

# Obesity and cardiovascular disease: an ESC clinical consensus statement

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The global prevalence of obesity has more than doubled over the past four decades, currently affecting more than a billion individuals. Beyond its recognition as a high-risk condition that is causally linked to many chronic illnesses, obesity has been declared a disease *per se* that results in impaired quality of life and reduced life expectancy. Notably, two-thirds of obesity-related excess mortality is attributable to cardiovascular disease. Despite the increasingly appreciated link between obesity and a broad range of cardiovascular disease manifestations including atherosclerotic disease, heart failure, thromboembolic disease, arrhythmias, and sudden cardiac death, obesity has been underrecognized and sub-optimally addressed compared with other modifiable cardiovascular risk factors. In the view of major repercussions of the obesity epidemic on public health, attention has focused on population-based and personalized approaches to prevent excess weight gain and maintain a healthy body weight from early childhood and throughout adult life, as well as on comprehensive weight loss interventions for persons with established obesity. This clinical consensus statement by the European Society of Cardiology discusses current evidence on the epidemiology and aetiology of obesity; the interplay between obesity, cardiovascular risk factors and cardiac conditions; the clinical management of patients with cardiac disease and obesity; and weight loss strategies including lifestyle changes, interventional procedures, and anti-obesity medications with particular focus on their impact on cardiometabolic risk and cardiac outcomes. The document aims to raise awareness on obesity as a major risk factor and provide guidance for implementing evidence-based practices for its prevention and optimal management within the context of primary and secondary cardiovascular disease prevention.

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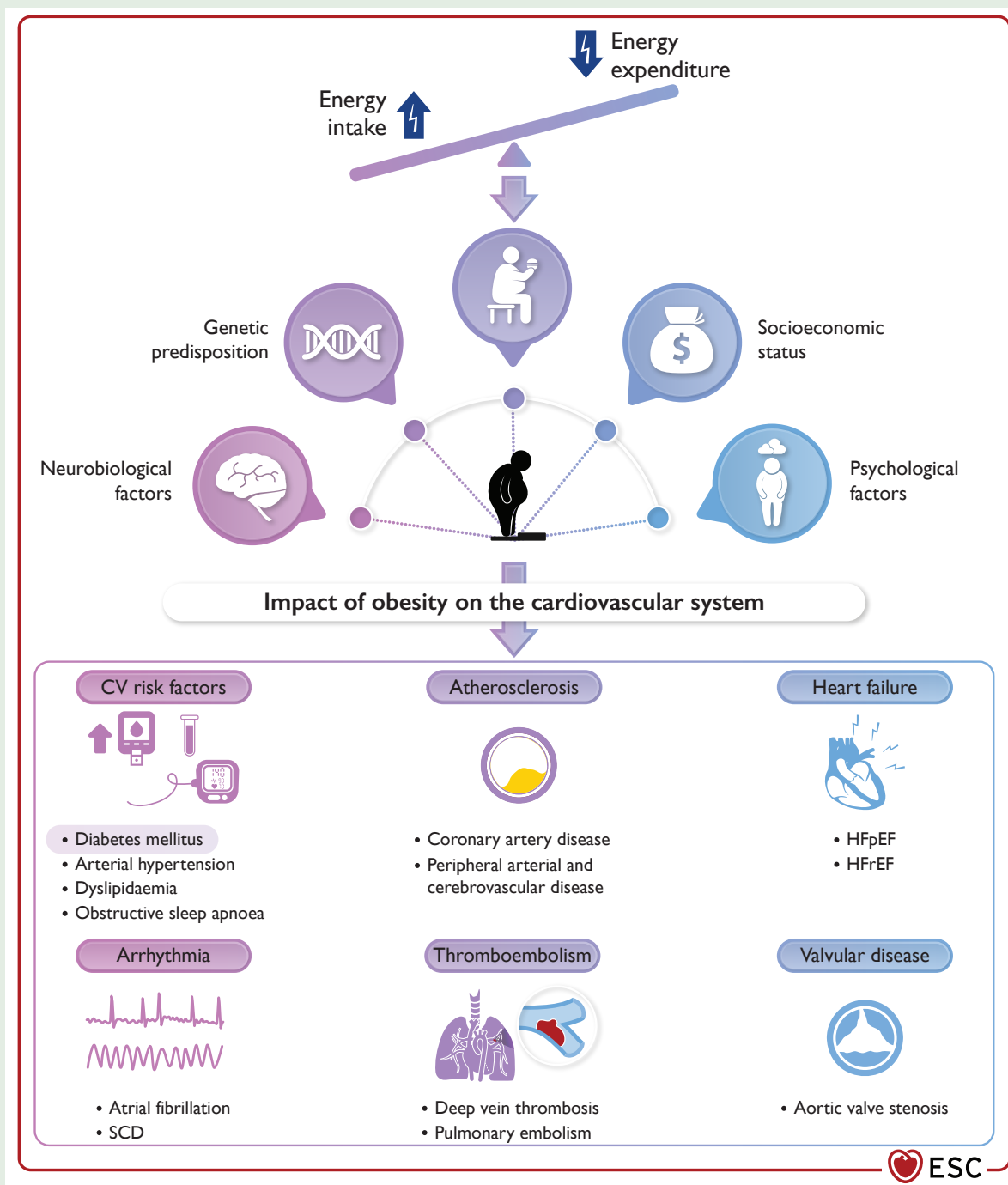
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## Graphical Abstract



Main causal factors and cardiovascular consequences of obesity. CV, cardiovascular; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; SCD, sudden cardiac death.

## Keywords

Anti-obesity drugs • Adipose tissue • Arrhythmia • Atherosclerosis • Bariatric interventions • Cardiovascular disease • Lifestyle interventions • Heart failure • Cardiovascular risk factors • Venous Thromboembolism • Valvular heart disease

## Preamble

European Society of Cardiology (ESC) Scientific Documents provide highly valuable advice for clinical management and interpretation of scientific evidence in areas of uncertainty not covered by ESC Clinical Practice Guidelines (CPGs). ESC Clinical Consensus Statements evaluate and summarize available evidence, and provide clinical advice as applicable with the aim of assisting health professionals in proposing the best diagnostic or therapeutic approach for an individual patient with a given condition (ESC Scientific Documents Policy available at <https://www.escardio.org/The-ESC/About/Policies/scientific-document-policy>). The clinical advice provided does not override the individual responsibility of health professionals to make appropriate and accurate decisions in consideration of each patient's health condition and in consultation with that patient or the patient's caregiver where appropriate and/or necessary. It is also the health professional's responsibility to verify the rules and regulations applicable in each country to drugs and devices at the time of prescription, and, where appropriate, to respect the ethical rules of their profession.

The members of this Clinical Consensus Statement Task Force were selected by the ESC to represent professionals involved with the medical care of patients with the pathology. Task Force members provided declarations of interest including all relationships that might be perceived as real or potential sources of conflicts of interest. Declarations of interest were reviewed according to the rules established in the ESC Declaration and Management of Conflict of Interest Policy (<https://www.escardio.org/The-ESC/About/Policies/esc-declaration-and-management-of-conflict-of-interest-policy>), and have been compiled in a report published as a [Supplementary data online, Supplementary Document](#). Task Force chairs and >75% of Task Force members were asked to comply with the policy criteria applicable to ESC Guidelines authors, while the rest of the Task Force members with criteria applicable to ESC Scientific Documents authors. Members of the Task Force with declared interests on specific topics did not author related sections in the manuscript but were requested to review them.

Upon validation of the content by all Task Force members, the document was peer-reviewed by members of the ESC Board, the ESC CPG Committee, and the ESC Scientific Documents Committee. The ESC Board provided final sign-off prior to the submission to the journal, where the document underwent independent peer-review.

## Introduction

Obesity, a complex, multifactorial condition characterized by excess body fat accumulation, has reached epidemic levels worldwide. Obesity is associated with adverse health outcomes and reduced life expectancy, and was declared a disease by the World Health Organization (WHO) in 1997 and by the European Commission in 2021.<sup>1</sup> A meta-analysis including >10 million individuals unequivocally showed a log-linear increase in all-cause mortality with body mass index (BMI) for values >25 kg/m<sup>2</sup>.<sup>2</sup> While obesity adversely affects different organs and is a risk factor for several chronic diseases (e.g. chronic kidney disease, cancer), 67.5% of deaths related to high BMI are attributable to cardiovascular disease (CVD).<sup>3</sup> Indeed, obesity contributes to well-established cardiovascular (CV) risk factors [type 2 diabetes mellitus (T2DM), dyslipidaemia, elevated blood pressure and arterial hypertension] but also has direct adverse effects on cardiac structure and function and leads to the development of CVD—both

atherosclerotic and non-atherosclerotic—independently of other CV risk factors.<sup>4</sup>

The obesity epidemic is a global health crisis, entailing not only adverse health outcomes but staggering costs placing a significant strain on health budgets. Among the multiple health risks associated with obesity, CV risk factors and CVD stand out as a primary contributor to the escalating healthcare costs because of their high prevalence in the population. The surge in obesity-related CVD diverts considerable healthcare resources away from other critical areas, due to direct costs of CVD treatment as well as indirect costs related to societal loss in productivity.

Obesity is both preventable and treatable. Comprehensive obesity treatment is based on multidisciplinary approaches including behavioural interventions, nutrition, physical activity, pharmacological therapy, and endoscopic procedures/bariatric surgery as appropriate. Despite the broad range of available treatment options, obesity management has received considerably less attention compared with other modifiable CV risk factors over the past decades, particularly among cardiologists. Newer anti-obesity medications have recently emerged as additional options for marked weight loss with proven effect on CV outcomes, fuelling interest in obesity as a therapeutic target.

This clinical consensus statement discusses the complex interplay between obesity, various CV risk factors, and CVD manifestations, and summarizes the impact of weight loss interventions on CV outcomes. The importance of public health policies beyond individual patient-level interventions is also critically discussed. The document aims to increase awareness on this major modifiable risk factor, and to provide guidance for implementing evidence-based treatment options for optimal management of excess adiposity and associated cardiometabolic risk. While this Task Force emphasizes the value of long-term maintenance of a healthy body weight (by preventing excessive weight gain or pursuing weight loss, as appropriate) in individuals without known CVD, and even though the implications of weight loss may differ in the context of primary vs. secondary CV prevention, management of obesity in patients with established CVD is a main focus of this ESC document.

## Definition of obesity

Overweight and obesity are defined as abnormal or excessive fat accumulation that may impair health. Obesity is typically classified using the BMI scale, based on a person's weight and height. The WHO cut-off points for normal weight, overweight, and obesity, as well as classes of obesity in adults are summarized in [Box 1](#). Lower, country-specific cut-off points apply to Asian subpopulations (e.g.  $\geq 24$  and  $\geq 28$  kg/m<sup>2</sup> for overweight and obesity, respectively, in China) (see [Supplementary data online, Table S1](#)),<sup>5</sup> and specific cut-off points apply to children and pregnant women. Potential issues arising from defining obesity based on BMI are discussed below.

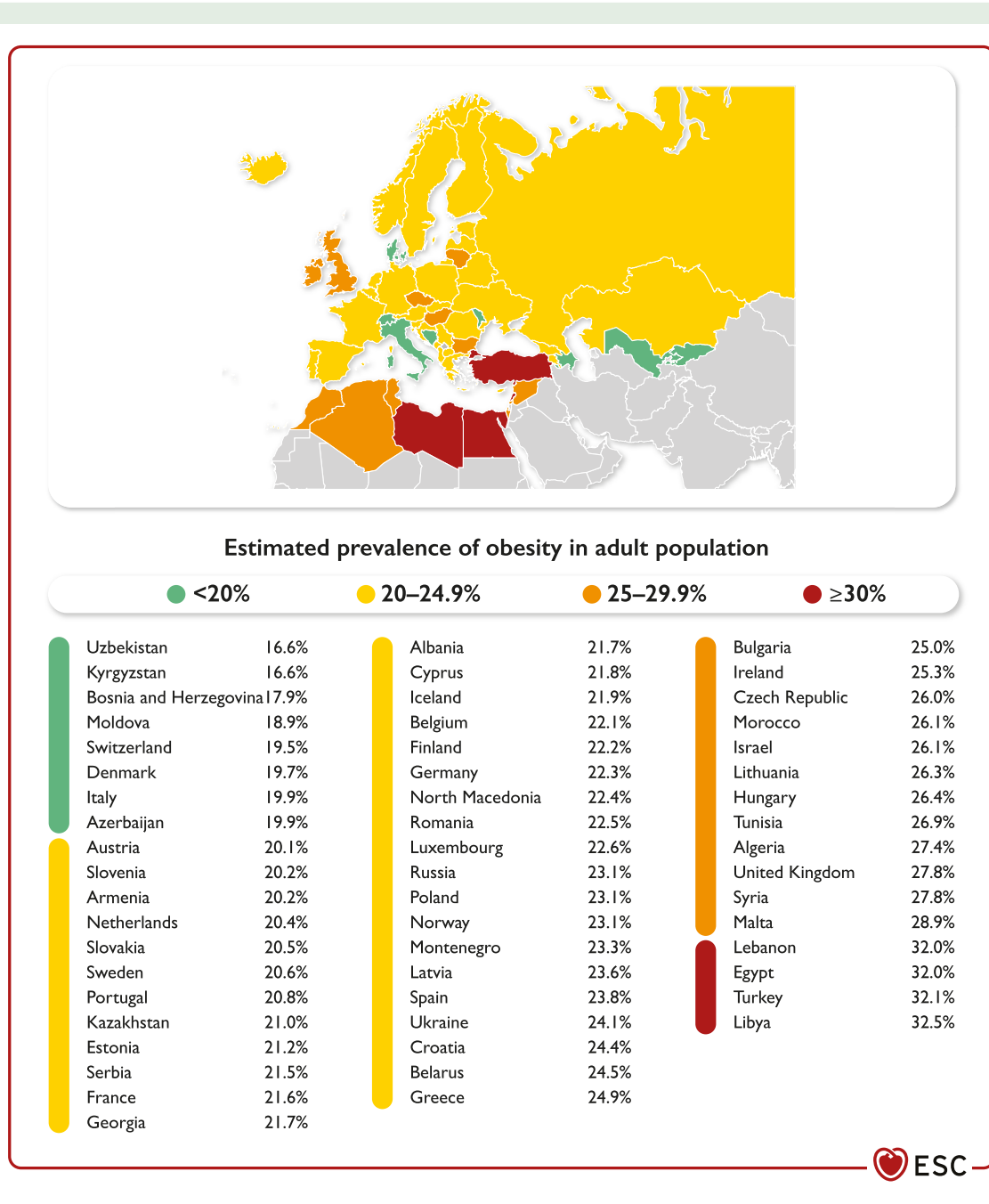
### Box 1 WHO classification of overweight and obesity in adults

- BMI 20 to <25 kg/m<sup>2</sup>: Normal weight
- BMI 25 to <30 kg/m<sup>2</sup>: Overweight
- BMI  $\geq 30$  kg/m<sup>2</sup>: Obesity
  - BMI 30 to <35 kg/m<sup>2</sup>: Obesity Class 1
  - BMI 35 to <40 kg/m<sup>2</sup>: Obesity Class 2
  - BMI  $\geq 40$  kg/m<sup>2</sup>: Obesity Class 3 (severe obesity)

## Epidemiology of obesity

According to 2021 ESC CVD statistics, it is estimated that 22.5% of adults across ESC member countries are obese, a prevalence that has more than doubled over the past 40 years (see [Supplementary data online, Figure S1](#)).<sup>6</sup> There are large differences between countries, with prevalence rates ranging from <20% to >30% in some countries ([Figure 1](#)). Overall, there is little difference by sex with prevalence of 22.7% in women and 22.2% in men.<sup>6</sup> However, women tend to be more overweight than men in middle-income countries while the opposite is true in high-income countries,<sup>6</sup> possibly reflecting different stages in the obesity transition.<sup>7</sup> Within countries,

socioeconomic disparities in relation to obesity are strong and increasing; in particular, lower educational level was linked to higher prevalence of obesity in European countries particularly among women<sup>8,9</sup> and clustering of socioeconomic disadvantages exacerbates these disparities.<sup>10</sup> It has been estimated that up to 50% of obesity can be attributed to inequalities in educational status.<sup>11</sup> Ethnic disparities have also been observed,<sup>11</sup> with higher obesity rates in Black ethnic groups and people from Middle Eastern and North African ancestry, and lower rates in Chinese ethnic groups. In a global perspective, obesity affected around 650 million adults in 2015,<sup>3</sup> corresponding to 10.8% of men and 14.9% of women worldwide.<sup>3,12</sup> It is estimated that >1 billion people worldwide are now living with



**Figure 1** Prevalence of obesity (BMI  $\geq 30$  kg/m<sup>2</sup>) across ESC member countries in 2019. Adapted from Timmis et al.<sup>6</sup>

obesity, and that obesity prevalence has more than doubled globally among adults since 1990.<sup>13</sup>

Understanding the patterns of overweight and obesity rates over the life course is essential to determine appropriate measures to tackle obesity on a population level. Currently, the prevalence of overweight and obesity is lower among younger people and increases markedly in the third to fifth decade of life,<sup>14</sup> whereas obesity-related cardiometabolic disorders and manifest CVD become exponentially more prevalent in the following decades. However, childhood obesity is expected to increase substantially, with most children remaining obese throughout adolescence and adult life.<sup>15</sup> In children, obesity in early infancy or at 3 years of age translates into an almost 90% risk of being overweight or obese in adolescence. Among obese adolescents, the most rapid weight gain was shown to have occurred between 2 and 6 years of age; most children who were obese at that age were obese in adolescence. Although medical treatment of obesity and overweight now may be within reach, more action is needed to prevent obesity from developing. Targeting action that could prevent weight gain over critical periods in children and the young, in particular among families with reduced socioeconomic potential, is pivotal.<sup>16,17</sup>

Obesity with BMI  $\geq 35$  kg/m<sup>2</sup> (Classes 2 and 3) has emerged as an almost entirely new phenotype in the past decades. Still, most cases of obesity-related CVD will arise from the large group with overweight and Class 1 obesity. If trends in overweight and obesity persist, the marked decline in death from coronary artery disease (CAD) seen over the last decades in many countries is likely (or has already started) to flatten, with a concomitant rise in other CV disorders such as heart failure (HF) and cardiomyopathy.<sup>18,19</sup>

## Key points

- Obesity affects about one in five adults in ESC member countries and one in eight adults worldwide.
- The prevalence of obesity has been rising over the past decades globally.
- While marked obesity (BMI  $\geq 35$  kg/m<sup>2</sup>) is an emerging phenotype, most cases of obesity-related CVD are expected to arise from persons with BMI  $< 35$  kg/m<sup>2</sup>.
- Preventive measures should focus particularly on childhood and early adulthood and address socioeconomic disparities.

## Aetiology

The process of obesity is complex and multi-factorial including individual-related and environmental factors. In broad terms, overweight and obesity are caused by an imbalance between energy intake and energy expenditure (*Graphical Abstract*). Energy intake and expenditure reflect individual decisions influenced by biological and genetic factors. However, the options available to the individual are shaped by financial, societal, and social network factors.<sup>20</sup> Importantly, the worldwide increase in the prevalence of overweight and obesity has largely been driven by these environmental factors.<sup>21</sup> For example, vast changes in food production and marketing (including growing consumption of easily accessible and lower-cost highly processed and ultra-processed foods, as well as eating alone as a result of changing social relationships particularly in industrialized and urban setting),<sup>22</sup> along with changes in transportation and job organization overall contribute to a widespread caloric imbalance favouring weight gain. The noticeable rise in sedentary behaviours over time, resulting in a decline in energy expenditure and thereby promoting weight gain, deserves particular attention. Mortality

rates are higher in people with sedentary lifestyle,<sup>23</sup> this association appears to be partly attenuated by more moderate-intensity physical activity (~60–75 min per day) among those with high sitting time.<sup>24</sup> Notably, in addition to being a contributing factor, a decline in physical activity and adoption of sedentary behaviour may be a consequence of advanced obesity, thereby potentially establishing a vicious cycle that augments unhealthy weight gain and associated cardiometabolic risk.

