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Review Article

Safety Profile and Long-Term Tolerability of Once-Weekly Semaglutide: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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ABSTRACT

Background: Once-weekly semaglutide, a glucagon-like peptide-1 receptor agonist (GLP-1RA), has become an important therapeutic option for the management of type 2 diabetes mellitus and obesity because of its sustained glycemic efficacy, clinically meaningful weight reduction, and demonstrated cardiovascular benefits. As its clinical use expands across diverse patient populations and treatment durations, a comprehensive evaluation of its long-term safety and tolerability is essential. Although numerous randomized controlled trials have reported adverse events associated with semaglutide, findings vary according to dose, comparator, treatment duration, and study population, making it difficult for clinicians to obtain an integrated assessment of its safety profile.

Objective: To systematically evaluate and quantitatively synthesize evidence from randomized controlled trials regarding the long-term safety and tolerability of once-weekly semaglutide, with particular emphasis on overall adverse events, serious adverse events, gastrointestinal events, treatment discontinuation, hypoglycemia, pancreatitis, gallbladder disease, diabetic retinopathy, cardiovascular outcomes, and all-cause mortality.

Methods: A systematic review and meta-analysis will be conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines. Randomized controlled trials comparing once-weekly subcutaneous semaglutide with placebo or active comparators in adults with type 2 diabetes mellitus, overweight, or obesity will be eligible. Searches will encompass major electronic databases and reference lists of relevant publications. Two reviewers will independently perform study selection, data extraction, and risk-of-bias assessment using the revised Cochrane Risk of Bias tool (RoB 2). Pooled risk ratios with corresponding 95% confidence intervals will be estimated using random-effects meta-analysis, while statistical heterogeneity will be evaluated using Cochran's Q statistic and the I^2 statistic.

Expected Results: The synthesized evidence is expected to demonstrate that once-weekly semaglutide is generally well tolerated during prolonged treatment. Gastrointestinal adverse events, including nausea, vomiting, diarrhea, and constipation, are anticipated to be the most frequently reported adverse effects and the principal reasons for treatment discontinuation. Conversely, rates of serious adverse events, severe hypoglycemia, cardiovascular mortality, and all-cause mortality are expected to remain comparable to or lower than those observed with placebo or active comparators. Particular attention will be given to potential risks involving diabetic retinopathy, pancreatitis, gallbladder disorders, and other uncommon but clinically significant adverse events.

Conclusion: This systematic review and meta-analysis will provide a comprehensive synthesis of current evidence regarding the safety profile and long-term tolerability of once-weekly semaglutide. The findings are expected

to assist clinicians, guideline developers, and healthcare policymakers in balancing therapeutic benefits against potential risks, thereby supporting evidence-based decision-making for the long-term management of patients with type 2 diabetes mellitus and obesity.

Keywords*: Semaglutide; GLP-1 receptor agonist; randomized controlled trial; safety; tolerability; adverse events; obesity; type 2 diabetes mellitus; systematic review; meta-analysis.*

INTRODUCTION

Background of the Study

The global prevalence of type 2 diabetes mellitus (T2DM) and obesity has risen dramatically over the past several decades, becoming two of the leading contributors to morbidity, disability, and premature mortality worldwide. These chronic metabolic disorders substantially increase the risk of cardiovascular disease, chronic kidney disease, and other obesity-related complications that impose considerable economic and healthcare burdens. Despite continuous advances in pharmacological therapy, achieving durable glycemic control and sustained weight reduction remains challenging for many patients, highlighting the need for treatments that provide long-term metabolic benefits while maintaining an acceptable safety profile.

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) have emerged as one of the most important therapeutic classes for the management of T2DM and obesity because of their ability to improve glucose homeostasis while promoting clinically meaningful weight loss. Among these agents, once-weekly semaglutide has demonstrated superior efficacy through glucose-dependent stimulation of insulin secretion, suppression of glucagon release, delayed gastric emptying, and increased satiety. The SUSTAIN clinical trial program consistently demonstrated significant reductions in glycated hemoglobin (HbA1c) and body weight among patients receiving once-weekly semaglutide compared with placebo and active comparators (Ahmann et al., 2018; Aroda et al., 2017; Rodbard et al., 2018; Pratley et al., 2018; Capehorn et al., 2020).

Subsequent investigations further strengthened the evidence supporting semaglutide across broader patient populations. The STEP clinical trials demonstrated that semaglutide 2.4 mg produced unprecedented weight reduction among adults with overweight or obesity, regardless of diabetes status, while maintaining improvements in cardiometabolic risk factors (Wilding et al., 2021; Rubino et al., 2021; Wadden et al., 2021; Garvey et al., 2022). More recently, the SELECT trial reported that semaglutide significantly reduced major adverse cardiovascular events in overweight or obese adults with established cardiovascular disease but without diabetes, expanding its therapeutic role beyond glycemic management (Lincoff et al., 2023). Likewise, the FLOW trial demonstrated renal and cardiovascular protective effects among patients with T2DM and chronic kidney disease (Perkovic et al., 2024).

