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REVIEW

Incretin-Based Polypharmacology and the Redefinition of Cardiometabolic Medicine

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Abstract: Within little more than a decade, agonists of the glucagon-like peptide-1 (GLP-1) receptor have moved from incremental glucose-lowering agents to the most consequential drug class in cardiometabolic medicine. The defining advance has been less a single molecule than a design strategy—rational polypharmacology—in which one peptide, or a fixed co-formulation, engages two or three nutrient-sensing receptors. In this narrative review, built from a documented search of the primary literature and graded by level of evidence, we trace the resulting efficacy ladder from single GLP-1 agonism (≈ 15% mean weight loss with semaglutide) through dual GLP-1/GIP agonism (tirzepatide, ≈ 21%) to triple GLP-1/GIP/glucagon agonism (retatrutide, 24% in phase 2, with provisional phase 3 topline results in the high-20% range). We argue that the class's significance lies less in weight than in convergent benefits across cardiovascular, renal, respiratory and hepatic disease; we synthesize the pivotal outcome trials (SELECT, FLOW, SURPASS-CVOT, SURMOUNT-OSA, SUMMIT, ESSENCE); quantify the principal safety signals in absolute terms; and confront the unresolved problems of durability, tolerability, lean-mass loss, special populations, cost and equitable access. Negative results—most notably the failure of oral semaglutide to slow early Alzheimer's disease in EVOKE and EVOKE+—are given equal weight.

Keywords: incretin polypharmacology, GLP-1 receptor agonists, cardiometabolic medicine, obesity, cardiorenal outcomes

1 Introduction

Obesity and type 2 diabetes are the central drivers of twenty-first-century chronic disease, and for decades pharmacology offered only modest help against them. That changed with the clinical maturation of the incretin hormones—gut peptides, chief among which is glucagon-like peptide-1 (GLP-1), which couple nutrient intake to insulin secretion, satiety, and energy balance [1, 2]. The first GLP-1 receptor agonists were developed as glucose-lowering agents; their capacity to produce double-digit weight loss was, at first, almost incidental. By 2026 that incidental property has reorganized an entire field. A class once measured by fractions of a percentage point of glycated haemoglobin is now measured by its effect on heart attacks, kidney failure, sleep apnoea and all-cause mortality, and tirzepatide was the world's best-selling medicine in 2025 [3].

This Review argues that the pivotal innovation underlying this transformation is conceptual rather than chemical: the deliberate design of single peptides that activate several nutrient-sensing receptors simultaneously. We follow the resulting efficacy ladder, examine the outcome trials that moved incretins from metabolic to cardiovascular, renal and hepatic medicine, and—because honest appraisal is essential for a class subject to extraordinary hype—give equal weight to what these drugs do not yet solve, including trials that failed.

2 Methods: literature search and evidence grading

This is a narrative, not a systematic, review. The procedures below are reported so that the evidence base can be audited and the risk of selective citation judged by the reader.

2.1 Sources and search

PubMed/MEDLINE and ClinicalTrials.gov were searched for records published between 1 January 2005 (first approval of a GLP-1 receptor agonist) and 2026, using the strings in Box 1. Reference lists of included trials and of major reviews were hand-searched. Because several pivotal events post-date peer-reviewed publication, we also consulted US Food and Drug Administration (FDA) prescribing information and safety communications, company filings to the US Securities and Exchange Commission, and sponsor topline announcements; these are identified as such wherever they are used. The search returned records, of which were screened in full text and are cited.

Box 1 | Search strategy

Databases: PubMed/MEDLINE; ClinicalTrials.gov. **Supplementary sources:** FDA labels and safety communications; SEC filings; sponsor press releases (topline data only, graded L3).

Window: 1 January 2005 – [final search date]. **Language:** English. **Final search run:** [date].

PubMed string (agents × design): (semaglutide OR tirzepatide OR retatrutide OR cagrilintide OR orforglipron OR "maridebart cafraglutide" OR liraglutide) AND (randomized controlled trial[pt] OR "phase 3" OR "outcome trial").

