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## A Saudi Heart Association Position Statement on Obesity and Cardiovascular Disease

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# A Saudi Heart Association Position Statement on Obesity and Cardiovascular Disease

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## Abstract

**Objectives:** The obesity pandemic is a major public health concern in Saudi Arabia, with significant impact on cardiovascular disease (CVD). This position statement aims to provide an overview of available evidence as well as the recommendations of the Saudi Heart Association on the management of obesity associated with CVD.

**Methods:** Under the auspices of the Saudi Heart Association, a multidisciplinary expert panel comprised of cardiologists and endocrinologists discussed available evidence and provided recommendations on the management of obesity in CVD. The expert panel discussions occurred between September of 2023 and May of 2024 and also took into consideration local expertise in addition to published data in the management of obesity and CVD in the Kingdom of Saudi Arabia.

**Results and conclusions:** The expert panel explored studies on obesity and its implication on CVD assessment modalities, while also examining the efficacy and cardiovascular safety of available interventions for weight reduction. The association between obesity and CVD is undeniable. The treatment of obesity, be it through lifestyle changes, pharmacological therapy or surgery, is an effective strategy for both weight loss as well as the primary and secondary prevention of CVD. The Saudi Heart Association position statement thus provides guidance and recommendations for the management of obesity/overweight and CVD in Saudi Arabia. This position statement is expected to contribute towards obesity and CVD prevention efforts in Saudi Arabia by promoting adequate and time-appropriate treatment of these conditions.

**Keywords:** Obesity, Cardiovascular diseases, Disease management, Saudi Arabia

## 1. Introduction

The obesity pandemic poses a major healthcare problem around the world. Overweight affected around 40% (1.9 billion) of adults in 2016, of

which 13% (650 million) were obese [1]. The obesity pandemic also extends to younger individuals, with obesity or overweight affecting 38.2 million children aged 5 years or younger (in 2019) and more than 340 million children and adolescents between the ages

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of 5 and 19 (in 2016) [1]. Obesity has also attained pandemic proportions in the Middle East, with more affluent countries especially affected [2]. Data indicate that the global average of obesity prevalence of 13% is at least doubled in Saudi Arabia [3,4]. However, an overview of data from the Global Health Observatory paints a far more dire situation, rendering obesity and overweight a health issue of national interest; the overall prevalence of overweight and obesity in 2016 had exceeded 60% in the adult Saudi population, and ranged from 20 to 60% in pediatric and adolescent groups [5]. The alarming prevalence of obesity in Saudi Arabia has been confirmed locally in the PURE-Saudi study [6].

Obesity and overweight were officially recognized as a complex chronic disease by medical societies and associations (such as the American Medical Association) [7]. Obesity-related mortality has sharply increased since 1990, with implications on modern human society overshadowing those of underweight and malnutrition [8]. Estimates from 2019 attribute approximately 5.4 million global deaths to high body mass index (BMI) [9]. More deaths in 2017 are attributable to or caused by obesity in Saudi Arabia compared to the global average (18% vs. 8%, and 116.7 per 100,000 vs 60 per 100,000, respectively) [10], due to the pervasiveness of this disease in the country. Moreover, the past three decades have seen the rise of high BMI to become the leading risk of years lost to disability in Saudi Arabia [11]. BMI is also one of the five risk factors that contributed to more than 50% of the risk of incident cardiovascular disease (CVD) and around 20% of deaths from any cause in a global cohort [12]. Clear associations have also been drawn between obesity specifically, cardiometabolic diseases and their risk factors [13]; individuals who are obese or have increased adiposity have higher likelihoods of cardiovascular (CV) mortality, and developing cardiometabolic diseases such as type 2 diabetes mellitus (T2DM), hypertension, and dyslipidemia [14–18]. A direct link between adiposity and high-risk CV traits (aortic diseases, heart failure (HF), atrial fibrillation (AF), etc.) has been established in genetic and population-based studies [19,20].

The need for early interventions to help in primary prevention and adequate management of obesity is therefore increasingly evident, especially in younger populations and in individuals with established CVD. This position statement therefore aims to outline the position of the Saudi Heart Association (SHA) on the management of obesity

#### Abbreviation

|        |   |
|--------|---|
| AF     | Atrial Fibrillation                           |
| BMI    | Body Mass Index                               |
| CAD    | Coronary Artery Disease                       |
| CCTA   | Coronary Computed Tomography Angiography      |
| CMR    | Cardiac Magnetic Resonance                    |
| CT     | Computed Tomography                           |
| CV     | Cardiovascular                                |
| CVD    | Cardiovascular Disease                        |
| DEXA   | Dual-Energy X-Ray Absorptiometry              |
| ECG    | Electrocardiogram                             |
| EMA    | European Medicines Agency                     |
| FDA    | United States Food and Drug Administration    |
| GIP    | Glucose-Dependent Insulinotropic Polypeptide  |
| GLP-1  | Glucagon-Like Peptide-1                       |
| HF     | Heart Failure                                 |
| LDL    | Low-Density Lipoprotein                       |
| LEPR   | Leptin Receptor                               |
| LVEF   | Left Ventricular Ejection Fraction            |
| MACE   | Major Adverse Cardiovascular Events           |
| MC4R   | Melanocortin-4 Receptor                       |
| MRI    | Magnetic Resonance Imaging                    |
| PCSK-1 | Proprotein Convertase Subtilisin/Kexin Type 1 |
| PET    | Positron Emission Tomography                  |
| POMC   | Proopiomelanocortin                           |
| RCT    | Randomized Controlled Trial                   |
| SCD    | Sudden Cardiac Death                          |
| SFDA   | Saudi Food and Drug Administration            |
| SGLT2  | Sodium-Glucose Transport Protein 2            |
| SHA    | Saudi Heart Association                       |
| SPECT  | Single-Photon Emission Computed Tomography    |
| T2DM   | Type 2 Diabetes Mellitus                      |
| TTE    | Transthoracic Echocardiogram                  |
| WC     | Waist Circumference                           |
| WHO    | World Health Organization                     |
| WHR    | Waist-Hip Ratio                               |

associated with CVD and to provide guidance to healthcare professionals highlighting the most recent evidence in this field.

## 2. Methods

A multidisciplinary panel of experts met under the auspices of the SHA in a series of meetings and online deliberations between September of 2023 and May of 2024 to discuss available evidence and formulate recommendations on the management of obesity in CVD. The panel was made up of cardiologists, endocrinologists and with extensive expertise and knowledge in the management of CVD in Saudi Arabia. Original articles, review papers and meta-analyses were included in the literature review and considered by the experts. PubMed and MEDLINE searches were conducted for relevant literature with no limits on date or language. Search terms (or combination of terms)

that were used included ‘obesity’, ‘epidemiology’ ‘Kingdom of Saudi Arabia’ ‘adiposity’, ‘cardiovascular disease’, ‘cardiovascular risk’, ‘coronary artery disease’, ‘atrial fibrillation’, ‘heart failure’, ‘hypertension’, ‘body mass index or BMI’, ‘waist circumference’, ‘waist-hip ratio’, ‘body composition’, ‘obesity paradox’, ‘weight loss’, ‘pharmacotherapy or medication’, ‘antiobesity’, and ‘bariatric surgery’.

### 3. Definition and measures

The World Health Organization (WHO) defines overweight and obesity as “*as abnormal or excessive fat accumulation that presents a risk to health*” [21]. The evaluation and classification of weight generally relies on the WHO’s BMI classifications of weight status (Table 1). Individuals who had a BMI between 25.0 and 29.9 kg/m<sup>2</sup> are classified as being overweight, while obesity corresponds to BMI ≥30.0 kg/m<sup>2</sup> [22,23]. However, these BMI categories are largely derived from studies on Caucasian populations, which potentially limits their applicability to other races-ethnicities with different body fat distribution. Ethnic-specific cutoff values for BMI become necessary with the emergence of ethnic differences in health risks associated with obesity [24,25]. BMI-based classifications were thus redefined for South Asian, Chinese and Japanese populations (Table 1) with lower BMI thresholds (overweight BMI ≥23.0 kg/m<sup>2</sup> and obesity BMI ≥25.0 kg/m<sup>2</sup>) adopted for overweight and obesity in these populations reflecting increased CV risk [26].

Despite its common use, BMI has several limitations in terms of assessment and prediction of CV risk; BMI does not reflect body fat composition or distribution possibly leading to weight status misclassification, nor does it consider relevant individual variables such as age, gender and race/ethnicity. As a result, individuals with a normal

weight based on BMI could have higher CV risk due to disproportionate fat distribution, while individuals with overall obesity could present with low visceral (abdominal) adiposity and by extension, could have a lower CV risk, or “metabolically healthy” obesity [27–29]. The evidence linking visceral adiposity to CV risk is mounting [30–32]. Alternative anthropometric measures were thus sought and explored for improved CV risk assessment. Waist circumference (WC) reflects body composition, particularly abdominal body fat, and may lead to better prediction of cardiometabolic and CVD as well as mortality [33–36]. The use of WC along with BMI is therefore widely recommended and gender-specific WC cutoff levels are recommended for the classification of disease risk (WC > 102 cm for men or >88 cm for women [23]). Evidence also suggests that waist-hip ratio (WHR) is a better predictor of fat distribution, central obesity and CVD compared with BMI [23,33]. A WHR of 0.9 or more in men or 0.85 or more in women was recommended by the WHO to identify increased risk of metabolic complications [23]. Another measure that could be useful for metabolic and CV risk-based stratification independently of body weight is WC to height ratio, a marker of central adiposity [37–40].

Other methods such as dual-energy x-ray absorptiometry (DEXA) and magnetic resonance imaging (MRI) techniques are available for the accurate detection of body fat and its distribution. However, these techniques require more time, expertise and cost compared to anthropometric measures such as BMI and WC. Moreover, results obtained from different methods of body composition assessment might not be concordant, as shown between DEXA and bioelectrical impedance analysis [41]. That being said, imaging modalities such as computed tomography (CT) and MRI can be used for the quantification of adipose tissue (i.e. liver, pancreas, heart, skeletal muscle) and ectopic fat depots (fat stored in non-adipose tissues) [42]. In this regard, body composition assessment can help prevent the misclassification of individuals (including children) with higher body fat (and by extension, higher CVD risk) based on relative body weight, or BMI [43–46].

Despite its correlation with CVD risk factors, it remains debatable whether percent body fat (body composition) is a superior predictor of CVD and its risk factors compared to BMI or WC [47–49]. Moreover, optimal cutoff values for percentage of body fat have yet to be established. However, it is important to note that the affordability and accessibility of non-anthropometric measures is

Table 1. WHO body mass index classifications of weight status [22,23,26].

| Classification                     | WHO general population Body mass index (BMI) classifications (kg/m <sup>2</sup> ) | WHO South Asian, Chinese and Japanese BMI classifications (kg/m <sup>2</sup> ) |
|------------------------------------|---|--|
| Underweight                        | <18.5   | <18.5  |
| Healthy weight                     | 18.5–24.9   | 18.5–22.9  |
| Overweight                         | 25.0–29.9   | 23.0–24.9  |
| Obese                              | ≥30.0   | ≥25.0  |
| Obesity Class I                    | 30.0–34.9   | 25.0–29.9  |
| Obesity Class II (morbid obesity)  | 35–39.9   | ≥30.0  |
| Obesity Class III (severe obesity) | ≥40.0   | –  |

increasing. CT and MRI have the highest accuracy for measuring adiposity but carry the risk of radiation exposure in addition to being costly and time-consuming. Ultrasonography and DEXA are accurate but impractical for adiposity measurement. Bioelectrical impedance analysis is the method with the highest ease of use but the lowest accuracy in determining body composition [50]. When considering any of these methods, the accuracy of each in minority or ethnically-diverse populations should not be dismissed.

## 4. Obesity and CVD

### 4.1. Obesity pathogenesis

Obesity is a chronic, relapsing multifactorial neurobehavioral disease with associations to a plethora of other conditions such as CVD, dyslipidemia, insulin resistance and diabetes, stroke, gallstones, fatty liver, sleep apnea and cancers.

