depots have been investigated. Although a number of pharmacological agents exist to reduce body fat, lifestyle interventions such as the Diabetes Prevention Program may be as effective as, if not more effective than, medications.<sup>75,76</sup> Randomized studies in both men and women across varying ages have found that exercise, usually 3 to 5 sessions per week for 12 to 52 weeks, reduces VAT compared with a nonexercise control group.<sup>77–79</sup> Well-controlled studies have demonstrated

that exercise can reduce VAT even in the absence of weight loss,<sup>77-79</sup> and a meta-analysis reported exercise to result in a 6.1% loss of VAT in the absence of weight loss.<sup>80</sup> Loss of VAT in the absence of weight loss may relate to increases in fat-free mass.<sup>81</sup> However, not all studies have demonstrated a significant reduction of VAT compared with control.<sup>82,83</sup> The most beneficial exercise interventions appear to be aerobic in nature; data on the reductions of VAT by only resistance training are equivocal.<sup>84,85</sup> Similarly, reductions in VAT with high-intensity exercise have not been consistently superior to those with moderate-intensity exercise,<sup>86,87</sup> and even 3 months of walking resulted in greater VAT reductions compared with control.<sup>88</sup> Meeting the current recommendations for physical activity of 150 min/wk may be sufficient to reduce VAT, with no further reductions with additional activity.<sup>89</sup> Interventions targeting weight loss through caloric restriction have also demonstrated effectiveness in reducing VAT.<sup>90,91</sup> Compared with dietary interventions, exercise interventions have demonstrated greater VAT reductions in most studies<sup>92,93</sup> and in a meta-analysis<sup>80</sup> but not in all studies.<sup>90,91,94</sup> Combined interventions carried out in the Diabetes Prevention Program and the Look AHEAD Trial (Action for Health in Diabetes) have reported greater VAT reductions compared with control groups.<sup>75,95</sup> Exercise interventions also appear to be effective at reducing hepatic<sup>96,97</sup> and epicardial and pericardial fat.<sup>98,99</sup> However, a meta-analysis did not find a significant reduction in epicardial fat with exercise.<sup>100</sup> Caloric restriction has been demonstrated to reduce hepatic<sup>101</sup> and epicardial and pericardial fat.<sup>100,102</sup>

## OTHER ADIPOSITY AND BODY COMPOSITION MEASURES

Although WC is meaningful on its own, the ratio of WC to height, which takes body size into account, may be a better predictor of CVD and may be considered a measure of adiposity.<sup>103,104</sup> Moreover, waist-to-hip ratio (WHR) has been shown to predict cardiovascular mortality independently of BMI. According to data from the National Health and Nutrition Examination Survey, those in the US population with a WHR indicative of central obesity had a higher risk of cardiovascular mortality compared with those with the same BMI but without central adiposity.<sup>34,105</sup> Nonanthropometric measures based on CT, MRI, ultrasonography, dual-energy x-ray absorptiometry, air displacement plethysmography, and bioelectric impedance analysis can be used to quantify body composition. Details on how these body composition measures relate to cardiovascular risk have been summarized in the American Heart Association scientific statement "Identification of Obesity and Cardiovascular Risk in Ethnically and Racially Diverse Populations."<sup>14</sup>

Thus, visceral adiposity as measured by WC, WHR, or detailed imaging methods has been shown to be a risk factor for CVD independently of BMI. Lifestyle interventions, particularly physical activity interventions or interventions combining dietary changes and physical activity, have been shown to reduce VAT and ectopic fat, in some cases independently of weight loss.

## PATHOPHYSIOLOGY OF CORONARY ARTERY DISEASE IN OBESITY

### Atherosclerosis and Coronary Artery Disease

The atherosclerotic process is initiated in childhood, with ingestion of cholesterol esters by macrophage foam cells and their deposition in vessel walls resulting in thickening of the arterial intima. Further lipid accumulation leads to the development of fatty streaks,<sup>106</sup> which appear to be nearly ubiquitously present in young adults.<sup>107</sup> Obesity accelerates these early atherosclerotic changes through several mechanisms, including insulin resistance and inflammation.<sup>108</sup> Obesity and several related downstream metabolic cardiovascular risk factors, including elevated blood pressure, dyslipidemia, and hyperglycemia, have been linked to the extent of atherosclerotic disease in autopsy studies of children and young adults.<sup>109,110</sup> However, obesity is associated with overt atherosclerotic lesions even after accounting for the impact of these metabolic cardiovascular risk factors. The association of obesity with raised atherosclerotic lesions among men in the Pathobiological Determinants of Atherosclerosis in Youth study was present only for those with a thick abdominal panniculus, indicating the fundamental role of central adiposity in the development of atherosclerotic disease.<sup>111</sup> Visceral adiposity promotes systemic and vascular inflammation, which is fundamental to all aspects of the atherosclerotic process, from fatty streak development to atherothrombosis.<sup>112,113</sup> Inflammation induced by obesity increases the likelihood of low-density lipoprotein oxidation,<sup>114</sup> which in turn promotes atherogenesis. Insulin resistance is associated with dyslipidemia (high triglycerides; low high-density lipoprotein cholesterol; small, dense low-density lipoprotein particles) and metabolic syndrome (multiplex CVD risk factor including abdominal obesity, atherogenic dyslipidemia, elevated blood pressure, insulin resistance with or without glucose intolerance, and proinflammatory and prothrombotic states), which are linked to atherosclerosis.<sup>115</sup> Endothelial dysfunction in obesity, principally caused by diminished bioavailability of nitric oxide in the setting of inflammation and oxidative stress,<sup>116</sup> is also fundamental to atherosclerosis progression. Carotid intima-media thickness as an early marker of atherosclerosis in young



adults is associated with obesity,<sup>117</sup> particularly chronically elevated weight from youth through adulthood.<sup>118</sup>

### Incident Coronary Artery Disease Events

Several prospective epidemiological studies demonstrate that obesity is associated with higher risk of incident coronary artery disease (CAD).<sup>119–122</sup> A meta-analysis of >300 000 adults with 18 000 CAD events demonstrated that BMI in the overweight and obese ranges was associated with elevated CAD risk.<sup>123</sup> Of clinical importance, at each level of BMI, higher measures of central adiposity, including WC and WHR, were associated with a greater risk of CAD and cardiovascular mortality, including among those with normal weight as assessed by BMI.<sup>31,34,105,124,125</sup> The degree and duration of obesity, as measured by total cumulative exposure to excess overall and abdominal adiposity and expressed as excess BMI-years and WC-years, have been shown to be stronger predictors of CAD events beyond BMI or WC alone.<sup>126</sup> There are conflicting results on the extent to which the association of obesity with CAD is independent of the metabolic cardiovascular risk factors linked to excess weight. Some large prospective analyses have indicated that the link between obesity and CAD is mediated largely by hypertension, dyslipidemia, diabetes, and other comorbidities,<sup>127</sup> whereas other prospective studies suggest a significant residual CAD risk in obesity even after accounting for these risk factors.<sup>120,128</sup> Similarly, some studies have indicated that obesity without metabolic syndrome is not associated with incident myocardial infarction,<sup>129</sup> in contrast to other studies.<sup>130,131</sup> A meta-analysis of 21 studies including 1.8 million individuals suggested that approximately half of the associations of overweight and obesity with CAD are explained by levels of blood pressure, cholesterol, and glucose.<sup>132</sup> However, this may be an underestimation resulting from residual confounding from cardiovascular risk factors assessed at a single time point or not measured directly in some studies. Production of adipocytokines, oxidative stress, and a prothrombotic state in individuals with metabolic syndrome may contribute to CAD risk beyond that explained by routinely measured cardiovascular risk factors.<sup>115</sup> Ectopic fat deposition, including within the pericardial and epicardial spaces, may further contribute to the burden of coronary atherosclerosis.<sup>133</sup> A pathological study in humans reported that part of the left anterior descending artery with an intramyocardial course was in perfect condition (ie, without any intimal atherosclerotic lesion), which was in contrast to the epicardial segment of the same artery in which atherosclerosis was documented.<sup>134</sup> Likewise, in hypercholesterolemic rabbits, epicardial coronary arteries surrounded by adipose tissue develop atherosclerosis, whereas the intramyocardial segments of the same arteries remain unaltered.<sup>135</sup> Thus, local

production of adipocytokines by epicardial fat may modulate blood vessel biology through paracrine signaling or through vasa vasorum.

