JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 81, NO. 5, 2023

PUBLISHED BY ELSEVIER

THE PRESENT AND FUTURE

JACC STATE-OF-THE-ART REVIEW

Challenges in Cardiovascular Evaluation and Management of Obese Patients

JACC State-of-the-Art Review

Rosana G. Bianchettin, MD,[a] Carl J. Lavie, MD,[b] Francisco Lopez-Jimenez, MD[a]

ABSTRACT

Many unique clinical challenges accompany the diagnosis and treatment of cardiovascular disease (CVD) in people living with overweight/obesity. Similarly, physicians encounter numerous complicating factors when managing obesity among people with CVD. Diagnostic accuracy in CVD medicine can be hampered by the presence of obesity, and pharmacological treatments or cardiac procedures require careful adjustment to optimize efficacy. The obesity paradox concept remains a source of confusion within the clinical community that may cause important risk factors to go unaddressed, and body mass index is a misleading measure that cannot account for body composition (eg, lean mass). Lifestyle modifications that support weight loss require long-term commitment, but cardiac rehabilitation programs represent a potential opportunity for structured interventions, and bariatric surgery may reduce CVD risk factors in obesity and CVD. This review examines the key issues and considerations for physicians involved in the management of concurrent obesity and CVD. (J Am Coll Cardiol 2023;81:490-504) © 2023 by the American College of Cardiology Foundation.

Physicians face a multitude of clinical challenges when managing cardiovascular disease (CVD) in people with overweight/obesity, from diagnosis through to long-term treatment, because of the complex, multifaceted, and progressive nature of obesity and its impact on CVD outcomes (**Figure 1**).[1,2] Obesity is a heterogenous chronic condition affecting many people seen in the cardiology department, and although the World Health Organization defines the severity of obesity according to body mass index (BMI), a range of anthropometric measures that more accurately capture central adiposity (eg, waist-hip ratio, waist circumference) may provide better means of assessing the associated CVD risk.[3-13] Overweight, obesity, and severe class III or (previously called) morbid obesity are typically described as having a BMI of 25-29.9, ≥30, and ≥40 kg/m^2, respectively, for Caucasian individuals, whereas lower thresholds exist for Asian populations.[8,14] Direct and indirect obesity-related mechanisms raise CVD risk via multiple pathways involving structural, functional, humoral, and hemodynamic alterations associated with the onset of cardiometabolic disease and complications associated with fat mass.[1,13]

People with CVD and overweight/obesity often need support to understand and address their level of CVD risk, and a long-term multidisciplinary approach may be required to achieve and maintain a healthier body weight. This narrative review explores the unique clinical challenges relating to the management of CVD in the setting of obesity as well as the

Listen to this manuscript's audio summary by Editor-in-Chief Dr Valentin Fuster on www.jacc.org/journal/jacc.

From the [a]Division of Cardiovascular Diseases, Mayo Clinic, Rochester, Minnesota, USA; and the [b]John Ochsner Heart and Vascular Institute, Ochsner Clinical School, The University of Queensland School of Medicine, New Orleans, Louisiana, USA.
The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received August 31, 2022; revised manuscript received October 12, 2022, accepted November 2, 2022.

ISSN 0735-1097/$36.00 https://doi.org/10.1016/j.jacc.2022.11.031

HIGHLIGHTS

- Obesity presents unique challenges to diagnosis and management of patients with known or suspected CVD.
- Excess adiposity can impede the performance and reduce the accuracy of standard modalities for diagnosis of cardiovascular disease.
- Weight reduction is an important adjunct to reduction of cardiovascular risk and management of CVD in obese patients, and when other measures are insufficient, bariatric surgery can improve outcomes.

key issues to consider when addressing obesity among people living with CVD. The **Central Illustration** presents an overview of the reciprocal clinical issues associated with the concurrent management of CVD and obesity, and this review focuses on patient-centric and evidence-based approaches to care for the improvement of treatment outcomes and quality of life.

COMMON DIAGNOSTIC TESTS IN CVD MEDICINE: CHALLENGES IN THE SETTING OF OBESITY

Multiple technologies are available for the assessment and diagnosis of obesity-related CVD, although the presence of adiposity can negatively affect the accuracy and performance of these modalities (**Table 1**).[15-19] Thick layers of soft tissue can make it difficult to access intravenous routes for imaging techniques.[18] Large cannula venous lines (eg, 18-gauge) and placement in larger caliber veins help to improve vascular opacification, enabling greater injection rates and lowering the probability of contrast media extravasation.[18]

ELECTROCARDIOGRAPHY. Morphological changes induced by obesity and technical challenges may negatively affect the diagnostic performance of electrocardiography. These include displacement of the heart (resulting from an elevated diaphragm in the supine position), cardiac hypertrophy (caused by increased cardiac workload) and widening of distance between the heart and the recording electrodes caused by the accumulation of fat in the chest wall subcutaneous tissue (and possibly increased epicardial fat).[19] Other complicating factors include chronic lung disease (potentially secondary to obstructive sleep apnea [OSA]/hypoventilation syndrome), low QRS voltage and leftward trend in the axis, nonspecific flattening of the T-wave in the inferolateral leads, and an increased incidence of false-positive criteria for inferior myocardial infarction.[19]

TRANSTHORACIC ECHOCARDIOGRAPHY. Transthoracic echocardiography will be limited in the presence of poor acoustic windows related to body habitus.[20] The thicker layer of subcutaneous adipose tissue in the thorax increases the depth needed to identify cardiac structures and deeper ultrasound beams require lower ultrasound frequency, decreasing spatial resolution. Differentiation between subepicardial adipose tissue and pericardial effusion can be difficult in people with obesity. Epicardial adipose tissue is a common cause of false-positive effusion (pseudo pericardial effusion).

STRESS TESTING. The accuracy of exercise stress test data may be suboptimal or compromised by lower heart rates and double product at maximal effort, because many people with obesity have difficulties in exercising.[17] ECG signals tend to have lower voltages in people with significant obesity, which can theoretically lower the sensitivity of tests conducted to identify ischemic ECG changes. Treadmill weight limits may be prohibitive (300-400 pounds, depending on the manufacturer), and single photon emission computed tomography scanning may be hampered by restricted table weights (<300-400 pounds, depending on the supplier) and limitations on radioisotope dosing because larger people require doses that exceed the maximum allowable level (usually calculated according to weight in mCi/kg).[18] Radioisotopes are degraded by the scatter of photons within the soft tissues, causing the signal-to-noise ratio to be decreased in the presence of excess adipose tissue.[18] Thalium-201 myocardial perfusion imaging accuracy is also reduced with increasing BMI.[17] Echocardiogram-based stress test has the same limitations inherent to obesity and ultrasound described in the previous text, and many institutions now recommend the positron emission tomography stress test for people with BMI >40 kg/m^2 because this method is considered to be minimally affected by body habitus, compared with other modalities. Studies examining the use of transesophageal dobutamine stress echocardiography with an adapted accelerated infusion protocol suggest that this approach may be useful for severely obese individuals.[21]

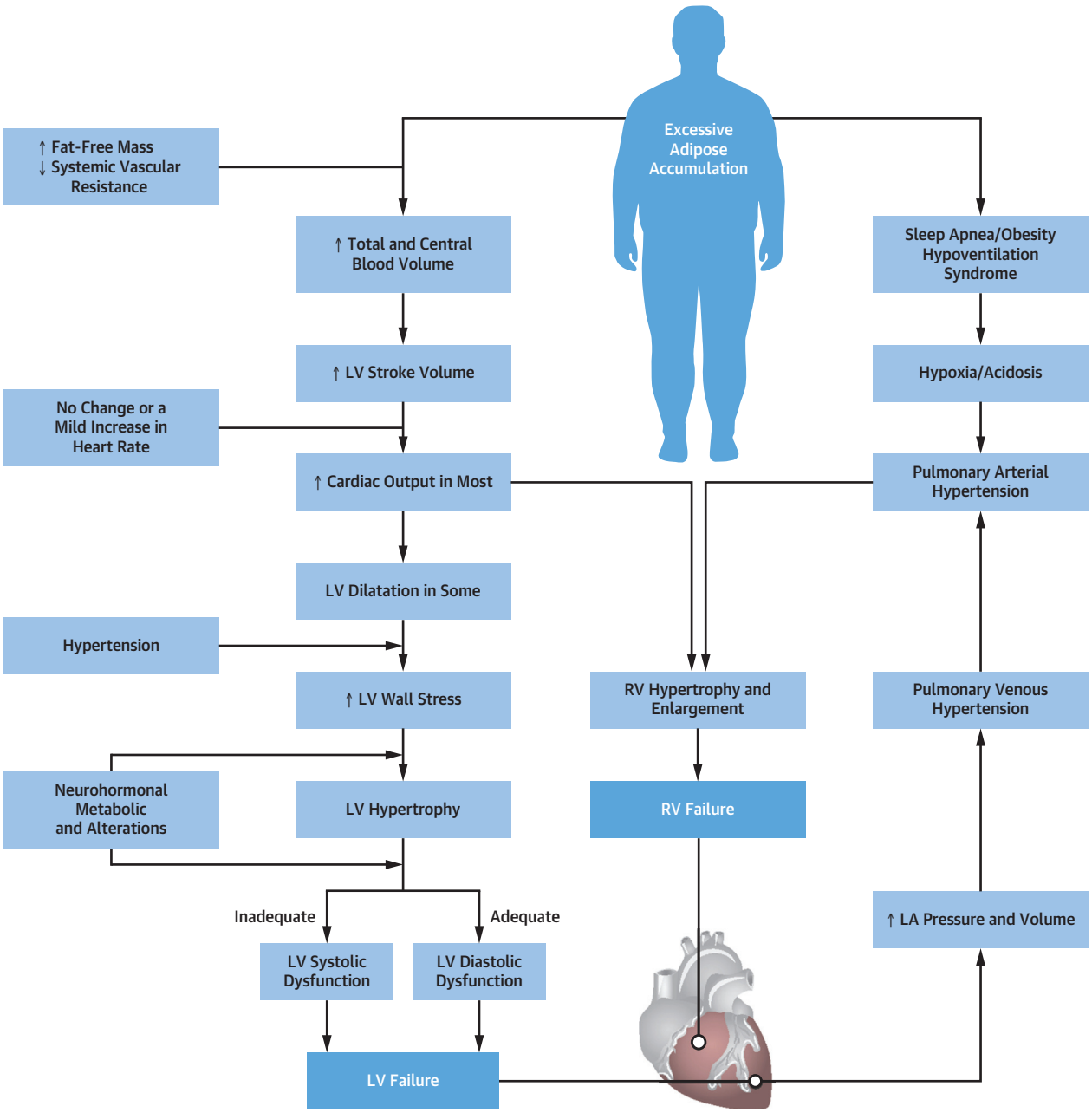
COMPUTERIZED TOMOGRAPHY CORONARY ANGIOGRAPHY. Computerized tomography coronary angiography