Individual factors that are at play include regulation of appetite and satiety in the brain by adipose tissue, gut, or liver hormones, with a dysregulated craving for food in individuals with obesity.<sup>21</sup> Understanding what drives the development of obesity in the individual is crucial to prevent weight gain and obesity during the life course. Hormonal changes over the course of life [particularly in pregnancy-related obesity,<sup>25</sup> in post-menopausal women,<sup>21</sup> and some endocrinological disorders (hypercortisolism, hypothyroidism, growth hormone deficiency)], as well as medications (e.g. antipsychotics, antidepressants, antihyperglycemics, antihypertensives, and corticosteroids) are precipitating factors that could lead to weight gain.

Monogenic, syndromic, and polygenic obesity are all genetic causes of obesity.<sup>26</sup> Parental adiposity has been linked to body composition in offspring,<sup>27</sup> and parental BMI has been positively associated with adult offspring BMI,<sup>28</sup> overall indicating that both parents may similarly contribute either with genetic traits, or by promoting an obesogenic family environment. Although observations from twin and adoption studies suggest that obesity might be an inherited disorder of energy homeostasis, changes in population genetic factors cannot explain the marked rise in obesity over the last decades.<sup>21</sup>

## Key point

- Genetic and biological factors influence individual development of obesity, but the worldwide obesity epidemic is largely driven by environmental/societal factors.

## Obesity phenotypes and metrics

Fat can be deposited in subcutaneous adipose tissue depots or in visceral, intramuscular, or other ectopic depots surrounding organs and blood vessels (e.g. the kidney, liver, or the epicardial/pericardial space). Different adipose tissue depots have different biological significance and contribution to metabolic health. Visceral adipose tissue carries the largest burden of metabolically unhealthy obesity (driving the 'apple-shape' or 'male-type' obesity), and its accumulation increases cardiometabolic risk.<sup>29,30</sup> Conversely, subcutaneous fat is metabolically inactive, and particularly the expansion of the gluteal depot ('gynoid-type' obesity) is inversely related with cardiometabolic risk.<sup>31</sup> Epicardial adipose tissue thickness and expansion may have value in cardiometabolic risk assessment<sup>32</sup> and has been linked to higher risk of acute coronary syndromes and post-cardiac surgery atrial fibrillation (AF).<sup>32</sup>

For a given fat mass, the risk of cardiometabolic complications varies considerably and is related to the distribution of fat as well as the amount of muscle tissue. Metabolically unhealthy normal weight is characterized by high visceral fat mass, low leg fat mass, and low muscle mass. Conversely, the term 'metabolically healthy obesity' has sometimes been used to describe individuals who are classified as obese based on their BMI but who do not exhibit typical metabolic abnormalities associated with obesity;<sup>33</sup> however, this likely represents a transient phenotype<sup>34</sup> and may simply reflect different stages in development of obesity and manifest cardiometabolic disorders or CVD.<sup>35</sup> In older people, overweight or mild (Class 1) obesity may paradoxically appear



to be protective,<sup>36</sup> whereas in people with comorbidities and chronic diseases, significantly reduced adipose tissue and weight loss is associated with increased mortality. In older adults, a catabolic state and inactivity may result in lower muscle mass with low BMI but partly preserved excess fat, termed sarcopenic obesity.<sup>37</sup>

BMI, the gold standard for obesity definition and classification, has been used in many studies to define and classify obesity, which facilitates comparisons across populations and studies. Although BMI provides the most useful population-level measure of overweight and obesity, it may not correspond to the same degree of adiposity in different individuals. BMI does not encompass the complex biology of excess adiposity, as it does not take muscle mass or the amount and distribution of fat into account. Individuals with similar BMI may have different cardiometabolic risk.<sup>38</sup> For example, women typically have a higher percentage of body fat and lower muscle mass compared with men for the same BMI.

Research indicates that the lowest all-cause mortality, the nadir of the U-shaped curve, is observed at a BMI of 20–25 kg/m<sup>2</sup> in both sexes. Men, however, exhibit a higher risk per excess BMI unit than women, corresponding to steeper legs of the U-shaped curve.<sup>2</sup> The nadir of CVD risk is similar across different global regions, except in East Asia, where the lowest risk of coronary heart disease is at a BMI of 18.5–20 kg/m<sup>2</sup>.<sup>2</sup>

Simple measurements such as the waist circumference, waist-to-hip or waist-to-height ratio reflecting visceral adipose tissue may better predict CV events than BMI alone.<sup>29,39,40</sup> These anthropometric measurements have therefore been proposed to complement BMI for phenotypic characterization of obesity,<sup>41</sup> but their clinical utility as well as optimal threshold values of these metrics across BMI categories remain to be defined and broadly accepted. For waist circumference in particular, current ESC Prevention Guidelines advise no further weight gain for values >94 cm in men and >80 cm in women, and weight reduction for values >102 cm in men and >88 cm in women.<sup>42</sup> Threshold values for adiposity measures beyond BMI are discussed in detail elsewhere,<sup>41,43</sup> as for BMI, different thresholds of these metrics apply to children, adolescents, and pregnant women.

## Key points

- Individuals with similar BMI may have different cardiometabolic risk.
- Optimal BMI range for the lowest mortality is similar in women and men.
- Metrics of abdominal adiposity including waist circumference, waist-to-height ratio and waist-to-hip ratio are useful to refine cardiometabolic risk stratification beyond BMI.

## Assessment of fat topography and body composition

Adipose tissue distribution can be visualized and quantified using various imaging modalities (Figure 2). Dual energy X-ray absorptiometry (DEXA) scan can roughly estimate general fat distribution in the body, whereas ultrasound provides a more accurate evaluation of the thickness of subcutaneous, gluteal and in some cases visceral fat in the chest or abdomen. Magnetic resonance imaging (MRI) provides excellent evaluation of adipose tissue distribution including volumetric assessment. Computed tomography (CT) is the gold standard for volumetric assessment of adipose tissue as well as ectopic fat depots (e.g. in the liver or skeletal muscle). Both MRI and CT can assess fat topography including visceral and subcutaneous adipose tissue. CT-based artificial intelligence post-processing methods can assess adipose tissue quality, adipocyte size, and adipose tissue texture and composition,

reflecting the inflammatory, and metabolic status of the tissue.<sup>45</sup> Positron emission tomography (PET) provides the gold standard in assessing the quality of adipose tissue at a macro-level, but its low spatial resolution does not allow evaluation of small depots like perivascular adipose tissue (Figure 2). Currently, imaging is not widely used to assess obesity, but due to the increasing number of imaging tests performed for other reasons (e.g. CT angiography as first-line investigation for chest pain), there is an opportunity to standardize the extraction and interpretation of volumetric assessment of visceral adiposity obtained from routine, clinically indicated imaging. Other methods that have been used to assess body composition include skinfold thickness, bio-electrical impedance analysis, and body plethysmography. Currently, commercially available mobile-health applications are increasingly being used to monitor body weight and composition, although their accuracy against gold-standard imaging modalities remains to be documented.<sup>46</sup>

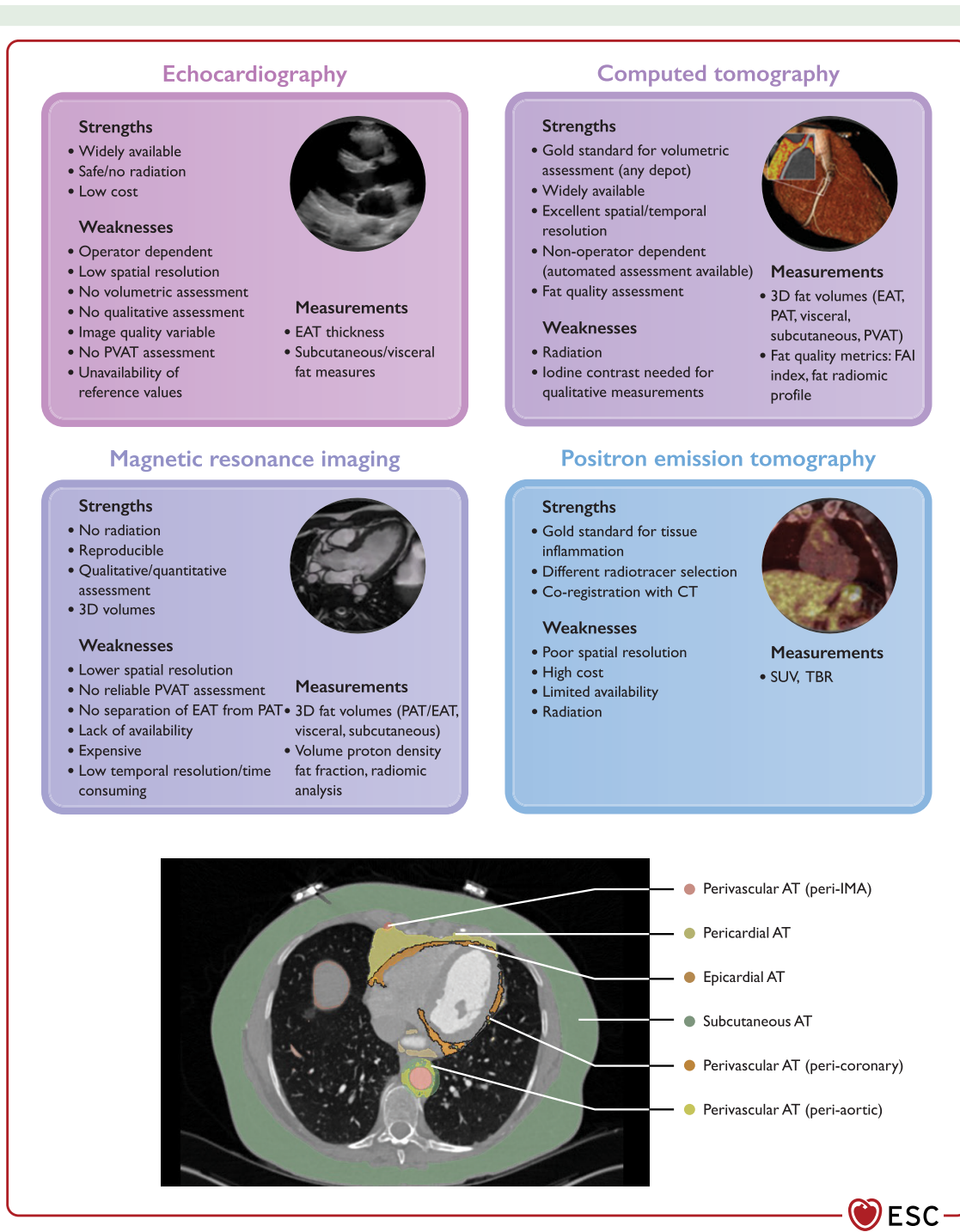
Obesity induces pericardial, epicardial, and perivascular adipose tissue. The total fat content surrounding the heart (the sum of epicardial and pericardial fat), has been associated with prevalent CVD independent of obesity metrics<sup>47</sup> and with future CV events among individuals free of clinical CVD.<sup>48</sup> Epicardial fat, the visceral fat between the outer wall of the myocardium and the visceral layer of the pericardium, is a good surrogate of visceral obesity and has been correlated with subclinical atherosclerosis and CAD.<sup>49</sup> Echocardiography can measure epicardial fat thickness but cannot assess adipose tissue quality.<sup>44,50</sup> CT can differentiate epicardial from pericardial adipose tissue and quantify perivascular adipose tissue around the coronary arteries.<sup>44</sup> CT imaging coupled with post-processing methods provide a metric of coronary inflammation, with prognostic value for future CV events as shown in studies not restricted to obese individuals.<sup>51,52</sup> Clinical use of these imaging metrics of perivascular adipose tissue for identifying the inflamed coronary arteries and personalizing CV risk estimation has emerged as one of the first applications of adipose tissue imaging in CV medicine,<sup>44</sup> although not yet implemented in clinical practice. Similarly, the evidence on epicardial adipose tissue volume holds promise for cardiometabolic risk stratification in the future. Measurement of pericardial adipose tissue from routine CV imaging tests is less standardized and the evidence supporting its value as a marker of metabolically dysfunctional adiposity is less robust.

## Key points

- Different imaging modalities can accurately assess fat topography and quality.
- Quantification of perivascular, epicardial, and pericardial adipose tissue may improve CV risk assessment, but its clinical role remains uncertain.

## Interplay between adipose tissue and the cardiovascular system

As reviewed in detail elsewhere,<sup>44</sup> different cell types within the human adipose tissue secrete various molecules, such as adipokines,<sup>50</sup> lipid species (e.g. ceramides, sphingolipids),<sup>53</sup> and large protein molecules like Wnt ligands.<sup>54</sup> When these molecules are secreted by the large 'remote' adipose tissue depots (visceral, subcutaneous, or gluteal fat), they enter the circulation and can exert endocrine effects on the vascular wall and myocardium, affecting CV physiology.<sup>55</sup> Molecules secreted by perivascular adipose tissue also exert paracrine (via diffusion) and possibly vasocrine (via the microcirculation) effects on the vascular wall (outside-to-inside signalling).<sup>55</sup> Similar paracrine effects are observed between the secretome of epicardial adipose tissue and the myocardium,



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**Figure 2** Main imaging modalities for assessment of adipose tissue. Upper part: Comparison of different imaging modalities for assessment of adipose tissue. Lower part: Distribution of adipose tissue around the heart. Axial view of the chest in computed tomography, showing subcutaneous, visceral abdominal, thoracic (including the pericardial and epicardial) adipose tissue. Perivascular adipose tissue is defined as the adipose tissue lying within a radial distance from the outer vessel wall equal to the vessel diameter (or at a maximum distance of 2 cm in the case of large vessels with diameter >2 cm, like the aorta). 3D, three-dimensional; CT, computed tomography; EAT, epicardial adipose tissue; PAT, pericardial adipose tissue; PVAT, perivascular adipose tissue; FAI, fat attenuation index; IMA, internal mammary artery; AT, adipose tissue; SUV, standardized uptake value; TBR, target-to-blood pool ratio. Modified from Antoniadou et al.<sup>44</sup>

thereby affecting cardiac function in obesity.<sup>55</sup> These molecules do not necessarily induce CV dysfunction; indeed, secretion of adiponectin or interleukin-10 exert protective effects by suppressing inflammation and

reducing CV oxidative stress.<sup>55</sup> Adipose tissue whose secretome shifts towards this anti-atherogenic profile, is considered as ‘metabolically healthy’. In the presence of insulin resistance, adipose tissue shifts its

secretome towards pro-inflammatory cytokines which have pro-atherogenic and pro-inflammatory effects.<sup>50</sup> Different adipose tissue depots have different secretome profile (i.e. visceral adipose tissue generates more pro-inflammatory/pro-atherogenic adipokines).<sup>50</sup>

Beyond its effects on the CV system, adipose tissue can sense signals coming from the CV system, modifying its structure and composition (inside-to-outside signals). Perivascular adipose tissue senses molecules from the vascular wall or the heart, such as oxidation products<sup>56,57</sup> or inflammatory molecules<sup>58</sup> and in response reprograms the secretory machinery into producing anti-inflammatory molecules like adiponectin; this serves as a defence homeostatic mechanism, by which perivascular adipose tissue may protect the CV system from oxidative or inflammatory injury. Similar effects are observed with remote adipose tissue depots, which sense distress signals from the CV system [e.g. myocardium-derived B-type natriuretic peptide (BNP) or tumour necrosis factor- $\alpha$  in HF], that lead to lipolysis/weight loss/cachexia and reprogramming of the adipocytes to produce large amounts of adiponectin as a compensatory mechanism in these chronic diseases.<sup>59</sup>

## Key point

- Remote and local adipose tissue exert pro-atherogenic and pro-inflammatory effects on coronary vascular wall and myocardium, but may also shift to anti-atherogenic effects.

## Obesity and cardiovascular risk factors

### Diabetes

Obesity and T2DM are strongly related with a similar rise in prevalence both on a European level and globally.<sup>6,60</sup> About 80%–85% of people with T2DM are also overweight or obese.<sup>61</sup> Conversely, individuals with obesity are nearly three times more likely to develop T2DM than normal weight individuals (20% vs. 7.3%).<sup>62</sup> While younger persons with weight in the upper normal range have higher risk of developing cardiometabolic disease, in particular T2DM, adolescents with obesity have a markedly higher relative risk.<sup>63</sup> It is generally agreed that individuals in high-risk groups including those with overweight or obesity should be regularly screened for diabetes, particularly after age 45 years.<sup>61</sup> In patients with established T2DM, weight loss interventions have shown positive effects on glycaemic control including remission to a non-diabetic state (Box 2).<sup>64</sup>

### Box 2 Impact of non-pharmacological weight loss interventions on diabetes

- In the Look AHEAD trial of overweight or obese patients with T2DM, intensive lifestyle intervention (reduced caloric intake and increased physical activity) when compared with control treatment resulted in greater weight loss (8.6% vs. 0.7%) and greater reduction in glycated haemoglobin (HbA1c) (0.7% vs. 0.1%) at 1 year.<sup>69</sup>
- A meta-analysis of 36 randomized controlled trials in selected patients with T2DM and obesity ( $n = 2141$ ) found greater BMI and HbA1c reductions and more frequent remission of diabetes with bariatric surgery vs. non-surgical therapy.<sup>70</sup> There is limited evidence for patients aged >65 years or with BMI <35 kg/m<sup>2</sup>, and no evidence so far comparing bariatric surgery vs. newer weight loss medications (glucagon-like peptide receptor agonists).

