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Review

A review of the evidence on cardiovascular outcomes from obesity treatment

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ABSTRACT

Background: Obesity is a chronic disease with a myriad of complications including cardiovascular disease. There is a growing interest to examine if obesity treatment is associated with cardiovascular outcomes.
Methods: In this narrative review, we focused on randomized controlled trials (RCT) with cardiovascular outcomes (CVO) from lifestyle intervention, bariatric surgery, glucagon-like peptide-1 analogues (GLP-1a) and other pharmacotherapy. Additionally, we provide a comprehensive look into the RCT of sodium glucose cotransporter 2 inhibitors (SGLT2i) and CVO in obesity, while also summarizing several ongoing randomized cardiovascular outcome controlled trials for the pharmacological treatment of obesity.
Results: To date, the results from the randomized controlled trials supported the association between obesity treatment and cardiovascular outcomes. Studies have large sample sizes, conducted over long duration, with the majority demonstrating superiority in primary cardiovascular outcome end points compared to placebo.
Conclusion: Future data from several ongoing anti-obesity medications cardiovascular outcome trials such as SELECT, SURPASS, SUMMIT and SURMOUNT-MMO hold promises. Further studies are warranted to investigate the long term cardiovascular outcomes following lifestyle intervention and bariatric surgery.

1. Introduction

Obesity is a chronic disease defined as excessive or abnormal adiposity which increases morbidity and mortality, leading to global public health challenges [1]. The rising prevalence of obesity has multiple implications for the risk of cancer, type 2 diabetes (T2D), obstructive sleep apnoea, non-alcoholic fatty liver disease, chronic kidney disease and cardiovascular disease (CVD) [2,3]. The management of obesity includes lifestyle modification, pharmacological therapy, and bariatric surgery, with the latter being the most effective treatment to date [4]. Additionally, psychotherapy may be an adjunct to lifestyle therapies, medications, and bariatric surgery [5,6].

Current guidelines recommend anti-obesity medication (AOM) in individuals with body mass index (BMI) $\geq$ 30 kg/m^2 or BMI $\geq$27 kg/m^2 with adiposity-related complications [7]. Only a few AOM received approval by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) such as semaglutide, liraglutide, tirzepatide (in T2D), orlistat and setmelanotide [8–12]. The estimated degree of weight reductions and the approval status for the AOM are presented in Table 1.

The Global Burden of Disease Obesity Collaborators showed an increase in the burden of elevated BMI, with high BMI accounting for 4 million deaths in 2015, in which over two-thirds were caused by CVD [13,14]. The development of CVD, most notably coronary artery disease, heart failure, and arrythmias, were driven by several obesity-related mechanisms that causes structural, humoral and haemodynamic changes such as altered atrial and ventricular pressure and hypoxia (in those with sleep apnoea), left ventricular remodelling and hypertrophy, atherosclerosis, thrombosis, and myocardial ischemia [15]. To date, evidence suggested that obesity treatments improve adverse cardiovascular events and CVD risk factors such as dyslipidaemia and hypertension [16–18]. These benefits were also seen in patients with pre-existing CVD [19].

There is a growing interest to examine if obesity treatment is associated with cardiovascular outcomes (CVO). In this narrative review, we searched PubMed from its inception until March 2023 for the term obesity and cardiovascular disease, limited to English language articles. We focused on randomized controlled trials (RCT) with CVO from lifestyle intervention, bariatric surgery, glucagon-like peptide-1 analogues (GLP-1a) and other pharmacotherapy. Additionally, the present review

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Table 1
The estimated degree of weight reduction with anti-obesity medications. Adapted with permission from Ref. [20].

