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Adverse Effects of GLP-1 Receptor Agonists: From Diabetic Complications to the Risk of Discontinuation - Systematic Analysis and Proposal of A Predictive Model for Personalization of Therapeutics

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Abstract

This work is a systematic and critical analysis of the safety profile of GLP-1 receptor agonists (GLP-1 RAs), the adverse effects whose incidence and severity are modulated by the presence of chronic complications of type 2 diabetes mellitus (T2DM), and their crucial role in the phenomenon of early therapeutic discontinuation. The primary objective is to construct a clinically usable map of documented adverse effects—gastrointestinal, cardiovascular, renal, thyroid, pancreatic, biliary, skin, and ophthalmological—by analyzing the underlying pathophysiological mechanisms, populations at increased risk, and management implications for each. The secondary objective, which constitutes the original contribution of the work, is to integrate this analysis with the proposal of a predictive discontinuation risk stratification model, intended for both clinical practice and medical affairs strategy.

Abbreviations: ADSC: Adipose-Derived Stem Cells; AGEs: Advanced Glycation End Products; AIFA: Italian Medicines Agency; AKI: Acute Kidney Injury; AUC: Area Under the Curve; CKD: Chronic Kidney Disease; CV: Cardiovascular; CVOT: Cardiovascular Outcome Trial; DAN: Diabetic Autonomic Neuropathy; T2DM: Type 2 Diabetes Mellitus 2; DPP-4: Dipeptidyl Peptidase-4; DWAT: Dermal White Adipose Tissue; EA-GI: Gastrointestinal Adverse Events; eGFR: estimated Glomerular Filtration Rate; EMA: European Medicines Agency; GIP: Glucose-dependent Insulinotropic Polypeptide; GLP-1: Glucagon-Like Peptide-1; GLP-1 RA: Glucagon-Like Peptide-1 Receptor Agonists; HbA1c: Glycated hemoglobin; HR: Hazard Ratio; HS: Hidradenitis Suppurativa (Hidradenitis Suppurativa); ICC: Intraclass Correlation Coefficient; MACE: Major Adverse Cardiovascular Events; MASH: Metabolic dysfunction-Associated SteatoHepatitis; MEN2:

Multiple Endocrine Neoplasia type 2; TCM: Medullary Thyroid Cancer; NAION: Non-Arteritic Anterior Ischemic Optic Neuropathy; NF-κB: Nuclear Factor kappa-B; PBPK: Physiologically Based Pharmacokinetic; PRAC: Pharmacovigilance Risk Assessment Committee; PSP: Patient Support Program; RAGE: Receptor for Advanced Glycation End Products; RCT: Randomized Controlled Trial; ROS: Reactive Oxygen Species; RWE: Real-World Evidence; SGLT-2i: Sodium-glucose cotransporter 2 inhibitors; SIRT1: Sirtuin 1

Introduction

The work is based on a narrative review of the scientific literature published between 2015 and 2026. The "systematic" nature of the analysis, as referenced in the title, refers to the classification of adverse effects by organ and system and their treatment according to a uniform framework (mechanism, severity of risk, susceptible populations, management implications). Relevant pivotal Randomized Controlled Trials (RCTs), large Cardiovascular Outcome Trials (CVOTs), meta-analyses, and Real-World Evidence (RWE) studies were analyzed. The main reference sources are the meta-analysis of the main CVOTs by Giugliano et al. **[1]**, the narrative review of real-world evidence by Thomsen et al. **[2],** the review on the safety profile of semaglutide by Smits and van Raalte **[3],** the review on the mechanisms of action of GLP-1 and dual GIP/GLP-1 agonists by Liu **[4],** and the experimental study by Xiang et al. on SIRT1-mediated muscle protection **[5].** Four more recent sources are added: the review by Cardoso et al. on precision medicine and the heterogeneity of the therapeutic effect of GLP-1 RAs **[6],** the review by Paschou et al. on the effects of GLP-1 RAs on inflammatory skin diseases **[7],** the narrative review by Alfaris et al. on single, dual, and triple agonists for T2DM and obesity **[8]** and the PBPK modeling study by Hooper et al. on drug interactions due to slowing of gastrointestinal motility **[9].** The SELECT trial with semaglutide in obese non-diabetic patients **[10]** and the FLOW trial with semaglutide on primary renal endpoints **[11]** complete the summary of the main trials published to date.

Mechanism of Action, Pharmacology, and Structural Differences Between Molecules

Glucagon-like peptide-1 (GLP-1) is an incretin hormone produced by L cells of the distal intestine in response to nutrient ingestion. Its physiological effects are mediated by activation of the specific GLP-1R receptor, distributed in multiple tissues: pancreatic beta cells, heart, kidneys, brain, gastrointestinal tract, lung, and—as evidenced by the most recent research—skin and dermal adipose tissue **[4]**. Mechanisms of action relevant to understanding the safety profile include: (i) glucose-dependent stimulation of insulin secretion with glucagon suppression, without hypoglycemic risk in monotherapy; (ii) dose-dependent slowing of gastric emptying, mediated by activation of GLP-1R receptors in the myenteric plexus and modulation of the afferent vagal nerve; (iii) reduction of appetite through central effects on the hypothalamus and area postrema; (iv) direct and indirect pleiotropic effects on the heart, kidneys, blood vessels, liver, and adipose tissue **[4].** From a structural point of view, the GLP-1 RA class includes molecules with significantly different pharmacokinetic characteristics, resulting in non-overlapping efficacy and safety profiles. Exendin-4 analogues (exenatide, lixisenatide) share only 53% homology with human GLP-1, while human GLP-1 analogues (liraglutide, semaglutide, dulaglutide, albiglutide) have approximately 90–97% homology **[4].** Tirzepatide, a dual GIP/GLP-1R agonist, represents a conceptual novelty: the simultaneous activation of the GIP receptor (expressed in adipose tissue) and the GLP-1R confers enhanced metabolic effects, with demonstrated superiority in glycemia and weight loss compared to mono-GLP-1R agonists **[4].**

Pharmacokinetically, the extremely short half-life of native peptides (1–2 minutes for endogenous GLP-1, degraded by DPP-4) has stimulated the development of analogues resistant to enzymatic degradation through:

amino acid substitutions at position 8 (resistance to DPP-4), acylation with fatty acids to prolong binding to albumin (liraglutide, semaglutide), fusion with large molecules such as albumin (albiglutide) or the Fc fragment of IgG4 (dulaglutide). These modifications allow for daily (exenatide IR, liraglutide, lixisenatide) or weekly (exenatide ER, semaglutide SC, dulaglutide, tirzepatide) dosing [4] as shown in **Table 1**.

Molecule	Structure	Administration	t½ approx.
Exenatide IR	Exendine-4 analogue	2×/die s.c.	~2,4 hours
Exenatide ER	Exendine-4 analogue	1×/week s.c.	~2,4 hours*
Liraglutide	Human GLP-1 analogue	1×/die s.c.	~13 hours
Semaglutide s.c.	Human GLP-1 analogue	1×/week s.c.	~7 days
Semaglutide os.	Human GLP-1 analogue	1×/die os.	~7 days
Dulaglutide	Human GLP-1 analogue	1×week s.c.	~5 days
Lixisenatide	Exendine-4 analogue	1×/die s.c.	~3 hours
Tirzepatide	GLP-1/GIP dual agonist	1×/week s.c.	~5 days

Table 1: Main GLP-1 antiretrovirals and pharmacokinetic characteristics [4]. *The half-life of the molecule is unchanged; weekly administration is made possible by the sustained release from the microspheres, which results in steady state being reached in 6-7 weeks.

The Clinical Paradox: From Trial to Real-World Evidence

Large randomized cardiovascular trials have demonstrated significant reductions in Major Cardiovascular Events (MACE) in high-risk patients, with benefits extending to cardiovascular mortality, all-cause mortality, hospitalization for heart failure, and renal progression [1,12–15]. The STEP and SURMOUNT programs have redefined weight loss expectations, with average reductions of approximately 15% with semaglutide 2.4 mg [16] and greater than 20% with tirzepatide 15 mg [17]. The SELECT trial extended the cardiovascular indications of semaglutide to obese patients without diabetes [10]. The FLOW trial demonstrated for the first time the superiority of a GLP-1 RA on prespecified primary renal endpoints [11]. However, an unresolved paradox emerges in daily clinical practice: discontinuation rates ranging from 20% to 50% within the first year of therapy, with dropouts concentrated in the first 3 months after titration, and frequent underdosing compared to the doses studied in trials [2]. In a public health system that supports the high cost of these drugs, this discrepancy between efficacy (trial) and effectiveness (real world) also represents a problem of economic sustainability.

Adverse Effects

Classification by Organ and System

A systematic understanding of the safety profile of GLP-1 RAs requires a classification of documented adverse effects by organ and system, distinguishing between class effects—common to all GLP-1 RAs by virtue of their shared mechanism of action—and molecule-specific effects.

- Gastrointestinal effects: nausea, vomiting, diarrhea, constipation, dyspepsia,

gastroesophageal reflux. They represent the most relevant category in terms of frequency and impact on adherence. Emerging signs in RWE include gastroparesis and intestinal obstruction.