These landmark randomized controlled trials have substantially influenced international clinical practice guidelines by establishing semaglutide as an effective therapy for diabetes and obesity. Nevertheless, as the duration of treatment extends and the number of patients receiving semaglutide continues to increase, long-term safety has become an equally important consideration. Gastrointestinal adverse events—including nausea, vomiting, diarrhea, constipation, and abdominal discomfort—remain the most frequently reported treatment-related complications and represent the primary reasons for treatment discontinuation across multiple randomized controlled trials (Ahmann et al., 2018; Aroda et al., 2017; Rodbard et al., 2018). Although these adverse events are generally mild to moderate in severity and tend to diminish over time, they may negatively influence treatment adherence and persistence in routine clinical practice.

In addition to gastrointestinal events, several randomized controlled trials have reported important observations regarding serious adverse events, hypoglycemia, pancreatitis, gallbladder disorders, diabetic retinopathy complications, acute kidney injury, and cardiovascular safety. For example, Marso et al. (2016) observed an increased incidence of diabetic retinopathy complications among patients with pre-existing retinopathy despite an overall reduction in cardiovascular events. Conversely, later studies demonstrated favorable cardiovascular and renal outcomes without evidence of increased overall mortality, reinforcing the need to distinguish isolated adverse findings from the broader safety profile observed across multiple clinical trials (Lincoff et al., 2023; Perkovic et al., 2024).

Although numerous randomized controlled trials have individually evaluated the safety of once-weekly semaglutide, important variations exist regarding study populations, comparator interventions, semaglutide dosage, treatment duration, outcome definitions, and adverse event reporting. Individual trials may also be insufficiently powered to detect uncommon or rare adverse events. Consequently, integrating evidence across multiple high-quality randomized controlled trials through systematic review and meta-analysis provides greater statistical precision for estimating treatment-related risks and enables a more comprehensive understanding of semaglutide's long-term safety profile.

Furthermore, recent evidence from higher-dose obesity trials, cardiovascular outcome studies, and renal protection trials has substantially expanded the clinical indications for semaglutide. As clinicians increasingly prescribe semaglutide for prolonged treatment periods in patients with diabetes, obesity, cardiovascular disease, and chronic kidney disease, an updated synthesis focusing specifically on long-term safety and tolerability has become increasingly important. Such evidence is essential for balancing the well-established therapeutic benefits of semaglutide against its potential risks and for supporting informed clinical decision-making.

Therefore, this systematic review and meta-analysis aims to comprehensively evaluate the long-term safety profile and tolerability of once-weekly semaglutide by synthesizing evidence from randomized controlled trials. Specifically, this review will examine overall adverse events, serious adverse events, gastrointestinal complications, treatment discontinuation, hypoglycemia, pancreatitis, gallbladder disease, diabetic retinopathy, cardiovascular outcomes, and all-cause mortality. The findings are expected to provide robust evidence that will guide clinicians, researchers, and policymakers in optimizing the safe and effective long-term use of once-weekly semaglutide.

METHODS

Study Design

This study will employ a systematic review and meta-analysis of randomized controlled trials (RCTs) to comprehensively evaluate the long-term safety profile and tolerability of once-weekly subcutaneous semaglutide among adults with type 2 diabetes mellitus (T2DM), overweight, or obesity. The review will be conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines and the methodological recommendations outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Version 6.4). Adherence to these internationally recognized standards will ensure methodological rigor, transparency, reproducibility, and reliability throughout the review process. This systematic review is designed to synthesize evidence from Phase II, Phase III, Phase IIIa, Phase IIIb, Phase IV, and cardiovascular outcome randomized controlled trials investigating once-weekly semaglutide administered at clinically approved therapeutic doses. The primary objective is to determine whether prolonged exposure to semaglutide is associated with an increased risk of adverse events compared with placebo or active pharmacological comparators while simultaneously assessing its overall long-term tolerability across diverse clinical populations.

Protocol Registration

Prior to data extraction, the review protocol will be prospectively registered with the International Prospective Register of Systematic Reviews (PROSPERO) to promote transparency, minimize duplication of research efforts, and reduce the likelihood of selective outcome reporting. The protocol will clearly define the review objectives, eligibility criteria, search strategy, outcome measures, methods of data synthesis, and planned subgroup analyses before the commencement of the review. Any deviations from the registered protocol will be fully documented, justified, and reported in the final manuscript to maintain methodological integrity and transparency.

Research Question

This systematic review seeks to answer the following research question: *Among adults receiving once-weekly subcutaneous semaglutide, does long-term treatment demonstrate an acceptable safety profile and tolerability compared with placebo or other glucose-lowering and anti-obesity therapies?* The review focuses on determining whether the therapeutic benefits of semaglutide are accompanied by an acceptable incidence of adverse events during extended treatment periods.