Medication	Mean and categorical weight reduction (%)*	Notes	Approval		References
			FDA	EMA	
Phentermine 15mg/d (oral)	Mean = 7 ≥5% = 46 ≥10% = 21 ≥15% = NA	Placebo group had 2% mean weight reduction, with 16% and 7% achieving ≥5% and ≥10% weight reduction respectively	2011	NA	[21,22]
Semaglutide 2.4 mg/week SC	Mean = 15 ≥5% = 86 ≥10% = 69 ≥15% = 51 ≥20% = 32	Placebo group had 2% mean weight reduction, with 32%, 12%, 5% and 2% achieving ≥5%, ≥10%, ≥15%, and ≥20% categorical weight reduction respectively	2021	2022	[12]
Liraglutide 3.0mg/d SC	Mean = 8 ≥5% = 63 ≥10% = 33 ≥15% = 14	Placebo group had 3% mean weight reduction, with 27%, 11% and 4% achieving ≥5%, ≥10%, and ≥15% categorical weight reduction respectively	2014	2015	[11]
Phentermine HCl/Topiramate Extended Release (oral) (top dose = phentermine 15mg/92 mg topiramate)	**EQUATE** Mean = 9 ≥5% = 66[a] ≥10% = 41[a]	Placebo group had 2% mean weight reduction, with 16% and 7% achieving ≥5% and ≥10% categorical weight reduction respectively	2012	NA	[21,23]
Medication	**Mean and categorical weight reduction (%)***	**Notes**	**Approval**		**References**
	SEQUEL Mean = 10 ≥5% = 79[a] ≥10% = 54[a] ≥15% = 32[a] ≥20% = 15[a]	Placebo group had 2% mean weight reduction, with 30%, 12%, 7% and 2% achieving ≥5%, ≥10%, ≥15%, and ≥20% categorical weight reduction respectively			
Naltrexone sustained release (SR) 32mg/d plus bupropion SR 360mg/d (oral)	Mean = 7 ≥5% = 56 ≥10% = 27 ≥15% = 10	Placebo group had 2% mean weight reduction, with 18%, 7% and 2% achieving ≥5%, ≥10%, and ≥15% categorical weight reduction respectively	2014	2015	[24]
Orlistat 120 mg three times/d (oral)	Mean = 9 ≥5% = 66 ≥10% = 39 ≥15% = NA	Placebo group had 6% mean weight reduction, with 44%, and 25% achieving ≥5% and ≥10% categorical weight reduction respectively	1999	1998	[8]
Setmelanotide 3.0mg/d SC	Mean = NR ≥10% = 32.3	In patients with impaired signalling of MC4R pathway only. Phase 3 trial, 14-week double-blind, placebo controlled followed by 52-week open label period	2022	2021	[9]
Medication	**Mean and categorical weight reduction (%)***	**Notes**	**Approval**		**References**
Tirzepatide dose (top dose 15 mg/week SC)	Mean = 21[a] ≥5% = 91[a] ≥20% = 57[a]	Placebo group had 3% mean weight reduction, with 35%, and 3% achieving ≥5% and ≥20% categorical weight reduction respectively	2022[b]	2022[b]	[10]

NR = Not reported. NA = Not approved. FDA = U.S. Food and Drug Administration. EMA = European Medicines Agency. MC4R = melanocortin-4 receptor.
*The values are not intended to represent head-to-head comparisons. Data are derived from different studies. In most cases, the percent weight reductions were dose dependent. Therefore, the listed mean values may be less than the percent weight reduction with the highest doses of anti-obesity medications.
[a] At the top dose of.
[b] Approved in T2D only. SC = subcutaneous.

provides a comprehensive look into the RCT of sodium glucose cotransporter 2 inhibitors (SGLT2i) and CVO in obesity, while also summarizing several ongoing randomized cardiovascular outcome controlled trials such as SELECT, SURPASS, SUMMIT and SURMOUNT-MMO for the pharmacological treatment of obesity.

2. Randomized controlled trials of lifestyle intervention with cardiovascular outcomes in obesity

The Look AHEAD (Action for Health in Diabetes) was the largest and the longest randomized control trial evaluating the effect of lifestyle intervention on CVO [25]. Participants who were affected by either overweight or obesity with T2D were randomized to an intensive lifestyle intervention or the standard care (n=5145). At baseline, the mean BMI and glycated haemoglobin (HbA_1c) were 36 kg/m^2 and 7.3% respectively. Intensive lifestyle intervention included group and individual counselling (weekly for the first 6 months, and subsequently tapered in the course of the trial), a 175 minutes of moderate-intensity physical activity per week, and a reduced caloric intake, aiming at achieving and maintaining at least a 7% weight loss. The standard care included diabetes group support and education, featuring three group sessions per year, focusing on diet, exercise, and social support from year one to four. This was followed by a reduction in the frequency to a session annually. To examine the effect on cardiovascular (CV) morbidity and mortality, the primary outcome was the composite of death from CV causes, nonfatal MI, nonfatal stroke or hospitalization for angina up to 13.5 years. However, the trial was discontinued at a median of 9.6 years following a futility analysis. The intensive lifestyle intervention group demonstrated greater weight loss (6.0% versus 3.5%), reduction in HbA_1c, improvement in fitness and all CV risk factors (except for LDL cholesterol). Compared to standard care, intensive lifestyle intervention did not reduce the rate of CV events in participants affected by overweight or obesity with T2D (HR 0.95, CI 0.83 – 1.09, p=0.51). A lower event rates in both groups, the lack of sufficient power, the need to achieve a higher weight loss in the intervention group, the provision of education sessions, use of statin and the effectiveness of medical intervention in the standard care group may have lessened the differences between the two groups [26]. A further post-hoc analyses of this trial