- Cardiovascular effects: modest increase in heart rate (class effect).
- Ocular effects: increased retinal complications documented in SUSTAIN-6 for semaglutide; risk of NAION associated with semaglutide in Scandinavian observational studies, recognized by the EMA in 2025 as a very rare side effect.
- Biliary effects: dose-dependent increased risk of cholelithiasis and cholecystitis, with a higher risk in obesity studies than in those of T2DM.
- Thyroid effects: C-cell hyperplasia in rodents; no solid evidence in humans.
- Pancreatic effects: asymptomatic increase in lipase and amylase; Unconfirmed signal for clinical acute pancreatitis in CVOTs.
- Renal effects: Class-wide nephroprotection; possible acute kidney injury due to dehydration in patients with severe GI disorders.
- Skin effects: Changes in dermal adipose tissue with complex molecular mechanisms.
- Effects on body composition: Reduction in fat mass with possible concomitant loss of lean mass.
- Psychiatric effects: No solid evidence of increased risk of depression or suicidality in RWE.

Incidence in pivotal studies and RWE: critical comparison

Incidence data for adverse effects in semaglutide pivotal trials provide a precise quantitative reference. In the SUSTAIN program trials for the subcutaneous formulation, nausea was reported in 11–24% of treated patients (versus 3–8% in the placebo group), vomiting in 4–12% (versus 2–3%), and diarrhea in 4–11% (versus 2–6%) **[3].** In the PIONEER program trials for the oral formulation, nausea reached 5–23% (versus 6–7% with placebo), with higher peaks in patients with moderate CKD **[3].** In the STEP program for semaglutide 2.4 mg for weight management, nausea was reported in 44.2% of active patients versus 16% of placebo, and vomiting in 24.8% versus 6.3% **[16] (Table 2).** The mechanisms underlying nausea and vomiting are not fully elucidated. A role for the central nervous system has been hypothesized: studies with exenatide analogues with reduced brain penetrance have shown less vomiting while maintaining glycemic efficacy, suggesting that the area postrema—lacking the blood-brain barrier—is a key site mediating emetic effects **[3].** Approximately 10% of patients discontinue semaglutide due to GI adverse events, with real-world data overlapping with those from trials **[3].** In contrast to trials, RWE documents much higher discontinuation rates and, in intention-to-treat analyses, weight reductions that are lower than those from trials, but comparable in high-adherence subgroups **[2];** persistence data are analyzed in Chapter 8.

Adverse Effect Frequency (Class): Timing, Clinical Relevance

Adverse effect	Frequency (class)	Timing	Clinical relevance
Nausea	Very common: 11-44% (dose-dep.)	Titration phase	High- First cause of dropout
Vomiting	Common: 4-25%	Titration phase	High

Diarrhea	Common: 4-15%	Titration phase	Medium
Constipation	Common: 1-10%	Variable	Medium
↑ Cardiac rate	Very common: +2-4 bpm	Persistent	Low-Medium
Cholelithiasis/cholecystitis	Uncommon in DMT2; RR 2,29 in obesity studies	Late	Medium-High
Gastroparesis (RWE)	HR 3,67 vs bupropione-naltrexone [18]	Variable	High in susceptible
Intestinal Ostruction	HR 4,22 vs bupropion-naltrexone [18]*	Rare	High (signal to be confirmed)
Retinopathy (SUSTAIN-6)	HR 1,76 (semaglutide) [13]	Early phase	High in pat. with DRP
NAION (semaglutide)	HR 2,19 vs unexposed; HR 2,81 vs SGLT-2i [19,20]	Emerging	Very rare (EMA 2025)
Cellular hyperplasia C tiroxine	Rodents; Not documented in humans	—	Controversial
AKI	Similar to placebo in CVOT [3]	Sporadic	Indirect GI Mechanism indiretto
↑ Lipase/amylase	Frequent, asymptomatic [3]	First weeks	Monitor

Table 2. Summary of documented adverse effects of GLP-1 RAs. *Methodologically challenged signal.

Gastrointestinal Adverse Effects and Diabetic Complications

From mechanism of action to adverse event

Understanding gastrointestinal adverse effects requires an analysis of the mechanism of action of GLP-1 RAs in the gastrointestinal tract. The distribution of GLP-1 receptors throughout the digestive tract—with high expression in the myenteric plexuses, the vagus nerve, and the area postrema—determines pathophysiologically consistent and predictable effects. Regarding the slowing of gastric emptying, the mechanism is partly mediated by the central nervous system. GLP-1 inhibits gastric motility through activation of GLP-1R receptors on vagal afferent fibers that transmit sensory signals to the brainstem; brain regions of the nucleus tractus solitarius (NTS) mediate the inhibitory effect on motility [4]. The dose threshold for inhibiting gastric emptying is 3,000–10,000 times lower than that required to suppress feeding behavior, indicating separate mechanisms for the two functions [4]. A notable aspect is the phenomenon of tachyphylaxis: prolonged and continuous exposure to GLP-1R (as with long-acting analogues) results in a progressive desensitization of the effect on slowing gastric emptying, whereas short-acting analogues maintain this effect for the duration of treatment [4]. This partly explains why GI adverse events tend to decrease over time during treatment with long-acting GLP-1 RAs. A relevant observation also deserves mention: nausea induced by GLP-1 RAs does not appear to contribute substantially to weight loss. A mediation analysis conducted in the SUSTAIN 1-5 trials attributed less than 0.5 kg of weight reduction to nausea/vomiting events [3], and similar analyses in the

STEP trials with semaglutide and the SURPASS trials with tirzepatide showed no association between EA-GI and the amount of weight loss [4].

Diabetic Autonomic Neuropathy as an Amplifying Factor

Diabetic Autonomic Neuropathy (DAN) is, from a pathophysiological perspective, a plausible and potentially relevant risk factor for the development of serious gastrointestinal adverse effects during GLP-1 RA therapy. Glycosylation of neuronal structural proteins and the accumulation of sorbitol due to activation of the polyol pathway—consequent to chronic exposure to hyperglycemia—lead to axonal dysfunction and neuronal death in the autonomic nerves of the gastrointestinal tract. From a pathophysiological perspective, intestinal autonomic damage compromises normal gastrointestinal motility across a spectrum ranging from mild reduction in gastric emptying to full-blown gastroparesis. Even in the absence of instrumentally diagnosable gastroparesis, a significant proportion of patients with long-standing T2DM exhibit subclinical alterations in gastric motility detectable by scintigraphy or breath testing. When these patients begin a GLP-1 RA, the pharmacological mechanism overlaps with preexisting autonomic damage, amplifying gastric distension and related symptoms. This scenario has fundamental strategic implications: patients with DAN are both those at greatest risk of intolerance to GLP-1 RAs and those who could benefit most from their cardiovascular and renal protective effects. Preventive risk stratification in this population is therefore clinically relevant and forms the foundation of the predictive model developed in Chapter 8. It should be noted, however, that no studies have specifically evaluated DAN as a predictor of intolerance to GLP-1 RAs in the literature reviewed. The role attributed to it in this work represents a pathophysiological hypothesis, which the model proposed in Chapter 8 and the RE-START study in Chapter 9 aim to test.

Diabetic Gastroparesis: Risk and Clinical Management

Diabetic gastroparesis represents the most critical scenario for the use of GLP-1 RAs. In these patients, the product information for all available GLP-1 RAs lists severe gastroparesis as a relative contraindication or caution, as further slowing gastric emptying can precipitate episodes of uncontrollable nausea and vomiting, dehydration, and deterioration of glycemic control due to unpredictable nutrient absorption. In practice, patients with diagnosed gastroparesis require a specialist gastroenterological evaluation before initiating GLP-1 RA therapy and—if the decision is made to proceed—an extremely slow titration with close monitoring. Emerging signs in RWE: intestinal obstruction and g Postmarketing reports of ileus and intestinal obstruction associated with GLP-1 RAs were partially supported by a cohort study of patients with obesity conducted by Sodhi et al. on a US insurance claims database, comparing new users of semaglutide and liraglutide with new users of bupropion-naltrexone. The study reported a hazard ratio of 4.22 (95% CI: 1.02-17.40) for intestinal obstruction and 3.67 (95% CI: 1.15-11.90) for gastroparesis [18]. However, this study has been subjected to significant methodological criticisms [2]: the choice of bupropion-naltrexone as the comparator introduces significant indication bias, as this molecule is typically prescribed to patients with fewer gastrointestinal comorbidities than those receiving a GLP-1 RA; The absolute numbers of events are very small, making HRs imprecise; and definitions of gastroparesis and intestinal obstruction in administrative databases based on diagnostic codes are subject to misclassification. In contrast, the observational cohort study by Rodriguez et al., comparing semaglutide and tirzepatide in 18,386 overweight or obese adults, found no significant difference in rates of gastroparesis (HR 0.73; 95% CI: 0.38-1.42) or intestinal obstruction between the two molecules [2,21]. The current position of regulatory agencies calls for monitoring this signal but does not

recommend changes to prescribing practice based on available evidence. The American Society of Anesthesiologists' recommendation to suspend GLP-1 RAs before elective surgical procedures to reduce the risk of aspiration related to delayed gastric emptying remains prudent [2].