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation
BMI = body mass index
CHD = coronary heart disease
CMR = cardiac magnetic resonance
CVD = cardiovascular disease
DOAC = direct-acting oral anticoagulant
GFR = glomerular filtration rate
HF = heart failure
OSA = obstructive sleep apnea
T2DM = type 2 diabetes mellitus

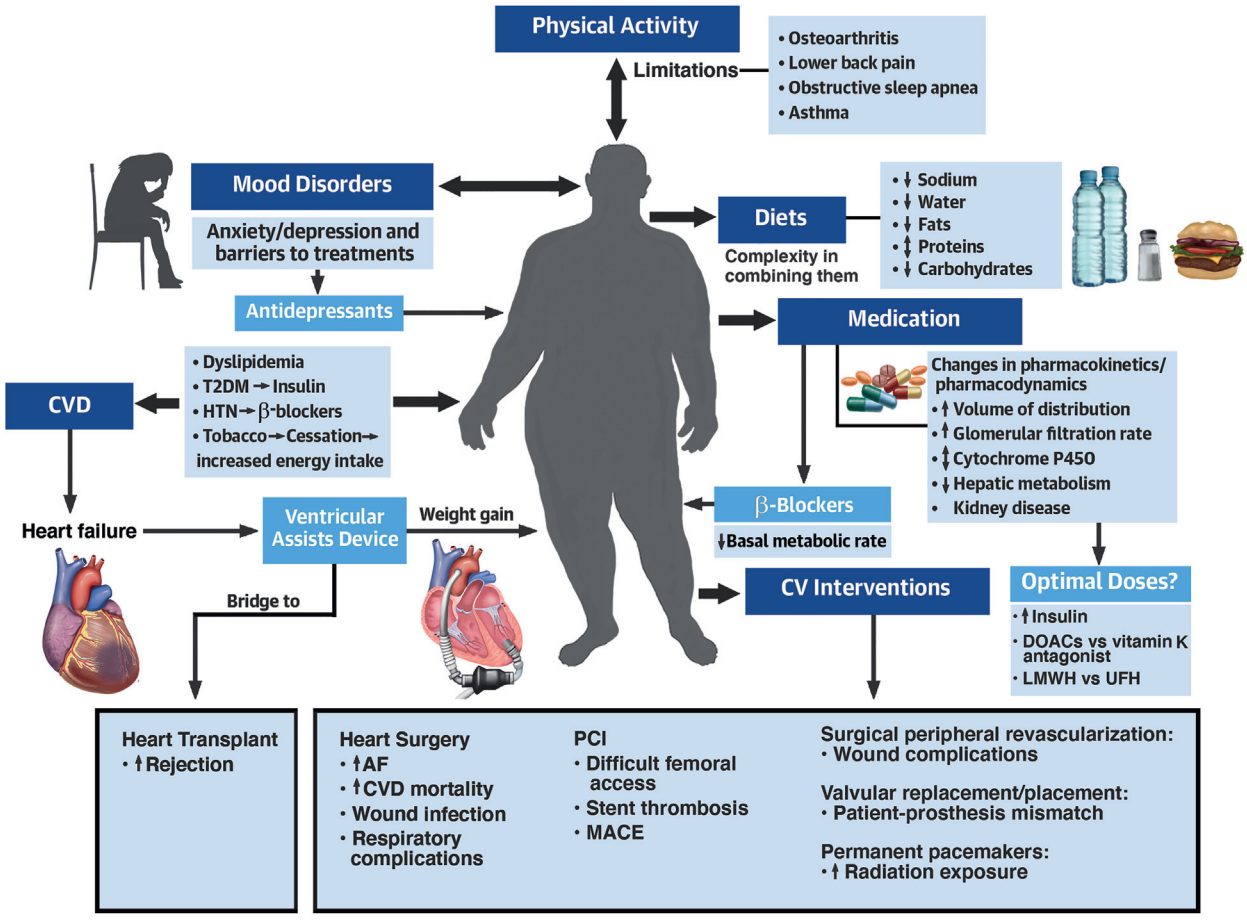
JACC VOL. 81, NO. 5, 2023
FEBRUARY 7, 2023:490–504

FIGURE 1 **Obesity and Cardiovascular Disease: Proposed Pathophysiology of Obesity Cardiomyopathy**



This diagram shows the central hemodynamic alterations that result from excessive adipose accumulation in severely obese patients and their subsequent effects on cardiac morphology and ventricular function. Left ventricular (LV) hypertrophy in severe obesity may be eccentric or concentric. Factors influencing LV remodeling and geometry include severity and duration of obesity; duration and severity of adverse LV loading conditions (particularly hypertension); and, possibly, neurohormonal and metabolic abnormalities such as increased sympathetic nervous system tone, activation of the renin-angiotensin-aldosterone system, insulin resistance with hyperinsulinemia, leptin resistance with hyperleptinemia, adiponectin deficiency, lipotoxicity, and lipoapoptosis. These alterations may contribute to the development of LV failure. LV failure, facilitated by pulmonary arterial hypertension from sleep apnea/obesity hypoventilation, may subsequently lead to right ventricular (RV) failure. Figure provided with kind permission from Lavie et al.[2] LA = left atrial.

CENTRAL ILLUSTRATION Clinical Challenges in People With Obesity and CVD



Bianchettin RG, et al. J Am Coll Cardiol. 2023;81(5):490–504.

The **direction of the arrows** represents the causal relationship. CVD = cardiovascular disease; DOAC = direct oral anticoagulants; HTN = hypertension; LMWH = low molecular weight heparin; MACE = major adverse cardiovascular events; PCI = percutaneous intervention; UFH = unfractionated heparin.

image quality degrades with rising BMI, and this type of angiography testing is usually precluded in people with BMI >40 kg/m^2.[16,20] Dual-source computerized tomography coronary angiography, using a specific obesity protocol, has shown improvement in image quality and noise when the radiation dose is elevated by 32% to 54%.[15,16] However, limits remain in place regarding table weight (standard computerized tomography table limits are usually 450 lbs/205 kg) and gantry diameter.[20,22]

CARDIAC MAGNETIC RESONANCE IMAGING. Equipment bore size can be restrictive for people with obesity undergoing cardiac magnetic resonance imaging (CMR), and the experience may induce claustrophobia.[16] Intolerance to repeated breath holding and the extended distance between the heart and chest coils reduces image quality.[16] Despite these issues, CMR is a diagnostic technique that is relatively unaffected by obesity.[20]

INTERVENTIONAL RADIOLOGY. Technical challenges associated with image-guided interventional procedures for people with obesity include visualization of the target areas, the available length of equipment (which may be too short) and accommodation of larger people within the computerized tomography or CMR scanners.[18] As highlighted in the previous text, higher doses of radiation may be required for larger individuals who would typically also need an elevated sedative dose before the intervention.[18] These challenges raise safety concerns for persons

TABLE 1 A Summary of Key Obesity-Related Challenges That May Affect the Diagnostic Performance of Cardiovascular Modalities

Cardiovascular Modality	Obesity-Related Challenges Affecting Diagnostics
Electrocardiogram	Displacement of the heart (because of elevation of the diaphragm in the supine position) Increased cardiac workload and associated cardiac hypertrophy Widening of distance between the heart and the recording electrodes Chronic lung disease Low QRS voltage + leftward trend in the axis Nonspecific T-wave flattening Increased incidence of inferior MI false-positive criteria Increased heart rate
Transthoracic echocardiography	Poor acoustic window (caused by pulmonary disease, body habitus and respiratory motion) Differentiation between subepicardial adipose tissue and pericardial effusion Epicardial adipose tissue (pseudo pericardial effusion) and pericardial fluid underestimation Adipose depots within the heart tissue
Stress testing	
Exercise echocardiography	Low sensitivity Difficulty exercising
SPECT	Table weight limits Radioisotope dosing limits Reduced signal-to-noise ratio
Thalium-201 myocardial perfusion imaging	Reduced accuracy
CTCA	Precluded in people with BMI >40 kg/m^2
CMR	Restrictive bore size Claustrophobia Reduced quality of image Extended distance between heart and chest coils
Interventional radiology	Poor visualization of target areas Restricted length of equipment Accommodation of larger individuals within CT or CMR scanners Radioisotope dosing limits Safety concerns regarding dosing where multiple procedures are required

CMR = cardiac magnetic resonance; CT = computerized tomography; CTCA = computerized tomography coronary angiography; MI = myocardial infarction; SPECT = single photon emission computed tomography.

undergoing various procedures, and clinicians should consider the provision of additional support during the postintervention recovery period.[18]

THERAPEUTIC CHALLENGES IN PEOPLE WITH CVD AND OBESITY

Pharmacological, procedural, and lifestyle interventions for CVD are associated with numerous challenges when treating a person with obesity. Table 2 summarizes some of the key therapeutic aspects that may be affected.[23-40]

PHARMACOLOGY IN OBESITY AND CVD. Obesity brings additional complexity to CVD prescribing as a consequence of altered pharmacokinetic and pharmacodynamic factors, as well as metabolic changes and obesity-related multimorbidity, such as the onset of type 2 diabetes mellitus (T2DM).[24,29,41-66]