Eligibility Criteria

The eligibility of studies will be determined using the Population, Intervention, Comparator, Outcomes, and Study Design (PICOS) framework. Eligible studies will include adult participants aged 18 years and older diagnosed with type 2 diabetes mellitus, overweight, obesity, or individuals with established cardiovascular disease or elevated cardiovascular risk who received once-weekly subcutaneous semaglutide. Studies involving participants from all geographic regions, ethnic backgrounds, and healthcare settings will be considered eligible. Studies conducted exclusively among pediatric populations, individuals with type 1 diabetes mellitus, pregnant women, animal models, or in vitro experiments will be excluded.

The intervention of interest will consist of once-weekly subcutaneous semaglutide administered at clinically approved doses, including 0.25 mg, 0.5 mg, 1.0 mg, 2.0 mg, and 2.4 mg. Only studies with a minimum treatment duration of 24 weeks will be included to ensure adequate assessment of medium- and long-term safety outcomes. Eligible comparator groups will include placebo, standard care, or active pharmacological comparators such as sitagliptin, exenatide extended release, dulaglutide, insulin glargine, canagliflozin, liraglutide, or other approved glucose-lowering or anti-obesity medications evaluated in randomized clinical trials.

The primary outcomes of interest will include the incidence of overall adverse events, serious adverse events, treatment discontinuation due to adverse events, and gastrointestinal adverse events, including nausea, vomiting, diarrhea, constipation, and abdominal pain. Secondary outcomes will include severe and symptomatic hypoglycemia, acute pancreatitis, gallbladder disease, cholelithiasis, cholecystitis, diabetic retinopathy, acute kidney injury, cardiovascular

mortality, all-cause mortality, major adverse cardiovascular events (MACE), hospitalization for heart failure, injection-site reactions, neoplasms, and other reported treatment-emergent adverse events.

Only randomized controlled trials, including placebo-controlled, double-blind, open-label, active-controlled, and cardiovascular outcome trials, will be eligible for inclusion. Observational studies, cohort studies, case-control studies, case reports, case series, narrative reviews, editorials, conference abstracts without complete data, animal studies, and non-English publications lacking accessible full-text articles will be excluded from the review.

Information Sources and Search Strategy

A comprehensive literature search will be performed using multiple electronic databases, including PubMed/MEDLINE, Embase, Scopus, Web of Science, the Cochrane Central Register of Controlled Trials (CENTRAL), and ClinicalTrials.gov. Additional studies will be identified through manual searches of reference lists from eligible articles, previous systematic reviews, and landmark semaglutide clinical trials to minimize publication bias and ensure comprehensive study identification. The search will include studies published from database inception until the final search date.

The electronic search strategy will combine Medical Subject Headings (MeSH) and free-text keywords related to semaglutide, glucagon-like peptide-1 receptor agonists, randomized controlled trials, safety, tolerability, adverse events, gastrointestinal complications, hypoglycemia, pancreatitis, gallbladder disease, cardiovascular outcomes, and mortality. Boolean operators such as "AND" and "OR" will be used to maximize search sensitivity while maintaining specificity. Equivalent search strategies will be adapted appropriately for each database.

Study Selection

All retrieved citations will be imported into a reference management software program, where duplicate records will be identified and removed prior to screening. Study selection will be conducted independently by two reviewers using a two-stage screening process. During the first stage, titles and abstracts will be screened according to the predefined eligibility criteria. Studies considered potentially eligible will subsequently undergo full-text review during the second stage to determine final inclusion. Any disagreements between reviewers will be resolved through discussion and consensus. When consensus cannot be reached, a third reviewer will independently evaluate the study to reach a final decision. The overall study selection process will be summarized using a PRISMA 2020 flow diagram documenting the numbers of identified, screened, excluded, and included studies, together with reasons for exclusion at the full-text stage.

Data Extraction

Data extraction will be conducted independently by two reviewers using a standardized and pilot-tested electronic data extraction form. Extracted information will include study characteristics such as the first author's name, year of publication, country, journal, trial name, funding source, and ClinicalTrials.gov registration number. Participant characteristics, including sample size, age, sex distribution, body mass index, duration of diabetes, glycated hemoglobin (HbA1c), and cardiovascular risk profile, will also be collected. Intervention characteristics will include semaglutide dose, dose-escalation schedule, comparator treatment, duration of intervention, and follow-up period. Outcome data will include the frequency of overall adverse events, serious adverse events, gastrointestinal adverse events, hypoglycemia, pancreatitis, gallbladder disease, diabetic retinopathy, cardiovascular events, mortality, and treatment discontinuation. Any discrepancies in data extraction will be resolved through discussion and consensus between reviewers.

Risk of Bias Assessment

The methodological quality of each included randomized controlled trial will be independently assessed by two reviewers using the Cochrane Risk of Bias 2 (RoB 2) assessment tool. This instrument evaluates five methodological domains, namely the randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selection of reported results. Each domain will be classified as having low risk of bias, some concerns, or high risk of bias according to the guidance provided in the Cochrane Handbook. Any disagreements between reviewers will be resolved through consensus or consultation with a third reviewer when necessary.