Pancreatitis Risk: Evidence and Controversy

An asymptomatic increase in markers of pancreatic exocrine function—lipase and amylase—is a frequent and consistent finding in trials with GLP-1 RAs. In a phase 2 study, oral semaglutide increased lipase levels by 9–55% in a dose-dependent manner, and subcutaneous semaglutide by 36% [3]. This enzyme increase occurs within the first hours of administration, is asymptomatic, and has not been associated with the onset of clinical pancreatitis in trial analyses [3]. Regarding clinical pancreatitis, pooled data from large CVOTs are reassuring. In SUSTAIN-6, acute pancreatitis occurred in 9 patients on semaglutide and 12 on placebo; in PIONEER 6, in 1 patient on oral semaglutide and 3 on placebo [3]. A meta-analysis of 11 CVOTs with GLP-1 RAs calculated a rate ratio for acute pancreatitis of 1.05 (95% CI: 0.78-1.41), which was not statistically significant [2]. The current consensus is that the risk of clinical pancreatitis is not significantly increased by the class of GLP-1 RAs, but pancreatitis remains listed as a potential adverse event in the product information. Pre-existing risk factors for pancreatitis require an individualized risk-benefit assessment. Significant data emerge from stratification by therapeutic indication. In the cohort study by Sodhi et al., reported in the review by Alfaris et al., in the population treated with GLP-1 RA for weight management without a diagnosis of diabetes, the risk of pancreatitis was significantly increased compared to the comparator bupropion-naltrexone (HR 9.09; 95% CI: 1.25-66.00), despite the methodological limitations discussed in paragraph 3.5 [8,18]. This contrasts with the absence of a significant increase documented in the meta-analyses of CVOT conducted on populations with T2DM. The most plausible interpretation is that the pancreatic risk profile is modulated by indication and comorbidities: obese patients without diabetes receiving GLP-1 RA for weight loss may have a different prevalence of baseline pancreatic risks compared to patients with T2DM included in CVOTs, or that higher doses used for weight management (semaglutide 2.4 mg versus 0.5-1 mg for T2DM) exert a greater exocrine pancreatic impact. These data reinforce the need for pre-therapy assessment of pancreatitis risk factors (hypertriglyceridemia, history of pancreatitis, cholelithiasis) regardless of therapeutic indication [8]. Drug interactions mediated by slowing gastrointestinal motili GLP-1 RAs do not generally induce classical pharmacokinetic interactions through inhibition of hepatic metabolism (cytochrome P450) or membrane transporters. However, their specific effect on slowing gastrointestinal motility—with extension of gastric emptying time and intestinal transit—introduces a clinically relevant but systematically underestimated category of drug interactions in prescribing practice [9]. A PBPK (Physiologically Based Pharmacokinetic) modeling study conducted by Hooper et al. with the Certara Simcyp™ V23 software simulated, in a virtual cohort of 1,000 obese adults, the effect of prolonged gastric emptying (1 to 4 hours) and extended small intestinal transit (3.32 to 9 hours), values derived from capsule endoscopy in patients with diabetes treated with liraglutide [9]. The model, validated on package insert data for semaglutide and liraglutide for five reference drugs, showed agreement within 20% for most substrates. In the exploratory analysis of drugs frequently co-prescribed with GLP-1 RAs (identified by the Medical Expenditure Panel Survey 2022), systemic exposure (AUC 0-24h) increased by 64% for rosuvastatin, 90% for valsartan, and 205% for dabigatran, with a delay in Tmax for all three drugs [9]. For rosuvastatin and valsartan, the increase in AUC was not accompanied by a proportional increase in Cmax, while dabigatran—an anticoagulant with a narrow therapeutic index—also showed an increase in Cmax, with potential implications for bleeding risk.

Sensitivity analyses revealed a methodologically crucial finding: the determining parameter for the increase in AUC is not gastric emptying time, but rather small intestinal transit time. BCS class II drugs (low solubility, high permeability), such as dabigatran and rosuvastatin, are particularly susceptible to this effect due to their dependence on the absorptive surface area of the small intestine. Gastric emptying time, on the other hand, determines the delay in Tmax. This distinction has immediate practical implications: rivaroxaban, absorbed predominantly in the stomach, shows no significant alterations in AUC or Tmax; apixaban, absorbed in the distal small intestine and colon, may conversely be more vulnerable to prolonged intestinal transit times [9]. The clinical implications are relevant for specific categories of patients receiving polytherapy. Regarding direct oral anticoagulants, the 205% increase in dabigatran AUC—although derived from a simulated model requiring prospective clinical validation—requires increased monitoring in patients initiating a GLP-1 RA co-administered with dabigatran, given the lack of a readily available specific antidote and the clinical diversity of its absorption profile. For statins, the increased exposure to rosuvastatin (+64%) may require dose reduction, particularly in patients with concomitant renal insufficiency. For antihypertensives, the increased exposure to valsartan (+90%) may potentiate the hypotensive effect, with a risk of orthostatic hypotension in elderly or bedridden patients. For oral contraceptives, package insert data for semaglutide and tirzepatide document changes in ethinyl estradiol AUC in opposite directions (+7% with semaglutide, -21% with tirzepatide), indicating that the interaction is not reducible to the motility mechanism alone and requires specific counseling for patients of childbearing age. For levothyroxine—for which a separation of at least 4 hours from interfering drugs is already recommended—prolonging gastric emptying may further alter the optimal administration window, with the risk of altering the binding dynamics with co-administered sequestrants (phosphate binders, multivitamin supplements) and further reducing their absorption [9]. The study's limitations must be explicitly addressed: the motility parameters were derived from patients with diabetes (and not obesity) treated with liraglutide, one of the less potent agents, likely underestimating the effects of semaglutide and tirzepatide; the model does not incorporate the increase in gastric pH (up to 20%) related to reduced acid secretion; the effect is modeled as constant, without considering tachyphylaxis. Active surveillance and dedicated clinical trials in the highest-risk groups (anticoagulants, epileptics, users of oral contraceptives) represent a pharmacovigilance priority for the class [9].

Cardiovascular Effects: Protection, Risks, and New Indications gastroparesis

Systematic Meta-Analysis of Eight CVOTs

Since 2008, the FDA has required all new agents for T2DM to exclude excess cardiovascular risk compared to placebo (non-inferiority) in high-risk patients; this requirement was revised by the FDA in 2020. For the GLP-1 RA class, these studies have produced remarkably favorable results for most of the agents examined. An updated meta-analysis conducted by Giugliano et al., which summarized data from eight CVOTs involving 60,080 adult patients with T2DM (72.4% with established cardiovascular disease) and a median follow-up of 1.3 to 5.4 years, provides the most robust estimate of class effects [1]. GLP-1 RAs reduced the risk of MACE by 14% (HR = 0.86; 95% CI: 0.79-0.94; p = 0.006), with non-significant heterogeneity between trials. The benefit was apparently more marked in patients with pre-existing cardiovascular disease (HR = 0.84; 95% CI: 0.79-0.90) compared to those without a history of cardiovascular disease (HR = 0.94; 95% CI: 0.83-1.06), although the interaction between subgroups was not statistically significant (p = 0.127) [1]. Analyzing the individual components of MACE, the 16% reduction in non-fatal stroke (HR=0.84; 95% CI: 0.76-0.94; p=0.007) was

statistically significant and without heterogeneity between trials (I^2=0%), while the 9% reduction in non-fatal myocardial infarction (HR=0.91; 95% CI: 0.81-1.01) did not reach statistical significance. Cardiovascular mortality was reduced by 13% (HR=0.87; 95% CI: 0.78-0.96; p=0.016), all-cause mortality by 12% (HR=0.88; 95% CI: 0.80-0.96; p=0.012), and hospitalizations for heart failure by 10% (HR=0.90; 95% CI: 0.83-0.98; p=0.023) [1]. Regarding renal outcomes, a meta-analysis of six CVOTs with renal endpoints showed a 17% reduction in the composite renal endpoint (HR = 0.83; 95% CI: 0.73-0.94), driven primarily by a 26% reduction in new macroalbuminuria (HR = 0.74; 95% CI: 0.67-0.82; p<0.001). The reduction in macroalbuminuria represents, in absolute terms, the most robust and consistent renoprotective effect documented for the class in CVOTs [1] (Table 3).

Trial	Moleule	N	MACE HR (95% CI)	Result
ELIXA [22]	Lixisenatide	6.068	1,02 (0,89-1,17)	Non inferiority
LEADER [12]	Liraglutide	9.340	0,87 (0,78-0,97)	Superiority
SUSTAIN-6 [13]	Semaglutide s.c.	3.297	0,74 (0,58-0,95)	Non inferiority†
EXSCEL [23]	Exenatide ER	14.752	0,91 (0,83-1,00)	Non inferiority
HARMONY [14]	Albiglutide	9.463	0,78 (0,68-0,90)	Superiority
REWIND [15]	Dulaglutide	9.901	0,88 (0,79-0,99)	Superiority
PIONEER 6 [24]	Semaglutide os.	3.183	0,79 (0,57-1,11)	Non inferiority
AMPLITUDE-O [25]	Efpeglenatide	4.076	0,73 (0,58-0,92)	Superiority
Meta-analisys [1]	8 GLP-1 RA	60.080	0,86 (0,79-0,94)	Superiority

Table 3: Summary of CVOTs for GLP-1 RAs and meta-analysis by Giugliano et al. [1]. †SUSTAIN-6 was designed for non-inferiority: the observed reduction in MACE is statistically significant, but superiority was not a prespecified hypothesis.

