Review Article

The Semaglutide Effect: Redefining Treatment Across Diabetes, Obesity, and Cardiometabolic Risk

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ABSTRACT

Semaglutide, a long-acting glucagon-like peptide-1 (GLP-1) receptor agonist, has become one of the most consequential pharmacologic agents introduced in endocrinology and metabolic medicine in the past decade. Originally developed for glycemic control in type 2 diabetes, semaglutide has since demonstrated substantial efficacy for chronic weight management and a reduction in major adverse cardiovascular events in patients with established cardiovascular disease and overweight or obesity. This review synthesizes current evidence on semaglutide's pharmacology, mechanism of action, and clinical efficacy across diabetes, obesity, and cardiovascular indications, drawing on data from the STEP, SUSTAIN, and SELECT trial programs. Safety considerations, including gastrointestinal, psychiatric, ophthalmologic, and dermatologic/facial adverse effects, are examined alongside practical considerations for nutritional support, weight-loss maintenance, and treatment discontinuation. The review concludes with a discussion of current clinical practice guidelines and unresolved questions that merit further investigation.

Key words: Semaglutide, Glucagon-Like Peptide-1 Receptor Agonist, Type 2 Diabetes Mellitus, Obesity, Weight Management, Cardiovascular Outcomes, Cardiometabolic Risk, Chronic Kidney Disease, MASLD/MASH, Safety and Tolerability.

Type 2 diabetes (T2D) is a chronic metabolic disorder characterized by insulin resistance and progressive pancreatic beta-cell dysfunction, resulting in sustained hyperglycemia. It accounts for the large majority of diabetes cases worldwide and is a leading cause of cardiovascular disease, chronic kidney disease, blindness, and lower-limb amputation. Its prevalence has risen sharply alongside global increases in obesity, sedentary lifestyles, and aging populations, making it one of the most significant chronic disease burdens facing health systems today. The pathophysiology of T2D is multifactorial, involving impaired insulin signaling in skeletal muscle, adipose tissue, and the liver, alongside a relative deficiency in insulin secretion as beta-cell function declines over time. This progressive nature means that many patients require escalating pharmacologic intervention over the course of their disease, moving from lifestyle modification and oral monotherapy toward combination regimens and, eventually, injectable therapies such as insulin or GLP-1 receptor agonists. The chronic, progressive character of T2D underscores why durable, well-tolerated pharmacologic options that can be intensified over time, as semaglutide's dose-ranging data illustrate, are of particular clinical value [1].

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1.2 Obesity: A Brief Overview

Obesity is a chronic, relapsing disease characterized by excess adiposity that impairs health, most commonly assessed clinically using body mass index (BMI) alongside waist circumference and the presence of weight-related complications. Obesity is closely linked mechanistically and epidemiologically to T2D, cardiovascular disease, metabolic dysfunction-associated liver disease, and certain cancers, and the two conditions frequently coexist and compound one another's cardiometabolic risk. Historically, sustained pharmacologic weight reduction was difficult to achieve, leaving lifestyle intervention and bariatric surgery as the primary options for meaningful, durable weight loss [2].

Excess adiposity, particularly visceral fat, drives a chronic low-grade inflammatory state and contributes to insulin resistance, dyslipidemia, and endothelial dysfunction, forming a mechanistic bridge between obesity and the downstream cardiovascular and renal complications discussed later in this review.

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Weight loss of even 5 to 10 percent of baseline body weight is associated with clinically meaningful improvements in glycemic control, blood pressure, and lipid profile, which is part of why agents capable of producing weight reductions well beyond this threshold, as semaglutide has demonstrated in the STEP program, represent such a significant advance over earlier pharmacologic options [2].

1.3 The Emergence of GLP-1 Receptor Agonists

The emergence of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) has fundamentally altered the treatment landscape for both conditions. Semaglutide, a modified analogue of native human GLP-1, was first approved for glycemic control in T2D and has since been developed and approved across multiple formulations (subcutaneous and oral) and doses for chronic weight management and cardiovascular risk reduction. Its clinical development program is among the most extensive in metabolic medicine, encompassing the SUSTAIN trials in diabetes, the STEP trials in obesity, and the SELECT cardiovascular outcomes trial, in addition to a growing body of mechanistic and pharmacovigilance literature [3,4].

This review aims to synthesize the pharmacological basis, clinical efficacy, safety profile, and practical management considerations associated with semaglutide therapy, and to highlight the evidence-based guidance now shaping its use in clinical practice. The scope of this review spans five broad domains: the molecular pharmacology and structural basis of semaglutide's action; its clinical efficacy across glycemic, weight-related, and cardiovascular endpoints; its emerging role in hepatic and renal outcomes; its safety and tolerability profile, including less-discussed signals in psychiatric and ophthalmologic domains; and the practical considerations nutritional, behavioral, and guideline-based — that shape its real-world use. Each domain is treated in turn, with an emphasis throughout on distinguishing well-established, high-certainty findings from areas where evidence remains preliminary or where causality has not been firmly established.

2. PHARMACOLOGY AND MECHANISM OF ACTION

Semaglutide exerts its effects through agonism of the GLP-1 receptor, a G-protein-coupled receptor expressed in pancreatic beta cells, the gastrointestinal tract, and regions of the central nervous system involved in appetite regulation. Receptor activation potentiates glucose-dependent insulin secretion, suppresses glucagon release, slows gastric emptying, and enhances satiety signaling in the hypothalamus, collectively producing improvements in glycemic control and reductions in caloric intake [4].

At the cellular level, GLP-1 receptor binding activates Gs-protein-coupled adenylate cyclase, raising intracellular cAMP and activating protein kinase A and Epac2, which potentiates glucose-stimulated insulin secretion in a strictly glucose-dependent manner, explaining semaglutide's low intrinsic hypoglycemia risk relative to insulin secretagogues such as sulfonylureas. In the central nervous system, GLP-1 receptors in the hypothalamic arcuate nucleus and brainstem (area postrema, nucleus tractus solitarius) integrate peripheral satiety signals; their activation reduces food intake by enhancing satiety and modulating reward-related eating behavior, helping explain semaglutide's greater weight-loss efficacy relative to earlier appetite-suppressant therapies acting through different pathways [4]. The principal mechanisms of semaglutide action are illustrated in the figure (Figure 1) [5].

