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REVIEW
CVD risk factors

Rethinking weight loss treatments as cardiovascular medicine in obesity, a comprehensive review

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The global escalation of obesity has made it a worldwide health concern, notably as a leading risk factor for cardiovascular disease (CVD). Extensive evidence corroborates its association with a range of cardiac complications, including coronary artery disease, heart failure, and heightened vulnerability to sudden cardiac events. Additionally, obesity contributes to the emergence of other cardiovascular risk factors including dyslipidaemia, type 2 diabetes, hypertension, and sleep disorders, further amplifying the predisposition to CVD. To adequately address CVD in patients with obesity, it is crucial to first understand the pathophysiology underlying this link. We herein explore these intricate mechanisms, including adipose tissue dysfunction, chronic inflammation, immune system dysregulation, and alterations in the gut microbiome.Recent guidelines from the European Society of Cardiology underscore the pivotal role of diagnosing and treating obesity to prevent CVD. However, the intricate relationship between obesity and CVD poses significant challenges in clinical practice: the presence of obesity can impede accurate CVD diagnosis while optimizing the effectiveness of pharmacological treatments or cardiac procedures requires meticulous adjustment, and it is crucial that cardiologists acknowledge the implications of excessive weight while striving to enhance outcomes for the vulnerable population affected by obesity. We, therefore, sought to overcome controversial aspects in the clinical management of heart disease in patients with overweight/obesity and present evidence on cardiometabolic outcomes associated with currently available weight management interventions, with the objective of equipping clinicians with an evidence-based approach to recognize and address CVD risks associated with obesity.

Keywords Cardiovascular disease • Cardiometabolic risk • Chronic inflammation • Anti obesity medication • Obesity pharmacotherapy • Cardiovascular outcomes

Introduction

The global health landscape is increasingly burdened by non-communicable diseases (NCDs), among which obesity and cardiovascular diseases (CVDs) are significant public health challenges. The World Health Organization estimates that NCDs account for 74% of all deaths globally, with CVDs being responsible for ~17.9 million deaths annually.[1] Obesity, a major risk factor for CVD, has risen dramatically, affecting over 650 million adults worldwide. Developed countries like the United States have particularly high rates, with ~42% of the adult population affected,[2] with countries in the European community rapidly narrowing the gap.[3] However, low- and middle-income countries are not immune; countries like Mexico and South Africa are experiencing burgeoning obesity rates, creating a dual burden alongside existing infectious diseases.[2] Cardiovascular diseases encompass a range of conditions, including coronary artery

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disease, heart failure (HF), and stroke. The prevalence of myocardial infarction, congestive HF, and stroke is 21, 3.5, and 3%, respectively, in individuals with obesity but without diabetes.[4,5] Furthermore, the prevalence of CVD risk factors such as hypertension, dyslipidaemia, and diabetes is also high, with rates of 51, 60–70, and 21%, respectively.[4] The Global Burden of Disease Study estimates that CVD is the leading cause of death worldwide, accounting for 31% of all global deaths.[6] The rising prevalence of obesity and CVD has profound implications for global health systems.[4] The economic burden is staggering, with the direct and indirect costs of treating these conditions running into hundreds of billions of dollars annually. Furthermore, the social implications are significant, affecting productivity, quality of life, and life expectancy.[6]

The relationship between obesity and CVD is complex and multifactorial, with chronic low-grade inflammation as the cornerstone in understanding this connection. This systemic inflammatory state is primarily orchestrated by adipose tissue dysfunction, acting as a central hub that connects a variety of pathological pathways, each contributing to the overall cardiovascular risk. These range from cellular dysfunction and immune cell infiltration to oxidative stress and external modulatory factors like diet and genetics.[7] The distribution of adipose tissue also matters: visceral adipose tissue is more strongly associated with insulin resistance, dyslipidaemia, a pro-thrombotic, and a pro-inflammatory state, all factors directly implicated in the pathogenesis of CVD.[8] The cumulative impact of these interconnected pathways significantly impairs cardiovascular health, setting the stage for the onset and progression of CVDs.[9]

While body mass index (BMI) is often used as a quick and convenient measure of obesity, it lacks the granularity to differentiate between types of adipose tissue and their metabolic activity.[10] Noteworthy, patients with CVD do not necessarily suffer from severe obesity. Far more prevalent is the presence of visceral obesity in the case of overweight, a critical risk factor for CVD, which is often overlooked in non-obesity focused clinical settings, representing a significant gap in current medical practice.[8,10] This oversight can lead to inadequate risk stratification and may miss opportunities for targeted interventions that could mitigate CVD risk: several studies have indeed demonstrated that weight loss can significantly reduce the risk of developing CVD, further emphasizing the interconnectedness of these conditions.[11,12] This underscores the need for more comprehensive adiposity assessment methods, such as waist circumference, in cardiology settings to better evaluate and treat the complex relationship between obesity and cardiovascular health.

The present narrative review summarizes the pathophysiology underlying the link between obesity and CVD, examining the variability of obesity-related cardiometabolic effects. Moreover, it gives an overview of the cardiovascular impact of weight loss providing evidence on the implications of weight excess in the treatment of patients with CVD.

Pathophysiology

Low-grade inflammation

Once considered a mere energy storage site, adipose tissue has emerged as a dynamic endocrine organ of paramount significance in the context of obesity. The development of chronic inflammation in obesity lies at the base of the link between CVD and weight primarily due to adipose tissue dysfunction.[13] In the obese state, adipocytes undergo hypertrophy and hyperplasia, leading to dysregulated adipokine secretion.[14] This shift in the secretory profile of adipose tissue results in an increased production of pro-inflammatory cytokines, including TNF-α, IL-6, and IL-1β, alongside a reduction in anti-inflammatory adipokines, such as adiponectin.[14] This shift in adipokine balance sustains the chronic inflammatory milieu and interferes with insulin signalling cascades within adipocytes and skeletal muscle cells. The ensuing insulin resistance culminates in compromised glucose uptake, emblematic of the dysregulated glucose metabolism that characterizes obesity and type 2 diabetes (T2D).[15]

The dysregulated adipokine secretion promotes the infiltration of immune cells into adipose tissue, particularly macrophages with a pro-inflammatory phenotype (M1). This infiltration sets up a positive feedback loop that perpetuates chronic inflammation. Activation of innate immune pathways, such as toll-like receptors (TLRs), by obesity-related factors like fatty acids and endotoxins, also plays a crucial role in chronic inflammation. Toll-like receptor activation initiates a cascade of pro-inflammatory signals, further fuelling the inflammatory response.[16]

The inflammatory milieu within adipose tissue in obesity also triggers perturbations in lipid metabolism. This leads to the liberation of free fatty acids into the bloodstream, exacerbating lipid imbalances typified by dyslipidaemia—a well-established risk factor for atherosclerosis and CVD. Moreover, elevated levels of free fatty acids in individuals with obesity, and mitochondrial dysfunction, amplify the generation of reactive oxygen species (ROS). The presence of ROS activates additional inflammatory signalling pathways, adding another layer to the complex interplay between obesity and chronic inflammation.[17]

The gut microbiome, dietary components, and genetic factors interact with the mechanisms above, exacerbating chronic inflammation in obesity. Dysbiosis in the gut microbiome can lead to increased production of pro-inflammatory metabolites. Dietary factors, particularly high-fat and high-sugar diets, contribute to oxidative stress and inflammation.[18]

Among the health complications ensuing from chronic inflammation in obesity, endothelial dysfunction is pivotal for vascular health. Diminished nitric oxide bioavailability, prompted by inflammatory signalling, hampers vasodilation, and increases vascular resistance. This sets the stage for hypertension, a precursor to CVD. Additionally, the vascular wall experiences heightened oxidative stress, promoting a pro-atherogenic environment. The up-regulation of adhesion molecules on the endothelial surface allows for the recruitment of leucocytes, initiating an inflammatory cascade that is a hallmark of atherosclerosis[19] (*Figure 1*).

Metabolically healthy obesity

However, a subset of individuals with obesity do not exhibit the metabolic complications commonly associated with obesity, such as insulin resistance, dyslipidaemia, chronic low-grade inflammation, and an elevated risk for CVD.[20] This subgroup delineates individuals with metabolically healthy obesity (MHO). The comparison of MHO and metabolically unhealthy obesity (MUO) is still a subject of controversy, with evidence suggesting that MHO might represent a transitional state. Notably, studies like the meta-analysis by Zheng *et al.*[21] propose that individuals with MHO may progress towards an unhealthy metabolic state, impacting cardiovascular risk more than overall mortality. Moreover, the multitude of diverse classifications and criteria used to define metabolic syndrome makes the distinctive identification of patients with MHO and differentiation from those with MUO complex.[22] Despite these intricacies, MHO presents a fascinating paradox that challenges the conventional understanding of obesity-related risks. The paradox of MHO suggests that all adipose tissue is not created equal.[23] In MHO individuals, adipose tissue functions more efficiently despite the excess weight. The hypertrophy and hyperplasia of adipocytes may occur in a manner that avoids hypoxia and minimizes pro-inflammatory cytokine production. Compared to visceral fat, subcutaneous fat is less metabolically active and less prone to induce systemic inflammation. Individuals with a higher proportion of subcutaneous fat may be protected from the pro-inflammatory state often seen in obesity. In MHO, the infiltration of macrophages into adipose tissue may be reduced, or the macrophages may adopt a more anti-inflammatory M2 phenotype as opposed to the pro-inflammatory M1 phenotype. This could result in a less inflammatory environment despite the surplus of adipose tissue.[22] Another possibility is the elevated production or effectiveness of anti-inflammatory adipokines like adiponectin. Higher adiponectin levels have been correlated with improved insulin sensitivity and a lower risk of CVD.[24] Some

