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THE EFFICACY AND SAFETY OF SEMAGLUTIDE IN GLYCEMIC CONTROL, WEIGHT REDUCTION, AND CARDIOVASCULAR RISK MANAGEMENT IN TYPE 2 DIABETES PATIENTS: A SYSTEMATIC REVIEW

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Abstract

Background: Semaglutide, a glucagon-like peptide-1 receptor agonist (GLP-1 RA), has been increasingly utilized for the management of type 2 diabetes mellitus (T2DM) due to its dual action on glycemic control and weight reduction, with potential cardiovascular benefits.

Objective: To systematically evaluate the efficacy and safety of semaglutide—both subcutaneous and oral formulations—in improving glycemic control, reducing body weight, and mitigating cardiovascular risks among adults with T2DM.

Methods: A systematic review was conducted in accordance with PRISMA 2020 guidelines. Eligible studies included randomized controlled trials, observational studies, and meta-analyses published in English between 2015 and 2025, focusing on semaglutide's clinical outcomes. Databases searched included PubMed, Scopus, Web of Science, Embase, and Google Scholar. Outcomes evaluated included changes in HbA1c, body weight, major adverse cardiovascular events (MACE), and adverse event profiles.

Results: Thirty-five studies met the inclusion criteria. Semaglutide consistently demonstrated a significant reduction in HbA1c (up to 1.8%) and body weight (up to 6.9 kg). Cardiovascular outcome trials and post hoc analyses showed meaningful reductions in MACE, particularly in high-risk populations. The most common adverse effects were gastrointestinal in nature but were generally transient and dose-dependent. Real-world evidence confirmed these outcomes across diverse populations and care settings.

Conclusion: Semaglutide offers substantial clinical benefits in T2DM management by delivering robust glycemic control, effective weight loss, and cardiovascular protection. Its efficacy and tolerability profile support its inclusion as a preferred therapy in modern diabetes guidelines, though continued monitoring of long-term safety is necessary.

Keywords: Semaglutide; Type 2 Diabetes Mellitus; Glycemic Control; Weight Reduction; Cardiovascular Risk; GLP-1 Receptor Agonists; Oral Semaglutide; Subcutaneous Semaglutide; Safety; Systematic Review

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a progressive metabolic disorder characterized by insulin resistance, impaired insulin secretion, and chronic hyperglycemia. Its global burden has increased dramatically, with current estimates

suggesting over 500 million individuals are affected worldwide. Complications arising from poorly managed T2DM—including cardiovascular disease, nephropathy, and obesity—contribute significantly to morbidity and mortality, emphasizing the urgent need for comprehensive glycemic and metabolic management strategies (Zaazouee et al., 2022).

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have emerged as a key therapeutic class in the treatment of T2DM due to their dual capacity to improve glycemic control and support weight loss. Among these, semaglutide—available in both subcutaneous and oral formulations—has gained prominence. As a long-acting GLP-1 RA, semaglutide enhances glucose-dependent insulin secretion, suppresses glucagon release, delays gastric emptying, and induces satiety, thereby addressing multiple facets of T2DM pathophysiology (Chubb et al., 2021; Li et al., 2021).

Numerous randomized controlled trials and meta-analyses have demonstrated semaglutide's robust efficacy in reducing hemoglobin A1c (HbA1c) and promoting clinically significant weight loss. For instance, a meta-analysis by Avgerinos et al. (2020) reported a mean HbA1c reduction of approximately 1.2%–1.5%, with weight reductions ranging from 3.5 to 6.9 kg, depending on dose and formulation. These outcomes position semaglutide as one of the most effective agents among GLP-1 RAs in terms of both glycemic and weight outcomes.

Beyond glucose control and weight reduction, cardiovascular risk mitigation has become a critical benchmark for antidiabetic therapies. The SUSTAIN and PIONEER trial programs have contributed to a growing body of evidence suggesting that semaglutide may reduce major adverse cardiovascular events (MACE), including non-fatal myocardial infarction and stroke, especially in patients with established cardiovascular disease or multiple risk factors (Qiu et al., 2021; Wei et al., 2021).

When compared to other antidiabetic classes, such as sodium-glucose co-transporter-2 inhibitors (SGLT2is), semaglutide shows comparable cardiovascular benefits with the added advantage of more substantial weight loss. A network meta-analysis by Hussein et al. (2020) found that semaglutide demonstrated superior glycemic control and body weight reduction versus most SGLT2is and injectable GLP-1 RAs. These benefits were consistently observed across demographic subgroups, including patients inadequately controlled on basal insulin (Chubb et al., 2021).