SELECT: semaglutide in patients with obesity without diabetes

The SELECT (Semaglutide Effects on Cardiovascular Outcomes in People with Overweight or Obesity) trial, published in 2023, extended the evidence of cardiovascular benefit of semaglutide to a radically different population compared to previous CVOTs: 17,604 adults with BMI ≥ 27 kg/m² and pre-existing atherosclerotic cardiovascular disease, but without a diagnosis of T2DM [10]. Treatment with semaglutide 2.4 mg weekly with a mean follow-up of 39.8 months significantly reduced the primary MACE (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke) with a HR of 0.80 (95% CI: 0.72-0.90; p<0.001) [10]. Cardiovascular death, the first confirmatory secondary endpoint, did not reach statistical significance (HR=0.85; 95% CI: 0.71-1.01); Consequently, due to the trial's hierarchical design, subsequent confirmatory endpoints were not formally tested for superiority. All-cause mortality showed a HR of 0.81 (95% CI: 0.71-0.93), a finding consistent with a benefit, but should be interpreted as non-confirmatory [10]. SELECT demonstrates that the cardiovascular benefit of semaglutide is not dependent on the glucose-lowering effect—which is absent in non-diabetics—and raises fundamental questions about the underlying

mechanisms: reduction of inflammation, improvement of the lipid profile, reduction of blood pressure, direct anti-atherosclerotic effects. The trial also paves the way for the use of semaglutide in secondary cardiovascular prevention in obese patients without diabetes, with relevant implications for cardiology guidelines [4].

FLOW: the dedicated renal trial

The FLOW (Semaglutide and Kidney Outcomes in Patients with Type 2 Diabetes and Chronic Kidney Disease) trial, published in 2024, represents the first primary renal outcomes trial with a GLP-1 RA [11]. In 3,533 patients with T2DM and CKD (eGFR 25-75 mL/min/1.73 m²), semaglutide 1 mg weekly reduced the risk of a primary composite renal endpoint (sustained eGFR reduction ≥50%, end-stage renal disease, renal or cardiovascular death) by 24% (HR = 0.76; 95% CI: 0.66-0.88; p = 0.0003). Significantly for this safety profile, FLOW also demonstrated significant reductions in cardiovascular mortality (HR = 0.71; 95% CI: 0.56-0.89) and all-cause mortality (HR = 0.80; 95% CI: 0.67-0.95) in this particularly vulnerable population [11].

Cardiovascular Adverse Effects: Increased Heart Rate

The primary cardiovascular adverse effect of the GLP-1 RA class is a modest but consistent increase in resting heart rate. In SUSTAIN-6, the placebo-corrected increase was 2.75 bpm with semaglutide 0.5 mg and 3.2 bpm with semaglutide 1 mg [3]. This increase persisted throughout treatment and did not resolve with tachyphylaxis. The underlying mechanism is still a matter of debate: mechanistic studies have reported conflicting results regarding the activation of the sympathetic nervous system, while a mouse model has shown that GLP-1R stimulation on atrial cells induces a positive chronotropic effect in the presence of neuronal input [3]. There is no consensus on the definitive mechanism. The clinical implications of this increase are controversial but reassuring in terms of outcomes: despite the increase in heart rate, CVOTs have demonstrated a net benefit on cardiovascular events. In patients with diabetic DAN, this positive chronotropic effect may interfere with the already impaired autonomic modulation of heart rate, making it difficult to distinguish drug-induced tachycardia from autonomic dysfunction. In patients with paroxysmal atrial fibrillation or pre-existing sinus tachycardia, clinical monitoring is recommended.

Retinal complications and non-arteritic anterior ischemic optic neuropathy

Semaglutide is the only GLP-1 RA for which a statistically significant increase in diabetic retinopathy complications has been documented. In SUSTAIN-6, the frequency of retinal complications (laser photocoagulation, treatment with anti-VEGF agents, vitreous hemorrhages, diabetes-related blindness) was 3.0% in the semaglutide group versus 1.8% in the placebo group (HR = 1.76; 95% CI: 1.11-2.78) [13]. This signal was not replicated with the same strength in the liraglutide (LEADER) studies nor in the dulaglutide (REWIND) trials. The most widely accepted interpretation is not a direct effect of semaglutide on the retina, but rather the phenomenon of early worsening of retinopathy in response to rapid glycemic reduction: a similar manifestation had already been documented in patients with pre-existing retinopathy who began intensive insulin therapy. A mediation analysis of the SUSTAIN program demonstrated that participants achieving the retinal endpoint had the most pronounced HbA1c reduction in the first 16 weeks, regardless of randomization to semaglutide or placebo [3]. Studies from the AngioSafe group have not found an association between GLP-1 RA exposure and pathological retinal angiogenesis [3]. A distinct—and more recently emerging—safety signal concerns non-arteritic anterior ischemic optic neuropathy (NAION), a rare but important cause of sudden monocular blindness in adults. A US study conducted at a neuro-ophthalmology center first reported an increased risk of NAION in patients treated with semaglutide [26]. This finding was subsequently confirmed by two large Scandinavian cohort studies: Grauslund et al. [19]

documented an incidence rate of NAION of 2.3 per 10,000 person-years for semaglutide versus 0.9 for unexposed individuals, with an adjusted HR of 2.19 (95% CI: 1.54–3.12) in a Danish cohort of 424,152 people with T2DM; Simonsen et al., comparing new users of semaglutide with new users of SGLT-2 inhibitors in Danish and Norwegian registries, reported a pooled HR of 2.81 (95% CI: 1.67–4.75) **[20].** Causal interpretation of this signal requires caution: patients with T2DM already have a higher baseline risk of NAION than the general population, and it is not yet clear whether this risk is directly mediated by semaglutide or reflects confounding factors related to the duration and severity of diabetes and associated comorbidities. Based on the incidence rates reported by Grauslund et al. (2.3 versus 0.9 per 10,000 person-years), the absolute risk difference is approximately 1.4 events per 10,000 person-years, a modest number compared to the demonstrated cardiovascular and renal benefits **[19].** In June 2025, the EMA's PRAC, after reviewing the available evidence, concluded that NAION is a very rare side effect of semaglutide-containing medicines and recommended updating the product information **[27].** However, patients with risk factors for NAION (small optic disc with a "full disc," arterial hypertension, obstructive sleep apnea, long-standing diabetes) deserve ophthalmologic counseling and monitoring.

Thyroid, Pancreatic, and Gallbladder Effects

Medullary thyroid carcinoma: preclinical and clinical data

The risk of Medullary Thyroid Carcinoma (MTC) was the primary safety signal identified in preclinical studies with liraglutide, which demonstrated thyroid C-cell hyperplasia and the formation of medullary adenomas and carcinomas in rodents exposed to very high doses. The mechanism is activation of GLP-1R receptors expressed on rodent C-cells, resulting in proliferative stimulation. However, the translational relevance of these data to humans is limited by fundamental biological differences. Using validated antibodies, GLP-1R is only marginally expressed in the thyroid glands of nonhuman primates and humans **[3];** experiments in monkeys treated with more than 60 times the human therapeutic dose of liraglutide for 20 months did not produce C-cell abnormalities **[3].** In the SUSTAIN program studies for semaglutide, three adjusted thyroid malignancy events were identified: two in the semaglutide group (combined n=5,933) and one in the comparator group; None were MTC. Serum calcitonin levels showed no difference between treatment arms **[3].** A meta-analysis of 45 RCTs with GLP-1 RAs found a weak association with any thyroid disorder (RR = 1.28; 95% CI: 1.03-1.60), mainly attributable to liraglutide and dulaglutide, but no significant difference for thyroid cancer (RR = 1.30; 95% CI: 0.86-1.97) **[2].** However, the evidence is not unequivocal. A subsequent meta-analysis of 64 RCTs of at least 52 weeks duration found a modest but statistically significant increase in overall thyroid cancer risk (MH-OR 1.52; 95% CI: 1.01-2.29; fragility index of 1), with no significant associations for either papillary or medullary thyroid cancer alone (MTC: MH-OR 1.44; 95% CI: 0.23-9.16) **[28].** A nested case-control study in the French national health database also reported an increased risk of thyroid cancer (adjusted HR 1.58; 95% CI: 1.27-1.95) and MTC (adjusted HR 1.78; 95% CI: 1.04-3.05) in association with 1-3 years of exposure to GLP-1 RAs **[29].** Two large Scandinavian observational studies have not found an increased risk of thyroid cancer with GLP-1 RAs versus DPP-4 inhibitors **[2].** The current regulatory position maintains the contraindication in cases of personal or family history of MTC or MEN2; a causal link in humans has not yet been demonstrated, but the heterogeneity of the results justifies continued surveillance. More granular data on the risk of thyroid disorders by single molecule are reported in the review by Alfaris et al. **[8]:** liraglutide is associated with a 37% increased risk of thyroid disorders (RR 1.37), dulaglutide with a 96% increase (RR 1.96), while no

statistically significant risk was detected for semaglutide, lixisenatide, exenatide, and albiglutide [8]. These data suggest intra-class heterogeneity in thyroid signaling, potentially related to structural differences in binding affinity to the thyroid GLP-1R or duration of receptor exposure. In any case, the position of the EMA's Pharmacovigilance Risk Assessment Committee (PRAC), published in October 2023, did not consider the available evidence sufficient to support a causal association between GLP-1 RAs and thyroid cancer [8].