### Obesity and Microvascular Disease

In addition to the effects of excess adiposity on epicardial coronary vessels described above, obesity is linked to abnormalities in the coronary microvasculature, a key regulator of coronary blood flow.<sup>136,137</sup> Coronary microvascular disease often coexists with and compounds the effects of obstructive or nonobstructive CAD on myocardial ischemia and CAD events.<sup>138,139</sup> Coronary microvascular disease is pathophysiologically linked to endothelial dysfunction and possibly to small vessel remodeling; this microvascular disease is independently associated with higher BMI<sup>140</sup> and provides independent prognostic information on cardiovascular risk among those with obesity.<sup>141</sup> In prospective studies, weight loss via bariatric surgery has been associated with improvements in coronary microvascular function.<sup>142</sup>

### DIAGNOSIS OF CAD IN OBESITY

CAD assessment can be challenging in patients with obesity. The baseline ECG may be influenced by obesity, and patients with obesity have impaired maximal exercise testing capacity (dyspnea, mechanical limitations, left ventricular [LV] diastolic dysfunction [LVDD]).<sup>27</sup> Thus, other modalities such as nuclear medicine approaches, stress echocardiography, or pharmacological stress and stress cardiac MRI may be of interest in the evaluation of CAD in this population. CAC screening and CT coronary angiography can be used in diagnosing CAD, but ultimately, coronary angiography remains the gold standard test for identifying the presence and extent of CAD. Here, we review specific considerations for the use of noninvasive and invasive modalities to assess CAD in patients with obesity (summarized in Table 1).

### Noninvasive CAD Assessment in Obesity

#### *Electrocardiographic Assessment*

Obesity has the potential to affect the ECG in several ways: displacing the heart by elevating the diaphragm in the supine position, increasing the cardiac workload, and increasing the distance between the heart and the recording electrodes.<sup>27</sup> Several electrocardiographic changes are associated with obesity (Table 2). More frequent ST-segment depression is seen in patients with overweight and CAD,<sup>143</sup> and insulin concentration may be related to the development of the ST-segment depression over time.<sup>144</sup> Multiple electrocardiographic criteria for LV hypertrophy (LVH) are present more regularly in patients with severe obesity compared with individuals with normal weight but less frequently than

**Table 1. Considerations for Use of Noninvasive and Invasive Diagnostic Tools in Patients With Obesity**

Diagnostic tool	Strengths	Limitations
Noninvasive diagnostic tools		
ECG	Widely available, cheap	Low sensitivity and specificity
Treadmill stress test	Widely available Functional testing	Patients may stop because of symptoms unrelated to CVD
SPECT	Available, good precision	Irradiation, technical limitation because of body size Residual uncorrected attenuation
PET (rubidium)	Nuclear imaging technique of choice for patients with obesity	Less radiation exposure than SPECT but technical limitations because of body size
Stress echocardiography	Widely available, valid technique in patients with obesity Radiation free Has no weight limits Functional testing	Highly operator dependent Can be limited because of poor acoustic windows related to pulmonary disease, breast size, obesity, and respiratory motion
Stress cardiac MRI	Accurate assessment of the complex cardiac effect of chronic pressure overload and high cardiac output in patients with obesity	Table weight limit WC may limit access depending on bore diameter Length of examination Claustrophobia
CT calcium scan	Inexpensive and reproducible technique to determine the presence and extent of CAC	Obesity may limit the diagnostic accuracy and value of cardiac CT calcium scan Gantry/bore diameter limitations
Invasive diagnostic tools		
Cardiac CT coronary angiography	Sensitivity and negative predictive values are high in patients with obesity	Image quality degrades as BMI increases Degradation is related to an increase in back-ground noise, subsequent reduced signal-to-noise ratio, and low vessel opacification
Intravascular ultrasound	Allows in vivo assessment of plaque burden, plaque morphology (ie, stages of plaque development, high-risk plaque features)	Invasive technique

BMI indicates body mass index; CAC, coronary artery calcium; CT, computed tomography; CVD, cardiovascular disease; MRI, magnetic resonance imaging; PET, positron emission tomography; SPECT, single photon emission computed tomography; and WC, waist circumference.

would be expected on the basis of the high prevalence of echocardiographic criteria for LVH.<sup>27</sup> Therefore, LVH is probably underdiagnosed according to the usual ECG criteria in individuals with severe obesity. In LVH and in obesity, the heart is oriented more horizontally in the mediastinum, which may explain the usefulness of the R wave in AVL.<sup>27</sup> Thus, it has been proposed that for men of all ages, LVH is considered present on the basis of the QRS voltage alone when the amplitudes of the R wave in lead AVL and the S wave in lead V<sub>3</sub> are >35 mm. For women, the same criteria were set at >25 mm.<sup>27</sup> When electrocardiographic voltage criteria were compared with LV mass estimated by echocardiography, a sensitivity of 49%, specificity of 93%, and overall accuracy of 76% were reported.<sup>27</sup> These percentages representing the Cornell score are higher than other widely used criteria such as the Sokolow-Lyon voltage or Romhilt-Estes score.

### Treadmill Stress Test

Standard treadmill stress test performance is limited in patients with obesity by several factors. Electrocardiographic abnormalities seen with obesity might limit accurate interpretation, and aerobic capacity can be

diminished because of pulmonary dysfunction, orthopedic limitations, and LVDD.<sup>145</sup> Many patients with obesity fail to achieve 80% to 85% of the age-predicted heart rate needed for diagnostically valid results.<sup>146,147</sup> Chronotropic competence can be reduced in obesity, with a prior study showing that peak heart rate, heart rate recovery, and chronotropic index are lower in patients with obesity, regardless of fitness level.<sup>146</sup> Higher systolic and diastolic blood pressures also may be observed during the exercise stress test in patients with obesity.<sup>148</sup> However, standard Bruce and modified Ramp protocols achieve valid results in most patients with obesity, with patients terminating the test because of fatigue, leg pain, or dyspnea.<sup>149</sup>

### Single Photon Emission CT

Single photon emission CT can be used with exercise, vasodilator (dipyridamole), and dobutamine stress. Two-day protocols with larger tracer doses, which are weight based, are recommended in patients who weigh 250 to 350 lb (113–160 kg). Attenuation artifacts, most commonly resulting from attenuation by the diaphragm or breast, are common in obesity. Tissue attenuation

**Table 2. Electrocardiographic Changes That May Occur in Individuals With Obesity**

Clinically significant
↑ Heart rate
↑ QRS interval
↑ QTc interval
False-positive criteria for inferior myocardial infarction
Less clinically significant
↑ PR interval
↑ QRS voltage
↑ QT dispersion
↑ SAECG (late potentials)
↑ ST-T abnormalities
↑ ST-segment depression
Left axis deviation
Flattening of the T wave (inferolateral leads)
Left atrial abnormalities

SAECG indicates signal-averaged ECG.

Adapted from Poirier et al.<sup>27</sup> Copyright © 2006, American Heart Association, Inc.

decreases single photon emission CT image quality and thus diagnostic accuracy. Improved cameras, software, and CT-based attenuation correction algorithms are techniques that enable a reduction of attenuation artifacts. Technetium sestamibi is the marker of choice in patients with obesity because of greater energy emission, which generates better images.<sup>150</sup> Disadvantages include the limitations of relative perfusion imaging with reduced ability to detect triple-vessel or left main stem disease and residual uncorrected attenuation. Weight-based limitations might occur at 350 lb (160 kg), which might necessitate planar imaging. Newer and more sensitive cameras might eliminate some of these issues, but their use still leads to table weight and size issues because proper positioning of the patient is required with this system. Thus, single photon emission CT is generally avoided when the patient's BMI is >35 kg/m<sup>2</sup> because of the above limitations, and positron emission tomography (PET) is recommended in those cases when looking for myocardial ischemia and an imaging modality is indicated.

### PET Rubidium

PET rubidium has a 91% sensitivity and 89% specificity; is faster than sestamibi single photon emission CT; and produces less radiation exposure, better-quality images, correction for attenuation, a greater degree of diagnostic precision, and a reduced need for invasive examinations. Normal PET myocardial perfusion imaging is associated with very low cardiac death rates in all categories of obesity.<sup>151</sup> PET allows the ability to quantify absolute coronary blood flow, adding to the diagnostic and prognostic capabilities beyond relative

perfusion imaging, especially in the detection of triple-vessel and left main stem disease. Therefore, PET rubidium is the nuclear imaging technique of choice for patients with obesity.