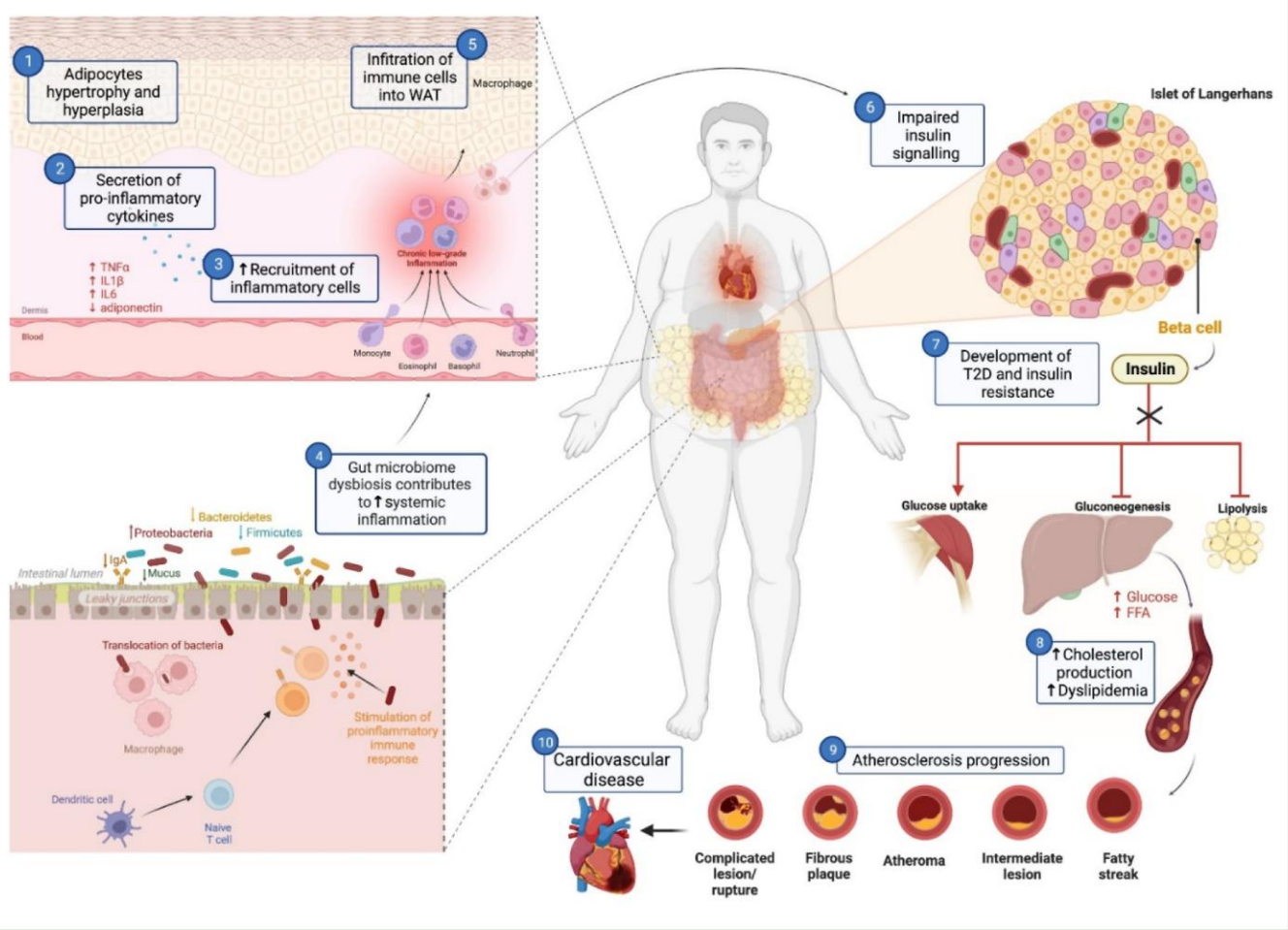

Figure 1 The pathophysiology underlying the link between excessive fat accumulation and the development of cardiovascular disease.

individuals may have genetic variants that protect them against inflammation and CVD despite the presence of obesity.[23] Epigenetic modifications, influenced by factors like diet, physical activity, and even the microbiome, could also modulate the expression of genes related to inflammation and cardiovascular health.[25] Indeed even without weight loss, physical activity has been shown to improve the metabolic profile and reduce inflammation.[26] Diet quality, independent of caloric intake, may also play a role. For instance, a diet abundant in foods known for their anti-inflammatory properties, such as fruits, vegetables, and fish, could potentially lower the associated risks.[27] However, it should be noted that several individuals with MHO eventually develop complications over time, at a point that the concept of MHO is not universally accepted. Additionally, they still have a significantly higher risk compared with metabolically healthy lean subjects[28,29] (*Figure 1*).

Implications on weight excess in the treatment of cardiovascular disease

In cardiology, individuals with excess weight ranging from obesity to visceral obesity, despite having a normal BMI, present unique challenges. These challenges extend from diagnosis to treatment and have long-term implications for patient outcomes. *Table 1* provides a workflow outlining how to manage a patient with obesity and CVD, offering a step-by-step guide for clinicians. First, it is crucial to distinguish between different forms of weight excess. While obesity is commonly assessed using BMI, it may not capture the entire picture. Visceral obesity, characterized by an accumulation of fat around internal organs, can be present in individuals who are not categorized as with obesity based on BMI alone. Both obesity and visceral obesity have been linked to adverse cardiovascular outcomes.[8]

In the SELECT trial, subjects in secondary prevention had an average BMI of 33.3 (5.04); 28.5% were overweight (BMI = 27 – < 30) at baseline. The majority of participants (42.5%) had Class 1 obesity (BMI = 30 – < 35), while 19% had Class 2 (BMI = 35 – < 40), and 10% had Class 3 (BMI ≥ 40).[30] These baseline characteristics are important because they help physicians in recognizing CVD in non-extreme obesity, suggesting that only severe obesity is harmful is incorrect.

The impact of obesity on the clinical presentation, diagnosis, and outcomes of coronary artery disease

Clinical presentation

Although obesity and visceral adiposity do not necessarily correlate with a higher incidence of unusual symptoms during cardiac events, individuals with metabolic syndrome, and particularly those with T2D—which are common complications of obesity—may exhibit less specific symptoms or silent ischaemia (lack of blood flow to the heart muscle).[31,32]

Table 1 Workflow outlining how to manage a patient with obesity and cardiovascular disease

Steps	Component	Obesity-related aspects to be implemented
Medical assessment	Patient history	Ask for family history for diabetes and obesity
	Physical examination	Examine for signs of obesity complications (i.e. large neck circumference for OSAS)
		Evaluate clinical symptoms and signs indicative of heart failure, being aware that NYHA grading is to be considered in light of excess BMI
		Record waist circumference, weight and height to calculate BMI: self-declared height and weight are very different from reality, increased waist circumference is very common in patients with CVD even in the absence of frank obesity
	Biochemistry	Interpret NT-proBNP levels considering reduced levels in obesity
	ECG Interpretation	Increased heart rate
		Increased PR interval, wider QRS complex
		Decreased/increased QRS voltage
		Increased corrected QT (QTc) interval
		Abnormal late potentials
		ST wave and T wave abnormalities
		Left axis deviation and T-wave flattening
		Left atrial abnormalities
		False positive MI criteria
	Echocardiographic Evaluation	Increased LV Stiffness
		Increased End Diastolic Pressure
		Increased Pulmonary Artery Pressure
		Altered Atrial and Ventricular Pressure in sleep apnoea
Therapeutic work-up	Medical treatment	Consider weight loss medications
		Prefer 'weight neutral' CVD medications
	Referral	Consider referral to obesity specialist rather than advising for 'all-hypo-diet')

BMI, body mass index; NYHA, New York Heart Association; OSAS, obstructive sleep apnoea syndrome; MI, myocardial infarction, NT-pro BNP, N-terminal pro-B-type natriuretic peptide; CVD, cardiovascular disease; LV, left ventricular; ECG, electrocardiogram.

Diagnosis

Examining patients with obesity in cardiology can be challenging, leading to missed or delayed diagnoses. For example, it can impede the identification of cardiac murmurs or other findings during a medical examination. Additionally, interpreting electrocardiograms can be challenging in individuals with obesity due to alterations in body habitus, which can lead to potential misdiagnosis.[33] Traditional diagnostic tests, such as treadmill stress testing, may also be less effective in individuals with obesity due to limitations in exercise capacity. Furthermore, imaging studies, such as echocardiograms or cardiac MRIs, can also be technically challenging, which can reduce their sensitivity and specificity in detecting cardiac abnormalities.[34] As such, clinicians should be aware of these limitations when assessing and diagnosing cardiac conditions in patients with obesity, and alternative diagnostic and screening strategies may need to be considered.

Outcomes

It is interesting to note that some studies have found an 'obesity paradox' where people who are overweight or mild obesity seem to have better outcomes after acute cardiac events compared to their leaner counterparts.[35] However, these studies use BMI as the parameter to classify obesity. Body mass index is a simple tool for categorizing individuals based on their weight relative to height. However, it has significant limitations as it cannot differentiate band fat mass or to specify the fat distribution. As a result, BMI may underestimate the level of fat excess in individuals and potentially misclassify them into 'healthier' weight categories.[10]

The distinction between intentional and unintentional weight loss may hold the key to understanding the obesity paradox, particularly in cardiology. Intentional weight loss, achieved through lifestyle modifications such as diet and exercise, is generally associated with improved cardiovascular outcomes.[36] In contrast, unintentional weight loss, often observed in severe illnesses such as cancer or advanced stages of CVD, can indicate increased morbidity and a worse prognosis. In such cases, the 'normal' weight category may act as a confounding factor, falsely suggesting that lower weight is associated with worse outcomes when, in reality, the weight loss is a symptom of an underlying disease.[37] Understanding the nuances of intentional and unintentional weight loss is crucial for accurate risk stratification and effective management of CVD. The role of muscle mass and overall nutritional status adds another layer of complexity. Individuals with higher muscle mass may have elevated BMIs but lower cardiovascular risk than those with similar BMIs but higher fat mass.[38] Furthermore, good nutritional status, often better preserved in individuals with overweight or mild obesity, may confer a protective effect during acute illnesses, including cardiac events.[38] Given these complexities, it may be more accurate to consider the obesity paradox as a manifestation of the limitations of BMI as a measure and the confounding effects of underlying diseases that cause unintentional weight loss. In this light, what appears as a paradox may be a nuanced interplay of various factors including body composition, the cause of weight loss, and overall health status.