Pancreatitis: State of the Art and Asymptomatic Lipase/Amylase Signal

As discussed in section 3.6, asymptomatic elevations of serum lipase and amylase are a frequent and early finding in trials with GLP-1 RAs, which, however, has not translated into a clinically relevant increased risk of acute pancreatitis in pivotal trials or CVOTs [3]. The aggregate CVOT data reported in section 3.6 are complemented by evidence from RWE: in patients with T2DM, numerous database studies have confirmed the absence of a significant increase in risk [2]. For patients treated with higher doses for weight management, data are more limited: an observational study reported pancreatitis rates of 4.6–7.9 events per 1,000 person-years for semaglutide and liraglutide versus 1.0 for the comparator, but this study has been methodologically criticized (see section 3.5) [2,18]. The regulatory agencies' position is that acute pancreatitis remains listed as a potential adverse event in the product information, with recommendations to suspend treatment if a suspected episode occurs and not restart it after diagnosis. Preexisting risk factors for pancreatitis require an individualized risk-benefit assessment.

Gallbladder and biliary tract disease: a dose-dependent risk

Biliary disease—particularly cholelithiasis (gallstones) and cholecystitis—represents one of the most robustly documented adverse effects of GLP-1 RAs, yet it is often overlooked in clinical trials. A 2022 meta-analysis of 76 RCTs involving 103,371 patients quantified a relative risk of 1.37 (95% CI: 1.23-1.52) for gallbladder or biliary disease in patients treated with GLP-1 RAs compared with placebo or other non-GLP-1 RAs [2]. This estimate shows significant heterogeneity by therapeutic indication: the relative risk for studies on T2DM is 1.27 (95% CI: 1.14-1.43), while for studies on obesity it reaches 2.29 (95% CI: 1.64-3.18) [2]. This difference is likely explained by the extent of weight loss: in patients treated for obesity, rapid weight loss per se—regardless of the pharmacological mechanism—significantly increases the risk of gallstone formation, due to changes in bile composition and volume. A direct pharmacological mechanism is hypothesized, however, since biliary disease is not observed with SGLT-2 inhibitors, which also cause weight loss, albeit to a more modest extent [3]. Proposed mechanisms include: reduced gallbladder motility with bile stasis and sludge formation (evidenced in acute studies with exenatide and albiglutide); changes in bile acid composition; and direct effects of GLP-1R on the gallbladder wall [3]. Clinically, cholelithiasis can progress to acute cholecystitis, requiring surgical intervention, and to biliary tract complications. The risk is highest during the phase of rapid weight loss and in patients with predisposing factors (obesity, female gender, family history, hypertriglyceridemia). Practical recommendations include: pre-therapy assessment of risk factors for cholelithiasis; patient counseling regarding the possibility of biliary symptoms; periodic ultrasound monitoring in high-risk patients; adequate dietary fatty acid intake to stimulate gallbladder motility; and early management of any symptoms suggestive of biliary colic or cholecystitis.

Renal Effects: Nephroprotection and Risks in Patients with CKD

Mechanisms of Nephroprotection and CVOT Data

Nephroprotection is one of the most relevant pleiotropic effects of GLP-1 RAs, consolidated in

cardiovascular studies with prespecified renal endpoints and now demonstrated as the primary endpoint in the FLOW trial. In LEADER, liraglutide reduced the composite renal risk (new macroalbuminuria, doubling of creatinine, need for renal replacement therapy, renal death) [12]. Similar results in SUSTAIN-6 and REWIND confirmed the class-specific nature of this benefit [13,15]. The Giugliano 2021 meta-analysis quantifies a 17% reduction in the composite renal endpoint and a 26% reduction in new macroalbuminuria, with notable statistical robustness (I^2=11% for macroalbuminuria) [1]. The mechanisms of nephroprotection are multiple. Indirect effects include reduction in systolic blood pressure (mediated by natriuresis and vasodilation), improved glycemic control with a reduction in renal glycotoxicity, and weight loss with a consequent reduction in intraglomerular pressure. Direct effects include activation of GLP-1 receptors in the proximal renal tubule, with effects on sodium transport and reduction of intraglomerular pressure, and local anti-inflammatory actions that reduce oxidative damage at the tubular cell level [4]. The FLOW trial definitively demonstrated that these mechanisms translate into a significant reduction in the primary renal composite endpoint even in patients with moderate-to-severe CKD (eGFR 25-75 mL/min/1.73 m^2) [11]. Acute kidney injury: mechanism and incidence Acute kidney injury (AKI) was one of the first safety signals of GLP-1 RAs, reported primarily in case reports with exenatide in patients also taking diuretics and/or renin-angiotensin-aldosterone system inhibitors [3]. The proposed pathophysiological mechanism is indirect: dehydration induced by severe nausea, vomiting, and diarrhea compromises renal circulation, particularly in patients with impaired renal reserve or co-therapy with nephrotoxic drugs. A direct mechanism has been hypothesized based on evidence that GLP-1 RAs increase natriuresis and diuresis, but this effect is considered clinically relevant only in scenarios of marked volume depletion. In pivotal trials and CVOTs, AKI did not show a significant increase compared to placebo. In SUSTAIN-6, acute renal failure had a similar incidence between semaglutide and placebo [3]. In PIONEER 6, AKI occurred in 2.0% of patients with oral semaglutide versus 2.3% with placebo [3]. In FLOW, semaglutide did not increase the risk of AKI compared to placebo in patients with pre-existing CKD, confirming the safety of acute kidney injury even in this vulnerable population [11].

Adverse effects in patients with advanced chronic kidney disease

Despite the documented renoprotective benefits, patients with advanced CKD—stages 3b-5, corresponding to eGFR < 45 mL/min/1.73 m^2—present a specific risk profile for GI adverse events. In PIONEER 5, conducted in patients with moderate CKD (eGFR 30-59 mL/min), the rates of nausea and vomiting with oral semaglutide were higher than in patients with preserved renal function, suggesting that CKD amplifies susceptibility to GI adverse events [3]. Pharmacokinetically, exenatide—which is eliminated primarily by the kidney—is contraindicated with eGFR <30 mL/min and requires caution in moderate CKD. Liraglutide and semaglutide, which are proteolyticly metabolized, do not require dosage adjustments in mild, moderate, or severe renal impairment, but their use is not recommended in end-stage renal disease (eGFR <15 mL/min/1.73 m^2). Patients with advanced CKD on GLP-1 RA therapy require: more frequent monitoring of renal function and electrolytes; particular attention to preventing dehydration in the event of vomiting or diarrhea; and dosage adjustments consistent with the regulatory indications for the prescribed drug.

Skin Effects, Body Composition, and Aging

Ozempic Face: Clinical Phenomenon and Aesthetic Impact

With the growing popularity of GLP-1 RAs, an aesthetic side effect has emerged and gained visibility in the scientific literature: the "Ozempic Face"

phenomenon. This term describes a pattern of accelerated facial aging observed in patients treated with GLP-1 RAs, characterized by soft tissue ptosis, the appearance or accentuation of deep wrinkles, reduced cheek and lip volume, and alterations in facial proportions [30]. The clinical presentation mimics that observed in patients who have lost weight rapidly for other reasons. Histological studies on skin biopsies from patients with massive weight loss after bariatric surgery have highlighted structural alterations in the dermis, with a reduction in the density of collagen and elastin fibers, suggesting that rapid weight loss may alter skin architecture beyond simple changes in fat volume [31,32]. However, as highlighted in the mini-review by Paschou et al., the most up-to-date scientific evidence suggests that the phenomenon cannot be explained exclusively by facial fat loss, but that GLP-1 RAs may directly interfere with the cellular and molecular mechanisms of skin aging [30].