### Stress Echocardiography

Despite some limitations, exercise stress echocardiography is a valid technique in patients with obesity.<sup>152,153</sup> Stress echocardiography is highly feasible in most cases for patients with obesity through either physiological stress (treadmill exercise) or pharmacological stress (dobutamine). It is widely available, low cost, and radiation free and has no weight limits. However, stress echocardiography is highly operator dependent and can be limited in the presence of poor acoustic windows related to pulmonary disease, breast size, obesity, and respiratory motion.<sup>154</sup> Excellent 1-year outcomes have been shown in patients with obesity and normal stress echocardiography.<sup>155</sup> Contrast injection can be used to improve the number of heart segments visualized.<sup>155</sup> In a prospective study of patients with overweight and obesity who underwent coronary angiography and dobutamine stress echocardiography with and without contrast, contrasted images improved sensitivity and specificity (82% versus 70% and 78% versus 67% with and without contrast, respectively).<sup>154</sup> Retrospectively, Lerakis et al<sup>156</sup> assessed dobutamine stress echocardiography as a preoperative screen for CAD in a bariatric surgery population. Adequate imaging was obtained in 97% of patients in light of intravenous echocardiographic contrast use in 72% of cases. Indeed, higher rates of contrast use have been reported in patients with severe obesity who undergo transthoracic dobutamine echocardiography.<sup>152,153,157,158</sup> If severe limitations exist, transesophageal echocardiography with dobutamine might be useful.<sup>159,160</sup>

### Stress Cardiac MRI

Stress cardiac MRI is a technique that allows the assessment of perfusion defects, regional wall motion abnormalities, and LV ejection fraction and the detection of scar with the use of gadolinium. It allows accurate assessment of the complex cardiac effect of chronic pressure overload and high cardiac output in patients with obesity.<sup>153,155</sup> Stress cardiac MRI and PET are likely the diagnostic techniques least affected by obesity. Newer-generation MRIs have larger bore sizes (70 instead of 60 cm) and greater magnet strengths, which have accommodated patients with obesity more easily and led to improved image quality. The usefulness of stress cardiac MRI was studied in 285 participants with an average BMI of 34 kg/m<sup>2</sup> who underwent testing and long-term follow-up. Of the patients imaged, 89% had diagnostic image quality.<sup>161</sup> The presence of ischemia predicted adverse events at 5 years of follow-up, regardless of whether scar was present. Lack of inducible ischemia is associated with a low annual major adverse coronary

events (MACEs) rate of 0.3% at 2 years in patients with obesity.<sup>161</sup> Table weight limit, bore diameter, and length can be significant limitations, and some centers might not be able to accommodate patients with more severe obesity despite the benefits of diagnosis. Besides the weight limit of 335 lb (152 kg) that comes with MRI tables, higher WC and claustrophobia might also limit the feasibility of MRI in patients with severe obesity.<sup>155</sup>

### CT Calcium Scan

Obesity is associated with elevated CAC, a marker of coronary atherosclerosis that is predictive of cardiovascular events<sup>162,163</sup> and more rapid CAC progression.<sup>164</sup> The presence of high CAC score offers an inexpensive and reproducible technique to determine the presence and extent of calcified coronary artery plaque. Despite advances in CT scanners, obesity may limit the diagnostic accuracy and value of cardiac CT calcium scan. CT equipment has table weight limits of 350 to 450 lb (160–204 kg) and is also limited by gantry/bore diameter. Studies suggest that WC and WHR provide more useful prognostic information than BMI on the likelihood of elevated CAC,<sup>165,166</sup> again indicating the importance of abdominal obesity in the pathophysiology of atherosclerosis.

### Cardiac CT Coronary Angiography

CT coronary angiography is emerging as an alternative approach for the quantification of both coronary calcified and noncalcified plaque. This approach may be particularly useful in specific subsets of symptomatic patients with obesity, unknown CVD, and equivocal or uninterpretable stress tests or in cases when a discrepancy exists between clinical presentation and stress test results. CAC score allows risk stratification and plaque burden assessment, whereas CT coronary angiography allows evaluation of luminal stenosis and plaque characterization and quantification. Registry data showed that those with obesity who were symptomatic were more likely than patients without obesity to have any CVD at CT coronary angiography.<sup>167</sup> Imai et al<sup>168</sup> studied 553 patients who underwent serial CT coronary angiography and observed that the risk of noncalcified plaques became higher as abdominal visceral adiposity was higher, with the highest quartile conferring the greatest risk, regardless of underlying cardiovascular risk factors. One major challenge with CT coronary angiography is that image quality degrades as BMI increases; this degradation is related to an increase in background noise and subsequent reduced signal-to-noise ratio. In addition, low vessel opacification may occur in patients with overweight or obesity because of differences in the distribution of blood volume in peripheral venous and central circulation when contrast is injected,<sup>169</sup> which ultimately leads to a higher rate of nonevaluable segments in patients with overweight or

obesity. Nevertheless, sensitivity and negative predictive values are invariably high even in patients with obesity.

## Invasive Evaluation of CAD in Obesity

### Coronary Angiography

Individuals with obesity have several limitations when undergoing evaluation in the catheterization laboratory. Potential technical difficulties include suboptimal radiographic visualization that may limit detection of angiographic results and may result in a greater likelihood of complications. Vascular access may be laborious; radial access is preferred in this population because of fewer vascular complications, especially bleeding, earlier ambulation, and a shorter hospital stay.<sup>170,171</sup> When cardiac catheterization is pursued for diagnostic or therapeutic purposes for those with severe obesity, radial artery access has been associated with a 3 times lower rate of complications than a transfemoral approach.<sup>170</sup> The radial approach is particularly useful for patients with limited capability to tolerate supine positions because upright mobilization can be immediate after the procedure. If the femoral approach is used, vascular closure devices should be used to accelerate ambulation in patients with obesity.<sup>172</sup> The fluoroscopy needed to achieve adequate x-ray penetration and sufficient image quality may also result in higher radiation exposure to both patients with obesity and staff.<sup>173</sup> In addition to issues with vascular access and radiographic imaging, the engineering parameters and physical limitations of the catheterization table and its supporting structures may limit patients' ability to undergo clinically indicated coronary angiography.

### Intravascular Ultrasound

Several intravascular imaging techniques such as intravascular ultrasound, virtual histology intravascular ultrasound, and optical coherence tomography allow in vivo assessment of plaque burden, plaque morphology (ie, stages of plaque development, high-risk plaque features), and response to therapy, particularly for higher-risk patients. In a large retrospective database of 3158 patients designed to evaluate plaque characteristics, 32% of patients with BMI >25 kg/m<sup>2</sup> demonstrated evidence of high-risk plaque features (positive remodeling, spotty calcification, and low-attenuation plaque), and BMI itself was an independent predictor of future acute coronary syndrome events.<sup>174</sup> Abdominal visceral adiposity independently predicted the presence and extent of noncalcified coronary plaque that also contained multiple features of plaque vulnerability.<sup>175</sup> Thus, numerous tests can diagnose atherosclerosis, myocardial ischemia, or both. The appropriate choice of test to assess CVD depends on local expertise, the relative strengths and weaknesses of each modality, and individual patient characteristics that contribute to the



pretest likelihood of CVD and the risk/benefit ratio of using a given modality.

## CLINICAL MANAGEMENT AND TREATMENT OF CAD IN OBESITY

### The Obesity Paradox

Obesity is a strong risk factor for the development of CVD because patients with obesity experience CVD events at an earlier age, live with CVD for a greater proportion of their lifetime, and have a shorter average life span than individuals with normal weight.<sup>176</sup> However, in patients with overweight or obesity, particularly among those who develop symptomatic CVD, BMI and other parameters of body composition are not consistent cardiovascular risk factors for adverse short-term CVD outcomes ( $\leq 10$  years).<sup>177–179</sup> This reversal of traditional epidemiology, called the obesity paradox, is now well documented in numerous studies, particularly in diverse populations who have overweight or class 1 obesity. The underlying cause of the obesity paradox is unclear. The paradox may relate to potential lead time bias that occurs when patients with overweight or obesity develop CVD earlier in their lifetime or are tested earlier for CVD than patients with normal weight, resulting in earlier diagnoses and treatment and confounding differences in outcomes. In addition, differences in cardiorespiratory fitness may explain more favorable CVD outcomes regardless of BMI. Finally, some propose that a “lean paradox” may exist in which low body fat percentage and low BMI with less reserve to avoid cardiac cachexia may be the more pertinent predictors of poor CVD outcomes.<sup>177–179</sup>

### Weight Loss and CAD Risk

Lifestyle modification, with associated weight loss, improves both the diagnostic components of metabolic syndrome and associated pathophysiologic abnormalities such as systemic inflammation and endothelial dysfunction.<sup>27,180,181</sup> Interventional trials of medical weight loss have not demonstrated a clear reduction in CAD rates.<sup>182–184</sup> In contrast, reduced CAD risk has been demonstrated in prospective studies comparing patients undergoing bariatric surgery with nonsurgical patients with obesity, with the Swedish Obesity Study finding significantly lower rates of fatal and nonfatal cardiovascular events in those undergoing bariatric surgery.<sup>185</sup> The reason for the disparate results of medical and surgical weight loss studies is likely the degree of weight loss achieved (5–10 kg with medical weight loss versus 10–40 kg with surgery) and the risk factor reduction seen with bariatric surgery.<sup>186</sup> Modest short-term weight loss may not be sufficient to fully overcome the deleterious effects of long-term obesity on the vasculature.

