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SUPPLEMENT: SEMAGLUTIDE FOR WEIGHT MANAGEMENT – AN INTRODUCTION FOR PRIMARY CARE

Cardiometabolic risk factors efficacy of semaglutide in the STEP program

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ABSTRACT

People with overweight or obesity often suffer from associated cardiometabolic diseases and comorbidities. Current therapies for obesity include lifestyle intervention, bariatric surgery, and pharmacotherapy. The magnitude of weight loss achieved with these therapies can determine the level of improvement in various comorbidities. Once-weekly subcutaneous semaglutide 2.4 mg is a glucagon-like peptide-1 receptor agonist recently approved by the US Food and Drug Administration for the treatment of obesity. This article reviews data from the global phase 3 Semaglutide Treatment Effect in People with obesity (STEP) program, comparing the efficacy of once-weekly subcutaneous semaglutide 2.4 mg versus placebo for weight loss and improvements in cardiometabolic parameters across the STEP 1 to 5 trials. In STEP 1 to 3 and STEP 5, semaglutide led to greater reductions from baseline versus placebo in body weight, waist circumference, body mass index, systolic blood pressure (SBP), and diastolic blood pressure, as well as positive changes in glycated hemoglobin (HbA_{1c}), C-reactive protein, and lipid levels. In STEP 4, all participants had a 20-week run-in period on semaglutide before either continuing on semaglutide or switching to placebo at week 20 in a 2:1 ratio for 48 weeks. At week 68, continued semaglutide led to further reductions from week 20 in HbA_{1c}, improvements in lipid profile, and stabilization of SBP. Overall, across the STEP trials, treatment with semaglutide 2.4 mg versus placebo improved cardiometabolic risk factors associated with obesity, illustrating an effective treatment option for people with overweight (and associated comorbidities) or obesity.

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KEYWORDS
Semaglutide 2.4 mg; obesity; overweight; weight loss; cardiometabolic parameters; anti-obesity medication

1. Introduction

The prevalence of obesity in the US has nearly tripled since 1980 [1,2], increasing from 15% to approximately 42% in 2018 [1], and has become a major public health issue due to the increased risk of premature mortality [3,4], financial burden [5], and the negative impact on health-related quality of life [6,7]. Obesity is associated with a number of cardiometabolic diseases and comorbidities that can cause disability and decrease life expectancy [8], including hypertension, dyslipidemia, insulin resistance, type 2 diabetes (T2D), nonalcoholic fatty liver disease (NAFLD), and obstructive sleep apnea [9,10]. Accumulation of intra-abdominal fat increases the risk of cardiometabolic disease [11] and correlates with an increase in waist circumference (WC) [12]. Therefore, elevated WC is considered a cardiometabolic disease risk factor [13]. Obesity, WC, and other forms of ectopic fat deposition are all associated with enhanced cardiovascular mortality [14].

Weight loss is the basis of obesity management. Significant clinical improvements in the associated comorbidities have been shown to occur when a sustained weight loss of 5% to ≥15% is achieved [9,10]. Weight loss of 3–5% can lead to improvements in some obesity-related comorbidities [15]; however, guidelines consider a weight loss of ≥5% to be the recommended minimum target for the treatment of obesity and associated comorbidities [10]. Five percent or greater weight loss can lead to improvements in hyperglycemia and hypertension (systolic blood pressure [SBP] and diastolic blood pressure [DBP]) [16]. It has also been shown to improve NAFLD and dyslipidemia (elevated triglycerides and reduced high-density lipoprotein cholesterol) [9,17,18]. Weight loss of ≥10% is associated with significant improvements in obstructive sleep apnea and nonalcoholic steatohepatitis (NASH) and decreases the likelihood of developing T2D [9,19]. Weight loss of 15% or greater can lead to T2D remission and reduce cardiovascular mortality [9,20].

Glucagon-like peptide-1 receptor agonists have been shown to be effective in weight management in people with and without T2D and have demonstrated improvements in cardiometabolic risk factors [21–23]. Once-weekly subcutaneous (s.c.) semaglutide 2.4 mg has recently been approved for use in the US by the Food and Drug Administration and in Europe by the European Medicines Agency for the treatment of obesity [24,25]. The global phase 3 Semaglutide Treatment Effect in People with obesity (STEP) program investigated the efficacy and safety of semaglutide 2.4 mg for weight reduction as well as the effects on cardiometabolic parameters and associated obesity-related comorbidities [26–31]. This article describes the effect of semaglutide 2.4 mg on cardiometabolic risk factors associated with obesity across the STEP 1 to 5 trials [26–31].

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Article overview and relevance to your clinical practice

- Using results from the phase 3 STEP clinical trial program, this supplement reviews the effects of the glucagon-like peptide-1 analog semaglutide 2.4 mg in weight management.
- Article 1 in this supplement by Amaro et al. reviewed STEP trial evidence demonstrating that once-weekly s.c. semaglutide 2.4 mg provides substantial and sustained weight loss in adults with overweight or obesity and is generally well tolerated.
- This second article in the supplement initially revisits the burden of obesity-related comorbidities, weight loss recommendations for achieving improvements in cardiometabolic risk factors, and current strategies in obesity management.
- We then draw on the results of the STEP 1 to 5 trials to explore the effects of semaglutide 2.4 mg on cardiometabolic risk factors and comorbidities in adults with overweight or obesity, with or without T2D.
- The improvements in cardiometabolic risk factors and comorbidities with semaglutide 2.4 mg described herein may help inform treatment selection for obesity management in clinical practice.