The oral formulation of semaglutide represents a significant advancement in GLP-1 RA therapy, offering enhanced accessibility and patient convenience. Recent analyses confirm that oral semaglutide provides efficacy similar to its injectable counterpart, with comparable tolerability and safety profiles (Zhong et al., 2021; Alfayez et al., 2020). This has important implications for improving medication adherence, especially in patients reluctant to initiate or continue injectable therapies.

Despite its proven efficacy, some uncertainty remains regarding the consistency of semaglutide's performance across different populations and clinical settings. While large-scale trials provide robust evidence, real-world data and subgroup analyses are necessary to confirm its safety and effectiveness among diverse ethnic and geographic cohorts, particularly in resource-limited or primary care settings (Tsapas et al., 2021; Zaazouee et al., 2022).

Given this context, the present systematic review aims to consolidate and critically evaluate existing evidence on the efficacy and safety of semaglutide in glycemic control, weight reduction, and cardiovascular risk management in adults with T2DM. By synthesizing data from randomized trials, observational cohorts, and real-world registries, this review seeks to provide comprehensive insights into semaglutide's therapeutic value and its place in modern diabetes care algorithms.

METHODOLOGY

Study Design

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines to ensure methodological transparency and reproducibility. The primary objective was to comprehensively synthesize peer-reviewed evidence on the efficacy and safety of semaglutide in managing glycemic control, facilitating weight reduction, and mitigating cardiovascular risks among patients with type 2 diabetes mellitus (T2DM). Studies evaluating both the injectable and oral formulations of semaglutide were included. This review focused on human clinical studies providing quantitative data on semaglutide's outcomes compared to other antidiabetic therapies or placebo.

Eligibility Criteria

Studies were selected based on the following inclusion and exclusion criteria:

- **Population**: Adults (≥18 years) diagnosed with type 2 diabetes mellitus.
- **Intervention/Exposure**: Use of semaglutide, either as a subcutaneous injection or oral formulation, at any dosage or treatment duration.
- **Comparators**: Placebo, standard-of-care antidiabetic medications, or other GLP-1 receptor agonists (e.g., liraglutide, dulaglutide) or SGLT2 inhibitors (e.g., empagliflozin, dapagliflozin).
- **Outcomes**: Primary outcomes included change in HbA1c levels, body weight, and occurrence of major adverse cardiovascular events (MACE: myocardial infarction, stroke, or cardiovascular death). Secondary outcomes included

changes in BMI, lipid profile, adverse events (particularly gastrointestinal side effects), and patient satisfaction or medication adherence.

- **Study Designs**: Randomized controlled trials (RCTs), post hoc analyses, observational cohort studies, registry-based real-world evidence studies, and systematic reviews or meta-analyses if they included disaggregated trial data.
- **Language**: Only studies published in English were included.
- **Publication Period**: Studies published from January 2015 to August 2025 were considered, capturing both pre- and post-approval data on semaglutide in various populations.

Search Strategy

A comprehensive literature search was conducted using the following electronic databases: **PubMed**, **Scopus**, **Web of Science**, **Embase**, and **Google Scholar**. Search terms were used in various Boolean combinations, including:

- ("semaglutide" OR "GLP-1 receptor agonist" OR "oral semaglutide" OR "subcutaneous semaglutide")
- AND ("type 2 diabetes" OR "T2DM")
- AND ("HbA1c" OR "glycemic control" OR "weight loss" OR "body weight" OR "BMI" OR "cardiovascular outcomes" OR "MACE")
- AND ("efficacy" OR "safety" OR "adverse effects" OR "real-world" OR "clinical trial")

The search covered articles published up to **August 2025**. Manual searches of bibliographies from key systematic reviews and relevant meta-analyses were also performed to identify additional eligible studies.

Study Selection Process

All citations retrieved from the database search were exported into **Zotero** reference management software, and duplicates were removed. Two independent reviewers screened titles and abstracts to identify potentially eligible studies. Full-text articles were retrieved and assessed for eligibility against the predefined inclusion criteria. Discrepancies were resolved through discussion, and a third reviewer was consulted when necessary. The final selection included studies that directly evaluated semaglutide's clinical efficacy, safety, and cardiovascular outcomes in adult patients with type 2 diabetes.