Table 2 Medications frequently used in a cardiological setting which can lead to weight gain

Drug Class	Metabolic profile and efficacy	Side effects and Limitations
Beta-blockers	May lead to weight gain; newer generation may have a more favourable metabolic profile.	Reduced energy expenditure; potential contributor to obesity.
Calcium channel blockers	Neutral or slightly beneficial metabolic profile; effective across different BMI categories.	Increased risk of peripheral oedema in patients with obesity.
ACEIs and ARBs	Favourable metabolic profiles; potential renal protection; may be particularly effective in obesity.	None mentioned.
Direct renin inhibitors	Target the RAAS system; may offer advantages in obesity.	Data not as extensive as for ACEIs and ARBs.
Thiazide diuretics	Deterioration of glucose control; dose-dependent effect.	Particularly important in patients with diabetes; less relevant in those with normal glucose control.

ACEI, Angiotensin-converting enzyme inhibitors; ARBs, Angiotensin Receptor Blockers; RAAS, renin–angiotensin–aldosterone system.

The impact of obesity on the clinical presentation, diagnosis, and outcomes of heart failure

Clinical presentation

Obesity and especially visceral obesity are strongly associated with HF with preserved ejection fraction (HFpEF),[39] with a hazard ratio (HR) of 1.3 for every 4-unit increase in BMI.[5] The metabolic inflammation and increased cardiac preload associated with visceral obesity contribute to diastolic dysfunction, a hallmark of HFpEF. The diagnosis and management of HFpEF are notoriously challenging,[40] and obesity further complicates the clinical approach as recently discussed in a joint position paper by the World Heart Federation and World Obesity Federation.[41]

More generally, obesity and visceral obesity often lead to atypical presentations of HF. Breathlessness, a hallmark symptom, might be attributed to obesity itself rather than underlying cardiac dysfunction. Moreover, obesity-related comorbidities like sleep apnoea and obesity hypoventilation syndrome can confound the clinical picture, making it difficult to discern the aetiology of symptoms.[42]

Diagnosis

Echocardiographic imaging can be less reliable due to poor acoustic windows, and the interpretation of natriuretic peptides, key biomarkers in HF diagnosis, especially the HFpEF subtype, can be complicated by obesity. These peptides NT-proBNP levels are inversely correlated with body weight and are often lower in individuals with obesity, even in the presence of HF, potentially leading to missed or delayed diagnoses.[5,34]

Outcomes

As for coronary artery disease (CAD), some studies have suggested an 'obesity paradox' in HF, where patients with overweight or mild obesity have better short-term outcomes than their leaner counterparts. The abovementioned considerations apply, necessitating cautious interpretation. There is also an important correlation between unintentional weight loss after discharge for HF and mortality, with a 3.2 times higher risk for cardiac events and poor outcomes reported.[43] As previously mentioned, the efficacy and safety of Semaglutide 2.4 mg in patients suffering from obesity and HFpEF have been established. In the study, Semaglutide 2.4 mg resulted in more significant reductions in symptoms and physical limitations, improved exercise function, and greater weight loss compared to the placebo.[44]

Moreover, medications used in HF, such as diuretics and beta-blockers, may negatively impact glucose and/or lipid metabolism, something to be considered while treating individuals with obesity.[45] Moreover, beta-blockers may lead to some degree of weight gain due to a variety of mechanisms including inhibited sympathetic tone, decreased lipolysis, reduced exercise tolerance, increased fatigue, and reduced resting energy expenditure[46] (*Table 2*). New generation beta-blockers seem to exert neutral or even positive metabolic effects, supporting their use as opposed to old-generation ones.[45,47]

The impact of obesity on the clinical presentation, diagnosis, and outcomes of stroke

Clinical presentation

Individuals with visceral or total body obesity often present with a unique set of challenges when experiencing a stroke. Traditional symptoms like sudden numbness or weakness may be masked or misinterpreted due to pre-existing limitations in mobility or other obesity-related comorbidities, and silent ischaemia is more common in individuals with metabolic syndrome.[48] Additionally, obesity may exacerbate post-stroke complications such as respiratory distress, making acute care more challenging.

Diagnosis

The diagnostic process for stroke in individuals with overweight or obesity can be complicated. Standard imaging techniques, such as computed tomography scans and MRIs, may be less reliable or require specialized protocols due to body habitus. Similarly, the interpretation of biomarkers associated with stroke and neuronal damage, like neuron-specific enolase, may differ in individuals with obesity, who tend to have higher baseline values, requiring a more nuanced approach to diagnosis.[49]

Outcomes

As for CAD and HF, some studies have pointed to an 'obesity paradox' in stroke. However, this paradox is not always confirmed, possibly due to selection bias and inaccuracy of the obesity definition.[50,51] The presence of obesity also complicates the post-stroke rehabilitation process. Reduced mobility, combined with other comorbid conditions like diabetes or hypertension, can hinder the effectiveness of rehabilitative therapies.[52] Glucagon-like peptide-1 (GLP-1) receptor agonists have been proven to be highly effective in reducing the risk of stroke within the 3-point major adverse cardiovascular events (3p-MACE) in subjects with T2D.[53] However, there is still a lack of data on the effects of GLP-1 receptor agonists (RAs) in individuals with obesity and without diabetes. The SELECT trial, which is set to be published in November

2023, will provide information as to whether the same effects can be observed in such patients.

The impact of obesity on the clinical presentation, diagnosis, and outcomes of peripheral artery disease

Clinical presentation and diagnosis

The impact of obesity or visceral obesity on peripheral artery disease (PAD) first manifests in its clinical presentation. Peripheral artery disease traditionally presents with intermittent claudication or critical limb ischaemia. However, if diagnosis itself is not particularly challenging in individuals with obesity, these symptoms may be attributed to musculoskeletal conditions related to weight, or they may be masked by underlying conditions such as diabetes-related polyneuropathy or lumbar spine diseases. Furthermore, obesity can exacerbate claudication severity, leading to reduced mobility and a more sedentary lifestyle, which in turn can worsen PAD symptoms.[54]

Outcomes

Research indicates that individuals with obesity face worse outcomes in PAD, including increased rates of amputation and cardiovascular events. However, akin to the 'obesity paradox' observed in other cardiovascular conditions, some data suggest that individuals with mild obesity may have better short-term outcomes.[55] Most authors agree that this may be due to frequent sarcopenia and unintentional weight loss in those with PAD categorized in a 'healthy' BMI.[54]

Cardiologist-managed risk factors in subjects with obesity

Hypertension

Hypertension is often labelled as the 'silent killer' due to its largely asymptomatic nature, and presentation is usually not different in individuals with obesity. However, diagnosis can be more difficult: traditional blood pressure cuffs may not fit properly, and the presence of excess adipose tissue can affect readings.[56] Additionally, blood pressure variability is often higher in patients with obesity, complicating the diagnosis and requiring more frequent or prolonged monitoring for accurate assessment.[57]

Pharmacologic treatment of hypertension may require special considerations in individuals with obesity. Thiazide Diuretics led to a small but significant deterioration of glucose control, with a dose-dependent effect.[58] This is particularly important in patients with T2D, but may be less relevant in those with normal glucose control.

As stated above, beta-blockers may lead to some degree of weight gain due to a variety of mechanisms. Interestingly, energy expenditure was found to be massively reduced in those chronic beta-blocker users compared to weight-matched controls, to the point that some authors even suggested that the obesity pandemic may be at least partially caused by the widespread use of these medications so beneficial on CV health.[59] When selecting a medication regimen, clinicians must therefore weigh the therapeutic advantages against the potential metabolic consequences. Newer generation beta-blockers may offer a more favourable metabolic profile, but the risk of weight gain should still be factored into the clinical decision-making process.[45,47]

Calcium Channel Blockers appear to have a neutral or slightly beneficial metabolic profile and are considered effective across different BMI categories. However, patients with obesity are more likely to experience peripheral oedema as a side effect of the treatment when compared with lean patients, posing a potential limitation to their use in these individuals.[60]

Angiotensin-converting enzyme inhibitors (ACEIs) and Angiotensin II Receptor Blockers (ARBs) are often recommended for these patients due to their favourable metabolic profiles and potential renal protection. Some studies suggest that ACEIs and ARBs may be particularly effective in individuals with obesity, possibly due to the increased activity of the renin–angiotensin–aldosterone system (RAAS) in obesity as well as the effect of ACE inhibition on leptin levels.[61] Direct renin inhibitors also target the RAAS system and may offer advantages in patients with obesity, though the data is not as extensive as for ACEIs and ARBs[62] (*Table 2*).

Dyslipidaemia

Independent of body weight, dyslipidaemia is usually asymptomatic until it contributes to a cardiovascular event. Diagnosing dyslipidaemia relies primarily on laboratory tests, including total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides. Obesity or visceral obesity can influence these lipid profiles, often resulting in elevated triglycerides and reduced HDL-C, thus often necessitating a more comprehensive approach to lipid management, rather than focusing solely on LDL-C lowering.

Non-HDL cholesterol has been proposed as a primary therapeutic target for individuals living with obesity, as it may provide a more comprehensive assessment of cardiovascular risk compared to LDL-C.[63] Moreover, the interpretation of these values may require additional considerations, such as the presence of other metabolic syndrome components, to accurately assess cardiovascular risk.[64] It is important to pay attention to the residual risk factors in patients with obesity, such as excess weight, high triglycerides, smoking habits, and dysglycemia, as they can have a significant impact on cardiovascular health. Fortunately, medication for obesity can help reduce this risk. For instance, GLP1-RA can not only induce weight loss, but also improve lipid profile, blood pressure, and inflammation. Additionally, naltrexone and bupropion can help reduce smoking habits and promote weight loss.

Although the management of dyslipidaemia often involves pharmacologic agents like statins, fibrates, or PCSK9 inhibitors, lifestyle modification is a cornerstone, and individuals with obesity are often prompted to weight loss instead of being prescribed lipid-lowering drugs, despite potentially very high CV risk. Noteworthy, the impact of dietary treatments and weight loss on dyslipidaemia is statistically significant but clinically marginal with 1.27 mg/dL reduction in LDL-C being reported per kilograms weight loss.[65] Therefore, the habit of postponing pharmacotherapy in these individuals until weight loss is obtained and maintained should probably be abandoned.

