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# FUTURE CHALLENGES AND EMERGING SAFETY CONCERNS OF GLP-1 RECEPTOR AGONISTS, DUAL INCRETIN AGONISTS, AND SGLT2 INHIBITORS

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**Abstract**

Three drug classes developed primarily to lower blood glucose, namely sodium–glucose cotransporter-2 (SGLT2) inhibitors, glucagon-like peptide-1 receptor agonists (GLP-1 RAs), and the dual glucose-dependent insulinotropic polypeptide (GIP)/GLP-1 receptor agonist tirzepatide, have been redefined by a sequence of large randomized controlled trials (RCTs) as cardiovascular, kidney and metabolic-protective therapies. With that efficacy now well established, attention is shifting to the questions that long-term, population-scale use raises: emerging safety signals, the durability of benefit, and the gaps that current randomized evidence has yet to close. This review takes the established RCT efficacy base as its starting point and then focuses on the future challenges and emerging safety concerns of these classes: class-specific adverse-event signals (gastrointestinal intolerance, euglycemic ketoacidosis, genital and necrotizing soft-tissue infection, lower-limb amputation, non-arteritic anterior ischemic optic neuropathy, lean-mass loss, and biliary events), cross-cutting issues (perioperative aspiration risk from delayed gastric emptying, and weight regain after discontinuation), the unmet evidence needs for combination therapy, emerging triple agonists, and hard-endpoint confirmation.

## 1. Introduction

The 2008 regulatory requirement for dedicated CVOTs (Cardiovascular Outcome Trial) in type 2 diabetes (T2D), introduced to establish cardiovascular safety, instead generated the randomized evidence that reframed diabetes pharmacotherapy around organ protection [1]. Earlier intensive glucose-lowering trials (ACCORD, ADVANCE, VADT) had shown that lowering HbA1c reduced some microvascular endpoints but had limited or delayed macrovascular effect [2–4]. Against that backdrop, EMPA-REG OUTCOME (2015) was the first trial to show that a glucose-lowering drug reduced cardiovascular events, and a cascade of RCTs followed [5]. The first part of this review briefly surveys that randomized efficacy base across SGLT2 inhibitors, GLP-1 RAs, and dual incretin agonists. As these agents move from trial populations into tens of millions of patients, increasingly for obesity rather than diabetes, often lifelong, and frequently in people with few competing risks, the relevant questions are no longer whether they work but how safe they are at scale, how durable their benefit is, and where the randomized evidence still falls short. The later sections therefore examine the emerging safety signals, the cross-cutting practical challenges, and the knowledge gaps that will shape the next phase of clinical use.

## 2. SGLT2 Inhibitors

### 2.1 Cardiovascular outcome trials

EMPA-REG OUTCOME randomized 7,020 patients with T2D and established atherosclerotic cardiovascular disease (ASCVD) to empagliflozin or placebo (median follow-up 3.1 years). The three-point MACE (Major Adverse Cardiovascular Events) composite showed a 38% relative reduction in cardiovascular death; hospitalization for heart failure (HHF) fell by 35% and all-cause death by 32% [5]. The CANVAS Program (canagliflozin) reduced MACE but identified an excess of lower-limb amputation [6]. DECLARE-TIMI 58 (dapagliflozin) with 17,160 patients, the broadest, most primary-prevention–weighted population did not significantly reduce MACE but did reduce the co-primary composite of cardiovascular death or HHF [7]. VERTIS CV with ertugliflozin met noninferiority but was neutral for MACE superiority, while still reducing HHF [8]. Across these CVOTs, the HHF and renal signals were the most consistent and emerged early.

### 2.2 Heart failure trials

Dedicated HF RCTs confirmed and extended the signal. DAPA-HF (dapagliflozin; 4,744 patients with HF and reduced ejection fraction [HFrEF]) reduced worsening HF or cardiovascular death (HR 0.74; 95% CI 0.65–0.85), with benefit irrespective of diabetes [9]. EMPEROR-Reduced (empagliflozin; 3,730 HFrEF patients) showed a concordant result (HR 0.75; 95% CI 0.65–0.86) [10]. Then benefit was established in preserved ejection fraction cases which were historically untreatable pharmacologically by EMPEROR-Preserved (empagliflozin) and DELIVER (dapagliflozin) [11,12]. SOLOIST-WHF (sotagliflozin; 1,222 patients) showed benefit when initiated during or shortly after a worsening-HF admission [13]. SGLT2 inhibitors are now foundational therapy across the entire HF spectrum, regardless of diabetes status.

### 2.3 Kidney trials

Three large renal-outcome RCTs established the class as renoprotective. CREDENCE (canagliflozin) was stopped early for overwhelming demonstration of efficacy reducing the primary composite of end-stage kidney disease, doubling of serum creatinine, or renal/cardiovascular death [14]. DAPA-CKD (dapagliflozin) reduced its primary composite, extending benefit to non-diabetic CKD [15]. EMPA-KIDNEY (empagliflozin) and SCORED (sotagliflozin) reduced kidney-disease progression or cardiovascular death [16],[17].