The pathogenesis of obesity implicates impairment of energy balance due to the regulation of energy utilization and appetite, along with complex interactions with environmental and genetic factors. While the etiology of obesity remains debated, current management practices focus on correcting the positive energy imbalance resulting from higher consumed vs expended calories. This can in turn be linked to environmental, social and economic variables mainly pertaining to the availability and consumption of highly rewarding and energy-dense food (i.e., fast food) [51,52]. Family history and lifestyle also contribute to the pathogenesis of obesity, as individuals (particularly children) have a higher likelihood of becoming obese if one or both of their parents are obese [53,54], or if they or their caretakers follow poor dietary and exercise choices [55,56]. Although the exact mechanisms of this association remain unclear, dysbiosis, or imbalance of microbial populations in the human gut, has been suggested as a contributor to the pathogenesis of obesity and its associated comorbidities [57,58]. Sex-specific variations in obesity and associated CVDs occurrence have also been noted, with possible implication of sociocultural, environmental, and physiological factors as contributors to the risk gap between males and females [59]. While the influence of environmental factors on obesity pathogenesis is undeniable, genetic and epigenetic susceptibilities to fat accumulation compound these effects. Genetic factors contribute to up to 70% of the obesity variation in humans [60]. Genetic obesity triggers can be related to a variation or mutation in a single

gene (monogenic), several genes (polygenic) or neurodevelopmental and organ/system malformations (syndromic). Several genes (such as AgRP (Agouti-related peptide), PYY (orexogenic), or the melanocortin-4 receptor (MC4R) are recognized causes of monogenic obesity through a disruption of appetite and weight regulation as well as metabolic hormonal regulation (ghrelin, leptin, insulin). These monogenetic mutations can cause high levels of hunger, poor appetite control (binge eating), lower satiety, higher fat accumulation, and metabolic dysregulation leading to dramatic obesity in young children as well as adults [61–65].

### 4.2. Pathophysiology of CVD in obesity

Before exploring the pathophysiology of CV conditions in association with obesity, it is necessary to distinguish between the types of adiposity and their correlation with CV risk. Adipose tissue beneath the skin is known as subcutaneous adipose tissue and visceral adipose tissue denotes adipose (fat) tissue stored within the abdominal cavity. Ectopic fat refers to depots that accumulate on organs such as the liver, heart, pancreas and muscles. Of interest in CVD, ectopic fat depots of the pericardial and epicardial regions have both been linked to the development of CVD and events [66–69]. Despite the majority of evidence focusing on visceral adiposity, both visceral and subcutaneous adipose tissue have been associated with cardiometabolic risk [70]. Moreover, correlations were established between adipose and ectopic fat depots [71,72]. That being said, the distribution of fat between subcutaneous, and intra-abdominal/visceral adipose tissue shows considerable variation between individuals at any BMI value [42,73,74]. This could lead to the previously mentioned “metabolically healthy” obesity in case of low visceral adiposity, or increased CV risk in cases of excess visceral adiposity despite low risk classification by BMI [27–29,42,74,75]. As evidence of the link between visceral adiposity and CV risk continues to rise [30–32], and considering the pathophysiological associations between obesity and CVDs (Fig. 1), it is important to incorporate adequate assessments of visceral adipose tissue in the management of patients with obesity and CVD.

#### 4.2.1. Coronary artery disease and atherosclerosis

Systemic and local inflammation have both been linked to obesity and adiposity as associations emerge between inflammatory markers and measures of adiposity as well as cardiometabolic risks [76]. It is thought that dysfunction in lipid pathway

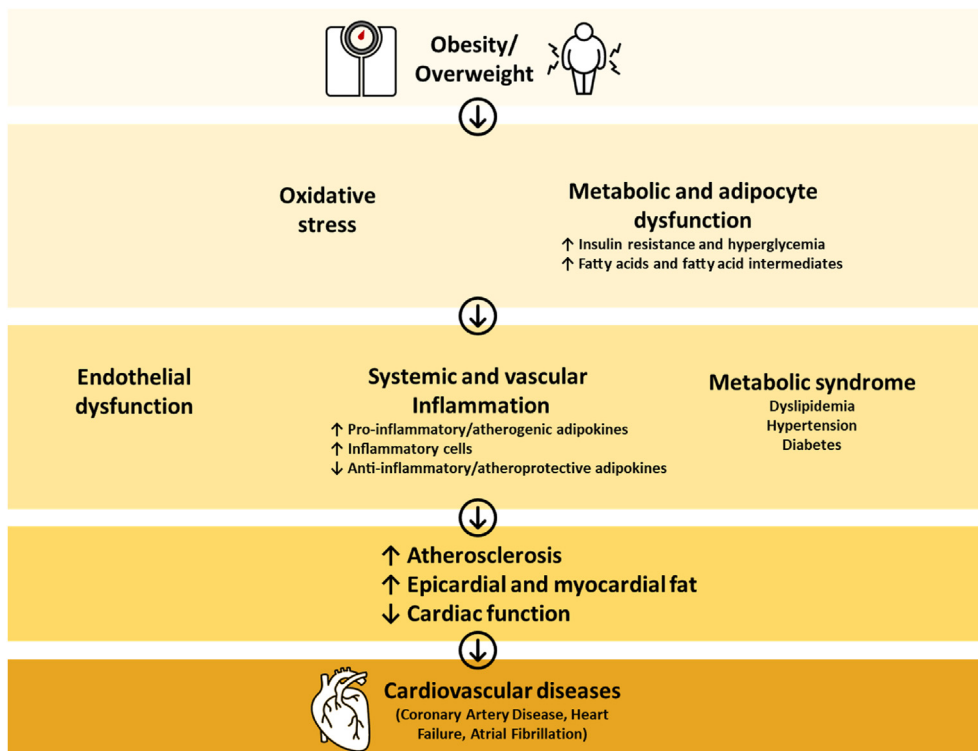


Fig. 1. Pathophysiology of cardiovascular diseases in obesity and overweight.

and the resulting buildup of fatty acids and their intermediates can promote inflammation and metabolic dysregulation by causing oxidative stress [77,78]. Obesity can thus also be referred to as “metabolic inflammation” with implications in the pathogenesis of cardiometabolic diseases. In fact, the early atherosclerotic changes experienced throughout childhood are accelerated by obesity through insulin resistance and inflammation [79]. The extent of atherosclerotic disease can actually be linked to obesity and its downstream metabolic risk factors (hypertension, dyslipidemia, diabetes) and seems to be closely related to visceral adiposity [80–82]. Fatty streak development and atherothrombosis are examples of atherosclerotic processes that result from systemic and vascular inflammation, which in turn are promoted by visceral adiposity [83,84]. Obesity also contributes to the onset of atherosclerosis via insulin resistance, metabolic syndrome and endothelial dysfunction [85,86].

As a result, individuals who are obese have a significantly greater risk of incidence coronary artery disease (CAD) [87–90]. The elevated risk of CAD with obesity also extends to individuals who are overweight [91]. More importantly, there is a marked positive association between central (visceral) adiposity and risk of CAD and CV

mortality which persists in individuals who have a normal weight according to BMI [92–96]. However, it is also important to remember that metabolic CV risk factors such as hypertension, dyslipidemia and diabetes seem to largely mediate the association between obesity and CAD [97,98], although some evidence is also available to the contrary [88,99].

#### 4.2.2. Heart failure

Obesity-related excess adiposity and comorbidities carry direct and indirect effects on cardiac function, leading to hemodynamic changes (increased cardiac output, reduced systemic vascular resistance, increased myocardial stiffness and filling ventricular pressure), higher blood pressure, and myocardial fat accumulation [15,100]. Obesity is a major risk factor for the development of HF considering its implication as a risk factor for conditions implicated in HF development such as hypertension, CVD, and left ventricular hypertrophy [101,102]. This led clinicians and researchers to recognize an obesity phenotype in HF with preserved ejection fraction [103]. Epidemiological studies have confirmed that the incidence of HF increases along the BMI spectrum. Moreover, with every 1-unit BMI increase, the incidence of HF is increased by 5% and 7% in men and women,

respectively, even after accounting for risk factors [104–106]. Of note that increased BMI might be more strongly correlated with HF with preserved ejection fraction rather than HF with reduced ejection fraction [107,108] (see Fig. 2 for a depiction of the pathophysiology of obesity and HF with preserved ejection fraction).

However, the obesity paradox has been noted in HF (see section 5 for more details).

#### 4.2.3. Atrial fibrillation, arrhythmias and sudden cardiac death

Obesity is a major contributor to AF through structural and electric remodeling. Epicardial fat infiltration of the myocardium might be responsible for voltage abnormalities, conduction block and AF vulnerability [109]. There is increasing evidence linking epicardial adipose tissue with arrhythmogenic substrate development, which could be a major contributor to HF in obesity [67–69]. Obese individuals have a higher likelihood of presenting with greater left atrial pressure and volumes, left atrial remodeling, and impaired contractility even when accounting for CV risk factors [67,110]. It is currently estimated that obesity accounts for 20% of AF cases [111–113]. Generally, incident AF in later life shows links with weight gain (higher BMI) in mid-life [114,115]; the risk of incident AF actually rises by close to 30% for every 5-unit increase in BMI [116]. The likelihood

of AF progression is also affected by obesity and is positively correlated with BMI, with class 2 obesity incurring an 87% surge in the risk of progression from paroxysmal to permanent AF [117]. In addition to AF, individuals with mild or severe obesity are at a higher risk of both ventricular tachycardia and ventricular fibrillation [118,119]. Arrhythmic substrate is also implicated in the development of ventricular tachycardia and ventricular fibrillation and is seen concomitantly with increased left ventricular diameter and mass [120], concentric left ventricular hypertrophy [121], left ventricular diastolic dysfunction [120,122] and repolarization abnormalities. Obesity is also an recognized risk factor for sudden cardiac death (SCD) [123,124]; the risk of SCD increases by 16% for every 5-unit increment in BMI [125]. While evidence suggests obesity as the most frequent non-ischemic cause of SCD [126], body fat distribution may affect the relationship between the two conditions. Abdominal adiposity seems to be a marker of SCD potentially due to left ventricular hypertrophy, QT prolongation, premature ventricular complexes, and autonomic imbalance [127–129]. Moreover, epicardial adipose tissue leads to a higher risk of both SCD and ventricular tachycardia/ventricular fibrillation [130–134]. SCD can be independently predicted by QRS fragmentation and fibrosis [135,136], further supporting the association between obesity and arrhythmias.



Fig. 2. Pathophysiology of obesity and heart failure with preserved ejection fraction.

#### 4.2.4. Obstructive sleep apnea, obesity and CVD

Obstructive sleep apnea is a sleep disorder characterized by episodic cycles of breathing disruption that are associated with both acute and chronic physiological stressors. Obesity is established as an important risk factor for obstructive sleep apnea [137], most likely due to mass loading in the upper airway. Obstructive sleep apnea is also highly frequent in individuals suffering from CVD and CV risk factors such as hypertension, HF, CAD, pulmonary hypertension, AF and stroke, with estimates of obstructive sleep apnea in these populations varying between 40 and 80% [138]. In fact, obstructive sleep apnea can independently predict AF even in the absence of other CVDs [139]. While a causal relationship has yet to be proven, the high likelihood of obstructive sleep apnea in AF patients is likely related to the shared risk factors of the two conditions, which include obesity and hypertension. Possible mechanisms of AF emergence due to obstructive sleep apnea include structural and functional atrial remodeling and subsequent atrial fibrosis resulting from chronic changes in intrathoracic pressure [139]. The link between AF and obstructive sleep apnea is reflected clinically by AF reversal upon obesity management; Sufficient weight loss ( $\geq 10\%$ ) carries significant benefit in terms of arrhythmic free survival rate, AF burden, and symptom severity [140]. However, this benefit is not observed with lesser degrees of weight loss (5% weight loss) [141]. By contrast, the relationship between obstructive sleep apnea and HF is two-pronged; A diagnosis of obstructive sleep apnea is linked to an increased risk of HF, while patients diagnosed with HF are at an increased risk for coexisting obstructive sleep apnea and central sleep apnea, as well as a higher risk of adverse clinical outcomes [142]. Obstructive sleep apnea most likely contributes to the progression of HF through sympathetic activation, increased inflammation, increased left ventricular transmural pressure and left ventricular afterload, and endothelial dysfunction [143]. Evidence suggests that treatment of central sleep apnea through adaptive servo-ventilation, or obstructive sleep apnea through continuous positive airway pressure, can improve heart function and quality of life [144–148]. However, data are generally insufficient for the establishment of appropriate treatment approaches. It also remains controversial whether treatment of obstructive sleep apnea will improve CV outcomes in CAD [149], despite the implication of oxidative stress and systemic inflammation resulting from obstructive sleep apnea in the onset of coronary atherosclerosis and acute myocardial infarction events.

