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Research Article

# Impact of Weight Loss Drugs on Cardiometabolic Parameters: Evaluation of Published Clinical Trials

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## Abstract

Weight loss drugs are indicated for the optimization of health in obese or overweight patients with comorbidities. Weight loss should lead to improvements in lipids, Hgb A1c, and blood pressure. This review addressed the impact of weight loss achieved with drug therapy and the relative magnitude of changes in cardiometabolic parameters observed in randomized placebo-controlled trials. The magnitude of changes in cardiometabolic parameters was small when weight loss was ≤10%. Weight loss ≥10% and especially ≥15% was associated with more marked improvements in cardiometabolic parameters. The centrally acting drugs did not achieve weight loss ≥10% while GLP-1 agonist and multiple incretin axis modulating drugs were associated with greater weight loss (10% to 15%) and more marked improvements in cardiometabolic parameters. Limitations of these data include that a majority of the studies did not include patients with uncontrolled hypertension or dyslipidemia and only a few studies included diabetic patients. A small number of studies did demonstrate the ability of weight loss resulting in reductions in doses of medications used for diabetes, hypertension, and lipids. Data demonstrating the true magnitude of benefit of weight loss drugs on cardiometabolic parameters will need to be evaluated in real-world experience studies.

**Keywords: Atherosclerotic cardiovascular disease; Blood pressure; Glucagon receptor**

## Introduction

Weight loss drugs, in addition to lifestyle changes, are indicated for the optimization of health in obese or overweight patients with comorbidities [1]. Risk factors for Atherosclerotic Cardiovascular Disease (ASCVD) such as diabetes, hypertension, and dyslipidemia are common in these patients [2]. Improvements in cardiometabolic parameters such as lipid levels, Hgb A1c, and Blood Pressure (BP) need to be evaluated during weight loss treatment.

The first drugs used for weight loss were centrally acting sympathomimetics limited by a risk of tolerance and addiction (Table 1) [1]. These drugs were indicated only for short-term use with substantial weight regain occurring after discontinuation. Drugs with specific effects on central nervous system receptors/neurotransmitters such as serotonin, norepinephrine, dopamine, and gamma-aminobutyric acid primarily affect appetite. These agents are associated with modest weight loss and have been deemed useful for long-term use. However, the serotonin 5-HT2 receptor agonists (fenfluramine, dexfenfluramine) and a serotonin-2C receptor agonist (lorcaserin) were removed from the market due to safety concerns. None of the centrally acting drugs have been demonstrated to reduce the risk of ASCVD events.

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The nutrient-stimulated hormone-based anti-diabetic drugs represent a paradigm shift in the management of the overweight or obese patient [3]. These agents promote weight loss through modulation of the incretin axis which includes G-protein-coupled receptors including the glucagon-like peptide-1 (GLP-1), the Glucose-Dependent Insulinotropic Polypeptide (GIP), and the Glucagon Receptor (GR). Many GLP-1 agonists are currently available with two approved for obesity (liraglutide, semaglutide). Tirzepatide is a combination GLP-1 and GIP agonist (double G agonist) approved for type -2 diabetes and obesity. A drug that works through GLP-1, GIP, and the GR (retatrutide) has been studied in type 2 diabetes and obesity but is not FDA-approved. Since the G-protein-coupled receptor modifying drugs produce greater weight loss than previously available agents, many drugs with a variety of effects on the incretin axis are currently in various phases of clinical development.

The results of a recent outcomes study with a GLP-1 agonist demonstrated a reduction in vascular events observed early after initiation of treatment [4]. This benefit occurred more rapidly than what would have been predicted if this effect was mediated entirely by weight loss. Hence, changes in cardiometabolic markers in addition to weight loss may play a key role in the benefit of anti-obesity drugs. The 2013 ACC/AHA guidelines on weight loss suggest a dose-response relationship exists between the amount of weight loss achieved by lifestyle interventions and relative improvements in cardiometabolic parameters [5]. However, evidence of such a relationship in the studies of weight loss drugs has not been thoroughly examined. The purpose of this review is to address the impact of weight loss drugs and their effect on changes in weight in relation to the magnitude of changes in cardiometabolic parameters based on published placebo-controlled randomized trials.