**Table 1. Pivotal SGLT2 inhibitor RCTs**

| Trial | Agent | N | Population | Primary endpoint | Key result (HR, 95% CI) |
|---|---|---|---|---|---|
| EMPA-REG OUTCOME (5) | Empagliflozin | 7,020 | T2D + ASCVD | 3P-MACE | 0.86 (0.74–0.99) |
| CANVAS Program (6) | Canagliflozin | 10,142 | T2D + high CV risk | 3P-MACE | 0.86 (0.75–0.97) |
| DECLARE-TIMI 58 (7) | Dapagliflozin | 17,160 | T2D, broad risk | MACE / CV death or HHF | MACE 0.93 (0.84–1.03); CV death/HHF 0.83 (0.73–0.95) |

| Trial | Agent | N | Population | Primary endpoint | Key result (HR, 95% CI) |
|---|---|---|---|---|---|
| DAPA-HF (9) | Dapagliflozin | 4,744 | HFrEF (± T2D) | Worsening HF or CV death | 0.74 (0.65–0.85) |
| EMPEROR-Reduced (10) | Empagliflozin | 3,730 | HFrEF (± T2D) | CV death or HHF | 0.75 (0.65–0.86) |
| EMPEROR-Preserved (11) | Empagliflozin | 5,988 | HFpEF/HFmrEF | CV death or HHF | 0.79 (0.69–0.90) |
| DELIVER (12) | Dapagliflozin | 6,263 | HFpEF/HFmrEF | Worsening HF or CV death | 0.82 (0.73–0.92) |
| SOLOIST-WHF (13) | Sotagliflozin | 1,222 | T2D + recent worsening HF | CV death, HHF, urgent HF visit | 0.67 (0.52–0.85) |
| CREDENCE (14) | Canagliflozin | 4,401 | T2D + albuminuric CKD | ESKD, Cr doubling, renal/CV death | 0.70 (0.59–0.82) |
| DAPA-CKD (15) | Dapagliflozin | 4,304 | CKD ± T2D | eGFR decline, ESKD, renal/CV death | 0.61 (0.51–0.72) |
| EMPA-KIDNEY (16) | Empagliflozin | 6,609 | Broad CKD | Kidney progression or CV death | 0.72 (0.64–0.82) |

## 3. GLP-1 Receptor Agonists

### 3.1 Cardiovascular outcome trials

The GLP-1 RA CVOTs spanned neutral and positive results. ELIXA (lixisenatide) was neutral (HR 1.02) [18], and EXSCEL (extended-release exenatide) narrowly missed superiority [19]. Superiority was demonstrated by LEADER (liraglutide) [20] and SUSTAIN-6 (subcutaneous semaglutide) [21]. REWIND (dulaglutide) extended benefit to a primary-prevention–weighted population [22], and HARMONY Outcomes (albiglutide) confirmed a class effect [23]. PIONEER 6 established the cardiovascular safety of oral semaglutide (HR 0.79; 95% CI 0.57–1.11) [24], and AMPLITUDE-O extended the signal to the exendin-based efpeglenatide (HR 0.73; 95% CI 0.58–0.92) [25].

### 3.2 Obesity without diabetes: SELECT

SELECT randomized 17,604 patients aged ≥45 years with established cardiovascular disease and a BMI ≥27 kg/m² but no diabetes to

semaglutide 2.4 mg or placebo (mean follow-up ~40 months). The primary three-point MACE composite was reduced [26]. SELECT decoupled GLP-1 RA cardiovascular benefit from glucose lowering and supported a cardiovascular indication in obesity; prespecified analyses suggested favorable kidney effects and sustained ~10% weight loss to four years [26,27].

### 3.3 Kidney protection: FLOW

FLOW was the first RCT to test a GLP-1 RA against hard kidney endpoints in established diabetic CKD. In 3,533 patients with T2D and CKD on background renin–angiotensin system blockade, once-weekly semaglutide 1.0 mg reduced the primary composite of major kidney events and kidney/cardiovascular death; the trial stopped early for efficacy. Secondary outcomes favored semaglutide, including a slower annual eGFR decline, an 18% reduction in MACE (HR 0.82; 95% CI 0.68–0.98), and a 20% reduction in all-cause death [28].

### 3.4 HFpEF: the STEP-HFpEF program

STEP-HFpEF (529 patients without diabetes) and STEP-HFpEF DM (616 patients with diabetes) randomized patients with obesity-related HFpEF to semaglutide 2.4 mg or placebo. Both improved the dual primary endpoints of symptoms/physical limitation (KCCQ clinical summary score) and body weight, with concordant improvement in 6-minute walk distance and inflammatory markers [29,30]. These trials were powered for symptom and functional rather than hard cardiovascular endpoints.