PHARMACOKINETICS IN PEOPLE WITH OBESITY. Data are currently lacking regarding the influence of obesity on drug pharmacokinetics, but the parameters most affected are volume distribution and clearance. Drug affinity for adipose tissue will vary and will be unique to the properties of the individual agent (eg, lipophilicity, polarity). Distribution will therefore be affected by the absolute volume and proportion of adipose tissue.[41] Because lipophilic drugs (eg, steroids, tricyclic antidepressants) have a higher volume distribution in people carrying greater fat mass, tissue perfusion will be reduced, and both the half-life and clearance may be altered.[41,66] Physiological changes associated with rising body weight influence drug elimination.[41,42,66] Greater cardiac output and increased blood flow to the liver and kidneys can maintain or elevate clearance in people with obesity who do not have hepatic or renal failure, and those with nonalcoholic fatty liver disease will have reduced hepatic blood flow and lower drug elimination rates.[41,42,66] Studies indicate that the activity of cytochrome P450 (CYP450) 3A4 decreases in individuals living with obesity, whereas CYP450 2E1 activity is raised.[43] Mild-to-moderate obesity is associated with an increase in effective renal plasma flow and glomerular filtration rate (GFR), and overweight/obesity is linked with hyperfiltration and hyperperfusion in the kidneys, but there is an absence of convincing evidence regarding the impact on renal drug clearance.[44,66] Microalbuminuria is highly prevalent in people with obesity (without T2DM), suggesting the involvement of renal hyperfiltration.[45] Studies conducted in populations of African descent living with obesity have shown that GFR, effective renal plasma flow, and filtration fraction are typically elevated and prevalence of glomerular hyperfiltration is higher compared with normal weight populations.[46] Initial rises in GFR are not necessarily associated with increased renal drug clearance, and this might be explained by the long-term decline in GFR observed in many individuals resulting from persistent elevation of intraglomerular pressure.[48] In practice, estimation of GFR for dose-adjustment purposes should consider total body weight for moderate to highly lipophilic agents and lean body weight for calculations relating to renal clearance in chronic dosing regimens.[42,49] Corrections for lean body weight or use of the ideal body weight should be applied for initial dosing of some drugs to minimize the overdose risk.[50] Adjustments for hydrophobic drugs are best calculated using the ideal body weight or the percentage in excess of this value.[50] Initial doses of lipophilic agent are complex to adjust according to body size because not all of the drug will inevitably be distributed extensively in the adipose tissue, and it may be appropriate to correct

TABLE 2 Therapeutic Challenges in People With CVD and Obesity

Therapeutic Factors	Challenges in People With CVD and Obesity
Lifestyle modifications	
Diets	Multiple and conflicting dietary recommendations: low calorie, high/low protein, low fat, low sodium, low fluids, high/low green vegetables.
Physical activity	Obstacles to regular exercise participation with obesity: • Lower back pain, knee or hip osteoarthritis; • Sever deconditioning, leading to significant dyspnea; • OSA: increases feelings of tiredness; • Asthma.
Smoking cessation	Induces weight gain and increases risk of T2DM because of increased food intake and decreased suppressant effects of nicotine from the central nervous system.
Pharmacology	Tailoring pharmacotherapy is difficult because of unique pharmacokinetics and pharmacodynamics factors in people with obesity that alter distribution, metabolism, and elimination of drugs. Each drug also has special properties that must be considered when it is administrated.
Pharmacokinetics	Increase volume of distribution: increase in fat mass generates higher volume of distribution of lipophilic drugs. The loading dose of drugs with distribution restricted to lean tissues should be based on the ideal body weight of patients with obesity. Increase/decrease hepatic metabolism: increase hepatic blood flow. In the presence of nonalcoholic fatty liver disease, blood flow decrease. Activity of CYP450 3A4 decreases and CYP450 2E1 activity increases. Obesity can increase renal clearance caused by higher cardiac output. It can also lead to kidney disease resulting in lower GFR.
Pharmacodynamics	Disparities in receptor expression and affinity. Excessive adipose tissue increases intrinsic insulin cleaving activity, leading to increase insulin requirements. Increased tumor necrosis factor-α, increases insulin resistance. Metabolic syndrome is related to high on-treatment platelet reactivity. Antiplatelet therapy should be tailored to each patient. Prasugrel and ticagrelor seems to have better platelet inhibition. Anticoagulants: difficult to determine optimal dose. Thromboembolism vs bleeding. DOACs do not have label indications on dose adjustment for body weight. Limited data on LMWH and unfractionated heparin. Beta-blocker therapies have a metabolism impact and weight gain. Reduction in resting and total energy expenditure, increased feelings of tiredness, decreased exercise tolerance, and nonexercise thermogenesis. Avoid metoprolol tartrate. HTN treatment: first line would be ACEI or angiotensin II receptor blocker.
Cardiac procedures	
PCI	Difficult femoral access and hemostasis. Radial arterial access is preferred. Higher risk of stent thrombosis, especially after bare-metal stent implantation.
Open heart surgery	Higher CVD mortality in BMI $\geq$35 kg/m^2. Higher AF events. Increased risk of wound infection resulting from larger incisions, decreased blood supply within the adipose tissue and less sternal blood supply caused by bilateral use of the internal mammary artery. Increased risk for mediastinitis, acute renal failure, prolonged ventilation, pneumonia, and VTE.
Surgical peripheral revascularization	Increased risk for wound complications, surgical site infections, graft failure, and sepsis.
Valvular replacement	Higher risk for patient-prosthesis mismatch when body surface area is used.
Heart transplantation	High risk for rejection.
Therapeutic measures	May lead to weight gain or make weight loss more difficult.
Smoking cessation	Weight gain leads to reduced glycemic control. People with diabetes who quit smoking may need closer metabolic follow-up.
Insulin therapy	The anabolic effect of insulin leads to an increase in truncal fat mass. It increases energy intake linked to a fear of hypoglycemia. Reduction in glycosuria, central effects on weight, and appetite regulation. Insulin therapy may generate hyperphagia and weight gain by reducing hypothalamic (arcuate nucleus) signaling and increasing anabolic peptides like neuropeptide Y and Agouti-related peptide. Insulin detemir is associated with least weight gain.
Beta-blockers	Insulin resistance and increased risk of developing T2DM. Other effects mentioned above.
VADs	Significant weight gain after implantation.
Bidirectional relationship	
Antidepressants	Depression has a strong relationship with obesity and some forms of CVD. At the same time, antidepressant therapy may promote weight gain.
Physical activity	PA is effective in the prevention of overweight and obesity, and also plays a key role in their treatment. Physical limitations and lack of adherence may worsen negative feedback.
CVD	Obesity is a main risk factor for developing CVD, but at the same time, CVD may be a limiting factor to weight loss. Not only for the detrimental effects of CVD but also for the side effects of therapeutic measures on weight management.

Multiple complications are associated with treatment, lifestyle options and cardiac procedures when managing CVD in people with obesity, with some aspects of management having a bidirectional relationship that can either exacerbate or improve CVD, obesity, and associated comorbidities.[23-40]

ACEI = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; BMI = body mass index; CVD = cardiovascular disease; CYP450 = cytochrome P450; DOAC = direct oral anticoagulants; GFR = glomerular filtration rate; HTN = hypertension; LMWH = low molecular weight heparin; OSA = obstructive sleep apnea PCI = percutaneous intervention; T2DM = type 2 diabetes mellitus; VAD = ventricular assist device; VTE = venous thromboembolism.

for lean body weight and index GFR for height.[50,51] The use of lean body weight appears to be the most practical approach when estimating creatinine clearance for drug dosing in people with overweight/obesity.[47]

PHARMACODYNAMIC CONSIDERATIONS WHEN TREATING PEOPLE WITH OBESITY AND CVD. Data are relatively scarce regarding the impact of obesity on pharmacodynamic factors, and each person will respond differently to any given drug as a result of disparities in receptor expression and affinity.[53] For example, higher insulin doses are required for some people with overweight/obesity because adipose tissue has an elevated intrinsic insulin cleaving activity, and excessive production of tumor necrosis factor-α in these individuals perpetuates insulin resistance.[53] Metabolic syndrome powerfully influences antiplatelet treatment response and might offer a better predictive measure of risk for people with obesity than BMI because it is associated with greater incidence of high on-treatment platelet reactivity as well as lower bleeding complications among people with BMI >30 kg/m^2, compared with those of normal weight.[42] This was described for clopidogrel and prasugrel in a study showing that prasugrel had superior efficacy and significantly lower high on-treatment platelet activity.[54] Increasing the dosage of clopidogrel (600 mg) has not been shown to inhibit platelet aggregation in overweight patients to the same extent as in normal-weight patients.[67] Although other studies suggest that ticagrelor performs better in terms of platelet inhibition, with no BMI correlation, more data and studies with larger samples are necessary to support recommendations about tailoring antiplatelet therapy in people with obesity.[68]

DOSING OF ANTICOAGULANTS IN OBESITY. Clinicians prescribing anticoagulant medications for people with obesity face difficulty in identifying the optimal dose to prevent venous thromboembolism (VTE) and ischemic stroke in individuals with nonvalvular atrial fibrillation (AF), while also avoiding bleeding. Direct-acting oral anticoagulants (DOAC), such as dabigatran, apixaban, edoxaban, and rivaroxaban, are efficacious with a good safety profile, but their licensed indications do not include instructions on dose adjustment for body weight or BMI. Each DOAC has unique pharmacokinetic characteristics, and when administered to people with obesity, there may be a risk of underdosing caused by decreased drug concentration.[55] A study of dabigatran showed that drug concentration was lowered by 20% in people with body weight >100 kg.[69] The ENGAGE AF-TIMI 48 (Effective aNticoaGulation with factor xA next Generation in Atrial Fibrillation-Thrombolysis In Myocardial Infarction study 48) trial indicated that edoxaban concentration did not vary significantly according to BMI, but women with high BMI were at increased risk of bleeding events compared with those with normal BMI.[70] In 2016, The International Society for Thrombosis and Haemostasis recommendations stated that DOAC treatments may be unsuitable for individuals with BMI >40 kg/m^2 (or those weighing >120 kg), and drug monitoring should be used where DOAC agents are prescribed in this population.[55] Unfortunately, drug monitoring facilities may not be available at all institutions. If levels dip below the expected range, a vitamin K antagonist might be appropriate rather than adjustment of the DOAC dosage.[55] Occurrences of VTE, pulmonary embolism, deep vein thrombosis, and bleeding within 12 months of an admission are considered to be similar when either DOAC or warfarin treatment are used in the obesity setting, although the evidence is limited with extreme degrees of severe obesity.[56]