Molecular mechanisms: ADSCs, fibroblasts, DWAT, and AGEs

Dermal white adipose tissue (DWAT) is a layer of metabolically active adipocytes, immune cells, fibroblasts, and adipose tissue-derived stem cells (ADSCs) located in the dermis. Expression of the GLP-1R receptor has been documented on both DWAT cells and ADSCs [30]. DWAT volume directly influences the skin aging process. ADSCs are mesenchymal cells with differentiation and regeneration capabilities: in response to stimulation, they produce cytokines, hormones, and growth factors with skin rejuvenation effects. In particular, ADSCs exert direct antioxidant effects on fibroblasts—likely through protective cytokines such as IGFs—protecting them from oxidative damage mediated by reactive oxygen species (ROS) [30]. Pharmacological activation of GLP-1 receptors on human ADSCs, according to available in vitro data, inhibits ADSC proliferation and differentiation, resulting in: (i) increased ROS production and oxidative damage to fibroblasts; (ii) reduced fibroblast migration and their synthetic capacity; (iii) reduced glucose uptake by ADSCs—a mechanism opposite to the effect of GLP-1 RAs on mature cells—with energy deficit, increased oxidative damage, and apoptosis [30]. An additional mechanism involves estrogen production: reduced ADSC activity decreases estrogen production by DWAT. Skin fibroblasts express estrogen receptors, whose stimulation increases collagen production; dermal estrogen deficiency therefore reduces collagen synthesis and increases the activity of metalloproteinases (MMPs), with degradation of the extracellular matrix [30]. In contrast to the pro-aging mechanisms described, GLP-1 RAs exert protective effects on skin aging through the reduction of advanced glycation end products (AGEs). AGEs are formed through the non-enzymatic glycation reaction between glucose and proteins, nucleic acids, and lipids; their production is accelerated in the chronic hyperglycemia of T2DM. At the skin level, AGEs accumulate in the extracellular compartment, promoting the cross-linking of collagen and elastin, resulting in tissue stiffening. The accumulation of AGEs in the epidermis compromises the skin barrier function and hinders healing. AGE receptors (RAGE) are distributed in numerous tissues, including the skin; their activation stimulates NF-κB with the production of pro-inflammatory cytokines (IL-6, TNF-α) and activation of NADPH oxidase, resulting in an increase in ROS [30]. GLP-1 RAs, as hypoglycemic agents, reduce AGE production by limiting glycation. Furthermore, they exert anti-inflammatory and antioxidant properties that interfere with post-receptor RAGE signaling pathways: liraglutide inhibits the AGE-induced NF-κB pathway in vascular smooth muscle cells; dulaglutide significantly reduced AGE levels in peripheral blood in a randomized controlled trial [30]. The described framework therefore outlines two potentially antithetical mechanisms, both mediated by GLP-1 RAs: pro-aging effects through the inhibition of ADSCs and the reduction of dermal estrogen production; and anti-aging effects through the

reduction of AGEs and the inhibition of RAGE. Paschou et al. propose that these two effects coexist and may alternately prevail depending on individual factors—baseline metabolic status, circulating AGE levels, extent of weight loss, and characteristics of the DWAT compartment—which currently do not allow for reliable clinical prediction of the resulting skin phenotype [30]. Potential beneficial effects on the cutaneous microcirculation have also been reported: studies suggest that GLP-1 RAs may increase dermal microvascular perfusion through direct effects on arterioles and capillaries, with potential benefits for the healing of diabetic skin lesions [30]. This area remains largely unexplored at the clinical and experimental level. The "Ozempic face" is therefore neither a universal nor inevitable effect of GLP-1 RA therapy, but a probabilistic phenomenon whose expression depends on the dynamic balance between opposing mechanisms. This opens up relevant translational research perspectives: the identification of predictive biomarkers of skin phenotype in response to GLP-1 RAs, and the development of dermatological co-treatment strategies for patients at greater aesthetic risk.

Muscle Loss and the SIRT1 Pathway

The rapid weight loss induced by GLP-1 RAs—particularly marked with semaglutide 2.4 mg and tirzepatide at maximal doses—raises relevant clinical questions about body composition. Analysis of trials with semaglutide and tirzepatide suggests that weight loss is predominantly fat mass, with a reduction in lean mass accounting for approximately one-third of total weight loss [4]. The ratio of fat mass to lean mass lost is similar to that observed with bariatric surgery and intensive lifestyle interventions (Look AHEAD study) [4]. A recent experimental study by Xiang et al. explored the molecular mechanisms by which liraglutide and semaglutide protect skeletal muscle from obesity-induced atrophy in C57BL/6J mice fed a high-fat diet (HFD) for 18 weeks [5]. The main findings document that both molecules: (i) reduce body weight and visceral fat while preserving lower limb muscle mass; (ii) improve muscle strength (grip strength) and limb suspension time; (iii) reduce intramuscular lipid infiltration and muscle fiber atrophy as detected by H&E staining; (iv) suppress muscle atrophy markers (Atrogin-1, MuRF-1) and increase myogenic differentiation markers (MyoD, Myogenin) [5]. The identified molecular mechanism is the SIRT1 (Sirtuin 1) pathway, a key regulator of muscle metabolism and antioxidant response. HFD feeding suppresses SIRT1 expression in skeletal muscle; treatment with liraglutide and semaglutide restores SIRT1 and GLUT4 (the main glucose transporter in muscle) expression. Confirmation of the causal role of SIRT1 was obtained using the specific inhibitor EX-527: in the presence of this inhibitor, the protective effects of liraglutide and semaglutide on muscle atrophy and insulin resistance are abolished [5]. These preclinical data offer a possible molecular rationale for GLP-1 RAs protecting muscle quality and function, which in humans, however, coexists with the reduction in lean mass described at the beginning of this paragraph. SIRT1 activation could represent a relevant therapeutic target for mitigating lean mass loss in the context of sarcopenic obesity. However, it is important to emphasize that these data are based on a murine model: translation to humans requires specific clinical studies on body composition using validated DXA or bioimpedance analysis methods. Clinically, the risk of iatrogenic sarcopenia in patients treated with GLP-1 RA requires attention, particularly in elderly patients, those with pre-existing sarcopenia, and those with reduced protein intake. Practical recommendations include: adequate protein intake (≥ 1.2 g/kg/day in elderly patients or those at risk of sarcopenia), encouraging physical activity with a resistance training component, and monitoring body composition with appropriate methods in at-risk patients. Skin complications of diabetesThe skin complications of diabetes—from necrobiosis lipoidal disease to diabetic dermatopathies, from cheiroarthropathy to neuropathic ulcers—largely

depend on the same pathophysiological substrate that determines accelerated skin aging: chronic hyperglycemia with AGE accumulation, reduced dermal microcirculation, fibroblast dysfunction, and impaired wound healing. By reducing HbA1c and AGE levels, GLP-1 RAs may exert a favorable effect on this substrate, improving skin health in diabetic patients. Data on skin microcirculation suggest that GLP-1 RAs may increase dermal microvascular perfusion, with potential benefits for the healing of diabetic skin lesions [30]. However, the reduction of DWAT and inhibition of ADSCs may potentially compromise local tissue repair. The mechanistic network of these opposing effects has not been systematically studied in the specific context of skin complications of T2DM and represents a clinically relevant area of research.

Immunomodulatory Effects on Inflammatory Skin Diseases: Psoriasis and Hidradenitis Suppurativa

In addition to the pro- and anti-aging mechanisms described in the previous sections, a rapidly expanding line of research documents immunomodulatory effects of GLP-1 RAs on specific inflammatory skin diseases, particularly psoriasis and Hidradenitis Suppurativa (HS). A literature review by Paschou et al. summarized the available evidence on these relationships [7].

Psoriasis: Molecular Mechanisms and Clinical Data

Psoriasis shares important pathogenetic mechanisms with T2DM and obesity: low-grade systemic inflammation, insulin resistance, and immune dysfunction constitute a common substrate for the potential involvement of GLP-1 receptors. The activation of Th17 cells and γδ T lymphocytes, with the production of pro-inflammatory cytokines (TNF-α, IL-12, IL-17, IL-23), is central to the pathogenesis of psoriatic disease [7]. Several molecular mechanisms explain the ameliorative effect of GLP-1 RAs on psoriasis. In invariant natural killer T (iNKT) cells, which express GLP-1R, receptor stimulation activates the cAMP/PKA/CREB pathway, which inhibits NF-κB and stimulates the production of the anti-inflammatory cytokine IL-10; GLP-1 RAs also redistribute iNKT cells from the skin to the circulation, reducing their infiltration into psoriatic plaques [7]. A second mechanism involves dermal γδ T cells, the main source of IL-17 in lesions: in a prospective study, exenatide or liraglutide reduced the percentage of γδ T cells in psoriatic biopsies (from 5.9±4.6% to 2.9±3.5%), correlating with PASI improvement [7]. GLP-1 RAs also reduce the levels of SDF-1, a chemokine that recruits CD4+ lymphocytes to the skin, and inhibit the PI3K pathway, limiting the proliferation and migration of immune cells [7]. Clinical evidence, although limited in number, is consistent. In 7 patients with T2DM and psoriasis, liraglutide 1.8 mg for 12 weeks reduced PASI from 15.7±11.0 to 2.2±3.0, with improvement preceding glycemic improvement [7]; In a small RCT of 11 patients, liraglutide reduced IL-23 and IL-17 to a greater extent than standard treatment alone [7]. A placebo-controlled RCT in obese patients with psoriasis without T2DM found no significant difference in PASI, suggesting that the benefit may be greater in the presence of diabetes [7].