Type 2 diabetes

The management of T2D in patients with obesity and cardiovascular risk necessitates a comprehensive and tailored approach. A multifaceted strategy involving lifestyle modifications, pharmacological interventions, and, in specific cases, bariatric surgery is crucial.[66]

In recent times, there has been a notable shift in the management approach for T2D from a 'treat to goal' to a more personalized 'treat to benefit' paradigm.[67] This signifies a move towards personalized treatment strategies that go beyond glycaemic control alone, taking into account the holistic management of T2D and its complications, including excess weight.[68] Prioritizing the selection of antidiabetic medications with a positive impact on weight, such as GLP1 receptor agonists or SGLT2 inhibitors, or those with a neutral impact, like biguanides, has become paramount in aligning with the broader goal of addressing both diabetes and obesity.[69] This shift underscores the importance of a tailored and comprehensive approach, emphasizing the multifaceted nature of T2D management to optimize overall patient outcomes. It is advisable to approach the utilization of insulin, sulphonamide, or thiazolidinedione with caution, employing these medications only when clinically indicated to avoid exacerbating weight-related concerns.[70] Recommending the use of GLP1 receptor agonists in individuals with diabetes and secondary cardiovascular risk, along with

SGLT2 inhibitors for those with HF, can provide targeted benefits. GLP1 receptor agonists have been shown to promote myocardial glucose uptake and utilization, reduce oxidative stress, and inhibit cardiomyocyte apoptosis, thereby offering cardiovascular benefits.[71] Furthermore, bariatric surgery is considered the most effective treatment option for patients with T2D, especially for those who have not achieved success with conventional medical therapies. The impact of bariatric surgery on diabetes remission is significant, with remission rates ranging from 33 to 90% for individuals with T2D,[72] underscoring the importance of a holistic and individualized approach to managing this complex interplay of conditions.

Cardiovascular impact of weight loss treatment

Dietary treatment

Dietary treatment for obesity often encompasses a multifaceted approach, including caloric restriction, macronutrient balance, and the inclusion of nutrient-dense foods. Studies have shown that even modest weight loss of 5–10% can significantly improve cardiovascular markers.[73] Caloric restriction, often achieved through a deficit of 500–1000 kcal/day has been shown to reduce serum LDL-C and triglycerides while increasing HDL-C levels. Moreover, dietary patterns, such as the Mediterranean diet, have been associated with improved endothelial function and reduced inflammation and insulin resistance.[73–75]

The Mediterranean diet is rich in fruits, vegetables, whole grains, nuts, and olive oil, with moderate fish and poultry and minimal red meat and dairy. This nutrient profile lowers non-HDL-C, reduces inflammation and hypertension, and improves insulin sensitivity, all of which are beneficial for cardiovascular health. Moreover, the Mediterranean diet's richness in omega-3 fatty acids and antioxidants, like polyphenols and resveratrol, further contribute to its heart-healthy effects. Long-term studies have confirmed its ability to reduce cardiovascular events, even in high-risk groups such as those with obesity.[76] Moreover, the Mediterranean diet has been shown to be beneficial for both primary and secondary prevention of CVD. The CORDIOPREV single-centre, randomized clinical trial, found that in patients with established coronary heart disease, the Mediterranean diet was superior to a low-fat diet in preventing the occurrence of new major cardiovascular events.[77] The diet is also palatable and culturally accepted, making it a sustainable choice for long-term health.[27]

Weight reduction has predominantly demonstrated efficacy as a strategy to enhance HbA1c levels and mitigate the risk of complications associated with excess weight.[78] In this regard, the Look AHEAD (Action for Health in Diabetes) study revealed that individuals at high risk of T2D, achieving a substantial weight loss (>10%) through 1-year lifestyle counselling in primary health care, experienced lasting benefits, including a reduction in cardiovascular events and all-cause mortality.[78,79]

A nutritional approach similar to the Mediterranean diet is the Dietary Approaches to Stop Hypertension diet, initially designed for hypertension management, which prioritizes fruits, vegetables, low-fat dairy, and whole grains while reducing sodium and saturated fats. Abundant in fibre, potassium, calcium, and magnesium, it supplies essential nutrients crucial for cardiovascular health. Not only does it effectively lower blood pressure, but it also improves lipid profile and insulin sensitivity. The diet's balance and inclusivity make it sustainable for long-term administration, and studies have shown it to reduce cardiovascular events over time.[80]

The influence of the ketogenic diet (KD) on cardiovascular health in the context of obesity remains a subject of debate.[81] Ketogenic diet is a low-carbohydrate diet in which macronutrient distribution and calorie intake may vary. The constant is a carbohydrate content fixed at <50 g/daily, a threshold under which ketosis may be achieved.[82] The diet's main advantage is significant weight loss, largely from reduced calories and increased satiety.[83] This weight loss can improve cardiovascular markers like lipid profile.[84] However, if high in saturated fats, the diet might elevate LDL-C while it generally boosts HDL-C and lowers triglycerides.[84] Moreover, genetic variations can impact the response to a KD by influencing the body's capacity to process and utilize fats.[85] The KD can also lower blood pressure, possibly due to weight loss and reduced insulin levels.[84] However, endothelial dysfunction may ensue if high in saturated fats. Additionally, ketosis exerts anti-inflammatory effects.[86] While short-term studies have shown some cardiovascular benefits,[84] given the scarce sustainability of the diet long-term, no long-term studies in the setting of obesity have been conducted, consequently, the lasting cardiovascular benefits remain uncertain (*Table 3*).

Pharmacotherapy

The pharmacological agents used in the treatment of obesity can be broadly categorized into appetite suppressants, such as the combinations phentermine–topiramate and bupropion–naltrexone; nutrient absorption inhibitors, like orlistat; and hormone analogues, such as liraglutide, semaglutide, and tirzepatide. Some of these medications are approved specifically for weight management. Obesity medications facilitate weight loss to some degree, which in itself is a significant cardiovascular risk reducer.[87]

Phentermine–topiramate combination therapy has demonstrated modest reductions in blood pressure after 1 or 2 years from treatment initiation, but phentermine can elevate heart rate and is generally not recommended for individuals with existing CVD.[88]

Similarly, the association bupropion–naltrexone was reported to be non-inferior to placebo regarding risk of major cardiovascular events.[89] Still, it had less beneficial results than placebo on weight loss-driven hypertension improvement,[43] making this medication generally not recommended for individuals with existing CVD. Its long-term cardiovascular safety remains to be established (*Table 3*).

Orlistat has been shown to induce a very small reduction in body weight, it is associated with a decrease in total and LDL-C improvements in blood pressure. A 37% risk reduction in diabetes progression was also reported at 4 years.[90,91]

Advanced anti-obesity drugs are about to become crucial in managing cardiovascular risk factors in patients living with obesity and CVD. Specifically, GLP-1 receptor agonists have shown significant benefits for cardiovascular health. These medications not only facilitate weight loss but also offer multiple cardioprotective effects. They aid in reducing atherosclerotic plaque formation, enhancing endothelial function, and optimizing myocardial energy metabolism. Incorporating these drugs into cardiovascular care algorithms represents a transformative approach that synergistically addresses metabolic and cardiovascular endpoints with a multi-targeted strategy.

Beyond weight loss *per se*, GLP-1 RAs have been shown to improve blood pressure, likely due to weight loss-induced reductions in peripheral resistance or direct vasodilatory effects.[92] GLP-1 RAs are highly effective in controlling blood sugar and cholesterol levels, which can help reduce the risk of T2D and dyslipidaemia. Liraglutide 3 mg, in the largest randomized controlled trial (RCT) for weight management, SCALE obesity, and pre-diabetes, demonstrated significant improvements in these areas[93] (*Table 3*).

These agents enhance insulin sensitivity and glucose utilization, which is critically important in the context of obesity, where insulin resistance is often present.[94] Moreover, GLP-1 RAs seem to have a role in reducing platelet aggregation and thrombus formation, thus exerting pleiotropic beneficial CV effects.[95] Finally, Semaglutide 2.4 mg once-weekly (OW) was also proved safe and effective in patients with obesity and HFpEF, a common and underdiagnosed obesity complication[44]

Table 3 Weight loss treatments, diets and surgery (with the population enrolled), mechanisms and components of the medications, cardiovascular benefits, and limitations/considerations on the weight loss treatments

Weight loss treatment Molecule/intervention, (population), main study	Mechanism/components	Cardiovascular benefits	Limitations/considerations
Dietary intervention			
The Mediterranean diet	High in fruits, vegetables, wh + C6:E18ole grains, nuts, olive oil; moderate in fish and poultry; low in red meat, dairy, sweets	Reduces LDL and triglycerides, increases HDL, reduces inflammation, improves endothelial function, and blood pressure regulation	Highly sustainable
DASH diet	High in fruits, vegetables, low-fat dairy, whole grains; low in sodium, saturated fats, added sugars	Lowers blood pressure, improves lipid profile, reduces vascular resistance, improves insulin sensitivity	Highly sustainable
Ketogenic diet	Low-carbohydrate (<30–50 g/day), high-fat/protein	Significant weight loss, increases HDL, reduces triglycerides, lowers blood pressure	Lack of long-term studies; potential to raise LDL if high in saturated fats
Surgical intervention			
Bariatric surgery (people with obesity), Swedish Obesity Study (SOS)	Caloric intake is reduced following Bariatric surgery (BS), with substantial changes in food preference and taste. BS increase the secretion of multiple intestinally derived peptides, including GLP-1, PYY, and FGF-19, and decrease the secretion of others, such as ghrelin. It induces profound changes in the microbiome and alters composition of circulating bile acids	Reduction in CV mortality, HF, MI, and ischaemic stroke incidence with follow-up duration ranging between 2 and 24 years. After 5 years superiority in achievement diabetes remission, lower body weight, waist circumference, waist-to-hip ratio, triglycerides and urinary albumin-to-creatinine ratio respect to intensive medical therapy; decrease in number of medications needed to treat hyperlipidaemia, hypertension and diabetes. Weight loss following a variety of BS procedures is 17% 5 years following surgery, 16% in 15 years, and 18% in 20 years post-surgery.	Mild anaemia, gastroesophageal reflux if vertical sleeve gastrectomy is performed, hypoglycaemic episodes (late dumping syndrome), mineral and vitamin deficiencies, rarely nephrolithiasis and cholelithiasis, 20% postoperative weight regain
Pharmacological intervention			
Liraglutide 1.8 mg once-daily (LEADER) (people with Type 2 Diabetes),	GLP1 acts in liver-increasing hepatic insulin sensitivity and reducing endogenous glucose production, *de novo* lipogenesis, lipotoxicity, and steatosis; in pancreatic islets-increasing beta-cell function and glucose-dependent insulin secretion and reducing beta-cell apoptosis and glucose-dependent glucagon secretion; in stomach-delaying gastric emptying; in central nervous system-reducing food intake and increasing satiety; in cardiovascular system-reducing fatty acid metabolism,blood pressure and inflammation	Significant reduction of 3-point MACE outcome (mainly driven by a significant decrease in death from cardiovascular causes), HbA1c value and SBP, lower rate of nephropathy events; Weight loss of 4.7% (5.0 kg) with liraglutide (1.8 mg dose) after 56 weeks in particular weight loss of 5% or greater occurred in 40.4% and weight loss greater than 10% occurred in 15.9% of patients	GI side effects: nausea (1.6%), vomiting(0.7%), diarrhoea (0.6%), rarely gallbladder-related events and pancreatitis, and slight increases in heart rate
Liraglutide 3.0 mg once-daily (SCALE) (Obesity and pre-diabetes)	Higher dosage of liraglutide for same mechanism	Weight loss of 8.0 ± 6.7% (8.4 ± 7.3 kg) after 56 weeks, in particular weight loss greater of 5% occurred in 51–73% and weight loss >10% occurred in 25–37% of patients. Reduction in SBP and DBP, HbA1c, fasting glucose and insulin levels, waist circumference. Improvements in all measures of fasting lipid levels, levels of high-sensitivity C-reactive protein, plasminogen activator inhibitor-1, and adiponectin.	More GI side effects (dose-dependent, usually occurring during the dose escalation period): nausea (40%), diarrhoea (21%), constipation (20%), vomiting (16%), dyspepsia (9%, rarely gallbladder-related events, and pancreatitis

