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Cardiovascular outcome trials in obesity: A review

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Summary

Obesity is a global epidemic associated with over 200 health complications and a significant risk of developing cardiovascular disease (CVD), partly by increasing classical risk factors such as lipid and glucose levels and blood pressure. Weight loss through lifestyle interventions, pharmacotherapy and/or bariatric surgery improves CV risk factors. Cardiovascular outcome trials (CVOTs) of anti-obesity medications aim to evaluate the CV safety and benefits of pharmacotherapy. Many CVOTs in obesity have either failed to demonstrate a CV benefit or have been terminated prematurely because of safety issues, prompting regulatory agencies to define new requirements (based on those for CVOTs in type 2 diabetes [T2D]). CVOTs of glucagon-like peptide-1 receptor agonists (GLP-1RAs) in T2D have demonstrated that some GLP-1RAs reduce CV risk and may help inform future CVOTs in obesity, given the approval of liraglutide 3.0 mg for obesity. In this review, the evidence for the link between obesity and CVD is considered in the context of studies showing that weight loss improves markers of CV risk and risk of adverse CV events. The review also examines the CVOTs in obesity that have been conducted to date and those under way, such as the SELECT trial with subcutaneous semaglutide of 2.4 mg.

KEYWORDS

anti-obesity medications, cardiovascular, obesity, outcome trial

Abbreviations: AOM, anti-obesity medication; AQCLAIM, A Qsymia™ CardiovascuLAr morbIdity and Mortality; BMI, body mass index; BP, blood pressure; CAD, coronary artery disease; CAMELLIA-TIMI 61, Cardiovascular and Metabolic Effects of Lorcaserin in Overweight and Obese Patients—Thrombolysis in Myocardial Infarction 61; CANVAS, CANagliflozin cardioVascular Assessment Study; CAROLINA, Cardiovascular Outcome Study of Linagliptin vs Glimepiride in Type 2 Diabetes; CHD, coronary heart disease; CHF, congestive heart failure; CI, confidence interval; CRESCENDO, Comprehensive Rimonabant Evaluation Study of Cardiovascular Endpoints and Outcomes; CV, cardiovascular; CVD, cardiovascular disease; CVOT, cardiovascular outcome trial; DBP, diastolic blood pressure; DECLARE-TIMI 58, Dapagliflozin Effect on CardiovascuLAR Events—Thrombolysis In Myocardial Infarction 58; ELIXA, Evaluation of LIXisenatide in Acute coronary syndrome; EMA, European Medicines Agency; EPIC-CVD, European Prospective Investigation into Cancer—Cardiovascular Disease; EXAMINE, Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care; EXSCEL, Exenatide Study of Cardiovascular Event Lowering; FDA, Food and Drug Administration; fen-phen, fenfluramine–phentermine; FPG, fasting plasma glucose; GLP-1RA, glucagon-like peptide-1 receptor agonist; HDL-C, high-density lipoprotein cholesterol; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HR, hazard ratio; hsCRP, high-sensitivity C-reactive protein; ILI, intensive lifestyle intervention; LEADER, Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; Look AHEAD, Look Action for Health in Diabetes; MACE, major adverse cardiovascular events; MI, myocardial infarction; OCM, obesity cardiomyopathy; PIONEER, Peptide Innovation for Early Diabetes Treatment; REWIND, researching cardiovascular events with a weekly incretin in diabetes; RIO, Rimonabant In Obesity; SAVOR-TIMI 53, Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus—Thrombolysis in Myocardial Infarction 53; SBP, systolic blood pressure; SCALE, Satiety and Clinical Adiposity—Liraglutide Evidence in Nondiabetic and Diabetic Individuals; SCOUT, Sibutramine Cardiovascular Outcomes Trial; SELECT, Semaglutide Effects on Heart Disease and Stroke in Patients With Overweight or Obesity; SOS, Swedish Obese Subjects; STAMPEDE, Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy; T2D, type 2 diabetes; TECOS, Trial Evaluating Cardiovascular Outcomes with Sitagliptin; WAT, white adipose tissue; XENDOS, XENical in the Prevention of Diabetes in Obese Subjects.

1 | INTRODUCTION

Globally, approximately 650 million people are living with obesity[1]; the global economic cost of obesity is ~1.8 trillion Euros, equivalent to 2.8% of gross domestic product.[2] Excess adipose tissue may lead to increased adipokine synthesis, lipid production, activation of the sympathetic nervous and renin–angiotensin–aldosterone systems and to a low-grade systemic inflammatory state.[3] Hence, obesity is associated with over 200 complications,[4] a number of which are risk factors for cardiovascular disease (CVD).

This article reviews the association between obesity and risk for CVD, explores the effect of weight loss on CVD risk and overviews cardiovascular outcome trials (CVOTs), to date, in people with obesity.

2 | ANTHROPOMETRIC INDICATORS OF OBESITY AND CV RISK

Obesity is an established risk factor for atherosclerosis, ischaemic heart disease, congestive heart failure and stroke.[4] In a pooled analysis of three prospective cohort studies (Nurses' Health Study I and II and the Health Professionals Follow-up Study) that included 225 072 people, those who were classified as having overweight (body mass index [BMI] 25.0–29.9 kg m^{-2}), obesity Class I (BMI 30.0–34.9 kg m^{-2}) or obesity Class II (BMI > 35.0 kg m^{-2}) had increased risk of CV death than had people with healthy weight (BMI 18.5–24.9 kg m^{-2}), with hazard ratio (HR) [95% confidence interval, CI]: 1.2 [1.15, 1.28], 1.6 [1.52, 1.74] and 2.7 [2.53, 2.97], respectively.[5] The Cardiovascular Disease Lifetime Risk Pooling Project reported that middle-aged men with obesity (BMI 30.0–39.9 kg m^{-2}) or severe obesity (BMI > 40.0 kg m^{-2}) had shorter overall survival time (27.2 and 23.4 years) than had those with healthy weight (BMI 18.5–24.9 kg m^{-2}; 29.1 years); those with severe obesity had greater risk for CV mortality than those with obesity or overweight (HR [95% CI]: 2.32 [1.69, 3.18] vs. 1.41 [1.28, 1.55] or 1.10 [1.02, 1.19]).[6]

The pan-European EPIC-CVD (European Prospective Investigation into Cancer and Nutrition—Cardiovascular Disease) study demonstrated that people with overweight (BMI ≥ 25 to <30 kg m^{-2}) or obesity (BMI ≥ 30 kg m^{-2}) had a higher risk of coronary heart disease (CHD) than those with healthy weight (BMI ≥ 18.5 to <25 kg m^{-2}) (HR [95% CI]: 1.26 [1.17, 1.36] and 1.28 [1.05, 1.56], respectively), even in the absence of metabolic syndrome, suggesting that obesity is an independent risk factor for CHD.[7] A meta-analysis of Mendelian randomization studies suggested that each standard deviation unit increase in BMI is associated with a 20% increased risk of coronary artery disease (CAD), independently of other risk factors.[8]