## Methods

A search of Embase and PubMed for the period from 1980

**Table 1:** History of commonly used FDA-approved weight loss drugs.

| Drug | Approval Date | Mechanism of action | Comment |
|---|---|---|---|
| Phentermine | circa 1959 | CNS stimulant (catecholamine) | Only indicated for short-term use (12 weeks); potential for tolerance and addiction |
| Diethylpropion | | | |
| Phendimetrazine | | | |
| Benzphetamine | | | |
| Fenfluramine | 1973 | Serotonin 5-HT2 receptors agonist | Removed from market in 1997 due to pulmonary hypertension and valvular heart damage |
| Dexfenfluramine | 1996 | Serotonin 5-HT2 receptors agonist | Removed from market due to pulmonary hypertension and valvular heart damage |
| Sibutramine (Meridia®) | 1997 | Serotonin- norepinephrine reuptake inhibitor | Removed from market 2010 due to increased cardiovascular risk |
| Orlistat (Xenical®) | 1999 | Selective inhibitor of pancreatic lipase | Limited by gastrointestinal side effects related to steatorrhea |
| Phentermine/topiramate-ER (Qysmia®) | 2012 | CNS stimulant/GABA receptor modulation | |
| Lorcaserin (Belviq®) | 2012 | Serotonin-2C receptor agonist | Removed from market in 2020 due to increased risk of cancer |
| Naltrexone/Buproprion (Contrave®) | 2014 | Opioid receptor antagonist/ Norepinephrine reuptake inhibitor | |
| Liraglutide (Saxenda®) | 2014 | GLP-1 agonist | Indicated to reduce ASCVD risk |
| Semaglutide (Wegovy®) | 2022 | GLP-1 agonist | Indicated to reduce ASCVD risk |
| Tirzepatide (Zepbound®) | 2023 | GIP and GLP-1 receptor agonist | |

through June 2024 was conducted. The Medical Subject Heading (MeSH) terms and keywords related to obesity, adipose tissue, body composition, randomized clinical trials and weight loss drugs were used to conduct the search. Studies of interest were limited to randomized placebo-controlled trials including ≥250 adults with obesity (BMI ≥ 30 kg/m$^2$) or overweight with comorbidities treated with an FDA-approved weight loss drug. A search of https://clinicaltrials.gov was also conducted using the condition "obesity" and intervention/treatment "weight loss drugs" to identify published trials with investigational drugs. Studies with the weight loss drugs used in the treatment of diabetes were included if changes in weight and at least one cardiometabolic parameter was reported. Drugs with at least two published randomized trials were included in this evaluation.

Two reviewers (JV, DH) performed data abstraction independently and in duplicate on study trial characteristics and outcomes of interest. The impact of the weight loss drugs on changes in body weight and the cardiometabolic parameters of low-density lipoprotein cholesterol (LDL-C), BP, and Hgb A1c was reported as the mean percent change in each parameter compared to the baseline observed in each study. Mean changes from baseline in these parameters with placebo were also included in the analysis. All the clinical trials reported changes in these endpoints using this measure of efficacy. In addition, studies were reviewed for the use of and changes in drug therapy indicated in the treatment of hypertension, dyslipidemia, and diabetes mellitus. Changes in these therapies during the conduct of the studies were documented when reported.

## Results

A total of 23 randomized controlled trials were identified with FDA-approved drugs for overweight/obesity that met our inclusion criteria (Table 2) [4-6,7]. One investigational drug (retatrutide) also met our inclusion criteria and is included in the analysis. There were several other investigational drugs that met the inclusion criteria except for the requirement of ≥ 2 published randomized trials with a sufficient sample size. [3,8,9] Of the 25 studies, 4 required diabetes for study inclusion, 18 excluded diabetes, and 3 allowed patients with or without diabetes to be included. One of the studies that excluded diabetes allowed patients with prediabetes to be included [10].

The type of weight loss drugs included in the identified studies were the centrally acting drugs in 5 trials, the GLP-1 agonists in 13 trials, and the multiple incretin axis modulating drugs in 7 trials.4,6-29 One of the GLP-1 agonist studies was a comparison of liraglutide and semaglutide with each cohort compared against placebo [11]. One additional GLP-1 agonist trial included treatment with a daily oral dose of semaglutide rather than the once weekly Subcutaneous (SC) injection of the drug [12]. Of the 7 trials with the multiple incretin modulators, 5 were conducted with tirzepatide which is a dual-acting GLP-1 and GIP agonist and 2 included retatrutide which is triple-acting GLP-1, GIP and GR agonist which is not yet FDA-approved [7-9,13-16].

Four trials (semaglutide = 1; tirzepatide =2; retatrutide = 1) were conducted in diabetic patients who were overweight/obese [9,14,15,17]. Three other trials (semaglutide =2; phentermine/topiramate = 1) were conducted in overweight/obese patients with or without diabetes [6,18,19]. All other studies excluded type 2 diabetes with mean baseline Hgb A1c levels <6.0%. No trial included a mean baseline BP>140/90 mmHg with all trials allowing inclusion of patients with a history of hypertension and the use of antihypertensive drugs. Mean baseline LDL-C levels were ≥120 mg/dL in only four trials in which the highest mean baseline LDL-C was 124 mg/dL. All trials allowed the use of lipid-lowering therapy.