Continued

Table 3 *Continued*

Weight loss treatment	Mechanism/components	Cardiovascular benefits	Limitations/considerations
Semaglutide 1 mg once-weekly (SUSTAIN-6) (people with diabetes and obesity)	Same mechanism of liraglutide but greater decrease in energy intake and meal duration and greater increase of satiety and half-life of the drug (once weekly vs. once-daily)	Significant reduction of 3-point MACE outcome (driven by the effect on non-fatal stroke), HbA1c, waist circumference, SBP and DBP, improvement of total cholesterol, LDL-cholesterol, HDL-cholesterol, and triglyceride levels. The proportion of patients achieving 5% weight loss across SUSTAIN 1–5 and 7 was 37–46% with 0.5 mg semaglutide and 45–66% with semaglutide 1.0 mg	GI side effects (dose-dependent, usually occurring during the dose escalation period): nausea(17–20%), diarrhoea (18%), vomiting (10–15%), rarely gallbladder-related events, hypoglycaemic events, and pancreatitis, slight increases in heart rate
Semaglutide 2.4 mg once-weekly (STEP1) (people with overweight and obesity)	HIGHER DOSES of semaglutide for same mechanism	After 68 weeks weight loss greater of 5% occurred in 86.4%, weight loss > 10% occurred in 69.1% and weight loss greater than 15% occurred in 50.5%, improvements in glycated haemoglobin, fasting plasma glucose, C-reactive protein, fasting lipid levels, waist circumference, body composition, SBP and DBP	More GI side effects (dose-dependent, usually occurring during the dose escalation period): nausea (44%), diarrhoea (31%), vomiting (25%), constipation (23%), and rarely gallbladder-related events
Oral Semaglutide 14 mg once-daily (PIONEER-6) (people with diabetes and obesity)	Oral semaglutide is currently the only oral medication within GLP1-RA class	CV safety profile of oral semaglutide was non-inferior to placebo; Decrease in HA1c,waist circumference, SBP, modest decrease of low-density lipoprotein cholesterol and triglycerides; The proportion of patients achieving weight loss of ≥5% across the PIONEER trials was from 13% to 44% with oral semaglutide 7 and 14 mg respectively	GI side effects (dose-dependent, usually occurring during the dose escalation period): nausea (2.9%), vomiting (1.5%), diarrhoea (1,4%) slight increases in heart rate, and rarely pancreatitis
Oral Semaglutide 50 mg once-daily (OSAS1) (people with overweight and obesity)	Higher dose of oral GLP1	Improvements in waist circumference, HbA1c, SBP e DBP, fasting lipids (HDL cholesterol, VLDL cholesterol and triglycerides) and high-sensitivity C-reactive protein, weight loss of 5% or more 85, 10 or more 69, 15 54% of patients at week 68	GI side effects (dose-dependent, usually occurring during the dose escalation period): nausea (52%), constipation (28%), diarrhoea (27%), vomiting (24%), slight increases in heart rate, and rarely gallbladder-related disorders
Tirzepatide 15 mg (SURMOUNT 1) (people with diabetes and obesity)	Tirzepatide is a glucose-dependent insulinotropic polypeptide receptor agonist and a glucagon-like peptide.1 receptor agonist whose benefits could go beyond that observed with selective GLP-1 RAs, including a more profound effect on carbohydrate control, blood pressure, lipid metabolism body weight, and reduction of hepatic and visceral fat	The mean percentage change in weight at week 72 was −15.0% with 5 mg weekly doses of tirzepatide, −19.5% with 10 mg doses, and −20.9% with 15 mg doses; at week 72, most (95.3%) of the participants with pre-diabetes at baseline in the tirzepatide groups had reverted to normoglycemia, reduction in total body fat mass, waist circumference, SBP, DBP, fasting insulin level, and lipid levels.	GI side effects (dose-dependent; safety profile of tirzepatide was consistent with other GLP-1 RAs): nausea (25–30%), diarrhoea (20%), constipation (10–15%), vomiting (8–10%), dyspesia (8–10%), rarely pancreatitis, and cholecystitis

Continued

Table 3 *Continued*

Weight loss treatment	Mechanism/components	Cardiovascular benefits	Limitations/considerations
Orlistat 120 mg (people with overweight and obesity)	Reversible inhibitor of gastrointestinal lipases; inhibits fat absorption up to 30% (dose-dependent)	Improvements in several lipid parameters including total cholesterol, low-density lipoprotein-cholesterol, triglycerides, and apolipoprotein B, beneficial effect on oral glucose tolerance tests status, waist circumference and systolic and diastolic blood pressure; at 1 year weight loss of 5% or more 50%, 10% or more 29–38% of patients (at maximum dosage)	GI side effects: oily spotting (26.5% of patients), flatus with discharge (23.9%) and faecal urgency (22.1%); Drug interactions
Naltrexone/Bupropione 8/90 mg (people with overweight and obesity)	Naltrexone is a μ-type opioid receptor antagonist- Bupropion is a (weak) inhibitor of dopamine and norepinephrine reuptake.These drugs act on the hypothalamus and the mesolimbic dopamine circuit decreasing food intake and modulating food cravings through an effect on the dopamine reward pathway	Bupropion, B–N, or naltrexone did not significantly increase the risk of MACE compared with placebo; significant improvement in waist circumference, triglycerides, HDL, HOMA-IR; at 1 year weight loss of 5% or more 45–66%, 10% or more 25–40% of patients (at maximum dosage)	Side effects: Nausea (33%), constipation (19%), headache (18%), vomiting (11%), dizziness (10%), insomnia (9%), diarrhoea (7%); Drug interactions; not administer to patients with uncontrolled hypertension and recent MI due to lack of evidence
Phentermine/ topiramate (people with overweight and obesity)	Phentermine a is sympathomimetic amine anorectic- Topiramate is a anti-epileptic drug. A single-dose combination of low-dose phentermine and topiramate extended-release was recently approved by FDA but not by EMA reduces appetite and increases energy expenditure	Reduction in SBP and DBP, improvements in serum triglyceride, high-density lipoprotein cholesterol and non-HDL-C levels. Available data do not indicate any increased cardiovascular risk associated with PHEN/TPM-ER; at 1 year weight loss of 5% or more 67–70%, 10% or more 47–18% of patients (at maximum dosage)	Slight increases in heart rate for the maximum dosage (15/92 mg), paraesthesia (19%), dry mouth (17%), constipation (14%), dysgeusia (8%), insomnia (7%). Contraindications: History of cardiovascular disease, Glaucoma, Hyperthyroidism, concomitant therapy with monoamine oxidase inhibitors

DASH, Dietary approaches to stop hypertension; DBP, Dyastolic blood pressure; EMA, European Medicines Agency; FDA, Food And Drug Administration; GI, gastrointestinal; GLP-1, Glucagon-Like Peptide-1; HF, heart failure; RA, receptor agonist; SBP, systolic blood pressure.

(*Table 3*). Using Semaglutide 2.4 mg to treat CVD marks a significant advancement in the management of obesity. Such effects have never been reported before, indicating a potential reduction in cardiovascular mortality and morbidity among patients with obesity. This breakthrough paves the way for future regulatory agreements regarding the use of these medications. Moreover, there is currently an oral version of Semaglutide 14 mg available for the treatment of T2D. Studies have shown a decrease in cardiovascular risk factors among patients with T2D as well as non-inferiority in cardiovascular risk when compared to placebo.[96] However, due to the short observation period a superiority of Semaglutide per os (p.o.) was not observed.

In addition, Semaglutide p.o. increased at the dosage of 50 mg in the OASIS 1 study, a RCT conducted on adults with overweight or obesity, showed promising results in terms of safety and efficacy. Specifically, the dosage of 50 mg taken once-daily led to significant reductions in weight, incidence of T2D, inflammation, blood pressure, and improved lipid profile.[97]

In November 2023, authors from the SELECT trial showed that the primary cardiovascular endpoint event (3P-MACE) occurred in 6.5% of the patients in the sub-cutaneous OW Semaglutide 2.4 mg group and in 8.0% in the placebo group (HR, 0.80; 95% confidence interval, 0.72–0.90; $P < 0.001$ for superiority), with a reduction of non-fatal myocardial infarction (HR, 0.72; 95% confidence interval, 0.72–0.85). These patients had either overweight or obesity and established CVD. This marks the first time a GLP1-RA has shown such a result in a cardiovascular outcome trial (CVOT) trial among patients with no history of diabetes, representing a groundbreaking achievement.[98]

Pharmacological future directions

Currently, researchers are exploring different compounds that have shown potential for weight loss in CVOT RCTs.