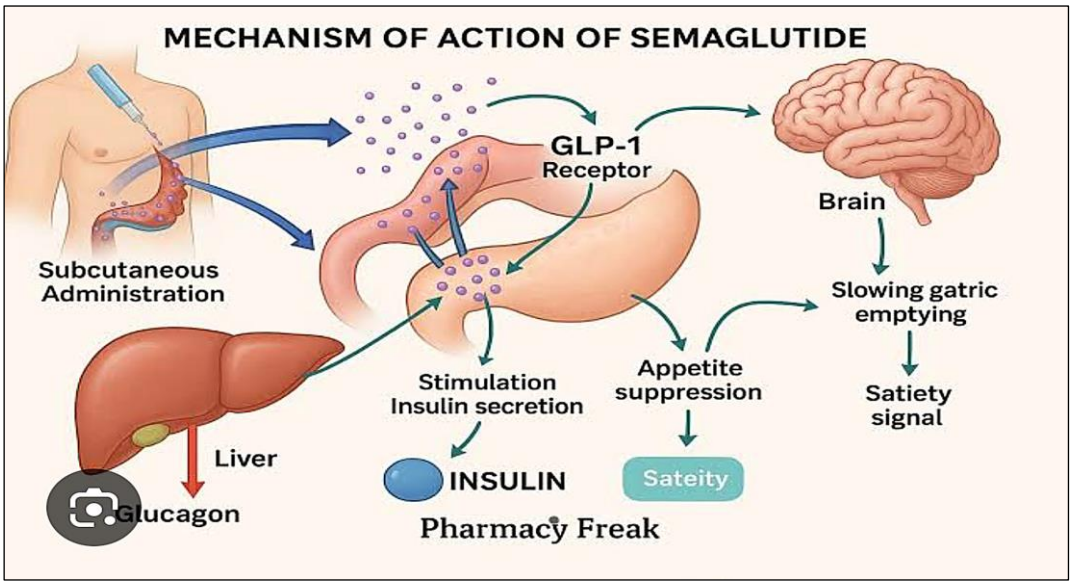


Figure 1. Mechanism of action of semaglutide via subcutaneous administration, GLP-1 receptor binding, insulin stimulation, appetite suppression, and gastric emptying effects. Source: Pharmacy Freak Editorial Team, "Mechanism of Action of Semaglutide (Ozempic/Wegovy)".

Beyond these canonical effects, mechanistic work has implicated semaglutide in adipose tissue browning, a process associated with increased energy expenditure, as well as anti-inflammatory, antioxidant, and mitochondrial biogenesis-related effects in skeletal muscle, suggesting a broader metabolic role beyond simple appetite suppression [4]. Preclinical evidence further suggests direct cardioprotective signaling: in a doxorubicin-induced cardiotoxicity model, semaglutide attenuated mitochondrial dysfunction via modulation of BNIP3 expression through the PI3K/AKT pathway, pointing to mechanisms that may partly underlie its favorable cardiovascular outcomes in clinical trials [6].

Pharmacokinetically, semaglutide is characterized by a long elimination half-life of approximately one week, a property conferred by structural modifications that reduce dipeptidyl peptidase-4 (DPP-4)-mediated degradation and promote albumin binding. This profile supports once-weekly subcutaneous dosing, while an oral formulation co-formulated with the absorption enhancer SNAC allows once-daily dosing despite the inherently poor oral bioavailability of peptide therapeutics. A systematic review of semaglutide's clinical pharmacokinetics found that exposure (AUC and Cmax) increases in a dose-dependent manner for both formulations, that drug-drug interactions are limited, and that no dose adjustment is required in patients with renal or hepatic impairment or upper gastrointestinal disease [7]. The absorption mechanism of oral semaglutide merits particular note, since peptide drugs are normally degraded almost completely by gastric and intestinal proteases before reaching the systemic circulation. SNAC (sodium N-[8-(2-hydroxybenzoyl)amino]caprylate) works by locally raising gastric pH around the dissolving tablet and by facilitating transcellular absorption of the semaglutide molecule across the gastric epithelium before enzymatic degradation can occur.

This mechanism explains several practical prescribing requirements for the oral formulation: it must be taken on an empty stomach with a small amount of plain water, and no other food, beverages, or oral medications may be taken for at least 30 minutes afterward, since co-administered food or fluid dilutes the local SNAC concentration and substantially reduces absorption [7].

2.1 Structural Basis of Receptor Binding

From a structural pharmacology standpoint, semaglutide's amino acid substitutions relative to native GLP-1 (including an Aib residue at position 8 and an arginine substitution at position 34) confer resistance to enzymatic cleavage, while its C18 fatty diacid side chain, attached via a spacer at the modified lysine residue at position 26, enables reversible, high-affinity albumin binding that markedly extends systemic half-life [3,8].

Molecular docking analyses against solved GLP-1 receptor structures can further illustrate the specific extracellular domain contacts and transmembrane binding-pocket interactions that distinguish semaglutide's receptor engagement from that of native GLP-1 and from other class members such as tirzepatide, which additionally engages the GIP receptor. Such structure-based approaches are a valuable complement to clinical outcome data, offering a mechanistic rationale for observed differences in potency and duration of action across the GLP-1 receptor agonist class. The structural features described above are illustrated in the structural diagram (Figure 2) [8].

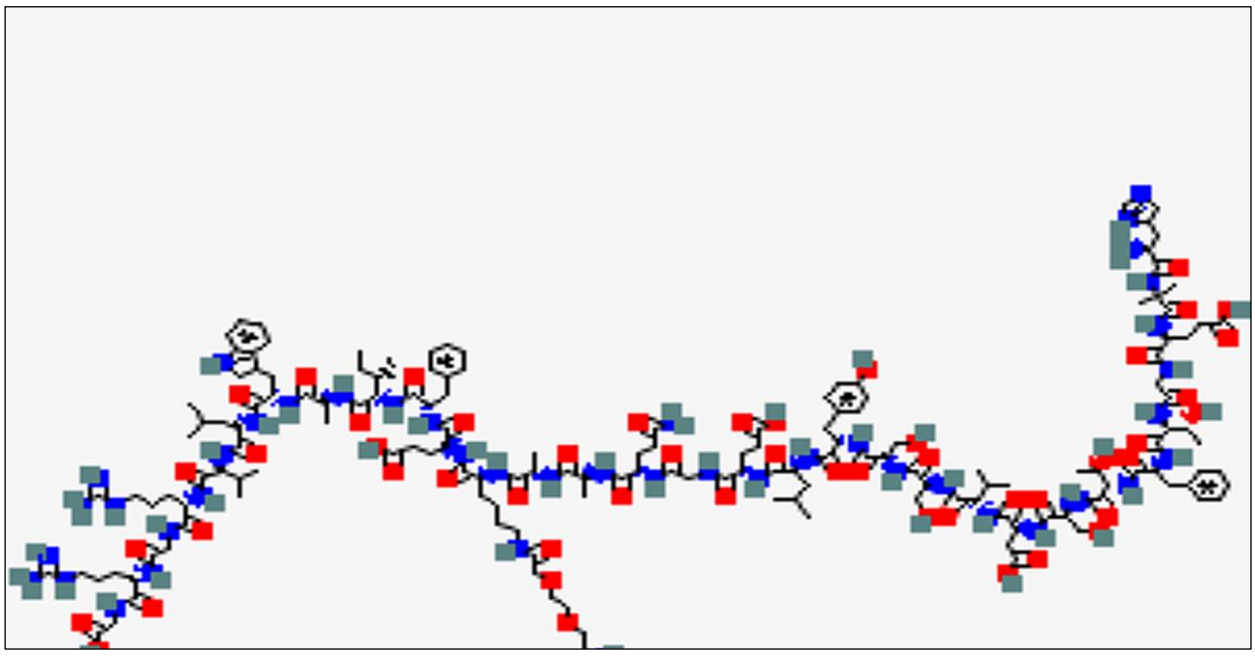


Figure 2. Two-dimensional structural diagram of semaglutide (C187H291N45O59), showing the full 31-residue backbone and C18 fatty diacid side chain. Source: National Center for Biotechnology Information, PubChem Compound Summary for CID 56843331

