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REVIEW ARTICLE

Clinical Impact of Weight-Loss Pharmacotherapy in Patients with Atherosclerotic Cardiovascular Disease

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Abstract

Obesity is associated with the development and progression of multiple cardiovascular risk factors, such as hypertension, dyslipidemia, and type 2 diabetes mellitus, and is an important contributor to the global burden of atherosclerotic cardiovascular disease (CVD). Guidelines suggest that clinicians provide lifestyle counseling and promote lifestyle modifications before considering weight-loss surgery. However, despite lifestyle modifications and increased physical activity, most patients with obesity will not lose significant weight or will experience weight regain. Weight-loss pharmacotherapy added to lifestyle modification has long been perceived as a bridge between lifestyle modifications alone and weight-loss surgery. However, since its inception, weight-loss pharmacotherapy has been plagued by variable efficacy and concern about cardiovascular safety. Following requirements from regulatory authorities, efficacy and cardiovascular safety trials have been conducted for the currently available weight-loss pharmacotherapeutic agents. Overall, these trials have shown that weight-loss pharmacotherapy is only modestly efficient for the inducement of weight loss. Recent trials have also demonstrated the cardiovascular safety of some of these agents. We review these trials with a focus on the clinical impact of these weight-loss pharmacotherapeutic agents in patients with atherosclerotic CVD.

Key Points

Cardiovascular disease is one of the most severe complications of obesity. Yet, in patients with established cardiovascular disease, options to treat obesity and data regarding the benefits of losing weight are lacking.

Weight-loss pharmacotherapy could be of interest but has been plagued by variable efficacy and concern about cardiovascular and noncardiovascular safety.

Recent data suggest that some agents may reduce cardiovascular events, although this benefit may not be intrinsically related to weight loss.

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1 Introduction

Obesity is a growing worldwide problem. In 2014, 1.9 billion people had a body mass index (BMI) ≥ 25 kg/m^2, and > 650 million of these people were obese (BMI ≥ 30 kg/m^2), accounting for 39% and 13% of the global adult population, respectively [1]. This pandemic is even more pronounced in high-income countries, especially in the USA, where 39.8% of adults were obese in 2015–2016 [2].

In parallel with the rising prevalence of obesity, the burden of metabolic and cardiovascular diseases (CVDs) associated with excess weight is expected to increase. Of these, atherosclerotic coronary and peripheral artery disease are highly prevalent and represent severe complications of obesity. Obesity per se is recognized as an independent and causal cardiovascular risk factor [3–6], although it is often associated with dyslipidemia, arterial hypertension, and type 2 diabetes mellitus (T2DM), which may in part confound the effect of weight on cardiovascular risk. Furthermore, excess weight and obesity are highly prevalent in patients with CVD [7–9]. Obesity is also associated with premature death [10].

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Lifestyle interventions, including dietary, exercise, and behavioral changes, are the basis of any approach to weight loss. In patients with severe obesity (BMI > 35 kg/m^2 with comorbidities), weight-loss surgery may be indicated [11–14]. Weight-loss pharmacotherapy, with an efficacy level that falls between that of lifestyle and surgical interventions, has long been perceived as the missing link between lifestyle measures and weight-loss surgery.

The magnitude of weight loss through dietary measures and lifestyle modifications in patients with excess weight or with obesity and atherosclerotic CVD varies depending on the population studied and the intensity of the interventions (Fig. 1) [15]. Most data available in this population (patients with obesity and coronary artery disease [CAD]) are from studies of cardiac rehabilitation programs with dietary management and supervised physical activity. In this setting, depending on the type of intervention, weight loss compared with placebo ranges from −4.1 to + 0.9 kg after 1 year [16–23]. This notwithstanding, few data assess the role of weight loss through lifestyle intervention to decrease major adverse cardiac events (MACE) in patients with obesity and atherosclerotic CVD. Bariatric surgery has not yet been studied prospectively in this specific population.

Current cardiovascular prevention guidelines do not include specific recommendations on weight-loss pharmacotherapy or weight-loss surgery strategies in patients with obesity and atherosclerotic CVD [24]. In addition, the concept of the obesity paradox, whereby patients with obesity and established CAD seem to have a better prognosis than their leaner counterparts, may mislead the clinician regarding the importance of weight loss in patients with atherosclerotic CVD [25].

This article reviews currently approved medications for weight loss, focusing on their efficacy in terms of weight loss and cardiovascular safety (i.e., cardiovascular events), in studies that included patients with established atherosclerotic CVD.