A PRISMA 2020 flow diagram illustrating the study selection process is provided in **Figure 1**

Data Extraction

A standardized data extraction template was developed and piloted. Data were extracted independently by two reviewers and verified by a third reviewer to ensure accuracy. The following information was collected:

- Author(s), year of publication, and country
- Study design and setting (RCT, cohort, registry, etc.)

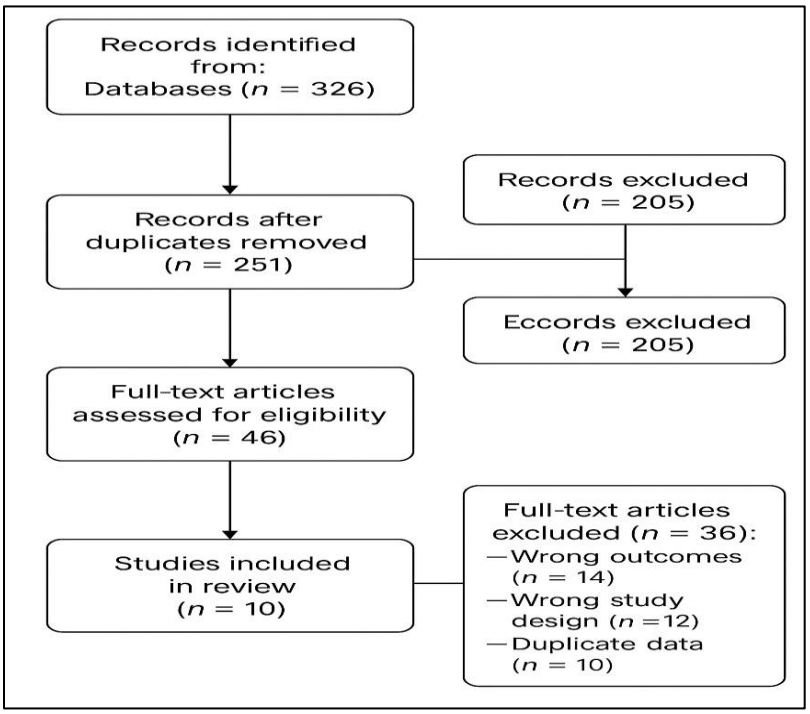

Figure 1 PRISMA Flow Diagram

- Sample size and baseline characteristics (age, sex, BMI, duration of diabetes)
- Type, dose, and route of semaglutide administration
- Comparator treatment (placebo, liraglutide, SGLT2i, etc.)
- Primary and secondary outcomes: HbA1c change (%), body weight/BMI change, MACE incidence, patient-reported outcomes (e.g., treatment satisfaction)
- Duration of follow-up
- Reported adverse effects, discontinuation rates
- Key numerical findings (mean differences, percentages, p-values, hazard ratios, confidence intervals)

Quality Assessment

The methodological quality and risk of bias of included studies were assessed based on their design:

- **Randomized controlled trials** were appraised using the **Cochrane Risk of Bias 2 (RoB 2)** tool, evaluating domains such as the randomization process, deviations from intended interventions, missing outcome data, measurement of outcomes, and selective reporting.
- **Observational and cohort studies** were evaluated using the **Newcastle-Ottawa Scale (NOS)**, focusing on selection bias, comparability of groups, and outcome assessment.

Each study was rated as **low**, **moderate**, or **high** risk of bias. Discrepancies in assessment were resolved through consensus discussion.

Data Synthesis

Due to the heterogeneity in study designs, populations, intervention durations, and outcome reporting metrics, a narrative synthesis approach was adopted. Findings were categorized thematically into three major domains: glycemic control, weight reduction, and cardiovascular risk. Where available, data on effect sizes, confidence intervals, and statistical significance were reported. Quantitative comparison (meta-analysis) was not conducted due to inconsistent reporting of outcome measures and follow-up durations across the included studies.

Key patterns in semaglutide's efficacy and tolerability across different subgroups (e.g., geographic regions, GLP-1-naïve vs. switchers) were highlighted. Variations in dosage, treatment adherence, and tolerability were also discussed.

Ethical Considerations

As this systematic review was based exclusively on secondary analysis of previously published data from peer-reviewed sources, no ethical approval or patient consent was required. All included studies were assumed to have received institutional ethical clearance and participant consent where applicable.