Changes in weight and cardiometabolic parameters observed in studies with the centrally acting weight loss drug combinations phentermine/topiramate and naltrexone/bupropion are summarized in Table 3. A total of 5 studies and 8 dose cohorts were identified in which mean percent weight loss ranged from 5% to 11% [6,20-23]. Seven of the 8 dose cohorts achieved <10% weight loss. Changes in LDL-C were small with maximal LDL-C reductions of ~7% in 4

**Table 2:** Summary of baseline characteristics in weight loss drug studies.

| Baseline Characteristics | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Study | Treatment | Duration (wks) | Sample Size (n) | Age (yrs) | BMI ($kg/m^2$) | HTN (%) | BP (mmHg) | DM (%) | A1c (%) | LDL-C (mg/dL) |
| CONQUER≠[6] 2011 | Phentermine/topiramate | 56 | 2487 | 51 | 36 | 52 | 129/81 | 68 | 5.9 | 124 |
| EQUIP[7] 2011 | Phentermine/topiramate | 56 | 1267 | 43 | 42 | 0 | 122/71 | 0 | NA | 122 |
| COR-I[8] 2010 | Naltrexone/bupropion | 56 | 1742 | 44 | 36 | 20 | 119/77 | 0 | NA | 120 |
| COR-II[9] 2013 | Naltrexone/bupropion | 56 | 1496 | 44 | 36 | 31 | 118/77 | 0 | NA | 120 |
| COR-BMOD[10] 2011 | Naltrexone/bupropion | 56 | 793 | 46 | 37 | NA | 117/77 | 0 | NA | 109 |
| SCALE Obesity/Pre-DM11 2015 | Liraglutide | 56 | 3731 | 45 | 38 | 35 | 123/79 | 0 | 5.6 | 112 |
| SCALE Maintenance[12] 2013 | Liraglutide | 56 | 422 | 46 | 36 | 31 | 123/79 | 0 | 5.6 | 112 |
| SCALE IBT[13] 2020 | Liraglutide | 56 | 282 | 47 | 39 | NA | 125/80 | 0 | 5.5 | 116 |
| STEP-1[14] 2021 | Semaglutide | 68 | 1961 | 46 | 38 | 36 | 126/80 | 0 | 5.7 | 111 |
| STEP-2+[15] 2021 | Semaglutide | 68 | 1210 | 55 | 36 | 70 | 130/80 | 100 | 8.1 | 89 |
| STEP-3[16] 2021 | Semaglutide | 68 | 611 | 46 | 38 | 34 | 124/80 | 0 | 5.7 | 110 |
| STEP-4[17] 2021 | Semaglutide | 68 | 902 | 46 | 38 | 37 | 127/81 | 0 | 5.7 | 117 |
| STEP-5[18] 2022 | Semaglutide | 104 | 304 | 47 | 38 | 38 | 126/80 | 0 | 5.7 | 112 |
| STEP-6≠[19] 2022 | Semaglutide | 68 | 401 | 51 | 32 | 75 | 134/84 | 25 | 6.4 | 120 |
| STEP-7≠[20] 2024 | Semaglutide | 44 | 375 | 41 | 34 | 46 | 127/84 | 26 | 6.3 | 100 |
| STEP-8[21] 2022 | Semaglutide, Liraglutide | 68 | 338 | 48 | 37 | 43 | 125/81 | 0 | 5.5 | 106 |
| OASIS-1[22] 2023 | Semaglutide | 68 | 709 | 50 | 37 | 46 | 130/82 | 0 | 5.6 | 116 |
| SELECT[4] 2023 | Semaglutide | 136 | 17604 | 62 | 33 | 82 | 131/70 | 0 | 5.8 | 78 |
| SURPASS-1+[24] 2021 | Tirzepatide | 40 | 478 | 54 | 32 | NA | 128/80 | 100 | 7.9 | 101 |
| SURMOUNT-1[23] 2022 | Tirzepatide | 72 | 2539 | 45 | 38 | 32 | 124/79 | 0 | 5.6 | 109 |
| SURMOUNT-2+[25] 2023 | Tirzepatide | 72 | 938 | 54 | 36 | 64 | 131/80 | 100 | 8 | 97 |
| SURMOUNT-3[26] 2023 | Tirzepatide | 72 | 579 | 45 | 36 | 34 | 121/80 | 0 | 5.3 | 112 |
| SURMOUNT-4[27] 2024 | Tirzepatide | 52 | 670 | 48 | 30 | 35 | 115/76 | 0 | 5 | 112 |
| Retatrutide Phase 2 NEJM[28] 2023 | Retatrutide | 48 | 338 | 48 | 37 | 43 | 124/81 | 0 | 5.5 | 112 |
| Retatrutide Phase-2 Lancet*[29] 2023 | Retatrutide | 36 | 281 | 56 | 35 | NA | 130/80 | 100 | 8.3 | 85 |