Hidradenitis suppurativa

Hidradenitis suppurativa (HS) is a chronic inflammatory disease of the hair follicle with an immune-mediated component (TNF-α, IL-1, IL-12, IL-17, IL-23), in which obesity is the most frequent comorbidity [7]. GLP-1 RAs can act on two levels: body weight reduction, provided it is not too rapid (excess redundant skin can paradoxically worsen the disease), and direct immunoregulatory effects, with inhibition of TNF-α/NF-κB and reduction of IL-17, IL-23, and MCP-1 [7]. Available studies, on limited case series, document favorable responses: in 14 obese patients with HS, liraglutide 3 mg/day for 3 months improved the Hurley score, DLQI, and systemic inflammatory markers; In a cohort of 30 patients treated with semaglutide (median 8.2 weeks), the DLQI decreased from 13 to 9; marked responses have also been described in individual cases treated with liraglutide and tirzepatide [7].

Clinical implications and research perspectives

This evidence is of practical relevance: in patients with T2DM or obesity and psoriasis or HS, choosing a GLP-1 RA may offer an additional dermatological benefit, and communicating these data to dermatologists, who do not prescribe GLP-1 RA in daily practice, constitutes a specific area of Medical Affairs strategy. However, adequately sized RCTs with primary dermatological endpoints (PASI 75, DLQI, Hurley Stage) are needed to distinguish the contribution of weight loss from the direct immunological one [7].

Predictive Factors for Discontinuation and Stratification Model

Analysis of Discontinuation Rates in Updated Real-World Evidence

Early discontinuation of GLP-1 RAs represents the main obstacle to translating the benefits demonstrated in clinical trials into sustainable clinical outcomes in real-world practice. The narrative review by Thomsen et al., which summarized the available real-world evidence on populations with obesity or T2DM, provides the most up-to-date and comprehensive characterization of the phenomenon [2]. For patients treated for T2DM in European settings, persistence on therapy at one year is approximately 80%, with better results in Northern European countries compared to the USA (where it drops to 50%) and Israel [2]. For patients treated for obesity alone—the new major indication for GLP-1 RAs—the situation is much more critical. A US study of 4,066 obese people without T2DM who started any GLP-1 RA documented only 32% persistence at one year; Three additional US studies report 35–50% persistence at one year [2]. Particularly illuminating is a Danish cohort study of 110,749 semaglutide initiators for weight management: 50% were still on treatment after one year, but—equally relevant—only 10% followed the recommended 4-weekly dose escalation protocol, and only 12% reached the target dose of 2.4 mg by the fifth prescription [2]. One in three patients continued on the 1.0 mg dose for extended periods, well below the exposure required for maximal weight-metabolic efficacy. Pivotal trials, by comparison, document 65–85% persistence, with 13–27% of patients discontinuing due to adverse events in the active arms [2]. The gap between trials and RWE reflects not only differences in tolerability but also contextual factors: restrictive patient selection in trials excludes the more complex comorbidities present in real-world practice; structured educational support and the fact that the drug is free in trials promote adherence; and easy affordability—without insurance, the monthly cost of semaglutide exceeds $1,000 in the US—represents an insurmountable barrier for many patients. More granular data on discontinuation in randomized clinical trials are provided by a meta-analysis of 60 RCTs reported in the review by Cardoso et al., which documents that discontinuation due to adverse events is significantly more frequent with GLP-1 RAs compared to placebo over a median follow-up of 25 months (12.7% versus 9.2%; HR 1.51; 95% CI: 1.18-1.94), while the overall frequency of serious adverse events is not increased (HR 0.95; 95% CI: 0.90-1.01) [6]. Single-molecule analysis highlights significant heterogeneity: injectable semaglutide has the highest odds ratio for discontinuation (OR 2.61; 95% CI: 1.56-4.37), followed by exenatide (OR 2.39; 95% CI: 1.14-4.98) and liraglutide (OR 2.15; 95% CI: 1.26-3.69); dulaglutide does not show a significantly different discontinuation rate from placebo (OR 1.41; 95% CI: 0.86-2.29), a fact that distinguishes it from other long-acting agents and may guide therapeutic choice in patients at greater risk of gastrointestinal intolerance [6]. In real-world evidence, the variability in discontinuation rates is even more marked: available data show rates ranging from 21.2% to 45.2%, with a study conducted in the UK National Health System—where universal coverage eliminates confounding related to financial access—reporting a discontinuation rate of 31.2% one year after starting treatment [6]. This variability is partly attributable to different definitions of discontinuation and different capture methods in

administrative sources: prescription gaps of 90–180 days are commonly used to infer discontinuation, but can also capture temporary interruptions due to supply issues or planned titrations [6].

Socioeconomic and Clinical Determinants of Treatment Discontinuation

Analysis of the determinants of discontinuation reveals a worrying pattern of health inequalities. Scandinavian observational data (unpublished data, reported in the review by Thomsen et al.) indicate that early discontinuation of semaglutide for weight loss is associated with low income and residence in socioeconomically disadvantaged areas, mental health problems, multiple comorbidities, and young age [2]. Paradoxically, these characteristics coincide with populations that bear the greatest burden of obesity-related disease and would benefit most from effective treatment. Lower education, lower income, older age, and ethnic minority background are associated with a 10–50% lower likelihood of receiving a GLP-1 RA—compared to other antidiabetic drugs—in analyses of US databases [2]. This finding suggests that barriers to initial access and persistence to therapy have structural dimensions that go well beyond individual tolerability. Clinically, identifiable causes of discontinuation include: GI adverse effects (estimated 30–50% of early dropouts); subjective perception of ineffectiveness in the first few months; Logistical difficulties related to self-injection; unaffordable costs without insurance coverage; and lack of structured educational support. In patients with T2DM, therapeutic motivation is strengthened by the need for glycemic control, which explains the higher persistence rates compared to patients with obesity alone.

Clinical and genetic predictors of response to GLP-1 RAs: towards precision medicine

The review by Cardoso et al. summarizes the available evidence on the heterogeneity of the therapeutic effect of GLP-1 RAs, identifying clinical and genetic factors that systematically modulate the response to key outcomes [6]. This dimension is crucial not only for understanding discontinuation, but also for guiding personalized prescription. Regarding glycemic response (reduction in HbA1c), the most robust clinical predictors are: higher baseline HbA1c (greater effect in those starting from lower values—a pattern common to all hypoglycemic agents); female gender, with a greater glycemic response in women than in men, partly attributable to higher circulating concentrations of GLP-1 RAs at the same dose; shorter duration of diabetes, which is associated with a better response regardless of baseline HbA1c; and better residual β-cell function, assessed by fasting C-peptide and clinical markers such as the ability to reduce HbA1c with diet alone—since GLP-1 RAs act as enhancers of glucose-dependent insulin secretion and require adequate β-cell functional reserve. Asian ethnicity is associated with a greater glycemic response than non-Asian ethnicities, likely related to lower baseline BMI [6]. For weight response, the most consistent predictors are: higher baseline BMI (greater absolute weight loss); female gender; younger age; and lower baseline HbA1c (apparently paradoxically, patients with higher glycemic levels show less weight loss, possibly due to alterations in appetite regulation, the microbiome, and susceptibility to drug therapy related to insulin deficiency) [6]. Metabolic syndrome features such as hypertension, fatty liver disease, and obstructive sleep apnea appear to be associated with a reduced weight response, independent of other factors [6]. For discontinuation, predictors identified in an observational study conducted in the UK National Health System include: older age, longer duration of diabetes, and a history of previous metformin discontinuation due to gastrointestinal intolerance. Women have higher discontinuation rates at 3 and 6 months after starting therapy, but comparable rates to men at 12 months. South Asian and Black ethnicities show higher discontinuation rates than White ethnicities. A BMI less than 30 kg/m² and an eGFR less than 75 mL/min/1.73 m² are associated with a higher risk of discontinuation [6]. These predictors,

documented for overall discontinuity, are only partially included in the score in section 8.4 (gastrointestinal intolerance to metformin and renal function), as the score is specifically oriented to the risk of gastrointestinal intolerance. The remaining predictors (gender, age, diabetes duration, ethnicity, BMI) will be collected as covariates in the RE-START study to verify whether they improve the model's predictive capacity. On a genetic level, rare variants of the ARRB1 gene (arrestin-β1) have been associated with a reduction in HbA1c of 2.2 mmol/mol greater than in non-carriers, while variants of the PAM gene appear to reduce the glycemic response to liraglutide and exenatide **[6].** A study of 6,750 individuals in 9 biobanks found no association between polygenic risk scores for T2DM or BMI and weight loss induced by GLP-1 RAs **[6].** Using routine clinical data, a Bayesian model developed on 27,319 individuals in UK primary care identified a clinically relevant glycemic benefit from GLP-1 RAs in 20.3% of patients, superior to that of SGLT-2 inhibitors **[6].**

The predictive model: risk stratification score (0-10 points)

The core proposal of this work is a predictive model that converts risk factors for gastrointestinal intolerance into a quantitative and operationally usable clinical tool. The proposed score (0-10 points) is constructed from four categories of clinical variables with varying predictive weights, operationally defined based on standard diagnostic criteria. It is an expert-based score: the weights assigned to the variables and the risk thresholds are proposed a priori, based on the pathophysiological rationale and evidence discussed in the previous chapters, and are not derived from an estimate based on cohort data. For this reason, the tool requires prospective validation (chapter 9) before any use in clinical practice.