2. Current strategies and unmet needs in the management of obesity

Obesity can be managed through a variety of interventions including dietary, lifestyle, intensive behavioral therapy (IBT), pharmacologic, and/or surgical interventions [15]. The magnitude of cardiometabolic improvement is generally proportional to the degree of weight loss achieved with these strategies [32]. Obesity is a chronic metabolic disease and as such requires a tiered management approach that is consistent with an individual's personal circumstances [9]. Lifestyle modification is a foundational therapy for obesity, just as it is for diabetes, and should include culturally appropriate healthy nutrition along with physical activity [9,12,33]. This healthy nutrition plan should be acceptable to the patient with a calorie-deficit calculated to achieve weight loss [9,12]. According to guidelines, physical activity should be started incrementally with a goal of reaching at least 150 minutes a week of moderate-intensity physical activity, including both aerobic and resistance exercises [9,12]. Some patients may be able to achieve sustained weight loss and improvement of cardiometabolic risk factors through lifestyle and dietary modification alone; however, most are unable to achieve and/or sustain these benefits [21]. In these patients, bariatric surgery and medications may be necessary for obesity management [34]. Bariatric surgery is effective at producing short- and long-term weight losses of ≥15% [34]. Combining lifestyle modification with pharmacotherapy may facilitate the achievement and maintenance of weight loss and by doing so, bridge the gap in weight loss magnitude between lifestyle modifications and bariatric surgery [35,36]. However, the value and benefit of continued lifestyle approaches should be emphasized [9,12]. It is notable that exercise has an impact on other important outcomes including reduction in cancer and cardiovascular disease (CVD), which are independent of its effects on weight, therefore its benefit in this regard should be highlighted [9,12].

The STEP trial program explored the combination of lifestyle modification and pharmacological therapy by investigating the efficacy and safety of once-weekly s.c. semaglutide 2.4 mg versus placebo in people with overweight or obesity as an adjunct to lifestyle intervention [26–31].

Key clinical take-home points: Current strategies and unmet needs in the management of obesity

- There are a variety of treatment options in the management of obesity.
- Improvement in cardiometabolic parameters is related to the degree of weight loss achieved.
- Lifestyle intervention, including dietary modification and exercise, should be the foundation of obesity management strategies, and should be continued in conjunction with any other interventions for optimal weight management.
- Combining pharmacotherapy with lifestyle intervention may facilitate the achievement of weight loss goals.
- The STEP trial program explored the effects of pharmacotherapy with semaglutide 2.4 mg as an adjunct to lifestyle intervention in people with overweight or obesity.

3. STEP 1 to 5 trial methods and procedures

The STEP 1 to 5 trials were randomized, double-blind, and placebo-controlled studies. The STEP 1 to 4 trials were conducted for a duration of 68 weeks (randomization occurred at week 20, after an open-label run-in period in STEP 4) [26–29] and STEP 5 was 104 weeks long [30]. STEP 1 had an extension phase that followed a subset of participants after treatment cessation at week 68 until the end-of-trial visit at week 120 [31].

The STEP 1 and 3 to 5 trials included adults (male or female) aged ≥18 years with a body mass index (BMI) of ≥30 kg/m^2, or ≥27 kg/m^2 with ≥1 weight-related comorbidity, and with ≥1 self-reported unsuccessful dietary effort to lose weight [26,28–30]. The STEP 2 trial included participants with a BMI of ≥27 kg/m^2 and was the only one of the STEP trials to include participants with T2D [27]. Previous surgical obesity treatment was a key exclusion criterion across all five STEP trials [26–31]. Across the STEP 1 to 5 trials, semaglutide was initiated at a dose of 0.25 mg once weekly for the first 4 weeks and then increased every 4 weeks to reach a maintenance dose of 2.4 mg weekly, by week 16. In STEP 1, participants were randomized in a 2:1 ratio to receive either once-weekly s.c. semaglutide 2.4 mg or placebo for 68 weeks as an adjunct to lifestyle intervention, consisting of a reduced calorie diet (500-kcal per day deficit relative to the energy expenditure estimated at the time of randomization) and increased physical activity (150 minutes per week) [26]. Overall, 94.3% of participants completed the trial and 81.1% adhered to treatment [26]. STEP 3

Table 1. Patient baseline demographics and clinical characteristics across the STEP 1 to 5 trials for total population [26–30,37].

Characteristic	STEP 1	STEP 2[a]	STEP 3	STEP 4[b]	STEP 5
No. of participants	1,961	1,210	611	902	304
Age, years	46.5 ± 12.7	55.3 ± 10.6	46.2 ± 12.7	46.4 ± 11.9	47.3 ± 11.0
Female sex, no. (%)	1,453 (74.1)	616 (50.9)	495 (81.0)	717 (79.5)	236 (77.6)
Mean BMI, kg/m^2	37.9 ± 6.7	35.7 ± 6.3	38.0 ± 6.7	38.3 ± 7.0	38.5 ± 6.9
Type 2 diabetes, N	N/A	N = 1,210	N/A	N/A	N/A
Duration, years	N/A	8.0 ± 6.1	N/A	N/A	N/A
Blood pressure, mmHg					
Systolic	126.5 ± 14.3	130.0 ± 13.5	124.4 ± 14.8	126.4 ± 14.3	125.5 ± 14.5
Diastolic	80.3 ± 9.6	79.8 ± 9.0	80.5 ± 9.7	80.9 ± 9.9	80.1 ± 9.4
Waist circumference, cm	114.7 ± 14.7	114.6 ± 14.1	113.0 ± 15.5	115.1 ± 15.6	115.7 ± 14.8
Body weight, kg	105.3	99.8	105.8	107.2	106.0
Glycated hemoglobin, %	5.7 ± 0.3	8.1 ± 0.8	5.7 ± 0.3	5.7 ± 0.3	5.7 ± 0.3
Glycemic status, n (%)					
Normoglycemia	1,106 (56.4)	N/A	306 (50.1)	493 (54.7)	163 (53.6)
Prediabetes	855 (43.6)	N/A	305 (49.9)	408 (45.3)	141 (46.4)
Coexisting conditions at the time of screening					
Dyslipidemia – no. (%)	725 (37.0)	826 (68.3)	212 (34.7)	288 (35.9)	107 (35.2)
Hypertension – no. (%)	706 (36.0)	848 (70.1)	212 (34.7)	298 (37.1)	118 (38.8)
Obstructive sleep apnea – no. (%)	230 (11.7)	176 (14.5)	77 (12.6)	94 (11.7)	51 (16.8)
Nonalcoholic fatty liver disease – no. (%)	163 (8.3)	261 (21.6)	35 (5.7)	55 (6.8)	31 (10.2)

Data are mean ± standard deviation, unless stated otherwise. Baseline mean values for lipids have not been included in this table as they were presented differently across the STEP trials and their respective primary publications. [a]Participant with type 2 diabetes. [b]Data is at enrollment (week 0) not randomization at week 20.
BMI, body mass index; N/A, not applicable.