Disparities exist concerning the optimal dosing of low molecular weight heparin treatments, and most studies focus on the use of enoxaparin. For people with BMI <40 kg/m^2 who are undergoing bariatric surgery, enoxaparin is recommended at 40 mg once daily for thromboprophylaxis.[57] The dose should be increased to 40 mg twice daily for those with BMI ≥40 kg/m^2.[57] In the case of nonbariatric surgery, enoxaparin may be considered for thromboprophylaxis at a dose of 0.5 mg/kg once or twice daily (or tinzaparin 75 IU/kg), although data are limited to support this recommendation.[57] Weight-based dosing of enoxaparin (1 mg/kg twice daily) is recommended in the treatment setting for people with BMI <40 kg/m^2, whereas reduced weight-based dosing should be applied when calculating the dosage if BMI is ≥40 kg/m^2.[57]

Studies examining the use of unfractionated heparin prophylaxis against VTE support dosing at 5,000 U subcutaneously every 8 hours in people weighing <100 kg, but data are limited in people with BMI ≥40 kg/m^2.[58] It is important to note that elevated doses (7,500 U subcutaneously every 8 hours) may increase the risk of major bleeding without providing additional protection against VTE in people weighing ≥100 kg.[59,60]

BETA-BLOCKER THERAPIES AND THEIR IMPACT ON METABOLISM. People prescribed beta-blocker therapies for hypertension and heart failure (HF) experience a mean weight gain of 1.2 kg, making the management of body weight and its associated

CVD risk ever more complex.[25,27,29,62,65] Data indicate that metoprolol tartrate is associated with weight gain in people who already have overweight/obesity, although carvedilol does not appear to have the same effect.[63,71] Proposed mechanisms for beta-blocker-related weight gain indicate a reduction in resting and total energy expenditure by approximately 4% to 6% (100-200 kcal/d).[29] Basal metabolic rate is reduced by up to 12%, diet-induced thermogenesis is suppressed by 50%, and fat oxidation rate reduced by 32%.[29,64] Individuals treated with beta-blockers often experience increased levels of tiredness, have poorer exercise tolerance, and have lower nonexercise thermogenesis.[29] Insulin resistance will be exacerbated in these individuals and their risk of developing T2DM can rise by as much as 28%.[27,29,61]

CHALLENGES DURING CARDIAC PROCEDURES. The relationship between BMI and outcomes following cardiac procedures is complex.[30] Obesity appears to be associated with better outcomes in the short term, but studies have shown that long-term mortality risk may be similar (at best) or worse for people with moderate-severe obesity compared with normal weight individuals.[72,73] These data reflect the concept of the obesity paradox, which we discuss in more detail later.

PERCUTANEOUS INTERVENTIONS. People with obesity undergoing percutaneous intervention usually have a lower rate of bleeding events compared with people of normal weight, which may be a consequence of earlier diagnosis (younger age) and treatment, and renal function being relatively unaffected by the aging process.[30] In addition, people with obesity are likely to receive a lower dose of antithrombotic medications relative to their body mass, because most are not dosed according to body weight.[30] Although BMI is not a predictor of 5-year mortality or CVD mortality in people undergoing percutaneous intervention, population-based data reveal underweight/normal-weight individuals to be significantly more likely to have renal failure and peripheral vascular disease at the time of the intervention.[74,75] Improved outcomes in people with obesity might also, in part, be caused by the greater likelihood of receiving guideline-recommended medical therapy within 12 months of intervention.[74]

It is generally more difficult to establish femoral access and achieve hemostasis in individuals with obesity, but radial arterial approaches are used marginally more often in these cases and can help to overcome issues.[30,76] Bleeding complications and access site injuries occur significantly less in people with BMI >40 kg/m^2 when using a transradial approach.[77]

Studies indicate that BMI is a predictor of stent thrombosis following implantation, although appropriate stent type selection may help correct the risks in some cases.[78] People with BMI >30 kg/m^2 have higher rates of major adverse cardiac events and 9-month angiographic stenosis following bare-metal stent implantation.[78]

OPEN HEART SURGERY IN PEOPLE WITH OVERWEIGHT/OBESITY. The association between BMI and open heart surgery outcomes is complicated. Studies reveal total mortality to be highest among postcoronary artery bypass graft recipients with low BMI, although CVD mortality is greatest among those with severe obesity (BMI ≥35 kg/m^2) when followed up over 1.8 years, potentially as a consequence of extensive coronary heart disease (CHD) and increased postoperative complications in those with severe obesity.[31] For each 5-unit increase in BMI, AF may be increased by 10% to 29% after cardiac surgery and catheter ablation.[79] Individuals with severe obesity undergoing coronary artery bypass graft are, on average, 4 years younger than normal weight graft recipients, which might be related to earlier onset of CHD secondary to other high-risk CVD factors and metabolic disorders.[31] Although there is no difference regarding in-hospital outcomes following coronary artery bypass graft according to body weight, each unit BMI increase is associated with a higher (11%) adjusted risk of 5-year CVD mortality, and people with obesity are more likely to have multiple CHD risk factors.[73] Over 5 years of follow-up, people with BMI ≥35 kg/m^2 have a higher overall mortality rate.[80]

Studies including people with BMI >40 kg/m^2 have shown an unequivocal increased risk of mortality (risk-adjusted OR: 1.57; $P = 0.02$) following cardiac surgery, compared with people of normal weight.[32] They also have a greater risk of complications like superficial and deep sternal wound infection. This is because of the need for larger incisions in intertriginous areas that have a relatively poor circulatory supply within the adipose tissue and bilateral use of the internal mammary artery that reduces sternal blood supply. Other complications are mediastinitis, acute renal failure (2-fold increase in risk), prolonged ventilation, pneumonia, and VTE.[32,79,81]

Data from a cohort of 7,446 people undergoing coronary artery bypass showed that greater waist circumference was significantly associated with adverse clinical events, independently of BMI, indicating that measures of central adiposity are

likely to be useful in predicting risk during cardiac surgery.[82]

SURGICAL PERIPHERAL REVASCULARIZATION. Systematic review data indicate that people with BMI ≥30 kg/m² have a lower 30-day postoperative mortality rate and fewer 30-day cardiac and respiratory complications following vascular surgery compared with people of normal weight.[83] These data suggest, once again, that factors involved in the obesity paradox (eg, younger age, earlier presentation, less comorbidities) influence surgical outcomes in this group. However, wound complications and surgical site infections are more prevalent in people with obesity, which may increase occurrence of graft failure, limb salvage, and sepsis and can affect recovery and the ability to return to functional health.[83,84]

VALVULAR REPLACEMENT OR PLACEMENT AND PERMANENT PACEMAKERS. Patient-prosthesis mismatch can occur following cardiac valve replacement or implantation when body surface area is used to index aortic valve area for individuals with obesity because valve area is more dependent on height than on body weight, leading to selection of inappropriately small valves for the size of the subject.[85-87] Electronic cardiac device implantation may be conducted safely and effectively in people with obesity, with the presence of additional subcutaneous fat potentially providing protection against pneumothorax, although radiation exposure in this group will be significantly higher.[88]

HEART TRANSPLANTATION, VENTRICULAR ASSIST DEVICES, AND OBESITY. The 2016 International Society for Heart Lung Transplantation criteria for heart transplantation recommended weight loss for people with BMI ≥35 kg/m² before heart transplantation listing because higher BMI is associated with worse outcomes after surgery, including shorter time to high-grade acute rejection and increased annual high-grade rejection frequency.[33,34] People with advanced HF receive ventricular assistance devices either as a destination or "bridge to weight loss" strategy. Significant weight gain (≥10%) has been observed in people with BMI ≥35 kg/m² following implantation of a ventricular assistance device.[34] However, a systematic review and meta-analysis showed that ventricular assistance devices recipients with obesity could improve candidacy for heart transplantation through weight loss programs that include bariatric surgery.[89]

CHALLENGES IN MAKING LIFESTYLE MODIFICATIONS. Reduction in body fat and maintenance of a healthier weight requires high and prolonged commitment on the part of the person with obesity in general, and more so in people with CVD. Additional challenges are presented when balancing the complexity of specific dietary approaches for each of the conditions/comorbidities that an individual may be living with (eg, T2DM, HF, end-stage kidney disease, hypertension). Some long-standing dietary recommendations (eg, low protein intake for people with proteinuria) have been challenged in trials. For example, low-calorie, high-protein diets have shown benefit for renal function and proteinuria among those who have diabetic nephropathy and obesity.[90] Such approaches might include supplementation of a healthy diet with a formula-based nutrition system (eg, high-protein drink) to achieve weight reduction and potential renal function benefits in the short term.[90] Despite theoretical concerns in people with advanced systolic HF and lower survival rates related to normal or low weight in this population, reduction in body fat could help to resolve comorbid conditions and improve access to heart transplantation or mechanical support.[91] Although dietary advice usually focuses on restriction of sodium and fluid intake, no clinical trials have specifically examined calorie-controlled weight loss models in the HF setting.[91] Sometimes diet recommendations given by different specialists become a complex and confusing puzzle that the patient must solve.

Emerging data suggest that some newer pharmacotherapies for weight loss may be of value when used alongside existing lifestyle interventions for overweight/obesity, and a number of clinical trials are ongoing to examine the impact of such treatments on CVD risk and mortality (eg, the SELECT [Semaglutide Effects on Heart Disease and Stroke in Patients With Overweight or Obesity; [NCT03574597]).[92,93]

Certain drugs make weight loss more challenging, even when consistent efforts are made regarding diet. People with overweight/obesity and T2DM under insulin treatment can experience weight gain through multiple mechanisms.[23,26,28,94] People taking beta-blockers may put on weight, as we have already discussed.[62] Studies suggest that around 48% of people with HF experience depressive symptoms, and antidepressant therapies should be chosen carefully to avoid side-effects such as weight gain.[95,96]

BARIATRIC SURGERY AND CVD. Bariatric surgery should be considered as an alternative approach to reducing CVD risk in those with class II to III obesity, and as a means of lowering 10-year risk of CVD events and death.[97] Studies indicate that bariatric surgery is associated with lower incidence of major adverse CVD

events, death, new myocardial infarction, and new-onset HF in people with CVD and obesity when conducted by experts at specialized centers, and large-scale randomized trials would be of value in corroborating these data.[98,99] A study examining treatment outcomes in a cohort of 189,770 Medicare beneficiaries with obesity, followed up over 4 years, showed that bariatric surgery was associated with risk reduction for all-cause mortality (37%), new-onset HF hospitalization (54%), MI (37%), and ischemic stroke (29%).[100] After 2.5 years, individuals who have undergone Roux-en-Y surgery may lower their BMI by 30%, and up to 63% achieve their weight loss goal with major improvement in several metabolic risk factors linked to CVD.[101] The procedure is generally associated with extremely low perioperative mortality among people with obesity and CVD and represents a strategy to increase access to transplant and improved long-term survival for those with HF CVD.[101,102]

