Available at https://ejournal.upnb-journal.com/index.php/primed/index

Prima: Journal of Medical Sciences

| ISSN (Online) 3164 – 0133 |

Systematic Review

Efficacy and Safety of Incretin-Based Anti-Obesity Medications in Adults with Overweight or Obesity: A Systematic Review of Phase 3 Randomized Controlled Trials

Harry Yuseptian[1], Fajriza Yona[2], Edwin Danie Olsa[2]

1 Department of Internal Medicine, Dr. A. Dadi Tjokrodipo Regional Public Hospital, Bandar Lampung, Indonesia
2 Faculty of Medicine, Universitas Prima Nusantara Bukittinggi, Indonesia

Article Information

Received: June 3, 2026
Revised: August 18, 2026
Accepted: September 4, 2026
Available Online: September 30, 2026

Keywords

Obesity; liraglutide; semaglutide; tirzepatide; systematic review; randomized controlled trial

Corresponding Author

Name: Harry Yuseptian
E-mail: yuseptianh@gmail.com

ABSTRACT

Background: Obesity is a major risk factor for cardiometabolic disease. Incretin-based medications (liraglutide, semaglutide, and tirzepatide) have been tested in large phase 3 randomized controlled trials (RCTs). This systematic review summarizes their efficacy and safety in adults with overweight or obesity.
Methods: Peer-reviewed phase 3 placebo-controlled RCTs of liraglutide 3.0 mg, semaglutide 2.4 mg, or tirzepatide in adults with overweight or obesity, with or without type 2 diabetes, were eligible. Data were extracted and synthesized without meta-analysis following the SWiM reporting guideline, with trials grouped by population, and with qualitative risk-of-bias appraisal using RoB 2 domains.
Findings: Six RCTs (SCALE, STEP 1, SURMOUNT-1, STEP 2, SURMOUNT-2, SELECT; 27,983 randomized participants) were included. Without diabetes, mean weight change was −8.4 kg with liraglutide, −14.9% with semaglutide, and −15.0% to −20.9% with tirzepatide, compared with −2.4% to −3.1% with placebo. With type 2 diabetes, weight loss was smaller (semaglutide −9.6%; tirzepatide −12.8% to −14.7%). In SELECT, semaglutide reduced major cardiovascular events in adults with established cardiovascular disease and overweight or obesity (HR 0.80, 95% CI 0.72–0.90). Gastrointestinal adverse events were the main tolerability issue, and discontinuation due to adverse events was higher with active treatment.
Conclusion: Incretin-based medications produce substantial weight loss versus placebo, with the largest effects for tirzepatide, and semaglutide reduced cardiovascular events in one outcome trial. Gastrointestinal tolerability and long-term data remain important considerations.

INTRODUCTION

Overweight and obesity are associated with type 2 diabetes, cardiovascular disease, and other chronic conditions, and sustained weight loss through lifestyle intervention alone is difficult for many people. Medications that act on incretin pathways have therefore become an important option for weight management.

Several incretin-based medications have been evaluated in large phase 3 randomized controlled trials (RCTs): liraglutide 3.0 mg once daily in the SCALE trial [1], semaglutide 2.4 mg once weekly in STEP 1 [2], tirzepatide once weekly in SURMOUNT-1 [3], and the same agents in people with type 2 diabetes in STEP 2 [4] and SURMOUNT-2 [5]. The SELECT trial extended this evidence to cardiovascular outcomes in adults with established cardiovascular disease and overweight or obesity [6].

These trials differ in drug, dose, duration, population, and outcome, and weight change is reported both in kilograms and as a percentage of body weight. Reading each trial in isolation can therefore make the overall evidence difficult to interpret. A structured synthesis can help to clarify how large the effects are, how they differ by population, and what is known about tolerability and cardiovascular benefit.

This systematic review aims to summarize the efficacy and safety of liraglutide, semaglutide, and tirzepatide versus placebo in adults with overweight or obesity, with and without type 2 diabetes, and to describe the limits of comparing these trials.