Table 2. Cardiometabolic secondary and exploratory endpoints investigated across STEP 1 to 5 [26–31].

Secondary endpoint	STEP 1[a]	STEP 1 extension[b]	STEP 2[a]	STEP 3[a]	STEP 4[a]	STEP 5[c]
Waist circumference	Confirmatory	Not evaluated	Confirmatory	Confirmatory	Confirmatory	Confirmatory
Systolic blood pressure	Confirmatory	Exploratory	Confirmatory	Confirmatory	Confirmatory	Confirmatory
HbA_{1c}	Supportive	Exploratory	Confirmatory	Supportive	Supportive	Supportive
Diastolic blood pressure	Supportive	Exploratory	Exploratory	Supportive	Supportive	Supportive
Lipids	Supportive	Exploratory	Exploratory	Supportive	Supportive	Supportive
C-reactive protein	Supportive	Exploratory	Exploratory	Supportive	Not evaluated	Supportive
Fasting plasma glucose	Supportive	Not evaluated	Exploratory	Supportive	Supportive	Supportive
Fasting serum insulin	Supportive	Not evaluated	Exploratory	Supportive	Supportive	Supportive
ALT	Exploratory[d]	Not evaluated	Exploratory	Not evaluated	Not evaluated	Not evaluated
AST	Exploratory[d]	Not evaluated	Exploratory	Not evaluated	Not evaluated	Not evaluated

[a]Change from randomization to week 68. [b]Change from week 68 to week 120. [c]Change from baseline to week 104. [d]Not a prespecified endpoint.
Confirmatory secondary endpoints are tested in analyses corrected for multiple comparisons, whereas supportive secondary and exploratory endpoints are not. Exploratory endpoints are subject to descriptive statistics only.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; HbA_{1c}, glycated hemoglobin.

followed a similar protocol as STEP 1 but included IBT (defined as 30 individual therapy visits), which consisted of a low-calorie diet (1000–1200 kcal/day) with provision of a partial meal-replacement program for the first 8 weeks and then a transition to a hypocaloric diet of conventional foods (1200–1800 kcal/day) for the remaining 68 weeks (prescribed calorie intake based on body weight at randomization). Participants were also prescribed 100 minutes of physical activity per week (spread across 4–5 days), which increased by 25 minutes every 4 weeks, to reach 200 minutes/week [28]. A similar proportion of participants to STEP 1 completed the trial in STEP 3 (92.8%) and 82.7% completed the trial in the on-treatment period [28]. In STEP 2, participants were randomized in a 1:1:1 ratio to receive either s.c. semaglutide 2.4 mg, semaglutide 1.0 mg, or placebo once weekly for 68 weeks as an adjunct to the same lifestyle intervention that was delivered in STEP 1 [27]. Of the randomized participants in STEP 2, a total of 96.2% completed the trial and 87.4% completed the trial in the on-treatment period [27]. In STEP 5, participants were randomized 1:1 to receive once-weekly s.c. semaglutide 2.4 mg or placebo plus lifestyle intervention for 104 weeks, comprising a reduced calorie diet (500 kcal deficit/day relative to the energy expenditure estimated at randomization) and increased physical activity (150 minutes/week) [30,37]. Similar to STEP 3, 92.8% of participants in STEP 5 completed the trial and 79.9% adhered to treatment [30]. The design of STEP 4 differed from the other trials in that all participants had a 20-week run-in period with once-weekly s.c. semaglutide 2.4 mg before randomization in a 2:1 ratio to continue with semaglutide 2.4 mg or switch to placebo from week 20 to week 68. All participants received lifestyle intervention from week 0 to week 68, which was identical to that delivered in STEP 1 and 2 [29]. Of the randomized participants in STEP 4, 98.0% completed the trial and 92.3% completed treatment [29].

The baseline characteristics assessed across the STEP 1 to 5 trials included WC, SBP, DBP, glycated hemoglobin (HbA_{1c}), lipid levels, and the presence of coexisting conditions including obstructive sleep apnea and NAFLD [26–30,37]. A summary of the baseline patient demographics and clinical characteristics relevant to cardiometabolic comorbidities across the STEP 1 to 5 trials can be found in Table 1. Across the studies in which T2D was an exclusion criterion (STEP 1 and 3 to 5) [26,28–30], more than one-third of participants had dyslipidemia and approximately the same proportion had

hypertension. Obstructive sleep apnea and NAFLD were present in approximately 10% to 17% and 5% to 10% of these participants, respectively. In STEP 2, in which all participants had T2D, the prevalence of dyslipidemia (68.3%), hypertension (70.1%), and NAFLD (21.6%) were higher [27], compared with STEP 1 and 3 to 5 (all coexisting conditions and comorbidities were self-reported at screening).

3.1. Outcomes across the STEP trial program

The co-primary endpoints across the STEP 1 to 3 [26–28] and 5 [30] trials included percentage change in body weight and the proportion of participants achieving at least 5% weight loss from baseline to end of treatment. The primary endpoint for STEP 4 was percentage change in body weight from randomization (week 20) to week 68 [29] (all primary endpoints across the STEP trials are discussed in detail by Amaro et al. in Article 1 of this supplement).

Cardiometabolic secondary (confirmatory and supportive) and exploratory endpoints investigated across the STEP 1 to 5 trials are summarized in Table 2 (all secondary confirmatory, secondary supportive, and exploratory endpoints across the STEP trials are reviewed by Amaro et al. in Article 1 of this supplement).