2 Criteria for US FDA Approval and Historical Studies

Since the early days of thyroid hormone supplements, 2,4-dinitrophenol, and amphetamines, weight-loss pharmacotherapy has been regarded, by both patients and physicians, as ineffective and potentially dangerous [26]. Historically, determining whether a weight-loss medication was clinically effective or not has been a subject of debate. Current regulatory criteria for approval of weight-loss medications are based on evidence suggesting that a 5% reduction in body weight leads to substantial reductions in lipid levels, blood pressure, and insulin resistance. Hence, based on the effects found in large pharmacological prevention trials studying these CVD risk factors, it is assumed that reductions in these parameters may in turn lead to a decrease in cardiovascular events [27–29]. Therefore, for regulatory approval by the US FDA, drug manufacturers must conduct randomized controlled trials with ≥ 3000 patients for a duration of at least 1 year [28]. To demonstrate efficacy, new study drugs must meet one of the following criteria at the end of the trial: (1) the mean difference in weight loss between pharmacotherapy and placebo must be ≥ 5% or (2) a greater proportion (≥ 35% and double that of the placebo group) of patients on pharmacotherapy must have lost ≥ 5% more weight than patients on placebo [28]. The European Medicines Agency (EMA) requires that patients taking the drug lose ≥ 10% of their baseline body weight and that they must also lose ≥ 5% more weight than patients on placebo [30]. The proportion of patients losing > 10% body weight is considered as an alternative endpoint.

The first drug to meet these thresholds was dexfenfluramine [31], a serotonin reuptake inhibitor and releasing agent. It was approved in the USA in 1996 for patients with a BMI > 30 kg/m^2 or > 27 kg/m^2 with a comorbid condition such as T2DM, arterial hypertension, or dyslipidemia. Subsequently, these criteria have become the standard indications for weight-loss pharmacotherapy. However,

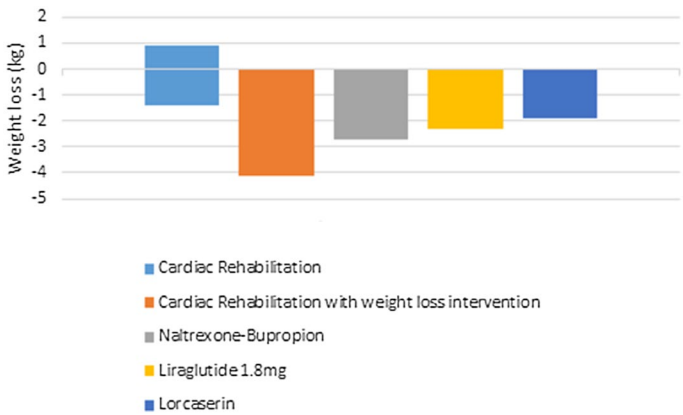

Fig. 1 Reported weight loss according to intervention/medication in patients with cardiovascular disease [16–18, 21, 22, 39, 52, 61]. For cardiac rehabilitation, range of results are for studies with data at 1 year of follow-up

amidst the success of the drug, reports of carcinoid-like left-sided heart valve lesions and pulmonary hypertension began to emerge, which eventually led to its withdrawal from the market [32]. Next came sibutramine [33, 34], a noradrenaline and serotonin reuptake inhibitor that was rapidly challenged because of concerns about its adverse effects on blood pressure and heart rate [35]. Despite claims that the favorable effect of weight loss on lipids would yield a favorable cardiovascular profile, regulatory authorities called for a cardiovascular safety trial [28]. The SCOUT trial enrolled 9804 patients with CVD (75%) or T2DM and another cardiovascular risk factor. In this high-risk cohort, after a median follow-up of 3.4 years, sibutramine increased the risk of the composite of MACE (hazard ratio [HR] 1.16; $P = 0.02$), driven essentially by nonfatal myocardial infarction and stroke [36]. Of note, in patients with established CVD, weight loss was associated with reduced cardiovascular mortality [37]. Following the SCOUT trial, sibutramine was also withdrawn from the market, and, consequently, the FDA requires cardiovascular outcomes trials (CVOTs) for every new weight-loss pharmacotherapy to determine cardiovascular safety (Table 1). Rimonabant, a cannabinoid-receptor inhibitor followed suit with a large cardiovascular safety trial, which also led to its withdrawal because of increased suicides and suicide attempts [38].

The recently published CAMELLIA-TIMI 61 trial [39] evaluated the cardiovascular safety of lorcaserin, a high-affinity serotonin receptor 2C agonist, in 12,000 patients with a BMI > 27 kg/m^2 with atherosclerotic CVD or at high CVD risk. After a median follow-up of 3.3 years, the primary safety outcome (composite of cardiovascular death, myocardial infarction, or stroke) was 2% per year in the lorcaserin group and 2.1% per year in the placebo group ($P < 0.001$ for noninferiority). Among the patients for whom echocardiographic data were available at baseline and at 1 year (echocardiographic substudy), there was no significant increase in new or worsening valvulopathy or pulmonary hypertension in the lorcaserin group, although this study was not powered to assess differences in these endpoints. However, with trial results showing an increased occurrence of cancer with the use of lorcaserin, the FDA issued a request that the manufacturer withdraw the weight-loss drug from the US market in January 2020 [40]. The trial found that more patients taking lorcaserin ($n = 462$ [7.7%]) were diagnosed with cancer than were those taking placebo ($n = 423$ [7.1%]).