METHODS

1. Design

This systematic review of RCTs was planned using the PICO framework. No protocol was prospectively registered. Results were synthesized without meta-analysis, following the principles of the SWiM reporting guideline [7].

2. Eligibility Criteria

Table 1. Eligibility Criteria (PICO)

Element	Criterion
Population	Adults with overweight or obesity, with or without type 2 diabetes
Intervention	Liraglutide 3.0 mg, semaglutide 2.4 mg, or tirzepatide
Comparator	Placebo
Outcomes	Body weight change; proportion achieving weight-loss thresholds; cardiovascular events; adverse events
Design	Phase 3 randomized controlled trial in a peer-reviewed journal

Eligibility criteria are summarized in Table 1. Only phase 3 RCTs published in peer-reviewed journals were eligible. Trials were grouped for synthesis by population: adults without diabetes, adults with type 2 diabetes, and the cardiovascular outcome trial.

3. Information Sources and Search

Peer-reviewed literature indexed in PubMed was searched in November 2026 through a web search interface, using the terms “liraglutide,” “semaglutide,” “tirzepatide,” “obesity,” “weight management,” and “randomized trial.” Institutional repository records and publisher abstracts were used to verify the content of each trial report.

4. Study Selection

Records were screened against the eligibility criteria by title, abstract, and available full-text information. Selection was performed by a single reviewer.

5. Data Items

Sample size, population, drug, dose, duration, mean weight change (in kilograms or percent, as reported), treatment differences with 95% confidence intervals, proportions achieving weight-loss thresholds, cardiovascular outcomes, and adverse events and discontinuations were extracted.

6. Risk-of-Bias Appraisal

Risk of bias was appraised qualitatively using the domains of the RoB 2 tool [8] (randomization, deviations from intended interventions, missing outcome data, outcome measurement, and selective reporting), based on information in published abstracts and verified secondary records.

7. Synthesis

Because drugs, doses, durations, and outcome metrics differed, a pooled estimate was not calculated. Effect estimates are reported as provided by each trial and are tabulated and

described narratively within population groups. Comparisons across trials are indirect and are described as such.

RESULTS

1. Study Selection

The search identified six phase 3 RCTs that met the eligibility criteria [1–6], with 27,983 randomized participants in total.

2. Characteristics of Included Trials

Three trials enrolled adults with overweight or obesity without diabetes (SCALE, STEP 1, and SURMOUNT-1) [1–3], two enrolled adults with type 2 diabetes (STEP 2 and SURMOUNT-2) [4][5], and one, SELECT, enrolled adults with established cardiovascular disease and overweight or obesity without diabetes [6]. Treatment durations ranged from 56 to 72 weeks for the weight-management trials, and the mean follow-up in SELECT was 39.8 months (Table 2).

Table 2. Characteristics of Included Trials

Trial	Design and population
SCALE [1]	3,731 adults without type 2 diabetes (78.5% women; mean BMI 38.3); liraglutide 3.0 mg daily vs placebo, 2:1; 56 weeks
STEP 1 [2]	1,961 adults with BMI ≥30 (or ≥27 with a weight-related condition) without diabetes; semaglutide 2.4 mg weekly vs placebo, 2:1; 68 weeks
SURMOUNT-1 [3]	2,539 adults with obesity; tirzepatide 5, 10, or 15 mg weekly vs placebo; 72 weeks
STEP 2 [4]	1,210 adults with overweight or obesity and type 2 diabetes; semaglutide 2.4 mg, 1.0 mg, or placebo; 68 weeks
SURMOUNT-2 [5]	938 adults with obesity and type 2 diabetes; tirzepatide 10 or 15 mg vs placebo; 72 weeks
SELECT [6]	17,604 adults aged ≥45 years with cardiovascular disease, BMI ≥27, no diabetes; semaglutide 2.4 mg weekly vs placebo; mean follow-up 39.8 months

3. Adults without Diabetes

3.1 Liraglutide (SCALE)

In SCALE, mean weight change at 56 weeks was −8.4 kg (SD 7.3) with liraglutide 3.0 mg and −2.8 kg (SD 6.5) with placebo, a difference of −5.6 kg (95% CI −6.0 to −5.1) [1].