Insulin resistance, a key factor in T2DM development manifesting long before the onset of diabetes,<sup>65</sup> is also a major feature of obesity.<sup>66</sup> Insulin resistance predicts the risk of developing CVD, even in the absence of diabetes,<sup>67</sup> and promotes atheroma plaque formation.<sup>68</sup>

### ESC Guidelines recommendation on management of overweight or obesity in T2DM

- It is recommended that individuals with diabetes living with overweight or obesity aim to reduce weight and increase physical exercise to improve metabolic control and overall CVD risk profile (Class I, level of evidence A).<sup>61</sup>

## Hypertension

Increased BMI, from overweight to all classes of obesity is linearly related to the prevalence of hypertension.<sup>71</sup> In the Framingham offspring study, people with overweight or obesity were more prone to develop hypertension than normal weight individuals; relative risk estimates attributable to adiposity were 78% in men and 65% in women aged 20–49 years.<sup>72</sup> Conversely, clinically significant long-term reductions in blood pressure can be achieved even with modest weight loss (Box 3).<sup>73</sup>

### Box 3 Impact of non-pharmacological weight loss interventions on blood pressure

- In the Look AHEAD trial overweight or obese patients with T2DM who received intensive lifestyle intervention (reduced caloric intake and increased physical activity), a 5–10% weight loss was associated with a 56% and 48% greater likelihood of achieving a 5-mmHg decrease in systolic and diastolic blood pressure, respectively. Greater weight loss was associated with larger blood pressure reductions.<sup>80</sup>
- A meta-analysis of 19 randomized controlled trials ( $n = 1353$ ) including selected patients with T2DM and obesity found greater reductions in systolic blood pressure (–3.9 mmHg) and diastolic blood pressure (–2.7 mmHg) with bariatric surgery vs. non-surgical treatment.<sup>70</sup>

Body fat distribution plays a major role in hypertension development, with visceral fat accumulation accounting for the strongest association with hypertension.<sup>74</sup> Obesity is associated with an increased blood volume and fluid retention, especially in the adipose tissue, which in turn increases blood venous return and cardiac output.<sup>75</sup> Moreover, obesity is associated with prematurely increased arterial stiffness not only in adults but also in children, concurring to hypertension onset.<sup>76</sup>

The development of hypertension in obesity is mediated in part by adverse changes in renal function.<sup>77</sup> Retroperitoneal fat excess compresses renal vasculature and nerves with subsequent increased intrarenal pressure, increased plasma renin activity, angiotensinogen, angiotensin-converting enzyme activity, angiotensin II, and aldosterone, all leading to hypertension.<sup>77</sup> Additional mechanisms linking obesity to hypertension development include obstructive sleep apnoea (OSA),



supranormal activation of the sympathetic nervous system,<sup>77</sup> insulin resistance, and hyperleptinaemia.<sup>78</sup>

### ESC Guidelines recommendations on management of obesity and hypertension

- It is recommended to aim for a stable and healthy BMI (20–25 kg/m<sup>2</sup>) and waist circumference values (<94 cm in men and <80 cm in women) to reduce blood pressure and CVD risk (Class I, level of evidence A).<sup>79</sup>
- Blood pressure-lowering drug treatment is recommended for people with pre-diabetes or obesity when confirmed office blood pressure is  $\geq 140/90$  mmHg or when office blood pressure is 130–139/80–89 mmHg and the patient is at predicted 10-year risk of CVD  $\geq 10\%$  or with high risk conditions, despite a maximum of three months of lifestyle therapy (Class I, level of evidence A).<sup>79</sup>

### Dyslipidaemia

Low-density lipoprotein cholesterol (LDL-C), a causal factor of atherosclerotic disease,<sup>81</sup> does not appear to be linearly associated with body weight,<sup>82</sup> rather, an inverse U-shaped correlation between BMI and LDL-C has been reported.<sup>83,84</sup> However, obesity is associated with an atherogenic lipoprotein phenotype including elevation of both fasting and post-prandial triglycerides, Apolipoprotein B (ApoB), and small dense LDL particles, and low high-density lipoprotein cholesterol (HDL-C) and apolipoprotein A1 (ApoA1) levels.<sup>85</sup> Small, dense LDLs are prone to oxidation and rapidly accumulate in the arterial wall inducing atheromatous plaques.<sup>86</sup> Moreover, high levels of very-low-density lipoproteins (VLDL) that vehicle plasma triglycerides were found to explain 40% of the excess risk of myocardial infarction associated with higher BMI.<sup>87</sup> Weight loss can lower levels of atherogenic lipids (Box 4).

### Box 4 Impact of non-pharmacological weight loss interventions on dyslipidaemia

- A meta-analysis of 73 randomized controlled trials found that weight loss decreased triglycerides and LDL-C and increased HDL-C, with the greatest effects on triglycerides.<sup>89</sup>
- 5%–10% weight loss can decrease triglyceride levels by 20%.

### ESC Guidelines recommendation on lipid measurements

- ApoB analysis is recommended for risk assessment in certain subgroups, including people with obesity, as an alternative to LDL-C, if available, as the primary measurement for screening, diagnosis, and management of dyslipidaemia (Class I, level of evidence C).<sup>88</sup>

### Obstructive sleep apnoea

Obstructive sleep apnoea *per se* is a risk factor implicated in the development of hypertension<sup>90</sup> and the progression of HF, pulmonary hypertension, and AF,<sup>90,91</sup> overall reflecting how obesity exerts multiple direct and

indirect deleterious CV effects. In patients with OSA, a 10% body weight loss reduces the apnoea–hypopnoea index (AHI) (a metric of OSA severity, defined as the number of apnoeas and hypopnoeas per hour) by 26%–32%, while a 10% weight gain increases AHI by 32% and is associated with a six-fold increase in the risk of developing moderate to severe OSA.<sup>92</sup> Weight loss in combination with continuous positive airway pressure (CPAP) reduces other CV risk factors, such as insulin resistance, circulating levels of triglycerides, and blood pressure.<sup>93</sup>

Obesity increases the amount of neck adipose tissue reducing pharyngeal airway lumen size with increased propensity for collapse of the airway during sleep;<sup>94</sup> therefore, measuring the neck circumference represents standard practice in the physical examination of people with OSA since it predicts the severity of OSA better than BMI.<sup>95</sup>

### ESC Guidelines recommendation on sleep disorders in persons with obesity

- In patients with obesity, regular screening for non-restorative sleep is indicated (e.g. by the question: 'how often have you been bothered by trouble falling or staying asleep or sleeping too much?'). (Class I, level of evidence C).<sup>42</sup>

### Key points on clinical management of CV risk factors and obesity

- Overweight and obese individuals should regularly be screened for T2DM, particularly after age 45.
- In patients with obesity and T2DM, hypertension, dyslipidaemia, or OSA, reducing weight is a cornerstone of treatment.

### Treatment strategies for obesity: lifestyle interventions

Because obesity is caused by a chronic positive energy intake vs. expenditure imbalance,<sup>21</sup> treatment strategies for obesity are based on the concept that calorie intake must not exceed calories expended. Treatment of obesity requires a comprehensive medical approach that includes a combination of behavioural strategies such as dietary, physical activity, and/or psychological interventions, potentially complemented by pharmacotherapy and bariatric procedures, overall aiming to achieve the individually defined weight loss, health status, and quality of life goals.<sup>96</sup> Educational and informative programmes—either alone or as a core component of multidisciplinary and structured weight loss programmes—promote patients' awareness of their individual CV risk and the rationale for lifestyle interventions. Patient education could facilitate long-term adherence to lifestyle interventions.<sup>97</sup> Mobile health (mHealth) applications that include recording of daily physical activity and monitoring of body composition are used increasingly for helping people adopt healthier lifestyles, and they reportedly result in greater weight loss compared with standard counselling alone.<sup>98</sup>

It is important to note that prevention of excessive weight gain or long-term weight maintenance following intentional weight loss ('primary' or 'secondary' prevention of obesity) require prolonged and sometimes laborious efforts by motivated individuals amidst largely 'obesogenic' environments in many modern societies. These efforts should include consistent, lifelong adoption of healthy lifestyle behaviours, including qualitatively and quantitatively healthy dietary habits

and regular physical activity; these measures go beyond the simple concept of consuming fewer calories than those expended for a limited period of time, and are a cornerstone for primary prevention of CVD.<sup>42</sup> The interventions described below typically reflect shorter periods in time (e.g. a number of weeks in the context of structured obesity programmes, or ~1 year in most trials of non-pharmacological obesity treatments), which most likely explains the modest effects seen on weight reduction or on CVD risk.

It is also important to carefully differentiate in nutritional recommendations and provide tailored, individualized guidance. Patients with established diseases (such as advanced HF, chronic obstructive pulmonary disease, or cancer) have a catabolic dominance. At these disease stages, patients may risk losing weight as a consequence of the chronic disease. Advocating nutritional restriction under these circumstances should be avoided or done with great caution.

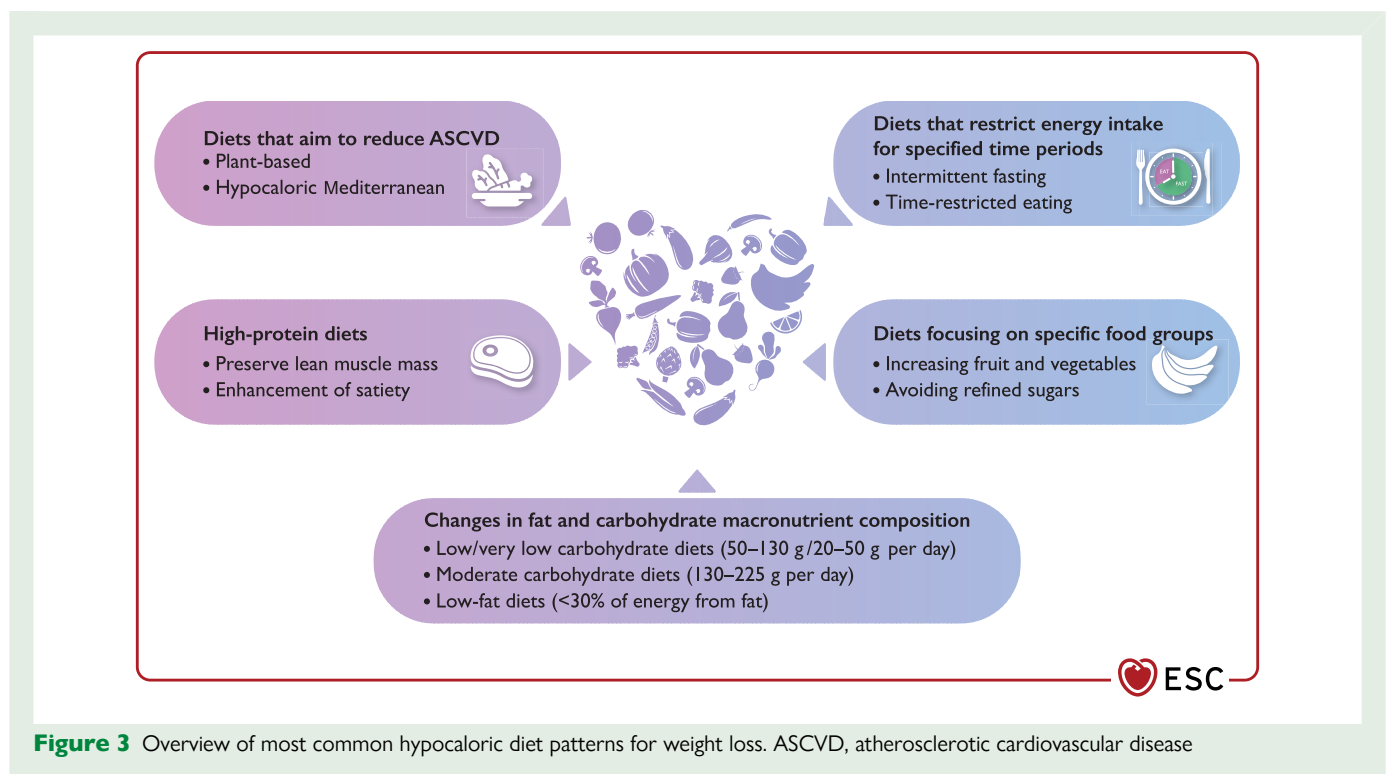
## Dietary interventions

Nutrition recommendations for adults of all body sizes should be personalized to meet individual values, preferences, and treatment goals to support a dietary approach that is safe, effective, nutritionally adequate, culturally acceptable, and affordable for long-term adherence. Potential contraindications to caloric restriction and intentional weight loss, such as morbidities characterized by catabolic dominance, also need to be taken into account. In general, dietary interventions aim for reduced caloric intake with a 500–750 kcal/day energy deficit that need to be adjusted for individual body weight and activity.<sup>99</sup> The energy deficit can be achieved by specific strategies including portion size control, reduction or elimination of ultra-processed foods such as sugar-sweetened beverages, reduction of alcohol consumption, and increased fruit and vegetable intake. Healthy eating approaches can be selected based on individual preference, metabolic risk, and likelihood of long-term adherence. In studies with a duration <2 years, successful weight reduction in the range

of 5%–10% was shown for nutritional approaches such as low fat-vegan, vegetarian style, low carbohydrate, and Mediterranean diets.<sup>99</sup> Figure 3 provides an overview of the most common patterns of hypocaloric diet for weight loss. According to a meta-analysis comparing dietary macronutrient patterns and dietary programmes for weight and CV risk factor reduction in overweight and obese adults, most dietary patterns resulted in broadly similar, modest short-term weight loss (within six months) with substantial improvements in CV risk factors; at later follow-up (12 months), the effects on weight loss and risk factors largely diminished, while the benefits of the Mediterranean diet tended to persist.<sup>100</sup> Supplementary data online, Table S2 summarizes the least and most effective types among common hypocaloric diets with respect to their impact on body weight and cardio-metabolic risk parameters.

In large, randomized trials, dietary interventions were typically assessed in combination with increased physical activity in the context of intensive lifestyle interventions. In the Diabetes Prevention Program in individuals with a BMI  $\geq 24$  kg/m<sup>2</sup> and pre-diabetes, lifestyle intervention led to a significant reduction of the incidence of T2DM (notably, to a greater extent than metformin), greater reduction of body weight and HbA1c compared with controls over a follow-up of 2.8 years.<sup>101</sup> In the Look AHEAD trial, 5145 patients with a BMI  $> 25$  kg/m<sup>2</sup> and T2DM, 14% with a history of CVD, were randomized to an intensive lifestyle intervention (weight loss promotion through reduced caloric intake and increased physical activity) or control (diabetes support and education). After 1 year, participants in the lifestyle intervention achieved greater weight loss (8.6% vs. 0.7%), and greater reduction in HbA1c and blood pressure levels. Differences in weight loss and HbA1c diminished but remained significant after a median of 9.6 years. The intensive lifestyle intervention did not reduce the rate of CV events, i.e. the study's primary outcome,<sup>69,102</sup> although a post-hoc analysis did show a significant reduction in CV events in patients achieving  $\geq 10\%$  weight loss.<sup>103</sup>

While some evidence demonstrates weight loss and improved CVD risk factors with other popular weight loss approaches including time-



**Figure 3** Overview of most common hypocaloric diet patterns for weight loss. ASCVD, atherosclerotic cardiovascular disease

restricted eating, intermittent fasting, or ketogenic diet, these have not yet been broadly endorsed and may require dietitian support.<sup>99</sup> The weight and body fat loss in case of intermittent fasting diets appear to be equivalent to continuous energy restriction when matched for energy intake.<sup>104</sup> Beyond hypocaloric diets to facilitate weight reduction, life-long adoption of a healthy diet is important for prevention of weight regain and more broadly for reduction of CVD risk; in this respect, a Mediterranean or similar diet is generally advocated, as shown in dietary randomized controlled trials (RCTs) for primary<sup>105</sup> or secondary CV prevention.<sup>106</sup> With respect to prevention of childhood obesity, dietary interventions are discussed in detailed elsewhere.<sup>16</sup>

## Physical activity

Combined physical activity and dietary interventions are used as first-line obesity treatment to achieve sustained loss of fat mass while avoiding loss of muscle mass. Physical activity, typically defined as bodily movements produced by skeletal muscles that require energy expenditure, has the potential to shift fat mass to muscle-mass and modify fat distribution, but the average effects on weight loss are typically modest—at least for the limited time periods during which physical activity interventions have typically been tested in the context of structured programmes or clinical trials. Larger effects can be expected in case of long-term adoption of increased physical activity and particularly exercise training—i.e. a subcategory of physical activity that involves structured, repetitive, and purposeful physical activity aimed at improving physical fitness, performance, and health.<sup>107</sup> In addition to contributing to weight loss, loss of fat mass, and supporting weight maintenance, exercise improves cardio-metabolic health and is prescribed for the treatment of CV risk (improved blood lipid profiles, delayed onset of T2DM, reduced blood pressure), and has the potential to enhance mental health and improve CV outcomes.<sup>108,109</sup>

To improve weight loss maintenance, frequent body weight self-monitoring and increased physical activity are important strategies.<sup>110</sup> Moderate-intensity continuous aerobic exercise (defined as 50%–70% of maximal heart rate) is associated with decreased visceral adiposity and modest weight loss of 2–3 kg through increased energy expenditure.<sup>107,108</sup> In addition, muscle strength or resistance training aims at preserving lean/fat-free mass during weight loss.<sup>107</sup> Aerobic training during weight loss has been shown to increase maximal oxygen consumption, and resistance training during weight loss leads to lower loss in lean body mass and increased muscle strength.<sup>111</sup> Whether a person primarily benefits from endurance or strength training seems to depend on individual factors.<sup>111</sup> A network meta-analysis including 84 RCTs showed that aerobic exercise at more vigorous intensities (including high-intensity interval training) is more effective than other exercise types (aerobic exercise at moderate intensities and resistance training) in reducing visceral adipose tissue in persons with overweight or obesity.<sup>112</sup> Importantly, prescription of exercise regimen based on high-intensity interval training is advised only after thorough assessment of CV risk.<sup>108</sup> With respect to the cardiometabolic effects of different types of exercise, resistance training is optimal for enhancing muscle strength and lipid profiles, while aerobic training excels in providing CV benefits and managing glucose levels in overweight and obese individuals.<sup>113</sup>

In current ESC guidelines for CVD prevention,<sup>42</sup> the common recommendation for the general adult population is at least 150–300 min per week of moderate or at least 75–150 min per week of vigorous physical activity to reduce all-cause mortality, CV mortality, and morbidity, with further recommendations for additional strength

exercises two to three times a week.<sup>110</sup> These general recommendations are largely applicable to individuals with obesity, whereas the European Association for the Study of Obesity advises a high volume of aerobic exercise (200–300 min/week of moderate-intensity exercise) to maintain a healthy weight after initial weight loss.<sup>108</sup>

Barriers to physical activity and exercise in obese persons should be taken into account, and individuals who cannot achieve the aforementioned exercise goals should stay as active as their abilities allow. Along these lines, healthcare professionals can encourage people with obesity to switch to non-sedentary behaviours throughout the day, such as walking for 2 min each hour or use of stairs.<sup>108</sup> Recently, wearable activity trackers, step counters and heart rate monitor watches emerged as effective motivation tools to further encourage and maintain increased physical activity.<sup>114</sup> Despite many barriers, an initial daily activity goal could be an additional 1800 steps per day on average.<sup>114</sup>

## Psychological interventions

Obesity is stigmatized in the public, even among healthcare professionals, and is associated with negative attitudes and discrimination.<sup>115</sup> Establishing a supportive environment for patients with obesity can be facilitated firstly with examination tables and chairs that accommodate all body sizes. Staff training on obesity and bias may improve the patient experience, including asking patients' permission to be weighed and providing alternatives including weighing in a private room or self-report of weight. Evidence-based counselling strategies can help initiate treatment discussions with patients. For example, the 5As (Assess, Advise, Agree, Assist, Arrange) can guide shared decision-making.<sup>116,117</sup> Each 'A' can occur when appropriate during the clinician–patient discussion and over several visits, and each additional counselling step is associated with increased patient motivation to lose weight.<sup>116</sup> Patients are more likely to lose weight when clinicians communicate using a supportive, non-judgmental approach.<sup>116</sup>

Food is often a coping mechanism for managing negative emotions, perpetuating cycles of emotional coping, and unhealthy eating behaviours.<sup>118</sup> Depression related to obesity may trigger unhealthy dietary habits, thus fuelling a vicious cycle. Family-based, multi-component weight management interventions are advised for people living with obesity. Interventions mainly target health behaviours and use behaviour change techniques attempting to directly improve diet and physical activity as behavioural outcomes. These interventions may show some improvements in psychological wellbeing, but there is limited consideration or understanding of the underlying mechanisms of action which indirectly influence engagement and the sustainability of the behaviour change.<sup>118</sup>

## Multidisciplinary approaches and structured obesity programmes

Intensive, multicomponent behavioural interventions represent an important strategy of obesity management. There are several evidence-based commercial multimodal programmes available.<sup>99,110,117,119</sup> Moderate- to high-intensity programmes typically include 12 or more sessions in the first year, followed by a maintenance phase for ~24 months.<sup>110</sup> Multimodal interventions include group, individual, or technology-based delivery for lifestyle changes, education, peer support, self-weighing, coaching, self-monitoring, cognitive restructuring, and goal setting.<sup>119</sup> Interventions may also address insufficient sleep and chronic stress. Moderate- to high-intensity interventions often produce 5%–10% weight loss with maximal loss achieved between 6 and 12

months.<sup>110</sup> Arranging follow-up visits for patients can promote weight loss, potentially by influencing behaviour change and accountability.<sup>120</sup> In the outpatient setting, close follow-up, ideally every four to six weeks, enables supporting lifestyle changes and addressing potential adverse effects of obesity management.