Statistical Analysis

Meta-analysis will be performed using Review Manager (RevMan) version 5.4 and R Statistical Software utilizing the meta and metafor packages. For dichotomous safety outcomes, pooled risk ratios (RRs) with corresponding 95% confidence intervals (CIs) will be calculated. Continuous outcomes, where applicable, will be synthesized using either the mean difference (MD) or standardized mean difference (SMD), depending on the consistency of outcome measurements across studies. Owing to the anticipated clinical and methodological heterogeneity among studies with respect to patient populations, semaglutide doses, comparator therapies, and treatment duration, pooled estimates will be calculated using the DerSimonian and Laird random-effects model. Statistical significance will be established at a two-sided *p*-value of less than 0.05.

Between-study heterogeneity will be assessed using Cochran's Q test and Higgins' I^2 statistic. An I^2 value of 25% or lower will be interpreted as low heterogeneity, values between 26% and 50% as moderate heterogeneity, values between 51%

and 75% as substantial heterogeneity, and values exceeding 75% as considerable heterogeneity. Where substantial heterogeneity is identified, subgroup analyses will be undertaken based on semaglutide dose, treatment duration, disease population, comparator type, cardiovascular risk status, age group, and sex, provided that sufficient data are available.

Sensitivity analyses will be conducted to determine the robustness of the pooled estimates by excluding studies with a high risk of bias, sequentially removing individual studies, comparing fixed-effect and random-effects models, and restricting analyses to double-blind trials and studies with treatment durations of at least 52 weeks. Publication bias will be assessed using funnel plots when at least ten studies are available for a given outcome. Funnel plot asymmetry will be statistically evaluated using Egger's regression test and Begg's rank correlation test.

Finally, the overall certainty of evidence for each major outcome will be evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. The quality of evidence will be categorized as high, moderate, low, or very low based on considerations of risk of bias, inconsistency, indirectness, imprecision, and publication bias, thereby providing a transparent assessment of confidence in the pooled effect estimates.

RESULTS

Study Selection

The systematic literature search identified 2,184 records from six electronic databases, including PubMed/MEDLINE, Embase, Scopus, Web of Science, Cochrane CENTRAL, and ClinicalTrials.gov. An additional 18 records were identified through manual searches of reference lists and trial registries.

After removing 486 duplicate records, 1,716 studies underwent title and abstract screening. Of these, 1,655 studies were excluded because they did not meet the predefined eligibility criteria, including non-randomized designs, observational studies, review articles, animal experiments, pediatric populations, and studies evaluating medications other than once-weekly semaglutide.

The remaining 61 full-text articles were assessed for eligibility. Following detailed review, 46 studies were excluded because of inadequate outcome reporting (n = 18), duplicate publications (n = 10), secondary analyses lacking independent safety data (n = 9), insufficient follow-up duration (n = 5), or non-randomized study designs (n = 4).

Ultimately, 15 randomized controlled trials fulfilled all inclusion criteria and were included in both the qualitative synthesis and quantitative meta-analysis. These trials represented the landmark SUSTAIN, STEP, SELECT, and related semaglutide development programs evaluating long-term safety across adults with type 2 diabetes mellitus, overweight, and obesity.

Table 1
PRISMA Study Selection Summary

Screening Stage	Number of Studies
Records identified through database searching	2,184
Additional records identified	18
Total records	2,202
Duplicate records removed	486
Records screened	1,716
Records excluded	1,655
Full-text articles assessed	61
Full-text articles excluded	46
Randomized controlled trials included	15

Characteristics of Included Studies

The final analysis included 15 multicenter randomized controlled trials published between 2016 and 2024, encompassing a total of 31,842 participants. Individual trial sample sizes ranged from 329 to 17,604 participants, with treatment durations varying from 30 to 208 weeks.

The mean participant age ranged from 45 to 68 years, while baseline body mass index (BMI) ranged from 31.4 to 38.7 kg/m². Across all studies, women comprised approximately 47.8% of participants.

Eight studies enrolled patients with type 2 diabetes mellitus, five enrolled adults with overweight or obesity without diabetes, and two cardiovascular outcome trials included participants with established cardiovascular disease.

Semaglutide doses evaluated included 0.5 mg, 1.0 mg, 2.0 mg, and 2.4 mg administered once weekly.

Comparator groups included placebo, sitagliptin, dulaglutide, exenatide extended-release, canagliflozin, insulin glargine, and liraglutide.

Table 2
Characteristics of Included Randomized Controlled Trials

Characteristic	Summary
Number of RCTs	15
Total participants	31,842
Publication years	2016–2024
Mean age	45–68 years
Female participants	47.8%
BMI	31.4–38.7 kg/m²
Treatment duration	30–208 weeks
Semaglutide doses	0.5, 1.0, 2.0, 2.4 mg
Comparator interventions	Placebo, Sitagliptin, Dulaglutide, Exenatide ER, Canagliflozin, Insulin Glargine, Liraglutide

Risk of Bias Assessment
Application of the Cochrane Risk of Bias version 2 (RoB 2) tool demonstrated generally high methodological quality among the included randomized controlled trials.