## 5. Obesity paradox

As established in the previous section, people who are obese are more likely to develop CVD in comparison with people who are of normal weight. However, adverse short-term CVD outcomes cannot be consistently predicted by BMI and other body composition parameters in those who are overweight or obese [101,150,151]. This is known as the obesity paradox. Several studies have documented this reversal of traditional epidemiology, particularly in overweight or class I obesity classifications. In HF, studies suggest better CV outcomes in patients who are obese and have HF with reduced ejection fraction, HF with preserved ejection fraction and acutely decompensated HF [101,102,151]. Better CV outcomes have been observed in HF patients who are overweight or obese (class 1) compared to patients who have comparable HF but have a normal weight. Similarly controversial results have been reported from several systematic reviews including CAD and HF patients [152–154]. However, most studies on the subject were retrospective and observational, with limited to no differentiation between intentional and unintentional weight loss. Unintentional weight loss may reflect undiagnosed disease such as cancer and act as a significant confounder of study results. In this regard, it was evident that intentional weight loss was associated with clinical benefit [155–157], while a recent meta-analysis associated unintentional or unspecified weight loss with higher mortality in HF patients who are obese or overweight [158]. Moreover, the obesity paradox could be due to the potential confounding effect of lead time bias, or in other words, earlier assessment and diagnosis of CVDs in those who are obese than would be practiced in normal weight individuals. Cardiorespiratory fitness could also play a role in the observation of more favorable CVD outcomes irrespective of BMI.

Obesity is not only a confounding factor when examining CV outcomes in patients with HF, it also affects the interpretation of natriuretic peptide levels. Normally, natriuretic peptides play a vital role in the diagnosis and management of HF [159]. However, individuals who are obese have low circulating natriuretic peptide levels even in the absence of HF [160]. This translates into the impaired reliability of natriuretic peptide measurement for HF diagnosis in obese patients seeing as measured levels are lower than what is expected from HF severity [161,162]. For more details on the use of biomarkers for the management of HF, please refer to the Saudi Heart Association Position Statement on the Use of Biomarkers for the



Management of Heart Failure and Acute Coronary Syndrome [159].

## 6. Impact of obesity on CVD management

### 6.1. *Imaging in obesity*

Detailed CV screening allows the diagnosis and treatment of subclinical CVD and should therefore be done for obese patients, even if they are asymptomatic [163]. Cardiac hypertrophy is commonly observed in patients with obesity and is the most typical cardiac change among children who are obese [164]. Obesity can also result in changes in left ventricular ejection fraction (LVEF), mostly increased [165] or less frequently decreased LVEF [166]. Other cardiac indices (strain, torsion, and contraction synchrony) are also impaired in patients with obesity (including asymptomatic children [167,168]), and allow the detection of systolic alterations in asymptomatic subjects [169]. Moreover, these parameters have a higher sensitivity for the prediction of cardiac function and mortality than LVEF [170].

However, while different non-invasive and invasive modalities may be used to accurately detect cardiac changes in obese subjects (such as hypertrophy and ischemia/fibrosis), it is important to recognize how obesity might limit their diagnostic accuracy and/or feasibility. Considerations for the use of diagnostic tools in obese subjects include technical limitations due to body size/weight in several tools (i.e. Single-photon emission computed tomography (SPECT), positron emission tomography (PET)), as well as poor acoustic window and attenuation artifacts with echocardiography and nuclear cardiology, among other limitations that will be detailed in the following sections.

#### 6.1.1. *Imaging: non-invasive assessments*

6.1.1.1. *Electrocardiogram.* Electrocardiogram (ECG) is a widely available and affordable non-invasive diagnostic tool that may be used in the CV assessment of individuals who are obese. However, it should be noted that obesity can affect the ECG by causing the elevation of the diaphragm in the supine position and consequently, displacing the heart. Obesity also leads to higher cardiac workload, and increased distance between the heart and the recording electrodes [171]. Clinically relevant electrocardiographic changes that can be expected with obesity include a higher frequency of ST-segment depression (increased QRS interval and QTc interval) [172], increased heart rate and false-positive

criteria for inferior myocardial infarction [171]. Left ventricular hypertrophy underdiagnosis is more likely in individuals who are severely obese, hence the need to adopt modified left ventricular hypertrophy criteria based on the R wave in aVL to improve the overall accuracy of ECG assessments (R wave amplitude in lead aVL and S wave amplitude in lead V3 >35 mm for men and >25 mm for women) [171].

Obesity also limits the performance of the standard treadmill stress test; obesity-related electrocardiographic abnormalities affect the accuracy of test interpretation while diminished aerobic capacity (fitness) prevent the achievement of diagnostically-valid heart rate results [173–175]. Patients may also opt to terminate the test due to factors unrelated to CVD, such as fatigue, leg pain, dyspnea [176]. However, it is still possible to achieve valid results with standard or modified protocols.

6.1.1.2. *Echocardiography.* Echocardiography is a widely available radiation-free imaging technique that might be valid in individuals who are obese. The typical change in obese individuals is the increase in myocardial mass/hypertrophy. The hypertrophy could take the form of concentric with increases in both mass and wall thickness that are frequently linked to increased mortality. Other forms that may be seen are eccentric hypertrophy with increased mass but normal wall thickness or concentric remodeling where the mass is normal while the wall thickness increases. Most transthoracic echocardiogram (TTE) research has found obese individuals to have either normal or increased LVEF [177,178]. As an alternative to LVEF, advanced indices such as strain, torsion, and contraction synchrony are considered to be more sensitive indices of function and future mortality [170].

There is evidence that these parameters may detect systolic alterations early before disease symptoms will be overt, which is ideal for monitoring asymptomatic subjects [169]. Subclinical systolic dysfunction [179] and lower values of strain rates and torsion have been reported in obese patients with preserved LVEF [180–185]. Despite the confounding role of CV risk factors, obesity may also be associated with diastolic dysfunction [180,184,185]. BMI is also correlated with both left atrial dimensions and progressive dilation irrespective of blood pressure [186]. Left atrium enlargement can occur concomitant with left ventricular hypertrophy, and that it is a risk factor for AF. Left atrial dimensions should be accurately determined in subjects who are obese. To that end, indices other than left atrial index should be used in

order to avoid underestimating left atrium dimensions. Alternative indices that should be used include linear diameter in parasternal view or using lower thresholds for defining left atrial dilatation (normal  $\leq 28$  mL/m<sup>2</sup>) or left atrium size indexed to height [187]. The assessment of the right ventricle with conventional 2D echocardiography is also highly limited by obesity and would be better assessed by 3D echocardiography and cardiac magnetic resonance (CMR) [188]. The increase in right ventricle mass, end-diastolic volume, stroke volume and decreased right ventricle ejection fraction were independent of left ventricular dimension and hypertension [189]. Cardiac stiffness might be recognized by the epicardial fat, which points to increased cardiometabolic risk [190]. Epicardial fat was found to be a better index to evaluate the carotid stiffness than the hip/waist ratio and was linked to a high prevalence of CVD in sex and age-matched controls. Qualitative assessment of epicardial fat is less sensitive. TTE with contrast can be used for the identification of early subclinical changes in both the left and right ventricle and should therefore be done prior to referral for CMR. TTE can be combined with a stress test, either physiological (treadmill exercise) or pharmacological (dobutamine) in order to assess cardiac function. However, this technique remains limited by its high operator dependency and poor acoustic windows [191]. The diagnostic accuracy of echocardiography can be and often is improved with the use of a contrast injection, which increases the number of heart segments that are visualized [191,192].

**6.1.1.3. Single photon emission computed tomography and positron emission tomography.** SPECT can be used for the assessment of CV function in individuals who are obese. Deconditioning pharmacologic stress with vasodilator (dipyridamole), and dobutamine stress add extra value to diagnose a possible underlying ischemic heart disease.

Moreover, patients who weigh 113–160 kg would be better assessed via two-day protocols with larger tracer doses. Another limitation of note in subjects who are obese is soft tissue attenuation of radioactive tracers, usually Technetium-99, which has a photopeak of gamma-ray emission of 140.5 keV, and half of that energy will be attenuated every 5 cm of chest wall thickness, leading to artifacts and poor signal-to-noise ratios in SPECT imaging [193]. It is therefore important to distinguish between artifacts and actual perfusion defects when assessing individuals who are obese. The quality of images could also be improved by the use of markers with greater energy emission, such as Technetium

sestamibi [194]. Moreover, weight-based limitations are faced with SPECT when evaluating patients who weigh at least 160 Kg (or have a BMI  $>35$  kg/m<sup>2</sup>), even with the use of ultrafast, high-efficiency SPECT cameras. That being said, the use of ultrafast, high-efficiency SPECT cameras has improved the sensitivity over the conventional SPECT cameras in morbidly obese subjects, allowing for assessment of coronary flow reserve.

The issue of the attenuation artifact in the obese can be overcome by using a cardiac PET-CT scan, which is not widely available because it utilizes positron emission (511 KeV) with a very short half-life (minutes) and requires having cyclotron on the premises. A cardiac PET-CT allows accurate attenuation correction and reduction of false-positive results. PET rubidium is the preferred nuclear imaging modality in individuals who are obese. It can generate higher quality images, correction for attenuation, less radiation exposure and higher diagnostic precision when compared to sestamibi SPECT [195]. Moreover, it can accurately assess myocardial perfusion across all obesity classes and allows the quantification of coronary blood flow [195].

Obese patients with heart failure demonstrate altered indices of cardiac sympathetic innervation on I-123 metaiodobenzylguanidine imaging, linking obesity to sympathetic impairment.

**6.1.1.4. Coronary Computed Tomography Angiography.** Coronary Computed Tomography Angiography (CCTA) is an alternative imaging modality that can be used for the quantification of coronary plaque, both calcified and non-calcified. It is also useful for the quantification of myocardial ischemia and the measurement of epicardial fat. The diagnostic accuracy of CCTA remains high in individuals who are obese, although increasing BMI is associated with worsening image quality due to the rise in background noise and reduced signal-to-noise ratio. There may also be higher rates of non-evaluable segments with CCTA in individuals who are overweight or obese due to blood volume distribution variations when contrast is injected in these populations [196]. Moreover, CCTA makes use of nephrotoxic contrast agents and ionizing radiation, which might limit its routine application.

**6.1.1.5. Cardiac magnetic resonance.** CMR is an imaging modality that can be used for the detection of perfusion defects and the evaluation of cardiac function, morphology and wall motion/thickness. CMR can reflect the cardiac changes due to chronic pressure overload and high cardiac output in obese patients [192,197]. CMR can also identify myocardial

fibrosis, allow extracellular volume fraction calculation, and quantify of epicardial fat. More importantly, obese patients can be better accommodated by newer-generation MRIs due to their large bore sizes and stronger magnets. Diagnostic image quality can be achieved with CMR in the majority (approx. 90%) of obese patients [198]. That being said, the use of CMR in individuals who are obese (particularly severe obesity) might not be feasible due to table weight limits, bore diameter and length (in older-generation MRIs) [192].

### 6.1.2. Imaging: invasive assessment

**6.1.2.1. Coronary angiography.** Limitations of coronary angiography for individuals who are obese include technical difficulties such as suboptimal radiographic visualization, higher complications and difficult vascular access. Radial access is associated with fewer complications in patients who are obese and is therefore preferred [199,200]. In the event that femoral access is used in patients who are obese, ambulation should be accelerated via vascular closure devices [201]. Issues with radiographic imaging can also be expected with obesity, as higher radiation exposure is necessary to reach adequate x-ray penetration and acceptable image quality [202]. In addition to these limitations, coronary angiography for obese patients might be challenged by the physical limitations of the catheterization table.

### 6.2. Treatment

Not only does obesity increase the risk of developing a CVD such as HF and cardiac arrhythmias (as mentioned in section 4.2.), it can also impact their management. Patients who are obese might experience altered drug properties, particularly in relation to volume of distribution and elimination [203]. This change in pharmacokinetics is observed in lipophilic drugs, possibly necessitating weight-based dose adjustments when treating obese patients with concomitant CVDs. For example, the volume distribution of lipophilic beta-blockers (such as propranolol) routinely used for rate control in AF and other CVDs was decreased in patients who are obese [204,205]. Lipophilicity is not the only factor implicated in reduced drug efficacy in obesity. For example, the treatment of AF also relies on anticoagulation via warfarin or direct oral anticoagulants (DOACs). While there is no evidence of decreased DOAC efficacy in obese patients [206], warfarin dose adjustment (dose increase) would be ideal to achieve international normalized ratio

within the therapeutic range as body weight increases [207]. Obesity can also affect the response to rhythm control strategies, be they pharmacological or surgical; antiarrhythmic drugs (calcium channel blockers) generally have decreased efficacy and higher rates of nonresponse in obese patients [208]. In a similar vein, the frequency of cardioversion failure and AF recurrence after catheter ablation is increased with obesity [116,209].