3 Current Weight-Loss Pharmacotherapeutic Agents

Currently, five drugs are approved in the USA: phentermine, phentermine–topiramate, orlistat, naltrexone–bupropion, and liraglutide. Phentermine and phentermine–topiramate are not approved in Canada or Europe.

Phentermine is contraindicated in patients with CVD [41] and is not approved for chronic use (maximum 12 weeks). As such, it has not been studied in patients with obesity and CVD, which are chronic conditions that may require lifelong therapy.

Table 1 Major cardiovascular safety trials

Study drug	Number of patients	Follow-up (years)	CVD (%)	Diabetes (%)	Age (years)	Women (%)	BMI (kg/m²)	Weight loss (kg)[a]	Outcome (HR)	p-value	Comment
Sibutramine[36]	9 804	Mean 3.4	15.8	24.3	63.2	42.4	33.7	2.4	1.16; 95% CI 1.03-1.31	0.02 (inferiority)	Excess non fatal MI and non fatal stroke
Rimonabant[38]	18 695	Mean 1.15	56.6	60.3	64	36.1	33.1	N/A	0·97, 95% CI 0·84–1·12	0.68 (superiority)	Trial prematurely teminated
Naltrexone-Bupropion[52]	8910	Median 2.3	32.1	85.2	61	54.5	36.6	2.7	0.95; 99.7% CI, 0.95-1.38	N/A	Trial prematurely teminated
Liraglutide[52]	9340	Median 3.8	72.4	100	64.3	35.7	32.5	2.3	0.87; 95% CI, 0.78-0.97	<0.001 (non-inferiority), 0.01 (superiority)	
Lorcaserin[39]	12 000	Median 3.3	74.7	56.8	64	35.8	35	1.9	0.99; 95% CI, 0.85-1.14	<0.001 (non-inferiority)	

Coloured shading indicates direction of the observed effect of the medication. Red - increase in major adverse cardiac events; Gray - No significant effect on major cardiac events; Green - decrease in major cardiac events

All trials were randomized controlled trials comparing one to one with placebo with lifestyle interventions in both groups. The primary outcome was MACE, defined as nonfatal MI, nonfatal stroke, and cardiovascular death in all trials except the SCOUT trial, which included resuscitation after cardiac arrest in the composite endpoint. Analyses were by modified intention to treat

BMI body mass index, *CI* confidence interval, *CVD* established cardiovascular disease, *MACE* major adverse cardiovascular event, *MI* myocardial infarction, *NA* not available, *T2DM* type 2 diabetes mellitus

[a]Compared with placebo at study completion/termination

Data presented as hazard ratio (95% CI) unless otherwise indicated

All trials discussed hereafter were double-blind randomized controlled trials with lifestyle and diet interventions applied to both groups. Thus, the degree of weight loss reported is not solely explained by the medication tested but reinforced by the nonpharmacological weight-loss approaches. Second, patients enrolled in these trials satisfied the indications for weight-loss medications (BMI > 30 kg/m^2 or > 27 kg/m^2 with a comorbidity such as T2DM, dyslipidemia, or hypertension). Lastly, in the efficacy trials, the population studied differed significantly from patients with atherosclerotic CVD, as the majority of patients enrolled were young women (aged < 50 years) in whom the prevalence of atherosclerotic CVD is low.

3.1 Orlistat

Orlistat is a pancreatic lipase inhibitor that exerts its activity in the intestinal lumen. Inhibition of the pancreatic lipase inhibits lipid absorption and is therefore most efficient in patients who specifically eat too much fat. Efficacy for orlistat is derived from a total of 17 randomized trials in diverse settings. By far the largest of these, the Xendos trial [42], enrolled 3305 patients with a BMI > 30 kg/m^2 and randomized them to orlistat or placebo. The primary endpoints were the onset of new T2DM and weight loss. After a follow-up of 4 years, orlistat provided a relative risk reduction of 37.3% ($P < 0.0032$) for new onset of T2DM and a mean weight loss of 3.6 versus 1.4 kg in the placebo group ($P < 0.001$). In this trial and in clinical practice, the use of orlistat is hampered by inconvenient gastrointestinal side effects (91% of patients within the first year) [42] such as flatulence, steatorrhea, and fecal incontinence.

In the Xendos trial, blood pressure, fasting glucose, low-density lipoprotein (LDL) cholesterol and the LDL/high-density lipoprotein (HDL) ratio were significantly and durably reduced despite a lesser increase in HDL cholesterol with orlistat (Table 2) [42]. The reduction in triglycerides was comparable between placebo and orlistat. No data on mortality or MACE were reported.