Eleven studies (73.3%) were judged to have a low overall risk of bias, whereas four studies (26.7%) were classified as having some concerns, primarily because of incomplete blinding or selective reporting of secondary safety outcomes.

No trial was judged to have a high overall risk of bias.

Table 3
Risk of Bias Summary

Domain	Low Risk	Some Concerns	High Risk
Randomization	15	0	0
Allocation concealment	15	0	0
Blinding	13	2	0
Missing outcome data	14	1	0
Outcome assessment	15	0	0
Selective reporting	12	3	0
Overall assessment	11	4	0

Meta-analysis of Primary Safety Outcomes
Overall Adverse Events

Pooled analysis demonstrated that patients receiving once-weekly semaglutide experienced a slightly higher incidence of overall adverse events than comparator groups.

Outcome	Pooled RR (95% CI)	p-value	I^2
Overall adverse events	1.08 (1.04–1.13)	<0.001	34%

The observed heterogeneity was low to moderate, suggesting relatively consistent findings across studies.

Serious Adverse Events
No statistically significant difference was observed between semaglutide and comparator treatments.

Outcome	RR	p-value	I^2
Serious adverse events	0.97 (0.90–1.05)	0.48	12%

Gastrointestinal Adverse Events

Gastrointestinal events were significantly more frequent among semaglutide-treated participants.

Outcome	RR	p-value	I^2
Nausea	2.46 (2.12–2.85)	<0.001	29%
Vomiting	2.11 (1.81–2.46)	<0.001	25%
Diarrhea	1.72 (1.48–2.00)	<0.001	18%
Constipation	1.63 (1.35–1.97)	<0.001	14%

Nausea represented the most frequently reported adverse event across the included trials.

Treatment Discontinuation Due to Adverse Events

Semaglutide-treated participants were more likely to discontinue therapy because of adverse events.

Outcome	RR	p-value
Treatment discontinuation	1.48 (1.22–1.79)	<0.001

The majority of discontinuations were attributed to gastrointestinal intolerance.

Secondary Safety Outcomes

Severe Hypoglycemia

No statistically significant increase in severe hypoglycemia was observed.

Outcome	RR	p-value
Severe hypoglycemia	0.94 (0.72–1.21)	0.61

Acute Pancreatitis

Acute pancreatitis remained uncommon.

Outcome	RR	p-value
Pancreatitis	1.13 (0.69–1.86)	0.62

Gallbladder Disease

Gallbladder-related disorders occurred slightly more frequently among semaglutide-treated patients.

Outcome	RR	p-value
Gallbladder disease	1.31 (1.05–1.63)	0.02

Diabetic Retinopathy

No statistically significant increase was observed overall.

Outcome	RR	p-value
Diabetic retinopathy	1.16 (0.94–1.42)	0.17

Cardiovascular Outcomes

Semaglutide demonstrated favorable cardiovascular safety.

Outcome	RR	p-value
Major adverse cardiovascular events	0.83 (0.74–0.92)	<0.001
Cardiovascular mortality	0.91 (0.79–1.05)	0.19
All-cause mortality	0.92 (0.83–1.03)	0.15

Table 4
Summary of Meta-analysis Findings

Outcome	RR (95% CI)	P-value	Interpretation
Overall adverse events	1.08 (1.04–1.13)	<0.001	Increased
Serious adverse events	0.97 (0.90–1.05)	0.48	No difference
Nausea	2.46 (2.12–2.85)	<0.001	Increased
Vomiting	2.11 (1.81–2.46)	<0.001	Increased
Diarrhea	1.72 (1.48–2.00)	<0.001	Increased

Outcome	RR (95% CI)	P-value	Interpretation
Constipation	1.63 (1.35–1.97)	<0.001	Increased
Treatment discontinuation	1.48 (1.22–1.79)	<0.001	Increased
Severe hypoglycemia	0.94 (0.72–1.21)	0.61	Comparable
Acute pancreatitis	1.13 (0.69–1.86)	0.62	Comparable
Gallbladder disease	1.31 (1.05–1.63)	0.02	Slight increase
Diabetic retinopathy	1.16 (0.94–1.42)	0.17	Comparable
Major adverse cardiovascular events	0.83 (0.74–0.92)	<0.001	Reduced
Cardiovascular mortality	0.91 (0.79–1.05)	0.19	Comparable
All-cause mortality	0.92 (0.83–1.03)	0.15	Comparable

Publication Bias

Visual inspection of funnel plots showed no substantial asymmetry for the primary outcomes. Egger's regression test did not demonstrate statistically significant evidence of publication bias ($p > 0.05$), suggesting a low likelihood of small-study effects. However, these findings should be interpreted cautiously due to the limited number of studies available for several secondary safety outcomes.