### Benefits of Weight Loss on CAD

The general goals of weight loss and management are, at a minimum, to prevent further weight gain, to reduce body weight, and to maintain a lower body weight over the long term. Patients should have their BMI and WC measured not only for the initial assessment of the degree of overweight and obesity but also as a guide to the efficacy of weight loss treatment.<sup>187</sup> The Mediterranean diet decreases MACEs in patients with high cardiovascular risk and is an interesting option for this population.<sup>188</sup> Future studies should determine how much adherence to a Mediterranean dietary pattern is needed or how best to personalize diets on the basis of genetic or other objective factors for CVD risk reduction in obesity.<sup>189</sup> Moreover, no studies have shown a clear reduction of CVD or mortality with weight loss through lifestyle modification. Look AHEAD, one of the largest clinical trials of lifestyle modification for obesity treatment in patients with type 2 diabetes, failed to show a significant reduction of MACEs or cardiovascular mortality after 9.6 years, which may be related to the limited differential weight loss between the intervention and control groups by the end of the trial.<sup>182</sup> Post hoc analyses of Look AHEAD showed that participants who lost  $\geq 10\%$  of their body weight had significant reductions in cardiovascular events.<sup>190</sup> In addition, physical activity, particularly aerobic exercise, is associated with improved insulin sensitivity, endothelial function, and reduction in proinflammatory markers independently of weight loss,<sup>189</sup> but more data are needed in populations with CVD. Liraglutide has been shown to reduce MACEs and cardiovascular death in the LEADER trial (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results), but this was in a population with type 2 diabetes who were using the 1.8-mg dosing specified for diabetes treatment.<sup>191</sup> Lorcaserin appeared to be safe in terms of CVD, but no benefits in cardiovascular mortality or CVD events were demonstrated (Lorcaserin was removed from the US market by the US Food and Drug Administration in 2020).<sup>192</sup> An interim analysis of the LIGHT trial (Cardiovascular Outcomes Study of Naltrexone SR/Bupropion SR in Overweight and Obese Subjects With Cardiovascular Risk Factors) showed that naltrexone-bupropion has cardiovascular safety; however, no solid conclusion can be drawn from this trial given that it was terminated early because of public release of the interim data by the sponsor.<sup>193</sup> A retrospective study of 20235 surgical and nonsurgical patients<sup>194</sup> showed that bariatric surgery is associated with a lower incidence of macrovascular disease (first occurrence of CAD or cerebrovascular events) driven mainly by a lower incidence of CAD (acute myocardial infarction, unstable angina, percutaneous coronary intervention [PCI], or coronary artery bypass grafting [CABG]).<sup>194</sup> The SOS study (Swedish

Obese Subjects), which is a nonrandomized prospective controlled study, also demonstrated a reduction of cardiovascular death in the bariatric surgery group compared with the control group.<sup>185</sup> To date, there is no randomized controlled trial on the effects of bariatric surgery on MACE incidence.

## PCI and Obesity

### Short-Term Outcomes After PCIs

The CathPCI Registry examined in-hospital complications of 83861 patients with severe obesity, including patients after myocardial infarction.<sup>195</sup> After multivariable adjustment, obesity was independently associated with a greater mortality rate and a lower bleeding rate.<sup>195</sup> Although obesity affects weight-based dosing protocols for unfractionated heparin, patients with severe obesity are underrepresented or even excluded from major trials.<sup>196</sup> A doubling in the time necessary to obtain adequate anticoagulation in patients weighing 110 kg with an initial infusion rate based on a nomogram was reported.<sup>196</sup> Another study of 227042 registry patients, including patients after myocardial infarction, with 37.2% (n=84479) having obesity and 7.4% (n=16730) having severe obesity,<sup>197</sup> reported that patients with severe obesity had significantly more contrast-induced nephropathy, nephropathy requiring dialysis, and vascular complications (almost exclusively femoral) compared with patients with overweight.<sup>197</sup> Gastrointestinal bleeding and MACE incidences were not statistically different. The British Cardiovascular Intervention Society Registry reported adverse in-hospital outcomes and mortality of 345192 patients undergoing PCI.<sup>198</sup> At 30 days after PCI, there was evidence of the obesity paradox, with lower mortality observed in patients with BMI  $\geq 25$  kg/m<sup>2</sup>. Up to 5 years after PCI, BMI  $>25$  kg/m<sup>2</sup> was an independent predictor of greater survival compared with normal weight, regardless of the clinical presentation (unstable angina, non-ST-segment-elevation myocardial infarction or ST-segment-elevation myocardial infarction).<sup>198</sup> The APPROACH registry (Alberta Provincial Project for Outcomes Assessment in Coronary Heart Disease) reported mortality in 30258 patients who had PCI and showed further evidence of the obesity paradox given that the 6-month mortality was lower in patients who were in the overweight or obese category compared with patients with normal BMI.<sup>199</sup>

### Long-Term Outcomes After PCIs

Patients with low BMI tend to have more events after PCI than patients with obesity.<sup>200,201</sup> A study of 23181 patients from 11 prospective PCI studies used a BMI of 22.5 to 24.9 kg/m<sup>2</sup> as the reference category. The risk of major cardiovascular events was higher among patients with a lower BMI ( $<18.5$  kg/m<sup>2</sup>) and declined among

patients with a higher BMI ( $>30.0$  kg/m<sup>2</sup>).<sup>202</sup> A recent meta-analysis of 865774 patients undergoing PCI or CABG confirmed these findings and demonstrated a U-shaped association across all BMI categories for all-cause mortality and MACEs after PCI or CABG.<sup>203</sup> This obesity paradox seems to wane when severe obesity is taken into consideration.<sup>199,204</sup> The APPROACH registry demonstrated that the 5- and 10-year mortality rate after PCI in patients with class 3 obesity and high-risk coronary anatomy was higher than that of patients with normal BMI (odds ratio, 1.78 at 5 years and 1.57 at 10 years).<sup>199</sup>

## Antiplatelet Therapy in Obesity

Compared with patients with normal weight, individuals with obesity display higher platelet reactivity in a number of ex vivo assays of platelet function, including platelet aggregation.<sup>205,206</sup> Adipose tissue produces multiple bioactive substances and hormones such as leptin, adiponectin, TNF- $\alpha$  (tumor necrosis factor- $\alpha$ ), interleukin-6, and resistin, all of which may directly or indirectly affect platelet function.<sup>206,207</sup> High levels of platelet aggregation and turnover are also found in patients with insulin resistance and hyperglycemia.<sup>208</sup> High on-aspirin platelet reactivity is the laboratory-defined failure of aspirin to appropriately inhibit platelet thromboxane production or to inhibit platelet function. Several studies have linked obesity to an elevated risk of high on-aspirin platelet reactivity.<sup>209</sup> In comparisons with individuals without obesity, postaspirin platelet reactivity was higher in the group with obesity at peak 1 hour after aspirin administration and trough 24 hours after aspirin administration time points.<sup>210,211</sup> In a pharmacokinetic/pharmacodynamic comparison of aspirin formulations in patients with obesity and type 2 diabetes, high on-aspirin platelet reactivity was highest with enteric-coated aspirin because of the increase in esterase and phase II conjugation enzymes in obesity.<sup>212</sup> Obesity-related endothelial dysfunction and persistent, low-grade inflammation can cause higher platelet consumption, leading to higher platelet turnover and acceleration of COX-1 (cyclooxygenase 1) renewal and resulting in a faster recovery of thromboxane-dependent platelet function and the loss of aspirin effect.<sup>213,214</sup> Similar correlations between patients' BMI and residual platelet reactivity under treatment were observed with clopidogrel and prasugrel in patients with obesity. However, patients with obesity but without metabolic syndrome had a better response to thienopyridines compared with patients with obesity and metabolic syndrome and had a response similar to that of patients without obesity, suggesting that metabolic status is a better correlate of platelet inhibition than BMI.<sup>206,215</sup> Some data suggest that patients with obesity receiving prasugrel had lower rates of high on-treatment platelet reactivity than those taking clopidogrel. However, a comparison of patients

with and without obesity on prasugrel revealed that 28% of patients with obesity had high on-treatment platelet reactivity compared with 4% of patients without obesity ( $P<0.01$ ). Although it seems that prasugrel is more effective in obesity compared with clopidogrel, it should be noted that additional data suggest that obesity might lead to a variable response effect to prasugrel compared with nonobesity.<sup>206,215</sup> Conversely to thienopyridines, no correlation was reported between BMI and high on-treatment platelet reactivity with ticagrelor; patients with obesity do not express significantly higher levels of platelet reactivity, whereas ticagrelor seems to induce significantly higher platelet inhibition than prasugrel in patients with obesity.<sup>206,216</sup> Although studies suggest that obesity may promote platelet activation and blunt effects of antiplatelet medications, clinical observations have pointed to an obesity paradox, namely that patients with obesity may have better post-acute coronary syndrome outcomes and may have a lower risk of reinfarction or death. Data involving platelet assays are often conflicting and involve sample sizes too small to draw decisive conclusions about clinical outcomes and to make recommendations about dosing adjustments of antiplatelet therapy in obesity.<sup>206</sup>