2.2 Dosing and Titration

Across its formulations and indications, semaglutide is initiated at a low dose and gradually titrated upward, a strategy designed to minimize gastrointestinal adverse effects while allowing the gut and central nervous system to adapt to sustained GLP-1 receptor stimulation. For the subcutaneous formulation used in T2D, treatment typically begins at 0.25 mg once weekly, a dose intended primarily for gastrointestinal tolerability rather than glycemic efficacy, before escalating at four-week intervals toward maintenance doses of 0.5 mg, 1.0 mg, or, per the SUSTAIN FORTE data discussed below, 2.0 mg weekly [1].

For chronic weight management, the subcutaneous formulation follows a more gradual step-up schedule, beginning at 0.25 mg weekly and increasing every four weeks through 0.5 mg, 1.0 mg, and 1.7 mg before reaching the target maintenance dose of 2.4 mg weekly used in the pivotal STEP trials. The oral formulation follows an analogous principle: therapy begins at 3 mg once daily for the first month, primarily to improve gastrointestinal tolerability rather than to achieve meaningful glycemic effect, before increasing to 7 mg and, if needed, 14 mg daily maintenance dosing. In each formulation, slower titration or temporary dose maintenance at a lower step is a recognized strategy for patients experiencing significant gastrointestinal symptoms during escalation, underscoring that the titration schedule itself functions as a key tolerability tool rather than a fixed, one-size-fits-all protocol (Table 1) [9,10].

3. CLINICAL EFFICACY IN TYPE 2 DIABETES

Semaglutide's foundational indication remains glycemic management in T2D. The SUSTAIN trial program established consistent, clinically meaningful reductions in HbA1c across dose levels and comparator arms. The SUSTAIN FORTE trial specifically addressed the subset of patients, estimated at 20 to 30 percent, who fail to reach glycemic targets on the standard 1.0 mg weekly dose. In this 40-week, double-blind, active-controlled trial, once-weekly semaglutide 2.0 mg produced superior HbA1c reduction compared with 1.0 mg, along with additional weight loss and a comparable safety profile, supporting dose intensification as a treatment strategy in inadequately controlled patients [1].

Cardiovascular safety in the T2D population was addressed in the SUSTAIN-6 trial, which enrolled patients with or at high risk for cardiovascular disease. Subsequent analyses of coronary artery disease outcomes from this trial provided reassurance regarding semaglutide's cardiovascular risk profile in this population, complementing the broader cardiovascular outcomes evidence later generated in non-diabetic populations by the SELECT trial [11]. Beyond glycemic and cardiovascular endpoints, the broader SUSTAIN program (encompassing multiple sequentially numbered trials beyond SUSTAIN-6 and SUSTAIN FORTE) evaluated semaglutide against a range of active comparators from other antidiabetic drug classes, including DPP-4 inhibitors, SGLT2 inhibitors, and other GLP-1 receptor agonists, across patients at varying stages of disease progression and background therapy. Taken together, this program was instrumental in establishing semaglutide's position as a preferred injectable, and in some regions oral, second- or third-line agent for T2D, particularly in patients for whom additional weight loss or cardiovascular risk reduction is a clinically relevant secondary goal alongside glycemic control. [1,11]

3.1 Oral Semaglutide: The PIONEER Program

Efficacy data for the oral formulation come from the PIONEER phase 3a program, which evaluated oral semaglutide (3 mg, 7 mg, or 14 mg) against placebo and several active comparators, empagliflozin (PIONEER 2), sitagliptin (PIONEER 3 and 7), and liraglutide (PIONEER 4), across more than 9,500 patients spanning different stages of T2D and background therapy regimens [10]. Across the program, oral semaglutide 14 mg produced HbA1c reductions of approximately 1.0 to 1.4 percentage points at 26 weeks (primary analysis time point, except PIONEER 7 at 52 weeks), consistently exceeding placebo, empagliflozin, and sitagliptin, and achieving reductions similar to liraglutide [10]. (Table 2) (Figure 3)

PIONEER 6 additionally established the cardiovascular safety of the oral formulation in patients with T2D at high cardiovascular risk: oral semaglutide met its primary non-inferiority endpoint for major adverse cardiovascular events versus placebo, and was associated with a 21 percent reduction in first major cardiovascular events along with a nearly 50 percent reduction in cardiovascular and all-cause mortality over a median follow-up of roughly 16 months, though the trial was not powered to demonstrate superiority [12]. From a practical prescribing standpoint, the oral and subcutaneous formulations occupy somewhat different clinical niches despite sharing the same active molecule. The oral formulation offers an option for patients who decline injectable therapy or who prefer the convenience and privacy of a tablet, but its strict administration requirements, fasting, minimal water, and a 30-minute waiting period before other oral intake, pose an adherence burden that the once-weekly subcutaneous formulation avoids entirely. Clinicians selecting between formulations must therefore weigh needle aversion and patient preference against the practical demands of oral dosing, alongside formulation-specific cost and insurance coverage considerations that vary considerably by health system.

4. CLINICAL EFFICACY IN OBESITY AND WEIGHT MANAGEMENT

The STEP (Semaglutide Treatment Effect in People with obesity) program represents the pivotal evidence base for semaglutide 2.4 mg as a chronic weight-management therapy.