The INTERHEART study reported that abdominal obesity (waist/hip ratio > 0.90 in men and >0.83 in women) is also an important predictor of adverse CV outcomes and is only modestly correlated to BMI.[9] Abdominal obesity was significantly related to acute myocardial infarction (MI; HR [99% CI]: 1.62 [1.45, 1.80] for the top vs. lowest tertile and 1.12 [1.01, 1.25] for the middle vs. lowest tertile; population attributable risk 20.1% for the top two tertiles vs. lowest tertile).[9] Waist circumference was shown to correlate with direct measurement of visceral adiposity[10] and is also an independent risk factor for CHD.[7]

It should be noted that the above-mentioned studies included US and European populations and risks may be different for other populations, including Asian populations who have been observed to have greater health risks at lower BMI than have Western populations.[11]

3 | THE PATHOPHYSIOLOGY OF OBESITY AND CVD

Both abdominal (visceral) fat and insulin resistance may contribute to CVD in obesity. Visceral fat is predominantly white adipose tissue (WAT). WAT has a prominent role in energy homeostasis; it is a reservoir for energy storage, senses energy demands and secretes endocrine factors such as leptin to regulate appetite.[12] In obesity, prolonged positive energy balance increases both the size and number of adipocytes. In addition, obesity can cause WAT to become severely dysfunctional; unhealthy expansion of WAT is associated with local hypoxia, altered adipokine secretion and mitochondrial dysfunction, which can lead to inflammation and fibrosis within adipose tissue.[13] Eventually, adipose tissue expansion becomes impossible owing to cell and tissue expansion limitations, and this induces ectopic fat deposition in the muscle, liver and pancreas. This is known as lipotoxicity and is associated with insulin resistance in the muscle and liver, together with beta-cell dysfunction, increasing the risk for type 2 diabetes (T2D). The resultant systemic chronic inflammatory state then results in endothelial dysfunction mediated through adipokines. Fat accumulation, insulin resistance, inflammation and dyslipidaemia may, therefore, all contribute to the development of atherosclerosis and CVD.[14]

As adipose tissue accumulates, numerous alterations in cardiac structure occur in individuals with obesity, even in the absence of comorbidities.[15] In obesity, circulating blood and plasma volume and cardiac output increase to meet increased metabolic needs. This then increases venous return to the ventricles, producing dilation of these cavities and increasing wall tension.[15] This, together with increased blood pressure (BP), results in left ventricular (LV) hypertrophy, which may be followed by systolic dysfunction. Diastolic dysfunction is also common in obesity and may lead to heart failure with preserved ejection fraction.[15] These functional, morphological and metabolic abnormalities related to the heart that are caused by obesity can result in obesity cardiomyopathy (OCM). OCM is caused by changes to the structure and function of the heart in the absence of other cardiac risk factors, such as coronary artery disease, hypertension and significant valvular disease. The American Heart Association classifies OCM as a subtype of dilated cardiomyopathy, characterized by alterations in ventricular morphology and function including LV dilatation, eccentric or concentric LV hypertrophy, LV systolic and diastolic dysfunction and right ventricular dysfunction, occurring in the setting of morbid obesity (BMI ≥ 35 kg m^{-2}).[16] OCM is associated with increased risk

for heart failure.[16] Obese heart failure with preserved ejection fraction is a distinct subtype of heart failure related to OCM.[17] A study of cardiac structure and LV function in 74 normotensive people with BMI ≥ 35 kg m^{-2} (i.e. people with OCM) with or without heart failure identified five factors that increase the risk of developing heart failure: the duration of morbid obesity, LV internal dimension in diastole, LV end-systolic wall stress, left atrial dimension and right ventricular internal dimension.[16] Therefore, systemic and pulmonary hypertension, CHD and heart failure all occur with disproportionately high frequency in obesity, increasing the risk of sudden cardiac death.[15]

4 | EFFECTS OF WEIGHT LOSS ON CVD RISK FACTORS AND OUTCOMES

Excess adiposity leads to major classical risk factors and common chronic diseases such as hypertension, dyslipidaemia, T2D, CHD and chronic kidney disease (Figure 1).[3] Excess adiposity is also an important source of cytokines and contributes to the proinflammatory milieu present in people with obesity.[18] Hence, it is hypothesized that weight reduction and the subsequent reduction in proinflammatory markers and inflammation may lead to improvements in CVD risk factors (soft endpoints), which in turn may lead to better CV outcomes (hard endpoints).

4.1 | Intentional weight loss

Observational studies have suggested that weight loss is associated with improvements in CVD risk factors and adverse CV events.[19,20] A prospective observational study that followed up people with overweight (BMI ≥ 27 kg m^{-2}) and T2D for 12 years reported a 25% reduction in total mortality with intentional weight loss.[19] In contrast, a meta-analysis of 26 studies demonstrated that intentional weight loss in people with overweight (BMI ≥ 25 to <30 kg m^{-2}) had a neutral effect on all-cause mortality (relative risk 1.01).[20]

4.2 | Lifestyle interventions

The Look Action for Health in Diabetes (Look AHEAD) trial, which studied the effects of intensive lifestyle intervention (ILI) over 10 years in people with overweight (BMI > 25 kg m^{-2}) or obesity (BMI > 27 kg m^{-2}) and T2D, observed no significant reductions in the incidence of CVD in the total population (p for trend = 0.17); however, a post hoc analysis suggested an association between the magnitude of weight loss and incidence of CVD[21] (Table 1). Furthermore, ILI resulted in reduced medication usage for diabetes, hypertension and dyslipidaemia at 1 year.[22] The Chinese Da Qing study assessing the long-term effects of a 6-year trial of lifestyle intervention (diet ± exercises) in people with impaired glucose tolerance and mean BMI of 25.7 kg m^{-2} (weight loss encouraged only in those with BMI > 25 kg m^{-2}) showed that after 30 years of follow-up, people who received the lifestyle intervention had delay in diabetes onset, reduced incidence of CVD events and deaths and increased life expectancy versus people in the control group[23] (Table 1).