## Costs considerations for lifestyle interventions

The costs of obesity rise exponentially with higher levels of BMI and, consequently, modelling studies find that the potential cost reductions for a given percent reduction in BMI are greater if targeting individuals with higher BMI. The cost-savings are also greater with concomitant diabetes.<sup>121</sup> Behavioural counselling and other weight management programmes have limited costs and are generally recommended for overweight and obese patients with CVD. Cost-effectiveness analyses have found that these are more cost-effective in patients with higher BMI and higher burden of comorbidity.<sup>122</sup> The Look AHEAD trial, while not showing significantly improved CV event rates, found a small but significant weight reduction in the lifestyle intervention group at 10-year follow-up. Cost-analysis concluded that the intervention led to reductions in hospital admissions and medications resulting in 7% reduction in costs or 10-year cost savings of \$5280 per person.<sup>123</sup> In the Diabetes Prevention Program, including individuals aged  $\geq 25$  years with impaired glucose tolerance and in which 38% of the lifestyle intervention group lost  $>7\%$  of their weight, the cost per quality-adjusted life-year (QALY) was  $\sim$ \$8800 for the lifestyle intervention and \$29 900 for the metformin intervention.<sup>124</sup> Therefore, provided they are effective, investing in behavioural counselling and lifestyle interventions may yield significant long-term health benefits at acceptable costs.

## Key points on non-pharmacological treatment of obesity

- Dietary interventions generally aim for a 500–750 kcal/day energy deficit. Adjustments to individual body weight and activity are needed.
- Weight reduction in the range of 5%–10% can be achieved with various nutritional and multidisciplinary approaches but maintenance of effects is a key issue.
- Physical activity interventions typically have modest effects on weight loss but are important for weight loss maintenance and reduction of overall CV risk.

## Treatment strategies for obesity: pharmacological treatment

Modification of lifestyle behaviour remains the cornerstone for the management of obesity. However, if sufficient weight loss cannot be achieved by means of lifestyle interventions, initiation of anti-obesity medication is a reasonable addition<sup>125</sup> that has been shown to reduce cardiometabolic risk in people with obesity.<sup>126,127</sup> These medications are typically indicated, in conjunction with lifestyle modification, at a BMI  $\geq 30$  kg/m<sup>2</sup>, or BMI  $\geq 27$  kg/m<sup>2</sup> with at least one weight-related comorbidity.<sup>119,125</sup>

There are currently six drugs approved both by the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) for long-term weight management in patients with obesity: orlistat, naltrexone extended release (ER)/bupropion (ER), liraglutide, semaglutide, tirzepatide, and setmelanotide for treatment of rare obesity-related monogenetic deficiencies. They predominantly

decrease energy intake by means of reducing appetite, increasing satiety, and slowing gastric emptying.<sup>96,128,129</sup> The approved drugs achieve weight loss of at least 5% (Figure 4); in principle, weight loss of 5%–10% or greater should be targeted to achieve risk reduction in CV and metabolic complications of obesity.<sup>103,119</sup> Landmark randomized controlled trials of approved medications are summarized in Table 1. Table 2 summarizes common side effects and contraindications.

## Approved anti-obesity medication

### Orlistat

Orlistat acts in the intestinal lumen by inhibiting selective gastric and pancreatic lipases and decreasing dietary fat absorption.<sup>130</sup> Weight loss compared with placebo is modest (Table 1) but associated with a significant reduction in the risk of developing diabetes. Orlistat was shown to lower HbA1c in overweight or obese diabetic patients independently of weight loss.<sup>131</sup> There are no CV outcomes trials of orlistat and patients with CVD were not included in the major trials (Table 1).

### Naltrexone/bupropion

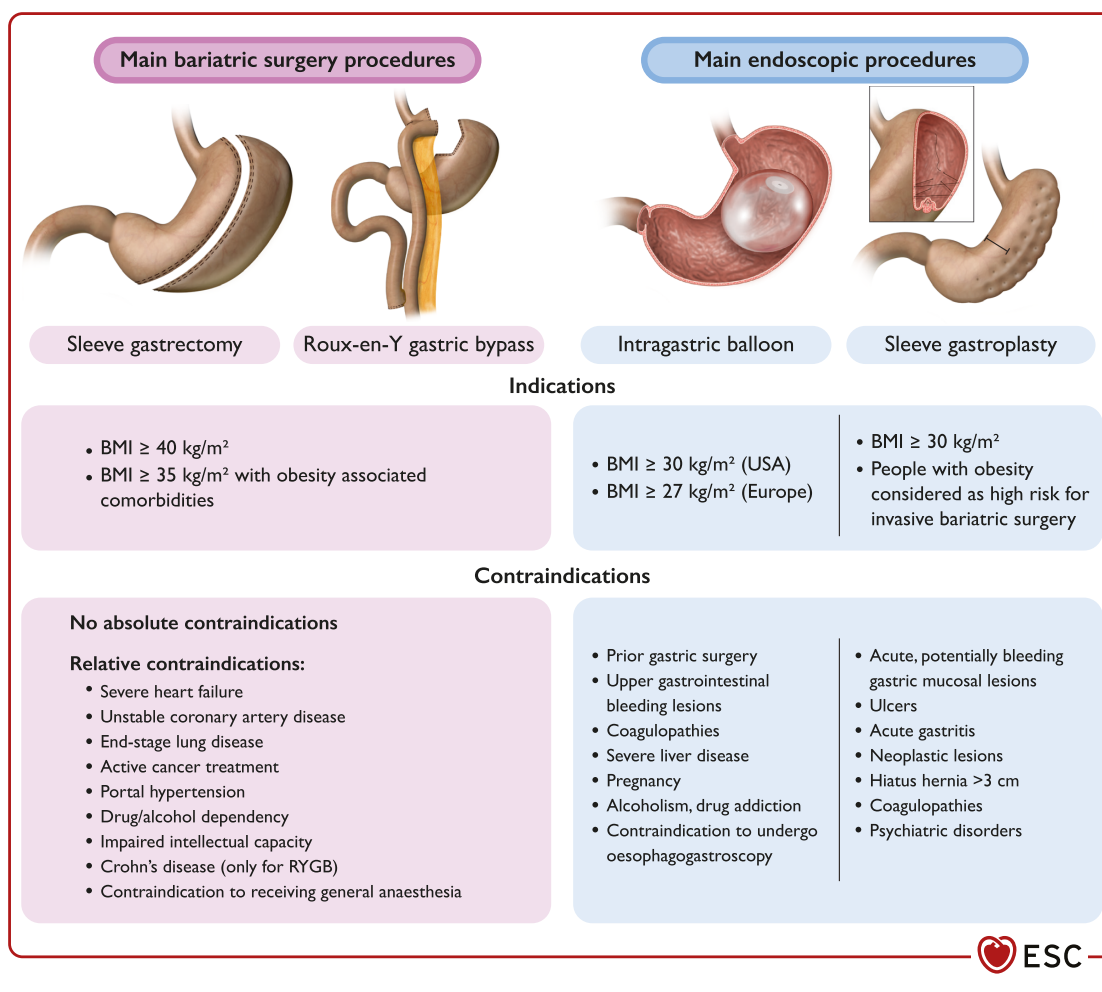
Bupropion, a dopamine and norepinephrine reuptake inhibitor, and naltrexone, an opioid receptor antagonist, work synergistically to stimulate the central secretion of proopiomelanocortin leading to reduced food craving and increased satiety.<sup>132</sup> In the largest randomized trial, the COR-III trial, the placebo-corrected weight loss with the 32/360 mg dose was 5.2% at 1 year, and the proportion of individuals achieving  $\geq 5\%$  weight loss was 50.5% vs. 17.1% with placebo.<sup>133</sup> A meta-analysis of four RCTs found a small but significant reduction of baseline body weight by 2.5 kg (1.9–3.2) with naltrexone/bupropion compared with placebo.<sup>134</sup> One RCT examined its effects on major adverse CV events (MACE) but was ended prematurely.<sup>135</sup> In the view of uncertainties regarding long-term CV safety, the medication—initially approved by the EMA in 2015—is currently under review, thus prescription of the drug in patients with CVD requires caution.<sup>136</sup>

### GLP-1 receptor agonists: liraglutide and semaglutide

Liraglutide and semaglutide are glucagon-like peptide 1 receptor agonists (GLP-1RAs) that enhance incretin effect, increase insulin secretion, delay gastric emptying, and decrease intestinal motility. Moreover, they act centrally and decrease appetite.<sup>137</sup> The GLP-1RAs, initially developed to lower glucose levels in patients with T2DM, were shown to elicit cardioprotective effects.<sup>138</sup> In addition to obesity management adjunct to lifestyle modifications in adults, both drugs have been approved by the EMA and FDA for use in adults and in children aged  $\geq 12$  years with obesity. To reduce side effects, both GLP-1 RAs should be up-titrated over several weeks.

RCTs in the SCALE programme examined the effects of subcutaneous liraglutide 3 mg once daily vs. placebo on weight loss in patients with obesity.<sup>139–143</sup> In these trials, patients with known CVD were either excluded, or comprised 8.5%<sup>140</sup> to 15%<sup>141</sup> of the study population. With liraglutide added to caloric reduction and increase of physical activity in patients without diabetes, the placebo-corrected weight loss was 5.4% at 1 year and 4.4% at 3 years.<sup>140,142</sup> In patients with T2DM, the placebo-corrected weight loss at 1 year was 3.9%.<sup>141</sup> In a weight loss maintenance study, liraglutide 3 mg plus an exercise programme was more effective in lowering body weight (–15.7% of pre-treatment weight) than liraglutide alone (–13.4%), exercise alone (–10.9%), or placebo (–6.7%).<sup>126</sup> With respect to CV outcomes, in patients with T2DM (mean baseline BMI of 32.5 kg/m<sup>2</sup>) treated with liraglutide 1.8 mg per day (i.e. not the 3 mg dose approved for obesity treatment),





**Figure 4** Main intragastric and surgical bariatric interventions. BMI, body mass index; RYGB, Rouen-en-Y gastric bypass

MACE were reduced by 13% and CV death by 22% compared with placebo.<sup>144</sup> No CV outcome trial has been conducted with liraglutide 3 mg in patients with overweight/obesity, with or without T2DM.

The STEP programme evaluated the effects of subcutaneous semaglutide 2.4 mg once weekly vs. placebo on weight loss in patients with obesity (mean baseline BMI 37.9 kg/m<sup>2</sup>). In the STEP 1 trial adjunct to lifestyle counselling, semaglutide 2.4 mg led to placebo-corrected body weight loss of 12.4% after 68 weeks; 32% of patients treated with semaglutide vs. 1.7% with placebo achieved a weight loss of  $\geq 20\%$ —a goal previously achievable only with bariatric surgery.<sup>145</sup> The weight loss was accompanied by favourable changes in systolic blood pressure and LDL-C levels. There was no further weight loss after 60 weeks of treatment, but weight loss was sustained for >2 years in patients who remained on treatment.<sup>146</sup> A meta-analysis of three RCTs showed a placebo-corrected body weight loss of 12.6% for semaglutide 2.4 mg in patients with obesity.<sup>147</sup> A meta-analysis including five trials with 3890 overweight or obese non-diabetic individuals showed a significant reduction in HbA1c with semaglutide 2.4 mg compared with placebo.<sup>148</sup> With respect to the impact on body composition as assessed by DEXA, 39% of weight loss in patients treated with semaglutide was lean body mass, whereas 61% was fat mass in the STEP1 trial.<sup>145</sup> With respect to CV outcomes, in patients with T2DM and high CV

risk, semaglutide 0.5 or 1.0 mg once weekly (i.e. not the 2.4 mg dose approved for obesity treatment) achieved a 26% reduction in MACE compared with placebo in a trial designed as non-inferiority trial.<sup>149</sup>

The SELECT trial is the first dedicated RCT to evaluate the effect of semaglutide on CV outcomes in patients with pre-existing CVD with overweight or obesity (BMI  $\geq 27$  kg/m<sup>2</sup>) but no diabetes. Of the 17 604 included patients, 82.1% had known CAD at baseline (prior myocardial infarction in 76.3%), and 24.3% had chronic HF [HF with preserved ejection fraction (HFpEF) in 12.9%]. Semaglutide 2.4 mg once weekly was superior to placebo at 40 months mean follow-up in reducing incidence CV death, non-fatal myocardial infarction, or non-fatal stroke (hazard ratio 0.80; 95% confidence interval 0.72–0.90).<sup>150</sup> Patients lost a mean of 9.4% of body weight over the first 2 years with semaglutide vs. 0.88% with placebo. Semaglutide also led to a significant reduction in systolic blood pressure, HbA1c, high-sensitivity C-reactive protein (hsCRP), LDL-C, and triglycerides.<sup>150</sup> In a head-to-head comparison, semaglutide 2.4 mg was more effective in lowering body weight than liraglutide 3 mg once daily in individuals with overweight and obesity without diabetes,<sup>151</sup> with a mean difference in body weight loss of 9.4% at 68 weeks. As a most recent development, oral semaglutide 50 mg once daily (currently not EMA- or FDA-approved) showed a placebo-corrected body weight change of



**Table 1** Landmark randomized controlled trials of approved anti-obesity medications on treatment efficacy for weight reduction and improvement of cardiovascular risk factors

Phase 3 randomized controlled trials	I: Intervention (n) C: control (n)	Mean BMI (kg)/mean age (years)/females (%)	Body weight change from baseline (kg) Least square mean diff.	Proportion (%) of participants losing ≥5% of baseline weight	Proportion (%) of participants losing ≥10% of baseline weight	Fasting blood glucose % change from baseline	Fasting insulin % change from baseline	HbA1c % change from baseline	LDL-C % change from baseline	SBP % change from baseline	IWQOL- Life score change from baseline	Proportion of participants discontinuing treatment due to adverse events (%)
<b>Orlistat</b>												
Sjöström, 1998 PMID 9683204	I: Orlistat 120 mg (343) C: Placebo (340) + hypocaloric diet 52 weeks BMI: 28–47 kg/m <sup>2</sup>	I: 36.0/45.2/82.8 C: 36.1/44.3/83.2	I: -10.2 kg C: -6.1 kg 3.9 kg	I: 68.5% C: 49.2%	I: 38.8% C: 17.7%	I: -3.2% C: -1.0%	I: -1.5% C: 7.6%	-	I: -1.2% C: +5.2%	I: -0.6% C: +1.2%	-	I: 6.7% C: 2.6%
Davidson, 1999 PMID 9918478	Drug treated DM excluded I: Orlistat 120 mg (668) C: Placebo (224) + hypocaloric diet 52 weeks BMI: 30–43 kg/m <sup>2</sup>	I: 36.2/43.3/82.8 C: 36.5/44.0/88.3	I: -8.8 kg C: -5.8 kg 5.8 kg	I: 65.7% C: 43.6%	I: 38.9% C: 24.8%	-	-	-	-	I: -0.01% C: +0.01%	-	-
Torgerson, 2004 XENDOS PMID 14693982	Drug treated DM excluded I: Orlistat 120 mg (1640) C: Placebo (1637) + lifestyle changes 1 year BMI: ≥30 kg/m <sup>2</sup> DM excluded	I: 37.3/43.0/55.2 C: 37.4/43.7/55.3	I: -10.6 kg C: -6.2 kg	I: 72.8% C: 45.1%	I: 41.0% C: 20.8%	I: +0.1% C: +0.2%	I: -26.5% C: -17.0%	-	I: -12.8% C: -5.1%	I: -7.3% C: -5.2%	-	-
Torgerson, 2004 XENDOS PMID 14693982	I: Orlistat 120 mg (1640) C: Placebo (1637) + lifestyle changes 4 years BMI: ≥30 kg/m <sup>2</sup> DM excluded	I: 37.3/43.0/55.2 C: 37.4/43.7/55.3	I: -5.8 kg C: -3.0 kg 2.7 kg	I: 52.8% C: 37.3%	I: 26.2% C: 15.6%	I: +0.1% C: +0.2%	I: -32.0% C: -20.6%	-	I: -11.4% C: -1.6%	I: -4.9% C: -3.4%	-	-
<b>Naltrexone/bupropion</b>												
Greenway, 2010 COR-1 PMID 20673995	I: NIB 16/360 mg (578) C: NIB 32/360 mg (583) C: Placebo (581) No specific co-intervention 56 weeks BMI: 27–45 kg/m <sup>2c</sup> DM excluded	I: 36.2/44.4/85 I: 36.1/44.4/85 C: 36.2/43.7/85	I: -5.0 kg I: -6.1 kg C: -1.3 kg	I: 39% I: 48% C: 16%	I: 20% I: 25% C: 7%	I: -1.9% I: -2.6% C: -0.7%	I: -11.8% I: -17.1% C: -4.6%	-	I: -1.5% I: -2.0% C: -0.5%	I: 0.3% I: -0.1% C: -1.9%	I: +11.7 I: +12.7 C: +8.6	I: 21.4% I: 19.5% C: 9.8%
Wadden, 2011 COR-BMOD PMID 20559296	I: NIB 32/360 mg (591) C: Placebo (202) + intensive behaviour modification (BMOD) 56 weeks BMI: 27–45 kg/m <sup>2c</sup> DM excluded	I: 36.3/45.9/89.3 C: 37.0/45.6/91.6	I: -9.3 kg C: -5.1 kg	I: 66.4% C: 42.5%	I: 41.5% C: 20.2%	I: -1.5% C: 0.0%	I: -28.0% C: -15.5%	-	I: +7.1% C: +10.0%	I: -0.03% C: -0.01%	I: +13.4 C: +10.3	I: 16% C: 3.5%