evaluated the magnitude of weight loss within the first year of the study and the incidence of CV disease. The composite primary outcome was similar to the main study while the secondary outcome was a composite of primary outcome plus coronary artery bypass, carotid endarterectomy, percutaneous coronary intervention, heart failure hospitalization, peripheral vascular disease or total mortality. In this analyses, participants who lost at least 10% of their bodyweight in the lifestyle intervention group was associated with a 20% lower risk of primary outcome (adjusted HR 0.8, p=0.039) and a 21% lower risk of secondary outcome (adjusted HR 0.79, p=0.11) [27].

3. Randomized controlled trials of bariatric surgery and cardiovascular outcomes in obesity

Bariatric surgery has been shown to be associated with reduction in all-cause mortality (HR 0.55), CV mortality (HR 0.59), incidence of heart failure (HR 0.5), myocardial infarction (HR 0.58) and stroke (HR 0.64, p <0.001 vs control for all interactions) [19]. These associations were derived from a number of prospective and retrospective cohort studies [19,28].

In participants with severe obesity and T2D, data from RCT of bariatric surgery have shown consistent benefit in diabetes outcome and CV risk factors [4,29–31]. In an open-label single-centre RCT, 60 participants with obesity and T2D were randomized to either medical treatment, Roux-en-Y gastric bypass or biliopancreatic diversion. At 5 years follow up, 50% of participants in the surgical group achieved diabetes remission compared to medical therapy (p = 0.0007). The surgical group also achieved a reduction in CV risk, plasma lipid levels and medication usage compared to medical therapy [30]. In the STAMPEDE trial, 150 participants with obesity and T2D were randomly treated with either intensive medical therapy alone or intensive medical therapy plus Roux-en-Y bypass or sleeve gastrectomy. At 5 years, 29% of the surgical group achieved the primary end point ($HbA_1c \leq 6\%$ with or without the use of diabetes medications) compared to the non-surgical group (adjusted p = 0.03, intention to treat p = 0.08) [31]. The findings from these RCT demonstrated the effectiveness of bariatric surgery in diabetes remission and reducing CV risk. However, none were designed to evaluate the impact of surgery on major composite CVO or mortality compared to placebo. The results from the two most recent large observational studies [28,32] which demonstrated significant probability of reduction in major adverse cardiovascular events (MACE) suggested the need of a CVO trial in bariatric surgery [33].

4. Randomized controlled trials of Glucagon-like Peptide-1 analogues (GLP-1a) and cardiovascular outcomes in obesity

GLP-1a promotes glucose dependent insulin secretion, suppresses glucagon, improves satiety, reduces gastric motility and appetite, and contributes to an intermediate to a high level of weight loss outcome [34,35]. The effectiveness of high dose liraglutide (3.0 mg) and semaglutide (2.4 mg) in participants living with obesity either with and without diabetes or pre-diabetes were demonstrated in the SCALE and STEP clinical trials [36]. To date, the cardioprotective effects of GLP-1a in obesity were derived from RCT involving patients with T2D. However, not all patients with T2D included in these studies had obesity. There are several ongoing GLP-1a trials involving participants with obesity and these are covered in the later section of this article.

The Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) trial was designed to examine the CV safety outcomes of lixisenatide in participants with T2D and recent acute coronary syndrome (n=6068). The mean BMI was 30.1 kg/m^2 at recruitment while the mean HbA_1c was 7.6% respectively. In the treatment group, participants were treated with lixisenatide (10–20 mcg daily). After a median follow up of 25 months, there was no difference in the occurrence of the composite primary outcome event (CV death, myocardial infarction, stroke, or hospitalization for unstable angina) in the lixisenatide group compared to placebo (HR 1.02, 95% CI 0.89 – 1.17). HbA_1c and BMI were better in the lixisenatide group compared to the placebo, with an average between-group difference of −0.27% and −0.7 kg (p<0.001 for both), respectively [37].