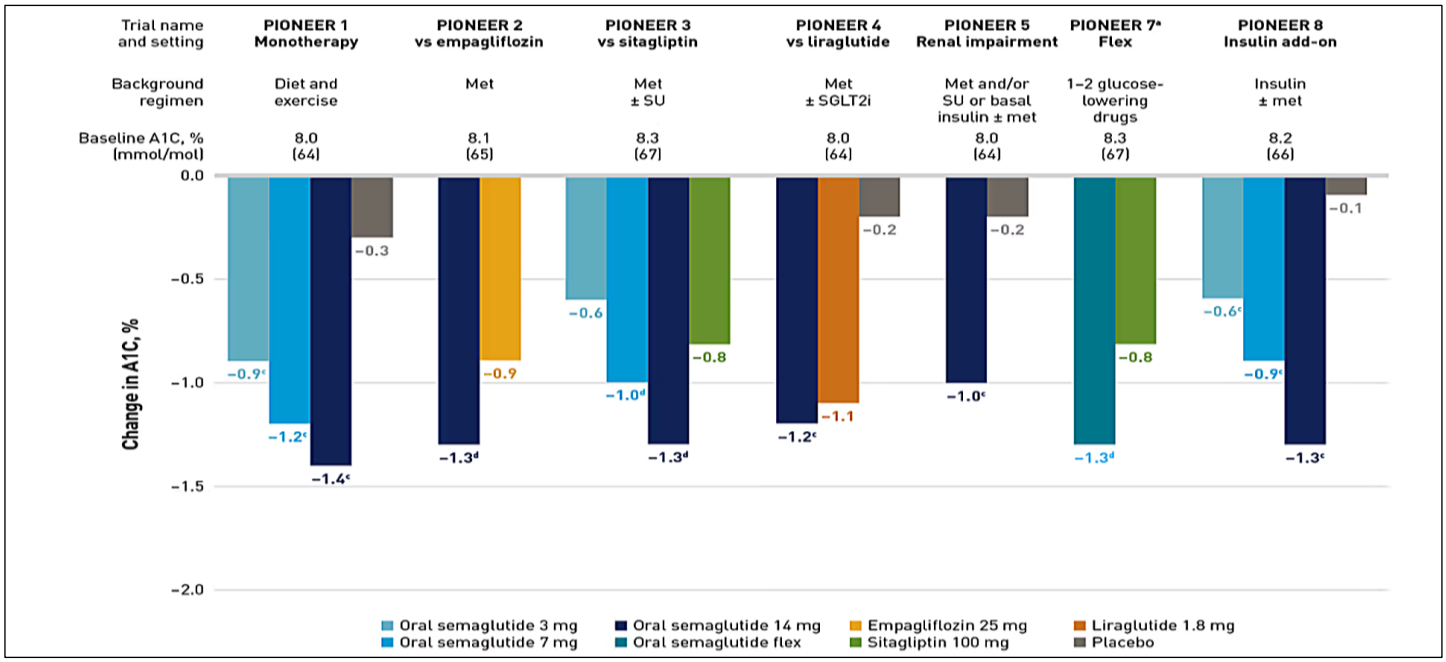


Figure 3. Reduction in HbA1c levels with oral semaglutide and comparators across the PIONEER 1–8 trials at the primary analysis time point.

Table 1. Recommended dose-titration schedules for semaglutide across its subcutaneous (type 2 diabetes and obesity) and oral (type 2 diabetes) formulations.

Indication / Formulation	Start	Step 2	Step 3	Step 4	Maintenance Dose
Type 2 Diabetes (subcutaneous)	0.25 mg (Wk 0)	0.5 mg (Wk 4)	1.0 mg (Wk 8)	—	1.0–2.0 mg weekly (Wk 12+)
Obesity / Weight Management (subcutaneous)	0.25 mg (Wk 0)	0.5 mg (Wk 4)	1.0 mg (Wk 8)	1.7 mg (Wk 12)	2.4 mg weekly (Wk 16+)
Type 2 Diabetes (oral)	3 mg (Month 1)	7 mg (Month 2)	14 mg (Month 3+)	—	7–14 mg daily

Table 2 summarizes the major clinical trials of semaglutide discussed throughout this review, spanning its glycemic, weight-management, cardiovascular, and renal indications.

Trial	Population	Design / Comparator	Duration	Key Result
SUSTAIN-6 [11]	T2D, high CV risk	Semaglutide vs placebo	104 wk	Cardiovascular safety established
SUSTAIN FORTE [1]	T2D, uncontrolled on 1.0 mg	2.0 mg vs 1.0 mg	40 wk	Superior HbA1c reduction with 2.0 mg
PIONEER 6 [12]	T2D, high CV risk (oral)	Oral semaglutide vs placebo	~16 mo	21% ↓ major CV events; ~50% ↓ CV/all-cause mortality
STEP 2 [9]	Overweight/obesity + T2D	2.4 mg vs 1.0 mg vs placebo	68 wk	Superior weight loss with 2.4 mg
STEP 5 [13]	Overweight/obesity	2.4 mg vs placebo	104 wk	77.1% achieved ≥5% weight loss vs 34.4% placebo
STEP 8 [14]	Overweight/obesity	Semaglutide 2.4 mg vs liraglutide 3.0 mg	68 wk	15.8% vs 6.4% mean weight loss
SELECT [15]	Overweight/obesity + established CVD, no diabetes	2.4 mg vs placebo	208 wk	20% ↓ MACE; 10.2% sustained weight loss
FLOW [16]	T2D + chronic kidney disease	1.0 mg vs placebo	Median 3.4 yr	24% ↓ composite kidney/CV/death outcome (HR 0.76)

STEP 2 evaluated semaglutide in adults with overweight or obesity and T2D, a population that typically demonstrates a blunted weight-loss response relative to non-diabetic individuals; even so, the trial demonstrated superior and clinically meaningful weight reduction with semaglutide 2.4 mg compared with both the lower 1.0 mg dose and placebo [9].

The broader STEP program extended well beyond the trials discussed in detail here, including studies in adolescents, patients maintaining weight loss after intensive behavioral intervention, and those combining semaglutide with structured lifestyle coaching delivered through varying intensities of clinical support. Across this program, a consistent finding has been that the magnitude of weight loss with semaglutide 2.4 mg substantially exceeds that achieved with earlier-generation anti-obesity pharmacotherapies, including orlistat, phentermine-topiramate, and naltrexone-bupropion, positioning it, alongside newer dual and triple incretin agonists, as part of a new generation of obesity pharmacotherapy capable of approaching the magnitude of weight loss historically associated only with bariatric surgery, albeit generally still smaller in magnitude than surgical outcomes [13,14].

STEP 5 extended the evidence base to two years of continuous treatment in adults with overweight or obesity, finding that 77.1 percent of semaglutide-treated participants achieved at least 5 percent weight loss from baseline at week 104, compared with 34.4 percent on placebo, confirming that weight loss is sustained rather than transient with continued therapy [13]. Gastrointestinal adverse events, though mostly mild to moderate, were more frequent with semaglutide (82.2 percent) than placebo (53.9 percent) across this longer follow-up period [13]. Head-to-head data from STEP 8 compared once-weekly semaglutide 2.4 mg with once-daily liraglutide 3.0 mg, the prior-generation GLP-1 RA approved for obesity. Semaglutide produced significantly greater weight loss at 68 weeks, a mean reduction of 15.8 percent versus 6.4 percent with liraglutide, reinforcing its position as a more potent option within the class [14]. A systematic review and meta-analysis restricted to individuals with obesity without diabetes, pooling four randomized controlled trials and 3,613 participants, found a mean weight reduction of 11.85 percent favoring semaglutide over placebo. However, the same analysis noted that the risk of treatment discontinuation due to adverse events was more than twice as likely, and the risk of serious adverse events (predominantly gastrointestinal and hepatobiliary, including pancreatitis and cholelithiasis) was 1.6 times higher with semaglutide, underscoring that its efficacy must be weighed against a non-trivial tolerability burden [17].

Optimizing outcomes in practice requires more than pharmacotherapy alone. A review by Noronha and colleagues emphasized that combining GLP-1 therapy with structured dietary and exercise interventions produces additive weight-loss effects compared with either approach in isolation, and detailed specific strategies, including protein intake above 1.2 g/kg/day, to preserve lean mass during rapid weight loss [18].