Parameter 1 — Diabetic Autonomic Neuropathy and Gastroparesis (0-4 points): This parameter receives the greatest weight, due to the pathophysiological rationale discussed in section 3.3. A diagnosis of overt DAN or instrumentally confirmed gastroparesis (labeled meal scintigraphy, C-octanoic acid breath test) yields the maximum score (4 points). The presence of symptoms suggestive of gastrointestinal autonomic dysfunction (chronic early satiety, postprandial fullness, nausea unrelated to organic causes) without instrumental confirmation yields 2 points. The absence of any clinical or instrumental signs yields 0 points.

Parameter 2 — Chronic Kidney Disease (0-2 points): The presence of CKD stages 3b-4 (eGFR 15-44 mL/min/1.73 m²) yields 2 points. This choice reflects both the higher frequency of EA-GI documented in patients with moderate CKD (PIONEER 5) **[3]** and the pharmacokinetic implications for some molecules in this class. CKD stage 3a (eGFR 45-59 mL/min/1.73 m²) scores 1 point. Preserved renal function (eGFR ≥ 60 mL/min/1.73 m²) scores 0 points.

Parameter 3 — History of gastrointestinal intolerance to metabolic drugs (0-2 points): A documented history of discontinuation of metformin, acarbose, or other hypoglycemic drugs due to gastrointestinal adverse events—coded in the medical record or noted in the history— scores 2 points. A history of GI AE requiring dose adjustments without discontinuation scores 1 point. No relevant history: 0 points.

Parameter 4 — Reduced basal gastric emptying rate (0-2 points): A slowing of gastric emptying documented by instrumentation (scintigraphy, breath test) that does not meet the diagnostic criteria for gastroparesis scores 2 points. The presence of uninvestigated chronic dyspeptic symptoms is worth 1 point. Absence of symptoms and/or negative investigations: 0 points. To avoid double counting, the same finding or symptom cannot be attributed to multiple parameters: if a score has been assigned in Parameter 1 (confirmed gastroparesis or symptoms suggestive of gastrointestinal autonomic dysfunction), Parameter 4 only considers additional instrumental findings not already counted **(Table 4).**

Score	Risk level	Therapeutic recommendation
0-3	LOW	Standard titration according to the technical data sheet. Follow-up at 4 and 12 weeks.
4-6	MODERATE	Slow titration: duration doubled at each minimum dose. Nutritional support. Biweekly follow-up during titration.
7-10	HIGH	Pre-therapy gastroenterological screening. Evaluate pre-treatment with a prokinetic. Ultra-slow titration. Weekly monitoring for the first month.

Table 4: Risk stratification score for GI intolerance to GLP-1 RAs and associated treatment recommendations.

Decision-making algorithm and implications for the M The decision-making algorithm derived from the score is structured in three phases: (i) systematic collection of clinical variables before starting therapy, integrated into the prescreening visit's anamnesis form; (ii) score calculation and risk level assignment; (iii) customization of the titration protocol and monitoring plan. From a Medical Affairs strategy perspective, this model allows for a shift from generic communication of adverse effects to a personalized approach, which identifies at-risk patients before a tolerability crisis occurs. The underdosing documented in the RWE (section 8.1) reflects not only poor individual compliance, but also an inadequate patient support system for drugs with such a complex tolerability curve. The implementation of a score-based Patient Support Program (PSP)—with proactive contact from specialized nurses or clinical pharmacists during the weeks of greatest risk—allows early detection of intolerance signals and interventions (dietary modifications, motivational support, and possible temporary dosage reduction) before the patient decides to discontinue therapy. A PSP model that explicitly addresses socioeconomic barriers—reimbursement information, simplified access procedures, and support for populations with low health literacy—would be consistent with the data on inequality of access documented in the RWE.

Pilot Study Proposal: RE-STart(REal-world STratification to Adherence in GLP-1-RA Therapy)

Rationale and Objectives

The RE-START pilot study proposal arises from the need to prospectively validate the risk stratification model described in Chapter 8. The current literature on GLP-1 RA discontinuation is based primarily on retrospective analyses of administrative databases, summarized in the narrative review by Thomsen et al. [2], which—while valuable for quantifying the phenomenon—do not allow for evaluating the effectiveness of personalized preventive interventions or prospectively identifying at-risk patients prior to the discontinuation event. The primary objective is to demonstrate that the systematic application of the risk stratification score, combined with a personalized titration protocol and a structured PSP, reduces the early discontinuation rate by 25% in relative terms compared to standard practice at 6 months after starting therapy.

Study Design, Population, and Intervention

RE-START is proposed as a pragmatic, prospective, multicenter interventional study, with cluster randomization at the prescribing center level, within the Italian National Health System (NHS). Because center allocation to the management strategy is randomized, the study qualifies as an interventional study and requires approval from the relevant Ethics Committee.

— **Design**: Pragmatic, prospective, multicenter interventional study, cluster randomized (10-15 NHS diabetes and internal medicine centers).

— **Population**: Approximately 500 patients with T2DM or obesity (BMI ≥ 30 kg/m²), eligible for initiation of a GLP-1 RA for the first time. This estimate is preliminary; the final sample size will be determined with a formal statistical power calculation that takes into account the intracluster correlation coefficient (ICC). The analysis will be stratified by indication (T2DM versus obesity) and by drug access modality (reimbursed by the National Health Service or paid by the patient), a potentially determining factor for persistence. Exclusion criteria: severe symptomatic gastroparesis, CKD stage 5 or dialysis, history of MTC or MEN2, history of acute pancreatitis in the last 12 months.

— Arm A (intervention centers): systematic application of the pre-therapy score; personalized titration based on risk level; dedicated PSP with proactive contacts at 2, 4, 8, 12, and 24 weeks.

— Arm B (control centers): standard clinical practice according to current ADA/EASD guidelines.

Endpoints and expected impactedical Affairs Strategy

The primary endpoint is the rate of persistence in therapy at 6 months, calculated as the proportion of patients who continue therapy with the GLP-1 RA without interruptions exceeding 4 consecutive weeks; achievement of the target dose is assessed separately as a secondary endpoint. Secondary endpoints include: discontinuation rate at 3 months; proportion of patients reaching the target dose within 6 months; change in HbA1c at 6 months; body weight reduction at 6 months; health-related quality of life (EQ-5D-5L) at 3 and 6 months; frequency and severity of AE-GI (NCI-CTCAE scale); and cost per patient-month on therapy (health-economic analysis). The expected impact extends beyond validation of the predictive model. A study conducted in centers within the Italian National Health System with unselected patients would provide value-based healthcare evidence directly applicable to regulatory authorities (AIFA) and HTA bodies, demonstrating that optimizing the therapeutic start-up phase—addressing both clinical and educational barriers—reduces pharmaceutical waste and improves clinical outcomes.

Conclusions

This review addressed the complexity of the safety profile of GLP-1 RAs with the aim of constructing a systematic map of documented adverse effects, analyzing their pathophysiological mechanisms in depth, and identifying the risk factors that modulate their clinical expression, with particular attention to their impact on therapeutic discontinuation. GLP-1 RAs remain drugs with an overall favorable safety profile. The meta-analysis by Giugliano et al. in 60,080 patients, it documents 14% reductions in MACE, 13% reductions in cardiovascular mortality, and 12% reductions in all-cause mortality **[1];** SELECT and FLOW extend this evidence to obese non-diabetic patients with cardiovascular disease and to patients with T2DM and moderate-to-severe CKD **[10,11].** Among the emerging safety signals, worthy of attention are biliary disease, with a relative risk of 2.29 in obesity studies **[2];** NAION associated with semaglutide (HR 2.19-2.81 in Scandinavian studies **[19,20]),** recognized by the EMA as a very rare side effect **[27];** and intestinal obstruction, which requires confirmation in more methodologically robust studies; and drug interactions resulting in slowed motility, with simulated increases in AUC of 64-205% for rosuvastatin, valsartan, and dabigatran **[9].** Skin effects—from the "Ozempic face," in which pro- and anti-aging mechanisms coexist **[30]**, to the immunomodulatory effects on psoriasis and hidradenitis suppurativa **[7]**—and muscle protection mediated by the SIRT1 pathway in the murine model **[5]** represent research frontiers that remain largely unexplored clinically. Early discontinuation—32-50% in the first year in the obese population **[2]**—and

frequent underdosing remain the main obstacle to translating demonstrated benefits into real-world outcomes. The proposed stratification score (0-10 points) aims to offer a simple-to-use tool for early identification of patients at greatest risk of intolerance; its prospective validation through the RE-START study represents the next step.

Ultimately, optimizing adherence to GLP-1 RAs is a public health and equity imperative: populations with the greatest disease burden—low income, mental health problems, multiple comorbidities—are also those with the highest discontinuation rates **[2],** and addressing this inequity is the task of Medical Affairs strategy as much as health policy.

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