While not extensive, current evidence supports the consideration of obesity and BMI when choosing and personalizing CVD management strategies in order to achieve optimal clinical outcomes.

## 7. Interventions for weight reduction: efficacy, safety and cardiometabolic outcomes

Weight reduction in overweight and obese patients significantly improve CV risk factors. Weight management through lifestyle intervention includes medical nutrition therapy, exercise and increased physical activity, behavioral changes and pharmacotherapy. The choice of weight management approach should be staged in a step wise approach that depends on the patient profile (CVD risk factors, established CVD, medical history, previous weight loss attempts, etc.). Multidisciplinary lifestyle interventions might be more appropriate for CVD prevention in obese people, while more advanced interventions (i.e. pharmacotherapy and/or surgery) might be more appropriate for the management of obesity in individuals with established atherosclerotic CVD. Metabolic surgery is another way of long-term weight management.

In addition to weight reduction, management of conditions such as hypertension, dyslipidemia, and diabetes should be targeted. In addition to being common CVD and obesity risk factors, some disorders, particularly hypertension, may arise as a direct result of obesity (see Fig. 3). For further information, please refer to relevant published SHA guidelines and position statements, which address the management of these conditions in the context of CVD. These include but are not limited to:

- National Heart Center/Saudi Heart Association 2023 Guidelines on the Management of Hypertension [210].
- Saudi Heart Association Guidelines on Best Practices in the Management of Chronic Coronary Syndromes [211].
- NHC/SHA 2023 Focused update of the 2019 guidelines for the management of heart failure [212].

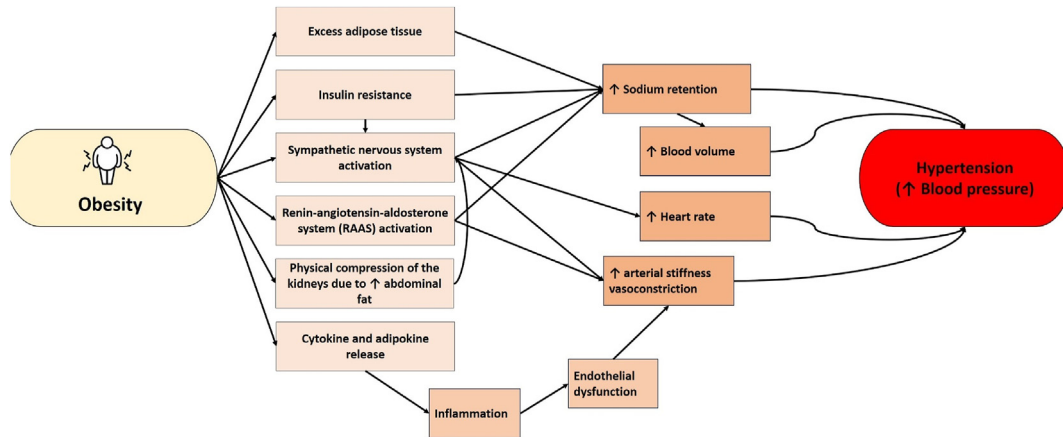


Fig. 3. Pathophysiology of obesity and hypertension.

- A Saudi Heart Association Position Statement on cardiovascular diseases and diabetes mellitus (under review as of date of publication)

### 7.1. Lifestyle interventions

Multidisciplinary lifestyle interventions are a crucial gateway into the short- and long-term management of obesity, acting through a two-pronged approach. First, it leads to improved CV risk factors [213] and might lower the risk of progression to T2DM of patients with prediabetes [214]. People achieving weight reduction (i.e. >10% of body weight reduction) were found to have lower CV mortality, non-fatal acute myocardial infarction, non-fatal stroke, and hospital admission for CV-related causes [215]. Second, nutritional intervention adopted in most lifestyle interventions seems to carry its own impact on CV outcomes.

#### 7.1.1. Diet

Diets such as the Mediterranean diet, low-fat diets and low carbohydrate diets are associated with better CV health in general, and lower risk of developing CVD [216–218], thus emphasizing the importance of limited red meat consumption and increased inclusion of vegetables, fruits and fibers in diets [217,219,220]. While other dietary approaches such as intermittent fasting, ketogenic diet and very low calorie diets lead to weight reduction, they remain controversial with no evidence of long-term CV benefits, as opposed to the Mediterranean and low fat diets [216,221,222]. For example, three models of intermittent fasting can be distinguished: time restricted eating (limited feeding window each day), alternate day fasting (free eating one day; fasting the next), and the 5:2 diet (free eating 5 days;

fasting 2 non-consecutive days). While all three models are associated with reduced body weight, long-term data are lacking and distinctions have been made in other parameters [223,224]; the time restricted eating model leads to reductions in fat mass and blood pressure but also reduces lean muscle mass. Alternate day fasting also reduces fat mass in addition to improving lipid profile, but has shown to be difficult to maintain. The 5:2 diet improves insulin sensitivity but has comparable effects to continuous caloric restriction, leading to lower desire to maintain the diet. The variable impact of different diets is summarized in Table 2. Regardless, there is a scarcity of long-term CV outcome studies for the establishment of a specific dietary approach for primary or secondary prevention of CVD, that calls for further research.

#### 7.1.2. Exercise

Dietary improvements are usually supplemented by exercise to reduce weight in people who are overweight or obese. Lifestyle interventions consisting of both dietary changes and physical activity for a healthy lifestyle such as the Diabetes Prevention Program have been shown to be at least as effective as pharmacotherapy [225,226]. There are actually robust data demonstrating that a consistent exercise regimen in itself can reduce visceral adipose tissue across both men and women, even without overall weight loss [227–229]. Aerobic exercise and resistance exercise have both been shown to decrease visceral adiposity [230,231]. Increasing exercise intensity does not lead to additional benefit on reducing visceral adiposity compared to moderate intensity exercise [232,233]. The current recommendation for physical activity of 150 min per week may be enough to decrease visceral adipose tissue [234]. In fact, a simple exercise regimen consisting of

Table 2. Comparison between the effect of various diets and their potential benefits.

|                                | ↓A1C | ↓Wt | ↓LDL | ↑HDL | ↓TG | ↓CVD | Inconclusive |
|--------------------------------|------|-----|------|------|-----|------|--------------|
| Mediterranean-style            | ✓    |     |      |      | ✓   | ✓    |              |
| Vegetarian/Vegan               | ✓    | ✓   | ✓    |      |     |      |              |
| Low- and Very Low-Fat          |      | ✓   |      |      |     |      |              |
| Low- and Very Low-Carbohydrate | ✓    | ✓   |      | ✓    | ✓   | ✓    |              |
| DASH                           |      | ✓   |      |      |     |      |              |
| Paleo                          |      |     |      |      |     |      | ✓            |

A1C: Glycated Hemoglobin; CVD: cardiovascular disease; HDL: high-density lipoprotein; LDL: Low-Density Lipoprotein; DASH-Dietary Approaches to Stop Hypertension; TG: Triglycerides; Wt: Weight.

Mediterranean style: plant-based food (vegetables, fruits and whole-grains) and healthy fat (olive oil). Dairy products and red meat allowed in low to moderate quantities; Vegetarian: plant-based food, includes egg and/or dairy products; Vegan: plant-based food, animal-derived products not allowed; Low-fat: vegetables, fruits, starches, lean protein sources and low-fat dairy products. Total fat intake  $\leq 30\%$  of total calories and saturated fat intake  $\leq 10\%$ ; Very low-fat: fiber-rich vegetables, beans, fruits, whole-grains, non-fat dairy and egg whites. Total fat intake  $\leq 10\%$  of total calories; Low-carbohydrate: vegetables low in carbohydrates, fat (from animal foods, oils, butter, avocado), protein and (optional) fruits. Carbohydrates comprise only 26–45% of total calories; Very low-carbohydrate: Similar composition to low-carbohydrate. Carbohydrates comprise  $< 26\%$  of total calories; DASH: vegetables, fruits, and low-fat dairy products, whole-grains, poultry, fish, and nuts; limited saturated fat, red meat, sugar and (optional) sodium; Paleo: lean meat, fish, shellfish, vegetables, eggs, nuts, and berries. No grains, dairy, salt, refined fats, and sugar.

Adapted from Evert AB et al. *Diabetes Care*. 2019; 42(5):731–754.

regular walking (60 min/3 times a week) has been reported to reduce visceral adipose tissue and improve insulin sensitivity in just 3 months [235]. Exercise is a fundamental intervention that should be included in any weight management program considering its effect in improving metabolic and CV function. These improvements include reduction in insulin levels, improvement of glucose tolerance, improvement of insulin sensitivity, better quality of life and reduction in vascular resistance, which usually persist even without achievement of overall weight reduction [236–238]. Physical activity has also been linked to better cardiorespiratory fitness and consequently, decreases in CVD risk, CV outcomes and CV mortality in both primary and secondary prevention studies [239–242]. Extant data support a multicomponent exercise approach consisting of combining training modalities such as continuous endurance training, interval training, and resistance training for the improvement of cardiometabolic health in individuals who are overweight or obese [243]. That said, the benefit of exercise regimens can vary according to patient characteristics, such as gender (i.e. higher cardiometabolic benefit with hybrid-type training vs. combined training among females) [243]. It is therefore important to initiate exercise regimens in an intensity and duration tailored to the CV risk and CV history of each patient, with careful monitoring of higher-risk individuals.

### 7.1.3. Psychological behavior

Lifestyle interventions should not only aim to reduce weight and/or visceral adipose tissue, but also target underlying eating and psychological behaviors that might be contributing to obesity.

Several randomized controlled trials (RCTs) have demonstrated the role of mindfulness-based interventions (such as meditation) in conjunction with standard weight-loss approaches in reducing stress, and ameliorating eating behaviors in obesity [244,245]. Similarly, cognitive behavioral therapy was associated with weight loss, increased cognitive restraint and reduced emotional eating [246]. Further studies are needed to investigate whether adopting a holistic approach to weight reduction through dietary, exercise and behavioral changes might be best for achieving and sustaining treatment outcomes in obesity.

Part of lifestyle intervention includes adjustment of some medications, especially those that increase body weight like antipsychotic medications and few diabetes medications like pioglitazone, sulphonylureas and insulin [247].

### 7.2. Medications

The history of weight-loss medication is riddled with emerging agents that reduce appetite and/or enhance energy expenditure thought to be promising but later hastily withdrawn due to an unacceptable side effects profile. One of the earliest drugs used for weight loss were centrally acting sympathomimetics desoxyephedrine, phentermine and diethylpropion, which were popular in the mid-20th century until concerns of their CV risk led to their decline in popularity [248]. Despite this, the 1990s saw the combined use of phentermine and fenfluramine or dexfenfluramine, serotonin (5-HT)-releasing agents associated with primary pulmonary hypertension [249]. However, reports of cardiac valvulopathy with this combination led to the

withdrawal of both fenfluramine and dexfenfluramine from the market [250]. Similar experiences were reported with sibutramine, a dual monoamine (noradrenaline and serotonin)-reuptake inhibitor associated with limited weight loss through the modulation of energy intake and energy expenditure; post-marketing clinical data revealed the drug's CV risk, leading to the suspension of its marketing authorization by the European Medicines Agency (EMA) in 2010 [251]. Other risks associated with weight-loss medication include serious psychiatric problems, such as anxiety, depression and suicide ([http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Press\\_release/2009/11/WC500014774.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2009/11/WC500014774.pdf)), leading to the termination of several CB1-receptor-antagonist-based anti-obesity drugs (e.g. rimonabant, taranabant, otenabant, surinabant and ibipinabant).