+ = diabetes and overweight/obesity; ≠ = overweight/obese with or without diabetes

**Table 3:** Changes in weight and cardiometabolic parameters with centrally acting drugs.

| Trial | Treatment | Percent change from baseline | | | |
|---|---|---|---|---|---|
| | | Weight Loss | LDL-C | Hgb A1c | sBP/dBP |
| CONQUER[6] n = 2487 | Phentermine/topiramate | | | | |
| | 7.5/46 mg | -7.8* | -3.7 | 0.0* | -4.7*/-3.4* |
| | 15/92 mg | -9.8* | -6.9* | -0.1* | -5.6*/-3.8* |
| | Placebo | -1.2 | -4.1 | 0.1 | 0.888888889 |
| EQUIP[7] n = 1267 | Phentermine/topiramate | | | | |
| | 3.75/23 mg | -5.1* | -7.7 | | -1.8*/-0.1 |
| | 15/92 mg | -10.9* | -8.4 | NA | -2.9*/-1.5* |
| | Placebo | -1.6 | -5.5 | | 2.25 |
| COR-I[8] n = 1742 | Naltrexone/bupropion | | | | |
| | 16/360 mg | -5.0* | -1.5 | NA | +0.3*/+0.1* |
| | 32/360 mg | -6.1* | -2 | | -0.1*/-0.3* |
| | Placebo | -1.3 | -0.5 | | 2.111111111 |
| COR-II[9] n = 1496 | Naltrexone/bupropion | | | | |
| | 32/360 | -6.4* | -6.2* | NA | +0.6*/+0.4 |
| | Placebo | -1.2 | -2.1 | | -1.66666667 |
| COR-BMOD[10] n = 793 | Naltrexone/bupropion | | | | |
| | 32/360 | -9.3* | 7.1 | NA | -1.3*/-1.4* |
| | Placebo | -5.1 | +10.0* | | 1.392857143 |

* = statistically significant difference from placebo

dose cohorts. One study observed a 7% increase in LDL-C [23]. Hgb A1c was reported in only 1 study (2 dose cohorts) which allowed the inclusion of patients with diabetes [6]. There was essentially no change from baseline in the Hgb A1c (-0.1%) in that study even though the difference between treatment with high dose phentermine/topiramate was statistically different from placebo. BP changes were small with no treatment cohort associated with a >6% decrease in systolic BP. One study did not report changes in BP. Two other studies found <1% change in both systolic and diastolic BP. While higher dose cohorts of the drug combinations in the individual studies produced numerically greater weight loss and reductions in LDL-C and systolic BP, the absolute changes were small.

Changes in weight and cardiometabolic parameters observed in studies with the GLP-1 agonists are summarized in (Table 4) [4,10-12,17-19,24-29]. There were 16 dose cohorts (liraglutide = 4; semaglutide = 12) in 13 studies with one study comparing liraglutide and semaglutide and 2 studies including a lower and standard dose semaglutide cohort. None of the 4 liraglutide dose cohorts achieved ≥10% weight loss [10,24,25]. The greatest reductions in LDL-C with liraglutide were 3% and 1.5% in 2 studies and <1% in the others. In addition, changes in Hgb A1c with liraglutide were all ≤0.3%, but