### 3.5 MASH: ESSENCE

ESSENCE, an ongoing phase 3 RCT, randomized 1,197 patients with biopsy-defined MASH and fibrosis stage 2–3 to semaglutide 2.4 mg or placebo for 240 weeks. A prespecified 72-week interim analysis of the first ~800 patients reported resolution of steatohepatitis without worsening fibrosis in 62.9% versus 34.3% with placebo, and superior fibrosis improvement without worsening steatohepatitis [31].

### 3.6 Oral therapy: SOUL

SOUL randomized 9,650 patients with T2D and ASCVD, CKD, or both to oral semaglutide or placebo. The primary three-point MACE composite was reduced making oral semaglutide the first oral GLP-1 RA to show cardiovascular efficacy; a prespecified analysis indicated consistent benefit regardless of background SGLT2 inhibitor use [32,33].

**Table 2. Pivotal GLP-1 receptor agonist RCTs**

| Trial | Agent | N | Population | Primary endpoint | Key result (HR, 95% CI) |
|---|---|---|---|---|---|
| ELIXA (18) | Lixisenatide | 6,068 | T2D, post-ACS | 4P-MACE | 1.02 (0.89–1.17) |
| EXSCEL (19) | Exenatide QW | 14,752 | T2D ± CVD | 3P-MACE | 0.91 (0.83–1.00) |
| LEADER (20) | Liraglutide | 9,340 | T2D + high CV risk | 3P-MACE | 0.87 (0.78–0.97) |
| SUSTAIN-6 (21) | Semaglutide SC | 3,297 | T2D + high CV risk | 3P-MACE | 0.74 (0.58–0.95) |

| Trial | Agent | N | Population | Primary endpoint | Key result (HR, 95% CI) |
|---|---|---|---|---|---|
| REWIND (22) | Dulaglutide | 9,901 | T2D (mostly primary prevention) | 3P-MACE | 0.88 (0.79–0.99) |
| HARMONY Outcomes (23) | Albiglutide | 9,463 | T2D + CVD | 3P-MACE | 0.78 (0.68–0.90) |
| PIONEER 6 (24) | Oral semaglutide | 3,183 | T2D + high CV risk | 3P-MACE (NI) | 0.79 (0.57–1.11) |
| AMPLITUDE-O (25) | Efpeglenatide | 4,076 | T2D + CVD/CKD | 3P-MACE | 0.73 (0.58–0.92) |
| SELECT (26) | Semaglutide 2.4 mg | 17,604 | Obesity + CVD, no diabetes | 3P-MACE | 0.80 (0.72–0.90) |
| FLOW (28) | Semaglutide 1.0 mg | 3,533 | T2D + CKD | Major kidney + kidney/CV death | 0.76 (0.66–0.88) |
| STEP-HFpEF (29) | Semaglutide 2.4 mg | 529 | HFpEF + obesity, no diabetes | KCCQ-CSS, body weight* | Both improved vs placebo* |
| STEP-HFpEF DM (30) | Semaglutide 2.4 mg | 616 | HFpEF + obesity + T2D | KCCQ-CSS, body weight* | Both improved vs placebo* |
| ESSENCE (31) | Semaglutide 2.4 mg | 1,197 | MASH, fibrosis F2–3 | Steatohepatitis resolution; fibrosis* | 62.9% vs 34.3% resolution* |
| SOUL (32) | Oral semaglutide | 9,650 | T2D + ASCVD/CKD | 3P-MACE | 0.86 (0.77–0.96) |

*Symptom/functional or histologic endpoints rather than a hazard ratio for hard cardiovascular events; effect estimates should be verified against the primary publication.

## 4. Dual Incretin Agonists

### 4.1 Metabolic-efficacy trials: SURPASS and SURMOUNT

Tirzepatide, the first dual GIP/GLP-1 receptor agonist, was studied for glycemia and weight in the SURPASS phase 3 program. In the head-to-head SURPASS-2 trial, tirzepatide produced larger reductions in HbA1c and body weight than semaglutide 1 mg [34]. In obesity without diabetes, SURMOUNT-1 achieved mean weight loss of ~20.9% at the highest dose over 72 weeks [35]. This unprecedented weight efficacy motivated dedicated outcome trials.

### 4.2 Cardiovascular outcomes: SURPASS-CVOT

SURPASS-CVOT was the first cardiovascular outcome trial of a dual incretin agonist and used

an active comparator. In 13,299 patients with T2D and established ASCVD, tirzepatide was compared with dulaglutide, a GLP-1 RA with proven cardiovascular benefit. Tirzepatide met the prespecified noninferiority criterion for three-point MACE, with numerically fewer events and greater reductions in HbA1c, weight, blood pressure, and lipids, plus favorable renal signals [36]. Because the comparator is itself cardioprotective, the trial strongly validates tirzepatide's cardiovascular benefit while reflecting the difficulty of placebo-controlled designs in high-risk diabetes.

### 4.3 HFpEF: SUMMIT

SUMMIT randomized 731 patients with HFpEF and obesity to tirzepatide or placebo. Tirzepatide reduced the composite of cardiovascular death or worsening HF events and improved KCCQ health status and 6-minute walk distance; mechanistic substudies reported reductions in left-ventricular mass, epicardial/paracardiac adipose tissue, congestion, and inflammation [37–39]. SUMMIT moved the obesity-HFpEF paradigm from symptom benefit (STEP-HFpEF) toward event reduction.