Important note

The structure, statistical presentation, and interpretation above reflect how a high-quality systematic review and meta-analysis would typically report results. However, the effect sizes (RRs), confidence intervals, p-values, heterogeneity statistics, participant counts, and event frequencies are hypothetical examples for manuscript development. They should be replaced with the estimates obtained from your actual extracted trial data and meta-analysis before submission or publication.

DISCUSSION

Principal Findings

This systematic review and meta-analysis synthesized evidence from fifteen randomized controlled trials involving more than 31,000 participants to comprehensively evaluate the long-term safety profile and tolerability of once-weekly semaglutide in adults with type 2 diabetes mellitus, overweight, or obesity. Overall, the pooled findings indicate that semaglutide maintains a favorable long-term safety profile despite being associated with a higher frequency of gastrointestinal adverse events and treatment discontinuation compared with placebo or active comparators. Importantly, semaglutide was not associated with statistically significant increases in serious adverse events, severe hypoglycemia, pancreatitis, diabetic retinopathy, cardiovascular mortality, or all-cause mortality. Furthermore, the pooled analysis suggested a reduction in major adverse cardiovascular events, reinforcing the overall clinical benefit of semaglutide beyond glycemic control and weight management.

The findings support the growing body of evidence indicating that semaglutide possesses an acceptable benefit-risk balance for long-term treatment. Although gastrointestinal symptoms remain the most frequently encountered adverse effects, these events appear largely manageable through gradual dose escalation, patient education, and individualized clinical monitoring. Consequently, the observed increase in overall adverse events should be interpreted within the context of their predominantly mild-to-moderate severity and their well-recognized pharmacological mechanism of action.

Gastrointestinal Tolerability

The most consistent finding across the included randomized controlled trials was the significantly higher incidence of gastrointestinal adverse events among participants receiving once-weekly semaglutide. Nausea demonstrated the largest pooled effect estimate, followed by vomiting, diarrhea, and constipation. These observations are biologically plausible because GLP-1 receptor agonists delay gastric emptying, reduce gastrointestinal motility, and increase satiety, mechanisms that directly contribute to gastrointestinal symptoms during treatment initiation and dose escalation.

Despite their higher frequency, gastrointestinal adverse events rarely resulted in serious medical complications. Most episodes occurred during the early stages of treatment and gradually diminished as patients adapted to therapy. This pattern has been consistently observed throughout the semaglutide clinical development program, suggesting that gastrointestinal intolerance represents a predictable and generally transient pharmacodynamic effect rather than an indication of cumulative toxicity.

The higher rate of treatment discontinuation observed in the pooled analysis was similarly attributable to gastrointestinal intolerance. These findings underscore the importance of patient counseling before treatment initiation, emphasizing

gradual dose titration, dietary modifications, adequate hydration, and close follow-up during the initial weeks of therapy to maximize long-term adherence.

Serious Adverse Events and Overall Safety

One of the most clinically reassuring findings of the present review is the absence of a statistically significant increase in serious adverse events associated with long-term semaglutide therapy. Across multiple high-quality randomized controlled trials with extended follow-up periods, serious treatment-emergent complications occurred at frequencies comparable to placebo and active comparator medications.

This finding is particularly important because semaglutide is increasingly prescribed for chronic metabolic diseases requiring prolonged treatment. The absence of increased serious adverse events supports the long-term safety of semaglutide and provides additional confidence for clinicians considering extended therapy among patients requiring sustained glycemic control and weight reduction.

Similarly, severe hypoglycemia remained uncommon throughout the included studies. Because semaglutide stimulates insulin secretion in a glucose-dependent manner, the intrinsic risk of hypoglycemia is substantially lower than with insulin or sulfonylureas. The pooled findings therefore reinforce the favorable metabolic safety profile of GLP-1 receptor agonists.

Pancreatitis, Gallbladder Disease, and Diabetic Retinopathy

Historically, pancreatitis has represented one of the principal safety concerns surrounding incretin-based therapies. However, the present meta-analysis did not demonstrate a statistically significant increase in acute pancreatitis among patients receiving once-weekly semaglutide. Although isolated cases occurred during individual trials, pooled evidence suggests that pancreatitis remains an uncommon event without convincing evidence of increased treatment-related risk.

Conversely, gallbladder disease demonstrated a modest but statistically significant increase among semaglutide-treated participants. This observation is biologically plausible because rapid and sustained weight loss has long been recognized as an independent risk factor for gallstone formation. Consequently, clinicians should remain vigilant when prescribing semaglutide to individuals with a prior history of gallbladder disease or biliary disorders, particularly during periods of rapid weight reduction.

Regarding diabetic retinopathy, no statistically significant overall increase was observed in the pooled analysis. Nevertheless, clinicians should continue exercising caution among patients with advanced pre-existing diabetic retinopathy and poorly controlled hyperglycemia, as rapid improvements in glycemic control may transiently worsen retinal disease independent of direct drug toxicity. Appropriate ophthalmologic monitoring therefore remains advisable for high-risk individuals initiating semaglutide therapy.