Key clinical take-home points: Overview of the STEP 1 to 5 trials

- STEP 1 and 3 to 5 enrolled adults with overweight and ≥1 weight-related comorbidity, or obesity, without T2D.
  - STEP 1 investigated the effect of semaglutide 2.4 mg versus placebo over 68 weeks as an adjunct to lifestyle intervention (consisting of a reduced calorie diet and increased physical activity).
  - The STEP 1 extension trial followed a subset of participants from STEP 1 after treatment was withdrawn at week 68, until the end-of-trial visit at week 120.
  - STEP 3 investigated the effect of semaglutide 2.4 mg versus placebo over 68 weeks as an adjunct to IBT (a low-calorie diet provided as meal replacements for 8 weeks followed by a reduced calorie diet for the remaining 60 weeks both in conjunction with increased physical activity).
  - STEP 4 investigated the effect of semaglutide 2.4 mg continuation or withdrawal (switch to placebo) after a 20-week semaglutide run-in period, as an adjunct to lifestyle intervention (consisting of a reduced calorie diet and increased physical activity).
  - STEP 5 assessed the treatment effect of semaglutide 2.4 mg versus placebo over a long-term, 2-year period (104 weeks), as an adjunct to lifestyle intervention (consisting of a reduced calorie diet and increased physical activity).
  - In contrast to the other studies, STEP 2 enrolled patients with overweight or obesity who had T2D and investigated the efficacy of semaglutide 2.4 mg and 1.0 mg, and placebo, as an adjunct to lifestyle intervention.
  - In contrast to the other studies, STEP 2 enrolled patients with overweight or obesity who had T2D and investigated the efficacy of semaglutide 2.4 mg and 1.0 mg, and placebo, as an adjunct to lifestyle intervention.

4. Improvements in cardiometabolic risk factors and comorbidities in people with obesity treated with semaglutide (STEP 1 to 5)

4.1. Waist circumference

WC can be used as a reliable proxy for obesity in people with a higher cardiometabolic risk and might be a more accurate predictor of CVD than BMI, due to the association of increased central adiposity with a range of metabolic comorbidities [38]. Across the STEP 1 to 5 trials, greater improvements in WC were achieved with semaglutide 2.4 mg versus placebo, respectively (STEP 1: −13.5 cm vs −4.1 cm [$P < 0.001$] [26]; STEP 2: −9.4 cm vs −4.5 cm [$P < 0.001$] [27]; STEP 3: −14.6 cm vs −6.3 cm [$P < 0.001$] [28]; Figure 1). In STEP 4, during the randomized period (weeks 20–68), participants who had continued in the semaglutide 2.4 mg treatment arm achieved a reduction in WC of −6.4 cm versus an increase of 3.3 cm in those who had switched to placebo [$P < 0.001$] (this followed a mean reduction in WC of −10.1 cm during the 20-week run-in) (Figure 1) [29]. Greater reductions from baseline to week 104 in WC were seen with semaglutide 2.4 mg versus placebo in STEP 5 (−14.4 cm with semaglutide vs −5.2 cm with placebo; $P < 0.001$), showing the long-term efficacy of semaglutide 2.4 mg for reducing WC (Figure 1) [30]. WC was not measured in the STEP 1 extension phase [31].

The results from STEP 1 to 5 show that semaglutide significantly reduces WC in people with overweight or obesity regardless of the presence of T2D [26–31].

4.2. Glycated hemoglobin

In STEP 2, which included participants with T2D, HbA_{1c} markedly improved by week 68 in both semaglutide treatment groups (1.0 mg and 2.4 mg) versus placebo (−1.5% and −1.6% vs −0.4%, respectively; $P < 0.0001$) [27] (Figure 2). The proportion of patients achieving HbA_{1c} levels of ≤6.5% by week 68 in the semaglutide 2.4 mg and 1.0 mg treatment arms versus the placebo arm was 67.5% and 60.1% versus 15.5%, respectively. The proportion of patients achieving HbA_{1c} levels of <7.0% by week 68 was 78.5% and 72.3% in the semaglutide 2.4 mg and 1.0 mg treatment arms, versus 26.5% in the placebo arm.

Greater changes in HbA_{1c} from baseline to week 68 with semaglutide 2.4 mg versus placebo were seen in STEP 1, 3, and 4 [26,28,29] (Figure 2). STEP 4 also found a significant treatment difference for HbA_{1c}; after an initial reduction of −0.4% during the