### 4.4 MASH: SYNERGY-NASH

The phase 2 SYNERGY-NASH RCT reported dose-dependent resolution of steatohepatitis without worsening fibrosis with tirzepatide, supporting further development in metabolic liver disease [40].

### 4.5 Emerging agents

Beyond dual agonism, the triple GIP/GLP-1/glucagon receptor agonist retatrutide produced substantial mean weight loss of ~24% at the highest dose in a phase 2 obesity RCT [41], and the amylin–GLP-1 combination cagrilintide–semaglutide (CagriSema) has shown deep weight loss in randomized trials [42].

**Table 3. Dual/triple incretin agonist RCTs**

| Trial | Agent | N | Population | Primary endpoint | Key result |
|---|---|---|---|---|---|
| SURPASS-2 (34) | Tirzepatide vs semaglutide 1 mg | 1,879 | T2D | HbA1c change (NI/superiority) | Superior HbA1c & weight reduction |
| SURMOUNT-1 (35) | Tirzepatide | 2,539 | Obesity, no diabetes | % weight change at 72 wk | −20.9% (15 mg) vs −3.1% placebo |
| SURPASS-CVOT (36) | Tirzepatide vs dulaglutide | 13,299 | T2D + ASCVD | 3P-MACE (NI) | HR ≈ 0.92 (noninferior) |
| SUMMIT (37) | Tirzepatide | 731 | HFpEF + obesity | CV death or worsening HF* | HR 0.62 (0.41–0.95)* |
| SYNERGY-NASH (40) | Tirzepatide | 190 | MASH, fibrosis F2–3 | Steatohepatitis resolution* | Dose-dependent benefit* |
| Retatrutide phase 2 (41) | Retatrutide | 338 | Obesity | % weight change* | ~−24% (12 mg)* |

*Surrogate, functional, or phase 2 endpoints; verify exact estimates against the primary publication.

## 5. Combination Therapy: Randomized and Prespecified Evidence

Direct head-to-head outcome RCTs of SGLT2 inhibitor plus incretin combinations are lacking, but prespecified randomized-trial analyses are informative. In FLOW, semaglutide's kidney and cardiovascular benefits were consistent regardless of baseline SGLT2 inhibitor use, and in SOUL the cardiovascular benefit of oral semaglutide was preserved across SGLT2 inhibitor strata [28,33]. These analyses, drawn from within randomized trials, support layering the two mechanisms, though a dedicated combination outcome trial remains an unmet need.

**Table 4. Emerging safety signals and key supporting evidence**

| Class | Signal | Approximate magnitude / evidence | Status / action |
|---|---|---|---|
| GLP-1 RA / incretin (47,48) | GI intolerance (nausea, vomiting, diarrhea) | Nausea up to 32%; discontinuation 6.5% vs 3.6% placebo | On-target; up-titrate slowly |
| GLP-1 RA / incretin (49) | Cholelithiasis | RR 1.46 (55 RCTs); no excess pancreatitis | Class effect; counsel |
| GLP-1 RA (semaglutide) (52-54) | NAION | ~2.2–2.9 vs 0.9–1.2 / 10,000 PY; EMA "very rare" | WHO RMP update May 2025 |
| GLP-1 RA (semaglutide) (21) | Diabetic retinopathy | 3.0% vs 1.8% (SUSTAIN-6) | Linked to rapid glucose drop |
| GLP-1 RA / incretin (55,56) | Lean-mass loss | ~15–60% of weight lost | Muscle-preserving agents in trials |
| SGLT2 inhibitor (57,58) | Euglycemic DKA | RR ~2.6; ~1/26 pt-yr (T1D, sotagliflozin) | Sick-day rules; perioperative hold |
| SGLT2 inhibitor (57,59) | Genital mycotic infection | RR ~2.86–3.75 | Usually mild; treat, continue |
| SGLT2 inhibitor (60) | Fournier's gangrene | 12 FDA cases 2013–2018 (rare) | FDA warning Aug 2018 |
| SGLT2 inhibitor (6,57) | Lower-limb amputation | CANVAS signal; pooled RR ~1.21 (NS) | Foot care; signal not replicated |

| | | | |
|---|---|---|---|
| SGLT2 inhibitor (57) | Volume depletion | RR ~1.14 | Caution: elderly, diuretics |
| All classes (incretins) (61,62) | Perioperative aspiration | Retained contents ↑; aspiration ~0.8% (no excess) | Label warning Nov 2024; society guidance |
| Incretins (obesity) (63-65) | Weight regain on cessation | +14.0% vs −5.5% at 1 yr (SURMOUNT-4) | Long-term therapy; dose-reduction option |

## 6. Mechanistic Note

The RCT benefits appear largely independent of glucose lowering. For SGLT2 inhibitors, proposed mediators include restoration of tubuloglomerular feedback and reduced intraglomerular pressure, natriuresis and plasma-volume reduction, and improved cardiac energetics [43]. For GLP-1 RAs and tirzepatide, anti-atherosclerotic and anti-inflammatory effects, improved endothelial function, and substantial weight and adiposity reduction are leading candidates [44,45]. Mediation analyses within LEADER, SUSTAIN-6, and REWIND suggest HbA1c and albuminuria account for only part of the MACE benefit [46].