3.2 Phentermine–Topiramate

Phentermine is an amphetamine derivative, and its primary action is to stimulate the release of noradrenalin, thereby suppressing appetite. The mechanisms leading to weight loss with topiramate, an anti-epileptic drug, are incompletely understood but may include inhibition of high-voltage-activated calcium channels and modulation of glutamate and γ-aminobutyric acid (GABA) signaling. The association of phentermine and topiramate was assessed in two trials (CONQUER [43], 2487 patients; EQUIP [44], 1267 patients). Both trials randomized patients to placebo, phentermine–topiramate 15/92 mg, and an intermediate dose of phentermine–topiramate (7.5/46 mg). After 1 year, patients on phentermine–topiramate 15/92 mg lost 8.8 and 10.8 kg more than patients on placebo in CONQUER and EQUIP, respectively ($P < 0.0001$ for both comparisons). Alternatively, 70 and 67% of patients on phentermine–topiramate lost ≥ 5% compared with 21 and 17% in the placebo groups in CONQUER and EQUIP, respectively ($P < 0.0001$ for both comparisons). As such, phentermine–topiramate is associated with the most impressive weight reductions reported in trials of weight-loss drugs versus placebo. Frequent side effects include dry mouth, paresthesia, constipation, and headaches.

This impressive weight reduction is associated with improvements in the cardiometabolic profile (blood pressure, lipids, glucose metabolism) (Table 2). However, phentermine is contraindicated in patients with CVD [41], and neither phentermine alone nor its association with topiramate have been examined in a CVOT.

3.3 Naltrexone–Bupropion

Naltrexone is approved as monotherapy for opioid addiction and alcohol dependence, whereas bupropion is approved as monotherapy for depression, smoking cessation, and seasonal affective disorder [45, 46]. Naltrexone blocks opioid-mediated pro-opiomelanocortin auto-inhibition, and bupropion inhibits reuptake of dopamine and noradrenalin [45, 47]. The mechanism of action of the combination relates to complex central pathways of reward and satiety.

The association of naltrexone and bupropion was assessed in four trials: COR (Contrave Obesity Research)-1 [48], COR-2 [49] (1496 patients), COR-BMOD [50] (with added intensive lifestyle intervention, 793 patients), and COR-Diabetes [51] (505 patients with diabetes). In the COR-1 trial, 1742 patients were randomized to naltrexone–bupropion 32/360 mg, naltrexone–bupropion 16/360 mg, or placebo and lost 6.1, 5.0, and 1.3% of their body weight, respectively ($P < 0.0001$ vs. placebo). Significantly more patients lost > 5% of their body weight in the 32/360 mg (48%) and the 16/360 mg (39%) groups compared with those in the placebo group (16%; $P < 0.0001$ for both comparisons). Frequent side effects included nausea (29.8% of patients in the 32/360 mg group), headache, constipation, dizziness, vomiting, and dry mouth. The other three COR trials [49–51] reported similar results, including in patients with T2DM.

In the COR trials, naltrexone–bupropion decreased triglycerides and increased HDL cholesterol, whereas reductions in LDL cholesterol and fasting glucose were less consistent (Table 2) [48–51]. Of note, in the naltrexone–bupropion cohorts, blood pressure was higher than in the placebo groups.

Table 2 Net difference in cardiometabolic parameters in randomized trials of clinical efficacy and cardiovascular safety