4.3 | Bariatric surgery

Bariatric surgery is an effective strategy for weight reduction for people with severe obesity (BMI ≥ 35.0 kg m^{-2}), and long-term studies demonstrate that it is associated with improvements in several CVD risk factors.[26] A retrospective observational study of 1330 people with no history of CVD undergoing bariatric surgery between 2010 and 2016 suggested that those with severe obesity and high risk of CVD benefit more from the procedure than those with obesity and low CV risk.[27]

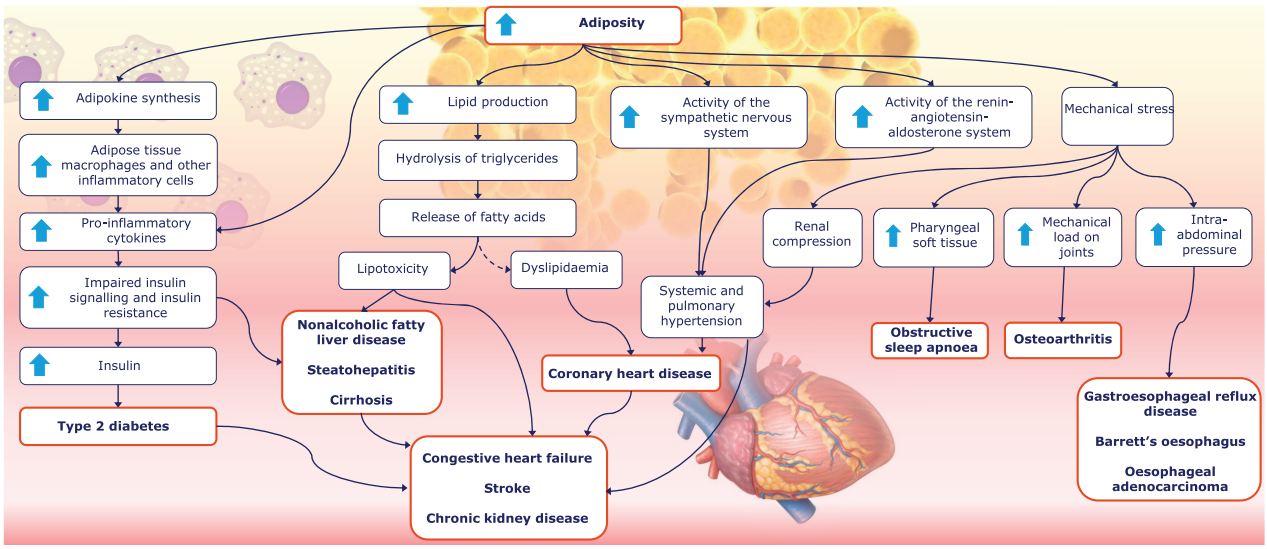

FIGURE 1 Association of excess adiposity with major risk factors and chronic conditions.[3] Common chronic diseases are shown in red boxes. The dashed arrow denotes an indirect association

TABLE 1 Obesity trials with positive outcomes

Obesity trials	Results
Look AHEAD post hoc analysis[21]	People who achieved ≥10% weight loss compared with those who did not achieve ≥10% weight loss had: • a significant 21% reduction (95% CI [0.64, 0.98]) in the risk of CVD • a significant 24% risk reduction (95% CI [0.63, 0.91]) for the first occurrence of nonfatal acute MI or stroke, hospitalization for angina or CHF, or CV death plus coronary artery bypass grafting, carotid endarterectomy, percutaneous coronary intervention, peripheral vascular disease or total mortality
Chinese Da Qing study[23]	Lifestyle intervention (diet and/or exercise) compared with control resulted in: • median delay in diabetes onset: 3.96 years (95% CI [1.25, 6.67]) • fewer CVD events (hazard ratio 0.74, 95% CI [0.59, 0.92]) • lower incidence of microvascular complications (0.65, 95% CI [0.45, 0.95], $p = 0.025$) • fewer CVD deaths (0.67, 95% CI [0.48, 0.94], $p = 0.022$) • fewer all-cause deaths (0.74, 95% CI [0.61, 0.89], $p = 0.0015$) • average increase in life expectancy of 1.44 years (95% CI [0.20, 2.68], $p = 0.023$) • BMI reduction of -1.1 kg m^{-2}
SCOUT trial[24]	Cardiovascular mortality for responders (who lost weight): • hazard ratio (per 1 kg weight loss): 0.93 95% CI [0.89, 0.97], $p = 0.001$
SOS trial[25]	Bariatric surgery vs. no surgery was associated with: • reduced number of CV deaths (28 events in 2010 participants in surgery group vs. 49 events in 2037 participants in control group; adjusted HR 0.47, 95% CI [0.29, 0.76], $p = 0.002$) • lower number of CV events (199 in 2010 vs. 234 in 2037; adjusted HR 0.67, 95% CI [0.54, 0.83], $p < 0.001$)

Abbreviations: CHF, congestive heart failure; CI, confidence interval; CV, cardiovascular; CVD, cardiovascular disease; MI, myocardial infarction.

Two- and 10-year follow-up data from the Swedish Obese Subjects (SOS) study demonstrated that bariatric surgery leads to T2D remission, as well as improvements in hypertension and hypertriglyceridaemia in some cases (at 10 years, 36%, 19% and 46% of people who had surgery achieved remission from these conditions vs. 13%, 11% and 24% who did not have surgery, respectively).[28] A 5-year follow-up of the randomized controlled STAMPEDE study involving 150 people with T2D and BMI of 27–43 kg m^{-2} demonstrated that $HbA_{1c} \leq 6.0\%$ was achieved by 2/38 (5%) people who received medical therapy alone versus 14/49 (29%) who underwent gastric bypass and 11/47 (23%) of those who had sleeve gastrectomy.[29] In the SOS study, after a median follow-up of 14.7 years, bariatric surgery was associated with lower incidence of CV death ($p = 0.002$) and MI or stroke ($p < 0.001$) versus no surgery (Table 1).[25] A meta-analysis of randomized controlled trials with a 2-year follow-up demonstrated that bariatric surgery, versus no surgery, led to a higher rate of T2D remission.[30] A retrospective cohort study, which included a mean follow-up of 7.1 years, demonstrated that bariatric surgery, compared with no surgery, was associated with mortality risk reductions of 56% and 92%, in people with CAD and T2D, respectively.[31]

Of note, a major limitation of the trials on bariatric surgery is that a majority of them are not randomized controlled studies.