One such compound is CagriSema 2.4 /2.4 mg, a combination of Semaglutide 2.4 mg and Cagrilintide 2.4 mg (an amylin analogue). This compound, administered OW has already demonstrated effectiveness in weight loss and glucose control.[99] It is currently being investigated in the REDEFINE 3 study (clinicaltrial.gov #NCT05669755) to evaluate its potential as a secondary prevention measure for patients with obesity, with or without T2D.

Tirzepatide is a new drug that acts on both Gastric inhibitory polypeptide (GIP) and GLP-1 receptors, and has been proven safe and effective for treating T2D, obesity, and showed reduction of cardiovascular risk factors.[100,101] Currently, it is being investigated for its potential in primary and secondary cardiovascular prevention in people with obesity through the SOURMOUNT-MMO study (clinicaltrial.gov #NCT05556512). Additionally, the SUMMIT study (clinicaltrial.gov #NCT04847557) is being conducted to assess the drug's safety and efficacy in participants with HFpEF.

Orforglipron, a non-peptide daily oral GLP-1 RA, has been associated with weight reduction[102] and improvement of T2D.[103] It is currently under investigation to confirm its effectiveness in reducing CVD markers in individuals with obesity (clinicaltrial.gov #NCT05869903).

Retatrutide, OW GIP, GLP-1, and glucagon RA, which is the first triple agonist investigated in large RCTs for the treatment of obesity[104] and T2D,[105] led to significant improvements in both. Retatrutide is now being investigated in regard to efficacy and safety compared to placebo in participants with severe obesity and established CVD (clinicaltrial.gov #NCT05869903).

Surgery

Bariatric surgery encompasses various surgical procedures that aim to induce weight loss by restricting food intake, and controlling appetite via the gut–brain incretin axis and mechanical effect. Common types include Roux-en-Y gastric bypass, sleeve gastrectomy, and adjustable gastric banding. These surgeries result in significant weight loss and induce metabolic changes, including improvements in lipid profiles, insulin sensitivity, and inflammatory markers. Significant and sustained weight loss is one of bariatric surgery's most immediate and impactful outcomes.[106] Weight reduction has been shown to correlate with improvements in several cardiovascular risk factors, including dyslipidaemia, hypertension, and systemic inflammation.[107] Bariatric surgery has been shown to significantly improve lipid metabolism, including reductions in LDL-C and triglycerides, and an increase in HDL-C.[108] Moreover, it has been shown to reduce blood pressure levels, often leading to the discontinuation of antihypertensive medications.[109] Additionally, weight loss following bariatric surgery has been associated with beneficial cardiac remodelling, including reductions in left ventricular mass and improved diastolic function.[109] Bariatric surgery is also effective in improving insulin sensitivity and has been shown to induce remission or improve T2D in a significant proportion of patients.[110] While the short-term cardiovascular benefits of bariatric surgery are well-documented, long-term data also suggest sustained CVD risk reduction.[111] The Swedish Obese Subjects (SOS) study, which followed patients for up to 15 years post-surgery, showed a significant reduction in coronary artery disease, stroke, and myocardial infarction incidence. However, there was a conspicuous number of patients lost to follow-up[107] (*Table 3*). A meta-analysis that focused on cardiovascular outcomes after bariatric surgery, which included 39 cohort studies, found that there were significant decreases in both all-cause mortality (HR 0.55, $P < 0.001$) and cardiovascular death (HR 0.59, $P < 0.001$). The instances of HF, myocardial infarction, and stroke were notably reduced. However, there was no significant impact on atrial fibrillation observed.[112]

Conclusion

The diagnosis and treatment of CVDs and their risk factors become more complex when dealing with patients who have excess body fat, whether it is obesity or visceral adiposity. Fat excess can alter clinical presentations and pose challenges in pharmacological management and procedural interventions, necessitating a nuanced approach for effective cardiovascular care. As physicians enter a new era in the treatment of CVD among people living with obesity, it is imperative for cardiologists to not only address the implications of excess weight to improve outcomes for this already vulnerable patient population but also to become well-versed in the latest treatment options. This encompasses a responsibility to stay informed about emerging therapies and feeling confident in initiating these treatments in a clinical setting. Familiarizing themselves with these new approaches will enable cardiologists to provide comprehensive care that is both innovative and tailored to the unique needs of patients with obesity, ultimately enhancing patient outcomes in this critical area of health.

Authors contributions

Study conception and design: D.T. and M.W. Data collection: D.T., M.W., D.M., I.C., L.M., L.B.M., A.N., E.M. Draft manuscript preparation: M.W., D.T., D.M. Draft revision: M.W., D.T., I.C., E.M., A.N., L.G., N.N., S.M., F.G. All authors reviewed and approved the final version of the manuscript.

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References

1. World Health Organization. *Noncommunicable Diseases: key facts*. https://www.who.int/news-room/fact-sheets/detail/noncommunicable-diseases (19 September 2023)