Study drug	Study	Initial Sample size	Duration of follow-up	Weight loss	SBP (mmHg)	DBP (mmHg)	TC (%)	LDL-C (%)	HDL-C (%)	TG (%)	Fasting glucose (mmol/L)	HbA1c (%)
Efficacy trials												
Orlistat 120mg t.i.d.	Xendos[42]	3 305	4 years	**-2.8kg**	**-0.7**	**-1.5**	**-5.6**	**-7.7**	**-2.6**	**-2.0**	**-0.1**	
Phentermine/topiramate 15/92mg o.d.	EQUIP[44]	996[a]	56 weeks	**-10.8kg**	**-3.8**	**-1.9**	**-2.5**	**-2.9**	**+3.5**	**-14.3**	**-0.14**	
	CONQUER[43]	1960	56 weeks	**-8.8kg**	**-3.2**	**-1.1**	**-3.0**	**-2.8**	**+5.6**	**-15.3**	**-0.20**	**-0.2**
Naltrexone/bupropion 16/180mg b.i.d.	COR-I[48]	1 164[a]	56 weeks	**-4.7kg**	**+1.8**	**+0.9**		-1.5	**+7.2**	**-9.6**	**-0.11**	
	COR-II[49]	1 496[a]	56 weeks	**-4.9kg**	**+1.1**	+0.1		**-4.1**	**+4.5**	**-9.3**	-0.09	
	COR-BMOD[50]	793[a]	56 weeks	**-4.2%**	**+2.6**	**+1.4**		-2.9	**+6.6**	**-8.1**	-0.08	
	COR-Diabetes[51]	505[a]	56 weeks	**-3.2%**	+1.1	+0.4		-1.4	**+3.3**	**-10.6**	-0.44	**-0.5**
Liraglutide 3mg o.d.	SCALE Obesity & Prediabetes[58]	3 731[a]	56 weeks	**-5.6kg**	**-2.8**	**-0.9**	**-2.3**	**-2.4**	**+1.9**	**-9.3**	**-0.38**	**-0.23**
	SCALE Maintenance[55]	422	56 weeks	**-5.9kg**	**-2.7**	-0.3	-2.0	-3.4	0.0	**-9**	-0.4	-0.3
	SCALE Diabetes[59]	635[a]	56 weeks	**-4.2kg**	**-2.6**	-0.4	**-5.3**	-4.4	**+1.8**	**-14.3**	**-1.77**	**-0.93**
Cardiovascular safety trials												
Naltrexone/bupropion 16/180mg b.i.d.	Nissen et al[52]	8 910	121 weeks[b]	**-2.7kg**[c]	**+0.9**[c]							
Liraglutide 1.8mg o.d.	LEADER[61]	9 340	3.8 years[d]	**-2.3kg**	**-1.2**	**-0.6**						**-0.40**

Bold indicates statistically significant results

Net difference is calculated by subtracting the effect observed in the placebo cohort from the effect observed in the study drug cohort. Of note, baseline values, although similar, were not always the same despite randomization. Results in green indicate statistically significant improvements in cardiometabolic parameters. Results in red indicate statistically significant worsening in cardiometabolic parameters. Results in white were not statistically significant

bid twice daily, *BP* blood pressure, *DBP* diastolic BP, *HbA1c* glycated hemoglobin, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *od* once daily, *SBP* systolic BP, *TC* total cholesterol, *TG* triglycerides, *tid* three times daily

[a]The EQUIP trial randomized a third cohort, not presented here, to phentermine–topiramate 3.75/23 mg. The CONQUER trial randomized a third cohort, not presented here, to phentermine–topiramate 7.5/46 mg. The COR-I trial randomized a third cohort, not presented here, to naltrexone–bupropion 8/180 mg bid. The COR-II trial randomized patients to naltrexone–bupropion 32/360 mg versus placebo in a 2:1 ratio. The COR-BMOD trial randomized patients to naltrexone–bupropion 32/360 mg versus placebo in a 3:1 ratio. The COR-Diabetes trial randomized patients to naltrexone–bupropion 32/360 mg versus placebo in a 2:1 ratio. The SCALE Obesity & Prediabetes and the SCALE-Diabetes trials randomized patients to liraglutide 3 mg versus placebo in a 2:1 ratio. The SCALE-Diabetes trial randomized a third cohort, not presented here, to liraglutide 1.8 mg

[b]This trial was interrupted prematurely, median follow-up was 121 weeks. Patients discontinued the drug if they had not lost weight or if bp increased by > 10 mmHg after 16 weeks

[c]Results for weight and BP are derived from the analysis at 16 weeks

[d]Median follow-up for cardiovascular events. In the LEADER trial, analysis of cardiometabolic parameters including weight was performed after 36 months

After naltrexone–bupropion met the FDA requirement for efficacy, a cardiovascular safety trial was undertaken [52]. Overweight or obese patients ($N = 8910$) at high risk of or with atherosclerotic CVD (32.2%) were randomized to placebo or naltrexone–bupropion 32/360 mg. In this population, mean age was 61.0 years, and 54.5% were women. The primary outcome was noninferiority in terms of MACE, with a prespecified upper limit of the confidence interval (CI) of the HR of 1.4. Unfortunately, the trial ended prematurely because the sponsor disclosed confidential interim data [52]. Thus, noninferiority could not be ascertained (after 50% of planned events, HR for MACE 0.88; adjusted 99.7% CI 0.57–1.34). In fact, the HR increased at the end of the study (HR 0.95; 99.7% CI 0.65–1.38). Weight loss was less than in the previously cited studies, with a 2.5% reduction in the naltrexone–bupropion group compared with placebo (Fig. 1). Dropout was important, as only 37.5 and 26.3% of patients were still receiving treatment after 1 year in the naltrexone–bupropion and placebo groups, respectively.

At 16 weeks, systolic blood pressure increased more with naltrexone–bupropion than with placebo (Table 2).