4.4 | Effects of anti-obesity medications on CVD risk factors

Given as an adjunct to lifestyle intervention, use of anti-obesity medications (AOMs) improves CVD risk factors. The four large-scale, Phase 3 RIO (Rimonabant In Obesity) trials[32] showed that rimonabant (20 mg; now withdrawn) improved glycaemic control, lipid profile and high-sensitivity C-reactive protein (hsCRP) levels and also reduced the prevalence of metabolic syndrome. Covariate analyses of the RIO-Lipids trial suggested that only 60% of the increase in high-density lipoprotein cholesterol (HDL-C) and 45% of the reduction in triglycerides could be explained by the observed weight loss.[33] Sibutramine (20 mg; now withdrawn) also improved HbA_{1c}, HDL-C and triglycerides in a placebo-controlled double-blind trial.[34] In the XENDOS trial, orlistat 120 mg, compared with placebo, improved waist circumference, systolic and diastolic BP (SBP/DBP), fasting plasma glucose (FPG) and lipids and improved glucose tolerance, over 4 years.[35]

The COR-I trial of naltrexone–bupropion 32 mg/360 mg observed improvements in FPG, fasting insulin and insulin resistance versus placebo after 56 weeks.[36] The SCALE Obesity and Prediabetes study of liraglutide of 3.0 mg, compared with placebo, demonstrated improvements in HbA_{1c}, FPG, SBP/DBP, fasting lipids, hsCRP, plasminogen activator inhibitor-1 and adiponectin after 56 weeks.[37] At 160 weeks, more people in the liraglutide of 3.0 mg group versus placebo had regressed from prediabetes to normoglycaemia (66% vs. 36%, respectively).[38]

In 1997, fenfluramine–phentermine (fen-phen) was withdrawn from the market by its manufacturer because of reports linking its use with valvular regurgitation.[39] A Mayo Clinic case series showed significant valvular heart disease in 24 women who had taken fen-phen for ≥6 months.[40] A subsequent report revealed that 113/132 (86%) people who had taken fen-phen for 6 to 24 months had aortic and/or mitral regurgitation.[41] Dexfenfluramine, the active isomer of fenfluramine, was also withdrawn from the global market following reports of pulmonary arterial hypertension in addition to valvular regurgitation.[41] These reports have a clear geographic distribution in that they were all reported in the United States. This may be because in Europe, dexfenfluramine and fenfluramine were only approved for use for ≤12 weeks, and hence, cardiac valvulopathy was not a safety issue.[42]

The use of dexfenfluramine or fenfluramine together with another AOM such as phentermine ('phen') was contraindicated in Europe, and off-label use in this way was rare; hence, the fen-phen issue was also not reported.[42]

The regulatory standards required for licensing of an anti-obesity drug are much stricter than for other drugs. The safety criteria are particularly stringent because of the poor track record of AOMs approved so far. Anti-obesity drugs are constantly monitored for any potential safety issues that would necessitate drug withdrawals.[42,43]

5 | CARDIOVASCULAR OUTCOME TRIALS IN PEOPLE WITH OBESITY

In 2010, sibutramine was withdrawn from the market by its manufacturer following clinical trial data suggesting an increased risk for stroke and MI with its use.[44] The Sibutramine Cardiovascular Outcomes Trial (SCOUT) in 9804 people with overweight (BMI 25.0–26.9 kg m^{-2}) or obesity (BMI 27.0–45.0 kg m^{-2}) demonstrated an increased risk of nonfatal MI and nonfatal stroke in those with pre-existing CVD receiving sibutramine of 10–15 mg daily.[45] The SCOUT trial had no stopping criteria, with nonresponders (i.e. those who did not lose weight) continuing therapy.[45] In a post hoc analysis, which only analysed responders, weight loss with sibutramine was associated with a reduction in CV mortality for a 4- to 5-year period following trial completion (including people with established CVD; Table 1).[24]

After rimonabant (20 mg) was granted marketing authorization in the European Union (EU) in 2006, its effect on CV outcomes was evaluated in the Comprehensive Rimonabant Evaluation Study of Cardiovascular Endpoints and Outcomes (CRESCENDO) CVOT. The trial was discontinued prematurely because of serious adverse event concerns raised by regulatory authorities.[46] The marketing of rimonabant was suspended, and the drug subsequently withdrawn from use in the EU in 2009.[47] A meta-analysis of all published clinical trial data suggests that although rimonabant of 20 mg day^{-1} was associated with a 4.7-kg greater weight reduction after 1 year versus placebo, it increased the risk of depressed mood disorders and anxiety.[48]

The findings from these early trials and clinical experience with AOMs contributed to increased demand for robust and long-term CV and safety outcome investigations.

5.1 | Regulatory requirements for obesity CVOTs from 2012 onwards

In 2012, the Food and Drug Administration (FDA) set out new requirements for CVOTs in obesity,[49] based on similar guidance for CVOTs in T2D.[50] A requirement for approval is that the upper bound of the 95% CI for the estimated risk of major adverse cardiovascular events (MACE) compared with placebo should be less than 1.3. Strategies to ensuring that CVOTs include a sufficient number of events for detection of differences in MACE are as follows: pooling safety databases across Phase 2 and 3 clinical trials and performing a meta-analysis of all CV events with prospective adjudication by an independent, blinded committee and careful enrolment of people at high CVD risk.[49] In 2015, the European Medicines Agency (EMA) provided similar recommendations for evaluating CV safety of new medicinal products for the long-term treatment of certain CV and metabolic diseases (Figure 2).[51]

5.2 | Challenges and requirements for the design of obesity CVOTs

Some of the trial design challenges and requirements set out by the Department of Health and Human Services (DHHS) are outlined below.[52]

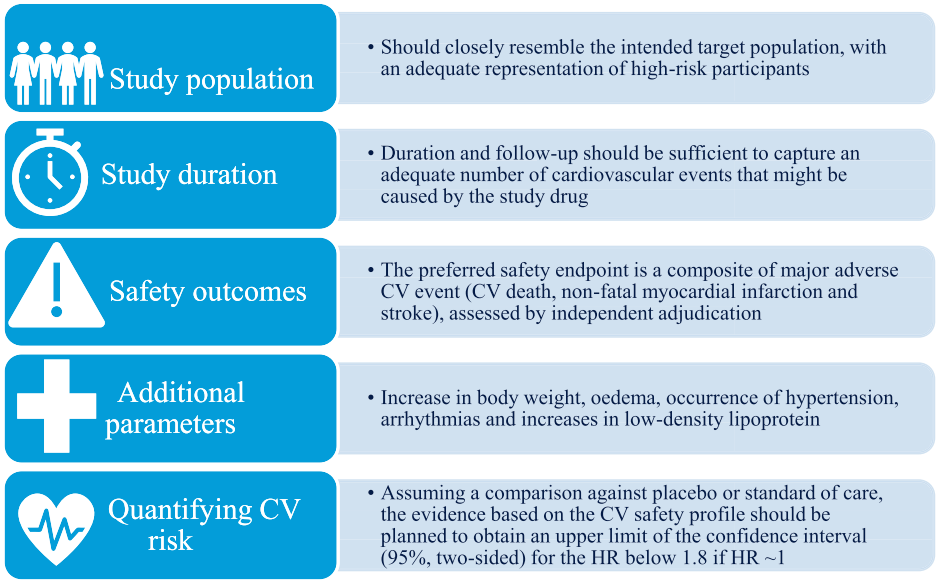

FIGURE 2 EMA recommendations for CV safety evaluation of new medicinal products.[51] CV, cardiovascular; HR, hazard ratio

5.2.1 | Superiority versus noninferiority trial

The primary objective of the trial should be to show CV benefit (superiority to placebo) or to rule out an unacceptable increase in CV risk (noninferiority to placebo). A larger sample size will be required to demonstrate superiority than to show noninferiority. The DHHS document contains a table with estimated sample sizes for both number of primary CV events and patient-years needed to observe the events. To show noninferiority, one needs to consider the degree of unacceptable CV risk that should be ruled out. The table in the DHHS document also provides the excess CV risk, as measured by the risk difference, that can be ruled out.