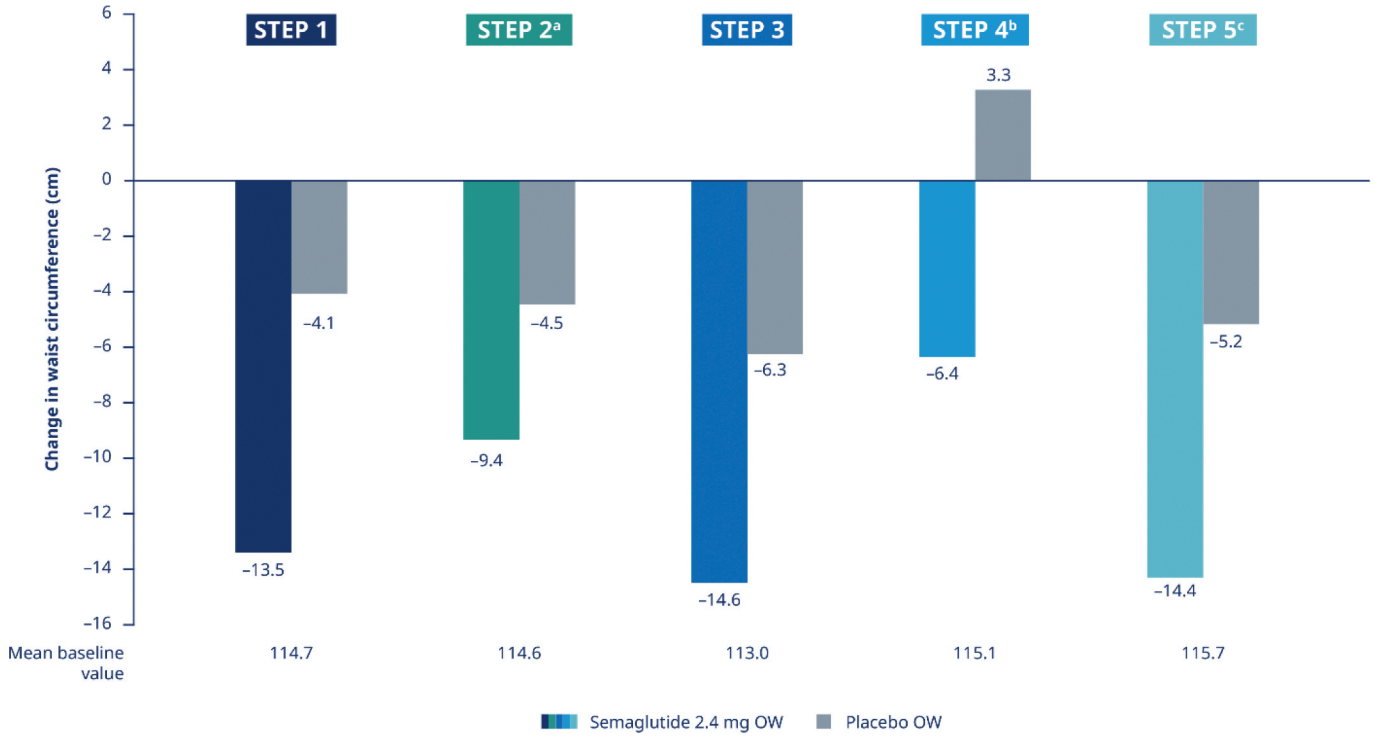

Figure 1. Change in waist circumference from randomization to week 68 (STEP 1 to 4) and week 104 (STEP 5) [26–30].

[a]Participants with type 2 diabetes at baseline. [b]Data shown are for the change from randomization at week 20 to week 68; for all other STEP trials, randomization occurred at week 0. [c]Data shown are from randomization to week 104. OW, once weekly.

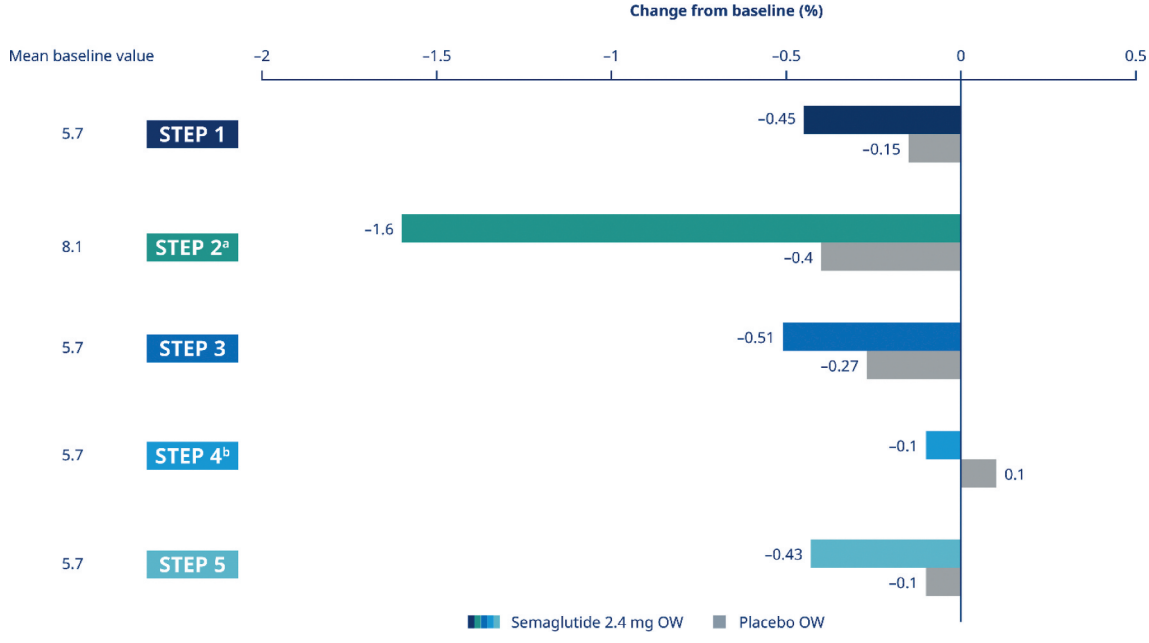

Figure 2. Change in HbA_{1c} (%) from randomization to end of treatment (STEP 1 to 5) [26–30].

[a]Participants with type 2 diabetes at baseline. [b]Data shown are for the change from randomization at week 20 to week 68; for all other STEP trials, randomization occurred at week 0. HbA_{1c}, glycated hemoglobin; OW, once weekly.

20-week run-in, those randomized to continue treatment with semaglutide 2.4 mg had an additional reduction of –0.1%, compared to an increase of 0.1% from week 20 to week 68 for those whose treatment was switched to placebo [29] (Figure 2).

In STEP 5, the change from baseline to week 104 in HbA_{1c} was greater in participants on semaglutide versus placebo (–0.4% points with semaglutide vs –0.1% points with placebo), showing the long-term efficacy of semaglutide for improving HbA_{1c} levels [30]. In the STEP 1 extension period, increases in mean HbA_{1c} were observed in both treatment arms after treatment cessation. The increase in HbA_{1c} from week 68 to week 120 was greater in the

Table 3. Change from randomization to week 68 (STEP 1 to 4) and week 104 (STEP 5) in systolic blood pressure and diastolic blood pressure [26–30].