3.4 Liraglutide

Liraglutide, a subcutaneous injectable glucagon-like peptide-1 (GLP-1) receptor agonist, is approved as an adjunct

therapy to diet and exercise for the management of T2DM at doses up to 1.8 mg once daily [53]. Results from clinical trials demonstrated the ability of GLP-1 analogs to induce weight loss [54]. Weight loss with liraglutide is dose dependent up to 3.0 mg once daily [55, 56] and is mediated by reduced appetite and energy intake [57].

The SCALE (Satiety and Clinical Adiposity–Liraglutide Evidence) Obesity-Prediabetes [58] trial studied liraglutide 3.0 mg daily as an adjunct to diet and exercise in a population of 3731 patients who were obese or overweight with comorbidities. After 56 weeks, the group treated with liraglutide 3.0 mg had a mean weight loss of 8.4 kg compared with 2.8 kg in the placebo group ($P < 0.001$). In the liraglutide group, 63.2% of the subjects lost ≥ 5% of total body weight compared with 27.1% in the placebo group ($P < 0.001$). Nausea was reported in 40.2% of patients treated with liraglutide. In SCALE-Diabetes [59] (846 patients with diabetes), weight loss was comparable. SCALE-Maintenance [55] randomized 422 patients who had previously lost > 5% body weight with a low-carbohydrate diet to liraglutide or placebo. After 56 weeks, mean weight loss decreased a further 6.2% in the liraglutide group, and more patients maintained the initial 5% weight loss in the liraglutide group than in the placebo group (81.4 vs. 48.9%; $P < 0.0001$).

Liraglutide treatment was associated with reductions in systolic blood pressure, fasting glucose, triglycerides, and LDL cholesterol, whereas HDL cholesterol levels increased (Table 2) [55, 58, 59].

No CVOT has been performed with liraglutide at the weight-loss dose of 3.0 mg, but a meta-analysis of the SCALE studies found no excess cardiovascular risk [60]. Furthermore, the LEADER trial [61] showed positive cardiovascular outcomes in patients with T2DM treated with liraglutide 1.8 mg daily, obviating the need for a CVOT for the 3 mg dose for the treatment of obesity. In the LEADER study, 9340 patients with T2DM (mean BMI 32.5 ± 6.3 kg/m^2) were randomized to receive either liraglutide or placebo. Participants had at least one coexisting cardiovascular condition, such as CAD, peripheral vascular disease, chronic kidney disease, or congestive heart failure, or at least one cardiovascular risk factor, such as hypertension or left ventricular hypertrophy. The primary outcome was first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. Of the 9340 patients (mean age 64.3 years, 35.7% women), the majority (6764 [72.4%]) had established CVD. The primary outcome occurred in significantly fewer patients in the liraglutide group (13.0%) than in the placebo group (14.9%) (HR for MACE 0.87; 95% CI 0.78–0.97; $P < 0.001$ for noninferiority; $P = 0.01$ for superiority). There were fewer deaths due to cardiovascular causes in the liraglutide group than in the placebo group (4.7 vs. 6.0%; $P = 0.007$), whereas the rates of myocardial infarction, stroke, and hospitalization for heart failure were not significantly lower with liraglutide than with placebo. Net weight loss was 2.3 kg in favor of liraglutide (1.8 mg daily) (Fig. 1). Acute gallstone disease emerged as a more frequent adverse event in the liraglutide group (3.1 vs. 1.9%; $P < 0.001$). Interestingly, side effects such as nausea were less frequent than in the SCALE trials, although this may simply be related to the lower dosage. Based on the results of the LEADER trial, liraglutide 1.8 mg is now indicated for the reduction of major cardiovascular events in adults with T2DM and CVD [62, 63].

Regarding the cardiometabolic profile, blood pressure and glycated hemoglobin were reduced with liraglutide (Table 2).

The SELECT (Semaglutide Effects on Cardiovascular Outcomes in People With Overweight or Obesity) CVOT of semaglutide in overweight/obese patients with CAD is underway. This study is expected to enroll 17,000 participants and last for about 2.5–5 years.

4 Clinical Outcomes

4.1 Efficacy Trials

Weight-loss pharmacotherapy has certainly proven some efficacy, at least according to the FDA and EMA regulations, albeit with frequent adverse side effects. However, analysis of the results suggests that efficacy is highly heterogeneous, as some patients lose > 5% body weight, others lose > 10%, and others do not seem to respond. This has led to the recommendation that the drug be discontinued if the patient has not lost > 5% body weight after a 3-month trial [64]. Likewise, according to these trials, adverse side effects leading to discontinuation only happen in a fraction of patients. Yet, no predictors of efficacy or susceptibility to adverse side effects, before initiation of therapy, have emerged, which hinders selection of the optimal patients (responders) who may benefit from weight-loss pharmacotherapy. Nevertheless, most trials demonstrated weight loss and improvements in blood pressure as well as lipid and glucose metabolism. Beyond cardiovascular outcomes, this may lead to, for example, delays in progression to diabetes, reductions in diabetes-related complications, fewer orthopedic problems, and improved quality of life.