Continued

**Table 1** Continued

Phase 3 randomized controlled trials	I: Intervention (n) C: control (n) study duration BMI inclusion range diabetes mellitus criteria	Mean BMI (kg)/mean age (years)/females (%)	Body weight change from baseline Least square mean diff. (kg)	Proportion (%) of participants losing ≥5% of baseline weight	Proportion (%) of participants losing ≥10% of baseline weight	Fasting blood glucose % change from baseline	Fasting insulin % change from baseline	HbA1c % change from baseline	LDL-C % change from baseline	SBP % change from baseline	IWQOL- Lite score change from baseline	Proportion of participants discontinuing treatment due to adverse events (%)
Apovian, 2013 COR-II PMID 23408728	I: NIB 32/360 mg (1001) C: Placebo (495) No co-intervention 56 weeks BMI: 27–45 kg/m <sup>2c</sup> DM excluded	I: 36.2/44.3/84.6 C: 36.1/44.4/84.8	I: -6.4% C: -1.2%	I: 50.5% C: 17.1%	I: 28.3% C: 5.7%	I: -2.9% C: -1.4%	I: -11.4% C: +3.5%	-	I: -0.05% C: -0.02%	I: +0.6 <sup>a</sup> C: -0.5 <sup>a</sup>	I: +10.9 C: +6.4	I: 24.3% C: 13.8%
Hollander, 2013 COR-Diabetes PMID 24144653	I: NIB 32/360 mg (835) C: Placebo (170) No co-intervention 56 weeks BMI: 27–45 kg/m <sup>2</sup> All had type 2 DM	I: 36.4/54.0/58.2 C: 36.4/53.5/52.9	I: -5.0% C: -1.8%	I: 44.5% C: 18.9%	I: 18.5% C: 5.7%	I: -7.4% C: -2.4%	I: -13.5% C: -10.4%	I: -0.6% C: -0.1%	I: -1.4% C: 0.0%	I: 0.0 <sup>a</sup> C: -1.1 <sup>a</sup>	-	I: 29.4% C: 15.4%
<b>Liraglutide</b> Pi-Sunyer, 2015 SCALE Obesity and Prediabetes PMID 26132939	I: Liraglutide 3.0 mg (2487) C: Placebo (1244) + lifestyle intervention 56 weeks BMI: ≥27 kg/m <sup>2c</sup> DM excluded	I: 38.3/45.2/78.7 C: 38.3/45.0/78.1	I: -8.0% C: -2.6% 5.6 kg	I: 63.2% C: 27.1%	I: 33.1% C: 10.6%	I: -7.1 C: +0.1	I: -12.6% C: -4.4%	I: -0.3% C: -0.1%	I: -3.0% C: -1.0%	I: -4.2% C: -1.5%	I: +10.6 C: +7.7	I: 10.6% C: 2.1%
Wadden, 2013 SCALE Maintenance PMID: 23812094	I: Liraglutide 3.0 mg (212) C: Placebo (210) + lifestyle intervention 56 weeks BMI: ≥27 kg/m <sup>2c</sup> DM excluded	I: 36.0/45.9/84 C: 35.2/46.5/79	I: -6.2% C: -0.2% 5.9 kg	I: 50.5% C: 21.8%	I: 26.1% C: 6.3%	-	-	I: -0.1% C: +0.1%	I: +0.2 <sup>a</sup> C: +0.1 <sup>a</sup>	I: +0.2 <sup>a</sup> C: +2.8 <sup>a</sup>	-	I: 8.5% C: 8.6%
Davies, 2015 SCALE Diabetes PMID 26284720	I: Liraglutide 3.0 mg (423) C: Liraglutide 1.8 mg (211) C: Placebo (212) + lifestyle intervention 56 weeks BMI: 27–45 kg/m <sup>2</sup> All had type 2 DM	I: 37.1/55.0/48.0 I: 37.0/54.9/48.8 C: 37.4/54.7/54.2	I: -6.0% I: -4.7% C: -2.0% 4.2 kg 3.8 kg	I: 54.3% I: 40.4% C: 21.4%	I: 25.2% I: 15.9% C: 6.7%	I: -10.4% I: -7.9% C: +0.6%	-	I: -1.3% I: -1.1% C: -0.3%	I: +0.6% I: -3.1% C: +5.0%	I: -2.8 <sup>a</sup> I: -3.5 <sup>a</sup> C: -0.4 <sup>a</sup>	I: +11.7 I: +9.1 C: +7.6	I: 9.2% I: 8.6% C: 3.3%
Le Roux, 2017 SCALE Obesity and Prediabetes Extension PMID 28237263	I: Liraglutide 3.0 mg (1505) C: Placebo (749) + lifestyle intervention 3 years BMI: ≥27 kg/m <sup>2c</sup> DM excluded	I: 38.8/47.5/76 C: 39.0/47.3/77	I: -6.1% C: -1.9% 4.6 kg	I: 49.6% C: 23.7%	I: 24.8% C: 9.9%	I: -6.7% C: +0.9%	I: -8.3% C: +1.7%	I: -0.4% C: -0.1%	I: -4.2% C: -3.3%	I: -3.2 <sup>a</sup> C: -0.5 <sup>a</sup>	I: +11.0 C: +8.1	I: 13% C: 6%

Continued

**Table 1** Continued

Phase 3 randomized controlled trials	I: Intervention (n) C: control (n)	Mean BMI (kg)/mean age (years)/females (%)	Body weight change from baseline (kg)	Proportion of participants losing ≥5% of baseline weight	Proportion of participants losing ≥10% of baseline weight	Fasting blood glucose % change from baseline	Fasting insulin % change from baseline	HbA1c % change from baseline	LDL-C % change from baseline	SBP % change from baseline	IWQOL-Life score change from baseline	Proportion of participants discontinuing treatment due to adverse events (%)
Wadden, 2020 SCALE-IBT PMID 32090517	I: Liraglutide 3.0 mg (142) C: Placebo (140) + intensive behaviour therapy (IBT)	I: 39.3/45.4/83.8 C: 38.7/49.0/82.9	I: -7.4% C: -4.0%	I: 61.5% C: 38.8%	I: 30.5% C: 19.8%	I: -4.3% C: 0.0%	-	I: -0.2% C: -0.1%	I: -1.4% C: +1.3%	I: -2.8% C: -0.6%	I: +14.9 C: +14.1	I: 8.5% C: 4.3%
56 weeks BMI: ≥30 kg/m <sup>2</sup> DM excluded												
<b>Semaglutide</b>												
Wilding, 2021 STEP 1 PMID 33567185	I: Semaglutide 2.4 mg (1306) C: Placebo (655) + lifestyle intervention	I: 37.8/46/73.1 C: 38.0/47/77.6	I: -14.9% C: -2.4% 12.7 kg	I: 86.4% C: 31.5%	I: 69.1% C: 12.0%	I: -8.4% C: -0.5%	-	I: -0.45% C: -0.15%	I: +1.0% C: +1.0%	I: -6.2% C: -1.1%	I: +14.7 C: +5.3	I: 7.0% C: 3.1%
68 weeks BMI: ≥27 kg/m <sup>2d</sup> DM excluded												
Davies, 2021 STEP 2 PMID 33667417	I: Semaglutide 2.4 mg (404) C: Semaglutide 1.0 mg (403) C: Placebo (403) + lifestyle intervention	I: 35.9/55/55.2 I: 35.3/56/50.4 C: 35.9/55/47.1	I: -9.6% I: -7.0% C: -3.4%	I: 68.8% I: 57.1% C: 28.5%	I: 45.6% I: 28.7% C: 8.2%	I: -2.1% I: -1.8% C: -0.1%	I: -12% I: -7% C: -6%	I: -1.6% I: -1.5% C: -0.4%	-	I: -3.9% I: -2.9% C: -0.5%	I: +10.1 I: +8.7 C: +5.3	I: 6.2% I: 5.0% C: 3.5%
68 weeks BMI: ≥27 kg/m <sup>2</sup> All had type 2 DM												
Wadden, 2021 STEP 3-IBT PMID 33625476	I: Semaglutide 2.4 mg (407) C: Placebo (204) + intensive behaviour therapy (IBT)	I: 38.1/46/77.4 C: 37.8/46/88.2	I: -16.0% C: -5.7% 10.6 kg	I: 86.6% C: 47.6%	I: 75.3% C: 27.0%	I: -6.7% C: -0.7%	I: -32.3% C: -15.0%	I: -0.5% C: -0.3%	I: -4.7 C: +2.6	I: -5.6% C: -1.6%	-	I: 5.9% C: 2.9%
68 weeks BMI: ≥27 kg/m <sup>2d</sup> DM excluded												
Rubino, 2021 STEP 4 Maintenance PMID 33755728	I: Continued semaglutide 2.4 mg (535) C: Switched to placebo (268) + lifestyle intervention	I: 34.5/47/80.2 C: 34.1/46/76.5	I: -7.9% C: +6.9% 13.2 kg	I: 88.7% C: 47.6% <sup>b</sup>	I: 79.0% <sup>b</sup> C: 20.4% <sup>b</sup>	I: -0.8% C: +6.7%	I: -18% C: 0%	I: -0.1% C: +0.1%	I: -1.0% C: +8%	I: +0.5% C: +4.4%	-	I: 2.4% C: 2.2%
104 weeks BMI: ≥27 kg/m <sup>2d</sup> DM excluded												
Garvey, 2022 STEP 5 PMID 36216945	I: Semaglutide 2.4 mg (152) C: Placebo (152) + lifestyle intervention	I: 38.6/47.3/80.9 C: 38.5/47.4/74.3	I: -15.2% C: -2.6% 12.9 kg	I: 77.1% C: 34.3%	I: 61.8% C: 13.3%	I: -0.4% C: +0.1%	I: -32.7% C: -7.2%	I: -0.4% C: +0.1%	I: -6.1% C: -2.7%	I: -5.7% C: -1.6%	-	I: 5.9% C: 4.6%
104 weeks BMI: ≥27 kg/m <sup>2d</sup> DM excluded												
Lincoff, 2023 SELECT PMID 37952131	I: Semaglutide 2.4 mg (8803) C: Placebo (8801) No specific co-intervention	I: 33.3/41.6/27.8 C: 33.4/41.6/27.5	I: -9.4% C: -0.9%	-	-	-	-	I: -0.3% C: 0.0%	I: -5.3% C: -3.1%	I: -3.8% C: 0.5%	-	I: 16.6% C: 8.2%
104 weeks BMI: ≥27 kg/m <sup>2b</sup> DM excluded												

Continued

**Table 1** Continued

Phase 3 randomized controlled trials	i: Intervention (n) C: control (n) co-intervention study duration	Mean BMI (kg)/mean age (years)/females (%)	Body weight change from baseline (kg) Least square mean diff. (kg)	Proportion (%) of participants losing ≥5% of baseline weight	Proportion (%) of participants losing ≥10% of baseline weight	Fasting blood glucose % change from baseline	Fasting insulin % change from baseline	HbA1c % change from baseline	LDL-C % change from baseline	SBP % change from baseline	IWQOL-Life score change from baseline	Proportion of participants discontinuing treatment due to adverse events (%)
Rubino, 2022 STEP 8 PMID 35015037	i: Semaglutide 2.4 mg (126) i: Liraglutide 3.0 mg (127) C: Placebo (85) + lifestyle intervention 68 weeks BMI: ≥27 kg/m <sup>2d</sup> DM excluded	i: 37.0/48/81.0 i: 37.2/49/76.4 C: 38.8/51/77.6	i: -15.8% i: -6.4% C: -1.9% 8.5 kg (i vs. i)	i: 87.2% i: 58.1% C: 29.5%	i: 70.9% i: 25.6% C: 15.4%	i: -8.3 <sup>a</sup> i: -4.3 <sup>a</sup> C: +3.3	i: -27.8% i: -15.4% C: -3.5%	i: -0.2% i: -0.1% C: +0.1%	i: -6.5% i: +0.9% C: -1.1%	i: -5.7 <sup>a</sup> i: -2.9 <sup>a</sup> C: +3.2 <sup>a</sup>	-	i: 3.2% i: 12.6% C: 3.5%
Knop, 2023 OASIS 1 PMID 37385278	i: Semaglutide 50 mg (334) C: Placebo (333) + lifestyle intervention 68 weeks BMI: ≥27 kg/m <sup>2d</sup> DM excluded	i: 37.3/49/74 C: 37.7/50/71	i: -15.1% C: -2.4% 13 kg	i: 85% C: 26%	i: 69% C: 12%	i: -0.5 <sup>a</sup> C: -0.1 <sup>a</sup>	i: -33.1% C: -8.1%	i: -0.2% C: +0.1%	i: -0.6% C: +1.7%	i: -6.6 <sup>a</sup> C: -0.3 <sup>a</sup>	i: +14.7 C: +4.2	i: 6% C: 4%
<b>Tirzepatide</b> Frias, 2021 SURPASS-2 PMID 34170647	i: Tirzepatide 15 mg (470) i: Tirzepatide 10 mg (469) i: Tirzepatide 5 mg (470) i: Semaglutide 1 mg (469) 40 weeks BMI: ≥25 kg/m <sup>2</sup> All had type 2 DM	i: 34.5/55.9/54.5 i: 34.3/57.2/49.3 i: 33.8/56.3/56.4 i: 34.2/56.9/52.0	i: -11.2% i: -9.3% i: -7.6% i: -5.7%	i: 80% i: 76% i: 65% i: 54%	i: 57% i: 47% i: 34% i: 24%	-	-	i: -2.3% i: -2.2% i: -2.0% i: -1.9%	i: -5.2% i: -5.6% i: -7.7% i: -6.4%	i: -6.5 <sup>a</sup> i: -5.3 <sup>a</sup> i: -4.8 <sup>a</sup> i: -3.6 <sup>a</sup>	-	i: 8.5% i: 8.5% i: 6.0% i: 4.1%
Jastreboff, 2022 SURMOUNT-1 PMID 35658024	i: Tirzepatide 15 mg (630) i: Tirzepatide 10 mg (636) i: Tirzepatide 5 mg (630) C: Placebo (643) + lifestyle intervention 72 weeks BMI: ≥27 kg/m <sup>2d</sup> DM excluded	i: 38.1/44.9/67.5 i: 38.2/44.7/67.1 i: 37.4/45.6/67.6 C: 38.2/44.4/67.8	i: -20.9% i: -19.5% i: -15.0% C: -3.1%	i: 90.9% i: 88.9% i: 85.1% C: 34.5%	i: 83.5% i: 78.1% i: 68.5% C: 18.8%	i: -10.6 <sup>a</sup> i: -9.7 <sup>a</sup> i: -7.7 <sup>a</sup> C: +0.9 <sup>a</sup>	i: -49.6% i: -48.9% i: -42.0% C: -9.7%	i: -0.5% i: -0.5% i: -0.4% C: -0.1%	i: -8.6% i: -6.6% i: -5.3% C: -0.9%	i: -7.6 <sup>a</sup> i: -8.2 <sup>a</sup> i: -7.0 <sup>a</sup> C: -1.2 <sup>a</sup>	-	i: 6.2% i: 7.1% i: 4.3% C: 2.6%
Garvey, 2023 SURMOUNT-2 PMID 37385275	i: Tirzepatide 15 mg (311) i: Tirzepatide 10 mg (312) C: Placebo (315) + lifestyle intervention 72 weeks BMI: ≥27 kg/m <sup>2</sup> DM excluded	i: 35.7/53.6/51 i: 36.0/54.3/51 C: 36.6/54.7/51	i: -15.7% i: -13.4% C: -3.3% 11.6 kg 9.7 kg	i: 82.8% i: 79.2% C: 32.5%	i: 64.8% i: 60.5% C: 9.5%	i: -2.7 <sup>a</sup> i: -2.7 <sup>a</sup> C: -0.6 <sup>a</sup>	i: -40.3% i: -29.6% C: -14.5%	i: -2.1 i: -2.1 C: -0.5	i: +3.2% i: +2.3% C: +6.3%	i: -7.7 <sup>a</sup> i: -5.9 <sup>a</sup> C: -1.2 <sup>a</sup>	i: 15.2 i: 14.3 C: 7.4	i: 7% i: 4% C: 4%
Wadden, 2023 SURMOUNT-3 PMID 37840095	All had type 2 DM i: Tirzepatide 10/15 mg (287) C: Placebo (292) + lifestyle intervention 72 weeks BMI: ≥27 kg/m <sup>2d</sup> DM excluded	i: 36.1/45.4/63.1 C: 35.7/45.7/62.7	i: -18.4% C: +2.5% 25.0 kg	i: 87.5% C: 16.5%	i: 76.7% C: 8.9%	i: -8.8 <sup>a</sup> C: -2.4 <sup>a</sup>	i: -39.1% C: -17.3%	i: -0.5% C: 0.0%	i: -6.1% C: +6.1%	i: -5.1% C: +4.1%	i: +13.9 C: +1.1	i: 10.5% C: 2.1%

Continued

**Table 1 Continued**

Phase 3 randomized controlled trials	I: Intervention (n) C: control (n)	Mean BMI (kg)/mean age (years)/females (%)	Body weight change from baseline (kg)	Proportion (%) of participants losing ≥5% of baseline weight	Proportion (%) of participants losing ≥10% of baseline weight	Fasting blood glucose % change from baseline	Fasting insulin % change from baseline	HbA1c % change from baseline	LDL-C % change from baseline	SBP % change from baseline	IWQOL-Lite score change from baseline	Proportion of participants discontinuing treatment due to adverse events (%)
Arome, 2024	I: Tirzepatide 10/15 mg (335) C: Placebo (335)	I: 30.3/49/70.4 C: 30.7/48/70.7	I: -5.5% C: +14.0% 15.8kg	I: 97.3% C: 70.3%	I: 92.1% C: 46.2%	I: -0.9 <sup>a</sup> C: +7.7 <sup>a</sup>	I: -15.4% C: 23.3%	I: -0.1% C: +0.3%	I: -3.4% C: +3.4%	I: +2.1% C: +8.4%	I: +4.3 C: -5.1	I: 1.8% C: 0.9%
SURMOUNT-4	I: Tirzepatide 5 mg (335) C: Placebo (335) + lifestyle intervention	I: 30.3/49/70.4 C: 30.7/48/70.7	I: -5.5% C: +14.0% 15.8kg	I: 97.3% C: 70.3%	I: 92.1% C: 46.2%	I: -0.9 <sup>a</sup> C: +7.7 <sup>a</sup>	I: -15.4% C: 23.3%	I: -0.1% C: +0.3%	I: -3.4% C: +3.4%	I: +2.1% C: +8.4%	I: +4.3 C: -5.1	I: 1.8% C: 0.9%
Maintenance	I: Tirzepatide 5 mg (335) C: Placebo (335) + lifestyle intervention	I: 30.3/49/70.4 C: 30.7/48/70.7	I: -5.5% C: +14.0% 15.8kg	I: 97.3% C: 70.3%	I: 92.1% C: 46.2%	I: -0.9 <sup>a</sup> C: +7.7 <sup>a</sup>	I: -15.4% C: 23.3%	I: -0.1% C: +0.3%	I: -3.4% C: +3.4%	I: +2.1% C: +8.4%	I: +4.3 C: -5.1	I: 1.8% C: 0.9%
PMID 38078870	I: Tirzepatide 5 mg (335) C: Placebo (335) + lifestyle intervention	I: 30.3/49/70.4 C: 30.7/48/70.7	I: -5.5% C: +14.0% 15.8kg	I: 97.3% C: 70.3%	I: 92.1% C: 46.2%	I: -0.9 <sup>a</sup> C: +7.7 <sup>a</sup>	I: -15.4% C: 23.3%	I: -0.1% C: +0.3%	I: -3.4% C: +3.4%	I: +2.1% C: +8.4%	I: +4.3 C: -5.1	I: 1.8% C: 0.9%

BMI, body mass index; DM, diabetes mellitus; HbA1c, glycated haemoglobin; IWQOL, Impact of 46.2% weight on quality of life; LDL-C, low-density lipoprotein cholesterol; NIB, naltrexone/bupropion; SBP, systolic blood pressure.  
<sup>a</sup>absolute change from baseline.  
<sup>b</sup>during entire trial including run-in phase.  
<sup>c</sup>BMI 27–30 kg/m<sup>2</sup> with hypertension and/or dyslipidaemia.  
<sup>d</sup>BMI 27–30 kg/m<sup>2</sup> with hypertension, dyslipidaemia, obstructive sleep apnoea, or CVD.  
<sup>e</sup>with an established CVD.

12.7% at 68 weeks in patients with overweight (BMI ≥27 kg/m<sup>2</sup> with CV risk) or obesity (BMI ≥30 kg/m<sup>2</sup>) without T2DM.<sup>152</sup> In patients with T2DM, the safety profile of oral semaglutide was similar to other subcutaneously administered GLP-1 RAs.<sup>153</sup>

In a recent cohort study,<sup>154</sup> the use of GLP-1 RAs compared with naltrexone/bupropion was associated with increased risk of gastrointestinal adverse events including pancreatitis, bowel obstruction, and gastroparesis but not biliary disease. Although these adverse events are overall rare, the potentially increased risk associated with the use of GLP-1 RAs needs to be considered, given the higher baseline risk for gastrointestinal adverse events in persons with obesity.