Fortunately, the failure of earlier lines of anti-obesity medication did not discourage the development of newer and safer medications for weight loss. Currently, there are 7 weight-loss medications approved by the United States Food and Drug Administration (FDA) for long term use. These are Bupropion-naltrexone (Contrave), Liraglutide (Saxenda), Orlistat (Xenical, Alli), Phentermine-topiramate (Qsymia), Semaglutide (Wegovy), Setmelanotide (Imcivree), and tirzepatide (Zepbound). Key clinical trials of approved medications are summarized in Table 3. An eighth drug, lorcaserin, was initially approved for weight loss but later withdrawn due to potential risk of cancer [252]. Other medications have also been used for weight management, albeit off-label. However, it is critical to consider the risk/benefit ratio of pharmacological agents used for weight reduction, particularly in conjunction with CVD. Another controversial topic of note is the use of herbal medicines for the management of obesity. The potential anti-obesity properties of traditional herbal medicines and their potential applications in drug design are mentioned in some studies [253,254], but there is currently no clinical data to support their use in the treatment of obesity. To note the possible implication of gender in the management of obesity; not only is obesity more prevalent among women [59], they also account for a higher number of prescriptions for weight reduction medication (72.4%–82.5% of prescriptions) and more often enroll in weight loss programs or trials compared to men [255,256]. While both men and women can expect to experience significant weight loss with appropriate interventions, men might lose more weight compared to women with non-pharmacological interventions (diet alone or combined with exercise) [257].

However, there is evidence to suggest the possible higher success of women on pharmacotherapy for weight loss compared to men [59]. Gender-related pharmacokinetic and pharmacodynamic factors have been hypothesized as possible mediators of a gender-dimorphic response to pharmacological obesity treatment, although no studies have been specifically designed to examine this [258].

### 7.2.1. Medications approved for weight loss

**7.2.1.1. Naltrexone/bupropion.** Bupropion is a norepinephrine-dopamine reuptake inhibitor approved for the treatment of major depressive disorder, seasonal affective disorder, and smoking cessation assistance and naltrexone is an opioid receptor antagonist indicated in alcohol and opioid dependence. The combination of both drugs is currently used for weight management as it mainly acts by suppressing appetite and promoting activation of brain regions implicated in self-control. Studies investigating naltrexone/bupropion in obese patients with comorbid diabetes, hypertension or hyperlipidemia found increased weight loss compared to placebo; Up to 33% of patients taking naltrexone/bupropion achieved 5% or higher weight loss after one year (mean weight loss of 4.7% across four phase 3 trials) [259]. To note that while significant weight loss has been reported with bupropion alone, the combination of naltrexone/bupropion leads to more weight loss and decreases in WC [260]. Naltrexone/bupropion has proven useful in combination with behavioral weight loss therapy for the management of binge-eating disorder [261]. Previous studies had shown that patients receiving naltrexone/bupropion had reduced frequency and intensity of food cravings [262–264], most likely owing to the synergistic effect of these drugs on the reward system associated with high energy and fat-laden food consumption.

Naltrexone/bupropion is currently approved by the FDA as an adjunct to lifestyle changes (a reduced-calorie diet and increased physical activity) for chronic weight management of adults who are overweight or obesity with at least one weight-related comorbidity (e.g. hypertension, T2DM, dyslipidemia).

Common side effects reported with the combination were nausea, constipation, vomiting, dizziness, and dry mouth [259]. A meta-analysis found that among included pharmacological therapies for weight management in 2016, naltrexone/bupropion had the second highest odds of treatment discontinuation due to an adverse event [255]. It is important to note that naltrexone/bupropion

Table 3. Summary of key clinical trials of approved weight loss medications.

| Medication             | Trial Name  | Participants   | Duration | Primary Outcome(s)   | Results  |
|------------------------|---|--|----------|--|--|
| Naltrexone + Bupropion | CONTRAVE Obesity Research-I (COR-I) [349]                         | 1742 adults with overweight or obese and dyslipidemia or hypertension                  | 56 weeks | Percent weight change at week 56<br><br>Proportion achieving $\geq 5\%$ weight loss at week 56         | –6.1% (naltrexone 32 mg + bupropion) and –5% (naltrexone 16 mg + bupropion) compared to –1.3% in placebo ( $p < 0.0001$ )<br>48% (naltrexone 32 mg + bupropion) and 39% (naltrexone 16 mg + bupropion) compared to 16% in placebo ( $p < 0.0001$ )                                   |
|                        | CONTRAVE Obesity Research-II (COR-II) [350]                       | 1496 adults with overweight or obese and dyslipidemia or hypertension                  | 56 weeks | Percent weight change at week 28<br><br>Proportion achieving $\geq 5\%$ weight loss at week 28         | –6.5% with naltrexone 32 mg + bupropion compared to –1.9% in placebo ( $p < 0.001$ )<br>55.6% with naltrexone 32 mg + bupropion compared to 17.5% in placebo ( $p < 0.001$ )   |
|                        | CONTRAVE Obesity Research- behavior modification (COR-BMOD) [351] | 793 adults with overweight or obese and dyslipidemia or hypertension                   | 56 weeks | Percent weight change at week 56<br><br>Proportion achieving $\geq 5\%$ weight loss at week 56         | –9.3% with naltrexone 32 mg + bupropion + behavioral modification compared to –5.1% in placebo + behavioral modification ( $p < 0.001$ )<br>66.4% with naltrexone 32 mg + bupropion + behavioral modification compared to 42.5% in placebo + behavioral modification ( $p < 0.001$ ) |
|                        | CONTRAVE Obesity Research-Diabetes Mellitus (COR-DM) [352]        | 505 adults with overweight or obese and type 2 diabetes                                | 56 weeks | Percent weight change at week 56<br><br>Proportion achieving $\geq 5\%$ weight loss at week 56         | –5.0% with naltrexone 32 mg + bupropion compared to –1.8% in placebo ( $p < 0.001$ )<br>44.5% with naltrexone 32 mg + bupropion compared to 18.9% in placebo ( $p < 0.001$ )   |
| Liraglutide 3 mg       | SCALE Obesity and Prediabetes [353]                               | 3731 adults without T2D, BMI $\geq 30$ or BMI $\geq 27$ with dyslipidemia/hypertension | 56 weeks | Change in body weight at week 56<br>Proportion achieving $\geq 5\%$ weight loss at week 56             | Liraglutide group lost 8.4 kg vs. 2.8 kg in placebo ( $p < 0.001$ )<br>63.2% with liraglutide vs 27.1% in placebo ( $p < 0.001$ )  |
|                        | BARI-OPTIMISE [354]   | 70 adults with poor weight loss post-bariatric surgery                                 | 24 weeks | Change in percentage body weight   | –8.82% with liraglutide compared to 0.54% in placebo ( $p < 0.001$ )   |
|                        | SCALE Maintenance [272]   | Adults who lost $\geq 5\%$ body weight during run-in period                            | 56 weeks | Percentage weight change from randomization<br>Proportion that lost $\geq 5\%$ of randomization weight | –6.2% with liraglutide compared to –0.2% in placebo ( $p < 0.0001$ )<br>50.5% with liraglutide compared to 21.8% in placebo ( $p < 0.001$ )  |
|                        | SCALE Diabetes [355]  | Adults with T2D, BMI $\geq 27$   | 56 weeks | Relative change in weight  | –6.0% with liraglutide vs. –2.0% in placebo ( $p < 0.001$ )  |

|                    |                         |  |           |   |   |
|--------------------|-------------------------|--|-----------|---|---|
| Semaglutide 2.4 mg | SCALE Sleep Apnea [274] | Adults with moderate/severe obstructive sleep apnea, BMI $\geq$ 30                     | 32 weeks  | Proportion achieving $\geq$ 5% weight loss<br>Proportion achieving $\geq$ 10% weight loss<br>Change in apnea-hypopnea index | 54.3% with liraglutide compared to 21.4% in placebo (p < 0.001)<br>25.5% with liraglutide compared to 6.7% in placebo (p < 0.001)<br>Significant improvement in apnea-hypopnea index with liraglutide compared to placebo (p < 0.001) |
|                    | STEP 1 [356]            | 1961 adults without diabetes with obesity or overweight $+\geq$ 1 comorbidity          | 68 weeks  | Percentage change in body weight<br>Proportion achieving $\geq$ 5% weight loss  | –14.9% weight reduction with semaglutide compared with –2.4% in placebo (p < 0.001)<br>86.4% with semaglutide compared with 31.5% in placebo (p < 0.001)  |
|                    | STEP 2 [357]            | 1210 adults with BMI $\geq$ 27 and type 2 diabetes                                     | 68 weeks  | Percentage change in body weight<br>Proportion achieving $\geq$ 5% weight loss  | –9.6% weight reduction with semaglutide compared with –3.4% with placebo (p < 0.0001)<br>68.8% with semaglutide compared with 28.5% in placebo (p < 0.0001)   |
|                    | STEP 3 [358]            | 611 adults without diabetes with obesity or overweight $+\geq$ 1 comorbidity           | 68 weeks  | Percentage change in body weight<br>Proportion achieving $\geq$ 5% weight loss  | –16.0% weight reduction with semaglutide + intensive behavioral therapy compared with –5.7% in placebo (p < 0.001)<br>86.6% with semaglutide + intensive behavioral therapy compared with 47.6% in placebo (p < 0.001)                |
|                    | STEP 4 [359]            | 803 adults without diabetes with obesity or overweight $+\geq$ 1 comorbidity           | 68 weeks  | Percentage change in body weight from week 20 to week 68  | –7.9% weight reduction with semaglutide compared with +6.9% weight increase in placebo (p < 0.001)  |
|                    | STEP 5 [360]            | 304 adults without diabetes with obesity or overweight $+\geq$ 1 comorbidity           | 104 weeks | Percentage change in body weight<br>Proportion achieving $\geq$ 5% weight loss  | –15.2% weight reduction with semaglutide compared with –2.6% in placebo (p < 0.0001)<br>77.1% with semaglutide + behavioral therapy compared with 34.4% in placebo (p < 0.0001)   |
|                    | STEP-HF [361]           | 529 adults with obesity-related heart failure with preserved ejection fraction (HFpEF) | 52 weeks  | Change in Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS)<br>Change in body weight               | +13.7 point increase in KCCQ-CSS with semaglutide compared to +8.7 points in placebo (p < 0.001)<br>–13.3% weight reduction with semaglutide compared to –2.6% with placebo (p < 0.001)   |

(continued on next page)



Table 3. (continued)

| Medication                | Trial Name                        | Participants   | Duration  | Primary Outcome(s)                          | Results   |
|---------------------------|-----------------------------------|--|-----------|---|---|
| Orlistat                  | XENDOS [362]                      | 3305 obese patients  | 4 years   | Time to onset of type 2 diabetes            | –37.3% risk reduction in diabetes incidence ( $p = 0.0032$ )  |
|                           |                                   |  |           | Change in body weight                       | –5.8 kg weight reduction with orlistat compared to 3.0 kg in placebo ( $p < 0.001$ )  |
|                           | Orlistat in Type 2 Diabetes [363] | 1200 overweight/obese patients with type 2 diabetes        | 1 year    | Change in body weight                       | –3.9% weight reduction with orlistat compared to –1.27% in placebo ( $p < 0.001$ )  |
|                           |                                   |  |           | glycemic control (change in HbA1c)          | HbA1c reduction of –0.62% with orlistat compared to –0.27% in placebo ( $p = 0.002$ )   |
| Orlistat in Obesity [364] |                                   | 743 obese patients   | 2 years   | Weight reduction during year 1              | –10.2% weight reduction with orlistat compared to 6.1% in placebo ( $p < 0.001$ )   |
|                           |                                   |  |           | Maintenance of lost weight during year 2    | 50% less weight regained compared to placebo ( $p < 0.001$ )  |
|                           | Orlistat in Adolescents [365]     | 539 obese adolescents                                      | 1 year    | Change in BMI                               | BMI reduction of –0.55 kg/m <sup>2</sup> with orlistat compared to an increase of +0.31 with placebo ( $p = 0.001$ )  |
| Phentermine topiramate    | EQUIP [366]                       | 1267 severely obese patients                               | 56 weeks  | Percent weight loss                         | –10.9% weight reduction with phentermine 15 mg/topiramate 92 mg and –5.1% with phentermine 3.75 mg/topiramate 23 mg compared to –1.6% in placebo ( $p < 0.0001$ ) |
|                           |                                   |  |           | Proportion achieving $\geq 5\%$ weight loss | 66.7% with phentermine 15 mg/topiramate 92 mg and 44.9% with phentermine 3.75 mg/topiramate 23 mg compared to –17.3% in placebo ( $p < 0.0001$ )                  |
|                           | CONQUER [297]                     | 2487 overweight/obese patients with $\geq 2$ comorbidities | 56 weeks  | Percentage change in body weight            | –9.8% weight reduction with phentermine 15 mg/topiramate 92 mg and –7.8% with phentermine 7.5 mg/topiramate 46 mg compared to –1.2% in placebo ( $p < 0.0001$ )   |
|                           |                                   |  |           | Proportion achieving $\geq 5\%$ weight loss | 70% with phentermine 15 mg/topiramate 92 mg and 62% with phentermine 7.5 mg/topiramate 46 mg compared to 21% in placebo ( $p < 0.0001$ )                          |
|                           | SEQUEL [298]                      | 676 patients from CONQUER study                            | 108 weeks | Percentage change in body weight            | –10.5% weight reduction with phentermine 15 mg/topiramate 92 mg and –9.3% with phentermine 7.5 mg/topiramate 46 mg  |