PHYSICAL ACTIVITY, EXERCISE, AND CARDIORESPIRATORY FITNESS. Adherence with physical activity (PA) programs is frequently poor, and people with overweight/obesity may need to overcome a number of additional health-related obstacles to participate regularly in exercise. The risk of lower back pain increases incrementally with rising BMI, from 2.9% (BMI 20-25 kg/m^2) to 5.2% (BMI 26-30 kg/m^2), 7.7% (BMI 31-35 kg/m^2), and finally 11.6% (BMI ≥36 kg/m^2).[36] Movement can be restricted among those with osteoarthritis (particularly of the knee), the risk of which may be increased by 2-fold to 10-fold as BMI rises.[35] Consultation with physical medicine professionals can help to tailor exercise recommendations to those with musculoskeletal limitations to improve compliance and to prevent complications resulting from exercise. Individuals can also feel tired and less motivated to participate in PA during the day as a consequence of OSA, which is highly prevalent in people with obesity (86%), and small body weight increases (10%) significantly elevate the risk of developing OSA.[35] Approximately 1 in 5 adults with BMI 25 to 28 kg/m^2 will have mild OSA, and 1 in 15 will have moderate OSA.[103] Prevalence will be higher among African Americans compared with other populations.[103] Excess body weight is associated with structural and functional alterations within the upper airway as well as changes in the body's oxygen demands, and overweight/obesity carries a 2- to 3-fold increase in a range of self-reported asthma outcomes.[103,104] Considerable evidence suggests that PA and cardiorespiratory fitness are more important predictors of survival than weight or even body fat or central obesity in those with CVD, including CHD and systolic HF.[105-109]

CARDIAC REHABILITATION: AN OPPORTUNITY FOR INTERVENTION. Cardiac rehabilitation (CR) is a cornerstone in secondary prevention for people who have experienced acute myocardial infarction or another CVD. Unfortunately, most rehabilitation programs do not contain a formal in-house weight management program to support participants in significantly improving their functional outcomes, such as metabolic equivalents and chronotropic competence.[110,111] Just 8% of cardiovascular programs in the United States deliver behavioral weight programs.[112] It seems that establishing longer programs for weight loss and group therapy, rather than individual therapy, improve outcomes during cardiac rehabilitation for populations with obesity.[110] The development of new technologies has created cost-efficient options, like home-based rehabilitation and telephone counseling, for long-term weight management in rural communities with limited access to preventive health services.[113,114] Motivated individuals will benefit from multicomponent approaches and should be encouraged to set specific, proximal, shared goals with their health care professional.[115] A multitude of tools are available to support self-monitoring (eg, smart phone applications, food diaries), and scheduled regular follow-up and feedback on progress can help to maintain motivation.[115]

MANAGEMENT OF MOOD DISORDERS. Mood disorders, such as anxiety and depression, are relatively prevalent among people with overweight/obesity.[37,38] The risk of depression is estimated to be 32% higher in individuals with obesity, and central obesity is associated with an OR for depression of 1.38 according to systematic review and meta-analysis data.[37,38] People with depression are 3 times more likely to be noncompliant with medical treatment recommendations, and women with overweight/obesity have higher prevalence of recurrent depression and lifetime depression/anxiety than men in all BMI categories (except BMI <18.5 kg/m^2).[116,117] There is considerable evidence that CR-induced increases in cardiorespiratory fitness correlate with marked reductions in depression, psychological distress, and stress-induced increased mortality that could be beneficial to people with obesity, stress, and CVD.[118]

SMOKING CESSATION. Smoking cessation is an important factor in reducing CVD risk; yet, weight gain associated with smoking abstinence represents a major barrier for people wishing to quit the habit.

Average weight gain is approximately 4 to 5 kg during the first 12 months after smoking cessation.[39] Importantly, weight gain is not universal, as 16% of quitters lose weight, whereas 13% gain >10 kg.[39] Weight increase is typically caused by the higher energy intake, likely because of people substituting the "hand to mouth" habit with eating, and reduced energy expenditure in addition to the removal of the appetite suppressant effects of nicotine from the central nervous system.[39,40,119] More intensive approaches to weight management (eg, low-calorie diets, PA programs) and medical interventions (eg, nicotine replacement therapy, varenicline, bupropion) should be made available to support people during smoking cessation efforts to minimize weight gain.[40,119] The weight gain associated with smoking cessation leads to reduced glycemic control, so people with diabetes who quit smoking may need closer metabolic follow-up and more aggressive approaches to avoid weight gain.[39,40,119] However, long-term quitters (>6 years) have lower all-cause and cancer mortality and incidence of CVD, underscoring the importance of smoking cessation, even if that may lead to some weight gain.[120,121] Where it is possible to achieve smoking cessation without weight gain, the total risk of CVD, CHD, and premature death is significantly lowered among people with T2DM, and mortality is reduced by 36% in those with CHD.[120,121]

THE OBESITY PARADOX IN CVD

The obesity paradox describes the inverse association between obesity and CVD mortality.[80,106,108,109,122-128] This phenomenon has been described for many CVDs, including HF, CHD and AF.[80,122-127] A review of the possible explanations of the obesity paradox goes beyond the scope of this paper. However, it important to underscore that the observed paradox does not indicate causality, similar to that of the smoker's paradox showing that people who smoke have a better prognosis after myocardial infarction compared with nonsmokers.[129-131]

The fundamental question when considering the obesity paradox is whether those with obesity and CVD would be better off after losing weight. A systematic review has described the long-term protective effects of intentional weight loss in the setting of lifestyle changes.[132] Studies involving bariatric surgery in subjects with CVD also suggest that better outcomes follow significant weight reduction.[89,97,98,101,102]

Furthermore, intentional weight loss has demonstrated clinical benefits in specific CVD populations like AF and HF with preserved ejection fraction.[133-137]

DIAGNOSTIC METHODS FOR OBESITY: CHALLENGES AND OPPORTUNITIES

BMI, the most commonly used clinical method for obesity detection and grading of severity, has poor diagnostic performance, especially in the normal weight range.[138-140] BMI cannot differentiate between body fat and lean mass, particularly in people with CVD, and does not provide an indication of fat distribution (peripheral fat vs central fat).[12,138-140]

For a better assessment of adiposity, it is prudent to investigate a range of complementary anthropometric parameters alongside standard BMI calculations (accounting for age, race, and sex), including measures of central obesity, such as waist circumference, waist-hip ratio and weight-height ratio.[12,138,141] Central fat distribution is an important indicator of adiposity-related risk, although manual waist circumference and waist-hip ratio assessment may be unreliable (even with specialist training). Waist circumference measurement errors of just 3.9 cm can equate to a 3 lb/1.4 kg variance in abdominal fat.[142,143] More recently, measurements of total adiposity using methods to assess body composition have increased in popularity, such as air-displacement plethysmography (Bod-Pod), dual energy x-ray absorptiometry, or electrical bioimpedance. Those techniques have shown validity in practice and are not necessarily expensive. Simpler methods such as the skinfold technique to estimate body adiposity have shown to be no better than BMI.[141]

The evaluation of changes in body composition after an exercise program is of particular relevance. BMI demonstrates poor performance when assessing changes in body adiposity after exercise programs, where lean mass or fat-free mass may replace fat mass so that overall body weight remains unchanged or even increased.[144,145]

CONCLUSIONS AND CONSIDERATIONS FOR CLINICAL PRACTICE

CVD and obesity are common conditions that frequently coexist. We cannot treat one of these conditions while ignoring the other. Diagnostic and therapeutic options for individuals with CVD and obesity have distinct limitations that clinicians need to be aware of. People with CVD struggle with multiple concurrent risk factors and comorbidities that affect their ability to lose weight, meaning that weight reduction therapies for people with CVD need to be tailored accordingly to those conditions. Multidisciplinary teams are extremely important in achieving therapeutic goals and long-term patient adherence.

Given the high prevalence of obesity in people with CVD and the unique challenges both conditions represent, cardiovascular guidelines need to take into consideration this special population when issuing diagnostic and therapeutic recommendations.

ACKNOWLEDGMENTS Medical writing services were provided on behalf of the authors by Rebecca Down at Copperfox Communications Limited. The authors appreciate the revision of the final draft and recommendations provided by Dr Kyla Lara-Breitinger.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Funding for medical writing services was provided by the Mayo Clinic. Dr Lopez-Jimenez has performed research related to 3D body assessment with Select Research, Inc, Mayo Clinic, and may benefit in the future if this technology gets commercialized; he has not received any monetary, financial or other type of compensation to date, in relationship to this arrangement, and 3D body technology, or any related technology, is not relevant to the contents of this paper. Dr Lopez-Jimenez is a member of the Scientific Advisory Board for Novo Nordisk. Dr Lavie is a member of the Data and Safety Monitoring Board for CagriSema, a trial sponsored by Novo Nordisk. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Francisco Lopez-Jimenez, Division of Cardiovascular Diseases, Mayo Clinic, 200 1st Street SW, Rochester, Minnesota 55905, USA. E-mail: lopez@mayo.edu. Twitter: @DrLopezJimenez, @MayoClinic, @MayoClinicCV.

REFERENCES

1. Powell-Wiley TM, Poirier P, Burke LE, et al. Obesity and cardiovascular disease: a scientific statement from the American Heart Association. *Circulation*. 2021:E984–E1010.

2. Lavie CJ, Laddu D, Arena R, Ortega FB, Alpert MA, Kushner RF. Healthy weight and obesity prevention: JACC health promotion series. *J Am Coll Cardiol*. 2018;72:1506–1531.

3. NCD Risk Factor Collaboration (NCD-RisC). Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19·2 million participants. *Lancet*. 2016;387:1377–1396.

4. Cornier M-A, Després J-P, Davis N, et al. Assessing adiposity. *Circulation*. 2011;124:1996–2019.

5. Rao G, Powell-Wiley TM, Ancheta I, et al. Identification of obesity and cardiovascular risk in ethnically and racially diverse populations. *Circulation*. 2015;132:457–472.

6. National Institute for Health and Care Excellence. Obesity: identification, assessment and management. 2014. Accessed September 29, 2022. https://www.nice.org.uk/guidance/cg189/resources/obesity-identification-assessment-and-management-pdf-35109821097925

7. Yumuk V, Tsigos C, Fried M, et al. European guidelines for obesity management in adults. *Obes Facts*. 2015;8:402–424.