The magnitude and consistency of weight loss achieved across the STEP program has also prompted a broader reconsideration of obesity as a treatable chronic disease within mainstream medical practice, rather than a condition addressed primarily through willpower-based lifestyle advice. This reframing has practical downstream consequences: it supports insurance coverage arguments for anti-obesity medications, informs how comorbid conditions such as osteoarthritis, obstructive sleep apnea, and infertility are approached in patients with obesity, and has driven demand that has, at times, outpaced drug manufacturing capacity, contributing to well-documented supply shortages of semaglutide products in several countries during the early years of widespread obesity-indication use.

5. CARDIOVASCULAR AND CARDIOMETABOLIC OUTCOMES

The SELECT trial marked a turning point in framing semaglutide not only as a weight-management agent but as a cardiovascular risk-reduction therapy in its own right. This double-blind, placebo-controlled trial enrolled 17,604 adults with established cardiovascular disease and overweight or obesity, without diabetes, and demonstrated a 20 percent relative reduction in major adverse cardiovascular events (MACE) with semaglutide 2.4 mg weekly [15,19].

The composite MACE endpoint in SELECT, consistent with standard cardiovascular outcomes trial methodology, captured cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke. The significance of demonstrating benefit on this hard composite endpoint, rather than surrogate markers such as blood pressure or lipid levels alone, cannot be overstated: it places semaglutide alongside a select group of pharmacotherapies with proven cardiovascular outcome benefit in a population defined primarily by adiposity and pre-existing atherosclerotic disease rather than by diabetes status, meaningfully broadening the population for whom cardiovascular risk reduction is now an evidence-based indication for GLP-1 receptor agonist therapy [15]. Long-term follow-up within SELECT showed that weight loss was not only substantial but durable: at 208 weeks, semaglutide-treated participants maintained a mean weight reduction of 10.2 percent, along with reductions in waist circumference and waist-to-height ratio, compared with minimal change in the placebo group [20]. A prespecified analysis focused on the subgroup with prevalent heart failure found that semaglutide reduced both MACE and composite heart-failure endpoints regardless of heart failure subtype, suggesting benefit extends across the spectrum of atherosclerotic cardiovascular disease severity [21].

Mechanistically, these clinical benefits are consistent with preclinical data showing direct cardioprotective signaling independent of weight loss, including mitigation of mitochondrial dysfunction in models of drug-induced cardiotoxicity [6], suggesting that semaglutide's cardiovascular benefit may reflect both indirect (weight- and metabolism-mediated) and direct pathways [6]. Several plausible direct mechanisms have been proposed to explain cardiovascular benefit beyond what weight loss alone would predict, including favorable effects on endothelial function and nitric oxide bioavailability, reductions in systemic and vascular inflammation, modest but consistent reductions in blood pressure, and improvements in lipid profile including reductions in triglycerides and small dense LDL particles. The relative contribution of these direct vascular and metabolic effects versus the indirect consequences of substantial weight loss remains an active area of investigation, and disentangling the two is complicated by the fact that weight loss itself drives many of these same downstream metabolic improvements [15].

6. HEPATIC AND METABOLIC EFFECTS (MASLD/MASH)

Metabolic dysfunction-associated steatotic liver disease (MASLD) shares substantial pathophysiological overlap with obesity and insulin resistance, making it a natural area of interest for GLP-1 RA therapy. A mechanistic review proposed that semaglutide improves hepatic steatosis through several convergent pathways: reduced caloric intake and consequent reduction in free fatty acid delivery to the liver; improved insulin sensitivity and reduced adipose tissue dysfunction; downregulation of de novo lipogenesis via suppression of ChREBP and SREBP-1c signaling; reduction in white and brown adipose tissue mass; and anti-inflammatory effects mediated in part through favorable alteration of the gut microbiota and reduced activity of GLP-1-expressing macrophages [22]. Clinically, this mechanistic rationale is supported by outcome data suggesting that semaglutide reduces markers of liver disease progression alongside cardiovascular risk in patients with obesity and cardiovascular disease, reinforcing the concept of semaglutide as a therapy with pleiotropic benefit across interconnected components of cardiometabolic syndrome [15,22].

This mechanistic rationale is further supported by direct clinical trial evidence: in a 72-week, placebo-controlled phase 2 trial in patients with biopsy-confirmed NASH and stage F1–F3 fibrosis, semaglutide 0.4 mg daily achieved NASH resolution without worsening of fibrosis in 59 percent of patients, compared with 17 percent on placebo ($P<0.001$), although the trial did not demonstrate a statistically significant between-group difference in fibrosis-stage improvement (43 percent vs. 33 percent, $P=0.48$) [23]. MASLD, and its more severe inflammatory subtype, metabolic dysfunction-associated steatohepatitis (MASH), represent an area of intense pharmaceutical development interest given the historical absence of approved pharmacotherapy specifically targeting liver fat and fibrosis. While the phase 2 trial above demonstrated clear benefit on NASH resolution, semaglutide is not yet approved with a dedicated MASLD or MASH indication, and its lack of significant effect on fibrosis-stage improvement in that trial leaves an important gap: larger, longer-duration phase 3 trials with fibrosis-focused endpoints are needed to confirm whether semaglutide can alter the histological course of the disease rather than steatosis and inflammation alone. Should such trials demonstrate benefit on fibrosis-specific endpoints, semaglutide would be positioned to address a substantial unmet need in a disease affecting a large proportion of patients with obesity and T2D, many of whom remain undiagnosed until advanced fibrosis or cirrhosis is present [22,23].

7. RENAL OUTCOMES: THE FLOW TRIAL

Patients with T2D and chronic kidney disease (CKD) face elevated risk of kidney failure, cardiovascular events, and death, and until recently no GLP-1 RA had been evaluated in a dedicated kidney-outcomes trial. The FLOW (Evaluate Renal Function with Semaglutide Once Weekly) trial addressed this gap directly, randomizing 3,533 adults with T2D and CKD (eGFR 24–75 mL/min/1.73 m² with elevated albuminuria) to once-weekly subcutaneous semaglutide 1.0 mg or placebo, both added to standard-of-care renin-angiotensin system inhibition [16]. Over a median follow-up of 3.4 years, semaglutide reduced the risk of the composite primary outcome of a persistent 50 percent or greater reduction in eGFR, kidney failure, kidney-related death, or cardiovascular death, by 24 percent relative to placebo (hazard ratio 0.76, 95% CI 0.66–0.88, $P = 0.0003$), with the trial stopped early on the recommendation of the independent data monitoring committee following a prespecified interim analysis [16]. Semaglutide also reduced the annual rate of eGFR decline by 1.16 mL/min/1.73 m² relative to placebo and lowered urinary albumin-to-creatinine ratio, alongside reductions in major cardiovascular events and all-cause mortality, with a generally favorable safety profile (serious adverse events occurred in 49.6 percent of the semaglutide group versus 53.8 percent of placebo) [16]. Together with the SELECT and SUSTAIN-6 cardiovascular findings, FLOW positions semaglutide as a therapy with benefit that extends across the kidney-heart-metabolic axis, rather than being confined to glycemic or weight outcomes alone(Figure 4) [16,24].