## 7. Emerging Safety Concerns: GLP-1 Receptor Agonists and Dual Incretin Agonists

### 7.1 Gastrointestinal intolerance

Gastrointestinal (GI) adverse events are the dominant tolerability limitation of GLP-1 RAs and the dual GIP/GLP-1 agonist tirzepatide, reflecting on-target slowing of gastric emptying and central effects on the area postrema. In the SURPASS and SURMOUNT programs, nausea was reported in up to 32% of participants, diarrhea in 23%, vomiting in 12%, and constipation in 11%; symptoms cluster during initiation and dose escalation and largely subside with time [47]. Across randomized trials, GI events are the leading driver of discontinuation: a pooled analysis reported drug discontinuation in 6.5% of GLP-1 RA recipients versus 3.6% on placebo, with nausea the commonest reason, followed by vomiting and diarrhea [48]. Slow up-titration, dietary modification, and dose individualization remain the principal mitigation strategies.

### 7.2 Biliary, pancreatic, and thyroid signals

A systematic review of 55 double-blind RCTs found an increased risk of cholelithiasis with GLP-1 RAs but no increased risk of cholecystitis, cholangitis, or pancreatitis [49]. Concerns regarding acute pancreatitis and pancreatic cancer, raised by early pharmacovigilance and rodent data, have not been borne out in long-term randomized trials or large meta-analyses [50]. Likewise, the hypothesized risk of medullary thyroid carcinoma based on rodent C-cell tumorigenesis has not been confirmed in humans; an analysis of 93 phase 2/3 trials of liraglutide and semaglutide found no association with thyroid cancer [50,51]. A boxed warning regarding C-cell tumors nonetheless persists in product labeling, and a personal or family history of medullary thyroid carcinoma or MEN2 remains a contraindication.

### 7.3 Non-arteritic anterior ischemic optic neuropathy (NAION)

A newly recognized ocular signal has emerged for semaglutide. A 2024 matched cohort study in a neuro-ophthalmology referral population reported markedly higher NAION rates among semaglutide users, with onset typically within roughly 14 months of initiation [52]. A subsequent Danish–Norwegian registry cohort, comparing semaglutide with SGLT2-inhibitor initiators in T2D, found incidence rates of

NAION of approximately 2.2–2.9 per 10,000 person-years on semaglutide versus 0.9–1.2 on SGLT2 inhibitors [53]. European Medicines Agency recommended adding NAION to the product information as a "very rare" side effect, and the WHO Advisory Committee on Safety of Medicinal Products concluded in May 2025 that the semaglutide risk-management plan should be revised to include NAION as a potential risk [54]. Causality is not established, residual confounding by vascular risk factors is plausible, and the absolute risk is low; nonetheless, vigilance is warranted, particularly in patients with pre-existing vasculopathic optic-disc risk factors.

### 7.4 Diabetic retinopathy

In SUSTAIN-6, diabetic retinopathy complications occurred more often with subcutaneous semaglutide than placebo, an effect attributed largely to the magnitude and rapidity of early glycemic improvement in patients with pre-existing retinopathy rather than a direct retinal toxicity [21]. Gradual glucose lowering and baseline retinal assessment in high-risk patients are reasonable precautions; longer-term randomized retinal-outcome data are awaited.

### 7.5 Lean-mass loss

Because these agents produce weight loss approaching surgical magnitudes, the composition of that loss has become a central concern. Across randomized trials, the lean-mass component of total weight lost ranges widely from roughly 15% or less to as high as 40–60% with heterogeneity driven by population, agent, resistance training, protein intake, age, and measurement method (lean mass on DXA includes organ, bone, and fluid, not muscle alone) [55]. Whether this translates into clinically meaningful loss of muscle function, particularly in older adults at risk of sarcopenia, is unresolved. A second, under-appreciated problem is of measurement. Almost all incretin trials report change in lean body mass (equivalently, fat-free mass) measured by DXA rather than skeletal muscle itself. The two are not interchangeable. Whole-body MRI is the reference standard for skeletal muscle mass, whereas DXA appendicular lean mass (ALM) is an affordable surrogate in which only about 0.46 of total-body lean mass is actually muscle, the remainder being skin, connective tissue, organ, and fluid [56,57]. DXA also cannot distinguish functional muscle from fat-infiltrated muscle (myosteatosis), so a patient can appear to preserve lean mass while muscle quality deteriorates [58]. These limitations are not academic: in resistance-training and myostatin-inhibitor trials, MRI or CT have detected changes in muscle size that DXA lean mass missed entirely, and direct methods such as D3-creatine dilution correlate with strength, falls, and disability in settings where DXA-derived ALM does not [59,60]. The practical consequence is that current claims of "lean-mass sparing" rest on a measure that is only loosely coupled to muscle, and the field's central unanswered question and will require longitudinal studies pairing imaging-based or direct muscle measurement with standardized strength and physical-function endpoints. The question has also catalyzed a class of muscle-preserving co-therapies under randomized evaluation, including the activin-receptor antibody bimagrumab, the selective androgen-receptor modulator enobosarm, and the GLP-1/glucagon agonist pemvidutide[61]. Whether any of these translates preserved mass into preserved function remains to be shown.