|               |   |  |          |  |  |
|---------------|---|--|----------|--|--|
|               | Phentermine/Topiramate in Adolescents [300] | 223 adolescents with obesity   | 56 weeks | Proportion achieving $\geq 5\%$ weight loss  | compared to $-1.2\%$ in placebo ( $p < 0.0001$ )<br>79.3% with phentermine 15 mg/topiramate 92 mg and 75.2% with phentermine 7.5 mg/topiramate 46 mg compared to 30% in placebo ( $p < 0.0001$ )               |
|               |   |  |          | Percentage change in BMI   | $-10.4$ percentage points difference in BMI with phentermine 15 mg/topiramate 92 mg and $-8.11$ percentage points with phentermine 7.5 mg/topiramate 46 mg compared to placebo ( $p < 0.001$ )                 |
| setmelanotide | POMC Deficiency Trial [367]                 | 10 patients with POMC deficiency   | 1 year   | Proportion achieving $\geq 10\%$ weight loss   | 80%  |
|               | LEPR Deficiency Trial [367]                 | 11 patients with LEPR deficiency   | 1 year   | Proportion achieving $\geq 10\%$ weight loss   | 45%  |
|               | Hypothalamic Obesity Trial [311]            | 16 patients with hypothalamic obesity  | 16 weeks | Proportion achieving $\geq 5\%$ reduction in BMI   | 89% ( $p < 0.001$ ); 15% mean reduction in BMI across all patients   |
| Tirzepatide   | SURMOUNT-1 [368]                            | 2539 adults with obesity or overweight with at least one weight-related comorbidity but without diabetes | 72 weeks | Percent change in body weight  | $-15.0\%$ weight reduction with 5-mg weekly doses of tirzepatide, $-19.5\%$ with 10-mg doses, and $-20.9\%$ with 15-mg doses compared to $-3.1\%$ with placebo ( $p < 0.001$ )                                 |
|               |   |  |          | Proportion achieving $\geq 5\%$ reduction in body weight   | 85% with 5-mg weekly doses of tirzepatide, 89% with 10-mg doses, and 91% with 15-mg doses compared to $-3.1\%$ with placebo ( $p < 0.001$ )  |
|               | SURMOUNT-2 [369]                            | 938 adults with obesity or overweight with type 2 diabetes   | 72 weeks | Percent change in body weight  | $-12.8\%$ weight reduction with tirzepatide 10 mg and $-14.7\%$ with tirzepatide 15 mg compared with $-3.2\%$ with placebo ( $p < 0.001$ )   |
|               | SURMOUNT-3 [370]                            | 579 adults with obesity or overweight with at least one weight-related comorbidity but without diabetes  | 72 weeks | Proportion achieving $\geq 5\%$ reduction in body weight<br>Additional mean per cent weight change from randomization to week 72 | 79%–83% with tirzepatide compared to 32% with placebo $-18.4\%$ weight reduction with tirzepatide after successful intensive lifestyle intervention compared to $+2.5\%$ increase with placebo ( $p < 0.001$ ) |
|               |   |  |          | Proportion achieving additional $\geq 5\%$ weight loss   | 87.5% with tirzepatide after successful intensive lifestyle  |

(continued on next page)

Table 3. (continued)

| Medication | Trial Name       | Participants  | Duration | Primary Outcome(s)   | Results   |
|------------|------------------|---|----------|--|---|
|            | SURMOUNT-4 [316] | 670 adults with obesity or overweight with at least one weight-related comorbidity but without diabetes | 88 weeks | Percent change in weight from week 36 (randomization) to week 88 | intervention compared to 16.5% with placebo ( $p < 0.001$ )<br>–5.5% weight reduction with continued tirzepatide compared with +14.0% increase in placebo (switch from tirzepatide) ( $p < 0.001$ ) |

cannot be used in patients with uncontrolled hypertension due to its sympathomimetic effects. Other restrictions are applicable to either naltrexone or bupropion alone, such as the inability to prescribe naltrexone concomitantly with opioid analgesics. The CV safety of naltrexone/bupropion remains uncertain, as analyses from the prematurely interrupted LIGHT trial provided conflicting and incomplete results [265].

**7.2.1.2. GLP-1 receptor agonists.** Glucagon-like peptide-1 (GLP-1) receptor agonists are a class of medications that are mainly used for the treatment of T2DM and have also been used for obesity. GLP-1 receptor agonists act through the incretin effect, effectively stimulating insulin secretion in response to glucose. This results not only in improved glycemic control, but also in lower blood pressure and cholesterol levels irrespective of the presence of T2DM [266]. Moreover, GLP-1 receptor agonists have shown benefit in terms of 3-point major adverse cardiovascular events (MACE) outcomes, such as CV death, myocardial infarction, stroke, mortality and HF-related hospitalization [267].

To note that severe, but rare, side effects could occur with the use of GLP-1 agonists; acute pancreatitis, acute gallbladder disease, and bowel obstruction have been reported with GLP-1 receptor agonists, with an increased risk compared to an older obesity medication naltrexone/bupropion [268]. While these remain relatively rare complications of this drug class (absolute risks  $<1\%$  per year of use [268]), they should be promptly addressed through treatment discontinuation once diagnosis is confirmed. GLP-1 receptor agonists may also cause anesthetic complications (regurgitation and pulmonary aspiration of gastric contents) during general anesthesia and deep sedation due to delayed gastric emptying. Although limited to anecdotal evidence, this potential risk of complications during anesthetic prompted the development of consensus recommendations for the management of patients on GLP-1 receptor agonists by the American Society of Anesthesiologists [269]: patients who are taking a GLP-1 receptor agonist that require emergency surgery should be managed as having a ‘full stomach’, while those undergoing elective surgery should have their treatment discontinued on the day of surgery (daily dosing) or a week before surgery (weekly dosing). One of the rumored severe side effects of GLP-1 receptor agonists is an increased risk of thyroid cancer, although it has yet to be demonstrated in humans outside of studies in rodents. Regardless, GLP-1 receptor agonist labels call for monitoring of thyroid function and signs of

thyroid cancer, and contraindicate the drugs in patient with a personal or family history of medullary thyroid carcinoma or Multiple Endocrine Neoplasia syndrome type 2. Suicidal ideation is another potential severe side effect of GLP-1 receptor agonists; however, investigation by the EMA found no causal relationship between GLP-1 receptor agonists (dulaglutide, exenatide, liraglutide, lixisenatide and semaglutide) and suicidal and self-injurious thoughts and actions [270]. Patients should be carefully monitored for signs of depression and suicidal ideation. Considering the circulation of mass media health information of questionable accuracy, physicians should carefully and comprehensively address patient fears and misconceptions as well as discuss expected treatment side effects to ensure patient adherence to therapy and treatment success.

Currently, only two GLP-1 agonists are currently indicated for the management of obesity: 3.0 mg liraglutide and 2.4 mg semaglutide. When using GLP-1 agonists, it is important to slowly titrate the dose up to the highest or maximally tolerated dose in order to avoid the onset of side effects expected with sudden initiation of higher doses.

- Liraglutide 3.0 mg

Liraglutide is a GLP-1 receptor agonist with a 97% homology to human GLP-1. The SCALE trial demonstrated that after 56 weeks of therapy, patients who are obese or overweight with concomitant dyslipidemia or hypertension lost a mean of 8.4 Kg of body weight with a high dose of liraglutide (vs. 2.8 in the placebo group). 63.2% of patients achieved 5% or higher reduction of their body weight, while 33.1% had weight reduction exceeding 10% of their body weight (vs 27.1% and 10.6% in the placebo group, respectively) [271]. The liraglutide group also maintained weight loss achieved with a low-calorie diet better than placebo, while additionally leading to additional weight loss [272]. Liraglutide (3.0 mg/daily) has also proven effective for weight loss in obese or overweight patients with concomitant T2DM (SCALE Diabetes trial) [273] as well as those with sleep apnea; in the SCALE Sleep Apnea trial, the liraglutide group showed significant weight loss and reduction of sleep apnea severity [274]. Taken collectively, data from RCTs and phase 3 studies suggests that patients without T2DM stand to benefit from a greater weight change compared to those with T2DM [275].

Liraglutide is currently indicated as an adjunct to lifestyle changes (a reduced-calorie diet and

increased physical activity) for weight management in adult patients who are obese or overweight with least one weight-related comorbidity.

Common side effects are nausea and vomiting, both of which tend to decrease after the first few weeks of treatment [273,276,277]. Patients could also experience diarrhea, constipation, dyspepsia and abdominal pain. The LEADER trial investigated CV outcomes with liraglutide in patients with advanced T2DM and high-baseline CV risk. The trial found CV benefit with liraglutide, as evidenced by the significant reduction in the primary outcomes (first occurrence of death from CV causes, non-fatal myocardial infarction or non-fatal stroke) with the drug compared to placebo [278]. Liraglutide also led to significantly lower nephropathy, but not retinopathy events [279].

- Semaglutide 2.4 mg

Semaglutide is another GLP-1 receptor agonist, with 94% homology with human GLP-1. The STEP trials (1–4) showed that a 2.4 mg once-weekly dose of semaglutide was effective for weight management. On average, patients taking semaglutide for 68 weeks experienced around 15% reduction of initial body weight by the end of treatment [280]. This weight loss was sustained over 104 weeks, as shown in the STEP 5 trial [281]. Semaglutide was also associated with CV benefit through its reduction of CV risk factors [280]. Same as liraglutide, semaglutide is indicated as an adjunct to reduced calorie intake and increased physical activity for chronic weight management in adults with obesity (BMI $\geq$ 30 kg/m<sup>2</sup>) or overweight (BMI $\geq$ 27 kg/m<sup>2</sup>) with at least one weight-related comorbidity.

The side effects profile of semaglutide is consistent with other GLP-1 receptor agonists, mainly consisting of gastrointestinal issues that are usually transient and prevalent during dose escalation. Daily formulations of semaglutide have been shown in CV outcomes trials to significantly reduce the risk of CV outcomes in patients with T2DM, including CV death, nonfatal myocardial infarction or nonfatal stroke [278,282]. The SELECT CV outcomes double-blind superiority study investigated the once-weekly 2.4 mg semaglutide formulation in 17,604 adults who are overweight or obese with preexisting CVD, finding a significant reduction in the incidence of death from CV causes, nonfatal myocardial infarction, or nonfatal stroke at a mean follow-up of 39.8 months compared to placebo [283]. The trial is by far the largest investigation of CV outcomes after a weight-loss strategy for obesity, with trial duration of at least 5 years. The STEP-HF trial demonstrated

that once-weekly 2.4 mg semaglutide led to higher weight loss, larger improvements in exercise function, and larger reductions in symptoms and physical limitations compared to placebo in patients who had HF with preserved ejection fraction and were obese [284].

**7.2.1.3. Orlistat.** Orlistat is a pancreatic lipase and gastric lipase inhibitor that contributes to weight loss by decreasing absorption of fatty acids [285,286]. Orlistat in conjunction with diet (in some cases with exercise and/or behavioral therapy) was associated with reductions in body weight, and WC in addition to reducing weight regain in both adolescent and adult obese patients [287–290]. 44% of patients taking orlistat achieve at least 5% weight loss [255]. Other than its weight-reducing effect, orlistat has been associated with lower cholesterol and low-density lipoprotein (LDL) levels [289], as well as a reduced incidence of diabetes in patients with impaired glucose tolerance [291].

Orlistat is currently indicated for weight loss in obese patients, as well as overweight patients who have concomitant risk factors such as hypertension, diabetes and dyslipidemia. Orlistat is also indicated for reducing the risk of weight regain after previous weight loss.