2. World Health Organization. *Obesity and Overweight*. https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight (19 September 2023)
3. Watanabe M, Risi R, De Giorgi F, Tuccinardi D, Mariani S, Basciani S, *et al.* Obesity treatment within the Italian national healthcare system tertiary care centers: what can we learn? *Eat Weight Disord* 2021;**26**:771–778.
4. Su W, Huang J, Chen F, Iacobucci W, Mocarski M, Dall TM, *et al.* Modeling the clinical and economic implications of obesity using microsimulation. *J Med Econ* 2015;**18**:886–897.
5. Redfield MM, Borlaug BA. Heart failure with preserved ejection fraction: a review. *JAMA* 2023;**329**:827–838.
6. Gregory AR, Damaris A, Kalkidan Hassen A, Abay SM, Cristiana A, Abbasi N, *et al.* Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2018;**392**:1736–1788.
7. Libby P, Ridker PM, Hansson GK. Progress and challenges in translating the biology of atherosclerosis. *Nature* 2011;**473**:317–325.
8. Després J-P, Lemieux I, Bergeron J. Abdominal obesity and the metabolic syndrome: contribution to global cardiometabolic risk. *Arterioscler Thromb Vasc Biol* 2008;**28**:1039–1049.
9. Lavie CJ, Milani RV, Ventura HO. Obesity and cardiovascular disease: risk factor, paradox, and impact of weight loss. *J Am Coll Cardiol* 2009;**53**:1925–1932.
10. Romero-Corral A, Somers VK, Sierra-Johnson JK, Korenfeld Y, Boarin S, Korinek J, *et al.* Normal weight obesity: a risk factor for cardiometabolic dysregulation and cardiovascular mortality. *Eur Heart J* 2010;**31**:737–746.
11. Ades PA, Savage PD, Toth MJ. High-calorie-expenditure exercise: a new approach to cardiac rehabilitation for overweight coronary patients. *Circulation* 2009;**119**:2671–2678.
12. Look AHEAD Research Group, Wing RR, Bolin P, Brancati FL, Bray GA, Clark JM, *et al.* Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. *N Engl J Med* 2013;**369**:145–154.
13. Hotamisligil GS. Inflammation and metabolic disorders. *Nature* 2006;**444**:860–867.
14. Tilg H, Moschen AR. Adipocytokines: mediators linking adipose tissue, inflammation and immunity. *Nat Rev Immunol* 2006;**6**:772–783.
15. Lumeng CN, Saltiel AR. Inflammatory links between obesity and metabolic disease. *J Clin Invest* 2011;**121**:2111–2117.
16. Shi H, Kokoeva MV, Inouye K, Tzameli I, Yin H, Flier JS. TLR4 links innate immunity and fatty acid–induced insulin resistance. *J Clin Invest* 2006;**116**:3015–3025.
17. Hotamisligil GS. Endoplasmic reticulum stress and the inflammatory basis of metabolic disease. *Cell* 2010;**140**:900–917.
18. Qin J, Li Y, Cai Z, Li S, Zhu J, Zhang F, *et al.* A metagenome-wide association study of gut microbiota in type 2 diabetes. *Nature* 2012;**490**:55–60.
19. Deanfield JE, Halcox JP, Rabelink TJ. Endothelial function and dysfunction: testing and clinical relevance. *Circulation* 2007;**115**:1285–1295.
20. Masi D, Risi R, Biagi F, Vasquez Barahona D, Watanabe M, Zilich R, *et al.* Application of a machine learning technology in the definition of metabolically healthy and unhealthy Status: a retrospective study of 2567 subjects suffering from obesity with or without metabolic syndrome. *Nutrients* 2022;**14**:373.
21. Zheng R, Zhou D, Zhu Y. The long-term prognosis of cardiovascular disease and all-cause mortality for metabolically healthy obesity: a systematic review and meta-analysis. *J Epidemiol Community Health* 2016;**70**:1024–1031.
22. Bluher M. Metabolically healthy obesity. *Endocr Rev* 2020;**41**:bnaa004.
23. Fall T, Hagg S, Ploner A, Mägi R, Fischer K, Draisma HH, *et al.* Age-and sex-specific causal effects of adiposity on cardiovascular risk factors. *Diabetes* 2015;**64**:1841–1852.
24. Kusminski CM, Scherer PE. The road from discovery to clinic: adiponectin as a biomarker of metabolic status. *Clin Pharmacol Ther* 2009;**86**:592–595.
25. Ling C, Ronn T. Epigenetics in human obesity and type 2 diabetes. *Cell Metab* 2019;**29**:1028–1044.
26. Beavers KM, Hsu F-C, Li S, Kritchevsky SB, Church T, Goodpaster B, *et al.* Long-term physical activity and inflammatory biomarkers in older adults. *Med Sci Sports Exerc* 2010;**42**:2189–2196.
27. Estruch R, Ros E, Salas-Salvado J, Covas M-I, Corella D, Arós F, *et al.* Primary prevention of cardiovascular disease with a Mediterranean diet supplemented with extra-virgin olive oil or nuts. *N Engl J Med* 2018;**378**:e34.
28. Eckel N, Li Y, Kuxhaus O, Stefan N, Hu FB, Schulze MB. Transition from metabolic healthy to unhealthy phenotypes and association with cardiovascular disease risk across BMI categories in 90 257 women (the Nurses' Health Study): 30 year follow-up from a prospective cohort study. *Lancet Diabetes Endocrinol* 2018;**6**:714–724.
29. Magkos F. Metabolically healthy obesity: what's in a name? *Am J Clin Nutr* 2019;**110**:533–539.
30. Lingvay I, Brown-Frandsen K, Colhoun HM, Deanfield J, Emerson SS, Esbjerg S, *et al.* Semaglutide for cardiovascular event reduction in people with overweight or obesity: sELECT study baseline characteristics. *Obesity (Silver Spring)* 2023;**31**:111–122.
31. Gazzaruso C, Solerte SB, De Amici E, Mancini M, Pujia A, Fratino P, *et al.* Association of the metabolic syndrome and insulin resistance with silent myocardial ischemia in patients with type 2 diabetes mellitus. *Am J Cardiol* 2006;**97**:236–239.
32. Chiariello M, Indolfi C. Silent myocardial ischemia in patients with diabetes mellitus. *Circulation* 1996;**93**:2089–2091.
33. Poirier P, Giles TD, Bray GA, Hong Y, Stern JS, Pi-Sunyer FX, *et al.* Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss: an update of the 1997 American Heart Association Scientific Statement on Obesity and Heart Disease from the Obesity Committee of the Council on Nutrition, Physical Activity, and Metabolism. *Circulation* 2006;**113**:898–918.
34. Powell-Wiley TM, Poirier P, Burke LE, Després J-P, Gordon-Larsen P, Lavie CJ, *et al.* Obesity and cardiovascular disease: a scientific statement from the American Heart Association. *Circulation* 2021;**143**:e984–e1010.
35. Bucholz EM, Beckman AL, Krumholz HA, Krumholz HM. Excess weight and life expectancy after acute myocardial infarction: the obesity paradox reexamined. *Am Heart J* 2016;**172**:173–181.
36. Sierra-Johnson J, Romero-Corral A, Somers VK, Lopez-Jimenez F, Thomas RJ, Squires RW, *et al.* Prognostic importance of weight loss in patients with coronary heart disease regardless of initial body mass index. *Eur J Cardiovasc Prev Rehabil* 2008;**15**:336–340.
37. Pack QR, Rodriguez-Escudero JP, Thomas RJ, Ades PA, West CP, Somers VK, *et al.* The prognostic importance of weight loss in coronary artery disease: a systematic review and meta-analysis. *Mayo Clin Proc* 2014;**89**:1368–1377.
38. Srikanthan P, Horwich TB, Tseng CH. Relation of muscle mass and fat mass to cardiovascular disease mortality. *Am J Cardiol* 2016;**117**:1355–1360.
39. Obokata M, Reddy YNV, Pislaru SV, Melenovsky V, Borlaug BA. Evidence supporting the existence of a distinct obese phenotype of heart failure with preserved ejection fraction. *Circulation* 2017;**136**:6–19.
40. Kitzman DW, Lam CSP. Obese heart failure with preserved ejection fraction phenotype: from pariah to central player. *Circulation* 2017;**136**:20–23.
41. Lopez-Jimenez F, Almahmeed W, Bays H, Cuevas A, Di Angelantonio E, le Roux CW, *et al.* Obesity and cardiovascular disease: mechanistic insights and management strategies. A joint position paper by the World Heart Federation and World Obesity Federation. *Eur J Prev Cardiol* 2022;**29**:2218–2237.
42. Caruana L, Petrie MC, Davie AP, McMurray JJ. Do patients with suspected heart failure and preserved left ventricular systolic function suffer from "diastolic heart failure" or from misdiagnosis? A prospective descriptive study. *BMJ* 2000;**321**:215–218.
43. Song EK, Lee Y, Moser DK, Dekker RL, Kang S-M, Lennie TA. The link of unintentional weight loss to cardiac event-free survival in patients with heart failure. *J Cardiovasc Nurs* 2014;**29**:439–447.
44. Borlaug BA, Kitzman DW, Davies MJ, Rasmussen S, Barros E, Butler J, *et al.* Semaglutide in HFpEF across obesity class and by body weight reduction: a prespecified analysis of the STEP-HFpEF trial. *Nat Med* 2023;**29**:2358–2365.
45. Kveiborg B, Christiansen B, Major-Petersen A, Torp-Pedersen C. Metabolic effects of beta-adrenoceptor antagonists with special emphasis on carvedilol. *Am J Cardiovasc Drugs* 2006;**6**:209–217.
46. Sharma AM, Pischon T, Hardt S, Kunz I, Luft FC. Hypothesis: beta-adrenergic receptor blockers and weight gain: a systematic analysis. *Hypertension* 2001;**37**:250–254.
47. Gammone MA, Efthymakis K, D'Orazio N. Effect of third-generation beta blockers on weight loss in a population of overweight-obese subjects in a controlled dietary regimen. *J Nutr Metab* 2021;**2021**:5767306.
48. Bokura H, Yamaguchi S, Iijima K, Nagai A, Oguro H. Metabolic syndrome is associated with silent ischemic brain lesions. *Stroke* 2008;**39**:1607–1609.
49. Wang SY, Zha XJ, Zhu XY, Li W-B, Ma J, Wu Z-W, *et al.* Metabolic syndrome and its components with neuron-specific enolase: a cross-sectional study in large health check-up population in China. *BMJ Open* 2018;**8**:e020899.
50. Oesch L, Tatlisumak T, Arnold M, Sarikaya H. Obesity paradox in stroke—myth or reality? A systematic review. *PLoS One* 2017;**12**:e0171334.
51. Dehlendorff C, Andersen KK, Olsen TS. Body mass index and death by stroke: no obesity paradox. *JAMA Neurol* 2014;**71**:978–984.
52. Sheffler LR, Knutson JS, Gunzler D, Chae J. Relationship between body mass index and rehabilitation outcomes in chronic stroke. *Am J Phys Med Rehabil* 2012;**91**:951–956.
53. Kristensen SL, Rorth R, Jhund PS, Docherty KF, Sattar N, Preiss D, *et al.* Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *Lancet Diabetes Endocrinol* 2019;**7**:776–785.
54. Lempesis IG, Varrias D, Sagris M, Attaran RR, Altin ES, Bakoyiannis C, *et al.* Obesity and peripheral artery disease: current evidence and controversies. *Curr Obes Rep* 2023;**12**:264–279.