5.2.2 | Primary endpoint

Three-point MACE (CV death, nonfatal MI and nonfatal stroke) should be the primary endpoint for the trials designed to show the CV benefit of the drugs. Trials sometimes include other endpoints such as hospitalization for unstable angina, heart failure and/or arterial or coronary revascularizations. These are more subjective endpoints and are challenging to define. The variability of these softer endpoints can bias the trial results towards the null, which is particularly concerning for noninferiority trials.

5.2.3 | Baseline characteristics of patient population

An event-driven CVOT would require large number of subjects and/or long treatment duration to reach the required number of MACE events. Hence, the trial needs to be enriched with subjects with high risk for MACE to capture more events while subjects are taking the drug. Although this may reduce or limit generalizability of the results, it will allow acceptable CV safety to be demonstrated in a high-risk population.

5.2.4 | Timing of interim analyses

The weight-loss efficacy of an obesity drug is usually the greatest at 6–9 months after initiation of the drug and often diminishes thereafter. This means that the CV efficacy/safety profile of the drug may change over time during the course of the trial. Although an interim analysis may be statistically valid, the timing of such analysis needs to be determined carefully as the results may provide the basis for regulatory approval of the drug.

5.2.5 | Primary analysis population

While analysing the primary results of a CVOT, it is important to identify the appropriate patient population, particularly because of the high dropout rates seen in trials of obesity drugs. Although an intention-to-treat population is considered the most appropriate for primary efficacy analysis, an on-treatment population may provide more information regarding the true CV efficacy/safety of the drug.

5.2.6 | Global representation within the trial population

A trial should be designed in such a way that the data produced can be applied to different populations around the world.

5.3 | CVOTs in obesity since 2012

Several CVOTs in people with overweight/obesity have been initiated since the new requirements were introduced (Figure 3). The Light study, which evaluated naltrexone–bupropion 32 mg/360 mg, was unblinded early and prematurely terminated because data from an interim 25% analysis showing a 41% reduction in MACE were accidentally 'leaked'.[53] Results from the completed, preplanned 50% interim analysis were less favourable than the earlier data cut-off and did not establish noninferiority for MACE (HR [95% CI]: 0.88 [0.57, 1.34]).[53] The AQCLAIM trial evaluating phentermine–topiramate extended release was authorized by the EMA in 2013, but the trial will probably not proceed.[54] Discussions between the manufacturer and the regulators are ongoing about a potential retrospective observational study rather than a CVOT.[54]

One of the major issues with obesity CVOTs and trials of obesity drugs in general is the high treatment discontinuation rates. This may be due to the fact that participants entering the trials are looking for a 'quick fix', and if they do not experience rapid weight loss they may drop out of the trial. One study looking into ways of maximizing participant retention in long-term, Phase 3 clinical trials of weight loss agents concluded that use of a dietitian screening interview to identify participants at high risk of dropout and monthly support conference calls to discuss strategies to enhance adherence resulted in better participant retention rates.[57]

The only completed CVOT to date is the CAMELLIA-TIMI-61 study, which confirmed CV safety but no CV benefit for lorcaserin.[55] Of note, the FDA requested the withdrawal of lorcaserin from the market in January 2020 owing to concerns over cancer risk from the same trial.[58]

Another issue is that BMI is not a perfect reflection of adiposity as it does not differentiate between adipose tissue and muscle mass. Although BMI is widely accepted to define overweight and obesity, it is not applicable globally with lower BMI associated with health issues in South Asians compared with Western populations. The use of an alternative measure of adiposity (e.g. waist/hip ratio or body volume index) in obesity CVOTs may, therefore, make their outcomes more widely applicable. Of note, in the obesity CVOTs conducted to date, more than 85% of the trial populations are White.[53,55]

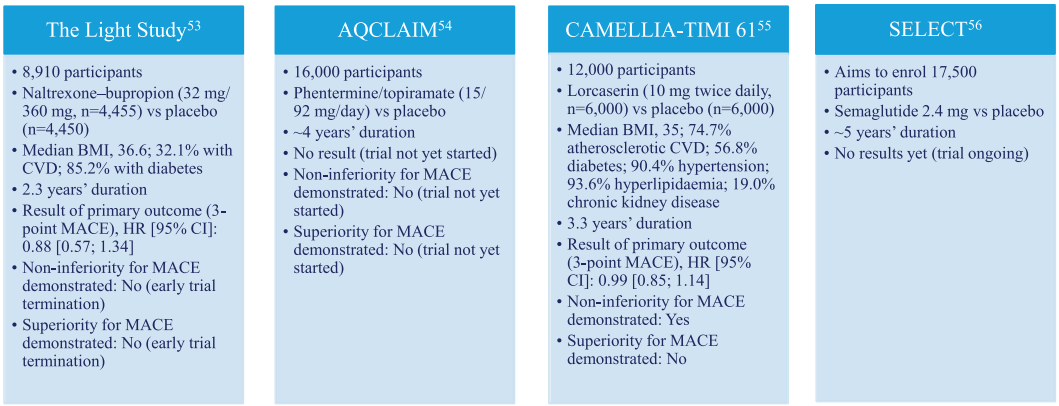

FIGURE 3 Overview of CVOTs in obesity since 2012. BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; MACE, major adverse cardiovascular event

Once-weekly semaglutide 2.4 mg (approved for the treatment of T2D at 0.5 and 1.0 mg)[59] is currently under investigation for the treatment of obesity in the Semaglutide Effects on Heart Disease and Stroke in Patients With Overweight or Obesity (SELECT) CVOT.[56] This trial aims to enrol 17 500 people with obesity and pre-existing CVD and differs notably from previous CVOTs in obesity (Figure 4).