The clinical significance of FLOW extends beyond its topline result: CKD in T2D is a leading cause of end-stage renal disease requiring dialysis or transplantation worldwide, and until the emergence of SGLT2 inhibitors as a first dedicated kidney-protective drug class, treatment options beyond renin-

angiotensin system blockade were limited. FLOW establishes semaglutide as a second, mechanistically distinct pharmacologic option for kidney protection in this population, raising practical questions for nephrology and endocrinology practice regarding optimal sequencing or combination of SGLT2 inhibitors and GLP-1 receptor agonists, an area of active prespecified subgroup analysis within the FLOW dataset itself, given that a substantial proportion of enrolled patients were also receiving SGLT2 inhibitor therapy at baseline [16].

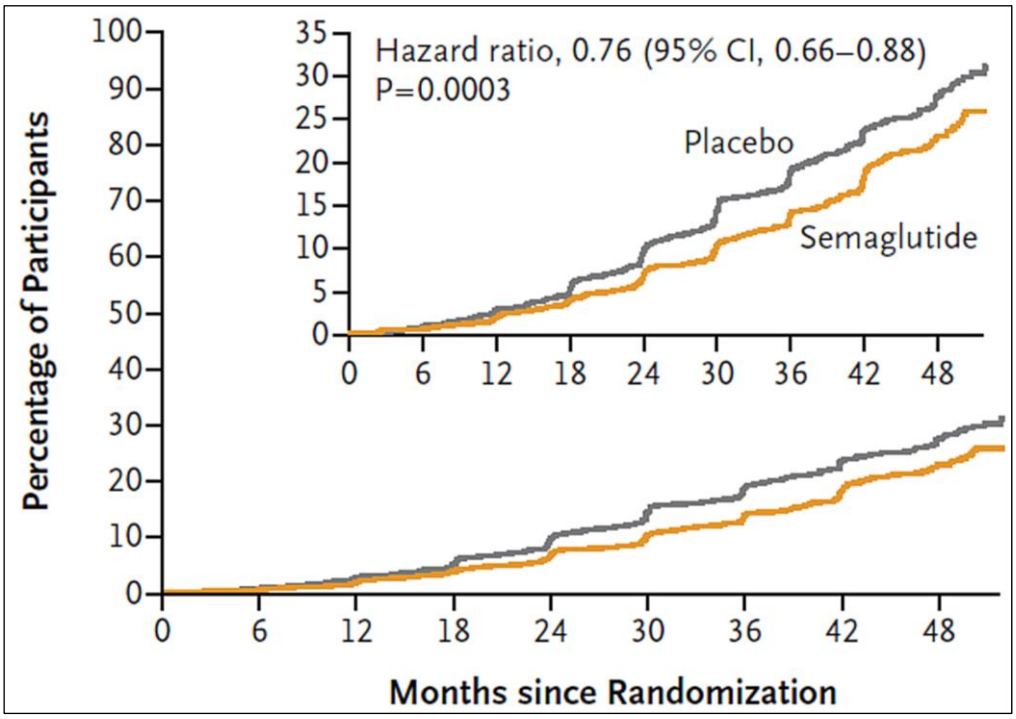


Figure 4. Kaplan-Meier cumulative incidence of the first major kidney disease event in the FLOW trial, comparing semaglutide versus placebo over 5 years of follow-up (hazard ratio 0.76, 95% CI 0.66–0.88, P = 0.0003).

8. SAFETY, TOLERABILITY, AND ADVERSE EFFECTS

Gastrointestinal adverse effects, nausea, vomiting, diarrhea, and constipation, remain the most common reason for treatment discontinuation and are directly related to semaglutide's mechanism of delayed gastric emptying. Meta-analytic data indicate that serious adverse events, including pancreatitis and cholelithiasis, occur at meaningfully higher rates than with placebo, even though absolute rates remain relatively low [17].

8.1 Gastrointestinal Effects (Established, RCT-Supported)

Nausea is typically the most frequently reported adverse effect, occurring predominantly during the initial weeks of treatment and following each dose escalation step, then generally attenuating with continued exposure as tolerance develops. Vomiting and diarrhea follow a broadly similar temporal pattern, while constipation may persist more consistently throughout treatment as a consequence of sustained delayed gastric and intestinal transit. Clinical management strategies commonly recommended in practice include eating smaller, lower-fat meals, stopping eating before feeling full, avoiding lying down immediately after meals, ensuring adequate hydration, and, when appropriate, temporarily pausing dose escalation or reverting to the previously tolerated dose rather than discontinuing therapy altogether. Acute pancreatitis, while uncommon, is a recognized and clinically significant risk across the GLP-1 receptor agonist class, and patients should be counseled to seek prompt medical attention for severe, persistent abdominal pain, particularly if radiating to the back or accompanied by vomiting. Cholelithiasis and cholecystitis are also observed at elevated rates relative to placebo, plausibly related to the rapid weight loss itself rather than a direct pharmacologic effect on biliary physiology, since rapid weight loss from any cause is independently associated with increased gallstone formation [17].

8.2 Psychiatric Safety Signal (Emerging Pharmacovigilance Signal)

A pharmacovigilance analysis of individual case safety reports submitted to the EudraVigilance database examined psychiatric adverse events associated with semaglutide, liraglutide, and tirzepatide. Depression was the most frequently reported psychiatric event, followed by anxiety and suicidal ideation. Nine deaths and eleven life-threatening outcomes were identified across the GLP-1 RA class in this dataset, occurring predominantly among men as a result of completed suicide attempts or severe depression [25]. It is important to interpret this pharmacovigilance signal cautiously: spontaneous case-

report databases like EudraVigilance capture suspected adverse events regardless of whether the drug caused them, are subject to reporting bias, and cannot be used to calculate a true incidence or population-level death rate attributable to semaglutide. No reliable, well-controlled population-based estimate of a semaglutide-specific "death rate" currently exists in the literature reviewed here; the case counts reported above should be read strictly as counts of reported cases, not as evidence of causation or absolute risk [25]. Nonetheless, the signal prompted regulatory investigation by the European Medicines Agency and warrants careful psychiatric screening and monitoring, particularly in patients with pre-existing mood disorders [25].

From a clinical practice standpoint, this signal reinforces the general principle that patients starting any new chronic medication, and particularly one associated with substantial physiological change such as rapid weight loss, benefit from baseline and periodic screening for mood symptoms, with clear guidance on when and how to seek help if new or worsening psychiatric symptoms emerge. It also illustrates a broader tension in pharmacovigilance: signals detected in spontaneous reporting systems are valuable for generating hypotheses and prompting regulatory scrutiny, but require confirmation through more rigorous epidemiological methods, such as active-comparator cohort studies or randomized trial data, before they can inform definitive causal claims or prescribing restrictions [25].