55. Lavie CJ, McAuley PA, Church TS, Milani RV, Blair SN. Obesity and cardiovascular diseases: implications regarding fitness, fatness, and severity in the obesity paradox. *J Am Coll Cardiol* 2014;**63**:1345–1354.
56. Palatini P, Asmar R, O'Brien E, Padwal R, Parati G, Sarkis J, *et al.* Recommendations for blood pressure measurement in large arms in research and clinical practice: position paper of the European society of hypertension working group on blood pressure monitoring and cardiovascular variability. *J Hypertens* 2020;**38**:1244–1250.
57. Piccirillo G, Vetta F, Viola E, Santagada E, Ronzoni S, Cacciafesta M, *et al.* Heart rate and blood pressure variability in obese normotensive subjects. *Int J Obes Relat Metab Disord* 1998;**22**:741–750.
58. Zhang X, Zhao Q. Association of thiazide-type diuretics with glycemic changes in hypertensive patients: a systematic review and meta-analysis of randomized controlled clinical trials. *J Clin Hypertens (Greenwich)* 2016;**18**:342–351.
59. Lee P, Kengne AP, Greenfield JR, Day RO, Chalmers J, Ho KKY. Metabolic sequelae of beta-blocker therapy: weighing in on the obesity epidemic? *Int J Obes (Lond)* 2011;**35**:1395–1403.
60. Liang L, Kung JY, Mitchelmore B, Cave A, Banh HL. Comparative peripheral edema for dihydropyridines calcium channel blockers treatment: a systematic review and network meta-analysis. *J Clin Hypertens (Greenwich)* 2022;**24**:536–554.
61. Masuo K, Mikami H, Ogihara T, Tuck ML. Weight reduction and pharmacologic treatment in obese hypertensives. *Am J Hypertens* 2001;**14**:530–538.
62. Schmieder RE, Philipp T, Gueregiaga J, Gorostidi M, Bush C, Keefe DL. Aliskiren-based therapy lowers blood pressure more effectively than hydrochlorothiazide-based therapy in obese patients with hypertension: sub-analysis of a 52-week, randomized, double-blind trial. *J Hypertens* 2009;**27**:1493–1501.
63. Hoenig MR. Implications of the obesity epidemic for lipid-lowering therapy: non-HDL cholesterol should replace LDL cholesterol as the primary therapeutic target. *Vasc Health Risk Manag* 2008;**4**:143–156.
64. Klop B, Elte JW, Cabezas MC. Dyslipidemia in obesity: mechanisms and potential targets. *Nutrients* 2013;**5**:1218–1240.
65. Hasan B, Nayfeh T, Alzuabi M, Wang Z, Kuchkuntla AR, Prokop LJ, *et al.* Weight loss and serum lipids in overweight and obese adults: a systematic review and meta-analysis. *J Clin Endocrinol Metab* 2020;**105**:dgaa673.
66. Grant B, Sandelson M, Agyemang-Prempeh B, Zalin A. Managing obesity in people with type 2 diabetes. *Clin Med (Lond)* 2021;**21**:e327–e231.
67. American Diabetes Association. Standards of care in diabetes-2023 abridged for primary care providers. *Clin Diabetes* 2022;**41**:4–31.
68. ElSayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, *et al.* 2. Classification and diagnosis of diabetes: standards of care in diabetes-2023. *Diabetes Care* 2023;**46**:S19–S40.
69. Lahiri SW. Management of type 2 diabetes in the setting of morbid obesity: how can weight gain be prevented or reversed? *Clin Diabetes* 2016;**34**:115–120.
70. Chaudhury A, Duvoor C, Reddy Dendi VS, Kraleti S, Chada A, Ravilla R, *et al.* Clinical review of antidiabetic drugs: implications for type 2 diabetes mellitus management. *Front Endocrinol (Lausanne)* 2017;**8**:6.
71. Ferhatbegovic L, Mrsic D, Macic-Dzankovic A. The benefits of GLP1 receptors in cardiovascular diseases. *Front Clin Diabetes Healthc* 2023;**4**:1293926.
72. Affinati AH, Esfandiari NH, Oral EA, Kraftson AT. Bariatric surgery in the treatment of type 2 diabetes. *Curr Diab Rep* 2019;**19**:156.
73. Jensen MD, Ryan DH, Apovian CM, Ard JD, Comuzzie AG, Donato KA, *et al.* 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. *Circulation* 2014;**129**:S102–S138.
74. Di Mauro A, Tuccinardi D, Watanabe M, Del Toro R, Monte L, Giorgino R, *et al.* The Mediterranean diet increases glucagon-like peptide 1 and oxyntomodulin compared with a vegetarian diet in patients with type 2 diabetes: a randomized controlled crossover trial. *Diabetes Metab Res Rev* 2021;**37**:e3406.
75. Tuccinardi D, Farr OM, Upadhyay J, Oussaada SM, Klapa MI, Candela M, *et al.* Mechanisms underlying the cardiometabolic protective effect of walnut consumption in obese people: a cross-over, randomized, double-blind, controlled inpatient physiology study. *Diabetes Obes Metab* 2019;**21**:2086–2095.
76. Laffond A, Rivera-Picon C, Rodriguez-Munoz PM, Juárez-Vela R, Ruiz de Viñaspre-Hernández R, Navas-Echazarreta N, *et al.* Mediterranean diet for primary and secondary prevention of cardiovascular disease and mortality: an updated systematic review. *Nutrients* 2023;**15**:3356.
77. Delgado-Lista J, Alcala-Diaz JF, Torres-Pena JD, Quintana-Navarro GM, Fuentes F, Garcia-Rios A, *et al.* Long-term secondary prevention of cardiovascular disease with a Mediterranean diet and a low-fat diet (CORDIOPREV): a randomised controlled trial. *Lancet* 2022;**399**:1876–1885.
78. Davies MJ, Aroda VR, Collins BS, Gabbay RA, Green J, Maruthur NM, *et al.* Management of hyperglycemia in type 2 diabetes, 2022. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* 2022;**45**:2753–2786.
79. Look AHEAD Research Group; Wadden TA, West DS, Delahanty L, Jakicic J, Rejeski J, *et al.* The Look AHEAD study: a description of the lifestyle intervention and the evidence supporting it. *Obesity (Silver Spring)* 2006;**14**:737–752.
80. Sacks FM, Svetkey LP, Vollmer WM, Appel LJ, Bray GA, Harsha D, *et al.* Effects on blood pressure of reduced dietary sodium and the dietary approaches to stop hypertension (DASH) diet. *N Engl J Med* 2001;**344**:3–10.
81. Watanabe M, Tuccinardi D, Ernesti I, Basciani S, Mariani S, Genco A, *et al.* Scientific evidence underlying contraindications to the ketogenic diet: an update. *Obes Rev* 2020;**21**:e13053.
82. Watanabe M, Tozzi R, Risi R, Tuccinardi D, Mariani S, Basciani S, *et al.* Beneficial effects of the ketogenic diet on nonalcoholic fatty liver disease: a comprehensive review of the literature. *Obes Rev* 2020;**21**:e13024.
83. Sumithran P, Prendergast LA, Delbridge E, Purcell K, Shulkes A, Kriketos A, *et al.* Ketosis and appetite-mediating nutrients and hormones after weight loss. *Eur J Clin Nutr* 2013;**67**:759–764.
84. Bueno NB, de Melo IS, de Oliveira SL, da Rocha Ataide T. Very-low-carbohydrate ketogenic diet v. low-fat diet for long-term weight loss: a meta-analysis of randomised controlled trials. *Br J Nutr* 2013;**110**:1178–1187.
85. Aronica L, Volek J, Poff A, D'Agostino D. Genetic variants for personalised management of very low carbohydrate ketogenic diets. *BMJ Nutr Prev Health* 2020;**3**:363–373.
86. Youm YH, Nguyen KY, Grant RW, Goldberg EL, Bodogai M, Kim D, *et al.* The ketone metabolite beta-hydroxybutyrate blocks NLRP3 inflammasome-mediated inflammatory disease. *Nat Med* 2015;**21**:263–269.
87. Bray GA, Fruhbeck G, Ryan DD, Wilding JPH. Management of obesity. *Lancet* 2016;**387**:1947–1956.
88. Jordan J, Astrup A, Engeli S, Narkiewicz K, Day WW, Finer N. Cardiovascular effects of phentermine and topiramate: a new drug combination for the treatment of obesity. *J Hypertens* 2014;**32**:1178–1188.
89. Sposito AC, Bonilha I, Luchiari B, Benchimol A, Hohl A, Moura F, *et al.* Cardiovascular safety of naltrexone and bupropion therapy: systematic review and meta-analyses. *Obes Rev* 2021;**22**:e13224.
90. Zavoral JH. Treatment with orlistat reduces cardiovascular risk in obese patients. *J Hypertens* 1998;**16**:2013–2017.
91. Torgerson JS, Hauptman J, Boldrin MN, Sjostrom L. XENical in the prevention of diabetes in obese subjects (XENDOS) study: a randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients. *Diabetes Care* 2004;**27**:155–161.
92. Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JFE, Nauck MA, *et al.* Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2016;**375**:311–322.
93. Pi-Sunyer X, Astrup A, Fujioka K, Greenway F, Halpern A, Krempf M, *et al.* A randomized, controlled trial of 3.0 mg of liraglutide in weight management. *N Engl J Med* 2015;**373**:11–22.
94. Rizzo M, Nikolic D, Patti AM, Mannina C, Montalto G, McAdams BS, *et al.* GLP-1 receptor agonists and reduction of cardiometabolic risk: potential underlying mechanisms. *Biochim Biophys Acta Mol Basis Dis* 2018;**1864**:2814–2821.
95. Nusca A, Tuccinardi D, Pieralice S, Giannone S, Carpenito M, Monte L, *et al.* Platelet effects of anti-diabetic therapies: new perspectives in the management of patients with diabetes and cardiovascular disease. *Front Pharmacol* 2021;**12**:670155.
96. Husain M, Birkenfeld AL, Donsmark M, Eliaschewitz FG, Franco DR, Jeppesen OK, *et al.* Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2019;**381**:841–851.
97. Knop FK, Aroda VR, do Vale RD, Holst-Hansen T, Laursen PN, Rosenstock J, *et al.* Oral semaglutide 50 mg taken once per day in adults with overweight or obesity (OASIS 1): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2023;**402**:705–719.
98. Lincoff AM, Brown-Frandsen K, Colhoun HM, Deanfield J, Emerson SS, Esbjerg S, *et al.* Semaglutide and cardiovascular outcomes in obesity without diabetes. *N Engl J Med* 2023;**389** 2221–2232.
99. Frias JP, Deenadayalan S, Erichsen L, Knop FK, Lingvay I, Macura S, *et al.* Efficacy and safety of co-administered once-weekly cagrilintide 2.4 mg with once-weekly semaglutide 2.4 mg in type 2 diabetes: a multicentre, randomised, double-blind, active-controlled, phase 2 trial. *Lancet* 2023;**402**:720–730.
100. Jastreboff AM, Aronne LJ, Ahmad NN, Wharton S, Connery L, Alves B, *et al.* Tirzepatide once weekly for the treatment of obesity. *N Engl J Med* 2022;**387**:205–216.

101. Rosenstock J, Wysham C, Frias JP, Kaneko S, Lee CJ, Fernández Landó L, *et al.* Efficacy and safety of a novel dual GIP and GLP-1 receptor agonist tirzepatide in patients with type 2 diabetes (SURPASS-1): a double-blind, randomised, phase 3 trial. *Lancet* 2021; **398**:143–155.
102. Wharton S, Blevins T, Connery L, Rosenstock J, Raha S, Liu R, *et al.* Daily oral GLP-1 receptor agonist orforglipron for adults with obesity. *N Engl J Med* 2023;**389**:877–888.
103. Frias JP, Hsia S, Eyde S, Liu R, Ma X, Konig M, *et al.* Efficacy and safety of oral orforglipron in patients with type 2 diabetes: a multicentre, randomised, dose-response, phase 2 study. *Lancet* 2023;**402**:472–483.
104. Jastreboff AM, Kaplan LM, Frias JP, Wu Q, Du Y, Gurbuz S, *et al.* Triple-hormone-receptor agonist retatrutide for obesity—a phase 2 trial. *N Engl J Med* 2023;**389**:514–526.
105. Rosenstock J, Frias J, Jastreboff AM, Du Y, Lou J, Gurbuz S, *et al.* Retatrutide, a GIP, GLP-1 and glucagon receptor agonist, for people with type 2 diabetes: a randomised, double-blind, placebo and active-controlled, parallel-group, phase 2 trial conducted in the USA. *Lancet* 2023;**402**:529–544.
106. Mechanick JI, Youdim A, Jones DB, Garvey WT, Hurley DL, McMahon MM, *et al.* Clinical practice guidelines for the perioperative nutritional, metabolic, and nonsurgical support of the bariatric surgery patient–2013 update: cosponsored by American association of clinical endocrinologists, the obesity society, and American society for metabolic & bariatric surgery. *Endocr Pract* 2013;**19**:337–372.
107. Sjostrom L, Peltonen M, Jacobson P, Sjöström CD, Karason K, Wedel H, *et al.* Bariatric surgery and long-term cardiovascular events. *JAMA* 2012;**307**:56–65.
108. Poirier P, Cornier MA, Mazzone T, Stiles S, Cummings S, Klein S, *et al.* Bariatric surgery and cardiovascular risk factors: a scientific statement from the American heart association. *Circulation* 2011;**123**:1683–1701.
109. Schauer PR, Bhatt DL, Kirwan JP, Wolski K, Aminian A, Brethauer SA, *et al.* Bariatric surgery versus intensive medical therapy for diabetes—5-year outcomes. *N Engl J Med* 2017;**376**:641–651.
110. Mingrone G, Panunzi S, De Gaetano A, Guidone C, Iaconelli A, Nanni G, *et al.* Bariatric-metabolic surgery versus conventional medical treatment in obese patients with type 2 diabetes: 5 year follow-up of an open-label, single-centre, randomised controlled trial. *Lancet* 2015;**386**:964–973.
111. Adams TD, Davidson LE, Litwin SE, Kolotkin RL, LaMonte MJ, Pendleton RC, *et al.* Health benefits of gastric bypass surgery after 6 years. *JAMA* 2012;**308**:1122–1131.
112. van Veldhuisen SL, Gorter TM, van Woerden G, de Boer RA, Rienstra M, Hazebroek EJ, *et al.* Bariatric surgery and cardiovascular disease: a systematic review and meta-analysis. *Eur Heart J* 2022;**43**:1955–1969.