6 | CARDIOVASCULAR OUTCOME TRIALS IN TYPE 2 DIABETES

Several CVOTs of T2D drugs have demonstrated CV benefit and safety.[60] Post hoc analyses of DECLARE-TIMI 58 (dapagliflozin)[61] that stratified participants by baseline BMI of 18.5 to <25, 25 to <30, 30 to <35, 35 to <40 and ≥40 kg m^{-2} showed that increasing BMI

FIGURE 4 Key features of the SELECT trial and potential implications. CV, cardiovascular; CVOT, cardiovascular outcomes trial; GLP-1RA, glucagon-like peptide-1 receptor agonist; HFpEF, heart failure with preserved ejection fraction; MACE, major adverse cardiovascular event; T2D, type 2 diabetes

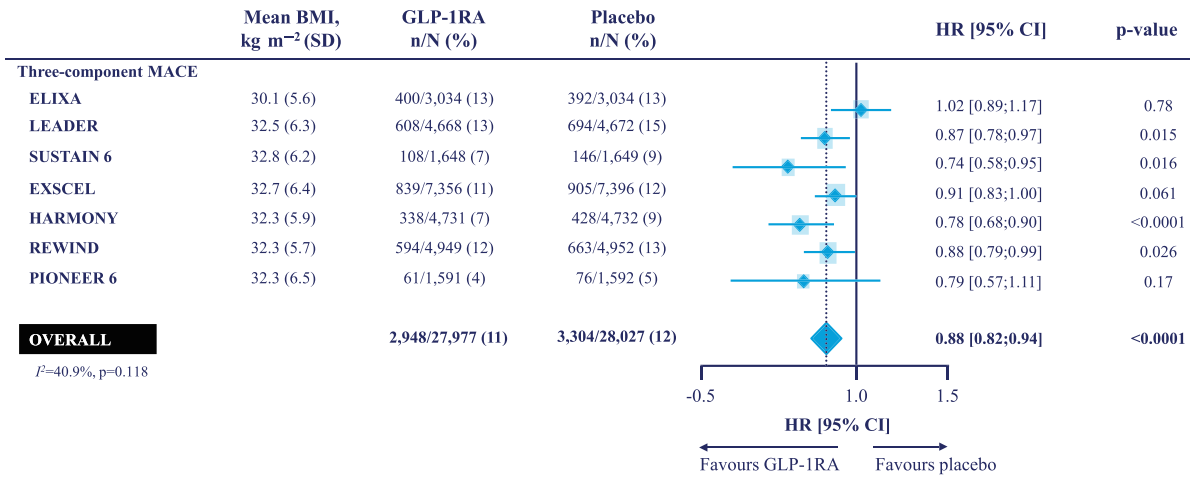

FIGURE 5 Cardiovascular outcome trials with glucagon-like peptide-1 receptor agonists in type 2 diabetes. Three-component MACE consisted of cardiovascular death, myocardial infarction and stroke. BMI, body mass index; CI, confidence interval; GLP-1RA, glucagon-like peptide-1 receptor agonist; HR, hazard ratio; MACE, major adverse cardiovascular event; SD, standard deviation

category was associated with a high risk of CVD/hospitalization for heart failure. A subanalysis of the CANVAS programme, which tested the consistency of canagliflozin across baseline BMI categories of <25, 25 to <30 and ≥30 kg m^{-2} showed that there was no difference in treatment-related outcomes across the BMI levels.[62] Post hoc analysis of LEADER/SUSTAIN 6[63] data stratifying participants by baseline BMI (<25, ≥25 to <30, ≥30 to <35 and ≥35 kg m^{-2}) showed that liraglutide and semaglutide improved CV and renal outcomes with no apparent differences across BMI groups. However, subgroup analysis of the EMPA-REG OUTCOME (empagliflozin) trial demonstrated a borderline trend for better outcomes for people with low BMI (<30 kg m^{-2}; HR for primary outcome 0.74) compared with those with high BMI (≥30 kg m^{-2}; HR for primary outcome 0.98).[64]

Data from seven CVOTs in T2D with glucagon-like peptide-1 receptor agonists (GLP-1RAs) (Figure 5) show that they have beneficial effects on CVD risk, all-cause mortality and renal outcomes.[65] Liraglutide (3.0 mg) was subsequently approved for obesity (by the FDA in 2014[66] and EMA in 2015[67]), and Phase 3 trials of semaglutide of 2.4 mg for weight management in people with or without T2D are underway.

7 | CONCLUSION

There is robust evidence to show that obesity and CVD are strongly linked and that weight loss improves surrogate markers of CVD risk. Post hoc analyses of large trials, such as Look AHEAD, SCOUT and the SOS, suggest that weight loss is positively correlated with CV benefits.[21,24,25] Several approved AOMs are considered appropriate for people with obesity and CVD; liraglutide of 1.8 mg reduced the risk of CV events in people with T2D in the LEADER trial, and this was accepted as evidence to support the CV safety of liraglutide of 3.0 mg by the regulators. Although bariatric surgery and liraglutide of 3.0 mg have been shown to improve CVD risk factors, more data on CV safety are lacking.[68,69] Adoption of AOMs by prescribers is still very low as compared with adoption of glucose-lowering agents for T2D.[70] Orlistat and liraglutide 3.0 mg are considered most appropriate for people with CVD,[68] but until further CVOTs in obesity are complete, it is unlikely that treatment algorithms and prescribing habits will evolve. Of note, no CVOT has yet demonstrated superiority of an AOM versus placebo in obesity. Although the ongoing SELECT trial holds promise, the focus on people with a high risk of CV events is an inherent limitation, and it may reduce the trial's generalizability to real-world practice.[60]

It is clear that large sample sizes and long trial durations are required to observe an adequate number of adverse CV events to enable suitably powered statistical comparison of the AOM being evaluated and its comparator, even if the population is enriched with patients at high risk of adverse CV events. If future obesity CVOTs are able to demonstrate reduction in observed risk of adverse CV outcomes and a CV benefit, we may see a gradual increase in the adoption of AOMs and updated guideline recommendations (as has occurred with the diabetes CVOTs).

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CONFLICT OF INTEREST

John Wilding reports receiving consultancy fees (paid to university) from AstraZeneca, Astellas, Boehringer Ingelheim, Janssen, Lilly, Mundipharma, Napp, Novo Nordisk, Rhythm Pharmaceuticals and Sanofi; grant and personal fees from AstraZeneca, Novo Nordisk and Takeda; and personal fees from Boehringer Ingelheim, Mundipharma, Napp and Sanofi. Stephan Jacob reports receiving personal fees from

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AUTHOR CONTRIBUTIONS

Both authors contributed to the conception of the review including discussion of proposals and guidance, critically reviewed for important intellectual content and approved the final version to be published.