8.3 Ophthalmologic Considerations (Emerging Pharmacovigilance Signal)

An analysis of FDA adverse event reporting data identified a disproportionate signal for vision impairment among semaglutide users relative to other diabetes and weight-loss medications. The authors emphasized that further studies are needed to characterize the absolute clinical risk and its implications for treatment decisions, but recommended vigilant post-marketing surveillance in the interim [26]. As with the psychiatric signal described above, this finding derives from spontaneous adverse-event reporting and disproportionality analysis; such designs can generate hypotheses but cannot establish causality, and no randomized controlled trial to date has confirmed a causal link between semaglutide and vision impairment [26]. A biologically plausible mechanism linking rapid glycemic improvement to a specific ophthalmologic condition, non-arteritic anterior ischemic optic neuropathy (NAION), has been proposed and studied following case reports and subsequent cohort analyses. Rapid correction of longstanding hyperglycemia, whether achieved through insulin, other glucose-lowering therapies, or GLP-1 receptor agonists, has long been recognized to transiently worsen diabetic retinopathy in some patients before longer-term benefit emerges, and a similar paradoxical short-term risk window has been hypothesized for optic nerve blood flow. Patients with pre-existing diabetic retinopathy or rapid, large reductions in HbA1c may warrant closer ophthalmologic monitoring during the early months of semaglutide therapy as this evidence continues to mature.

8.4 Dermatologic and Surgical Considerations (Established, Mechanism-Based)

Rapid, substantial fat loss associated with semaglutide has been linked to a cosmetic phenomenon colloquially termed "Ozempic face," characterized by facial volume depletion, wrinkling, and skin laxity. Clinicians prescribing semaglutide for weight loss frequently do not counsel patients on this possibility, creating a downstream referral burden for facial plastic surgeons [27]. The same review highlighted a practical perioperative concern: because semaglutide delays gastric emptying, its discontinuation should be considered prior to general anesthesia to reduce the risk of aspiration [27].

Beyond the face, similar volume-loss changes have been anecdotally described elsewhere on the body wherever subcutaneous fat is lost rapidly, sometimes accentuating the appearance of loose or sagging skin, particularly in older patients or those with larger amounts of total weight loss. While not medically dangerous, these cosmetic changes can meaningfully affect patient satisfaction and body image, and proactive counseling before treatment initiation, alongside resistance training to help preserve skin-supporting muscle mass, as discussed in the nutritional considerations below, may help set realistic expectations and mitigate psychological distress associated with rapid appearance change (Table 3) [18,27].

9. NUTRITIONAL AND LIFESTYLE CONSIDERATIONS DURING THERAPY

A joint advisory from several nutrition and obesity medicine societies emphasized that while GLP-1 receptor agonists reduce body weight by 5 to 18 percent in clinical trials, their use carries risks including nutritional deficiencies and loss of muscle and bone mass alongside fat mass [28]. Structured management of gastrointestinal side effects, prevention of nutrient deficiencies, and resistance training to preserve lean mass should therefore be considered standard components of care, alongside attention to drug access and food security, which shape real-world outcomes with GLP-1 therapy across patient populations [18,28]. In practice, this translates into a few concrete recommendations: prioritizing protein-forward, nutrient-dense meals given reduced overall food volume; incorporating structured resistance training to preserve skeletal muscle and bone density during rapid weight loss; and routine dietitian involvement to monitor for excessive weight loss or nutrient deficiency, particularly in older adults and those with lower baseline BMI [18].

Table 3. Summary of adverse events associated with semaglutide, indicating whether each is a class-wide GLP-1 receptor agonist effect or a semaglutide-specific signal, with recommended clinical actions.

Adverse Event	Frequency / Severity	Class-Wide or Semaglutide-Specific	Recommended Clinical Action
Nausea, vomiting, diarrhea	Common; most frequent during titration, attenuates over time	Class-wide (GLP-1 mechanism)	Smaller meals, slower titration, temporary dose hold if severe
Constipation	Common; may persist longer than other GI effects	Class-wide	Hydration, dietary fiber, routine monitoring
Acute pancreatitis	Uncommon but serious	Class-wide	Counsel on severe abdominal pain; discontinue and evaluate if suspected
Cholelithiasis / cholecystitis	Elevated vs. placebo	Likely weight-loss-related, not class-specific	Monitor for biliary symptoms, especially with rapid weight loss
Psychiatric symptoms (depression, anxiety, suicidal ideation)	Signal from spontaneous case reports; absolute risk unclear	Class-wide signal (semaglutide, liraglutide, tirzepatide)	Baseline and periodic mood screening; escalate if new/worsening symptoms
Vision impairment / NAION signal	Disproportionate reporting signal; causality unconfirmed	Semaglutide-specific signal in FDA data	Closer ophthalmologic monitoring with large, rapid HbA1c reductions
Facial volume loss ("Ozempic face")	Common with substantial/rapid weight loss	Not semaglutide-specific (weight-loss related)	Pre-treatment counseling; resistance training to preserve muscle/skin support
Delayed gastric emptying (perioperative risk)	Mechanism-based, relevant at any dose	Class-wide	Consider discontinuation before general anesthesia to reduce aspiration risk

10. WEIGHT REGAIN AND TREATMENT DISCONTINUATION

Obesity is increasingly understood as a chronic, relapsing condition, and data from the STEP 1 trial extension provide direct evidence for this framing in the context of semaglutide therapy. One year after discontinuation of semaglutide 2.4 mg and lifestyle intervention, participants regained approximately two-thirds of their prior weight loss, accompanied by reversal of associated cardiometabolic improvements [29]. This finding has significant implications for clinical practice and health-system planning, suggesting that, analogous to other chronic disease therapies, sustained benefit from semaglutide requires ongoing treatment rather than a finite treatment course [29].

The physiological basis for this rebound is well characterized: weight loss triggers compensatory adaptations, including reductions in resting energy expenditure disproportionate to the amount of weight lost, alongside increases in circulating ghrelin and reductions in satiety-promoting hormones, all of which favor weight regain once pharmacologic appetite suppression is withdrawn. These adaptations are not unique to semaglutide or to pharmacologically induced weight loss; they are observed following weight loss achieved through diet alone and are a central reason why long-term weight-loss maintenance through lifestyle intervention alone has historically proven so difficult to sustain at a population level [29]. These findings raise important, still largely unresolved questions for clinical practice and health policy: whether patients who achieve substantial weight loss and metabolic improvement might eventually be candidates for dose reduction or intermittent dosing strategies rather than indefinite maintenance dosing, how insurance systems and health budgets should account for a treatment model requiring lifelong therapy analogous to that used for hypertension or hyperlipidemia, and how patient expectations should be set at treatment initiation regarding the likely need for long-term or indefinite therapy to sustain benefit [29].