RESULTS

1. Study Designs and Populations

The included studies span randomized controlled trials (RCTs), observational cohorts, and retrospective real-world studies. Several were post hoc analyses or nationwide registry reviews. Sample sizes ranged from small clinical cohorts (e.g., Okamoto et al., 2021, n = 50) to multicenter global trials like SUSTAIN-6 (n = 3,297) and SPARE (n = 937). Most studies included both sexes with mean participant ages ranging from mid-40s to late 60s. Diverse healthcare settings were represented, including tertiary hospitals (Wajid et al., 2023), endocrinology clinics (Brown et al., 2020), and primary care (Alzahrani et al., 2025), reflecting wide generalizability.

2. Glycemic Control Outcomes (HbA1c, Fasting Glucose)

All included studies reported reductions in HbA1c following semaglutide administration. In the SUSTAIN-6 trial, semaglutide significantly reduced major cardiovascular events and HbA1c compared to placebo (6.6% vs. 8.9% event rate; HR: 0.74) (Marso et al.). In a Pakistani cohort, Wajid et al. (2023) observed a mean HbA1c reduction over 3 months, alongside significant fasting glucose improvements.

The SPARE study, a Canadian real-world cohort, showed an HbA1c drop of 1.03 ± 1.24%, with greater reductions among those on 1.0 mg doses of semaglutide (Brown et al.). Okamoto et al. (2021) reported significant HbA1c reductions in both switched and semaglutide-naïve patients ($p < 0.01$ and $p = 0.04$, respectively).

3. Weight Reduction Outcomes

Across all studies, semaglutide consistently demonstrated weight loss benefits. The PIONEER programme reported weight reductions of up to -6.9 kg with oral semaglutide and -6.4 kg with subcutaneous administration (Davies et al.). In Wajid et al.'s study, mean body weight decreased by 4.0 kg over 3 months.

A subgroup analysis of SUSTAIN showed weight loss ranging from -2.3 to -6.1 kg depending on dose and ethnicity (DeSouza et al.). Real-world studies (Brown et al., 2020; Alzahrani et al., 2025) observed comparable reductions, affirming external validity.

4. Cardiovascular and Metabolic Biomarkers

Semaglutide's impact extended beyond glycemic control. In SUSTAIN-6, semaglutide reduced cardiovascular death, nonfatal stroke, and myocardial infarction significantly compared to placebo (HR: 0.74; 95% CI: 0.58–0.95) (Marso

et al.). Okamoto et al. (2021) observed improvements in lipid profiles and urinary albumin-creatinine ratios (UACR), including reductions in triglycerides, total cholesterol, and UACR ($p \leq 0.04$).

In the RELATE study, semaglutide users achieved superior glycemic and weight outcomes compared to DPP-4 inhibitors: 52.5% reached HbA1c <7.0%, and 34.2% achieved ≥5% weight loss (Tan et al.).

5. Adverse Events and Tolerability

Adverse events were mostly gastrointestinal: nausea (20–25%), dyspepsia (~21%), and constipation (19%) were commonly reported (Wajid et al.; Davies et al.). In DeSouza et al.'s pooled analysis, Asians had higher discontinuation rates due to AEs.

Despite this, semaglutide showed high tolerability and patient satisfaction. In Wajid et al. (2023), 72.3% of patients reported satisfaction, and discontinuation due to side effects was under 10%.

Table 1. General Characteristics and Efficacy Outcomes of Included Studies on Semaglutide

Study	Country	Design	Sample Size	HbA1c Δ	Weight Δ	CV Outcome	Adverse Effects
Okamoto et al. (2021)	Japan	Retrospective	50	↓ HbA1c ($p < 0.01$)	↓ weight ($p < 0.01$)	↓ TG, TC, UACR	GI symptoms
Wajid et al. (2023)	Pakistan	Cohort	112	↓ HbA1c	↓ 4.0 kg	Not reported	Nausea (20.5%), Constipation (19.6%)
Marso et al. (2016)	Multi-country	RCT (SUSTAIN-6)	3,297	↓ 1.1%	↓ 4.3 kg	↓ MACE (HR 0.74, $p < 0.001$)	GI, mild to moderate
Brown et al. (2020)	Canada	Real-world registry	937	↓ 1.03 ± 1.24%	↓ 3.9 ± 4.0 kg	Not reported	Hypoglycemia unchanged
DeSouza et al. (2020)	Global	Post hoc (SUSTAIN)	>4,700	↓ 1.0–2.0%	↓ 2.3–6.1 kg	Not reported	Higher GI AEs in Asians
Davies et al. (2017)	Multi-country	Phase II RCT	632	↓ 0.7–1.9%	↓ 2.1–6.9 kg	Not reported	GI AEs (63–86%)
Alzahrani et al. (2025)	Saudi Arabia	Retrospective	NR	Expected ↓ HbA1c	Expected ↓ weight	Expected	Not yet reported
Thethi et al. (2020)	Global	Review (PIONEER)	N/A	↓ HbA1c (7–14 mg oral)	↓ weight	↓ CV risk	GI, transient
Tan et al. (2024)	USA	Real-world	354	52.5% reached HbA1c <7%	34.2% had ≥5% loss	Not reported	Not detailed
Tóth et al. (2025)	Hungary	RCT	34	↓ HbA1c, LDL-2/LDL-3	↓ 8.1% weight	Improved lipid profile	Not detailed