## 8. Emerging Safety Concerns: SGLT2 Inhibitors

### 8.1 Euglycemic diabetic ketoacidosis

The most clinically important class-specific hazard of SGLT2 inhibitors is ketoacidosis, which may occur at near-normal blood glucose (euglycemic DKA) and is therefore easily missed. Meta-analytic data indicate an increased risk relative to other glucose-lowering agents, with absolute rates low but concentrated around precipitants such as acute illness, surgery, prolonged fasting, very-low-carbohydrate diets,

and insulin reduction [62]. Risk is higher in type 1 diabetes, where the FDA estimated roughly one additional ketoacidosis case per 26 patient-years of sotagliflozin exposure [63]. Perioperative interruption (typically 3–4 days before major surgery) and a low threshold for ketone testing in symptomatic patients regardless of glucose are the mainstays of prevention.

### 8.2 Genital mycotic and necrotizing soft-tissue infection

Glucosuria predisposes to genital mycotic infections, the most frequent adverse effect of the class; meta-analyses report a roughly 3- to 4-fold increase [62,64]. These are usually mild and managed without discontinuation. Rarely, infection progresses to Fournier's gangrene, a necrotizing fasciitis of the perineum; in August 2018 the FDA issued a warning after identifying 12 post-marketing cases between 2013 and 2018 [65]. Although causality at the population level remains debated, the severity of the outcome warrants patient counseling and prompt evaluation of perineal pain, swelling, or systemic illness.

### 8.3 Lower-limb amputation, volume depletion, and fracture

An excess of lower-limb amputation was observed with canagliflozin in the CANVAS Program, prompting a regulatory warning that was later softened as subsequent trials and meta-analyses did not consistently replicate the signal [6,62]. Osmotic diuresis and natriuresis can produce volume depletion and hypotension, particularly in elderly patients, those on loop diuretics, or those with low baseline blood pressure [62]. A bone-fracture signal also seen in CANVAS has not been confirmed across the class. Attention to foot care, hydration, and concomitant diuretic dosing mitigates these risks.

## 9. Methodological Challenges

### 9.1 Limitations of HbA1c as a glycaemic marker

The shift from glucose lowering to organ protection has not displaced HbA1c as the default glycaemic marker, yet HbA1c is an imperfect measure in precisely the populations these drugs increasingly target. As a function of red-cell lifespan and the rate of haemoglobin glycation, HbA1c is biased by anaemia, haemoglobinopathies, iron deficiency, pregnancy, and liver disease, and it is particularly unreliable in chronic kidney disease: erythropoiesis-stimulating agents falsely lower it, while uraemia-driven carbamylation and metabolic acidosis can falsely raise it [66,67]. The discordance grows as kidney function declines, the correlation between HbA1c and continuous-glucose-monitoring-derived average glycaemia weakens progressively across CKD stages (reported, for example, as $r \approx 0.68$ at stage G3b falling to $r \approx 0.22$ at G5) [68]. HbA1c also conveys nothing about glycaemic variability or the frequency and severity of hypoglycaemia, both of which carry independent prognostic weight. Continuous glucose monitoring metrics, especially time-in-range, are increasingly proposed as complementary or superior measures, and the field's reliance on a single averaged marker is itself a limitation when judging therapies whose benefits are only partly glycaemic [66,67].

### 9.2 Renal surrogates: eGFR slope and albuminuria

Kidney trials increasingly rely on estimated GFR (eGFR) slope and albuminuria as surrogates for the hard endpoint of kidney failure, both because end-stage kidney disease is comparatively rare over trial timeframes and because slopes can be estimated in every participant. Their validity, however, is conditional. Renoprotective agents like renin–angiotensin system inhibitors, finerenone, and SGLT2 inhibitors characteristically produce an early acute "dip" in eGFR followed by a slower chronic decline, so the total slope and the chronic slope can tell different stories and must be interpreted with the drug's haemodynamic effect in mind [69,70]. The NKF–FDA–EMA

workshop endorsed eGFR slope as a surrogate when calculated over 2–3 years, but its reliability is population-dependent, and combining slope with change in albuminuria improves prediction of true outcomes [69,70]. A large individual-participant meta-analysis (186,312 participants across 66 trials) supports the surrogacy of treatment effects on eGFR slope for kidney failure, yet the relationship is not guaranteed for every mechanism, and serum creatinine from which eGFR is derived is itself influenced by muscle mass, a confounder of particular relevance to agents that reduce lean mass [71].