	Semaglutide 2.4 mg	Placebo	ETD (95% CI)	P value
STEP 1				
Systolic blood pressure (mmHg)	−6.2	−1.0	−5.10 (−6.3 to −3.9)	< 0.001
Diastolic blood pressure (mmHg)	−2.8	−0.4	−2.41 (−3.3 to −1.6)	N/R
STEP 2[a]				
Systolic blood pressure (mmHg)	−3.9	−0.5	−3.4 (−5.6 to −1.3)	0.0016
Diastolic blood pressure (mmHg)	−1.6	−0.9	−0.7 (−2.0 to 0.6)	N/R
STEP 3				
Systolic blood pressure (mmHg)	−5.6	−1.6	−3.9 (−6.4 to −1.5)	0.001
Diastolic blood pressure (mmHg)	−3.0	−0.8	−2.2 (−3.9 to −0.6)	0.008
STEP 4[b]				
Systolic blood pressure (mmHg)	0.5	4.4	−3.9 (−5.8 to −2.0)	< 0.001
Diastolic blood pressure (mmHg)	0.3	0.9	−0.6 (−0.2 to 0.9)	0.46
STEP 5				
Systolic blood pressure (mmHg)	−5.7	−1.6	−4.2 (−7.3 to −1.0)	0.0102
Diastolic blood pressure (mmHg)	−4.4	−0.8	−3.7 (−6.1 to −1.2)	N/R

[a]Participants with type 2 diabetes. [b]Randomization to remain on semaglutide or switch to placebo occurred at week 20, after an initial run-in period in which all patients were treated with semaglutide. In all other trials, randomization to semaglutide or placebo occurred at week 0.
CI, confidence interval; ETD, estimated treatment difference; N/R, not reported.

semaglutide versus placebo arm; however, the semaglutide arm maintained a small improvement relative to placebo in HbA_{1c} at week 120 [31].

According to the Centers for Disease Control and Prevention, an person with an HbA_{1c} level ranging between 5.7% and 6.4% is considered to have prediabetes [39]. In STEP 1, 84.1% of participants in the semaglutide group who had prediabetes at baseline reverted to normoglycemia (i.e. HbA_{1c} <5.7%) by week 68, compared with 47.8% of participants in the placebo group [26]. In the STEP 1 extension phase after treatment cessation, a greater proportion of patients in the semaglutide arm versus the placebo arm who had prediabetes at baseline reverted to normoglycemia by week 120 (43.3% vs 34.0%, respectively) [31]. Similar findings were observed in STEP 3, with 89.5% of participants with prediabetes at baseline reverting to normoglycemia by week 68 in the semaglutide 2.4 mg group, compared with 55.0% of those receiving placebo [40]. In STEP 4, a greater proportion of participants with prediabetes at week 0 had normoglycemia after 68 weeks of continued treatment with semaglutide (89.8%) compared with those who switched to placebo after the 20-week semaglutide run-in period (70.4%) [40]. In STEP 5, of participants with prediabetes at baseline, 79.7% treated with semaglutide reverted to normoglycemia by week 104, compared with 37.0% of participants on placebo [30].

The data across the STEP 1 to 5 trials therefore suggest that semaglutide 2.4 mg has beneficial effects on glucose metabolism in people with overweight or obesity, with or without T2D [26–31]. In addition, the effects on glucose metabolism are attenuated after discontinuation of semaglutide 2.4 mg (as shown in the STEP 1 extension trial and STEP 4) but are maintained if treatment continues beyond 1 year (STEP 5) [29–31].

4.3. Blood pressure and heart rate

Across most of the STEP trials, semaglutide improved blood pressure compared to placebo in patients with and without T2D. Greater decreases in SBP from baseline to end of treatment in participants on semaglutide 2.4 mg versus placebo were seen in STEP 1 to 3 and 5 (Table 3) [26–30]. In STEP 4, after a decrease from baseline during the 20-week semaglutide run-in, SBP significantly increased upon withdrawal (switch to placebo) and remained stable with continued semaglutide [29] (Table 3). Similarly, greater improvements in DBP from baseline to end of treatment were seen in STEP 1, 3, and 5 for semaglutide versus placebo [26,28,30]. In STEP 2 and 4, there was no significant difference between groups for DBP [27,29] (Table 3).

After treatment cessation in the STEP 1 extension phase, mean SBP and DBP were similar to baseline levels by week 120 in both treatment arms [31]. Across STEP 1 to 5, there was a small increase in mean heart rate of 1–4 beats per minute observed with semaglutide 2.4 mg compared with placebo [24,26–30].

4.4. Lipids

Semaglutide 2.4 mg versus placebo had a positive effect on lipid levels across the STEP 1 to 3 trials with a reduction in total cholesterol, low-density lipoprotein (LDL) cholesterol, very-low-density lipoprotein (VLDL) cholesterol, free fatty acids, and triglycerides, and an increase in high-density lipoprotein (HDL) cholesterol [26–28] (Table 4). In STEP 4, treatment withdrawal of semaglutide at week 20 saw a negative impact on total cholesterol, LDL cholesterol, VLDL cholesterol, and triglycerides, with significant increases between week 20 and week 68 for those who switched to placebo (Table 4) [29]. However, lipid levels continued to improve for participants in STEP 4 who remained on semaglutide 2.4 mg to week 68 (Table 4) [29].

As all participants in the STEP 2 trial had T2D, the results show that the effect of semaglutide on lipid levels remains beneficial regardless of the presence of T2D [27].

Compared with placebo, semaglutide also led to improvements in triglycerides from baseline to week 104 in STEP 5 [30] (Table 4).

After treatment withdrawal in the STEP 1 extension trial, improvements were maintained in lipid levels with an increase in HDL cholesterol and only a slight increase in LDL cholesterol (0.3%) in participants receiving semaglutide versus placebo at week 120 [31].

Table 4. Percentage change from randomization to week 68 (STEP 1 to 4) and week 104 (STEP 5) in lipid levels and C-reactive protein [26–30].