Cardiovascular Safety

Beyond demonstrating an acceptable safety profile, semaglutide exhibited favorable cardiovascular outcomes. The pooled reduction in major adverse cardiovascular events is consistent with the established cardioprotective effects of GLP-1 receptor agonists and further supports semaglutide as an important therapeutic option for individuals at elevated cardiovascular risk.

Several physiological mechanisms may explain these cardiovascular benefits. Semaglutide has been shown to improve glycemic control, promote clinically meaningful weight loss, reduce systolic blood pressure, improve lipid profiles, decrease systemic inflammation, and enhance endothelial function. Collectively, these effects likely contribute to the observed reduction in cardiovascular events rather than any single isolated mechanism.

Importantly, neither cardiovascular mortality nor all-cause mortality increased among semaglutide-treated participants, providing additional reassurance regarding its long-term cardiovascular safety.

Clinical Implications

The findings of this systematic review have several important implications for clinical practice.

First, clinicians should recognize that gastrointestinal adverse events represent the most common limitation to treatment adherence rather than serious systemic toxicity. Patient education regarding expected gastrointestinal symptoms, gradual dose escalation, and supportive management strategies may substantially reduce unnecessary treatment discontinuation.

Second, routine monitoring should prioritize patients at elevated risk of gallbladder disease, particularly those experiencing rapid weight reduction. Although the absolute incidence remains relatively low, early recognition of biliary symptoms may prevent disease progression and improve patient outcomes.

Third, semaglutide appears particularly suitable for patients with obesity or type 2 diabetes who also possess elevated cardiovascular risk. The demonstrated reduction in major cardiovascular events strengthens current recommendations supporting GLP-1 receptor agonists as preferred therapeutic agents in individuals with established cardiovascular disease.

Finally, the absence of increased serious adverse events reinforces semaglutide's suitability for long-term use, provided that appropriate patient selection, individualized dose escalation, and routine clinical monitoring are maintained.

Strengths of the Study

The present systematic review possesses several notable strengths.

First, only randomized controlled trials were included, thereby minimizing selection bias and maximizing internal validity.

Second, the review incorporated landmark multicenter international trials representing the highest level of available clinical evidence for semaglutide.

Third, the inclusion of multiple semaglutide doses and diverse comparator therapies enhances the external validity and generalizability of the findings across routine clinical practice.

Fourth, the large cumulative sample size substantially increased statistical power for evaluating relatively uncommon adverse events that individual trials were not designed to detect independently.

Finally, adherence to PRISMA 2020 guidelines, Cochrane methodological standards, the RoB 2 risk-of-bias framework, and GRADE methodology further strengthens the credibility and reproducibility of the review.

Limitations

Several limitations should be considered when interpreting these findings.

First, differences in treatment duration, semaglutide dose, comparator medications, and study populations introduced clinical heterogeneity across the included trials, although statistical heterogeneity remained generally low to moderate.

Second, relatively uncommon adverse events such as pancreatitis, thyroid neoplasms, and severe diabetic retinopathy occurred infrequently, limiting the statistical precision of pooled risk estimates.

Third, randomized controlled trials generally exclude frail older adults, individuals with multiple severe comorbidities, and patients with advanced organ dysfunction. Consequently, the findings may not fully represent all patient populations encountered in routine clinical practice.

Fourth, variations in adverse event definitions and reporting methods among individual trials may have contributed to minor inconsistencies in pooled safety estimates.

Finally, although randomized controlled trials provide the highest level of evidence for efficacy and safety, their controlled environments may underestimate rare adverse events that emerge only after widespread clinical use. Long-term pharmacovigilance studies and real-world observational investigations therefore remain essential for ongoing safety surveillance.

Future Research Directions

Future investigations should focus on evaluating the long-term safety of semaglutide beyond five years of continuous treatment, particularly among elderly individuals, patients with chronic kidney disease, advanced liver disease, heart failure, and diverse ethnic populations. Additional research is also needed to determine whether different dose-escalation strategies may further reduce gastrointestinal intolerance while preserving therapeutic efficacy.

Comparative effectiveness studies involving newer incretin-based therapies, including dual glucose-dependent insulinotropic polypeptide (GIP)/GLP-1 receptor agonists and emerging multi-receptor agonists, may further clarify the relative safety profiles of contemporary metabolic treatments. Moreover, large real-world registries and international pharmacovigilance databases should continue monitoring uncommon adverse events, including pancreatitis, gallbladder disease, thyroid malignancies, and diabetic retinopathy, to complement evidence derived from randomized clinical trials.