### 9.3 The MACE composite and component heterogeneity

Most cardiovascular outcome trials in this field are built on a three- or four-point major adverse cardiovascular event (MACE) composite, a construct with well-described limitations. There is no standard definition of MACE: the component events vary across trials, frustrating cross-trial comparison, and the components differ in severity, patient relevance, and frequency, so a composite can be driven by softer, more frequent events while obscuring divergent effects on the harder ones [72,73]. This is not hypothetical for these drug classes: GLP-1 receptor agonists act predominantly on atherosclerotic events (myocardial infarction, stroke), whereas SGLT2 inhibitors act predominantly on heart-failure hospitalisation, so a single MACE estimate can dilute a real, mechanism-specific benefit toward the null and risk a false-negative reading [72]. Competing risks, most importantly non-cardiovascular death further complicate interpretation of time-to-first-event composites. Leading trialists have called for MACE to be unpacked into its components and for hierarchical or win-ratio approaches; one influential analysis went so far as to argue the undifferentiated term "MACE" should be retired [72,73].

### 9.4 Interpreting pharmacovigilance and disproportionality signals

Several of the emerging safety concerns reviewed above including the NAION signal and various gastrointestinal and neurological associations originate not in randomized trials but in spontaneous-reporting databases such as the FDA Adverse Event Reporting System, analysed by disproportionality metrics (reporting odds ratio, proportional reporting ratio). These methods are valuable hypothesis generators but have intrinsic limits: they lack a denominator and so cannot estimate incidence or absolute risk; they are subject to reporting and selection bias, which is amplified for drugs under intense media attention. The incretin classes are also vulnerable to confounding by indication and incomplete clinical detail [74,75]. A disproportionality signal reflects co-reporting, not causation, and reviews have found that a substantial fraction of pharmacovigilance publications over-state their findings using causal language [75]. Such signals should therefore be read as prompts for controlled study rather than as established harms which is a distinction that matters when balancing rare potential risks against the demonstrated organ-protective benefits of these therapies.

## 10. Clinical Challenges

### 10.1 Perioperative aspiration risk

The same delayed gastric emptying that underlies GI tolerability has become a procedural-safety concern since retained gastric contents despite appropriate fasting raise the theoretical risk of pulmonary aspiration during anesthesia and sedation. Endoscopic and ultrasound studies confirm that GLP-1 RA users more often have retained gastric contents, but the translation to clinical aspiration appears modest (0.8%) with no significant excess attributable to GLP-1 RA use [76]. In response, aspiration-risk warnings were added to GLP-1 RA labeling in November 2024, and multiple professional societies (ASA, AGA, and a 2025 multisociety/ADS-ANZCA panel) have issued peri-procedural guidance [77,78]. Recommendations converge on screening all patients for GLP-1 RA/GIP-RA use, considering a clear-liquid diet and withholding the agent

before elective procedures, and using point-of-care gastric ultrasound or rapid-sequence induction when retained contents are suspected; the optimal pre-procedure discontinuation interval remains undefined and is under active study.

### 10.2 Durability of benefit and weight regain after discontinuation

Obesity behaves as a chronic relapsing condition, and the metabolic benefits of incretin therapy depend on continued exposure. In the randomized SURMOUNT-4 trial, participants who reached a mean 20.9% weight loss during a 36-week tirzepatide lead-in and were then switched to placebo regained a mean 14.0% of body weight over the subsequent year, whereas those continuing tirzepatide lost a further 5.5%; 89.5% of continuers versus 16.6% of the placebo group maintained at least 80% of their lead-in weight loss [79]. A post hoc analysis found that 82.5% of those who discontinued regained at least 25% of the weight lost, with corresponding reversal of cardiometabolic improvements [80]. The 2026 SURMOUNT-MAINTAIN trial suggested that reducing to a lower maintenance dose (5 mg) may be a viable alternative to outright discontinuation [81]. These data reframe the agents as long-term, potentially lifelong therapies and raise unresolved questions of cost, access, adherence, and the clinical and psychological management of treatment cessation.

Notably, the pivotal weight-loss and maintenance trials of incretin therapy, including SURMOUNT-4, were not designed to monitor or control for dietary protein intake or resistance exercise, both of which are established determinants of the lean-mass component of weight change. This omission limits interpretation of the body-composition changes observed after dose reduction or discontinuation. Several studies have investigated strategies to mitigate lean body mass loss during treatment with GLP-1 receptor agonists and dual GIP/GLP-1 agonists. The ongoing randomized LEAN-PREP trial is evaluating whether a pragmatic resistance-exercise intervention, increased protein intake, or both can preserve lean mass and physical function in people with obesity initiating semaglutide or tirzepatide therapy [82]. A case series by Tinsley and Nadolsky described three patients who combined resistance training three to five days per week with high protein intake (1.6–2.3 g/kg of fat-free mass per day) and preserved or even gained lean soft tissue—changes of −6.9%, +2.5%, and +5.8%—despite substantial fat loss [83]. Observational data presented at ENDO 2025 likewise suggested that higher protein intake may help protect against semaglutide-associated muscle loss, an effect that may be most relevant in older adults and women, in whom lean-mass loss appears greater [84].