The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial included participants with T2D and a high CV risk (n=9340). The mean BMI and HbA_1c at recruitment were 32.5 kg/m^2 and 8.7% respectively. In the treatment group, participants were treated with liraglutide up to 1.8mg/day (or the maximum tolerated dose), for a median of 3.8 years. There was a 13% reduction in the primary composite outcome (death from CV causes, non-fatal myocardial infarction, or non-fatal stroke) in the liraglutide group compared to placebo (HR 0.87, 95% CI 0.78 – 0.97, p<0.001). The liraglutide group had a mean difference in HbA_1c of −0.4% and 2.3 kg more weight loss than the placebo [38].

In the Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN-6) trial, 3297 participants with T2D and high CV risk (n=3297, 83% of participants had established CV disease) were randomized to either semaglutide (0.5 mg or 1.0 mg) or placebo. The mean BMI and HbA_1c were 33.0 kg/m^2 and 8.7% respectively. There was a 26% reduction in the primary outcome (composite of CV death, non-fatal myocardial infarction, or non-fatal stroke) in the semaglutide group compared to placebo (HR 0.74, 95% CI 0.58 – 0.95, p <0.001) after 104 weeks. However, there was a 76% increase in the onset of diabetes retinopathy (HR 1.76, 95% CI 1.11 – 2.78, p=0.02), in the semaglutide group. Compared to placebo, the mean HbA_1c reduction were −0.7% (semaglutide 0.5 mg), and −1.0% (semaglutide 1.0 mg) while the mean weight differences in the semaglutide group were −2.9 kg (semaglutide 0.5 mg) and −4.3 kg (semaglutide 1.0 mg) respectively [39].

The Exenatide Study of Cardiovascular Event Lowering Trial (EXSCEL) included 14,752 participants with T2D with or without CV disease. Over a median of 3.2 years, participants were randomized to either a once weekly exenatide (2.0 mg) versus placebo. The mean BMI and median HbA_1c were 32 kg/m^2 and 8.0% respectively. There was no difference in the primary composite outcome (death from CV causes, non-fatal myocardial infarction, or non-fatal stroke) in the exenatide group vs placebo (HR 0.91, 95% CI 0.83 – 1.0). The mean difference in HbA_1c and weight was −0.53% and −1.27 kg, favouring exenatide [40].

The Albiglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes and Cardiovascular Disease (Harmony Outcomes) included 9463 participants with T2D and CV disease. Over a median of 1.6 years, participants were randomized to either a weekly albiglutide 30 – 50 mg or a similar volume of placebo. At baseline, the mean BMI and HbA_1c were 32.3 kg/m^2 and 8.7% respectively. In the intention to treat analysis, there was a reduction in the primary composite outcome (death from CV causes, myocardial infarction, and stroke) in the albiglutide group compared to placebo (HR 0.78, 95% CI 0.68 – 0.9, p=0.006). Compared to placebo, mean HbA_1c and weight decreased more with albiglutide by 0.52% and 0.83 kg respectively [41].

In the Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND) trial, 9901 participants with T2D, with or without CV disease were included. In the treatment group, participants were treated with a weekly dulaglutide 1.5 mg. The primary composite outcome included non-fatal myocardial infarction, non-fatal stroke, or death from CV causes (including unknown causes). The baseline mean BMI and median HbA_1c were 32.3 kg/m^2 and 7.2% respectively. After a median of 5.4 years, there was a 12% reduction in the primary outcome in the dulaglutide group compared to the placebo (HR 0.88, 95% CI 0.79 – 0.99, p=0.026). The dulaglutide group demonstrated a reduction in the least-square mean (LSM) of HbA_1c, weight and BMI at −0.61%, −1.46 kg and −0.53 kg/m^2 respectively [42].

Further benefit from the subcutaneous GLP-1 analogue led to the development of the oral formulation. The Peptide Innovation for Early Diabetes Treatment (PIONEER) 6 was a phase 3a CVO trial for oral semaglutide. A total of 3183 participants with T2D and CV risk were randomized to either oral semaglutide 14 mg or placebo for a median of

15.9 months. The baseline BMI and HbA_1c were 32.3 kg/m^2 and 66 mmol/mol respectively. There was an absence in CV risk with the oral semaglutide. The primary composite outcome (first occurrence of death from CV causes, non-fatal MI or non-fatal stroke) was not inferior in the treatment group (HR 0.79, CI 0.57 – 1.11, p = 0.17 for superiority, p <0.001 for non-inferiority) compared to placebo. HbA_1c was slightly better in the treatment group (mean change of −1.0%) with mean weight loss of −4.2 kg compared to placebo [43].