Only one head-to-head randomized weight-loss drug comparison (liraglutide vs. orlistat) has been performed, with a 2-year follow-up period. In this trial, liraglutide induced more weight loss than orlistat (5.3 vs. 2.3 kg, respectively; $P < 0.001$) [56, 65]. In a Bayesian network meta-analysis by Khera et al. [66] (29,018 overweight and obese patients), orlistat, lorcaserin, naltrexone–bupropion, phentermine–topiramate, and liraglutide, compared with placebo, were each associated with achieving ≥ 5% weight

loss at 52 weeks. Phentermine–topiramate and liraglutide were associated with the highest odds of achieving at least 5% weight loss, but liraglutide was also associated with higher odds of discontinuation because of side effects. Naltrexone–bupropion displayed the same adverse effects profile with less efficacy. Orlistat and lorcaserin seemed to incur fewer adverse side effects but induced less weight loss [66].

In most trials, follow-up was limited to 1 year. Analysis of the weight-loss response under pharmacotherapy systematically shows a nadir weight after 6–12 months, with a progressive weight gain thereafter (Fig. 2). This is most evident in the few trials that extended follow-up after 1 year [42, 67, 68] and suggests that the efficacy of these drugs may wane over time. This may also reflect discontinuation of weight-loss therapy in intention-to-treat analyses with progressively fewer patients receiving the active drug.

Only three studies assessed weight gain after discontinuation of the active drug. In the BLOOM trial [68], patients receiving lorcaserin were re-randomized to lorcaserin or placebo after 1 year. Patients subsequently reassigned to placebo regained the weight loss attributable to lorcaserin within 6 months (Fig. 2). In the RIO trial, assessing the efficacy of rimonabant, patients initially on rimonabant who were subsequently randomized to placebo after 1 year also regained all weight lost [69]. Similar findings were reported with orlistat [70]. Thus, weight maintenance after drug discontinuation is problematic and implies a need for sustained therapy to maintain the benefit of initial weight loss, as is often the case with the management of other cardiovascular risk factors. The fact that prolonged therapy is necessary is also in line with the concepts of energy homeostasis and hormonal counter-regulation to weight loss [71, 72]. Therefore, these medications should be intended for prolonged use, and this raises concerns regarding long-term safety.

Substantial dropout rates (30–50%) were the hallmark of all the efficacy trials. To account for this, a modified intention-to-treat analysis was applied, where only patients with at least one follow-up visit were included in the final analysis, and the last observation was carried forward for subjects who withdrew. Rates of discontinuation were more important in the placebo groups. It has been suggested that many patients agreed to participate in these trials because they hoped to receive the drug then discontinued if they believed they did not. In active treatment groups, discontinuation was more often related to adverse effects. Although it is difficult to infer how these missing data influenced the systematic trend of weight regain, multiple sensitivity analyses yielded consistent results, suggesting that all of these trials demonstrated a small significant reduction in weight compared with placebo.

Lastly, the efficacy trials enrolled primary cardiovascular prevention populations (essentially young women) and were not powered to assess clinical cardiovascular event endpoints.

4.2 Cardiovascular Outcome Trials

The aforementioned CVOT studies suggest that the magnitude of weight loss with currently approved pharmacotherapy in overweight and obese patients with atherosclerotic CVD is modest at best. Furthermore, the clinical impact can only be inferred from CVOTs with a large majority of patients with atherosclerotic CVD as no clinical trial has been conducted in these patients exclusively. Additionally, the primary endpoint of these CVOTs was noninferiority. Superiority was only a secondary endpoint for which these trials with increasingly low event rates were not powered.

The mechanistic relationship between weight loss achieved by pharmacotherapy and its impact on atherosclerotic disease has only been studied with rimonabant. The STRADIVARIUS trial found no difference in change in percentage of atheroma volume by coronary intravascular imaging after 18 months of treatment despite a significant reduction in body weight (−3.8 kg vs. placebo; $P<0.001$) [73].

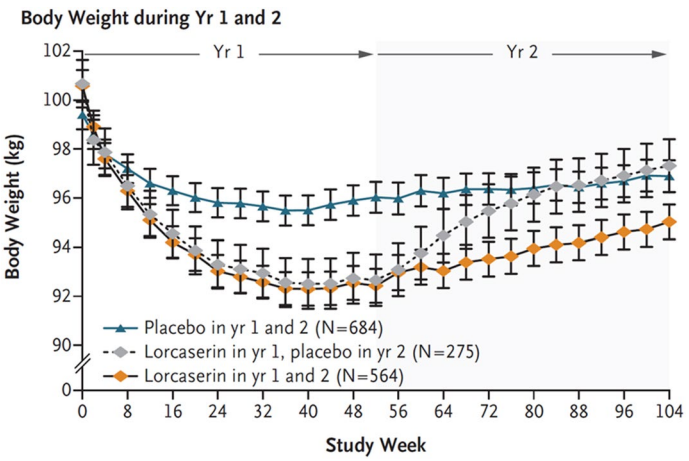

Fig. 2 Effects of lorcaserin 10 mg versus placebo on mean body weight during the first year (left). Then, during the second year (right), effect of lorcaserin 10 mg, placebo, and placebo after 1 year of lorcaserin. Reproduced with permission from Smith et al. [68]. *yr* year