## Surgical Revascularization

Obesity has been inconsistently associated with higher in-hospital mortality after CABG. An analysis of the Society of Thoracic Surgeons' database (559 004 patients who underwent isolated CABG between 1997 and 2000)<sup>217</sup> showed a higher risk of in-hospital mortality in patient with moderate obesity ( $n=42\ 060$ ; BMI, 35–39.9 kg/m<sup>2</sup>) and patients with severe obesity ( $n=18\ 735$ ; BMI >40 kg/m<sup>2</sup>) compared with patients with a BMI of 18.5 to 34.9 kg/m<sup>2</sup>. These results contrasted with previous studies that found no significantly greater postoperative mortality in patients with obesity after CABG.<sup>218,219</sup> A meta-analysis showed that the rate of in-hospital mortality after CABG was even less in the population with obesity.<sup>220</sup> A potentially protective effect was also shown in a retrospective multicenter cohort study,<sup>221</sup> which showed that 30-day operative mortality was highest in extreme BMI groups (BMI <20 and >40 kg/m<sup>2</sup>) and lowest near a BMI of 30 kg/m<sup>2</sup>, suggesting a U-shaped relationship.<sup>222</sup> Evidence on long-term mortality is still conflicting.<sup>171</sup> A meta-analysis found decreased long-term mortality (1–5 years) for the population with overweight and obesity.<sup>203,220</sup> In contrast, a recent retrospective study showed that obesity was associated with a higher rate of long-term mortality after CABG.<sup>223</sup> Several studies have documented the association between obesity and numerous postoperative CABG complications such as renal failure,<sup>224</sup> respiratory failure, arrhythmias, and greater intraoperative transfusion rate.<sup>27,225,226</sup> In contrast, postoperative cerebrovascular events,

myocardial infarction, and postoperative bleeding do not appear to be higher in patients with obesity.<sup>225,226</sup> A greater incidence of postoperative AF was reported in patients with obesity,<sup>227</sup> as was a longer length of stay.<sup>199</sup> In a large cohort study of patients who underwent isolated CABG, WC was associated with a higher risk of postoperative AF, prolonged mechanical ventilation and reintubation, renal failure and new postoperative renal replacement therapy, bloodstream infection, sternal wound infections, and intensive care unit and hospital length of stay independently of BMI.<sup>228</sup> Postoperative deep sternal wound infection is also more common in patients with obesity. CABG surgery using bilateral internal mammary artery instead of single internal mammary artery was associated with a higher risk of postoperative deep sternal wound infection without improving survival for patients with obesity.<sup>229</sup> The large, poorly vascularized panniculus, the higher incidence of dysglycemia among those with obesity, and the difficulty in wound surveillance may predispose to wound infections.<sup>199,230</sup> Obesity has also been identified as a risk factor for superficial wound infection and saphenous vein harvest site infection.<sup>218</sup>

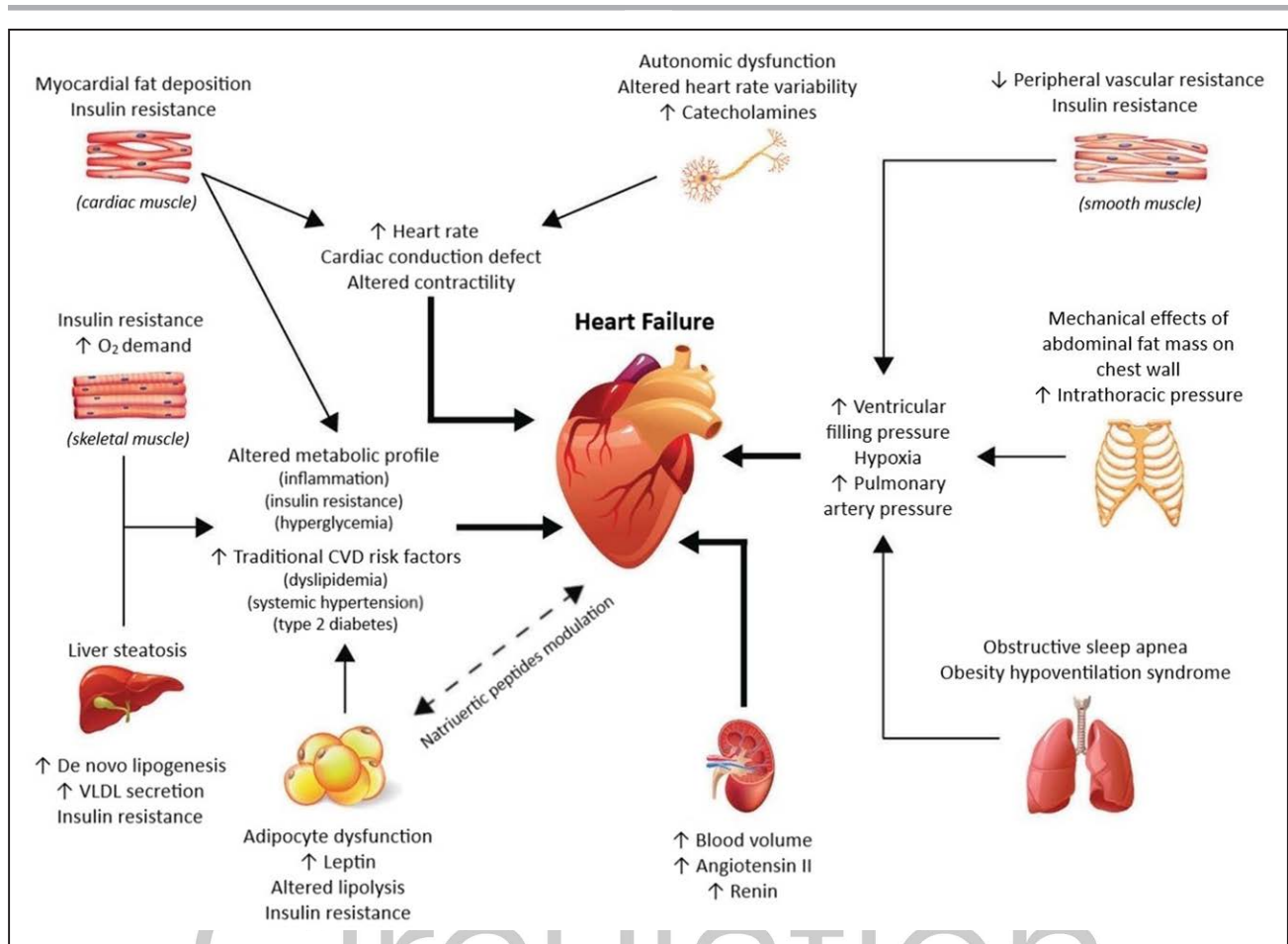
## PATHOPHYSIOLOGY OF HF AND ARRHYTHMIAS IN OBESITY

### Impact of Obesity on Heart Function

Excess adiposity promotes changes in cardiac function both directly through the effects on the myocardium and vasculature and indirectly through obesity-related comorbidities.<sup>231</sup> Excess adipose tissue accumulation leads to hemodynamic changes, including higher blood volume and cardiac output and a reduction in systemic vascular resistance.<sup>27</sup> Excess adiposity also leads to higher blood pressure as a result of activation of the renin-angiotensin-aldosterone and sympathetic nervous systems.<sup>232</sup> Obesity also directly affects the myocardium with myocardial fat accumulation and subsequent fibrosis that can lead to the development of LVDD and HF with preserved ejection fraction (HFpEF). Detailed phenotyping of patients with HFpEF with and without obesity compared with controls depicted that patients with obesity and HFpEF had greater concentric LV remodeling, right ventricular dilatation, and right ventricular dysfunction. There was also evidence of more pericardial restraint and ventricular interdependence for those with obesity and HFpEF in the setting of greater epicardial fat thickness and epicardial fat volume.<sup>233,234</sup> Patients with obesity and HFpEF also had significantly lower exercise capacity compared with patients without obesity with HFpEF and control subjects. This was one of the first studies to demonstrate a distinct pathophysiological phenotype of HFpEF in the setting of obesity.<sup>233</sup> Atherosclerotic heart disease related to obesity can lead







**Figure 1. Pathophysiology of heart failure in obesity.**

CVD indicates cardiovascular disease; and VLDL, very-low-density lipoprotein. Adapted from Rodriguez Flores et al<sup>240</sup> with permission from Taylor & Francis Ltd (<https://www.tandfonline.com>). Copyright © 2017, Taylor & Francis Ltd.