The AMPLITUDE-O trial evaluated the CV and renal outcome of efpeglenatide, involving 4076 participants with T2D and CV disease or current kidney disease, compared to placebo. The treatment group were treated with weekly efpeglenatide (4 mg or 6 mg) vs placebo for a median of 1.81 years. The baseline mean BMI and HbA_1c were 33 kg/m^2 and 8.9% respectively. There was a 27% reduction in the primary major adverse cardiovascular event (MACE), (HR 0.73, 95% CI 0.58 – 0.92, p<0.001) in the efpeglenatide group compared to placebo, independent of the baseline use of SGLT2i, metformin and baseline eGFR. The efpeglenatide group demonstrated a reduction in the LSM for HbA_1c and BMI at −1.24% and −0.9 kg/m^2 respectively [44].

5. Randomized controlled trials of other pharmacotherapy and cardiovascular outcomes in obesity

Sibutramine induces satiety and increases energy expenditure via noradrenaline and serotonin reuptake inhibition. It was approved as part of the obesity management in patients with low CV risk. The Sibutramine Cardiovascular Outcomes (SCOUT) trial evaluated the long term effect of sibutramine in participants with overweight or obesity with pre-existing CV disease, T2D or both. A total of 10,744 participants with mean BMI of 34 kg/m^2 were followed up over a mean of 3.4 years. The intervention group was treated with sibutramine 10 mg daily with an increase to 15 mg daily if weight loss was insufficient. Compared to placebo, the intervention group achieved and maintained further weight reduction (mean −1.7 kg) in addition to overall weight loss achieved by all participants during the run-in period (mean −2.6 kg). In this high CV risk population, a 16% increase risk of primary outcome (composite of non-fatal myocardial infarction, non-fatal stroke, resuscitation after cardiac arrest, or CV death) (HR 1.16, 95% CI 1.03 – 1.31, p = 0.02) was seen in the sibutramine group compared to placebo. Additionally, there was a 28% increased risk of non-fatal myocardial infarction (HR 1.28, 95% CI 1.04 – 1.57, p = 0.02) and a 36% increased risk of non-fatal stroke (HR 1.36, 95% CI 1.04 – 1.77, p = 0.03) against sibutramine [45]. Following this trial, marketing of sibutramine containing medicine was suspended across all European Union (EU).

Rimonabant has been shown to improve weight and several metabolic risk factors via its action as a selective cannabinoid-1 receptor antagonist. Previous placebo RCT involving rimonabant were between 12 to 18 months. To evaluate the effect of rimonabant on CVO, the Comprehensive Rimonabant Evaluation Study of Cardiovascular Endpoints and Outcomes (CRESCENDO) trial randomized 18,695 participants with obesity and high CV risks to either rimonabant (20 mg daily) or placebo. The baseline mean BMI was 33 kg/m^2. The primary endpoint was a composite of CV death, MI, or stroke. The trial was prematurely terminated at a mean follow up of 13.8 months following concern of suicides in the rimonabant group from 3 different health regulatory authorities. At the closure of the trial, there was no difference in the primary outcome (HR 0.97, 95% CI 0.84 – 1.12, p = 0.68) in both groups, with higher gastrointestinal, neuropsychiatric and serious psychiatric adverse events in the rimonabant group [46]. Following this trial, marketing of rimonabant was suspended across all EU.

Phentermine is a sympathomimetic agent with an appetite suppressant effect while topiramate is an antiepileptic agent that inhibits carbonic anhydrase enzyme which reduces appetite by altering the taste of food. The combination of phentermine-topiramate has been shown to induce significant weight loss [47] in addition to improvement in CV and metabolic variables [23]. The ACQLAIM (A Qysmia CardiovascuLAr morbidity and Mortality Study in Subjects with Documented Cardiovascular Disease) was a placebo RCT aimed to evaluate CV outcome of phentermine-topiramate involving 16,000 participants with obesity and CV disease. This trial ended prematurely and the marketing of phentermine-topiramate is currently suspended across all EU.