Similarly, the AUDITOR trial found no difference in carotid intima-media thickness after 30 months of therapy and weight loss of 3.2 kg compared with placebo ($P < 0.0001$) [74]. This contrasts with evidence of reduced CAD severity observed in trials on lifestyle intervention, albeit with different methods [21–23]. This may reflect that weight loss following lifestyle intervention could have a greater effect on atherosclerotic CVD than weight-loss pharmacotherapy alone, possibly related to mechanisms associated with exercise or specific diets that are independent of weight loss.

Interestingly, weight loss was less convincing in the three cardiovascular safety studies than in the initial efficacy trials. Indeed, patients on active drug treatment only lost 2.7, 1.9, and 2.3 kg compared with placebo with naltrexone–bupropion [52], lorcaserin [39], and liraglutide (albeit with the 1.8 mg dose) [61], respectively (Table 1, Fig. 1). This notwithstanding, some patients did present substantial losses and could therefore benefit from these drugs. However, the selection of such patients remains challenging in the absence of clear predictors of efficacy and adverse side effect profile.

With regards to cardiovascular benefit, on the one hand, the results of the LEADER [61] trial are highly encouraging in patients with obesity and T2DM. Positive results have also been replicated with other GLP-1 receptor agonists (semaglutide and dulaglutide) in the setting of diabetes, and these other agents also seem to induce weight loss [75–77]. The SELECT trial will provide important answers regarding the efficacy and safety of weight-loss pharmacotherapy in obese patients with CAD. On the other hand, results from the CAMELLIA-TIMI 61 [39] trial are quite disappointing as weight loss was minimal and no clear cardiovascular benefit was observed after > 3 years of treatment. Although cardiovascular safety data are inconclusive and minor increases in blood pressure remain a concern, naltrexone–bupropion could hold a niche indication for patients with atherosclerotic CVD wishing to quit smoking, as weight gain frequently occurs with smoking cessation. This strategy, which has not yet been studied, is supported by the primary use of bupropion as a smoking cessation aid [45]. It is unclear whether regulatory authorities will continue to approve naltrexone–bupropion if another CVOT is not undertaken. Finally, although phentermine–topiramate is not recommended in patients with CVD, it is surprising that the FDA has not asked for a CVOT as its impact on CVD, even in primary prevention or in patients with latent disease, is unknown.

Lastly, in trying to understand the relationships between these medications, weight loss, and cardiovascular events, these studies have several limitations. First, assessing obesity with BMI and attempting to correlate weight loss with reductions in cardiovascular events is probably overly simplistic as baseline body composition and changes in fat distribution contribute to the cardiovascular risk profile beyond simple variations in weight [78]. Second, specific diets may lead to reduced cardiovascular events beyond weight loss [79], but no specific information was reported with regards to diet in these studies. Moreover, patients with obesity often present with unhealthy eating habits (i.e., ultra-processed foods), which may have an impact on satiety in this specific study population.

5 Conclusion

Weight-loss pharmacotherapy has come a long way since its inception at the beginning of the century, and one of the lessons gleaned from this hazardous journey is that obesity can probably not be cured but should be treated over the long term, possibly indefinitely. However, despite increasing safety, long-term efficacy remains unsatisfactory probably because of the complexity of obesity and the mechanisms behind appetite, weight homeostasis, and weight loss. Moreover, perhaps the 5% weight loss required to meet weight-loss pharmacotherapy efficacy thresholds may be insufficient to translate into reductions in cardiovascular event rates. Therefore, clinicians face a lack of truly beneficial pharmacological agents to produce substantial and persistent weight loss, and further studies with novel agents are clearly required. Lastly, although prospective data regarding the role of bariatric surgery in primary prevention suggest impressive reductions in cardiovascular events and mortality, few data are available in patients with established CVD, and further evaluation of this approach in the management of the growing population of patients with obesity and atherosclerotic CVD is necessary.

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Declarations

Conflicts of interest Charles Pirlet, Paul Poirier, Tomas Cieza, Marie-Eve Piché, Laurent Biertho, Frédéric Maes, Zoltan Ruzsa, and Olivier F. Bertrand have no potential conflicts of interest that might be relevant to the contents of this manuscript.

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