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REFERENCES

1. World Health Organization. Obesity and overweight. Available from: https://www.who.int/en/news-room/fact-sheets/detail/obesity-and-overweight 2018. Accessed July 2020.
2. Dobbs R, Sawers C, Thompson F, et al. *Overcoming Obesity: An Initial Economic Analysis*. Jakarta, Indonesia: McKinsey Global Institute; 2014.
3. Heymsfield SB, Wadden TA. Mechanisms, pathophysiology, and management of obesity. *N Engl J Med*. 2017;376(3):254-266.
4. Yuen M, Earle R, Kadambi N, *et al*. A systematic review and evaluation of current evidence reveals 236 obesity-associated disorders (ObAD). Obesity Week: New Orleans, LA, USA 2016.
5. Yu E, Ley SH, Manson JE, et al. Weight history and all-cause and cause-specific mortality in three prospective cohort studies. *Ann Intern Med*. 2017;166(9):613-620.
6. Khan SS, Ning H, Wilkins JT, et al. Association of body mass index with lifetime risk of cardiovascular disease and compression of morbidity. *JAMA Cardiol*. 2018;3(4):280-287.
7. Lassale C, Tzoulaki I, Moons KGM, et al. Separate and combined associations of obesity and metabolic health with coronary heart disease: a pan-European case-cohort analysis. *Eur Heart J*. 2018;39(5):397-406.
8. Riaz H, Khan MS, Siddiqi TJ, et al. Association between obesity and cardiovascular outcomes: a systematic review and meta-analysis of Mendelian randomization studies. *JAMA Netw Open*. 2018;1(7):e183788.
9. Yusuf S, Hawken S, Ounpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case–control study. *Lancet*. 2004;364(9438):937-952.
10. Després JP, Lemieux I, Prud'homme D. Treatment of obesity: need to focus on high risk abdominally obese patients. *BMJ*. 2001;322(7288):716-720.
11. WHO expert consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *Lancet*. 2004;363:157-163.
12. Longo M, Zatterale F, Naderi J, et al. Adipose tissue dysfunction as determinant of obesity-associated metabolic complications. *Int J Mol Sci*. 2019;20(9):2358.
13. Carobbio S, Pellegrinelli V, Vidal-Puig A. Adipose tissue function and expandability as determinants of lipotoxicity and the metabolic syndrome. *Adv Exp Med Biol*. 2017;960:161-196.
14. Van Gaal LF, Mertens IL, De Block CE. Mechanisms linking obesity with cardiovascular disease. *Nature*. 2006;444(7121):875-880.
15. Poirier P, Giles TD, Bray GA, 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(6):898-918.
16. Albakri A. Obesity cardiomyopathy: a review of literature on clinical status and meta-analysis of diagnostic and clinical management. *Med Clin Arch*. 2018;2(3):1–13. https://doi.org/10.15761/MCA.1000134
17. 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(1):6-19.
18. Lyon CJ, Law RE, Hsueh WA. Minireview: adiposity, inflammation, and atherogenesis. *Endocrinology*. 2003;144(6):2195-2200.
19. Williamson DF, Thompson TJ, Thun M, Flanders D, Pamuk E, Byers T. Intentional weight loss and mortality among overweight individuals with diabetes. *Diabetes Care*. 2000;23(10):1499-1504.
20. Harrington M, Gibson S, Cottrell RC. A review and meta-analysis of the effect of weight loss on all-cause mortality risk. *Nutr Res Rev*. 2009;22(1):93-108.
21. Gregg EW, Jakicic JM, Blackburn G, et al. Association of the magnitude of weight loss and changes in physical fitness with long-term cardiovascular disease outcomes in overweight or obese people with type 2 diabetes: a post-hoc analysis of the Look AHEAD randomised clinical trial. *Lancet Diabetes Endocrinol*. 2016;4:913-921.
22. Redmon JB, Bertoni AG, Connelly S, et al. Effect of the look AHEAD study intervention on medication use and related cost to treat cardiovascular disease risk factors in individuals with type 2 diabetes. *Diabetes Care*. 2010;33(6):1153-1158.
23. Gong Q, Zhang P, Wang J, et al. Morbidity and mortality after lifestyle intervention for people with impaired glucose tolerance: 30-year results of the Da Qing Diabetes Prevention Outcome Study. *Lancet Diabetes Endocrinol*. 2019;7(6):452-461.
24. Caterson ID, Finer N, Coutinho W, et al. Maintained intentional weight loss reduces cardiovascular outcomes: results from the Sibutramine Cardiovascular OUTcomes (SCOUT) trial. *Diabetes Obes Metab*. 2012;14(6):523-530.
25. Sjöström L, Peltonen M, Jacobson P, et al. Bariatric surgery and long-term cardiovascular events. *JAMA*. 2012;307(1):56-65.
26. Buchwald H, Avidor Y, Braunwald E, et al. Bariatric surgery: a systematic review and meta-analysis. *JAMA*. 2004;292(14):1724-1737.
27. Blanco DG, Funes DR, Giambartolomei G, Lo Menzo E, Szomstein S, Rosenthal RJ. High cardiovascular risk patients benefit more from bariatric surgery than low cardiovascular risk patients. *Surg Endosc*. 2019;33(5):1626-1631.
28. Sjöström L, Lindroos AK, Peltonen M, et al. Lifestyle, diabetes, and cardiovascular risk factors 10 years after bariatric surgery. *N Engl J Med*. 2004;351(26):2683-2693.
29. Schauer PR, Bhatt DL, Kirwan JP, et al. Bariatric surgery versus intensive medical therapy for diabetes—5-year outcomes. *N Engl J Med*. 2017;376(7):641-651.
30. Gloy VL, Briel M, Bhatt DL, et al. Bariatric surgery versus non-surgical treatment for obesity: a systematic review and meta-analysis of randomised controlled trials. *BMJ*. 2013;347:f5934.
31. Adams TD, Gress RE, Smith SC, et al. Long-term mortality after gastric bypass surgery. *N Engl J Med*. 2007;357(8):753-761.
32. Van Gaal L, Pi-Sunyer X, Després JP, McCarthy C, Scheen A. Efficacy and safety of rimonabant for improvement of multiple cardiometabolic risk factors in overweight/obese patients: pooled 1-year data from the Rimonabant in Obesity (RIO) program. *Diabetes Care*. 2008;31(Suppl 2):S229-S240.
33. Waterlow M, Chrisp P. Rimonabant: the evidence for its use in the treatment of obesity and the metabolic syndrome. *Core Evid*. 2008;2(3):173-187.
34. Fujioka K, Seaton TB, Rowe E, et al. Weight loss with sibutramine improves glycaemic control and other metabolic parameters in obese patients with type 2 diabetes mellitus. *Diabetes Obes Metab*. 2000;2(3):175-187.