Evidence from phase 3 clinical trials demonstrated significant weight loss following the use of naltrexone and bupropion. Naltrexone is an opioid antagonist, and bupropion is a noradrenaline-dopamine reuptake inhibitor and nicotinic receptor antagonist. Although the mechanism of action is unclear, the combination of both drugs reduce hunger. The LIGHT study evaluated the effects of naltrexone-bupropion on the CV outcomes of 8910 participants who were affected by overweight or obesity with an increased CV risk. The intervention group was treated with naltrexone 32 mg/day and bupropion 360 mg/day. The baseline median body mass index was 36.6 kg/m^2. The primary endpoint was time to first confirmed occurrence of MACE (CV death, non-fatal stroke, or non-fatal MI). The trial ended due to a breach of confidentiality by the sponsor. At the 25% and 50% interim analyses, the HR for primary outcome in the treatment group were 0.59 (95% CI 0.39 – 0.9) and 0.88 (adjusted 99.7% CI 0.57 – 1.34) respectively, compared to placebo. Due to the unexpected termination of the study, it was impossible to determine the CV safety of naltrexone-bupropion as part of the management of obesity [48].

Through the inhibition of pancreatic and gastric lipase enzyme, orlistat has been shown to induce weight loss and is associated with improvement in a number of CV risk factors [49] and a reduction in CV mortality [50]. Setmelanotide is a melanocortin-4 receptor (MC4R) agonist, approved for the treatment for adult or children with obesity due to proopiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1) or leptin receptor (LEPR) deficiencies [51]. To date, there is no CVO RCT involving orlistat or setmelanotide.

Lorcaserin regulates appetite through the activation of the proopiomelanocortin (POMC) pathway and has been shown to aid weight loss. The CAMELLIA-TIMI-61 (Cardiovascular and Metabolic Effects of Lorcaserin in Overweight and Obese Patients-Thrombolysis in Myocardial Infarction-61) trial evaluated the CV outcome of lorcaserin compared to placebo in 12,000 participants who were affected by overweight or obesity with CV diseases or CV risk factors. The median BMI was 35 kg/m^2 and the median follow up duration was 3.3 years. The intervention group received lorcaserin 10 mg twice daily. The primary outcome was the composite of CV death, MI or stroke. The was a 3 times higher odds of losing 5% bodyweight with lorcaserin, compared to placebo (OR 3.01, 95% CI 2.74 – 3.3, p<0.001). There was no difference in the primary outcome between lorcaserin and placebo (HR 0.99, 95% CI 0.85 – 1.14, p <0.001 for non-inferiority). In this high risk population with overweight and obesity, lorcaserin did not demonstrated a higher CV event, with a significant weight loss benefit compared to placebo [52]. Further FDA review of the CAMELLIA-TIMI-61 and other trials involving lorcaserin demonstrated plausible increase in excess cancer risk [53] which led to withdrawal of lorcaserin from the EU and US market.

Overall, anti-obesity medications currently in use which do not have CVO trials are naltrexone-bupropion, orlistat and setmelanotide.

6. Ongoing randomized cardiovascular outcome controlled trials for pharmacological treatment of obesity

There are several ongoing randomized cardiovascular outcome controlled trials for the pharmacological treatment of obesity. The Semaglutide Effects on Heart Disease and Stroke in Patients With Overweight or Obesity (SELECT) included 17,500 participants with overweight or obesity with established CVD. The treatment group receives semaglutide 2.4 mg weekly versus placebo in the control group. The study is due to be completed in September 2023 [54].

Tirzepatide is a once weekly subcutaneous injectable peptide derived from the glucose-dependent insulinotropic polypeptide (GIP) sequence, with dual agonist activity at GIP and GLP-1 receptor [55], which

provided substantial and sustained reductions in body weight [10]. The SURPASS CVO (Study of Tirzepatide Compared With Dulaglutide on Major Cardiovascular Events in Participants With Type 2 Diabetes) trial included 13,299 participants with overweight or obesity with T2D and established CVD. Participants will be randomized to either tirzepatide or dulaglutide weekly. This study is due to be completed in October 2024 [56]. The primary outcome for both SELECT and SURPASS CVO trials is the time to first composite CV death, non-fatal MI and non-fatal stroke.

Another CVOT involving tirzepatide is the SUMMIT (A Study of Tirzepatide in Participants With Heart Failure With Preserved Ejection Fraction and Obesity) trial. This trial aims to recruit 700 participants with obesity and a diagnosis of heart failure with preserved ejection fraction. Participants will be randomized to either tirzepatide or placebo. The primary outcome is a hierarchical composite of all-cause mortality, heart failure events, 6-minute walk test distance and Kansas City Cardiomyopathy Questionnaire Clinical Summary Score category. The study is due to be completed in July 2024 [57].