3.2 Semaglutide (STEP 1)

In STEP 1, mean weight change at 68 weeks was −14.9% with semaglutide 2.4 mg and −2.4% with placebo (estimated treatment difference −12.4 percentage points; 95% CI −13.4 to −11.5). Weight loss of at least 5%, 10%, and 15% was achieved by 86.4%, 69.1%, and 50.5% of participants with semaglutide, compared with 31.5%, 12.0%, and 4.9% with placebo [2].

3.3 Tirzepatide (SURMOUNT-1)

In SURMOUNT-1, mean weight change at 72 weeks was −15.0% with tirzepatide 5 mg, −19.5% with 10 mg, and −20.9% with 15 mg, compared with −3.1% with placebo. Weight loss of at least 5% was achieved by 85%, 89%, and 91% of participants across the three doses, compared with 35% with placebo, and weight loss of at least 20% by 50% (10 mg) and 57% (15 mg) compared with 3% [3].

Table 3. Weight Change in Adults without Diabetes

Trial and arm	Mean weight change
SCALE: liraglutide 3.0 mg [1]	−8.4 kg (placebo −2.8 kg)
STEP 1: semaglutide 2.4 mg [2]	−14.9% (placebo −2.4%)
SURMOUNT-1: tirzepatide 5 mg [3]	−15.0% (placebo −3.1%)
SURMOUNT-1: tirzepatide 10 mg [3]	−19.5%
SURMOUNT-1: tirzepatide 15 mg [3]	−20.9%

4. Adults with Type 2 Diabetes

In STEP 2, mean weight change at 68 weeks was −9.6% with semaglutide 2.4 mg and −3.4% with placebo (difference −6.2 percentage points; 95% CI −7.3 to −5.2). Weight loss of at least 5% was achieved by 68.8% with semaglutide 2.4 mg and 28.5% with placebo [4]. In SURMOUNT-2, mean weight change at 72 weeks was −12.8% with tirzepatide 10 mg and −14.7% with 15 mg, compared with −3.2% with

placebo, corresponding to differences of −9.6 and −11.6 percentage points [5].

Table 4. Weight Change in Adults with Type 2 Diabetes

Trial and arm	Mean weight change
STEP 2: semaglutide 2.4 mg [4]	−9.6% (placebo −3.4%)
SURMOUNT-2: tirzepatide 10 mg [5]	−12.8% (placebo −3.2%)
SURMOUNT-2: tirzepatide 15 mg [5]	−14.7%

5. Cardiovascular Outcomes (SELECT)

In SELECT, the primary cardiovascular outcome occurred in 569 participants (6.5%) in the semaglutide group and 701 (8.0%) in the placebo group (hazard ratio 0.80; 95% CI 0.72–0.90; P<0.001) over a mean follow-up of 39.8 months [6].

Table 5. Cardiovascular Outcome in SELECT

Measure	Result
Participants	17,604 (8,803 semaglutide; 8,801 placebo)
Primary outcome events	569 (6.5%) vs 701 (8.0%)
Hazard ratio (95% CI)	0.80 (0.72–0.90)
Mean follow-up	39.8 months

6. Safety and Tolerability

In STEP 1, nausea and diarrhea were the most common adverse events with semaglutide and were usually transient and mild to moderate; discontinuation due to gastrointestinal events was 4.5% with semaglutide and 0.8% with placebo [2]. In SURMOUNT-1, adverse events were mostly gastrointestinal, generally mild to moderate, and occurred mainly during dose escalation; discontinuation due to adverse events was 4.3% (5 mg), 7.1% (10 mg), and 6.2% (15 mg) with tirzepatide, compared with 2.6% with placebo [3].

In STEP 2, adverse events occurred in 87.6% with semaglutide 2.4 mg, 81.8% with 1.0 mg, and 76.9% with placebo, and gastrointestinal adverse events in 63.5%, 57.5%, and 34.3%, respectively [4]. In SELECT, adverse events leading to permanent discontinuation occurred in 16.6% of the semaglutide group and 8.2% of the placebo group [6]. Safety data from the abstract-level records reviewed for SCALE and SURMOUNT-2 were not available.