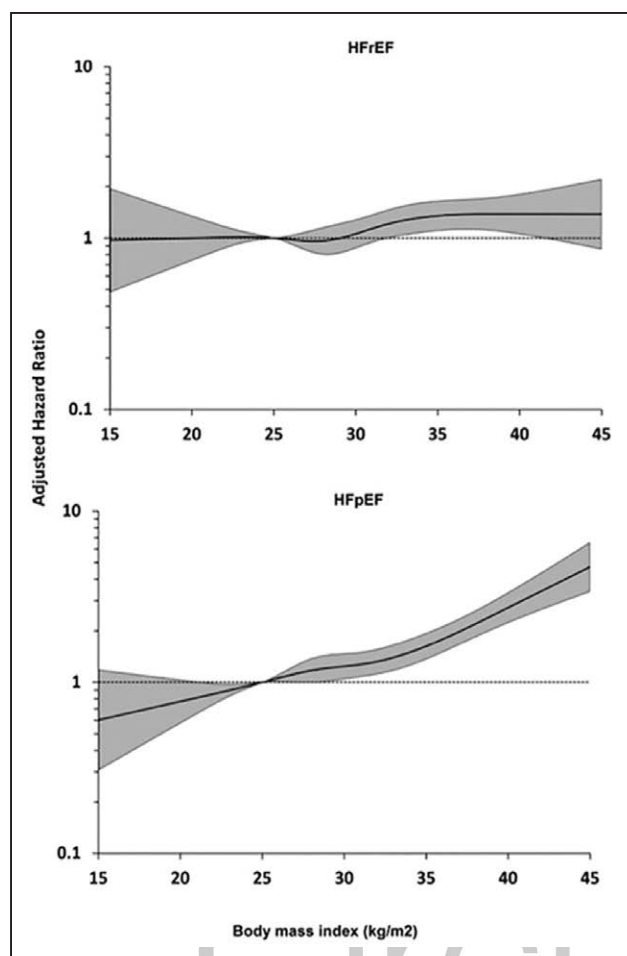
to systolic dysfunction and, ultimately, HF with reduced ejection fraction (HFrEF). Finally, comorbidities associated with obesity such as diabetes, sleep apnea, and hypoventilation syndrome can increase the risk for pulmonary hypertension and right ventricular and LV failure.<sup>231</sup>

## Obesity and HF

Numerous studies have established obesity to be a major risk factor for hypertension, CVD, and LVH, all strong risk factors for the development of HF.<sup>177,178</sup> In addition, obesity has potent adverse effects on LV systolic and, particularly, LV diastolic function. Multiple studies have established obesity as a major risk factor for the development of HF. In a study of 5881 Framingham Heart Study participants, HF incidence increased by 5% in men and 7% in women for every 1-unit BMI increase after adjustment for other risk factors, and the risk of HF increased across the entire spectrum of BMI.<sup>235</sup> This was subsequently confirmed in several large, prospective epidemiological studies.<sup>235–237</sup> Other anthropometric parameters of excess adiposity such as WC, WHR, and waist-to-height ratio have also been independently associated with HF risk, but they generally do not add substantive risk information for

HF beyond BMI measurement.<sup>236–239</sup> Visceral obesity has a number of local effects on the myocardium, including inducing cardiomyocyte hypertrophy, myocardial fibrosis, and activation of inflammatory pathways relating to macrophage infiltration and cytokine gene expression. Excessive fat accumulation in VAT and ectopic sites such as the pericardium/epicardium and liver results in higher circulating blood volume and local and systemic proatherogenic inflammatory factors, which act to increase stroke volume, cardiac wall stress, and myocardial injury, leading to concentric LVH, LV remodeling, and ultimately diastolic and systolic cardiac failure (Figure 1).<sup>240–242</sup> Recent work has also suggested that higher BMI is more strongly associated with the risk of HFpEF than with HFrEF.<sup>243</sup> In fact, in a pooled analysis using data from 3 large longitudinal studies, Pandey et al<sup>244</sup> demonstrated a greater association between higher BMI and risk of HFpEF, with participants with overweight and class 1 obesity having 38% and 56% higher risk of HFpEF, respectively, independently of other cardiovascular risk factors (Figure 2).<sup>244</sup> Low fitness has been associated with a significantly higher risk of HF across all BMI categories and may explain close to 50% of HF risk associated with BMI.<sup>245</sup>





**Figure 2.** Association between body mass index and risk of heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF).

Reprinted from Pandey et al<sup>243</sup> with permission from the American College of Cardiology Foundation. Copyright © 2018, American College of Cardiology Foundation.

## Obesity and HF Outcomes

Data support the presence of the obesity paradox in HF: Patients with overweight or class 1 obesity have better clinical outcomes than patients with normal weight and similar degrees of HF, and this is seen more for HFrEF than for HFpEF.<sup>177–179</sup> In addition, the protective effects of obesity on cardiovascular outcomes have now been noted for HFrEF, HFpEF, and acutely decompensated HF.<sup>177–179,237</sup> This obesity paradox has also been noted for BMI, WC, and percent body fat,<sup>178,179,237,246,247</sup> although a recent study in HFpEF suggested that higher WC was associated with better outcomes in univariate analysis but worse outcomes in multivariate analysis.<sup>248,249</sup> Epicardial adipose tissue has recently been found to be low in patients with HF compared with the general population, and a recent study found that low epicardial adipose tissue in HF was associated with higher HF mortality, another aspect of the obesity paradox.<sup>237,250,251</sup> Patients with obesity have lower levels of BNP (brain natriuretic peptide) than patients with normal weight, including in

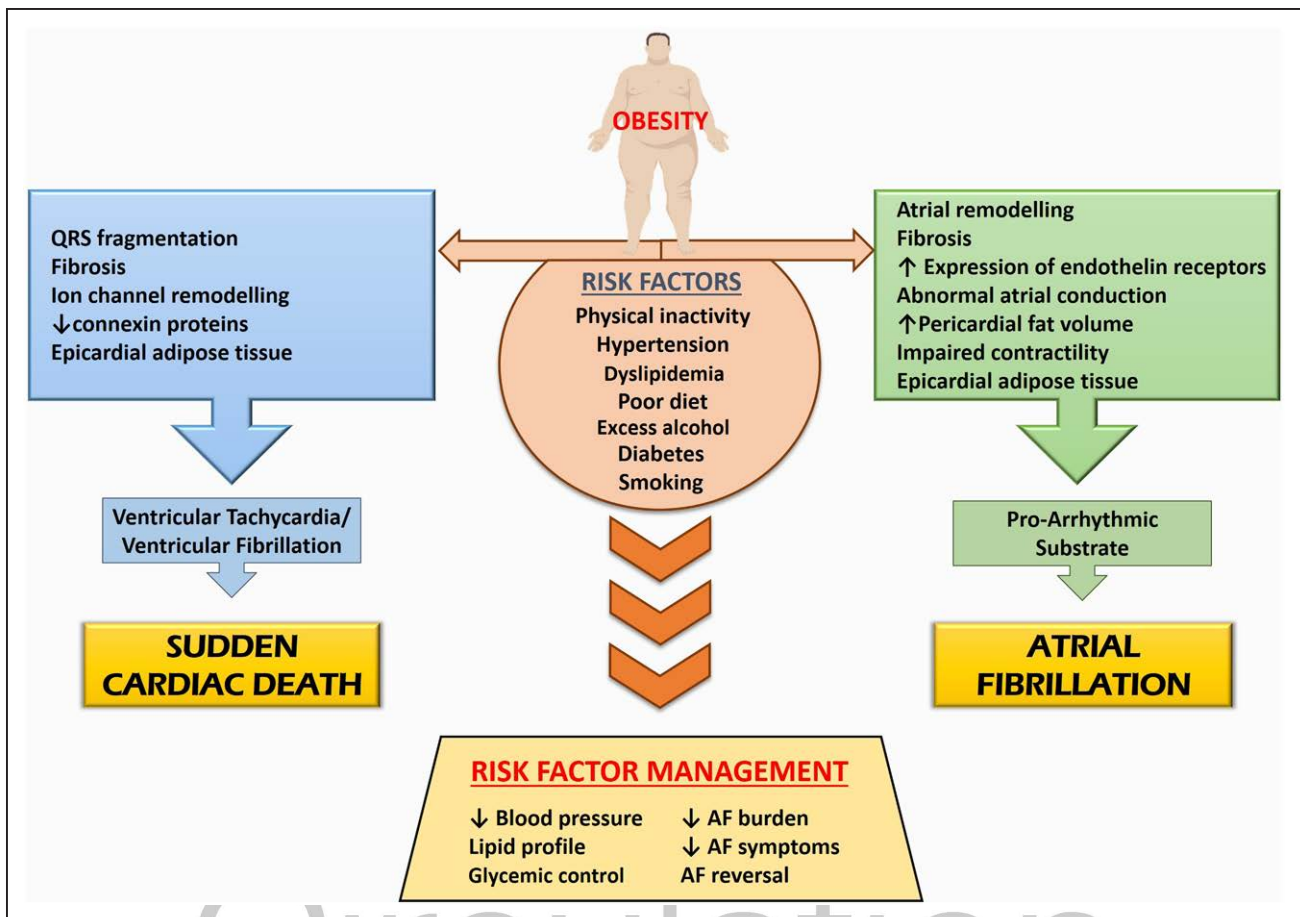
HF.<sup>177,178,237</sup> In patients with severe obesity, weight loss after bariatric surgery increases NT-proBNP (N-terminal pro-BNP) levels concomitantly with improved LVDD.<sup>252</sup> In advanced HF, extra adipose tissue and higher lean muscle mass may also provide reserves against cardiac cachexia and sarcopenia, which are associated with very poor cardiac prognosis in HF.<sup>253–255</sup> However, the exact reasons why those who have overweight and mild obesity with less severe forms of HF are also protected are not entirely clear.<sup>177–179</sup>