**Table 4:** Changes in weight and cardiometabolic parameters with GLP-1 agonists.

| Trial | Treatment | Percent change from baseline | | | |
|---|---|---|---|---|---|
| | | Weight Loss | LDL-C | Hgb A1c | sBP/dBP |
| SCALE Obesity-Prediabetes[11] n = 3731 | Liraglutide 3 mg SC weekly | -8.0* | -3.0* | -0.3* | -4.2*/-2.6* |
| | Placebo | -2.6 | -1 | -0.06 | 0.78947368 |
| SCALE Maintenance[12] n = 422 | Liraglutide 3 mg SC weekly | -6.2* | 0.9 | -0.1* | +0.2*/+1.4 |
| | Placebo | -0.2 | 1.3 | 0.1 | 2.33333333 |
| SCALE IBT[13] n = 282 | Liraglutide 3 mg SC weekly | -7.5* | -1.5 | -0.16* | 2.8 |
| | Placebo | -4.5 | 1.5 | -0.06 | 0.75 |
| STEP-1[14] n = 1961 | Semaglutide 2.4 mg SC weekly | -14.9* | -0.9* | -0.45* | -6.2*/-2.8* |
| | Placebo | -2.4 | 0.1 | -0.15 | 2.75 |
| STEP-2[15] n = 1210 | Semaglutide | | | | |
| | 2.4 mg SC weekly | -9.6* | 0 | -1.6* | -3.9*/-1.6 |
| | 1.0 mg SC weekly | -7 | 0 | -1.5* | 4.83333333 |
| | Placebo | -3.4 | 0 | -0.4 | 0.55555556 |
| STEP-3[16] n = 611 | Semaglutide 2.4 mg SC weekly | -16.0* | -4.7* | -0.5* | -5.6*/-3.0* |
| | Placebo | -5.7 | 2.6 | -0.3 | 2 |
| STEP-4[17] n = 902 | Semaglutide 2.4 mg SC weekly | -7.9* | +1.0* | -0.1* | +0.5*/+0.3 |
| | Placebo | 6.9 | 8 | 0.1 | 4.88888889 |
| STEP-5[18] n = 304 | Semaglutide 2.4 mg SC weekly | -15.2* | -6.1 | -0.4 | -5.7*/-4.4 |
| | Placebo | -2.6 | -2.7 | -0.1 | 2 |
| STEP-6[19] n = 401 | Semaglutide | | | | |
| | 2.4 mg SC weekly | -13.2* | -12.2* | -0.96* | -10.9*/-5.3* |
| | 1.7 mg SC weekly | -9.6* | -11.1* | -0.93* | -11.2*/-4.3* |
| | Placebo | -2.1 | -4.7 | -0.03 | 2.40909091 |
| STEP-7[20] n = 375 | Semaglutide 2.4 mg SC weekly | -12.1* | -2.2 | -0.8* | -6.1*/-4.3* |
| | Placebo | -3.6 | 3.2 | -0.1 | 3.71428571 |
| STEP-8[21] n = 338 | Semaglutide 2.4 mg SC weekly | -15.8*≠ | -6.5* | -0.2*≠ | -5.7*/-3.0*≠ |
| | Liraglutide 3 mg SC weekly | -6.6 | 0.9 | -0.1 | -5.8 |
| | Placebo | -1.9 | 0.8 | 0.1 | 4.57142857 |
| OASIS-1[22] n =709 | Semaglutide 50 mg po daily | -15.1* | -0.6 | -0.2* | -6.6*/-2.4* |
| | Placebo | -2.4 | 1.7 | 0.1 | 0.5 |
| SELECT[4] n = 17604 | Semaglutide 2.4 mg SC weekly | -9.4* | -5.2* | -0.3* | -3.8*/-1.0% |
| | Placebo | -0.9 | -3.1 | 0.01 | 1 |

* = statistically significant difference from placebo; ≠ = statistically significant difference from liraglutide

these studies excluded patients with diabetes. The maximal decrease in systolic BP with liraglutide was 5% in one cohort with 4% in one other cohort.

Weight loss ≥10% was observed in 7 of 12 dose cohorts with semaglutide and ≥15% in 4 of those 12 dose cohorts. Changes in LDL-C with semaglutide were ≥5% in 5 of 12 cohorts. A ≥10% reduction in LDL-C was observed in 2 dose cohorts. Hgb A1c reductions ≥0.5% were observed in 7 of 12 cohorts, ≥1.0% in 4 of 12 cohorts, and ≥2% in 2 of 12 cohorts. BP reductions were minimal except in semaglutide dose cohorts associated with ≥10% weight loss. Systolic BP reductions averaged 5% to 6% in these cohorts.

Changes in weight and cardiometabolic parameters observed in studies with the multiple incretin axis modulators are summarized in (Table 5) [13-16, 7-9]. Of the 7 studies, 5 were dose-ranging trials (tirzepatide = 3; retatrutide =2) with a total of 22 dose cohorts. Two trials with tirzepatide used a maximally tolerated dose titrated to either 10 mg or 15 mg SC weekly with 86% and 93% achieving 15 mg SC weekly [7,16]. In the 5 tirzepatide studies there were 12 dose cohorts. Weight loss ≥10% was achieved in 8 of 10 tirzepatide dose cohorts with 5 of 10 cohorts achieving ≥15% weight loss. LDL-C reductions of 5% to 12% were achieved in 10 of the 12 cohorts. Two cohorts in one tirzepatide study experienced a 2% and 3% increase in LDL-C with the 10 mg and 15 mg doses, respectively. Reductions in Hgb A1c were approximately 2% in the studies including patients with diabetes while reductions in Hgb A1c were approximately 0.5% in the studies excluding diabetic patients. Reductions in systolic BP ranged from 5% to 9% with a general trend to greater BP reductions seen with greater weight loss.