8. World Health Organization. Waist circumference and waist-hip ratio: report of a WHO expert consultation, Geneva, 8-11 December. 2008. Accessed September 29, 2022. https://apps.who.int/iris/bitstream/handle/10665/44583/9789241501491_eng.pdf?sequence=1

9. van Dis I, Kromhout D, Geleijnse JM, Boer JMA, Verschuren WM. Body mass index and waist circumference predict both 10-year nonfatal and fatal cardiovascular disease risk: study conducted in 20 000 Dutch men and women aged 20-65 years. *Eur J Cardiovasc Prev Rehabil*. 2009;16:729–734.

10. Fekri N, Khaloo P, Ramezankhani A, Mansournia MA, Azizi F, Hadaegh F. Association of body mass index with life expectancy with and without cardiovascular disease. *Int J Obes*. 2020;44:195–203.

11. World Health Organization. A healthy lifestyle - WHO recommendations. Body mass index - BMI. Accessed September 29, 2022. https://www.euro.who.int/en/health-topics/disease-prevention/nutrition/a-healthy-lifestyle/body-mass-index-bmi

12. Després J-P, Carpentier AC, Tchernof A, Neeland IJ, Poirier P. Management of obesity in cardiovascular practice: JACC focus seminar. *J Am Coll Cardiol*. 2021;78:513–531.

13. Lopez-Jimenez F, Almahmeed W, Bays H, et al. Obesity and cardiovascular disease: mechanistic insights and management strategies. A joint position paper by the World Heart Federation and World Obesity Federation. *Eur J Prev Cardiol*. 2022;29(17):2218–2237. https://doi.org/10.1093/eurjpc/zwac187

14. World Health Organization. *Obesity and overweight factsheet*. 2020. Accessed September 29, 2022. https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight

15. Leschka S, Stinn B, Schmid F, et al. Dual source CT coronary angiography in severely obese patients: trading off temporal resolution and image noise. *Invest Radiol*. 2009;44:720–727.

16. Murphy M, Krothapalli S, Cuellar J, et al. Prognostic value of normal stress echocardiography in obese patients. *J Obes*. 2014;2014:419724.

17. Bigvava T, Zamani SM, Pieske-Kraigher E, Gebker R, Pieske B, Kelle S. Prognostic value of non-invasive stress testing for coronary artery disease in obese patients. *Expert Rev Cardiovasc Ther*. 2015;13:1325–1332.

18. Uppot RN. Impact of obesity on radiology. *Radiol Clin North Am*. 2007;45:231–246.

19. Poirier P, Giles TD, Bray GA, et al. Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss. *Arterioscler Thromb Vasc Biol*. 2006;26:968–976.

20. Lim SP, Arasaratnam P, Chow BJ, Beanlands RS, Hessian RC. Obesity and the challenges of noninvasive imaging for the detection of coronary artery disease. *Can J Cardiol*. 2015;31:223–236.

21. Legault S, Sénéchal M, Bergeron S, et al. Usefulness of an accelerated transoesophageal stress echocardiography in the preoperative evaluation of high risk severely obese subjects awaiting bariatric surgery. *Cardiovasc Ultrasound*. 2010;8:30.

22. Uppot RN. Technical challenges of imaging & image-guided interventions in obese patients. *Br J Radiol*. 2018;91:20170931.

23. Brown A, Guess N, Dornhorst A, Taheri S, Frost G. Insulin-associated weight gain in obese type 2 diabetes mellitus patients: What can be done? *Diabetes Obes Metab*. 2017;19:1655–1668.

24. Cheymol G. Clinical pharmacokinetics of drugs in obesity. An update. *Clin Pharmacokinet*. 1993;25:103–114.

25. Reisin E, Weir MR, Falkner B, Hutchinson HG, Anzalone DA, Tuck ML. Lisinopril versus hydrochlorothiazide in obese hypertensive patients: a multicenter placebo-controlled trial. Treatment in Obese Patients With Hypertension (TROPHY) Study Group. *Hypertension*. 1997;30:140–145.

26. Wadsworth TG, Carr GG, Madaras-Kelly K, Remington R, Bell J. Weight gain associated with insulin detemir vs insulin glargine in clinical practice: a retrospective longitudinal cohort study. *Am J Health Syst Pharm*. 2021;78:401–407.

27. Grassi G, Seravalle G, Dell'Oro R, et al. Comparative effects of candesartan and hydrochlorothiazide on blood pressure, insulin sensitivity, and sympathetic drive in obese hypertensive individuals: results of the CROSS study. *J Hypertens*. 2003;21:1761–1769.

28. Schwartz MW, Porte D. Diabetes, obesity, and the brain. *Science*. 2005;307:375–379.

29. Sharma AM, Pischon T, Hardt S, Kunz I, Luft FC. Hypothesis: Beta-adrenergic receptor blockers and weight gain: a systematic analysis. *Hypertension*. 2001;37:250–254.

30. Lavie CJ, Arena R, Alpert MA, Milani RV, Ventura HO. Management of cardiovascular

diseases in patients with obesity. *Nat Rev Cardiol*. 2018;15:45–56.

31. Sharma A, Vallakati A, Einstein AJ, et al. Relationship of body mass index with total mortality, cardiovascular mortality, and myocardial infarction after coronary revascularization: evidence from a meta-analysis. *Mayo Clin Proc*. 2014;89:1080–1100.

32. Ghanta RK, LaPar DJ, Zhang Q, et al. Obesity increases risk-adjusted morbidity, mortality, and cost following cardiac surgery. *J Am Heart Assoc*. 2017;6(3):e003831. https://doi.org/10.1161/JAHA.116.003831

33. Mehra MR, Canter CE, Hannan MM, et al. The 2016 International Society for Heart Lung Transplantation listing criteria for heart transplantation: a 10-year update. *J Heart Lung Transplant*. 2016;35:1–23.

34. Jaiswal A, Truby LK, Chichra A, et al. Impact of obesity on ventricular assist device outcomes. *J Card Fail*. 2020;26:287–297.

35. Garvey WT, Mechanick JI, Brett EM, et al. American Association of Clinical Endocrinologists and American College of Endocrinology comprehensive clinical practice guidelines for medical care of patients with obesity. *Endocr Pract*. 2016;22(Suppl 3):1–203.

36. Smuck M, Kao M-CJ, Brar N, Martinez-Ith A, Choi J, Tomkins-Lane CC. Does physical activity influence the relationship between low back pain and obesity? *Spine J*. 2014;14:209–216.

37. Pereira-Miranda E, Costa PRF, Queiroz VAO, Pereira-Santos M, Santana MLP. Overweight and obesity associated with higher depression prevalence in adults: a systematic review and meta-analysis. *J Am Coll Nutr*. 2017;36:223–233.

38. Xu Q, Anderson D, Lurie-Beck J. The relationship between abdominal obesity and depression in the general population: a systematic review and meta-analysis. *Obes Res Clin Pract*. 2011;5:e267–e360.

39. Aubin H-J, Farley A, Lycett D, Lahmek P, Aveyard P. Weight gain in smokers after quitting cigarettes: meta-analysis. *BMJ*. 2012;345:e4439.

40. Svendsen M, Heggen E, Klemsdal TO, Tonstad S. Diet, eating behaviour and weight gain in men and women with overweight/obesity receiving varenicline for smoking cessation. *Clin Obes*. 2021;11:e12447.

41. Hanley MJ, Abernethy DR, Greenblatt DJ. Effect of obesity on the pharmacokinetics of drugs in humans. *Clin Pharmacokinet*. 2010;49:71–87.

42. Sankaralingam S, Kim RB, Padwal RS. The Impact of obesity on the pharmacology of medications used for cardiovascular risk factor control. *Can J Cardiol*. 2015;31:167–176.

43. Kotlyar M, Carson SW. Effects of obesity on the cytochrome P450 enzyme system. *Int J Clin Pharmacol Ther*. 1999;37:8–19.

44. Ribstein J, du Cailar G, Mimran A. Combined renal effects of overweight and hypertension. *Hypertension*. 1995;26:610–615.

45. Valensi P, Assayag M, Busby M, Pariès J, Lormeau B, Attali JR. Microalbuminuria in obese patients with or without hypertension. *Int J Obes Relat Metab Disord*. 1996;20, 574-549.

46. Wuerzner G, Pruijm M, Maillard M, et al. Marked association between obesity and glomerular hyperfiltration: a cross-sectional study in an African population. *Am J Kidney Dis*. 2010;56:303–312.

47. Pai MP. Estimating the glomerular filtration rate in obese adult patients for drug dosing. *Adv Chronic Kidney Dis*. 2010;17:e53–e62.

48. Smit C, de Hoogd S, Brüggemann RJM, Knibbe CAJ. Obesity and drug pharmacology: a review of the influence of obesity on pharmacokinetic and pharmacodynamic parameters. *Expert Opin Drug Metab Toxicol*. 2018;14:275–285.

49. Green B, Duffull SB. What is the best size descriptor to use for pharmacokinetic studies in the obese? *Br J Clin Pharmacol*. 2004;58:119–133.

50. Ghobadi C, Johnson TN, Aarabi M, et al. Application of a systems approach to the bottom-up assessment of pharmacokinetics in obese patients: expected variations in clearance. *Clin Pharmacokinet*. 2011;50:809–822.

51. Anastasio P, Spitali L, Frangiosa A, et al. Glomerular filtration rate in severely overweight normotensive humans. *Am J Kidney Dis*. 2000;35:1144–1148.

52. Nguyen MT, Fong J, Ullah S, Lovell A, Thompson CH. Estimating glomerular filtration rate in obese subjects. *Obes Res Clin Pract*. 2015;9:152–157.

53. Shank BR, Zimmerman DE. *Demystifying drug dosing in obese patients*. American Society of Health System Pharmacists; 2015.

54. Pankert M, Quilici J, Loundou AD, et al. Impact of obesity and the metabolic syndrome on response to clopidogrel or prasugrel and bleeding risk in patients treated after coronary stenting. *Am J Cardiol*. 2014;113:54–59.

55. Martin K, Beyer-Westendorf J, Davidson BL, Huisman MV, Sandset PM, Moll S. Use of the direct oral anticoagulants in obese patients: guidance from the SSC of the ISTH. *J Thromb Haemost*. 2016;14:1308–1313.