These conclusions should be interpreted in light of the limitations of the available withdrawal data. The STEP 1 extension followed a single trial population, adults without diabetes who had not previously used semaglutide, for only one year after discontinuation, and its open-label extension design may introduce differential dropout and reporting bias relative to the double-blind treatment period. Longer-term, multi-year follow-up, replication in other populations (including patients with type 2 diabetes and those on different maintenance doses), and prospective study of structured dose-tapering strategies remain necessary before firm conclusions can be drawn about the optimal approach to treatment discontinuation [29].

11. CLINICAL PRACTICE GUIDELINES

Reflecting the maturing evidence base, the American Diabetes Association's Obesity Association division has issued comprehensive, evidence-based standards of care for the

pharmacologic treatment of obesity in adults. These guidelines recommend selecting obesity medications through a person-centered, shared decision-making approach; prioritizing agents most likely to achieve and sustain treatment goals while accounting for cost, access, tolerability, and individual preference; and combining pharmacotherapy with nutrition, physical activity, and behavioral therapy as a matter of standard practice [2]. The guidelines also note the physiological basis for the chronicity of obesity treatment: weight-regulating hormones shift in response to weight loss in ways that favor regain, and reduced energy expenditure following weight loss further complicates maintenance, providing a mechanistic rationale consistent with the STEP 1 extension findings described above. The guidelines additionally recommend minimizing concomitant use of weight-promoting medications wherever clinically appropriate [2].

Patient selection in practice typically involves weighing BMI thresholds (generally 30 kg/m² or higher, or 27 kg/m² or higher in the presence of weight-related comorbidities) alongside individual risk-benefit considerations, prior treatment history, and patient preference. Contraindications and precautions relevant to prescribing decisions include a personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2, given a boxed warning derived from rodent studies showing thyroid C-cell tumors, as well as caution in patients with a history of pancreatitis, severe gastrointestinal disease, or diabetic retinopathy, given the safety considerations discussed above. Guidelines generally recommend regular follow-up during dose titration to assess tolerability, efficacy, and emerging adverse effects, with adjustment of the titration pace as clinically indicated rather than rigid adherence to a fixed schedule [2,17,26].

Guideline bodies have also increasingly addressed the question of treatment duration and discontinuation planning, generally recommending that patients and prescribers approach anti-obesity pharmacotherapy, including semaglutide, as a long-term or indefinite commitment analogous to management of other chronic diseases, rather than as a finite course of treatment with an expected endpoint. This framing has implications for how treatment goals are discussed at initiation, how success is defined over time, and how health systems structure coverage and reimbursement policies for what is, in effect, chronic disease management rather than a short-term intervention (Table 4) [2,29].

12. FUTURE DIRECTIONS AND RESEARCH GAPS

Several important questions remain incompletely resolved. First, strategies to improve long-term adherence and mitigate the substantial rates of weight regain after discontinuation require further study, including consideration of dose-tapering strategies, combination or staged intensive lifestyle management, and maintenance-phase protocols. Second, the psychiatric and ophthalmologic safety signals identified in pharmacovigilance data warrant prospective, mechanistic investigation to clarify causality and absolute risk. Third, cost-effectiveness and equitable access remain substantial barriers to population-level impact, particularly given the chronic treatment model that current evidence supports [17,20,29].

A fourth area of active investigation concerns special populations who remain comparatively understudied in the pivotal trial programs reviewed here, including adolescents and younger patients, pregnant or breastfeeding individuals (for whom semaglutide is currently not recommended given insufficient safety data), and patients with significant hepatic impairment. As real-world use expands well beyond the demographic profile of the original registration trials, post-marketing surveillance and dedicated trials in these populations will be important for refining prescribing guidance and identifying any population-specific safety considerations not captured in the existing evidence base [2]. From a structural and translational standpoint, computational approaches such as molecular docking and structure-based drug design offer a promising avenue for rational optimization of next-generation GLP-1-based and multi-agonist therapies. Comparative docking analyses across semaglutide and emerging agents may help clarify the structural determinants of differential potency, receptor selectivity, and duration of action within this rapidly expanding drug class, complementing the clinical outcomes literature reviewed here.

Table 4. Key patient-selection criteria and contraindications/precautions for semaglutide prescribing, based on current clinical practice guidelines.

Patient Selection Criteria	Contraindications & Precautions
BMI ≥30 kg/m², or ≥27 kg/m² with a weight-related comorbidity	Personal or family history of medullary thyroid carcinoma or MEN2 syndrome (boxed warning)
Prioritize agents likely to achieve and sustain treatment goals	Caution with prior history of pancreatitis or severe gastrointestinal disease
Account for cost, access, tolerability, and patient preference	Caution in patients with diabetic retinopathy, given the ophthalmologic safety signal
Combine pharmacotherapy with nutrition, physical activity, and behavioral therapy as standard practice	Not recommended in pregnancy or breastfeeding — insufficient safety data
Regular follow-up during dose titration to assess tolerability and efficacy	Minimize concomitant use of other weight-promoting medications wherever clinically appropriate

The broader competitive landscape also warrants continued attention: dual GIP/GLP-1 receptor agonists and emerging triple-agonist and oral small-molecule GLP-1 therapies are being developed with the aim of matching or exceeding semaglutide's efficacy while potentially improving tolerability or convenience. How semaglutide's well-established, multi-domain evidence base — spanning glycemic, weight, cardiovascular, hepatic, and renal outcomes — will compare against these newer agents as their own outcomes data matures represents one of the most consequential open questions in metabolic medicine over the coming several years. Finally, ongoing refinement of diagnostic criteria for "clinical obesity" and continued investigation into dietary modulation of endogenous GLP-1 secretion may further personalize and extend the reach of GLP-1-based therapeutics.

CONCLUSION

Semaglutide has established itself as a transformative therapy across type 2 diabetes, obesity, and cardiovascular risk reduction, supported by one of the most extensive clinical trial programs in metabolic medicine. Its efficacy is well documented and substantial, but it must be balanced against a meaningful burden of gastrointestinal, psychiatric, ophthalmologic, and dermatologic adverse effects, as well as the reality that benefits are not sustained without continued treatment. Optimal use of semaglutide in clinical practice requires an integrated approach that combines pharmacotherapy with structured nutritional support, resistance training, psychiatric monitoring, and shared decision-making, consistent with emerging clinical practice guidelines. Continued research into long-term safety, maintenance strategies, and next-generation agents informed by structural pharmacology will be essential to fully realizing semaglutide's potential in the management of cardiometabolic disease.

Taken as a whole, the evidence reviewed here, spanning glycemic control, weight management, cardiovascular risk reduction, hepatic and renal protection, and an increasingly well-characterized safety profile, supports semaglutide's position as one of the most consequential additions to the cardiometabolic pharmacopoeia in recent years. Its trajectory from a glucose-lowering diabetes therapy to a multi-system agent addressing several of the most significant chronic disease burdens in modern medicine illustrates both the promise and the complexity of GLP-1 receptor agonism as a therapeutic strategy, and underscores why continued rigorous evaluation of its long-term risks and benefits remains a priority for clinicians, researchers, and health systems alike.

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