## Obesity and Arrhythmias

There is now compelling evidence to support the importance of excess adiposity in determining arrhythmic risk, particularly focused on SCD and AF.<sup>256,257</sup>

## Obesity and SCD

There is an established association between obesity and SCD.<sup>258,259</sup> Every 5-unit increment in BMI confers a 16% higher risk of SCD,<sup>260</sup> and obesity has been identified as the most common nonischemic cause of SCD.<sup>261</sup> Data suggest that there may be an important role for body fat distribution, implicating abdominal adiposity as a marker of SCD.<sup>259,262</sup> The potential mechanisms for this association are varied and may include LVH, QT prolongation, premature ventricular complexes, and autonomic imbalance.<sup>257,263,264</sup> Both mild obesity and severe obesity are reported to be associated with greater risk of ventricular tachycardia (VT)/ventricular fibrillation (VF)<sup>265,266</sup> and late potentials,<sup>267</sup> highlighting a role in the formation of arrhythmic substrate. Clinical data reporting the substrate for VT/VF in obesity have come largely from autopsy studies, tissue Doppler, or endomyocardial biopsy. VT/VF in obesity is associated with increased LV diameter and mass,<sup>268</sup> concentric LV hypertrophy,<sup>269</sup> LVDD,<sup>268,270</sup> and repolarization abnormalities. A common finding in obesity and obesity-mediated SCD is QRS fragmentation, a surrogate for heterogeneous conduction.<sup>271,272</sup> Both QRS fragmentation<sup>273</sup> and fibrosis<sup>274</sup> are shown to be independent predictors of SCD, indicative of a potential role in mediating reentrant ventricular arrhythmias in obesity. Mechanistic studies from animal models have identified involvement of fibrosis, ion channel remodeling, and reduction of connexin proteins as likely drivers of lethal ventricular arrhythmias and SCD. In mice, rabbit, and rat models, high-fat diet has demonstrated (1) greater frequency of ventricular arrhythmias, attributed to oxidation RyR2 (ryanodine receptor type 2) and subsequently greater RyR2 calcium release; (2) changes in oxidative stress state, calcium handling, and putative components of the mitochondrial membrane permeability transition pore<sup>275</sup>; and (3) LVH and repolarization abnormalities.<sup>276</sup> However, it remains to be determined whether these changes can be replicated in ventricles



**Figure 3.** Relationships between obesity and cardiac arrhythmias. AF indicates atrial fibrillation.

of models with established obesity. Epicardial adipose tissue was reported to be associated with higher occurrence of premature ventricular contractions, VT/VF,<sup>277</sup> and all-cause long-term mortality<sup>277</sup> and mortality from SCD.<sup>278</sup> Furthermore, epicardial adipose tissue is significantly correlated with traditional SCD and VT/VF risk factors.<sup>63,65,279–281</sup> In a post-myocardial infarction ovine model, intramyocardial adiposity and discontinuous conduction at scar borders were found to be associated with altered electrophysiological properties and higher propensity for VT.<sup>282</sup> Perhaps even more important, epicardial adipose tissue infiltrations and subsequent fibrosis (as shown in the atria) may drive reentrant circuits for lethal arrhythmias and SCD (Figure 3). Given that SCD is responsible for approximately half of all deaths resulting from CVD, obesity also represents a modifiable target to reduce the public health burden of SCD in our society. Also of clinical importance is that, in patients with obesity, the efficacy of chest compressions and airway protection may be compromised because of body habitus in case of sudden cardiac arrest, and the problem is likely to worsen as the patient's weight increases. Higher thoracic impedance associated with an increase in BMI may also reduce defibrillation success.<sup>283,284</sup> It was shown that

severe obesity is associated with higher mortality after in-hospital cardiac arrest caused by either non-VF or VF arrest if it occurs late during hospitalization, and among survivors, discharge to home is significantly lower.<sup>285</sup>

### Obesity and AF

Estimates suggest that obesity may account for one-fifth of AF cases and 60% of recently documented population increases.<sup>286–288</sup> Weight gain and a higher midlife BMI are strongly correlated with incident AF in later life.<sup>289,290</sup> Every 5-unit increment in BMI confers an  $\approx 29\%$  greater risk of incident AF.<sup>291</sup> Moreover, these figures may underestimate the impact of adiposity when body fat distribution is considered. In addition, each 5-unit increment in BMI confers a 10% increase in postoperative AF and a 13% increase in postablation AF.<sup>291</sup> Progression of the disease has also been demonstrated in the context of obesity, with a BMI in the range of 30 to 34.9 kg/m<sup>2</sup> associated with a 54% increase in the likelihood of progression from paroxysmal to permanent AF and class 2 obesity (BMI 35.0 to 39.9 kg/m<sup>2</sup>) associated with an 87% increase in risk.<sup>292</sup> Overweight and obesity elevate the risk of AF through numerous mechanisms,

including structural and electric remodeling, which contribute to development of the arrhythmogenic substrate (Figure 3). Experimental studies in the ovine model have demonstrated short-term weight gain results in progressive remodeling of the atria, including a greater deposition of fibrous tissue, a greater expression of endothelin receptors, and abnormalities in atrial conduction, which in turn resulted in greater AF inducibility.<sup>293</sup> A subsequent chronic ovine model of obesity extended these findings and described a unique component of the substrate for AF. This study demonstrated a marked increase in pericardial fat volumes. Histological samples of the atrial myocardium from regions adjacent to pericardial fat depots showed epicardial fat infiltrating the myocardium, potentially resulting in voltage abnormalities, conduction block, and higher AF vulnerability.<sup>294</sup> Clinical data also demonstrate the role of obesity and epicardial fat in the promotion of AF. Early studies demonstrated that, compared with individuals with normal weight, patients with obesity undergoing electrophysiological studies were significantly more likely to have higher left atrial pressure and volumes.<sup>295</sup> In addition, individuals with obesity had significant left atrial remodeling and impaired contractility. These features remained significant after adjustment for common cardiovascular risk factors such as hypertension, sleep apnea, and diabetes. More recently, a larger cohort who were undergoing AF ablation were studied with cardiac MRI and electroanatomic mapping of the left atrium before undergoing ablation.<sup>296</sup> This study demonstrated that there was significantly more atrial remodeling, with areas of low voltage, conduction slowing, and increased fractionation of ECGs in patients with obesity. More distinct changes were noted in regions with greater epicardial fat depots, highlighting the role of epicardial fat in the promotion of AF. Epicardial adipose tissue has emerged as an important proarrhythmic substrate that may explain the excess risk of AF in obesity.<sup>296–298</sup> The strength of associations of AF with epicardial fat is greater than for measures of abdominal and overall obesity, raising the possibility that adiposity may be more influential than previously suspected when quantified through BMI alone.<sup>299</sup> The anatomic proximity of epicardial adipose tissue to the atrial myocardium lends credence to potential paracrine signaling.<sup>300</sup> Mechanisms by which adiposity may lead to a susceptible electrophysiological substrate in the atria include fatty infiltration, adipokine-mediated fibrosis, LVDD, and inflammation, among many possibilities.<sup>301</sup>

## TREATMENT OF HF AND ARRHYTHMIAS IN OBESITY

### Lifestyle Interventions in HF and Obesity

Currently, there is little evidence that weight reduction in HF leads to better major clinical outcomes or better

survival, but weight loss may reduce symptoms and improve quality of life and other medical conditions such as sleep apnea or diabetes.<sup>237</sup> In addition, weight loss in advanced HF could improve the candidacy of patients with obesity for aggressive interventions such as LV assist device implantation and heart transplantation.<sup>240,302</sup> Clearly, higher levels of physical activity and fitness have major impacts in reducing the development of HF,<sup>243–245</sup> and in patients with established HF, high fitness is a major determinant of prognosis.<sup>177–179</sup> Among patients with HF with preserved levels of fitness, several studies show a very good prognosis, regardless of BMI.<sup>177,178,237,303–305</sup> Therefore, greater physical activity and exercise training, especially with the goal of improving fitness, are highly encouraged for individuals with obesity with HF. For elderly populations with obesity who may be at greatest risk for HF, more work is needed to develop effective strategies for maintaining weight and improving functional outcomes as opposed to weight loss interventions.