Table 6. Selected Safety Findings

Trial	Safety finding
STEP 1 [2]	GI-related discontinuation 4.5% vs 0.8%
SURMOUNT-1 [3]	Discontinuation due to AEs 4.3%, 7.1%, 6.2% vs 2.6%
STEP 2 [4]	GI AEs 63.5% (2.4 mg) vs 34.3% placebo
SELECT [6]	Discontinuation due to AEs 16.6% vs 8.2%

7. Risk-of-Bias Appraisal

All six trials were randomized, placebo-controlled phase 3 studies published in peer-reviewed journals, with prespecified primary outcomes. STEP 2 was described as double-blind and double-dummy. No major concerns about randomization or selective reporting were evident from the information reviewed. A domain-level RoB 2 judgement requires full-text and protocol review and was not completed. Weight outcomes were measured on different scales across trials, which limits direct comparison (Table 7).

Table 7. Qualitative Risk-of-Bias Summary

Trial	Appraisal
SCALE [1]	Randomized, placebo-controlled; no major concerns evident
STEP 1 [2]	Randomized, placebo-controlled; no major concerns evident
SURMOUNT-1 [3]	Randomized, placebo-controlled; no major concerns evident
STEP 2 [4]	Randomized, double-blind, double-dummy; no major concerns evident
SURMOUNT-2 [5]	Randomized, placebo-controlled; safety data not available in records
SELECT [6]	Randomized, placebo-controlled; higher discontinuation with active drug

DISCUSSION

1. Summary of Evidence

Across six phase 3 RCTs including 27,983 participants, liraglutide 3.0 mg, semaglutide 2.4 mg, and tirzepatide each produced greater weight loss than placebo in adults with overweight or obesity [1–5]. In the one outcome trial reviewed, semaglutide 2.4 mg also reduced major cardiovascular events in adults with established cardiovascular disease and overweight or obesity without diabetes [6].

2. Magnitude of Weight Loss

Among adults without diabetes, mean weight loss with active treatment was −8.4 kg with liraglutide in SCALE [1], −14.9% with semaglutide in STEP 1 [2], and −15.0% to −20.9% with tirzepatide in SURMOUNT-1 [3]. Because SCALE reported weight change in kilograms while STEP 1 and SURMOUNT-1 reported percentages, and because trial durations and designs differed, these results are not directly comparable. No trial reviewed here compared the agents head-to-head, so conclusions about relative effectiveness remain indirect.

3. Dose Response with Tirzepatide

In SURMOUNT-1, mean weight loss increased from −15.0% with 5 mg to −19.5% with 10 mg and −20.9% with 15 mg, and the proportion achieving at least 20% weight loss was 50% with 10 mg and 57% with 15 mg [3]. A similar pattern was seen in SURMOUNT-2, with −12.8% for 10 mg and −14.7% for 15 mg [5]. These findings suggest a dose-response relationship, although the incremental benefit of the highest dose was smaller than that of the step from 5 to 10 mg in SURMOUNT-1.

4. Effect in People with Type 2 Diabetes

Weight loss was smaller in the trials enrolling people with type 2 diabetes than in those enrolling people without diabetes: −9.6% with semaglutide 2.4 mg in STEP 2 compared with −14.9% in STEP 1 [2][4], and −14.7% with tirzepatide 15 mg in SURMOUNT-2 compared with −20.9% in SURMOUNT-1 [3][5]. This is an indirect comparison across trials with different participants and should be interpreted cautiously, but the direction was consistent for both drugs.

5. Cardiovascular Outcomes

SELECT showed a lower rate of the primary cardiovascular outcome with semaglutide (6.5% vs 8.0%; HR 0.80, 95% CI 0.72–0.90) among adults with established cardiovascular disease, overweight or obesity, and no diabetes [6]. These results apply to that specific population. No cardiovascular outcome data for liraglutide 3.0 mg or tirzepatide were included in this review, so no conclusions can be drawn for those agents.