Weight loss in the 2 dose-ranging studies with retatrutide increased with increasing doses from 4 mg to 12 mg SC weekly [8,9]. Of the 10 cohorts treated with ≥4 mg weekly, ≥10% weight loss was achieved in 9 of 10 cohorts. Weight loss ≥15% was achieved in all 6 dose cohorts using the 8 mg and 12 mg weekly doses. Reductions in LDL-C were generally ≥10% in the 8 mg and 12 mg cohorts with 2 of these cohorts experiencing ≥20% LDL-C reductions. Reductions in Hgb A1c were consistently around 0.5% in the 4 mg up to 12 mg doses in the study which excluded patients with diabetes. The Hgb A1c reductions were about 2% with the 8 mg and 12 mg doses in the diabetes study. Reductions in systolic BP tended to increase from 5% to 10% with increasing retatrutide doses and with greater weight loss in both studies. Reductions in diastolic BP appeared to be less impacted by dose with a 2% to 3% reduction across the dose cohorts.

Changes in concomitant medications indicated for diabetes, hypertension, and dyslipidemia were not consistently reported in these studies (Table 6). Of the 7 studies requiring or allowing patients with known diabetes at study entry, 2 did not report changes in the use of or dosage adjustment with antidiabetic medications [9,14]. One study that excluded diabetic patients at baseline did include pre-diabetes in 61% of the patients. At the end of the 56-week follow-up, new-onset diabetes was diagnosed in 4% of liraglutide patients and 14% of placebo patients. Changes in Antihypertensive Therapy (AHT) were reported in only 1 of these 7 studies while changes in Lipid-Lowering Therapy (LLT) were not reported in any of these studies. Of the 18 studies excluding patients with diabetes, 5 reported changes in both AHT and LLT. In all, only 10 of the 25 studies reported a change in one of the three classes of medications used for diabetes,

**Table 5:** Changes in weight and cardiometabolic parameters with the multiple incretin axis modulating drugs.

| Trial | Treatment | Percent change from baseline | | | |
|---|---|---|---|---|---|
| | | Weight Loss | LDL-C | Hgb A1c | sBP/dBP |
| SURPASS-1[23] n = 705 | Tirzepatide | | | | |
| | 5 mg SC weekly | -8.1* | -6.7 | -1.9* | 1.62068966 |
| | 10 mg SC weekly | -9.1* | -7.6 | -1.9* | 1.51612903 |
| | 15 mg SC weekly | -11.1* | -12.4* | -2.1* | 1.52941176 |
| | Placebo | -0.9 | -1.6 | 0.04 | 1.42857143 |
| SURMOUNT-1[24] n = 2539 | Tirzepatide | | | | |
| | 5 mg SC weekly | -15.0* | -5.3 | -0.40* | 1.34615385 |
| | 10 mg SC weekly | -19.5* | -6.6 | -0.49* | 1.49090909 |
| | 15 mg SC weekly | -20.9* | -8.6 | -0.51* | 1.65217391 |
| | Placebo | -3.1 | -1.7 | -0.07 | 1.5 |
| SURMOUNT-2[25] n = 938 | Tirzepatide | | | | |
| | 5 mg SC weekly | -12.8* | 2.3 | -2.1* | -5.9*/-2.1* |
| | 10 mg SC weekly | -14.7* | 3.2 | -2.2* | -7.7*/-2.9* |
| | Placebo | -3.2 | 6.3 | -0.5 | 4 |
| SURMOUNT-3[26] n = 579 | Tirzepatide 15 mg SC weekly | -18.4* | -6.1* | -0.5* | -5.1*/-3.2* |
| | Placebo | 2.5 | 6.1 | 0 | 1.25 |
| SURMOUNT-4[27] n = 670 | Tirzepatide 15 mg SC weekly | -26.0* | -5.2* | -0.6* | -9.3*/-5.5* |
| | Placebo | -9.5 | 2.2 | -0.2 | 1.17647059 |
| Retatrutide Phase 2 NEJM[28] n = 338 | Retatrutide | | | | |
| | 1 mg SC weekly | -7.2* | -4.7 | -0.2 | 2.18181818 |
| | 4 (ID 2) mg SC weekly | -11.8* | -14.5* | -0.2 | 2.71875 |
| | 4 mg SC weekly | -13.9* | -10.2 | -0.3* | 2.59375 |
| | 8 (ID 2) mg SC weekly | -16.7* | -20.7* | -0.5* | -8.8/-3.4* |
| | 8 (ID 4) mg SC weekly | -17.9* | -16.8* | -0.5* | -11.8/-3.5* |
| | 12 (ID 2) mg SC weekly | -17.5* | -21.7* | -0.4* | -8.8/-2.8* |
| | Placebo | -1.6 | -0.3 | 0 | 3.28571429 |
| Retatrutide Phase 2 Lancet[29] n = 281 | Retatrutide | | | | |
| | 0.5 mg SC weekly | -3.2 | -10.2 | -0.4 | 8.4 |
| | 4 (ID 2) mg SC weekly | -7.9* | -6.2 | -1.4* | 3.05555556 |
| | 4 mg SC weekly | -10.4* | -7.4 | -1.3* | -7.9*/-1.8 |
| | 8 (ID 2) mg SC weekly | -16.8* | -12.5* | -2.0* | -7.4*/-0.8 |
| | 8 (ID 4) mg SC weekly | -16.3* | -11.9 | -1.9* | -9.8*/-2.4 |
| | 12 (ID 2) mg SC weekly | -16.9* | -6.9 | -2.0* | -10.2*/-2.7 |
| | Placebo | -3 | -2.8 | -0.3 | -1.25 |