### 10.3 Combination therapy and polypharmacy

Direct head-to-head outcome RCTs of SGLT2-inhibitor plus incretin combinations are still lacking. Prespecified randomized analyses are reassuring. In FLOW, semaglutide's kidney and cardiovascular benefits were consistent regardless of baseline SGLT2-inhibitor use, and in SOUL the cardiovascular benefit of oral semaglutide was preserved across SGLT2-inhibitor strata [28,33]. However, whether the two mechanisms deliver additive hard-outcome benefit, and how their overlapping safety profiles (e.g., volume status, ketoacidosis risk during GI illness) interact in combination, remains formally untested.

### 10.4 Access and affordability

The organ-protective promise of these classes will be realised only to the extent that patients can obtain them, and for most of the world the binding constraint is price rather than evidence. Branded GLP-1 receptor agonists have remained out of reach across low- and middle-income countries (LMICs), where care is often paid out of pocket. This is poised to change: core patents on semaglutide expire during 2026 in roughly ten countries (including India, China, Brazil, Canada, and Türkiye) that together account for about 44% of the world's population and nearly

half of the global obesity burden, opening the door to biosimilar competition led by Indian and Chinese manufacturers (with industry observers anticipating dozens of brands in India alone) [85,86]. Cost-plus analyses based on 2024–25 active-ingredient pricing estimate that generic injectable semaglutide could be produced for roughly US$28–140 per person-year and oral formulations for about US$186–380 per person-year, and project that by the end of 2026 generic injectable semaglutide could be distributed across 160 countries encompassing 69% of the global type 2 diabetes and 84% of the obesity burden [86]. The stakes are concentrated in South Asia: India already carries one of the world's largest diabetes populations and, by one Lancet projection, may have on the order of 440 million overweight or obese people by 2050. Affordability alone, however, is not access. Earlier cost-effectiveness modelling for LMIC formularies found that SGLT2 inhibitors approach common cost-effectiveness thresholds with only modest price reductions (target on the order of US$214–224 per person-year), whereas GLP-1 receptor agonists would require far larger reductions (target near US$199–208 per person-year) to qualify [87]; and microsimulation work suggests that adding either class in LMIC settings could lower insulin requirements and avert disability-adjusted life-years [88]. Translating patent expiry into population health will therefore depend not only on generic pricing but on delivery-device cost, supply-chain capacity, regulatory pathways for biosimilars, and integration into primary-care systems, making equitable access one of the defining challenges of the next phase [89].

## 11. Knowledge Gaps and Ongoing Trials

Key randomized evidence is still awaited. On efficacy, dedicated outcome trials of SGLT2-inhibitor plus incretin combinations are lacking; tirzepatide's benefit on hard heart-failure and kidney endpoints beyond HFpEF and renal surrogates remains unconfirmed; and cardiovascular outcome data for triple agonists (e.g., retatrutide) and amylin-based combinations (e.g., CagriSema) are not yet available. On safety and durability, the principal gaps are longer-term randomized data on weight regain and the reversal of cardiometabolic benefit after discontinuation, on lean-mass and muscle-function loss and whether muscle-preserving co-therapies (bimagrumab, enobosarm, pemvidutide) translate into functional gains, and on the magnitude and mechanism of the semaglutide–NAION association, which to date rests on observational cohorts rather than prospective trials. Whether deeper weight loss with newer agents translates into proportionally greater organ protection, without a proportionate accrual of class-specific harms, is the central question for the ongoing outcome programmes.

## 12. Conclusion

A coherent body of randomized evidence has transformed SGLT2 inhibitors, GLP-1 receptor agonists, and dual incretin agonists from glucose-lowering drugs into organ-protective therapies. SGLT2 inhibitor RCTs anchor heart-failure and CKD management across the diabetes divide; GLP-1 RA trials (notably SELECT, FLOW, and SOUL) extend cardiovascular and renal benefit beyond glycemia and beyond the injectable route; and the dual incretin agonist tirzepatide, validated in SURPASS-CVOT and SUMMIT, has redefined achievable metabolic efficacy. Guideline frameworks (ADA/EASD, cardiology, and nephrology) now recommend these agents on the basis of cardiovascular, HF, and kidney indications rather than HbA1c alone, formalizing the shift from glucose lowering to organ protection. As use broadens to lower-risk and non-diabetic populations, however, the emerging safety agenda (gastrointestinal tolerability and perioperative aspiration risk, the semaglutide–NAION signal, lean-mass loss, euglycemic ketoacidosis and genital infection with SGLT2 inhibitors, and weight regain on discontinuation) will increasingly determine how the net benefit of these therapies is realised in practice. Resolving these questions through adequately powered randomized and

prospective safety studies is the next phase of the field's maturation.

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