### ESC Guidelines recommendations on GLP-1RAs

- Glucose-lowering medications with effects on weight loss (e.g. GLP-1RAs) should be considered in patients with T2DM with overweight or obesity to reduce weight (Class IIa, level of evidence B).<sup>61</sup>
- GLP-1RAs with proven CV benefit (liraglutide, semaglutide s.c., dulaglutide, efpeglatide) are recommended in patients with T2DM and atherosclerotic CVD to reduce CV events, independent of baseline or target HbA1c and independent of concomitant glucose-lowering medication (Class I, level of evidence A).<sup>61</sup>
- The GLP-1 RA semaglutide should be considered in overweight (BMI >27 kg/m<sup>2</sup>) or obese chronic coronary syndrome patients without diabetes to reduce CV mortality, MI, or stroke. (Class IIa, level of evidence B).<sup>155</sup>

### Tirzepatide

Tirzepatide has a dual mode of action based on the stimulation of the endogenous glucose-dependent insulinotropic polypeptide (GIP) and GLP-1.<sup>156</sup> Chronic GIP agonism acts centrally by increasing satiety, and peripherally by delaying gastric emptying<sup>157</sup> and improving white adipose tissue health.<sup>158</sup> Subcutaneous tirzepatide showed greater weight loss and HbA1c reductions vs. semaglutide 1 mg once-weekly in patients with T2DM<sup>159</sup> (Table 1) but has not yet been tested against semaglutide 2.4 mg. In the SURMOUNT-1 trial, tirzepatide at doses of 5, 10, and 15 mg induced a mean body weight loss of 15.0%, 19.5%, and 20.9%, respectively, at 72 weeks compared with 3.1% with placebo, in overweight or obese patients without T2DM,<sup>160</sup> with more frequent reversal from pre-diabetes to normoglycaemia with tirzepatide vs. placebo. A post-hoc pooled analysis of SURPASS trials suggested that the improvement in glycaemic control is only in part mediated by weight loss-dependent mechanisms in diabetic patients.<sup>161</sup> The SURMOUNT-MMO trial is currently underway evaluating the effect of tirzepatide on CV outcomes in adults with obesity without T2DM (NCT05556512).

### Setmelanotide

Setmelanotide is a selective melanocortin-4 receptor (MC4R) agonist that is administered in very rare, genetically confirmed cases of deficiency disorders of the MC4R.<sup>162</sup> Setmelanotide reduces appetite, increases satiety and energy expenditure.<sup>163</sup> No data from RCTs are available for these rare genetic diseases.

### Anti-obesity medication in development

Several dual or triple agonist combinations, mostly based on the GLP-1RA mode of action, are currently in development. Mazdutide, an incretin-



**Table 2** Main adverse effects and contraindications for approved anti-obesity medications

Medication	Adverse effects	Contraindications
Orlistat	<ul style="list-style-type: none"> <li>Gastrointestinal symptoms: oily rectal leakage, abdominal pain, flatulence with discharge, faecal urgency, steatorrhoea, faecal incontinence, increased defaecation</li> </ul>	Chronic malabsorption syndrome; cholestasis; pregnancy
Naltrexone/bupropion	<ul style="list-style-type: none"> <li>Gastrointestinal symptoms: nausea, constipation, vomiting, diarrhoea, dry mouth</li> <li>Symptoms of the central nervous system: headaches, insomnia, sleep disorders</li> </ul>	Chronic opioid use; acute opioid withdrawal; uncontrolled hypertension; seizure disorder; bulimia or anorexia nervosa; abrupt discontinuation of alcohol, benzodiazepines, barbiturates, and antiseizure drugs; concomitant use of monoamine oxidase inhibitors; pregnancy
Liraglutide	<ul style="list-style-type: none"> <li>Gastrointestinal symptoms: nausea, vomiting, diarrhoea, constipation</li> <li>Symptoms of the central nervous system: headache</li> </ul>	Personal or family history of medullary thyroid carcinoma, multiple endocrine neoplasia syndrome type 2, pregnancy
Semaglutide	<ul style="list-style-type: none"> <li>Gastrointestinal symptoms: nausea, diarrhoea, vomiting, constipation, dyspepsia</li> <li>Symptoms of the central nervous system: headache</li> </ul>	Personal or family history of medullary thyroid carcinoma, multiple endocrine neoplasia syndrome type 2, pregnancy
Tirzepatide	<ul style="list-style-type: none"> <li>Gastrointestinal symptoms: Nausea, diarrhoea, decreased appetite, vomiting, constipation, dyspepsia, abdominal pain</li> </ul>	Personal or family history of medullary thyroid carcinoma, multiple endocrine neoplasia syndrome type 2, pregnancy, known serious hypersensitivity to tirzepatide or any of the excipients
Setmelanotide	<ul style="list-style-type: none"> <li>Hypersensitivity reaction at injection site, hyperpigmentation, sexual dysfunction</li> </ul>	Pregnancy

based poly-agonists combining GLP-1R with glucagon receptor agonism, achieved a placebo-corrected body weight loss of 10.3% after 24 weeks in a Phase II trial in Chinese adults with overweight or obesity.<sup>164</sup> A single-molecule tri-agonist approach with agonism at GLP-1R, GIPR, and GcgR is due to be tested in clinical studies.<sup>165</sup> Further approaches include combination of GLP-1 RAs with other types of anti-obesity medications such as the combination of 2.4 mg semaglutide with the amylin analogue cagrilintide, a peptide co-secreted with insulin; this combination achieved an average placebo-controlled weight reduction of 6.0%–7.4% at different doses tested after 20 weeks in a Phase I trial.<sup>166</sup>

## Costs considerations for pharmacological treatment of obesity

When addressing cost-effectiveness of drug therapy, it needs to be considered that the currently available drugs can lead to weight loss, but weight is typically regained after cessation of the treatment. Whether these drugs should be used life-long or as intermittent treatment over decades is unclear. Drugs that have shown efficiency for weight loss have been assessed for cost-effectiveness in overweight and obese individuals with assumptions on the duration of the treatment effects incorporated. Naltrexone/bupropion was assessed by the National Institute for Health and Care Excellence (NICE) to be cost-ineffective at a cost of \$34 824 per QALY but with substantial uncertainty of long-term clinical benefit.<sup>167</sup> In a comparative analysis by the Institute for Clinical and Economic Review of naltrexone/bupropion, the incremental cost over lifestyle modification per QALY gained was \$124 000.<sup>168</sup> In the same analyses, incremental costs over lifestyle modification for liraglutide was \$485 000 and for semaglutide \$238 000 per QALY gained.<sup>168</sup> Other studies have found that semaglutide is cost-effective under USA and UK willingness to pay (WTP) thresholds. For the US assuming 2-year treatment, 3 years to re-gain weight, and 30-year follow-up, semaglutide 2.4 mg/weekly had an incremental cost

effectiveness ratio (ICER) of \$122 549 per QALY when compared with diet and exercise.<sup>169</sup> An analysis with similar assumptions under UK conditions, where the price of semaglutide is set lower, yielded an ICER of £14 827 per QALY.<sup>170</sup> Notably, many cost-effectiveness assessments have authorship representation of manufacturers. Independent assessments that include the data from recent trials showing effect on CVD outcomes in secondary prevention and assuming a need for longer duration of treatment are yet to be made available.

Semaglutide (Wegovy) injection is approved by EMA for management of overweight in adults who have a BMI >30 kg/m<sup>2</sup> or BMI >27 kg/m<sup>2</sup> and at least one related health problem<sup>171</sup> and tirzepatide (Mounjaro) has recently gained approval.<sup>172</sup> As of April 2024, semaglutide has been marketed for weight loss in Norway, Denmark, UK, Germany, Iceland, Switzerland, Japan, UAE and the USA and tirzepatide in Germany, Switzerland, Poland, UK, and the USA. In March 2024, semaglutide label was extended by FDA to include prevention of CV events in adults with CVD and either obesity or overweight, in addition to reduced caloric intake and physical activity and EMA is likely to follow. The governments in Europe have so far taken a restrictive approach to reimbursement ranging from no reimbursement (Germany, Denmark, Norway) to limited coverage as part of a monitored weight management programme (Iceland, France) and full reimbursement by private insurance plans (Switzerland). In the UK, semaglutide is available in a pilot programme through the National Health Service (NHS) as part of a 2-year weight management programme for individuals with BMI >35 kg/m<sup>2</sup> or BMI >30 kg/m<sup>2</sup> and at least one risk factor, limiting access to ~35 000 individuals in the UK. The programme will be reassessed and similar considerations for tirzepatide are being made.<sup>173</sup>

Effective drug treatments may in some countries fall within the accepted WTP threshold of various funding parties. However, with ~30% of the populations in European countries being obese and annual costs of around 3000 Euros for a potentially life-long treatment, the

societal costs implied for general reimbursement are staggering. However, the overall costs of obesity to society are also staggering. The costs of accessibility to limited target populations within secondary prevention of CVD has yet to be calculated but would have similarities to the introduction of other expensive, evidence-based drugs in recent decades.

## Key points on pharmacological treatment of obesity

- Orlistat and bupropion/naltrexone should be used with caution as weight loss medications, particularly in patients with known CVD, in view of their modest effects on body weight, scarce evidence on CV safety, and concerns regarding potential long-term CV risk.
- GLP-1RAs are effective for weight loss and improvement in CV risk factors.
- Currently, the only weight loss intervention with proven outcomes effect in patients with established CVD without T2DM is semaglutide 2.4 mg/weekly.
- Treatment effects are limited to the duration of treatment. The long-term effects and maintenance of efficacy of weight loss medications requires further investigation.

## Treatment strategies for obesity: intragastric and surgical interventions

### Intragastric approaches

There are different endoscopic<sup>174</sup> and procedure-less<sup>175</sup> intragastric approaches that restrict gastric capacity, including various models of intragastric balloons as well as endoscopic sleeve gastropasty.<sup>176</sup> So far, only intragastric balloons that require an upper endoscopy have been approved by the FDA as well as in Europe.

The current indication spectrum for endoscopic procedures is a BMI ranging from  $\geq 30$  kg/m<sup>2</sup> to  $< 40$  kg/m<sup>2</sup>, or BMI  $> 27$  kg/m<sup>2</sup> in patients with one or more obesity-associated comorbidities (Figure 4).<sup>176</sup> Moreover, the FDA approved endoscopic sleeve gastropasty for patients with a BMI from 30 to 50 kg/m<sup>2</sup>.

Intragastric balloons restrict the space for solid food in the stomach, delay gastric emptying, and increase satiety.<sup>177,178</sup> Adverse effects include nausea, vomiting, and abdominal pain; potential complications include spontaneous deflation, intestinal occlusion, gut perforation, and mucosal ulcerations.<sup>179</sup> The devices are removed via endoscopy after 6–12 months. At nine months after intervention (three months post balloon removal), intragastric balloon therapy was shown to reduce body weight on average by 9.1% compared with an average 3.4% weight loss achieved by lifestyle intervention alone in a randomized trial of 255 individuals.<sup>177</sup> However, weight regain after balloon removal is frequently observed in clinical practice.

Endoscopic sleeve gastropasty is a procedure designed to reduce stomach volume.<sup>180</sup> In a multicentre randomized trial involving 209 subjects over 12 months, endoscopic sleeve gastropasty plus lifestyle modifications was associated with an average 13.6% weight loss compared with 0.8% in the lifestyle modifications group.<sup>180</sup> Intragastric procedures can be considered based on patient preference, eligibility, benefits, risks, and possible procedural contraindications (e.g. hiatal hernia or gastric ulcers).

### Bariatric surgery

Bariatric surgery, indicated for strictly selected individuals, is the most effective weight loss intervention.<sup>128</sup> Two procedure types comprise  $> 90\%$  of all surgeries. With laparoscopic sleeve gastrectomy (LSG),  $\sim 85\%$  of the stomach is removed by separation along the greater curvature. With laparoscopic Roux-en-Y gastric bypass (RYGB) surgery, a small gastric pouch is connected directly to the jejunum (Figure 4). Achieved weight loss and possible post-operative complications are shown in Box 5. To avoid malabsorption following the surgery, screening, and supplementation for micronutrients (thiamine, folate, iron, calcium, vitamins A, D, E, B12, and K, zinc, and copper) is advised.<sup>181</sup>

#### Box 5 Achieved weight loss and possible complications following bariatric surgery

- Average weight loss after 12 months: 25% after LSG and 30% after RYGB, with sustained weight loss for at least 5 years.<sup>181,183</sup>
- Early post-procedural complications: anastomotic leaks (LSG: 1%–7%; RYGB: 0.6%–4.4%), stenosis (LSG: 1%–9%; RYGB: 8%–19%), post-operative bleeding (11%), venous thromboembolic events.<sup>184</sup>
- Long-term complications: internal hernia, marginal ulceration, malabsorption of micronutrients, osteoporosis, depression.<sup>184,185</sup>

Bariatric surgery can be considered for individuals with BMI  $\geq 40$  kg/m<sup>2</sup>, or BMI  $\geq 35$  kg/m<sup>2</sup> with at least one obesity-related disease,<sup>117</sup> with lower thresholds applied to some Asian populations. The decision regarding the type of surgery should be made in collaboration with a multidisciplinary team, balancing the patient's expectations, medical condition, and expected benefits and risks of the surgery.<sup>117</sup> Nutrition and mental health evaluations prior to surgery are typically required, with additional evaluations determined by the surgeon.<sup>182</sup> There are no absolute contraindications to bariatric surgery, however relative contraindications include severe HF, unstable CAD, end-stage lung disease, active cancer treatment, portal hypertension, drug or alcohol dependency, and impaired intellectual capacity.

With respect to cardio-metabolic risk profile, bariatric surgery is effective in inducing T2DM remission lasting  $\sim 10$  years<sup>186</sup> and histological resolution of metabolic dysfunction-associated steatohepatitis.<sup>187</sup> Bariatric surgery results in greater reduction in HbA1c and more frequent remission of diabetes than non-surgical therapies among patients with diabetes according to a meta-analysis of randomized controlled trials,<sup>70</sup> greater reductions in systolic and diastolic blood pressure,<sup>188</sup> and greater reduction in LDL-C and increase in HDL levels compared with non-surgical obesity therapies.<sup>188</sup>

A meta-analysis of observational studies showed that bariatric surgery was associated with reduced all-cause and CV mortality, and a reduced incidence of HF, myocardial infarction, and stroke.<sup>189</sup> The Swedish Obese Subjects (SOS) study, a non-randomized retrospective study of 2007 patients ( $\sim 2\%$  with CVD at baseline) undergoing bariatric surgery vs. 2040 matched control patients receiving usual obesity care, showed a 23% lower risk of mortality in the surgery groups over a follow-up of 24 years;<sup>190</sup> still, median life expectancy in the surgery group was 5.5 years shorter than in a reference group from the general population. No prospective RCTs exist to assess the effect of bariatric surgery on CV outcomes.

### ESC Guidelines recommendations on bariatric surgery

- Bariatric surgery should be considered for obese high-risk individuals when lifestyle change does not result in maintained weight loss (Class IIa, level of evidence B).<sup>42</sup>
- Bariatric surgery should be considered for high and very high risk patients with T2DM and BMI  $\geq 35$  kg/m<sup>2</sup> when repetitive and structured efforts of lifestyle changes combined with weight-reducing medications do not result in maintained weight loss (Class IIa, level of evidence B).<sup>61</sup>

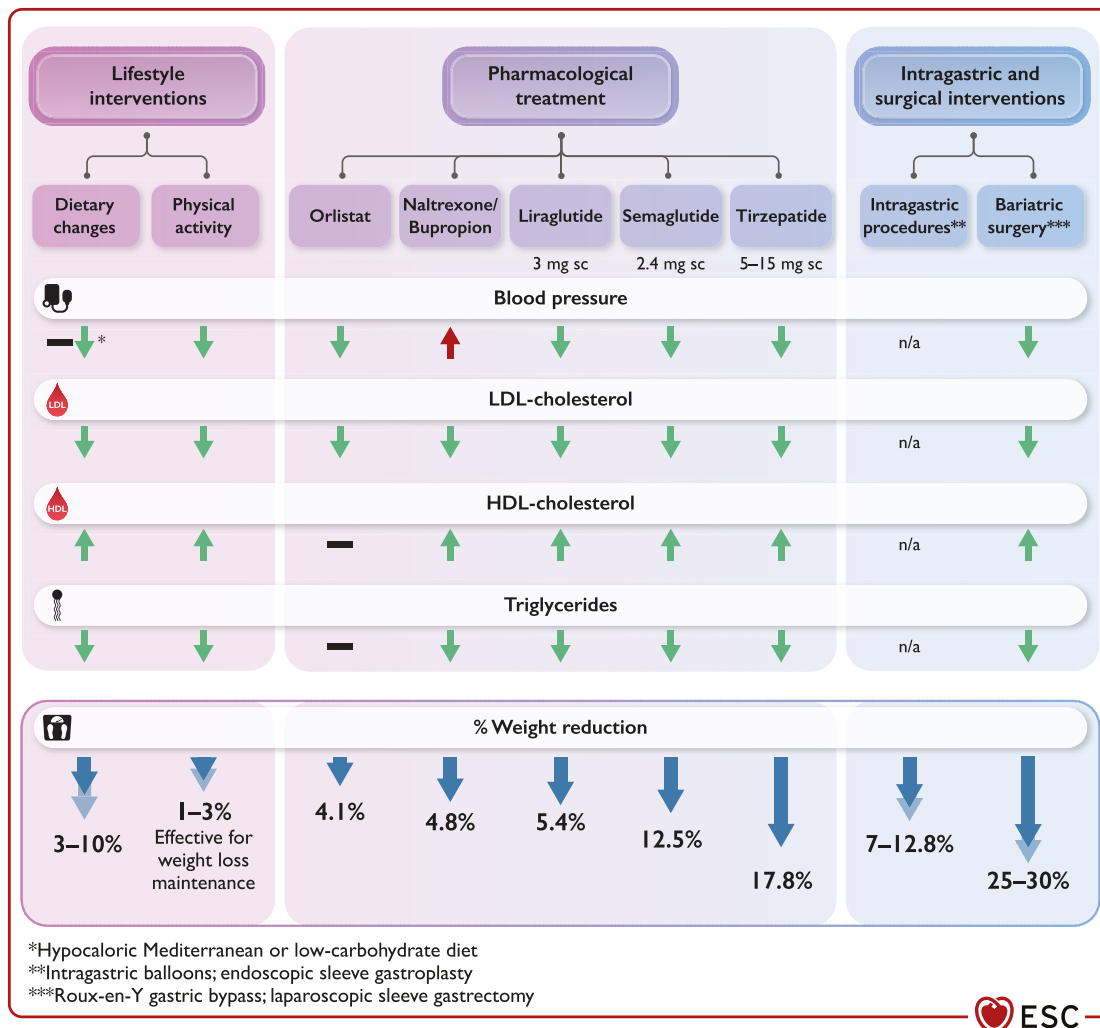
It is important to note that studies comparing bariatric surgery vs. new and more effective anti-obesity medications are lacking, and the

indications for bariatric surgery in the management of obesity might be adapted in the future in view of newer and/or upcoming pharmacologic therapeutic options.

### Costs considerations for bariatric surgery

Under the conditions generally used for indication of bariatric surgery (BMI  $\geq 40$  kg/m<sup>2</sup> or BMI  $\geq 35$  kg/m<sup>2</sup> and diabetes) the intervention has been shown to be cost effective. In a UK comparative economic evaluation of five weight management programmes: low, moderate, or high intensity (i.e. Look AHEAD), very low calorie diet, and bariatric surgery, the latter was the most cost-effective,<sup>191</sup> in particular among those with very high BMI ( $\geq 40$  kg/m<sup>2</sup>).<sup>192</sup>

The effects of pharmacologic and non-pharmacologic weight loss interventions on cardiometabolic risk factors and mean achieved weight loss are depicted in [Figure 5](#); the effects on CV outcomes are summarized in [Box 6](#).