Gastrointestinal side effects are common with orlistat. The addition of orlistat to diet has been shown to result in CV risk reduction among obese patients in several studies; orlistat was associated with lower blood pressure, improved lipid profile, and better glycemic control [292–294]. The favorable effect of orlistat on CV risk factors was also reported in patients with metabolic syndrome, treated uncontrolled hypertension, as well as those with T2DM [295,296].

**7.2.1.4. Phentermine-topiramate.** Phentermine and topiramate have several pharmaceutical applications. Topiramate on its own was used since its introduction in 1996 for partial-onset or primary generalized tonic-clonic seizures, Lennox-Gastaut syndrome, and as migraine prophylaxis. Topiramate is an anticonvulsant and a weak carbonic anhydrase inhibitor with antagonist activity on glutamate receptors, leading to appetite suppression and satiety enhancement. Phentermine is a central nervous system stimulant (sympathomimetic amine anorectic) that was introduced in 1959 as part of a combination therapy for obesity treatment, and has also been used alone in combination with lifestyle changes (exercise and caloric restriction) for short-term treatment of obesity. Phentermine alone is approved for short-term use (<12 weeks) for weight

management. In 2012, the FDA approved the combination of phentermine-topiramate for the long-term treatment of obesity or overweight in combination with a reduced-calorie diet and exercise in individuals who have at least one obesity-related comorbidity. However, this combination was not granted marketing authorization by the EMA due to safety concerns on the long-term CV effects of phentermine. To note that while phentermine-topiramate is FDA-approved, it has not received Saudi FDA (SFDA) approval as of April of 2024.

The CONQUER trial was a 56-week phase 3 trial that demonstrated that 62%–70% of overweight and obese adults achieved at least 5% reduction in body weight with phentermine-topiramate in combination with lifestyle interventions, compared to only 21% in the placebo group [297]. The 52-week extension study SEQUEL was then conducted in order to evaluate this combination treatment in obesity and overweight complicated by cardiometabolic disease (at least 2 weight-related comorbidities) [298]. Compared with placebo, phentermine-topiramate led to sustained weight loss over 2 years and a significantly higher number of patients achieving at least 5% (up to 80% vs. 30%), 10% (up to 53.9% vs 11.5%), and 15% (up to 31.9% vs 6.6%) weight loss. Patients in the phentermine-topiramate group also experienced improvement in CV and metabolic variables, as well as a reduced incidence of diabetes compared to placebo [298]. Taken collectively in a meta-analysis, data from six clinical trials showed that phentermine-topiramate led to a dose-dependent weight loss compared to placebo, ranging from an average of 3.55 kg with the 3.75/23 mg dose to 8.25 kg with the 15/92 mg dose [299]. Phentermine-topiramate also led to reductions in WC, blood pressure, glycemia and lipid levels. However, the risk of adverse events related to the nervous system was higher with the combination compared to placebo [299]. Phentermine topiramate can also be used for the treatment of adolescent obesity, where reductions in BMI can be expected along with improvement of lipid profiles [300].

In fact, caution is advised with the use of this combination. Phentermine-topiramate has several common side effects identified in clinical trials, namely dry mouth, constipation and paresthesia [297,299]. Increased resting heart rate has also been associated with phentermine-topiramate, hence the need for close monitoring of heart rate in all patients on this combination [301]. Psychiatric and cognitive disturbances (anxiety, depression, insomnia) have also been reported with phentermine-topiramate, in addition to cognitive impairment [302]. Phentermine-topiramate is also associated with metabolic

disturbances such as an increased risk of hypokalemia, metabolic acidosis and potentially, nephrolithiasis [303]. Moreover, abrupt withdrawal of phentermine-topiramate may cause seizures [304]. To note that phentermine-topiramate is contraindicated in women who are of childbearing potential and in those who are breastfeeding considering topiramate's teratogenicity and breastfeeding-associated side effects.

**7.2.1.5. Setmelanotide.** Setmelanotide is the first and currently only FDA approved medication [305] targeting MC4R pathway for the management of obesity caused by genetic deficiencies (proopiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), or leptin receptor (LEPR)), which are known to cause childhood-onset obesity. As a MC4R agonist, setmelanotide reverses hyperphagia caused by deficiencies or mutations in POMC, PCSK1 or LEPR and thereby promotes weight loss by lowering caloric intake and increasing energy expenditure [306,307].

A small Phase 3 clinical trial demonstrated the efficacy of setmelanotide for the management of obesity and hyperphagia due to POMC/PCSK1 or LEPR deficiency; the trial was conducted in 10 participants with POMC/PCSK1 deficiency and 11 participants with LEPR deficiency, among whom 80% and 45% achieved at least 10% weight loss at one year, respectively [308]. This was sufficient for Setmelanotide to gain FDA approval in 2020 for chronic weight management in adults and pediatrics six years of age and older due to the deficiency of POMC, PCSK1, or LEPR. The indication of setmelanotide was later expanded in 2022 to include Bardet–Biedel syndrome based on the positive results of another small phase 3 clinical trial; Of 20 included obese patients with Bardet–Biedel syndrome, clinically meaningful improvements in health-related quality of life measures and weight outcomes could be observed after 52 weeks among both pediatric and adult participants [309]. Another phase 3 trial confirmed the efficacy of setmelanotide in Bardet–Biedel syndrome, but results were inconclusive in patients with Alström syndrome [310]. A phase 2 trial recently showed that setmelanotide is also a novel effective treatment of hypothalamic obesity [311].

The most frequent adverse reactions reported with setmelanotide were injection site reactions, hyperpigmentation, and nausea [308,309]. Other notable side effects are sexual dysfunctions in both female and male patients, as well as depression and suicidal ideation. Moreover, setmelanotide is

contraindicated in premature and low-birth weight infants due to it containing benzyl alcohol, which can cause serious reactions such as gasping syndrome and death.

**7.2.1.6. GLP-1/GIP agonists.** Tirzepatide is a novel medication that acts as a dual receptor agonist for GLP-1 (similar to liraglutide and semaglutide) and glucose-dependent insulinotropic polypeptide (GIP). Tirzepatide was initially approved for the treatment of T2DM owing to its improvement of glycemic control in this patient population, but is not approved in T1DM [312].

The significant weight loss observed with tirzepatide in T2DM prompted its consideration for the treatment of obesity; a dose-dependent correlation with weight loss emerged that was similar to that seen with semaglutide, with 5.4 Kg weight reduction seen with 5 mg of tirzepatide and 10.5 Kg weight reduction seen with 15 mg tirzepatide [312]. As a result, clinical trials investigated the efficacy of tirzepatide for obesity. The SURMOUNT-1 trial included patients who are overweight or obese with at least one weight-related comorbidity, excluding diabetes [313]. Patients received either once-weekly tirzepatide (5 mg, 10 mg or 15 mg) or placebo for 72 weeks, which included a 20-week dose escalation period. The trial reported significant and sustained dose-dependent weight reductions with tirzepatide, although all investigated doses led to meaningful responses; patients experienced 15%–20.9% mean change in weight and on average 85%–91% of patients achieved a weight reduction of 5% or more with tirzepatide 5 mg–15mg [313]. The SURMOUNT-2 trial also reported significant and clinically meaningful weight reduction with tirzepatide in patients who were obese with concomitant T2DM. There was a 12.8% mean weight change in patients receiving 10 mg tirzepatide for 72 weeks, and 14.7% in those receiving the 15 mg dose (vs. 3.2% in placebo) [314]. Moreover, 79–83% of patients receiving tirzepatide had 5% or more reduction in weight, compared to 32% in placebo. Results from the SURMOUNT-3 [315] and SURMOUNT-4 trials [316] investigated the maximum tolerated dose of tirzepatide (10 or 15 mg) were also positive; 21.1% mean bodyweight loss was achieved by week 72 in the SURMOUNT 3 trial [315]. By contrast, the SURMOUNT 4 trial demonstrated the substantial regain of lost weight during a lead-in period (mean weight reduction of 20.9% by 36 weeks) when tirzepatide was withdrawn; participants randomized to placebo regained 14% of mean weight from week 36 to week 88, while those who remained on

tirzepatide experienced an additional 5.5% mean weight loss in this same period for a mean overall weight reduction of 25.3% from week 0 to week 88 [316]. A meta-analysis pooling results from 6 separate RCTs ranging from 12 to 72 weeks confirmed that substantial weight reduction of up to approximately 12 Kg and 12.4% change in bodyweight can be expected with tirzepatide [317]. Based on the positive outcomes of pivotal clinical trials, the FDA granted tirzepatide a fast track approval for the extension of its indication to include obesity. Tirzepatide is now approved for chronic weight management in adults with obesity or overweight with at least one weight-related condition (such as high blood pressure, T2DM or high cholesterol) in combination with dietary and physical interventions (a reduced calorie diet and increased physical activity).

In regards to safety, tirzepatide was relatively well-tolerated. The 10 and 15 mg doses of tirzepatide had the highest adverse event-related treatment discontinuation rates, with the most common adverse events being gastrointestinal (nausea, diarrhea, vomiting) [313] similar to GLP-1 agonists. The CV safety of tirzepatide was reported in a meta-analysis of phase 2 and 3 studies from the SURPASS clinical development program (in T2DM), with no increased risk of CV events [267]. It remains to be seen whether the same CV safety will be reported in analyses of obesity trials. That being said, the SURMOUNT 1 trial also assessed cardiometabolic outcomes and found that tirzepatide improved WC, blood pressure, fasting insulin level, and lipid levels in addition to reverting most participants with pre-diabetes to normoglycemia [313].

#### 7.2.2. Medications not approved for weight loss

Medications indicated for diabetes mellitus have been used for weight loss with variable results. However, this use is not indicated (off-label) and is not currently recommended.

**7.2.2.1. Metformin.** Metformin is the long-standing pillar of first-line T2DM management. It was found that in addition to its effect on glycemic control, metformin can also lead to weight loss; metformin was linked significant and sustainable decreases in both weight and WC in participants of the diabetes prevention program outcomes study, a large-scale RCT of metformin in prediabetes with a long-term (7–8 years) open-label extension [318]. A meta-analysis of 21 trials including obese or overweight participants with or without comorbidities such as T2DM and polycystic ovarian syndrome found only a modest reduction of BMI with metformin [319].

BMI reduction was most significant in more severe obesity classes (BMI >35 kg/m<sup>2</sup>) but was generally not sufficient to warrant the classification of metformin as a weight-loss drug. The mechanisms underlying the weight-loss benefit with metformin is still being researched, with current understanding linking it to modulation of hypothalamic appetite-regulatory centers and alteration in the gut microbiome [320]. However, as the weight loss benefit of metformin has not been consistent in published literature, the drug has not been approved by the FDA nor recommended by scientific/medical societies as an agent exclusively for weight loss.

**7.2.2.2. SGLT-2 inhibitors.** Sodium-glucose transport protein 2 (SGLT2) inhibitors include drugs such as Canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin which are approved by the US FDA as adjunct therapy to diet and exercise in the management of adults with T2DM. All SGLT2 inhibitors lead to reductions in glycated haemoglobin and fasting plasma glucose [321]. It was also noticed that SGLT-2 inhibitors led to significant weight reductions by inducing glucose excretion which directly causes body weight loss; A meta-analysis of 116 RCTs with a combined cohort of close to 100 thousand patients reported a mean weight reduction of 1.79 Kg with SGLT2 inhibitors compared with placebo [322]. Moreover, the dose-dependent weight reduction was consistent across all SGLT drug types, and was not restricted to diabetics [322]. When specifically considering non-diabetic adults who are overweight or obese, low-quality evidence suggests that SGLT2 inhibitors can lead to significant decreases in body weight and BMI, but possibly not in WC [323].

The above evidence prompted the off-label use of SGLT2 inhibitors for the management of obesity in conjunction with GLP-1 receptor agonists [324]. While promising, more evidence is needed on the role of SGLT-2 inhibitors in weight management and this drug class is not officially indicated for the treatment of obesity or overweight.

Despite their increased risk of female genital mycotic infections, urinary tract infections, increased urination, nausea, and constipation [325], SGLT-2 inhibitors have been associated with CV benefit. A meta-analysis confirmed that SGLT2 inhibitors have a substantial benefit in terms of CV and renal outcomes in patients with T2DM and high CVD risk, despite the risk of diabetic ketoacidosis [326]. SGLT-2 inhibitors have demonstrated benefits on atherosclerotic MACE in patients with

established ASCVD, with robust evidence supporting their reduction of HF hospitalization and progression of renal disease irrespective of existing CVD or HF [327]. SGLT-2 inhibitors have been shown to improve CV outcomes in patients with HF, particularly CV death, HF hospitalization and HF symptoms as well as quality of life [328–332]. Moreover, these benefits seem to extend to patients who do not have concomitant diabetes and are not related to ejection fraction. Based on this, SGLT2 inhibitors are actually recommended in addition to standard therapy for all patients with HF [212].