35. Torgerson JS, Hauptman J, Boldrin MN, Sjöström 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(1):155-161.
36. Greenway FL, Fujioka K, Plodkowski RA, et al. Effect of naltrexone plus bupropion on weight loss in overweight and obese adults (COR-I): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2010;376(9741):595-605.
37. Pi-Sunyer X, Astrup A, Fujioka K, et al. A randomized, controlled trial of 3.0 mg of liraglutide in weight management. *N Engl J Med*. 2015;373(1):11-22.
38. le Roux CW, Astrup A, Fujioka K, et al. 3 years of liraglutide versus placebo for type 2 diabetes risk reduction and weight management in individuals with prediabetes: a randomised, double-blind trial. *Lancet*. 2017;389(10077):1399-1409.
39. Federal Register. FDA withdrawal of fen-phen. Available from: https://www.govinfo.gov/content/pkg/FR-2015-09-29/pdf/2015-24619.pdf. Accessed July 2020.
40. Connolly HM, Crary JL, McGoon MD, et al. Valvular heart disease associated with fenfluramine-phentermine. *N Engl J Med*. 1997;337(9):581-588.
41. Cardiac valvulopathy associated with exposure to fenfluramine or dexfenfluramine: U.S. Department of Health and Human Services interim public health recommendations, November 1997. *MMWR Morb Mortal Wkly Rep*. 1997;46(45):1061-1066.
42. Heal DJ, Gosden J, Smith SL. Regulatory challenges for new drugs to treat obesity and comorbid metabolic disorders. *Br J Clin Pharmacol*. 2009;68(6):861-874.
43. Rodgers RJ, Tschöp MH, Wilding JP. Anti-obesity drugs: past, present and future. *Dis Model Mech*. 2012;5(5):621-626.
44. Medscape. FDA announces sibutramine has been withdrawn from the market. 2010. Available from: https://www.medscape.org/viewarticle/730515. Accessed July 2020.
45. James WP, Caterson ID, Coutinho W, et al. Effect of sibutramine on cardiovascular outcomes in overweight and obese subjects. *N Engl J Med*. 2010;363(10):905-917.
46. Topol EJ, Bousser MG, Fox KA, et al. Rimonabant for prevention of cardiovascular events (CRESCENDO): a randomised, multicentre, placebo-controlled trial. *Lancet*. 2010;376(9740):517-523.
47. European Medicines Agency. Rimonabant—withdrawal of the marketing authorisation in the European Union. 2009. Available from: https://www.ema.europa.eu/en/documents/public-statement/public-statement-acomplia-withdrawal-marketing-authorisation-european-union_en.pdf. Accessed July 2020.
48. Christensen R, Kristensen PK, Bartels EM, Bliddal H, Astrup A. Efficacy and safety of the weight-loss drug rimonabant: a meta-analysis of randomised trials. *Lancet*. 2007;370(9600):1706-1713.
49. Hiatt WR, Goldfine AB, Kaul S. Cardiovascular risk assessment in the development of new drugs for obesity. *JAMA*. 2012;308(11):1099-1100.
50. Food and Drug Administration. Guidance for industry: diabetes mellitus—evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes. US Department of Health and Human Services. December 2008. Available from: https://www.federalregister.gov/documents/2008/12/19/E8-30086/guidance-for-industry-on-diabetes-mellitus-evaluating-cardiovascular-risk-in-new-antidiabetic. Accessed July 2020.
51. European Medicines Agency. Reflection paper on assessment of cardiovascular safety profile of medicinal products. 2016. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-assessment-cardiovascular-safety-profile-medicinal-products_en.pdf. Accessed July 2020.
52. US Food and Drug Administration, Research. CfDEa. Summary minutes of the endocrinologic and metabolic drugs advisory committee meeting. March 28–29, 2012. Available from: https://wayback.archive-it.org/7993/20170404152004/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM303352.pdf. Accessed July 2020.
53. Nissen SE, Wolski KE, Prcela L, et al. Effect of naltrexone–bupropion on major adverse cardiovascular events in overweight and obese patients with cardiovascular risk factors: a randomized clinical trial. *JAMA*. 2016;315(10):990-1004.
54. EU Clinical Trials Register. A Qsymia™ CardiovascuLAr morbIdity and Mortality (AQCLAIM) Study in subjects with documented cardiovascular disease. 2013. Available from: https://www.clinicaltrialsregister.eu/ctr-search/search?query=AQCLAIM. Accessed July 2020.
55. Bohula EA, Wiviott SD, McGuire DK, et al. Cardiovascular safety of lorcaserin in overweight or obese patients. *N Engl J Med*. 2018;379(12):1107-1117.
56. ClinicalTrials.gov. Semaglutide Effects on Heart Disease and Stroke in Patients With Overweight or Obesity (SELECT), NCT03574597: 2018. Available from: https://clinicaltrials.gov/ct2/show/NCT03574597. Accessed July 2020.
57. Delahanty LM, Riggs M, Klioze SS, Chew RD, England RD, Digenio A. Maximizing retention in long-term clinical trials of a weight loss agent: use of a dietitian support team. *Obes Sci Pract*. 2016;2(3):256-265.
58. US Food and Drug Administration. FDA requests the withdrawal of weight loss drug Belviq, Belviq SR (lorcaserin) from the market Available at: https://www.fda.gov/drugs/drug-safety-and-availability/fda-requests-withdrawal-weight-loss-drug-belviq-belviq-xr-lorcaserin-market. Accessed July 2020.
59. Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2016;375(19):1834-1844.
60. Cefalu WT, Kaul S, Gerstein HC, et al. Cardiovascular outcomes trials in type 2 diabetes: where do we go from here? Reflections from a diabetes care editors' expert forum. *Diabetes Care*. 2018;41(1):14-31.
61. Kazuma O, Itamar R, Avivit C, et al. Effects of dapagliflozin on cardiovascular outcomes across body mass index categories in patients with type 2 diabetes mellitus in the DECLARE TIMI 58 trial. *J Am Coll Cardiol*. 2020;75(Suppl 1):660.
62. Ohkuma T, Van Gaal L, Shaw W, et al. Clinical outcomes with canagliflozin according to baseline body mass index: results from post hoc analyses of the CANVAS program. *Diabetes Obes Metab*. 2020;22(4):530-539.
63. Verma S, Bain S, Bhatt D, *et al*. The glucagon-like peptide-1 receptor agonists liraglutide and semaglutide improve cardiovascular and renal outcomes across most body mass index categories in type 2 diabetes: results of the LEADER and SUSTAIN 6 Trials. *Circulation* 2018;138:A14806.
64. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2015;373(22):2117-2128.
65. Kristensen SL, Rorth R, Jhund PS, 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(10):776-785.
66. Medscape. FDA approves liraglutide for weight loss. December 2014. Available from: https://www.medscape.com/viewarticle/837147. Accessed July 2020.
67. Medscape. Liraglutide gets okay from EU for obesity. January 2015. Available from: https://www.medscape.com/viewarticle/838630. Accessed July 2020.
68. Andrew CA, Saunders KH, Shukla AP, Aronne LJ. Treating obesity in patients with cardiovascular disease: the pharmacotherapeutic options. *Expert Opin Pharmacother*. 2019;20(5):585-593.

69. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2016; 375(4):311-322.
70. Thomas CE, Mauer EA, Shukla AP, Rathi S, Aronne LJ. Low adoption of weight loss medications: a comparison of prescribing patterns of antiobesity pharmacotherapies and SGLT2s. *Obesity (Silver Spring)*. 2016;24(9):1955-1961.

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