	Semaglutide 2.4 mg[c]	Placebo[d]	Relative difference (95% CI)
STEP 1[a]			
Total cholesterol, %	−3.0	0	−3.0 (−5.0 to −2.0)
HDL cholesterol, %	5.0	1.0	4.0 (2.0 to 5.0)
LDL cholesterol, %	−3.0	1.0	−4.0 (−6.0 to −2.0)
VLDL cholesterol, %	−22.0	−7.0	−16.0 (−19.0 to −13.0)
Free fatty acids, %	−17.0	−7.0	−11.0 (−17.0 to −6.0)
Triglycerides, %	−22.0	−7.0	−16.0 (−19.0 to −13.0)
C-reactive protein, %	−53.0	−15.0	−44.0 (−49.0 to −39.0)
STEP 2[a]			
Total cholesterol, %	−1.0	−1.0	−1.0 (−4.0 to 2.0)
HDL cholesterol, %	7.0	4.0	3.0 (0 to 5)
LDL cholesterol, %	0	0	0 (−4.0 to 5.0)
VLDL cholesterol, %	−21.0	−10.0	−12.0 (−17.0 to −7.0)
Free fatty acids, %	−16.0	−1.0	−16.0 (−22.0 to −9.0)
Triglycerides, %	−22.0	−9.0	−14.0 (−19.0 to −8.0)
C-reactive protein, %	−49.0	−17.0	−39.0 (−46.0 to −30.0)
STEP 3			
Total cholesterol, %	−3.8	2.1	−5.8 (−8.4 to −3.2)
HDL cholesterol, %	6.5	5.0	1.5 (−1.8 to 4.9)
LDL cholesterol, %	−4.7	2.6	−7.1 (−10.9 to −3.2)
VLDL cholesterol, %	−22.5	−6.6	−17.0 (−22.8 to −10.9)
Free fatty acids, %	−11.9	4.0	−15.3 (−25.0 to −4.3)
Triglycerides, %	−22.5	−6.5	−17.0 (−22.8 to −10.8)
C-reactive protein, %	−59.6	−22.9	−47.6 (−55.0 to −39.0)
STEP 4[b]			
Total cholesterol, %	5.0	11.0	−6.0 (−8.0 to −4.0)
HDL cholesterol, %	18.0	18.0	0 (−2.0 to 3.0)
LDL cholesterol, %	1.0	8.0	−6.0 (−9.0 to −3.0)
VLDL cholesterol, %	−6.0	15.0	−18.0 (−24.0 to −11.0)
Free fatty acids, %	−18.0	−14.0	−5.0 (−20.0 to 13.0)
Triglycerides, %	−6.0	15.0	−18.0 (−24.0 to −11.0)
C-reactive protein, %	N/A	N/A	N/A
STEP 5			
Total cholesterol, %	−3.3	1.4	−4.6 (−8.4 to −0.6)
HDL cholesterol, %	9.6	8.1	1.3 (−3.9 to 6.9)
LDL cholesterol, %	−6.1	−2.7	−3.4 (−9.1 to 2.6)
VLDL cholesterol, %	−18.9	3.3	−21.5 (−29.6 to −12.4)
Free fatty acids, %	0.3	7.0	−6.2 (−21.2 to 11.6)
Triglycerides, %	−19.0	3.7	−21.9 (−29.8 to −13.2)
C-reactive protein, %	−56.7	−7.8	−53.1 (−63.2 to −40.0)

Data are presented as percentage change. Comparison is the estimated relative percentage difference between groups. [a]These parameters were presented as estimated ratio to baseline (within treatment groups) and estimated treatment ratios in their respective publications. For consistency with STEP 3 and 4, these data are expressed as relative percentage change and estimated relative percentage difference between groups, respectively, and were calculated with the following formula: (estimated ratio − 1) × 100. [b]All participants had a 20-week run-in period with semaglutide 2.4 mg before being randomized to [c]continue semaglutide 2.4 mg or [d]switch to placebo at week 20 (in STEP 4 only).

CI, confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein; N/A, not applicable (not measured); VLDL, very-low-density lipoprotein.

4.5. C-reactive protein

High-sensitivity C-reactive protein (CRP) is an acute-phase inflammatory biomarker of which elevated levels can indicate an increased risk of CVD [8]. There is evidence that weight loss reduces CRP levels, which can be used as a marker to assess improvement of CVD risk [8]. In the STEP 1 to 3 trials, treatment with semaglutide compared with placebo showed greater improvements in CRP levels from baseline to week 68 [26–28] (Table 4). Moreover, the improvement in CRP remained over 2 years in the STEP 5 trial compared with placebo [30] (Table 4). CRP was not measured in the STEP 4 trial.

After treatment with semaglutide ended at week 68, CRP increased at week 120 but remained improved relative to the placebo arm in the STEP 1 extension trial [31].

4.6. Ongoing investigation of semaglutide 2.4 mg in people with overweight or obesity and established CVD – the SELECT trial

The Semaglutide Effects on Cardiovascular Outcomes in People with Overweight or Obesity (SELECT) trial is an ongoing, long-term, placebo-controlled cardiovascular outcomes trial designed to evaluate once-weekly s.c. semaglutide 2.4 mg versus placebo when added to standard of care for preventing major adverse cardiovascular events in patients with established CVD and overweight or obesity but without diabetes (NCT03574597) [41]. Approximately 17,500 male or female patients aged ≥45 years with a BMI of ≥27 kg/m^2 and evidence of CVD (prior myocardial infarction, prior stroke, or symptomatic peripheral arterial disease)

were enrolled. This ongoing trial will assess whether semaglutide 2.4 mg is superior to placebo in preventing major adverse cardiovascular events (cardiovascular death, or nonfatal myocardial infarction or nonfatal stroke) in this population and will therefore help further understanding of the cardiometabolic effects of semaglutide 2.4 mg in obesity management [41].