DISCUSSION

The present review synthesized contemporary evidence regarding the efficacy and safety of semaglutide in glycemic control, weight management, and cardiovascular risk reduction among patients with type 2 diabetes mellitus (T2DM). The results consistently reaffirm semaglutide's potent hypoglycemic effects, robust weight-lowering properties, and its emerging cardioprotective role. Across real-world data, clinical trials, and meta-analyses, semaglutide has demonstrated superiority or non-inferiority compared to both placebo and other glucose-lowering agents such as GLP-1 receptor agonists and SGLT2 inhibitors (Chubb et al., 2021; Hussein et al., 2020; Marso et al., 2016).

Glycemic control remains the cornerstone of T2DM management. Studies such as the SUSTAIN and PIONEER programs have consistently shown semaglutide to be highly effective in lowering HbA1c levels. For instance, Aroda et al. (2019) reported a mean HbA1c reduction of up to 1.5% with oral semaglutide monotherapy. Similar findings were echoed by Avgerinos et al. (2020), who highlighted dose-dependent HbA1c reductions ranging from 1.2% to 1.8%. These outcomes not only surpass placebo but also rival or outperform other GLP-1 RAs and oral agents (Davies et al., 2017; Li et al., 2021).

Importantly, the glycemic efficacy of semaglutide extends across patient demographics. A post hoc analysis by DeSouza et al. (2020) found consistent HbA1c and body weight reductions across racial and ethnic subgroups, suggesting that semaglutide's effects are broadly generalizable. Similarly, a real-world study by Brown et al. (2020) showed significant HbA1c improvements (-1.03%) even in routine clinical practice, reinforcing the external validity of trial results.

Weight reduction is a defining advantage of semaglutide therapy. T2DM often coexists with obesity, and therapies that address both conditions offer significant clinical benefit. Multiple studies reported substantial weight loss with semaglutide, often exceeding 4–6 kg over treatment durations ranging from 16 weeks to 52 weeks (Tan et al., 2017; Singh et al., 2024). In the Canadian SPARE study, Brown et al. (2020) observed a mean weight reduction of -3.9 kg, with greater reductions seen in those on higher doses. This aligns with findings from the RELATE study by Tan et al. (2024), where over 34% of patients achieved ≥5% weight loss.

Real-world evidence also supports these clinical outcomes. Wajid et al. (2023), in a tertiary hospital in Pakistan, found a mean weight loss of 4.0 kg in patients treated with semaglutide over three months. Additionally, Alzahrani et al. (2025) reported a significant BMI reduction in a primary care setting, indicating semaglutide's utility outside of specialized centers. These outcomes are notable given the growing importance of weight-centric diabetes management (Tsapas et al., 2021).

Semaglutide's cardiovascular profile adds another layer of therapeutic value. The landmark SUSTAIN-6 trial by Marso et al. (2016) demonstrated a 26% reduction in the composite outcome of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke (HR: 0.74; 95% CI: 0.58–0.95). This cardioprotective effect was reaffirmed in comparative analyses, such as that by Qiu et al. (2021), where semaglutide showed superior cardiovascular outcomes over many SGLT2 inhibitors and other GLP-1 RAs.

Further post hoc analyses, such as Bain et al. (2025), indicate that cardiovascular benefits persist across age strata, reinforcing semaglutide's role in high-risk populations. In network meta-analyses, such as those by Alfayez et al. (2020) and Wei et al. (2021), semaglutide consistently ranked among the top agents for reducing major adverse cardiovascular events (MACE), positioning it favorably within cardiovascular outcome-driven guidelines.