**Figure 5** Expected effects of weight loss interventions on cardiovascular risk factors and body weight. HDL, high-density lipoprotein; LDL, low-density lipoprotein; n/a, not available



### Box 6 Impact of weight loss interventions on cardiovascular outcomes

- Intensive lifestyle interventions combining nutritional interventions and physical activity in obesity have shown improved weight loss and improvement in cardiometabolic risk factors, but no significant effect on CV outcomes.
- Bariatric surgery has been associated with improved CV outcomes in observational studies. RCTs assessing CV outcomes are not available.
- Among anti-obesity drugs, semaglutide 2.4 mg once weekly showed clinical benefit in a dedicated CV outcome trial involving overweight or obese patients with pre-existing CVD and without diabetes. In CV outcome trials in patients with T2DM irrespective of the presence or the absence of obesity (but with mean baseline BMI of  $32.8 \pm 6.2$  and  $32.5 \pm 6.3$  kg/m<sup>2</sup>, respectively), both semaglutide 0.5 mg or 1.0 mg once weekly and liraglutide 1.8 mg once daily (i.e. doses approved for diabetes treatment and lower than the doses for obesity treatment) showed significant reductions in MACE.

## Impact of obesity on different cardiovascular disease manifestations

### Obesity and atherosclerotic cardiovascular disease

#### Specific aetiologic considerations

Obesity is strongly associated with an increased risk of developing atherosclerotic CVD (ASCVD).<sup>193</sup> This excess risk is in part mediated and magnified by the presence of obesity-associated risk factors (diabetes, hypertension, dyslipidaemia).<sup>194</sup> However, both overweight and obesity are associated with an increased risk of CAD or cerebrovascular disease even in the absence of these metabolic abnormalities,<sup>195</sup> suggesting that additional factors are in play. Visceral adiposity in particular is associated with the development of atherosclerosis, and obesity-induced low-grade inflammation is considered to play an important role in this context.<sup>196</sup> Patients with obesity have elevated levels of pro-inflammatory cytokines,<sup>197</sup> and elevated levels of hsCRP are associated with an increased CV risk in these patients. Interestingly and somehow counterintuitively, patients with moderately increased BMI (overweight or mild obesity) and heart disease may experience a more favourable prognosis and a survival benefit compared with patients with lower BMI,<sup>198</sup> whereas more advanced obesity is associated with impaired prognosis. Although the underlying mechanisms of this phenomenon (referred to by some as 'obesity paradox') remain incompletely understood, potential explanations include metabolic reserves in obese individuals, which may confer protection during times of stress, or bias introduced by inverse causality or collider stratification bias, referring to unmeasured confounding induced by selection bias. These observations raise questions about the complex interplay between body weight, metabolic factors, and CV outcomes.<sup>199</sup>

In addition to the elevated risk of obstructive atherosclerotic CAD, the risk of coronary microvascular dysfunction also appears to be increased in persons with obesity. Underlying mechanisms may include

oxidative stress, insulin resistance, reduced nitric oxide production, and imbalance between the sympathetic and parasympathetic systems.<sup>200</sup> An increase in body weight has been independently associated with abnormal circulatory function,<sup>201</sup> and a cohort study of 827 patients suggested that coronary microvascular dysfunction (defined as impaired coronary flow reserve in the absence of flow-limiting CAD) was independently associated with elevated BMI and adverse outcomes over a median follow-up of 5.6 years.<sup>202</sup>

#### Implications for diagnosis of ASCVD

Assessment of the clinical likelihood of CAD can be challenging in patients with obesity, as there is some overlap of symptoms suggestive of CAD (e.g. dyspnoea on effort or fatigue). Therefore, diagnosis or exclusion of CAD may rely to a greater extent on imaging or functional testing in people with overweight or obesity. Exercise stress testing may be limited by the presence of resting ECG changes (more frequent signs of left ventricular hypertrophy and ST-segment depression) and lower aerobic capacity in people with obesity. With respect to non-invasive imaging techniques, PET and single photon emission CT may have technical limitations because of attenuation artefacts (by the diaphragm or breast) and residual uncorrected attenuation that decreases diagnostic accuracy. Stress echocardiography is highly dependent on the performing operator and can be limited in obesity because of poor acoustic windows; image quality can be improved, however, with the use of contrast injection.<sup>203</sup> Cardiac MRI may be limited by the diameter of the bore as well as by limitations in the table weight, but these limitations are less relevant with newer-generation equipment that can provide improved image quality in obese patients. Similarly, CT coronary angiography may have limitations in image quality as BMI increases<sup>155</sup> due to background noise and reduced signal-to-noise ratio, as well as practical limitations related to table weight and bore diameter. CT angiography using dual-source CT appears to provide high diagnostic accuracy in both non-obese and obese patients.<sup>204</sup> If invasive coronary angiography is used to evaluate CAD in obese individuals, vascular access may be challenging; the radial approach should be the preferred access as in all other patients. If a femoral approach is used, vascular closure devices should be used. Radiographic visualization may be suboptimal, and higher radiation exposure is often required to achieve adequate X-ray penetration in patients with obesity. Practical limitations related to the catheterization table may pose additional challenges.

#### Implications for medical treatment of ASCVD

Obesity is associated with higher platelet reactivity in *ex vivo* studies, including higher on-treatment residual platelet reactivity under aspirin, clopidogrel, and prasugrel (but not ticagrelor) therapy.<sup>205</sup> These effects likely relate to pro-inflammatory cytokines and hormones secreted by adipose tissue which may affect platelet function.<sup>205</sup> Despite these findings of platelet assay studies suggesting higher platelet activation and reduced efficacy of antiplatelet medications in obese patients, observational studies have not suggested higher thrombotic risk in obese vs. non-obese patients after acute coronary syndromes.<sup>206</sup> Therefore, while for instance dose reduction is indicated for lower-weight patients (<60 kg) receiving prasugrel, there is no compelling evidence for dose adjustment in obese patients.<sup>207,208</sup> Collectively, medical treatment of patients with ASCVD does not differ between patients with and without obesity, since no data exist to show a clear difference in the clinical effectiveness of antiplatelet, antihypertensive, or lipid-lowering drugs.

Management of risk factors, including hypertension, diabetes, and dyslipidaemia in patients with established CVD should address obesity



as a cornerstone of secondary prevention. Few trials have addressed the effect of weight loss on CV outcomes in patients with established CVD. Recently, the SELECT trial reported a 1.5% absolute reduction in a composite CV endpoint in patients with CVD (see section 'GLP-1 receptor agonists: liraglutide and semaglutide').<sup>150</sup>

### Implications for interventional treatment of CAD

No prospective trials exist to compare the effectiveness of percutaneous coronary intervention (PCI) in patients with and without obesity. Two all-comers registries of patients undergoing PCI,<sup>209,210</sup> with inherent limitations common to observational studies, demonstrated lower mortality in patients with overweight or obesity compared with patients with normal BMI. Along the same lines, a pooled analysis of 13 trials with 22 922 patients suggested that, despite adjustment for multiple confounders, overweight and Class I obesity were associated with lower all-cause mortality as compared with patients with normal weight.<sup>211</sup> With respect to early post-PCI outcomes, a BMI  $\geq 40$  kg/m<sup>2</sup> has been associated with higher in-hospital mortality, particularly in patients with ST-elevation myocardial infarction.<sup>212</sup> A registry of 227 044 patients with PCI after myocardial infarction reported that patients with BMI  $\geq 40$  kg/m<sup>2</sup> more often developed contrast-induced nephropathy, nephropathy requiring dialysis, and vascular complications compared with overweight patients.<sup>213</sup> With respect to outcomes following coronary artery bypass surgery, an observational study including 22 666 patients showed higher 30-day mortality in patients with BMI  $< 21$  kg/m<sup>2</sup>, without significant differences among patients with higher BMI (normal-weight, overweight, or obese).<sup>214</sup>

### Key points on management of ASCVD in patients with obesity

- Medical treatment of ASCVD does not differ between patients with and without obesity.

### Obesity and heart failure

Obesity is a well-known risk factor for the development of HF.<sup>215–217</sup> It increases metabolic rate and, therefore, demand on the CV system, and raises the risk of atherosclerotic CAD which in turn can result in HF of ischaemic origin. In the Framingham Heart Study, each 1-unit increase in BMI was associated with a 5% increased risk of HF in men and 7% in women; obese individuals had twice the risk of HF compared with normal weight individuals.<sup>215</sup> A considerably steeper increase in risk of HF was observed among young men from the Swedish Conscript registry, starting to rise already in the normal weight range and was up to six- to nine-fold in the most obese categories over a follow-up of up to 42 years.<sup>218</sup> Data from the same registry demonstrated a strong relation between BMI in adolescence and long-term risk of cardiomyopathy, in particular dilated cardiomyopathy.<sup>18</sup>

Obesity is more strongly associated with the risk of developing HFpEF than with HF with reduced ejection fraction (HFrEF).<sup>219</sup> A study involving 51 451 participants showed a dose–response relationship between increased BMI and elevated risk for incident HFpEF, but not for HFrEF.<sup>216</sup> Possible pathophysiological links<sup>220</sup> include: (i) adverse myocardial remodelling, diastolic dysfunction and atrial myopathy; (ii) visceral and epicardial adiposity and intra-myocardial lipotoxicity; (iii) pulmonary vascular disease; (iv) neurohormonal activation, sodium retention and plasma volume expansion; and (v) systemic inflammation. Notably, several comorbidities that are highly prevalent in the setting of obesity, such as hypertension, T2DM and CAD, also lead to adverse myocardial remodelling, diastolic dysfunction and eventually HFpEF.<sup>221</sup>

Concomitant presence of T2DM is associated with a more severe form of obesity-related HFpEF with worse outcome.<sup>222</sup>

In HFpEF, obesity is associated with poor quality of life, more signs and symptoms of HF, a lower exercise capacity and more frequent HF hospitalizations.<sup>223,224</sup> Obesity-related HFpEF is characterized by a distinct haemodynamic profile, consisting of greater ventricular remodelling, more plasma volume expansion, impaired vasodilatation, enhanced pericardial restraint and ventricular interdependence, and worse exercise capacity.<sup>225</sup> Increased epicardial adipose tissue is thought to play a role in the syndrome of HFpEF.<sup>226–229</sup>

The prognostic importance of obesity in HF is less clear. An inverse relation of higher BMI with lower mortality has been extensively reported, both for HFrEF<sup>230,231</sup> and for HFpEF.<sup>230,232</sup> For HFrEF, in particular, a recent analysis from the PARADIGM-HF trial<sup>233</sup> challenged previous evidence<sup>230,231</sup> by showing that (i) the association between lower mortality and higher BMI ( $\geq 25$  vs.  $< 25$  kg/m<sup>2</sup>) was eliminated by adjustment for prognostic variables including disease severity, and (ii) the inverse relation between body weight and mortality was not observed when two indices incorporating waist circumference and height, but not weight, were used; all obesity metrics, including BMI, showed an association between greater adiposity and a higher risk of HF-related hospitalization, worse symptoms and health-related quality of life. For HFpEF, a large meta-analysis involving 69 273 patients with HFpEF showed a U-shaped association, with a summary hazard ratio for all-cause mortality 0.90 per 5 units increase in BMI and the nadir at a BMI of 32–34 kg/m<sup>2</sup>;<sup>2,234</sup> conversely, the association between increased BMI and the risk for HF hospitalization was linear, with a hazard ratio of 1.12 per 1-unit increase in BMI. However, there is a clear association with increased risk for mortality in HFpEF when more direct metrics for abdominal adiposity are used.<sup>235,236</sup> However, observational evidence on associations between body weight and outcome is prone to bias and cannot provide firm guidance on benefits of weight loss. For this, randomized trials of weight loss are essential.

The presence of obesity poses several diagnostic challenges, especially in HFpEF.<sup>220</sup> Typical HF symptoms such as dyspnoea and exercise intolerance may be attributable to obesity, clinical signs of congestion may be difficult to assess, and echocardiographic parameters incorporated in the HFA-PEFF diagnostic algorithm may be difficult to obtain.<sup>237</sup> Furthermore, levels of natriuretic peptides [BNP, N-terminal pro-B-type natriuretic peptide (NT-proBNP)] are typically lower, or even in the normal range, in HF (HFrEF or HFpEF) patients with when compared with those without obesity;<sup>238</sup> thereby, HFpEF in particular may be underdiagnosed in individuals with obesity due to the lower natriuretic peptide levels. Lower BNP/NT-proBNP concentrations in patients with HF and obesity result from lower release as well as enhanced clearance.<sup>239</sup> Obesity also attenuates BNP activity by decreasing natriuretic peptide receptor-A concentrations and BNP intracellular signalling pathways. In turn, reduced BNP levels and activity lead to reduced lipolysis, thus fostering an obesogenic vicious cycle.<sup>240</sup> In the view of the linear decrease in natriuretic peptide levels with increasing BMI, the Heart Failure Association of the ESC proposed to lower established cut-off concentrations of BNP/NT-proBNP for HF diagnosis by ~50% in persons with obesity; however, this needs to be validated.<sup>241</sup> Despite the lower circulating levels, natriuretic peptides levels retain prognostic performance in obese patients with HF.<sup>242</sup>

### Weight loss in HFrEF

Unintentional weight loss can indicate increased catabolism and can be associated with a poor prognosis. Conversely, modifying appetite to



generate negative calorie balance can be an effective treatment option for patients with HF and obesity, to improve HF symptoms and comorbidities. In patients with obesity and HFrEF, small RCTs as well as non-randomized data show that weight loss result in improvements in New York Heart Association (NYHA) classification, quality of life, and exercise capacity.<sup>243</sup> However, there are no randomized trials to support weight loss in patients with HFrEF to improve survival. Weight management advice including caloric restriction should be given with caution and under supervision, given that caloric restriction will increase the catabolic dominance that is inherent to HFrEF pathophysiology and is associated with development of cachexia and increased mortality.

Observational evidence supports a potential benefit of bariatric surgery in HFrEF with respect to HF hospitalizations.<sup>244</sup> In a retrospective, case series study, bariatric surgery in patients with established HF ( $n = 524$ ) was associated with a reduced rate of HF-related hospitalization and emergency room visits.<sup>245</sup> Bariatric surgery is being explored in the ongoing BRAVE RCT comparing bariatric surgery to medical weight management (NCT04226664) in patients with high-risk CV disease, including 35% of patients with symptomatic HF.

Regarding pharmacologic interventions, a small phase-2 RCT ( $n = 300$ ) including patients who had been recently hospitalized with HFrEF found no benefit of liraglutide 1.8 mg/day vs. placebo with respect to post-hospitalization clinical stability.<sup>246</sup> However, obesity was not an inclusion criteria and weight loss did not differ between groups [difference  $-1.8$  kg (95% CI  $-3.9$ – $0.3$ ),  $P = .09$ ]. In a sub-analysis of the EMPEROR-Reduced trial, the benefits of the sodium-glucose cotransporter 2 (SGLT2) inhibitor empagliflozin vs. placebo were consistent across all BMI categories (ranging from  $<20$  to  $>35$  kg/m<sup>2</sup>) in HFrEF patients.<sup>247</sup> Similarly, the effect of dapagliflozin in patients with HFrEF did not vary by BMI categories ( $P$ -value for interaction = .79 for the primary composite endpoint of worsening HF or CV death).<sup>248</sup> With respect to aldosterone blockade, a post-hoc analysis from the EMPHASIS-HF trial showed a more pronounced benefit of eplerenone in individuals with abdominal obesity defined by increased waist circumference ( $P$ -value for interaction = .01).<sup>249</sup>

### Weight loss in HFpEF

Obesity is of increasing interest as therapeutic target in HFpEF. An RCT demonstrated a benefit of either caloric restriction or aerobic exercise on exercise capacity in 100 older (mean age 67 years) obese patients with HFpEF, and the combination of both treatments was additive, with a mean weight loss of 10% in the combined treatment group.<sup>250</sup>

To date, randomized trials of bariatric surgery in patients with established HFpEF are lacking. In a retrospective registry-based study including 296 041 patients undergoing bariatric surgery, surgery was associated with lower risk of hospital admission related to 'diastolic HF', after adjustment for other CV risk factors.<sup>251</sup> Although registry data should be interpreted with caution, there is a pathophysiological basis for this observation, as bariatric surgery has been associated with an improvement in functional and structural myocardial abnormalities typically seen in HFpEF, reduction in epicardial and visceral adiposity,<sup>252,253</sup> reduction in adipose tissue inflammation and insulin resistance,<sup>254–256</sup> and improvement in invasively measured haemodynamics.<sup>257,258</sup>

Several pharmacological HF treatments are under scrutiny in obesity-related HFpEF. Obesity and adipose tissue dysfunction leads to excess secretion of aldosterone, enhanced neprilysin activity, and increased leptin signalling, causing neurohormonal activation, sodium

retention, myocardial inflammation, and fibrosis.<sup>259</sup> In the overall neutral TOPCAT trial comparing the mineralocorticoid receptor antagonist spironolactone with placebo in patients with HFpEF, a subgroup analysis of obese patients showed a decreased risk for the study's primary endpoint, CV death or HF hospitalizations, with spironolactone.<sup>260</sup> In a post-hoc analysis from the DELIVER trial of the SGLT2 inhibitor dapagliflozin in HFpEF/HF with mildly reduced ejection fraction, dapagliflozin reduced the risk for the primary outcome across all BMI categories, but led to greater symptom improvement in patients with vs. without obesity; moreover, dapagliflozin led to modest weight loss that was larger in the higher BMI categories.<sup>261</sup> No large clinical study or post-hoc analysis from a trial with sacubitril/valsartan has been performed in HFpEF patients with obesity; pre-clinical studies have suggested that sacubitril/valsartan might be superior to valsartan in reversing obesity-associated myocardial impairment.<sup>262</sup>

Two RCTs of semaglutide have compared semaglutide 2.4 mg once-weekly vs. placebo in obesity-related HFpEF, the STEP-HFpEF and the STEP-HFpEF-DM trial. In the STEP-HFpEF trial involving 529 patients with HFpEF (66% with NYHA Class II, 18.5% with known CAD at baseline) and BMI  $>30$  kg/m<sup>2</sup>, semaglutide led to a larger reduction in weight ( $-10.7$  kg difference), greater improvement in quality of life and 6-min walk distance,<sup>263</sup> and greater reduction in hsCRP. The benefits were observed in all BMI categories, with a dose-response relationship between the amount of weight loss and the treatment effect,<sup>264</sup> and across the different left ventricular ejection fraction (LVEF) categories (LVEF 45% to  $>60%$ ).<sup>265</sup> In the STEP-HFpEF-DM trial including 616 patients with symptomatic HFpEF with BMI  $>30$  kg/m<sup>2</sup> and T2DM,<sup>266</sup> semaglutide led to a larger decrease in body weight and HF-related symptoms and to a larger increase in 6-min walk distance. A pooled analysis of both trials showed a significant reduction in NT-proBNP levels and significant improvement in HF-related symptoms and physical limitations with semaglutide vs. placebo.<sup>267</sup> Currently, SGLT2 inhibitors comprise the only treatment with proven CV benefit (reduction in the risk of HF hospitalization or CV death) in patients with HFpEF irrespective of the presence of obesity;<sup>61,268</sup> whether the promising results of the STEP-HFpEF and STEP-HFpEF-DM trials may translate to positive CV outcomes of GLP-1 RAs in patients with obesity and HFpEF requires investigation in adequately powered trials. A randomized clinical trial evaluating tirzepatide in patients with HFpEF and obesity is currently ongoing (SUMMIT, NCT04847557).

Supplementary data online, Table S3 summarizes trial evidence of pharmacological and non-pharmacological interventions on patients with HF.