Finally, in the SURMOUNT-MMO (A Study of Tirzepatide on the Reduction on Morbidity and Mortality in Adults With Obesity) trial, 15,000 participants living with obesity with established or at risk of CVD will be randomized to either tirzepatide or placebo. The primary outcome within the following 5 years is reported to be the first occurrence to any component of composite CV outcome. This study is currently in the recruitment phase [58].

7. Randomized controlled trials of sodium glucose cotransporter 2 inhibitors (SGLT2i) and cardiovascular outcomes in obesity

SGLT2i is a group of medication that promotes glucosuria by inhibiting renal glucose absorption leading to a caloric loss of approximately 300 kcal/day which explains the average 2–3 kg weight loss achieved in the clinical trials [59,60]. To date, there are a few randomized trials demonstrating positive weight loss effects of SGLT2i (varying doses versus placebo) in participants living with overweight and obesity without T2D [22,61]. For example, in a dose-response analysis examining changes in body weight following 24 weeks with four once-daily and twice-daily licogliflozin doses (2.5–150 mg) versus placebo, Bays HE et al. showed that licogliflozin once daily or twice daily produced a significant dose-response signal for weight loss versus placebo ($p<0.0001$). However, mean adjusted percent changes in body weight following 24 weeks were modest, ranging from −0.45% to −3.83% (in the 50 mg twice daily group (95% CI: −5.26% to −2.48%); n=75) [62]. SGLT2i is not part of the FDA-approved pharmacotherapy in the management of obesity. Recent guidelines however, showed that SGLT2i is considered to have an intermediate action in promoting weight loss and is an option in treating patients with obesity and T2D [20,34]. Obesity and T2D are closely interlinked and all currently available CVO RCT involving SGLT2i included patients with T2D. However, not all patients with T2D included in these studies had obesity.

Over 7000 participants with T2D with established CVD were involved in the EMPA-REG OUTCOME (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients) trial. The active treatment group were treated to either empagliflozin 10 mg or 25 mg daily. The baseline HbA_1c and BMI were 8% and 30.6 kg/m^2 respectively. After a median follow-up of 3.1 years, there was a 14% reduction in the 3-point major adverse cardiovascular event (MACE) in the active treatment group compared to placebo (HR 0.86, 95% CI 0.74 – 0.99; p=0.04 for superiority) [63]. In addition, the treatment group had a significant 2 – 3 kg weight reduction [64]. Following this trial, empagliflozin was also proven to reduce the primary outcomes in participants with heart failure (HF) and reduced ejection fraction (HFrEF, EMPEROR-Reduced trial) [65], and participants with heart failure with preserved ejection fraction (HRpEF, EMPEROR-Preserved trial) [66]. As the EMPEROR-Reduced and EMPEROR-Preserved trials focused on the heart failure outcomes, they are beyond the scope of this paper.

The CANagliflozin cardioVascular Assessment Study (CANVAS) combined the participants from the CANVAS and the CANVAS-R (renal) trials. Over 10,000 participants were included to evaluate the effects of canagliflozin on CV and renal outcomes in participants with T2D and high CV risk. The dose of canagliflozin was either canagliflozin 100 mg or 300 mg (CANVAS trial) or 100 mg with the option to increase to 300 mg (week 13) in the CANVAS-R trial. The overall baseline BMI and HbA_1c was 32 kg/m^2 and 8.2% respectively. After a mean follow-up of 188.2 weeks, a 14% reduction in the primary outcome (composite of death from CV causes, non-fatal myocardial infarction, or non-fatal stroke) in the canagliflozin group compared to the placebo (HR 0.86, 95% CI 0.75 – 0.97; $p<0.001$) was seen. In addition, participants who were treated with canagliflozin had a mean weight differences of −1.6 kg compared to placebo [67]. In a further placebo controlled trial (CREDENCE) involving 4401 participants with T2D and kidney disease, canagliflozin (100 mg) was demonstrated to lower the CVO by 20%. However, as the primary aim was primarily focused on the renal outcome, it is not discussed in this publication [68].