4.7. Liver parameters and hepatic diseases (NAFLD/NASH)

Over 65% of patients with overweight or obesity seen in primary care also have NAFLD [42]. Glucagon-like peptide-1 receptor agonists such as semaglutide have shown promising results in the reduction of elevated liver enzymes and may be a potential treatment option for patients with NAFLD [43]. Although NAFLD/NASH were not assessed in the STEP trials, the effects of semaglutide 2.4 mg on liver enzymes (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) were investigated in the STEP 1 and 2 trials (assessed as an exploratory outcome but not tested for statistical significance) [26,27]. The ratio to baseline at week 68 for ALT levels was lower with semaglutide 2.4 mg than with placebo in STEP 1 (0.76 vs 0.94, respectively; estimated treatment ratio [ETR]: 0.81, 95% confidence interval [CI], 0.77 to 0.86 [26]) and STEP 2 (0.74 vs 0.85, respectively [treatment ratios for this parameter were not estimated in STEP 2] [27]). The ratio to baseline at week 68 for AST levels was also lower with semaglutide 2.4 mg than placebo in STEP 1 (0.89 vs 0.99, respectively; ETR: 0.90, 95% CI, 0.88 to 0.93 [26]) and STEP 2 (0.88 vs 0.93, respectively [treatment ratios for this parameter were not estimated in STEP 2] [27]). As results were similar between STEP 1 and 2, positive effects of semaglutide 2.4 mg on liver enzymes were demonstrated regardless of the presence of T2D [26,27].

Data from outside of the STEP program have also shown benefits favoring semaglutide for improvement in NAFLD and NASH. In a study by Newsome et al. (2019), the effects of semaglutide on liver enzymes and markers of inflammation in patients with T2D or obesity were assessed to evaluate semaglutide as a potential treatment for NAFLD/NASH. In patients treated with semaglutide at once-daily s.c. doses of 0.05, 0.1, 0.2, 0.3, or 0.4 mg for 52 weeks, results showed a dose-dependent decrease in ALT levels, with maximal reductions occurring around week 28 and remaining stable thereafter [44]. In another study by Newsome et al. (2021), patients with biopsy-confirmed NASH and liver fibrosis stage F1, F2, or F3 saw NASH resolution with no worsening of fibrosis achieved in 59% of the patient population on daily semaglutide 0.4 mg versus 17% in the placebo group after 72 weeks [45].

As semaglutide effectively treats obesity and T2D, there is growing evidence to suggest that semaglutide may reduce the risk of NAFLD and NASH and could be a potential treatment for these diseases [44–46]. Semaglutide 2.4 mg is currently being evaluated in a phase 3 trial for the treatment of NASH (NCT04822181).

Key clinical take-home points: Improvements in cardiometabolic risk factors and comorbidities in people treated with semaglutide

- Across the STEP trials, improvements in a range of cardiometabolic risk factors and other parameters were observed with semaglutide 2.4 mg versus placebo, including in WC, HbA_{1c}, blood pressure, lipid profile, CRP, and liver enzymes.
- The ongoing SELECT trial will determine whether semaglutide 2.4 mg prevents major adverse cardiovascular events in people living with overweight or obesity and established CVD.

5. Conclusion

Adults with overweight or obesity are at high risk of developing cardiometabolic diseases [10]. The patient populations across the STEP program had a high prevalence of cardiometabolic risk factors as well as other obesity-related comorbidities [26–31]. Across the STEP trials, treatment with once-weekly s.c. semaglutide 2.4 mg versus placebo demonstrated a beneficial effect on cardiometabolic risk factors and obesity-related comorbidities including WC, blood pressure, lipids, CRP, and HbA_{1c} levels, regardless of the presence of T2D [26–31]. A high rate of reversion to normoglycemia from prediabetes was achieved with semaglutide 2.4 mg in STEP 1, 3, and 4 [41] compared with placebo [26–28,31], and in STEP 1 and 2, semaglutide was associated with numerical improvements in liver enzymes [26,27].

After participants switched from semaglutide to placebo at week 20 in STEP 4, a gradual weight regain was seen with a loss of effect on the initial improvement seen at week 20 in WC, SBP, lipids, and HbA_{1c} levels [29]. Similarly, in the STEP 1 extension trial, treatment withdrawal at week 68 resulted in gradual weight regain and had a detrimental effect on cardiometabolic parameters, with increases in blood pressure, CRP, lipids, and HbA_{1c} levels, although the majority of these cardiometabolic parameters maintained a greater improvement versus placebo at week 120 [31]. By contrast, in STEP 5, semaglutide treatment for 2 years resulted in significant and sustained improvements in these cardiometabolic parameters [30].

One limitation of these STEP trials is that reduction in cardiovascular risk factors may differ by sex; however, across the STEP 1 to 5 trials, this was only assessed in STEP 1 [47]. In addition, it is believed that a reduction in CVD risk factors may reduce cardiovascular mortality; however, in obesity, this hypothesis remains unanswered whilst randomized clinical trials are ongoing.

Collectively, these results show that long-term treatment with semaglutide is necessary for maintaining weight reduction and improvements in cardiometabolic risk factors, and the benefits induced by semaglutide are similar in participants with and without T2D [26–31]. The magnitude of weight loss demonstrated with semaglutide across the STEP trials has been associated with improvements in obesity-

related complications and, with the addition of lifestyle modification, leads to optimal management of obesity and improvements in cardiometabolic risk factors [26–31].

Screening for cardiometabolic risk factors in people living with obesity allows for the identification of higher risk individuals, which enables primary care providers to counsel them accordingly and closely monitor their progress [9,12].

Abbreviations

ALT,	alanine aminotransferasex
AST,	aspartate aminotransferase
BMI,	body mass index
CI,	confidence interval
CRP,	high-sensitivity C-reactive protein
CVD,	cardiovascular disease
DBP,	diastolic blood pressure
ETD,	estimated treatment difference
ETR,	estimated treatment ratio
HbA_{1c},	glycated hemoglobin
HDL,	high-density lipoprotein
IBT,	intensive behavioral therapy
LDL,	low-density lipoprotein
NAFLD,	nonalcoholic fatty liver disease
NASH,	nonalcoholic steatohepatitis
s.c.,	subcutaneous
SBP,	systolic blood pressure
SELECT,	Semaglutide Effects on Cardiovascular Outcomes in People with Overweight or Obesity
STEP,	Semaglutide Treatment Effect in People with obesity
T2D,	type 2 diabetes
VLDL,	very-low-density lipoprotein
WC,	waist circumference

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