### Key points on management of obesity in heart failure

- Obesity even at younger age increases the risk of incident HF, particularly HFpEF.
- Weight loss by means of diet, exercise, or pharmacological intervention improves exercise capacity and symptoms in obese patients with HFpEF.
- Weight loss through lifestyle interventions may improve symptoms and exercise capacity in obese HFrEF patients, although more evidence is needed.
- Non-intentional weight loss is associated with increased mortality in patients with HFrEF.
- Trials of weight loss interventions in patients with HFrEF with morbidity and mortality outcomes are lacking.

## Obesity and arrhythmias

### Atrial fibrillation

Abundant observational evidence supports a causal association between obesity and AF.<sup>269,270</sup> In the Framingham cohort study, the age-adjusted incidence rates for AF were 9.7, 10.7, and 14.3 per 1000 person-years for normal weight, overweight, and obesity, respectively.<sup>271</sup> The Women's Health Study showed that increase in BMI over time was associated with incident AF.<sup>272</sup> A dose–response relationship was also reported between other anthropometric measurements of adiposity (beyond BMI) and the risk for incident AF.<sup>273,274</sup>

Obesity has also been associated with progression from paroxysmal to permanent AF.<sup>275</sup> While factors associated with obesity, such as hypertension, OSA, T2DM, and CAD, also increase the risk of AF,<sup>269</sup> a Mendelian randomization study showed that genetic variants related to obesity were associated with incident AF after adjustment for traditional AF risk factors, suggesting causality between obesity and AF.<sup>276</sup>

The association between obesity and risk for AF is largely mediated by structural and functional cardiac changes, particularly enlargement and stretching of the left atrium and diastolic dysfunction.<sup>269,277</sup> Moreover, peri-atrial adipose tissue thickness has been associated with AF burden, independent of age, BMI, or left atrial size,<sup>278</sup> and increased pericardial adipose tissue was associated with AF severity and higher AF recurrence after catheter ablation.<sup>279–282</sup> These observations suggest that peri-atrial adipose tissue expansion and local inflammation inducing paracrine signalling may lead to an arrhythmogenic substrate, and weight loss may facilitate substrate regression that could potentially reduce the risk of developing AF.<sup>283</sup>

In patients with prevalent AF, the association of obesity with outcomes is less clear. Increased BMI was associated with a lower risk of stroke or systemic embolic events and better survival, but increased risk of major bleeding in 21 028 patients in the ENGAGE AF-TIMI 48 trial.<sup>284</sup> In a registry including 10 220 patients with AF, higher mortality was observed in patients (men or women) in the lowest tertile of body weight and in women in the lowest tertile of BMI.<sup>285</sup>

Taken together, maintenance of a healthy body weight and weight reduction in obese persons appear to be effective for primary prevention of AF. Moreover, obesity may be a specific therapeutic target in patients with AF, as weight loss along with comprehensive risk factor management has the potential to reduce symptoms and AF burden. In the observational LEGACY study, long-term sustained weight loss was associated with a reduction in AF burden and maintenance of sinus rhythm.<sup>286</sup> In a randomized controlled study including 150 overweight or obese patients with symptomatic AF, intense weight reduction with CV risk factors management reduced AF symptom burden and severity along with favourable cardiac remodelling.<sup>287</sup> Severe obesity has been associated with reduced success of AF catheter ablation.<sup>288</sup> Intensive weight loss, aggressive risk factor management, and bariatric surgery have the potential to improve the success rate of AF ablation and reverse AF progression.<sup>289,290</sup> However, in the randomized SORT-AF trial, a weight loss intervention (combination of nutrition advice and physical training) resulting in 3.9% loss in weight over 12 months did not affect AF ablation outcomes.<sup>291</sup> Whether pharmacological interventions for obesity can prevent AF, delay the transition to permanent AF, affect AF ablation outcomes, or improve survival in patients with AF remains to be determined.

Patients with severe obesity are underrepresented in large trials comparing direct oral anticoagulants (DOAC) with vitamin K antagonists (VKA) for stroke prevention in AF. Observational data and post-hoc analyses of these trials reported comparable efficacy and safety

effects of DOACs over VKA.<sup>292–294</sup> While BMI can affect VKA dose requirement, the clinical relevance appears limited given routine international normalized ratio (INR) monitoring and consequent dose adjustments; however, closer INR surveillance may be required in obese patients.<sup>208</sup> Because of uncertainty related to very limited evidence for DOACs in patients with severe obesity (BMI  $\geq 40$  kg/m<sup>2</sup>),<sup>295</sup> the use of DOACs in preference to VKA may be questioned in these patients.<sup>208</sup> Moreover, because there remains uncertainty on the resorption of DOACs in patients who have undergone bariatric surgery,<sup>296,297</sup> it is reasonable to choose VKA over DOACs in these patients in the context of AF or other indications for oral anticoagulation therapy.

### ESC Guidelines recommendations on weight loss in patients with AF

- Weight reduction should be considered in obese individuals to prevent AF (Class IIa, level of evidence B).<sup>298</sup>
- Weight loss is recommended as part of comprehensive risk factor management in overweight and obese individuals with AF to reduce symptoms and AF burden, with a target of 10% or more reduction in body weight (Class I, level of evidence B).<sup>298</sup>

### Sudden cardiac death

The association between obesity and risk for sudden cardiac death (SCD) is long established. The Framingham Heart Study showed a strong association between increased weight and 26-year incidence of SCD, especially in men and irrespective of age.<sup>299</sup> A meta-analysis involving 3376 cases of incident SCD among 406 079 individuals showed a J-shaped relationship between BMI and risk for SCD, and a linear relationship between increased waist-to-hip ratio and SCD, with no association with waist circumference.<sup>300</sup> In a population-based study in 470 000 individuals in Finland, 21.8% of SCD cases were caused by non-*ischaemic* cardiomyopathy and within this subgroup, SCD was closely related to obesity.<sup>301</sup>

The underlying pathophysiological mechanisms may include a structural substrate involving, e.g. concentric remodelling, left ventricular hypertrophy,<sup>302</sup> epicardial and intramyocardial adiposity and myocardial fibrosis; and an electrophysiological substrate related to e.g. QT prolongation, premature ventricular complexes, late potentials and QRS fragmentation.<sup>303</sup>

Individuals with severe obesity appear less likely to be successfully resuscitated from in-hospital sudden cardiac arrest.<sup>304</sup> However, in SCD survivors, obesity has been associated with lower all-cause mortality,<sup>305</sup> although results are conflicting.<sup>306</sup>

While bariatric surgery is associated with reduced risk for all-cause and CV-related mortality,<sup>189</sup> no large observational studies have specifically investigated the association with the risk of SCD. Smaller observational studies have shown that bariatric surgery may potentially improve arrhythmogenic substrate for SCD, such as enhancement of heart rate variability and decreased mean heart rate,<sup>307</sup> improvement of ventricular conduction and repolarization,<sup>308,309</sup> and shortening of the QT interval.<sup>310</sup>

### Key points on obesity and arrhythmias

- Obesity is associated with the risk of incident AF and with transition to permanent AF.
- Obesity is associated with a higher thromboembolic risk in patients with prevalent AF.

- In obese persons, weight reduction should be encouraged for primary prevention of AF.
- Weight reduction and risk factor management may reduce AF symptom burden.
- In obese persons with prevalent AF, evidence that weight reduction improves survival is missing.
- Obesity is linked to higher risk of SCD, but there is no clear evidence supporting weight loss interventions for reducing this risk.

## Obesity and venous thromboembolism

Venous thromboembolism (VTE), encompassing deep vein thrombosis and pulmonary embolism, is relatively common, frequently recurring, associated with poor prognosis, and imposes a huge burden on health-care systems.<sup>311</sup> Risk factors include hospitalization (particularly including critically ill or surgical patients), older age, previous VTE, immobility, active cancer, trauma or fracture, oral contraceptive therapy, central venous lines, smoking, and obesity.<sup>312,313</sup> In a meta-analysis involving 63 552 patients, obesity had the strongest association with VTE among traditional CV risk factors with an odds ratio of 2.33 (95% CI 1.68–3.24).<sup>314</sup> While obesity is a relative weak risk factor compared with other known predisposing factors for VTE,<sup>315</sup> prevalence of obesity is very high and obesity interacts with other predisposing factors increasing the risk of first and recurrent VTE.<sup>316–318</sup> Consequently, presence of obesity is included in most risk scores that have been developed to guide clinicians on prophylactic treatment to prevent VTE event in hospitalized patients or on anticoagulation treatment for VTE, such as the Padua Prediction Score, the DAMOVES score and the HERDOO2 score.<sup>319–321</sup>

Clinical data on the use of DOACs for the treatment of VTE or as prophylaxis after elective hip and knee arthroplasty in patients with severe obesity is limited. In the view of growing available data showing similar safety and efficacy of DOACs vs. warfarin for the treatment of VTE,<sup>322,323</sup> a consensus document in 2021 concluded that standard dosage of rivaroxaban and apixaban are appropriate regardless of BMI for the VTE treatment or prophylaxis after elective hip and knee arthroplasty, whereas edoxaban or dabigatran were discouraged in patients with a BMI >40 kg/m<sup>2</sup> or body weight >120 kg (Box 7).<sup>324</sup>

### Box 7 Antithrombotic therapy in patients with obesity

- No dose adjustment is required for antiplatelet medications in patients with vs. without obesity.
- In patients who have indication for chronic oral anticoagulation therapy and have undergone bariatric surgery, it is reasonable to prefer VKAs over DOACs.
- In patients receiving warfarin and a GLP-1 RA, the INR should be carefully monitored.
- It is reasonable to avoid edoxaban and dabigatran for prevention or treatment of VTE in patients with a BMI >40 kg/m<sup>2</sup> or body weight >120 kg.

## Key point on obesity and VTE

- Obesity increases risk of developing VTE.

## Obesity and valvular heart disease

Adult obesity has been associated with incident aortic valve stenosis. In two large population-based Swedish cohorts free of CVD at baseline and a mean follow-up of 15.3 years, individuals with overweight and obesity had a 24% and 81% higher risk for incident aortic stenosis compared with normal weight adults, respectively.<sup>325</sup> In an analysis of the Copenhagen General Population Study applying Mendelian randomization design, genetically based obesity was associated with increased risk of aortic stenosis and aortic valve replacement.<sup>326</sup> In a genome-wide meta-analysis of over 11 million variants in 10 cohorts, obesity as well as dyslipidaemia and inflammation were found to be important aetiological factors of aortic stenosis.<sup>327</sup> In the large-scale Japan Collaborative Cohort Study, overweight and obesity were independent risk factors for mortality from non-rheumatic aortic valve disease with an HR of 2.83 in adults with a BMI  $\geq 27$  kg/m<sup>2</sup>.<sup>328</sup> Maintaining or achieving normal weight is expected to reduce incident aortic stenosis and associated mortality, though no RCT has provided evidence so far. Beyond BMI, presence of metabolic risk factors has been linked to prognosis in patients with severe aortic stenosis.<sup>329</sup> Of clinical relevance, in the presence of obesity, assessment of symptom burden of valvular heart disease is challenged.

With respect to treatment of severe aortic valve stenosis, a nationwide registry study including 42 315 patients who underwent transcatheter aortic valve implantation (TAVI), found a significantly lower risk of in-hospital mortality and post-procedural complications in patients with obesity.<sup>330</sup> In contrast, obesity with a BMI  $\geq 40$  kg/m<sup>2</sup>, or  $\geq 35$  kg/m<sup>2</sup> with obesity-related comorbidities has been associated with a higher risk of major vascular complications and lower device success, and abdominal obesity in particular has been associated with adverse long-term clinical outcomes following TAVI.<sup>331</sup> Based on the available evidence, TAVI should not be denied to patients with obesity, although caution with respect to vascular complications may be required in the context of severe obesity. The impact of weight loss interventions on aortic stenosis-related symptoms and on outcomes following interventions requires further investigation.

## Key points on obesity and valvular disease

- Obesity has been associated with an increased risk of aortic stenosis.
- Severe obesity appears to be associated with a higher risk of vascular complications in patients undergoing TAVI.

## Health economic considerations

As noted previously, the societal costs of obesity are staggering and a large proportion of these costs relate to management of downstream CV risk factors and CVD. Prevalence of obesity among cardiac patients is high across ESC countries. In the EUROASPIRE V monitoring risk factor control in patients with CAD, 82% had BMI  $\geq 25$  kg/m<sup>2</sup>, including 38% who were obese (BMI  $\geq 30$  kg/m<sup>2</sup>).<sup>332</sup> In the EORP-AF registry, ~70% of patients with AF were overweight or obese<sup>285</sup> and in the ESC Heart Failure Long-Term Registry, mean BMI was 28 kg/m<sup>2</sup>.<sup>333</sup> For the individual cardiac patient with obesity, not only physical limitations caused by excess weight but also psychological distress and social stigma associated with obesity compromise the overall quality of life.<sup>334</sup> Importantly, obesity and its CV consequences disproportionately affect already disadvantaged populations, exacerbating existing health inequalities.

## Overweight and obesity-related expenditures

Overweight and obesity are responsible for around 10% of the total disease burden (DALYs) in Europe.<sup>335</sup> The total societal costs of obesity have been estimated at 70 billion Euro, including both healthcare costs and lost productivity, and ~7% of national budgets across the EU is spent on non-communicable diseases associated with obesity.<sup>336</sup> The direct healthcare costs associated with obesity-related CVD are staggering. In addition to the costs related to management of conditions such as hypertension, diabetes, OSA, ASCVD, and HF, obesity often co-exists with several comorbidities, leading to more frequent and longer hospitalizations and emergency room visits, further amplifying healthcare costs.<sup>337,338</sup> The need for specialized care, diagnostic procedures and post-event rehabilitation also places a significant financial strain on healthcare systems.

## Policies

The global problem of obesity is unlikely to be resolved by medical, lifestyle or other interventions directed towards individuals alone. The epidemic of overweight, affecting now >60% of the population in Europe, results from societal and lifestyle changes and can be amended through effective public health policies. The passivity of European governments while the obesity epidemic has evolved over decades is noticeable. We live in an obesogenic environment in which circumstances, beyond the individual control, drive the obesity crisis. Structural factors shape choices and amplify health inequalities. Energy-dense food of low nutritional quality is often the cheapest option and is disproportionately promoted. Urban settings either discourage physical activity or promote sedentary behaviours such as reliance on cars over walking or biking. Screen-based entertainment and communication are on the rise. Policies must address these fundamental issues for sustainable solutions,<sup>334</sup> and ESC EU Advocacy is working ardently in that direction.

This inertia has also been witnessed in clinical management of CVD. In comparison to medical treatment of dyslipidaemia, hypertension, and diabetes, management of obesity has received minimal attention. Paradoxically, although shortness of breath is a cardinal symptom of both cardiac disease and obesity, there has been no strong, systematic incentive to address obesity to battle these symptoms. Clinical practice tends to address downstream consequences of obesity rather than the root causes. Discussions around problematic concepts such as 'the metabolically healthy obese' and 'the obesity paradox' may further perpetuate this inertia. Similarly, the dearth of supportive weight loss programmes available to cardiac patients pave the road for the need for effective but expensive novel medications.

We now have evidence from randomized trials that addressing obesity leads to improvement in health outcomes. While determining the future role of medical treatment of obesity, hopefully this development will spark renewed attention to combatting obesity on the societal level through public health and preventive measures and through greater availability of weight loss programmes.

## Key points

- 7% of national budgets across the EU is spent on non-communicable diseases associated with obesity, a large proportion of this related to CVD.
- Individual treatment of obesity in patients with CVD may be cost-effective in some but currently remains out of reach for most patients due to the costs to the individual as well as societal costs.

## Conclusions and future directions

Obesity poses an increasing challenge with one in six EU citizens classed as obese, and over half of adults being overweight. Obese individuals have a 50%–100% higher risk of death from all causes compared with normal-weight individuals, and most of the increased risk is due to CVD. Because the evolving obesity epidemic has largely stemmed from an increasingly obesogenic environment, efforts to reduce the obesity burden will require approaches that combine individual interventions with changes in the environment and society. From a population perspective, there is an urgent and imperative need for public health interventions at a governmental, non-governmental, and civil society level, involving all healthcare professionals towards this important goal.<sup>60</sup> In the view of the critical need for public health interventions, advocacy from the scientific community at policy-making level is crucial. As in any aspect of medicine, the Hippocratic concept that prevention is better than cure applies to management of obesity on an individual as well as population level. The substantial increase in obesity in children and adolescents urges for obesity prevention starting at very early age, considering that the risk of developing CV and non-CV complications depends not only to the severity but also on the duration of obesity over the life span.<sup>339</sup>

While the recent development of weight loss drugs with proven CV benefits represents a major step in the field for the management of patients with obesity, reliance on novel pharmacotherapies for the treatment of established obesity—as opposed to continuous efforts for obesity prevention based on sustainable healthy lifestyle changes—will currently be limited by associated costs and risk accentuating socioeconomic disparities if adequate reimbursement programmes are not put in place. It should also be kept in mind that the achieved weight loss, cardiometabolic benefits, and the reported CV benefit of novel anti-obesity medications occurred in the context of persistent, uninterrupted pharmacotherapy (thus leading to recommended chronic use), and that a substantial proportion (approximately one-half to two-thirds) of the weight lost is regained within 1 year of stopping treatment with semaglutide or tirzepatide.<sup>340</sup> Moreover, in view of the growing demand and the current shortage of supply for newer pharmacotherapies, off-label prescription of approved anti-obesity drugs and off-label use of anti-diabetic medications (GLP-1 RAs) for weight loss purposes should be discouraged.

Practicing physicians including cardiologists can contribute to the battle against obesity in multiple ways and at different levels, by becoming pro-active in the prevention and management of obesity, as they have been for decades with other modifiable CV risk factors. Firstly, we should consistently communicate the CV risk associated with obesity and stress the importance of life-long adoption of healthy lifestyles to maintain a healthy body weight throughout life. Secondly, in view of the strong association of obesity with a broad spectrum of CVD manifestations (*Graphical Abstract*), obesity needs to be appropriately integrated as a causal factor or risk enhancer into routine risk estimation and treatment guidance. Overall, more emphasis should be placed on primary prevention of obesity (maintenance of a healthy body weight and avoidance of excess weight gain), and also on management of obesity in persons without established CVD (*primary CV prevention*). In obese patients with established CVD (*secondary CV prevention*), weight management remains important to improve symptomatic status and comorbidities; however, while certain weight loss interventions have shown efficacy in improving CV outcomes (*Box 6*), this has not been the case in CVD conditions characterized by catabolic dominance (e.g. HFREF).

For patients presenting with obesity, cardiologists, and related healthcare professionals should appreciate the paradigm shift towards



combination strategies for managing obesity as a chronic disease. This evolution integrates lifestyle interventions, pharmacotherapy, and interventional or surgical procedures. Access to different treatment modalities should enable a patient-centred approach since persons with obesity comprise a heterogeneous group with distinct metabolic and CV risk profiles and differences in cultural backgrounds and preferences, requiring specific, individualized, and tailored treatments. In the context of interdisciplinary approaches and comprehensive, multi-level obesity treatment strategies, cardiologists should become involved in encouraging access to structured anti-obesity programmes, surgical treatment whenever indicated, and potentially newer pharmacotherapies according to local availability and resources. It should be appreciated, however, that lifestyle interventions remain first-line treatment for prevention of weight gain and for weight reduction, and that the effects of pharmacologic and lifestyle interventions on weight loss and cardiometabolic factors are additive.<sup>126,127</sup> Therefore, drug treatment—if applicable and locally supported—should be used as a complementary rather than substitutive treatment option; in this case, long-term adherence to a healthy lifestyle remains critical in order to potentiate and maintain the favourable drug effects.<sup>341</sup>

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## Supplementary data

Supplementary data are available at *European Journal of Preventive Cardiology* online.

## Declarations

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