In the large Dapagliflozin Effect on CardiovascuLAR Events (DECLARE-TIMI 58) trial, 17,160 participants with T2D with either established atherosclerotic CV disease or multiple risk factors for CVD, were randomized to either dapagliflozin 10 mg or placebo. The MACE outcome was a composite of cardiovascular death, myocardial infarction or ischaemic stroke and the median follow-up was 4.2 years. At baseline, the mean HbA_1c and BMI were 8.3% and 32.0 kg/m^2 respectively. Compared to placebo, dapagliflozin did not lower the risk of MACE (HR 0.93, CI 0.84 – 1.03, p=0.17) or CV death (HR 0.98, 95% CI 0.82 – 1.17). However, a 17% reduction in the composite CV death or hospitalization for heart failure were seen in the dapagliflozin group (HR 0.83, 95% CI 0.73 – 0.95, p=0.005), which was primarily driven by lowering the rate of heart failure hospitalization (HR 0.73, 95% CI 0.61 – 0.88). The least-squares mean difference in weight was −1.8 kg, favouring participants treated with dapagliflozin [69].

The Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes Trial (VERTIS CV) included 8246 participants with T2D and established CVD. Participants' mean baseline BMI and HbA_1c were 32 kg/m^2 and 8.2% respectively. The treatment group received either ertugliflozin 5 mg, or 15 mg and were compared to placebo for a mean of 3.5 years. There was no significant reduction in the primary outcome (composite of death from CV causes, non-fatal myocardial infarction, or non-fatal stroke) (HR 0.97, 95% CI 0.85 – 1.11) in the ertugliflozin group compared to placebo. At 1 year, the ertugliflozin group had a mean weight loss of 2.4 kg (ertugliflozin 5 mg) and 2.8 kg (ertugliflozin 15 mg) [70].

The Effect of Sotagliflozin on Cardiovascular and Renal Events in Participants with Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk (SCORED) trial (n=10,584) involved randomization of participants to either sotagliflozin 200 mg daily (with an increase to 400 mg if tolerated) or placebo. At baseline, the median BMI and HbA_1c was 31.8 kg/m^2 and 8.3% respectively. The trial was discontinued early due to loss of funding. Consequently, the endpoints underwent several changes. After a median follow-up of 16 months, the primary outcome (composite of the total number of deaths from CV causes, hospitalizations for HF and urgent visits for HF) was reduced by 26% (HR 0.74, 95% CI 0.63 – 0.88, $p<0.001$) in the sotagliflozin group compared to the placebo group [71].

8. Conclusion

To date, evidence from randomized controlled trials demonstrated that obesity treatment improves cardiovascular outcomes. The studies have large sample size of participants living with obesity with CVD or at high risk of CVD. Additionally, the trials were conducted over long duration, with the majority demonstrating superiority in primary CVO end points compared to placebo. It is important to highlight that SGLT2i and GLP-1a are designed primarily for treating T2D with intermediate and high weight loss efficacy respectively as part of the therapeutic

option in achieving and maintaining weight loss in patients with T2D. With rising evidence that both drugs reduce cardiovascular and renal outcomes [3], currently, broader recommendations for cardiorenal protection in people with diabetes at high risk of cardiorenal disease have taken place [34]. Other pharmacotherapies (excluding SGLT2i and GLP-1a) in the treatment of obesity did not show a consistent positive CVO.

Thus, future data from several ongoing CVO trials such as SELECT, SURPASS, SUMMIT and SURMOUNT-MMO hold promises. Finally, further studies are warranted to examine the CVO following lifestyle intervention and bariatric surgery.

CRediT authorship contribution

ClR conceptualize the manuscript. RAW conducts the literature review, and wrote the first draft. ClR and RAW reviewed the final manuscript and approved the final submission and publication.

Ethical review

Not applicable for this review article. This submission does not include any human subjects or volunteers. It represents an original work and any work and/or words of others are properly cited.

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Declaration of competing interest

RAW has no declaration of interest.

ClR reports grants from the Irish Research Council, Science Foundation Ireland, Anabio, and the Health Research Board. He serves on advisory boards of Novo Nordisk, Herbalife, GI Dynamics, Eli Lilly, Johnson & Johnson, Glia, and Boehringer Ingelheim. ClR is a member of the Irish Society for Nutrition and Metabolism outside the area of work commented on here. He was the chief medical officer and director of the Medical Device Division of Keyron in 2011. Both of these are unremunerated positions. ClR was a previous investor in Keyron, which develops endoscopically implantable medical devices intended to mimic the surgical procedures of sleeve gastrectomy and gastric bypass. The product has only been tested in rodents and none of Keyron's products are currently licensed. They do not have any contracts with other companies to put their products into clinical practice. No patients have been included in any of Keyron's studies and they are not listed on the stock market. ClR was gifted stock holdings in September 2021 and divested all stock holdings in Keyron in September 2021. He continues to provide scientific advice to Keyron for no remuneration.

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