### Medications for Weight Loss in HF

Although numerous medications are currently indicated for weight loss,<sup>177,237</sup> only orlistat, a lipase inhibitor, has limited efficacy and safety for the treatment of obesity with HF.<sup>306,307</sup> Several new classes of medications originally developed for patients with type 2 diabetes have shown promise for the treatment of both obesity and HF. Glucagon-like peptide agonists (at least liraglutide)<sup>191,308,309</sup> and sodium-glucose cotransporter 2 inhibitors<sup>310</sup> have demonstrated efficacy for weight loss and reduced hospitalization for HF and cardiovascular death. Trials of these agents are currently ongoing, focusing on both patients with HFrEF and those with HFpEF with and without diabetes, with results forthcoming over the next 5 years. Recently, it was reported in individuals with overweight/obesity and HFrEF that the risk of worsening HF or cardiovascular death was lower among those who received dapagliflozin than among those who received placebo, regardless of the presence or absence of diabetes.<sup>311</sup>

### Obesity Management in Advanced HF

Advanced HF is typically considered a contraindication for bariatric surgery, but small studies of bariatric surgery have indicated improvements in LV function, myocardial mechanics, and functional classification among patients with HF with obesity.<sup>237,240,312</sup> A recent retrospective study has also suggested that bariatric surgery reduces hospitalizations for HF in patients with a history of HF.<sup>313</sup> Although recent HF guidelines have not emphasized weight reduction, these guidelines recognize the high risk associated with severe obesity.<sup>237,314</sup> Clearly, efforts to reduce obesity and, especially, to reduce the progression of obesity to class



2 or 3 levels are needed.<sup>177</sup> Class 3 obesity is a relative contraindication for heart transplantation because patients with obesity who undergo heart transplantation have higher acute rejections and higher 5-year mortality than patients with normal weight receiving heart transplantation.<sup>302</sup> However, obesity has not universally been considered a contraindication for LV assist device implantation,<sup>240</sup> although there are adverse effects of obesity such as higher drive-line infection rates, and the clinical trials generally have excluded individuals with class 3 obesity. Clearly, there are opportunities to improve weight loss efforts in patients with an LV assist device with obesity who are anticipating heart transplantation, including a multidisciplinary approach with caloric restriction, physical activity/exercise training, and even bariatric surgery, that allow greater weight loss and greater ability to perform physical activity/exercise, allowing increases in muscle mass and function, possibly facilitating LV recovery, but certainly allowing the potential for better success with heart transplantation.<sup>302</sup>

### Obesity Management and AF

Convincing data now demonstrate the benefits of weight loss in patients with AF, supporting a strong causative role for adiposity in these patients.<sup>315</sup> A randomized controlled trial of 150 individuals demonstrated that an intense weight loss and cardiometabolic risk factor management program resulted in a greater reduction in cumulative time in AF, symptom burden, and severity scores and beneficial cardiac remodeling, as evidenced by a reduction in interventricular septal dimension and left atrial area, after 15 months of follow-up.<sup>316</sup> This approach was further validated in a cohort study that resulted in an almost 5-fold higher likelihood of freedom from AF after ablation for those who attended this clinic compared with control subjects.<sup>317</sup> Concomitant improvements in numerous other cardiovascular risk factors were observed, including a reduction in blood pressure and improved lipid profiles, commensurate with weight reduction.<sup>317</sup> Long-term follow-up at 5 years demonstrated the sustainability of this approach, with individuals able to achieve a  $\geq 10\%$  reduction in body weight and having an almost 6-fold higher likelihood of freedom from AF.<sup>315</sup> In addition, a reduced propensity for progression of the disease was observed, with greater degrees of weight loss associated with a reduced likelihood of progression to more permanent forms of the arrhythmia.<sup>318</sup> Collectively, these studies prove the dynamic nature of the AF substrate and solidify the role of cardiovascular risk factor management, in addition to rate and rhythm control and appropriate anticoagulation to mitigate stroke risk, as the essential fourth pillar of AF management.<sup>319</sup>

**Table 3. Summary of Recommendations for Future Research**

Evaluation of lifestyle interventions with randomized controlled trials to identify the role of intentional weight loss and decreased visceral adiposity for improving CVD outcomes in obesity
Development of dietary interventions with large randomized controlled trials to identify healthful dietary patterns or personalized diets for CVD risk reduction in obesity
Development of upstream interventions for primary prevention and better treatment of obesity as a chronic disease among young patients with severe obesity
Identification of best practices for use of glucagon-like peptide agonists and sodium-glucose cotransporter 2 inhibitors to reduce hospitalization for HF and cardiovascular death for patients with HFrEF and HFpEF with and without diabetes
Development of effective strategies for weight maintenance and improved functional outcomes as opposed to weight loss interventions in elderly populations at risk for HF

CVD indicates cardiovascular disease; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; and HFrEF, heart failure with reduced ejection fraction.

### CONCLUSIONS

Obesity is recognized as a heterogeneous condition in which individuals with similar BMIs may have distinct metabolic and CVD risk profiles. Thus, susceptibility to obesity-related cardiovascular complications is not mediated solely by overall body fat mass but depends largely on individual differences in regional body fat distribution, which negatively affect cardiac structure and function. With increasing prevalence of obesity in populations with a longer life span, there is a need to evaluate mechanisms underlying obesity-related cardiac dysfunction and to improve the management of patients with obesity and CVD through future research (Table 3). In addition, the dramatic increase in the proportion of young patients with severe obesity invokes the need for more upstream interventions for the primary prevention and better treatment of obesity as a chronic disease.

### ARTICLE INFORMATION

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

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### Writing Group Disclosures

Writing group member	Employment	Research grant	Other research support	Speakers' bureau/honoraria	Expert witness	Ownership interest	Consultant/advisory board	Other
Tiffany M. Powell-Wiley	National Institutes of Health	NIH (funded intramural investigator at NIH)†	None	None	None	None	None	None
Paul Poirier	Université Laval, Faculté de Pharmacie Institut Universitaire de Cardiologie et de Pneumologie de Québec (Canada)	None	None	Abbott*; Amgen*; AstraZeneca*; Bausch Health*; Bayer*; Boehringer Ingelheim*; Eli Lilly*; Janssen*; Novartis*; Novo Nordisk*; Sanofi*; Servier*; HLS Therapeutics*	None	None	Amgen*; Bausch Health*; Bayer*; Boehringer Ingelheim*; Eli Lilly*; Janssen*; Novartis*; Novo Nordisk*; Servier*; Sanofi*	None
Lora E. Burke	University of Pittsburgh	NIH†	None	None	None	None	None	NIH (principal investigator)†
Jean-Pierre Després	Université Laval, VITAM – Centre de recherche en santé durable (Canada)	Fondation IUCPQ-UL (coinvestigator)†; CIHR (PI)†	None	None	None	None	None 	None
Penny Gordon-Larsen	Gillings School of Global Public Health, University of North Carolina at Chapel Hill	NIH (principal investigator)*; NIH (coinvestigator)*	None	None	None	AstraZeneca (immediate family members)*; Amgen (immediate family members)*; Johnson & Johnson (immediate family members)*; Pfizer (immediate family members)*; Merck (immediate family members)*	NIDDK*; Boston Nutrition Obesity Research Center*	None
Carl J. Lavie	Ochsner Medical Center	None	None	AstraZeneca/FARXIGA*	None	None	AstraZeneca/FARXIGA*	None
Scott A. Lear	Simon Fraser University, St. Paul's Hospital (Canada)	Robert Wood Johnson Foundation†; Hamilton Health Sciences (research contract)†	None	None	None	None	None	None
Chiadi E. Ndumele	Johns Hopkins University	NIH (grant on mechanisms linking obesity to heart failure)†	None	None	None	None	None	None
Ian J. Neeland	University Hospitals Cleveland Medical Center and Case Western Reserve University School of Medicine	NIH/NIDDK (K23 career development grant)†	None	None	None	None	Merck*	None
Prashanthan Sanders	University of Adelaide and Royal Adelaide Hospital (Australia)	None	None	None	None	None	None	None
Marie-Pierre St-Onge	Columbia University, Irving Medical Center	None	None	None	None	None	None	None

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\*Modest.

†Significant.

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Leena P. Bharath	Merrimack College	None	None	None	None	None	None	None
Kevin P. Davy	Virginia Polytechnic Institute and State University	None	None	None	None	None	None	None
Francisco Lopez-Jimenez	Mayo Clinic	None	None	None	None	None	None	None
Eric D. Peterson	Duke Clinical Research Institute	Novo Nordisk*; AstraZeneca*; Janssen†	None	None	None	None	AstraZeneca*; Janssen*	None
Stephen Sidney	Kaiser Permanente	NHLBI (1RC2HL101666, relating to surveillance of cardiovascular disease, including stroke, in the Cardiovascular Research Network)†; NINDS (1U54NS081760-01, Stroke Prevention/Intervention Program [SPIRP])†	None	None	None	None	None	None

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