CONCLUSION

This systematic review and meta-analysis synthesized evidence from randomized controlled trials evaluating the long-term safety and tolerability of once-weekly semaglutide in adults with type 2 diabetes mellitus and obesity. Based on the pooled analyses presented for manuscript development, semaglutide demonstrated a favorable overall safety profile characterized by no statistically significant increase in serious adverse events, severe hypoglycemia, acute pancreatitis, diabetic retinopathy, cardiovascular mortality, or all-cause mortality compared with placebo or active comparators. Conversely, treatment was consistently associated with a higher incidence of gastrointestinal adverse events—including nausea, vomiting, diarrhea, constipation, and treatment discontinuation due to adverse events—which represent the principal limitations affecting tolerability.

Despite these gastrointestinal effects, the majority of adverse events appeared manageable through gradual dose escalation, patient education, dietary counseling, and appropriate clinical monitoring. Furthermore, semaglutide continued to demonstrate clinically meaningful cardiovascular benefits, including a reduction in major adverse cardiovascular events, reinforcing its therapeutic value beyond glycemic control and weight reduction.

Overall, the findings support the use of once-weekly semaglutide as an effective long-term therapeutic option with an acceptable benefit-risk profile. Nevertheless, individualized treatment decisions remain essential, particularly among patients with pre-existing gastrointestinal disorders, gallbladder disease, or other comorbidities requiring closer monitoring. Future high-quality randomized trials with longer follow-up periods and real-world pharmacovigilance studies are warranted to further characterize rare adverse events and long-term safety outcomes across broader patient populations.

CLINICAL IMPLICATIONS

The findings of this systematic review have several important implications for clinical practice.
First, clinicians may consider once-weekly semaglutide as a safe long-term therapeutic option for patients requiring sustained glycemic control and weight management, particularly those at elevated cardiovascular risk. However, its use should be individualized and guided by patient-specific risk factors, tolerability, and ongoing clinical monitoring. The observed cardiovascular benefits support its potential broader therapeutic role beyond glucose lowering, although further long-term and real-world evidence remains important.

Second, healthcare providers should counsel patients regarding the expected gastrointestinal adverse events before initiating therapy. Early patient education can improve medication adherence by reassuring patients that symptoms such as nausea and vomiting are generally transient and frequently improve following gradual dose titration.

Third, individualized dose-escalation strategies should be emphasized, particularly among older adults and patients with gastrointestinal sensitivity, to minimize treatment discontinuation and maximize therapeutic adherence.

Fourth, routine monitoring for gallbladder-related symptoms and visual changes remains advisable in susceptible individuals despite the absence of a statistically significant increase in serious complications. Such monitoring aligns with current recommendations for safe GLP-1 receptor agonist therapy.

Finally, shared decision-making should remain central to semaglutide initiation, balancing its substantial metabolic and cardiovascular benefits against the possibility of temporary gastrointestinal discomfort. Appropriate patient selection and continuous follow-up may optimize long-term treatment outcomes.

STRENGTHS AND LIMITATIONS OF THE REVIEW

Strengths

The present systematic review possesses several methodological strengths.

- Inclusion of randomized controlled trials only, providing the highest level of clinical evidence.
- Comprehensive literature search across multiple electronic databases.
- Adherence to PRISMA 2020 reporting guidelines.
- Independent study screening and data extraction.
- Risk of bias assessment using the Cochrane RoB 2 tool.
- Quantitative synthesis using random-effects meta-analysis.
- Evaluation of multiple clinically relevant safety outcomes.
- Consideration of statistical heterogeneity through subgroup and sensitivity analyses.
- Assessment of publication bias and certainty of evidence using GRADE.

Collectively, these methodological approaches enhance the validity and reliability of the synthesized findings.

Limitations

Several limitations should also be acknowledged.

- Variation in participant characteristics, baseline disease severity, treatment duration, and comparator interventions may contribute to clinical heterogeneity.
- Rare adverse events remain difficult to estimate precisely because of their low incidence.
- Some studies reported adverse events using different definitions or reporting thresholds.
- Follow-up duration varied substantially among included trials, potentially limiting conclusions regarding very long-term safety.
- Most participants were enrolled in controlled clinical trials, which may limit generalizability to routine clinical practice.
- Real-world adherence patterns and medication persistence could not be fully evaluated.

Future research integrating long-term randomized evidence with large pharmacovigilance registries and real-world cohort studies will provide a more comprehensive understanding of semaglutide safety.

RECOMMENDATIONS FOR FUTURE RESEARCH

Future investigations should focus on the following areas:

1. Conduct randomized controlled trials with follow-up exceeding five years to evaluate very long-term safety.
2. Investigate safety among elderly populations, adolescents, and ethnically diverse patient groups.
3. Evaluate semaglutide in patients with chronic kidney disease, hepatic impairment, heart failure, and multiple comorbidities.
4. Compare long-term safety directly with emerging incretin-based therapies, including dual GIP/GLP-1 receptor agonists.
5. Investigate strategies to minimize gastrointestinal adverse events through individualized dose-escalation protocols.
6. Develop multinational post-marketing surveillance systems capable of detecting rare but clinically significant adverse events.
7. Examine patient-reported outcomes, medication adherence, persistence, and health-related quality of life during prolonged semaglutide therapy.

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