6. Tolerability

Gastrointestinal adverse events were the main tolerability issue, with nausea and diarrhea common with semaglutide [2], and mostly mild to moderate events concentrated during dose escalation with tirzepatide [3]. Discontinuation due to adverse events was higher with active drug than placebo in the trials for which data were available [2][3][6]. Discontinuation reached 16.6% with semaglutide in SELECT, compared with 8.2% with placebo [6], which suggests that tolerability may limit long-term use in some patients.

7. Implications for Practice

The trials reviewed show clinically meaningful weight loss with incretin-based medications, but they were conducted under trial conditions with lifestyle intervention in both groups. The records reviewed did not include data on cost, access, weight regain after stopping treatment, or performance in Indonesian or other Southeast Asian populations. These considerations are important for clinical decisions in Indonesia and are not addressed by the trials summarized here.

8. Implications for Research

Future research should include head-to-head comparisons, long-term follow-up after treatment cessation, cardiovascular outcome

data for additional agents, and results from Asian populations, who may differ in body composition and cardiometabolic risk at a given body mass index.

9. Limitations

Several limitations should be acknowledged. Searching was performed through a web interface rather than an exportable multi-database search and no protocol was registered, so relevant trials may have been missed. Selection and extraction were performed by one reviewer, using published abstracts and verified secondary records. Six trials were included, a formal RoB 2 assessment was not completed, no pooled estimate was computed, and safety data were incomplete for two trials. Weight outcomes were reported on different scales, and comparisons across trials are indirect. The review should be repeated with a documented multi-database search and independent duplicate review before the findings are used for clinical recommendations.

CONCLUSIONS

Liraglutide 3.0 mg, semaglutide 2.4 mg, and tirzepatide produce substantial weight loss compared with placebo in adults with overweight or obesity, with the largest effects for tirzepatide and smaller effects in people with type 2 diabetes. Semaglutide reduced major cardiovascular events in one outcome trial of adults with established cardiovascular disease. Gastrointestinal adverse events and treatment discontinuation are important considerations.

Future work should include a pre-registered, multi-database systematic review with meta-analysis, formal risk-of-bias assessment, head-to-head and long-term evidence, and data from Indonesia and other Asian populations.

Author Contribution Statement

The author performed all aspects of this study.

REFERENCES

[1] Pi-Sunyer X, Astrup A, Fujioka K, et al. A randomized, controlled trial of 3.0 mg of liraglutide in weight management. *N Engl J Med.* 2015;373(1):11–22.

[2] Wilding JPH, Batterham RL, Calanna S, et al. Once-weekly semaglutide in adults with overweight or obesity. *N Engl J Med.* 2021;384(11):989–1002.

[3] Jastreboff AM, Aronne LJ, Ahmad NN, et al. Tirzepatide once weekly for the treatment of obesity. *N Engl J Med.* 2022;387(3):205–216. doi:10.1056/NEJMoa2206038

[4] Davies M, Færch L, Jeppesen OK, et al. Semaglutide 2.4 mg once a week in adults with overweight or obesity, and type 2 diabetes (STEP 2): a randomised, double-blind, double-dummy, placebo-controlled, phase 3 trial. *Lancet.* 2021;397(10278):971–984.

[5] Garvey WT, Frias JP, Jastreboff AM, et al. Tirzepatide once weekly for the treatment of obesity in people with type 2 diabetes (SURMOUNT-2): a double-blind, randomised, multicentre, placebo-controlled, phase 3 trial. *Lancet.* 2023;402(10402):613–626.

[6] Lincoff AM, Brown-Frandsen K, Colhoun HM, et al. Semaglutide and cardiovascular outcomes in obesity without diabetes. *N Engl J Med.* 2023;389(24):2221–2232. doi:10.1056/NEJMoa2307563

[7] Campbell M, McKenzie JE, Sowden A, et al. Synthesis without meta-analysis (SWiM) in systematic reviews: reporting guideline. *BMJ.* 2020;368:l6890. doi:10.1136/bmj.l6890

[8] Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ.* 2019;366:l4898.