56. Coons JC, Albert L, Bejjani A, Iasella CJ. Effectiveness and safety of direct oral anticoagulants versus warfarin in obese patients with acute venous thromboembolism. *Pharmacotherapy*. 2020;40:204–210.

57. Abildgaard A, Madsen SA, Hvas A-M. Dosage of anticoagulants in obesity: recommendations based on a systematic review. *Semin Thromb Hemost*. 2020;46:932–969.

58. Patanwala AE, Seaman SM, Kopp BJ, Erstad BL. Heparin dosing for venous thromboembolism prophylaxis in obese hospitalized patients: an observational study. *Thromb Res*. 2018;169:152–156.

59. Joy M, Tharp E, Hartman H, et al. Safety and efficacy of high-dose unfractionated heparin for prevention of venous thromboembolism in overweight and obese patients. *Pharmacotherapy*. 2016;36:740–748.

60. Mason SW, Barber A, Jones E, Chen S-L, Moll S, Northam K. Safety and efficacy of high-dose unfractionated heparin versus high-dose enoxaparin for venous thromboembolism prevention in morbidly obese hospitalized patients. *Am J Med*. 2020;133:e249–e259.

61. Gress TW, Nieto FJ, Shahar E, Wofford MR, Brancati FL. Hypertension and antihypertensive therapy as risk factors for type 2 diabetes mellitus. Atherosclerosis Risk in Communities Study. *N Engl J Med*. 2000;342:905–912.

62. Pischon T, Sharma AM. Use of beta-blockers in obesity hypertension: potential role of weight gain. *Obes Rev*. 2001;2:275–280.

63. Messerli FH, Bell DSH, Fonseca V, et al. Body weight changes with beta-blocker use: results from GEMINI. *Am J Med*. 2007;120:610–615.

64. Lee P, Kengne A-P, Greenfield JR, Day RO, Chalmers J, Ho KKY. Metabolic sequelae of β-blocker therapy: weighing in on the obesity epidemic? *Int J Obes (Lond)*. 2011;35:1395–1403.

65. Boxall BWJ, Clark AL. Beta-blockers and weight change in patients with chronic heart failure. *J Card Fail*. 2012;18:233–237.

66. European Medicines Agency. Reflection paper on investigation of pharmacokinetics and pharmacodynamics in the obese population. 2018. Accessed September 29, 2022. https://www.ema.europa.eu/documents/scientific-guideline/reflection-paper-investigation-pharmacokinetics-pharmacodynamics-obese-population_en.pdf

67. Sibbing D, von Beckerath O, Schömig A, Kastrati A, von Beckerath N. Impact of body mass index on platelet aggregation after administration of a high loading dose of 600 mg of clopidogrel before percutaneous coronary intervention. *Am J Cardiol*. 2007;100:203–205.

68. Deharo P, Pankert M, Bonnet G, et al. Body mass index has no impact on platelet inhibition induced by ticagrelor after acute coronary syndrome, conversely to prasugrel. *Int J Cardiol*. 2014;176:1200–1202.

69. Reilly PA, Lehr T, Haertter S, et al. The effect of dabigatran plasma concentrations and patient characteristics on the frequency of ischemic stroke and major bleeding in atrial fibrillation patients: the RE-LY Trial (Randomized Evaluation of Long-Term Anticoagulation Therapy). *J Am Coll Cardiol*. 2014;63:321–328.

70. Boriani G, Ruff CT, Kuder JF, et al. Relationship between body mass index and outcomes in patients with atrial fibrillation treated with edoxaban or warfarin in the ENGAGE AF-TIMI 48 trial. *Eur Heart J*. 2019;40:1541–1550.

71. Poirier P. Chapter 6: Pharmacological and surgical interventions that prevent or worsen type 2 diabetes. In: McGuire DK, Marx N, eds. *Diabetes in Cardiovascular Disease. A Companion to Braunwald's Heart Disease*. 1st ed. Saunders/Elsevier; 2015.

72. Oreopoulos A, Padwal R, Norris CM, Mullen JC, Pretorius V, Kalantar-Zadeh K. Effect of obesity on short- and long-term mortality postcoronary revascularization: a meta-analysis. *Obesity (Silver Spring)*. 2008;16:442–450.

73. Gurm HS, Whitlow PL, Kip KE. for the BARI Investigators. The impact of body mass index on short- and long-term outcomes inpatients undergoing coronary revascularization. Insights from the bypass angioplasty revascularization

investigation (BARI). *J Am Coll Cardiol*. 2002;39:834–840.

74. Lancefield T, Clark DJ, Andrianopoulos N, et al. Is there an obesity paradox after percutaneous coronary intervention in the contemporary era? An analysis from a multicenter Australian registry. *J Am Coll Cardiol Intv*. 2010;3:660–668.

75. Garcia-Labbé D, Ruka E, Bertrand OF, Voisine P, Costerousse O, Poirier P. Obesity and coronary artery disease: evaluation and treatment. *Can J Cardiol*. 2015;31:184–194.

76. Holroyd EW, Sirker A, Kwok CS, et al. The relationship of body mass index to percutaneous coronary intervention outcomes: does the obesity paradox exist in contemporary percutaneous coronary intervention cohorts? Insights from the British Cardiovascular Intervention Society registry. *J Am Coll Cardiol Intv*. 2017;10:1283–1292.

77. Hibbert B, Simard T, Wilson KR, et al. Transradial versus transfemoral artery approach for coronary angiography and percutaneous coronary intervention in the extremely obese. *J Am Coll Cardiol Intv*. 2012;5:819–826.

78. Nikolsky E, Kosinski E, Mishkel GJ, et al. Impact of obesity on revascularization and restenosis rates after bare-metal and drug-eluting stent implantation (from the TAXUS-IV trial). *Am J Cardiol*. 2005;95:709–715.

79. Wong CX, Sullivan T, Sun MT, et al. Obesity and the risk of incident, post-operative, and post-ablation atrial fibrillation: a meta-analysis of 626,603 individuals in 51 studies. *JACC Clin Electrophysiol*. 2015;1:139–152.

80. Lavie CJ, McAuley PA, Church TS, Milani R v, Blair SN. Obesity and cardiovascular diseases: implications regarding fitness, fatness, and severity in the obesity paradox. *J Am Coll Cardiol*. 2014;63:1345–1354.

81. Davenport DL, Xenos ES, Hosokawa P, Radford J, Henderson WG, Endean ED. The influence of body mass index obesity status on vascular surgery 30-day morbidity and mortality. *J Vasc Surg*. 2009;49:140–147, 147.e1; discussion 147.

82. Chassé M, Mathieu P, Voisine P, et al. The underestimated belly factor: waist circumference is linked to significant morbidity following isolated coronary artery bypass grafting. *Can J Cardiol*. 2016;32:327–335.

83. Galyfos G, Geropapas GI, Kerasidis S, Sianou A, Sigala F, Filis K. The effect of body mass index on major outcomes after vascular surgery. *J Vasc Surg*. 2017;65:1193–1207.

84. Arinze N, Farber A, Levin SR, et al. Perioperative outcomes after lower extremity bypass and peripheral vascular interventions in patients with morbid obesity and superobesity. *J Vasc Surg*. 2020;71:567–574.e4.

85. Buschur ME, Smith D, Share D, et al. The burgeoning epidemic of morbid obesity in patients undergoing percutaneous coronary intervention: insight from the Blue Cross Blue Shield of Michigan Cardiovascular Consortium. *J Am Coll Cardiol*. 2013;62:685–691.

86. Mohty D, Dumesnil JG, Echahidi N, et al. Impact of prosthesis-patient mismatch on long-term survival after aortic valve replacement: influence of age, obesity, and left ventricular dysfunction. *J Am Coll Cardiol*. 2009;53:39–47.

87. Ternacle J, Pibarot P, Herrmann HC, et al. Prosthesis-patient mismatch after aortic valve replacement in the PARTNER 2 trial and registry. *J Am Coll Cardiol Intv*. 2021;14:1466–1477.

88. Attanasio P, Lacour P, Ernert A, et al. Cardiac device implantations in obese patients: Success rates and complications. *Clin Cardiol*. 2017;40:230–234.

89. daSilva-deAbreu A, Alhafez BA, Curbelo-Pena Y, et al. Bariatric surgery in patients with obesity and ventricular assist devices considered for heart transplantation: systematic review and individual participant data meta-analysis. *J Card Fail*. 2021;27:338–348.

90. Saiki A, Nagayama D, Ohhira M, et al. Effect of weight loss using formula diet on renal function in obese patients with diabetic nephropathy. *Int J Obes (Lond)*. 2005;29:1115–1120.

91. Vest AR, Chan M, Deswal A, et al. Nutrition, obesity, and cachexia in patients with heart failure: a consensus statement from the Heart Failure Society of America Scientific Statements Committee. *J Card Fail*. 2019;25:380–400.

92. Pirlet C, Poirier P, Cieza T, et al. Clinical impact of weight-loss pharmacotherapy in patients with atherosclerotic cardiovascular disease. *Am J Cardiovasc Drugs*. 2021;21:271–281.

93. Ryan DH, Lingvay I, Colhoun HM, et al. Semaglutide effects on cardiovascular outcomes in people with overweight or obesity (SELECT) rationale and design. *Am Heart J*. 2020;229:61–69.

94. McFarlane SI. Insulin therapy and type 2 diabetes: management of weight gain. *J Clin Hypertens (Greenwich)*. 2009;11:601–607.

95. Westlake C, Dracup K, Fonarow G, Hamilton M. Depression in patients with heart failure. *J Card Fail*. 2005;11:30–35.

96. Schwartz TL, Nihalani N, Jindal S, Virk S, Jones N. Psychiatric medication-induced obesity: a review. *Obes Rev*. 2004;5:115–121.

97. Batsis JA, Romero-Corral A, Collazo-Clavell ML, et al. Effect of weight loss on predicted cardiovascular risk: change in cardiac risk after bariatric surgery. *Obesity (Silver Spring)*. 2007;15:772–784.

98. Doumouras AG, Wong JA, Paterson JM, et al. Bariatric surgery and cardiovascular outcomes in patients with obesity and cardiovascular disease: s population-based retrospective cohort study. *Circulation*. 2021;143:1468–1480.