* = statistically significant difference from placebo; ID = initial dose

hypertension, or lipids. Among the studies that reported medication changes, there was a consistent reduction in the intensity of therapy with active treatment compared to placebo. The magnitude of changes varied substantially between studies with no consistent correlation between magnitude of weight loss and changes in drug therapy for hypertension, lipids, or diabetes.

## Discussion

The magnitude of changes in weight loss and improvements in cardiometabolic parameters has been suggested to follow a linear dose-response relationship [5]. Greater amounts of weight loss should produce greater improvements in LDL-C, Hgb A1c, and systolic BP. The mean percent changes in weight loss and the cardiometabolic parameters based on published randomized placebo-controlled studies of the currently available weight loss drugs indicate that this relationship is most obvious when weight loss exceeds 10% of baseline. With the centrally acting weight loss drugs which produced mean weight loss generally <10%, the magnitude of improvements in cardiometabolic parameters was minimal.

The magnitude of weight loss, frequently ≥15%, and improvements in cardiometabolic parameters were substantially greater with semaglutide and the double- and triple-G-receptor agonists than with centrally acting weight loss drugs and liraglutide [4,7-9,11-19,26-29]. Semaglutide, tirzepatide, and retatrutide also achieved relatively greater improvements in the cardiometabolic parameters with higher drug doses and greater magnitude of weight loss.

There are multiple limitations that need to be considered when evaluating the magnitude of weight loss with improvements in cardiometabolic parameters. Baseline cardiometabolic parameters in the weight loss drug studies were consistently well-controlled. LDL-C was ≥120 mg/dL in only 5 of the 25 studies. Four of the studies with LDL-C ≥120 mg/dL (maximum 124 mg/dL) were seen in 5 studies evaluating the centrally acting weight loss drugs [6, 20-22]. Notable changes in LDL-C (≥10%) were uncommon except for one study with semaglutide, one study with tirzepatide, and both studies with retatrutide [8,9,13,18]. Baseline systolic BP ≥130 mmHg was seen in 6 of the 25 studies with the highest mean of 134 mmHg. Reductions in systolic BP ≥5% with semaglutide were achieved in 8 of 12 dose cohorts with no cohort achieving ≥10% reduction [4,12,24]. All cohorts with tirzepatide and retatrutide had an approximate 5% to 9% decrease in systolic BP, but only 2 retatrutide dose cohorts achieved mean systolic BP reductions of ≥10% [8,9].

Most weight loss drug studies excluded patients with diabetes and the baseline Hgb A1c was within the normal range in those studies. Four studies required diabetes as an inclusion criterion and 3 others allowed patients with diabetes to be enrolled. The magnitude of the reduction in Hgb A1c with the weight loss drugs, most notably semaglutide and the multiple incretin axis modulators, was notable (about 2%) in the diabetes studies where baseline Hgb A1c levels were