### 7.2.3. Anti-obesity therapy: what's in the pipeline?

A recent phase 1 trial investigated the combination of once-weekly semaglutide 2.4 mg with the amylin agonist cagrilintide. The combination led to significant outcomes, with 66% of patients receiving semaglutide 2.4 mg and cagrilintide achieving at least 15% weight loss in 20 weeks [333]. However, more research is needed to allow the use of this combination in routine clinical practice.

Another drug in the pipeline is the triple hormone receptor agonist retatrutide. Retatrutide is a GLP-1, GIP and Glucagon triple agonist that has been investigated in a double-blind placebo-controlled phase 2 trial and has been shown to lead to 24% weight loss at 48 weeks when administered at a dose of 12 mg. Moreover, the trial showed that most patients (92%) will achieve at least 5% weight loss at the lowest tested dose of 4 mg, while approximately 90% of patients receiving either the 9 mg or 12 mg dose can achieve at least 10% weight loss [334]. More importantly, the adverse effects profile of retatrutide was comparable to that of GLP-1 agonists.

Oral anti-obesity medications are also being investigated.

The OASIS-1 trial investigated the use of once daily oral 50 mg semaglutide in adults who are overweight or obese with bodyweight-related complications and comorbidities [335]. Recently published results indicated that compared with placebo, semaglutide led to a superior and clinically meaningful decrease in bodyweight after 68 weeks of therapy. Patients in the semaglutide groups had a mean bodyweight change of 15.1% compared to baseline versus 2.4% in the placebo group. Based on these results, around 85% of patients can expect to lose 5% of their bodyweight with semaglutide 50 mg [335].

Another daily oral nonpeptide GLP-1 agonist, Orforglipron, is also effective for weight loss among adults who are overweight or obese, ensuring 9.4%–14.7% weight loss by week 36 compared to 2.3% in placebo. Moreover, orforglipron led to

improvement in all prespecified weight-related and cardiometabolic measures [336].

### 7.3. Surgery

Surgical intervention could be considered for the treatment of obesity after failure of non-surgical approaches such as lifestyle modifications and pharmacological therapy (see section 8 for SHA recommendations on surgery).

Data on the benefits of bariatric surgery are widely available and range from observational studies to (small-scale) RCTs. A meta-analysis of 11 RCTs with pooled data from a total of 796 individuals showed that bariatric surgery ensures greater weight loss (26 kg difference) and a higher remission rate of T2DM compared to non-surgical treatment (i.e. diet, medication, and/or behavioral therapy) [337]. In the overall population, bariatric surgery carries significant benefits in terms of long-term all-cause mortality, CV mortality and incidence of both obesity-related diseases (T2DM, hypertension, dyslipidemia and ischemic heart disease) and CVD such as HF, myocardial infarction and stroke [338–344]. When considering bariatric surgery specifically in established CVD, fewer studies are available but results indicate a decrease in the incidence of MACE and CV mortality [345]. Moreover, the incidence of HF can be 5-fold lower in patients (with or without established comorbidities i.e. CAD, hypertension, diabetes) who underwent bariatric surgery compared to those who had non-surgical interventions [346]. There is evidence that in obese patients with preserved left ventricular function, bariatric surgery can lead to early ( $\leq 6$  months) improvement in subclinical myocardial function that was independently associated to a greater loss of visceral fat mass [347]. A recent meta-analysis of 19 studies with a total close to 450 thousand patients with HF reported that weight loss due to bariatric surgery reduced the risk of death in this patient population, but not weight loss due to medications or exercise [158]. Limited data suggests that pericardial fat decrease after surgical-induced weight loss is more prominent in paracardial compared to epicardial fat [348]. To note that pericardial fat has been linked to CVD development and CV event onset [66].

However, despite the benefits of bariatric surgery in weight loss and CV outcomes, real-life accessibility of these procedures remains relatively low compared to the number of individuals who are obese. With the recent advancements in pharmacotherapy, special consideration should be given when broaching the choice of surgical or pharmacological management approaches for obesity.



### 8. Conclusions and SHA recommendations for the management of obesity/overweight and CVD

Collectively, there is ample support for the management of obesity as a means for the primary and secondary prevention of CVD. Adopting healthier lifestyles involving an appropriate diet alone or combined with exercise will not only reduce the risk of developing CVD, but also improve cardiorespiratory fitness and CV outcomes as well as reduce CV mortality [216–218,239–242]. This primary and secondary prevention of CVD with dietary and physical lifestyle interventions is predominately mediated by decreased adiposity (or its prevention) and weight-loss, which could also be supplemented with behavioral therapies [244,245]. Pharmacological options for weight-loss are expanding, with emerging evidence of CV benefit in individuals who are obese or overweight. In particular, GLP-1 receptor agonists liraglutide and semaglutide have been shown to reduce the risk of death from CV causes, nonfatal myocardial infarction, stroke, and HF-related hospitalization

[267,278,283]. The use of other medications indicated for achievement of glycemic control, namely SGLT-2 inhibitors, could also improve CV outcomes both in patients with or without T2DM at high risk for developing CVD (primary prevention) [326] as well as in patients with established CVD such as atherosclerotic CVD and HF (secondary prevention) [327–332]. Surgical management of patients with obesity could yield further weight reduction when needed, with the added benefit of CVD prevention; in the general population, bariatric surgery reduces CV mortality and incidence of diseases associated with obesity (T2DM, hypertension, dyslipidemia and ischemic heart disease) as well as CVDs such as HF, myocardial infarction and stroke [338–344]. In terms of secondary prevention, data on bariatric surgery in patients with established CVD are more limited but confirm favorable CV outcomes (e.g. lower risk of MACE and CV mortality) [158,345].

Based on this evidence, the SHA recommendations for the management of obesity/overweight and CVD are provided below as well as in a clinical management algorithm (Fig. 4):

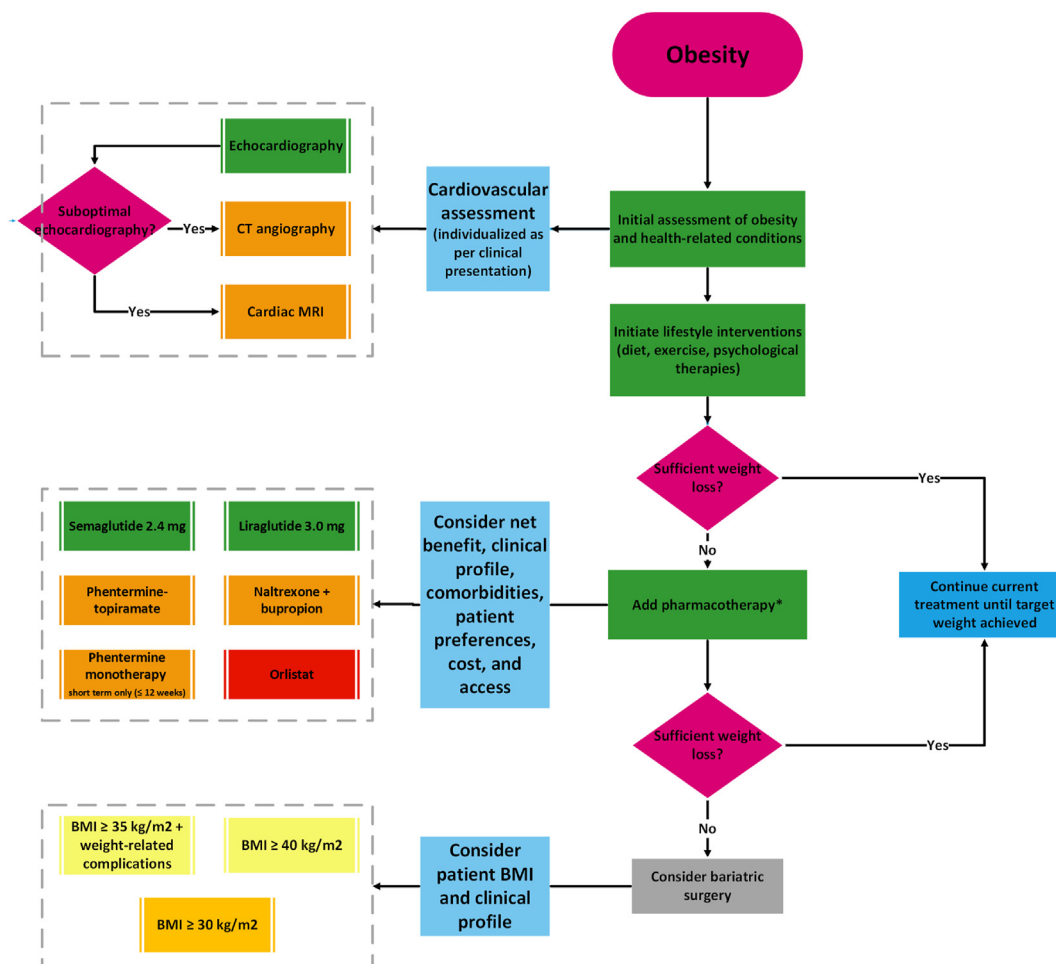


Fig. 4. Clinical management algorithm for obesity/overweight and CVD in Saudi Arabia.

### Imaging

- Echocardiography is recommended to detect and monitor cardiovascular complications such as left ventricular hypertrophy, diastolic dysfunction, and CAD, which are prevalent in obesity.
- CT angiography and cardiac MRI may be considered in obese patient enable assessment of cardiac structure and function, guide risk stratification, treatment strategies and effectiveness of weight management interventions, especially when the echocardiography is suboptimal.
- An individualized diagnostic approach is recommended as per the clinical presentation.

### Interventions for weight reduction: lifestyle interventions and medications

- Lifestyle interventions are recommended for the first-line management of adults with obesity or overweight.
- The addition of pharmacotherapy to lifestyle interventions is recommended in case of insufficient weight loss with lifestyle interventions alone.
- The selection of weight-loss medication should take into consideration the net benefit of the drug in question, as well as patient profile (i.e. comorbidities), patient needs and preferences, cost, and drug access.
- Semaglutide 2.4 mg is recommended in combination with lifestyle interventions for the treatment of obesity or overweight in adults.
  - Semaglutide 2.4 mg may be preferred over other weight-loss medications due to its net benefit in the long-term treatment of obesity
- Liraglutide 3.0 mg is recommended in combination with lifestyle interventions for the treatment of obesity or overweight in adults
  - Liraglutide 3.0 mg may be preferred over other weight-loss medications in patients with concomitant diabetes due to its gluco-regulatory benefits.
- Phentermine-topiramate may be used in combination with lifestyle interventions for the treatment of obesity or overweight in adults unless contraindicated (women of childbearing potential, history of cardiovascular disease and uncontrolled hypertension)
  - Phentermine-topiramate may be preferred in case of comorbid migraines due to its efficacy in treating migraine headaches.
- Phentermine monotherapy may be used in combination with lifestyle interventions for the short-term ( $\leq 12$  weeks) treatment of obesity in adults unless contraindicated (history of cardiovascular disease)
- Naltrexone-bupropion may be used in combination with lifestyle interventions for the treatment of obesity or overweight in adults unless contraindicated (seizure disorders, concomitant use of opiate medications)
  - Phentermine-topiramate may be preferred for individuals attempting smoking cessation, and in individuals suffering from depression.
- Orlistat is not recommended in combination with lifestyle interventions for the treatment of obesity or overweight in adults due to its small weight loss benefit and gastrointestinal adverse effects.
- The use of pharmacotherapy should be accompanied with careful monitoring of the occurrence of possible adverse effects (see section 7.2.) and gradual dose titration for adverse event mitigation (when applicable).

### Interventions for weight reduction: surgery

- Bariatric surgery offers significant benefit in terms of weight loss and improved clinical outcomes and should be considered in the following cases:
  - Patients with BMI of 40 kg/m<sup>2</sup> or higher.
  - Patients with BMI of 35 kg/m<sup>2</sup> or higher AND concomitant weight-related complications who can tolerate bariatric surgery.
- Bariatric surgery may be considered for patients with BMI of 30 kg/m<sup>2</sup> or higher in case of the failure of non-surgical weight-management approaches (lifestyle intervention + medications).

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### Conflict of interest

None declared.

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