99. Näslund E, Stenberg E, Hofmann R, et al. Association of metabolic surgery with major adverse cardiovascular outcomes in patients with previous myocardial infarction and severe obesity: a nationwide cohort study. *Circulation*. 2021;143:1458–1467.

100. Mentias A, Aminian A, Youssef D, et al. Long-term cardiovascular outcomes after bariatric surgery in the Medicare population. *J Am Coll Cardiol*. 2022;79:1429–1437.

101. Lopez-Jimenez F, Bhatia S, Collazo-Clavell ML, Sarr MG, Somers VK. Safety and efficacy of bariatric surgery in patients with coronary artery disease. *Mayo Clin Proc*. 2005;80:1157–1162.

102. Choudhury RA, Foster M, Hoeltzel G, et al. Bariatric surgery for congestive heart failure patients improves access to transplantation and long-term survival. *J Gastrointest Surg*. 2021;25:926–931.

103. Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: a population health perspective. *Am J Respir Crit Care Med*. 2002;165:1217–1239.

104. Farah CS, Salome CM. Asthma and obesity: a known association but unknown mechanism. *Respirology*. 2012;17:412–421.

105. Moholdt T, Lavie CJ, Nauman J. Sustained physical activity, not weight loss, associated with improved survival in coronary heart disease. *J Am Coll Cardiol*. 2018;71:1094–1101.

106. Pandey A, Patel K v, Lavie CJ. Obesity, central adiposity, and fitness: understanding the obesity paradox in the context of other cardiometabolic parameters. *Mayo Clin Proc*. 2018;93:676–678.

107. Moholdt T, Lavie CJ, Nauman J. Interaction of physical activity and body mass index on mortality in coronary heart disease: data from the Nord-Trøndelag health study. *Am J Med*. 2017;130:949–957.

108. McAuley PA, Artero EG, Sui X, et al. The obesity paradox, cardiorespiratory fitness, and coronary heart disease. *Mayo Clin Proc*. 2012;87:443–451.

109. Lavie CJ, Cahalin LP, Chase P, et al. Impact of cardiorespiratory fitness on the obesity paradox in patients with heart failure. *Mayo Clin Proc*. 2013;88:251–258.

110. Ades PA, Savage PD, Harvey-Berino J. The treatment of obesity in cardiac rehabilitation. *J Cardiopulm Rehabil Prev*. 2010;30:289–298.

111. Atti V, Devarakonda PK, Raina S. Differential effects of cardiac rehabilitation in obese and non-obese population. *Cureus*. 2021;13:e18227.

112. Ades PA, Savage PD. The treatment of obesity in cardiac rehabilitation: a review and practical recommendations. *J Cardiopulm Rehabil Prev*. 2021;41:295–301.

113. Perri MG, Limacher MC, Durning PE, et al. Extended-care programs for weight management in rural communities: the treatment of obesity in underserved rural settings (TOURS) randomized trial. *Arch Intern Med*. 2008;168:2347–2354.

114. Thomas RJ, Beatty AL, Beckie TM, et al. Home-based cardiac rehabilitation: a scientific statement from the American Association of Cardiovascular and Pulmonary Rehabilitation, the American Heart Association, and the American College of Cardiology. *Circulation*. 2019;140:e69–e89.

115. Mozaffarian D. Dietary and policy priorities for cardiovascular disease, diabetes, and obesity: a comprehensive review. *Circulation*. 2016;133:187–225.

116. Zhao G, Ford ES, Dhingra S, Li C, Strine TW, Mokdad AH. Depression and anxiety among US adults: associations with body mass index. *Int J Obes (Lond)*. 2009;33:257–266.

117. DiMatteo MR, Lepper HS, Croghan TW. Depression is a risk factor for noncompliance with medical treatment: meta-analysis of the effects of anxiety and depression on patient adherence. *Arch Intern Med*. 2000;160:2101–2107.

118. Tutor A, Lavie CJ, Kachur S, Dinshaw H, Milani RV. Impact of cardiorespiratory fitness on outcomes in cardiac rehabilitation. *Prog Cardiovasc Dis*. 2022;70:2–7.

119. Bush T, Lovejoy JC, Deprey M, Carpenter KM. The effect of tobacco cessation on weight gain, obesity, and diabetes risk. *Obesity (Silver Spring)*. 2016;24:1834–1841.

120. Liu G, Hu Y, Zong G, et al. Smoking cessation and weight change in relation to cardiovascular disease incidence and mortality in people with type 2 diabetes: a population-based cohort study. *Lancet Diabetes Endocrinol*. 2020;8:125–133.

121. Critchley JA, Capewell S. Mortality risk reduction associated with smoking cessation in patients with coronary heart disease: a systematic review. *JAMA*. 2003;290:86–97.

122. Padwal R, Mcalister FA, Mcmurray J, et al. The obesity paradox in heart failure patients with preserved versus reduced ejection fraction: a meta-analysis of individual patient data. *Int J Obes*. 2014;38:1110–1114.

123. Romero-Corral A, Montori VM, Somers VK, et al. Association of bodyweight with total mortality and with cardiovascular events in coronary artery disease: a systematic review of cohort studies. *Lancet*. 2006;368:666–678.

124. Kenchaiah S, Evans JC, Levy D, et al. Obesity and the risk of heart failure. *N Engl J Med*. 2002;347:305–313.

125. Wang ZJ, Zhou YJ, Galper BZ, Gao F, Yeh RW, Mauri L. Association of body mass index with mortality and cardiovascular events for patients with coronary artery disease: a systematic review and meta-analysis. *Heart*. 2015;101:1631–1638.

126. Elagizi A, Kachur S, Lavie CJ, et al. An overview and update on obesity and the obesity paradox in cardiovascular diseases. *Prog Cardiovasc Dis*. 2018;61:142–150.

127. Badheka AO, Rathod A, Kizilbash MA, et al. Influence of obesity on outcomes in atrial fibrillation: yet another obesity paradox. *Am J Med*. 2010;123:646–651.

128. Bezerra CO, de Lima Paiva RM, da Silva TL, et al. Obesity as a risk factor for heart failure: overview of systematic reviews. *Research Society and Development*. 2022;11:e0811124380. https://doi.org/10.33448/rsd-v11i1.24380

129. Carbone S, Canada JM, Billingsley HE, Siddiqui MS, Elagizi A, Lavie CJ. Obesity paradox in cardiovascular disease: where do we stand? *Vasc Health Risk Manag*. 2019;15:89–100.

130. Iliodromiti S, Celis-Morales CA, Lyall DM, et al. The impact of confounding on the associations of different adiposity measures with the incidence of cardiovascular disease: a cohort study of 296 535 adults of white European descent. *Eur Heart J*. 2018;39:1514–1520.

131. Joner M, Cassese S. The "smoker's paradox": the closer you look, the less you see. *J Am Coll Cardiol Intv*. 2019;12:1951–1953.

132. Pack QR, Rodriguez-Escudero JP, Thomas RJ, et al. The prognostic importance of weight loss in coronary artery disease: a systematic review and meta-analysis. *Mayo Clin Proc*. 2014;89:1368–1377.

133. Pathak RK, Middeldorp ME, Meredith M, et al. Long-term effect of goal-directed weight management in an atrial fibrillation cohort: a long-term follow-up study (LEGACY). *J Am Coll Cardiol*. 2015;65:2159–2169.

134. Pathak RK, Middeldorp ME, Lau DH, et al. Aggressive risk factor reduction study for atrial fibrillation and implications for the outcome of ablation: the ARREST-AF cohort study. *J Am Coll Cardiol*. 2014;64:2222–2231.

135. Abed HS, Wittert GA, Leong DP, et al. Effect of weight reduction and cardiometabolic risk factor management on symptom burden and severity in patients with atrial fibrillation: a randomized clinical trial. *JAMA*. 2013;310:2050–2060.

136. Romero Funes D, Gutierrez Blanco D, Botero-Fonnegra C, et al. Bariatric surgery decreases the number of future hospital admissions for diastolic heart failure in subjects with severe obesity: a retrospective analysis of the US National Inpatient Sample database. *Surg Obes Relat Dis*. 2022;18:1–8.

137. Sierra-Johnson J, Romero-Corral A, Somers VK, et al. Prognostic importance of weight loss in patients with coronary heart disease regardless of initial body mass index. *Eur J Cardiovasc Prev Rehabil*. 2008;15:336–340.

138. Oliveros E, Somers VK, Sochor O, Goel K, Lopez-Jimenez F. The concept of normal weight obesity. *Prog Cardiovasc Dis*. 2014;56:426–433.

139. Kesztyüs D, Lampl J, Kesztyüs T. The weight problem: overview of the most common concepts for body mass and fat distribution and critical consideration of their usefulness for risk assessment and practice overview of the most common concepts for body mass and fat distribution and critical consideration of their usefulness for risk assessment and practice. Risk assessment and practice. *Int J Environ Res Public Health*. 2021;18:11070.

140. Hsuan C-F, Lin F-J, Lee T-L, et al. The waist-to-body mass index ratio as an anthropometric predictor for cardiovascular outcome in subjects with established atherosclerotic cardiovascular disease. *Sci Rep*. 2022;12:804.

141. Rodriguez-Escudero JP, Pack QR, Somers VK, et al. Diagnostic performance of skinfold method to identify obesity as measured by air displacement plethysmography in cardiac rehabilitation. *J Cardiopulm Rehabil Prev*. 2014;34:335–342.

142. Medina-Inojosa J, Somers VK, Ngwa T, Hinshaw L, Lopez-Jimenez F. Reliability of a 3D body scanner for anthropometric measurements of central obesity. *Obes Open Access*. 2016;2:10.

143. Ross R, Neeland IJ, Yamashita S, et al. Waist circumference as a vital sign in clinical practice: a Consensus Statement from the IAS and ICCR Working Group on Visceral Obesity. *Nat Rev Endocrinol*. 2020;16:177–189.

144. Cruz P, Johnson BD, Karpinski SC, et al. Validity of weight loss to estimate improvement in body composition in individuals attending a wellness center. *Obesity*. 2011;19:2274–2279.

145. Pack QR, Rodriguez-Escudero JP, Thomas RJ, et al. Diagnostic performance of weight loss to predict body fatness improvement in cardiac rehabilitation patients. *J Cardiopulm Rehabil Prev*. 2013;33:68–76.

KEY WORDS body composition, body mass index, cardiovascular disease, obesity, obesity paradox, weight loss