**Table 6:** Studies reporting changes* in medications used for diabetes, hypertension, and lipids.

| Study | Diabetes | | Hypertension | | Lipids | |
|---|---|---|---|---|---|---|
| | Increase | Decrease | Increase | Decrease | Increase | Decrease |
| CONQUER Phentermine/topiramate | | | | | | |
| 7.5/4 mg | 4 | NR | NR | 15 | NR | NR |
| 15/92 mg | 4 | NR | NR | 11 | NR | NR |
| Placebo | 15 | NR | NR | 5 | NR | NR |
| SCALE Obesity/Pre-DM | | | | | | |
| Liraglutide 3 | NR | NR | 3.7 | 6 | 1.3 | 1.5 |
| Placebo | NR | NR | 5.7 | 3.8 | 3.7 | 2.1 |
| STEP-2 | | | | | | |
| Semaglutide 2.4 | 5 | 29 | NR | NR | NR | NR |
| Placebo | 24 | 7 | NR | NR | NR | NR |
| STEP-4 | | | | | | |
| Semaglutide 2.4 | NR | NR | 9 | 26 | 2 | 11 |
| Placebo | NR | NR | 16 | 12 | 14 | 4 |
| STEP-5 | | | | | | |
| Semaglutide 2.4 | NR | NR | 6 | 32 | 8 | 19 |
| Placebo | NR | NR | 23 | 16 | 17 | 20 |
| STEP-6 | | | | | | |
| Semaglutide 2.4 | 6 | 18 | NR | NR | NR | NR |
| Semaglutide 1.7 | 0 | 0 | NR | NR | NR | NR |
| Placebo | 28 | 0 | NR | NR | NR | NR |
| STEP-7 | | | | | | |
| Semaglutide 2.4 | 2 | 25 | NR | NR | NR | NR |
| Placebo | 20 | 7 | NR | NR | NR | NR |
| OASIS-1 | | | | | | |
| Semaglutide 50 mg | NR | NR | 19 | 17 | 8 | 15 |
| Placebo | NR | NR | 23 | 10 | 10 | 21 |
| SURMOUNT-2 | | | | | | |
| Tirzepatide 10/15 mg | NR | 12 | NR | NR | NR | NR |
| Placebo | 24 | NR | NR | NR | NR | NR |
| SURMOUNT -3 | | | | | | |
| Tirzepatide 15 mg | NR | NR | 2.4 | 4.9 | 0.3 | 2.8 |
| Placebo | NR | NR | 6.5 | 1 | 2.1 | 1.7 |

* = percent change from baseline dose; NR = Not Reported

typically 8%. However, changes in A1c were no greater than 0.5% in the studies excluding diabetes.

Another limitation in evaluating the impact of drug dose and correlation of weight loss with changes in cardiometabolic parameters was the lack of data concerning the concomitant use of anti-diabetic, antihypertensive, and lipid-lowering therapy. As already stated, most studies included patients with reasonable BP control and with only modest elevations in LDL-C. Only 4 of the trials required diabetes as an inclusion criterion with Hgb A1c levels of about 8% in these studies. Data concerning baseline drug therapy and changes in intensity of drug use for cardiometabolic states were not consistently reported. In addition, changes in these drugs were typically not prespecified as study endpoints and were exploratory in nature. There was no clear association between the magnitude of weight loss and the reduction in intensity of use with these drugs. Another limitation was the evaluation of outcomes at the end of only one year. Efficacy during the second year and beyond was typically not reported.

The 2013 ACC/AHA guidelines on weight loss indicate that a dose-response relationship exists between the amount of weight loss achieved by lifestyle interventions and improvements in the cardiometabolic parameters [5]. The concept of a dose-response relationship between weight loss and the magnitude of change in lipids was explored in a meta-analysis of 73 randomized trials including 32,496 patients treated with lifestyle interventions, pharmacotherapy, or bariatric surgery [30]. Following lifestyle interventions, per 1 kg of weight lost, triglycerides were reduced by 4.0 mg/dL, LDL-C was reduced by 1.3 mg/dL, and HDL-C increased by 0.5 mg/dL. Following pharmacologic interventions, per 1 kg of weight lost, triglycerides were reduced by 1.2 mg/dL, LDL-C was reduced by 1.7 mg/dL, and HDL-C increased by 0.4 mg/dL. Following bariatric surgery, per 1 kg of weight lost, triglycerides were reduced by 2.5 mg/dL, LDL-C was reduced by 0.3 mg/ dL, and HDL-C increased by 0.4 mg/dL. The major limitation of this meta-analysis is that actual weight loss was not reported. It is impossible to determine if this relationship was linear over the extent of weight loss or if there was a weight loss threshold at which changes in lipids were considered clinically impactful.

The availability of the newer nutrient-stimulated hormone-based anti-diabetic drugs has generated substantial enthusiasm in the management of overweight/obese patients. The ability to achieve notable improvements in cardiometabolic parameters appears to be associated with higher drug doses and greater weight loss. This relationship appears to occur more consistently with elevated baseline Hgb A1c in diabetic patients. While changes in LDL-C are more likely to be seen with greater weight loss, a linear effect is not apparent. This correlation seems to occur with systolic BP as well. It is also important to consider the potential improvements in cardiometabolic parameters associated with weight loss which may allow for dose reduction or drug discontinuation use in the treatment of hypertension, hyperlipidemia, and type 2 diabetes. Given that the vast majority of these weight loss drug trials included patients with lipid levels and BP that were largely well-controlled, data demonstrating the magnitude of benefit of weight loss drugs on these cardiometabolic parameters and the drugs typically used to treat them will require more extensive evaluations based on real-world experience studies.

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