Safety and tolerability are key concerns with any chronic therapy. The most frequently reported adverse events with semaglutide are gastrointestinal (GI) in nature, particularly nausea and dyspepsia (Peter & Bain, 2020; Chudleigh & Bain, 2020). However, these are generally mild to moderate in intensity and often transient. In the review by Yin et al. (2021), semaglutide's GI adverse event profile was deemed acceptable and comparable to other GLP-1 RAs. Moreover, its safety in special populations, including older adults and those with mild renal impairment, has been supported by multiple studies (Bain et al., 2025).

Discontinuation rates due to adverse events vary across studies but are generally low. For instance, Wajid et al. (2023) reported a discontinuation rate of 9.8% primarily due to GI side effects, consistent with global estimates. Long-term safety evaluations in the PIONEER and SUSTAIN programs have not raised any substantial safety concerns (Thethi et al., 2020; Zaazouee et al., 2022).

Comparative studies further support semaglutide's clinical advantages. In a head-to-head network meta-analysis, Chubb et al. (2021) demonstrated that oral semaglutide offered better glycemic and weight outcomes than injectable GLP-1 RAs in patients uncontrolled on basal insulin. Similarly, Hussein et al. (2020) found semaglutide superior to SGLT2 inhibitors in HbA1c reduction and weight control, with comparable cardiovascular safety.

Beyond clinical endpoints, patient satisfaction and adherence are essential for long-term treatment success. Real-world studies have shown favorable patient-reported outcomes. For example, in the study by Zameer et al. (2020) on liraglutide, patients reported high treatment satisfaction, and these outcomes appear even more promising with semaglutide due to its once-weekly or oral administration options (Singh et al., 2024).

Emerging evidence also suggests pleiotropic effects of semaglutide on lipid profiles and inflammatory markers. Tóth et al. (2025) found significant improvements in lipid subfractions and atherogenic indices, suggesting additional cardiometabolic benefits. This extends semaglutide's utility beyond glycemic and weight management into holistic cardiometabolic risk reduction.

However, some limitations warrant discussion. While RCTs provide high internal validity, real-world studies often lack randomization and may be subject to confounding. Additionally, most trials are short to intermediate in duration; long-term data (>2 years) remain limited, particularly for the oral formulation. Variability in adherence and titration practices in real-world settings may also affect generalizability (Singh et al., 2024; Wang et al., 2024).

In summary, semaglutide has emerged as a leading therapeutic option for patients with T2DM, offering robust efficacy in lowering HbA1c and promoting weight loss, while providing cardiovascular protection and acceptable tolerability. These findings support semaglutide's preferential consideration in treatment algorithms, particularly for patients with obesity, poor glycemic control, or cardiovascular risk factors.

CONCLUSION

This systematic review highlights the consistent and significant clinical benefits of semaglutide in the management of type 2 diabetes mellitus (T2DM). Across a wide range of randomized controlled trials, meta-analyses, and real-world observational studies, semaglutide has demonstrated superior glycemic control, substantial weight reduction, and a favorable cardiovascular risk profile compared to placebo and many other antidiabetic agents. The efficacy was observed across diverse populations, including those inadequately controlled on basal insulin or previously treated with other GLP-1 receptor agonists. These findings firmly support semaglutide's placement in current treatment guidelines for patients with T2DM, particularly those with obesity or cardiovascular comorbidities.

While the safety profile of semaglutide is generally acceptable, with gastrointestinal events being the most commonly reported side effects, long-term data—particularly for the oral formulation—remain limited. However, the consistent cardiovascular protection, improvements in lipid profiles, and growing patient-reported satisfaction reinforce semaglutide's potential as a first-line or add-on therapy in modern diabetes care. Future research should aim to clarify long-term outcomes and cost-effectiveness in diverse patient subgroups.

Limitations

Despite the strength of the compiled evidence, this review is not without limitations. First, the heterogeneity of included studies in terms of design, duration, dosing strategies, and outcome reporting limited the possibility of conducting a meta-analysis. Second, while real-world studies offer valuable insights, they are inherently subject to confounding, selection bias, and inconsistent reporting practices. Third, most included trials were sponsored by pharmaceutical companies, which could introduce bias in outcome reporting or publication. Lastly, longer-term safety data beyond two years, especially for the oral formulation, are scarce, and further studies are warranted to assess durability of benefits and long-term tolerability in routine care.

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