Outcome strings: … AND ("cardiovascular outcomes" OR MACE OR "chronic kidney disease" OR "sleep apnea" OR "heart failure" OR steatohepatitis OR MASH OR Alzheimer*).

Safety and durability strings: … AND (discontinuation OR persistence OR "adverse events" OR pancreatitis OR retinopathy OR aspiration OR "lean mass" OR "body composition").

Mechanism strings: (GLP-1 OR GIP OR glucagon) receptor AND (biased agonism OR β-arrestin OR cryo-EM OR "GIP receptor antagonist").

2.2 Eligibility

We included (i) phase 3 randomized controlled trials (RCTs) and cardiovascular, renal, hepatic or other hard-outcome trials of approved or late-stage incretin-based agents in adults; (ii) phase 2 RCTs only for agents without published phase 3 data; (iii) observational analyses only where no randomized comparison exists, and only with an explicit label; and (iv) mechanistic and structural studies for the mechanism section. We excluded non-English records, case reports, trials in type 1 diabetes, compounded or unapproved products, and analyses without a comparator.

2.3 Evidence grading

Each substantive claim is tied to one of five levels, listed for the key trials in Table 1. **L1**: peer-reviewed phase 3 or outcome RCT; **L2**: peer-reviewed phase 2 RCTs, or a substudy or secondary analysis of an RCT; **L3**: sponsors' topline or congress data not yet peer-reviewed; **L4**: observational, real-world or pharmacovigilance data; **L5**: mechanistic, structural or animal data. Commercial figures are analyst projections or company-reported revenue and are not graded as clinical evidence.

2.4 Appraisal and comparability

Formal risk-of-bias scoring was not undertaken. Instead, Table 1 reports design, comparator, population, size and duration for each pivotal trial, and the text flags open-label designs, randomized-withdrawal designs and non-inferiority margins where they bear on interpretation. All pivotal trials cited were industry-funded. Weight-loss figures are reported under the treatment-policy (treatment-regimen) estimand—the effect regardless of adherence—wherever it is available; where only an efficacy (on-treatment) estimate was reported, this is stated. Cross-trial comparisons of weight loss are descriptive only, because populations, durations and estimands differ.

3 The incretin system and the logic of polypharmacology

GLP-1 is released from intestinal L-cells after eating and acts through a class-B G-protein-coupled receptor expressed in pancreatic islets, the central nervous system and the cardiovascular system. Its physiological effects—glucose-dependent insulin secretion, suppression of glucagon, slowing of gastric emptying and reduction of appetite through hypothalamic and hindbrain circuits—make it an almost ideal anti-obesity and anti-diabetic target [1, 2, 4]. Critically, the appetite-suppressing action is largely *central*: GLP-1 receptors on neurons of the hindbrain and

Table 1 Pivotal evidence and evidence level

Trial (ref.)	Comparison	Population	N; duration	Key result	Level
SCALE [5]	Liraglutide 3.0 mg vs pbo	Obesity	3,731; 56 wk	Weight -8.0% vs -2.6%	L1
STEP 1 [6]	Semaglutide 2.4 mg vs pbo	Obesity, no T2D	1,961; 68 wk	Weight -14.9% vs -2.4%	L1
SURMOUNT-1 [7]	Tirzepatide 15 mg vs pbo	Obesity, no T2D	2,539; 72 wk	Weight -20.9% vs -3.1%	L1
SURMOUNT-5 [8]	Tirzepatide vs semaglutide (open-label)	Obesity, no T2D	751; 72 wk	Weight -20.2% vs -13.7%	L1
SURPASS-2 [9]	Tirzepatide vs semaglutide 1 mg	T2D	1,879; 40 wk	Greater HbA1c and weight reduction with tirzepatide	L1
Retatrutide phase 2 [10]	Retatrutide 12 mg vs pbo	Obesity	338; 48 wk	Weight -24.2% vs -2.1%	L2
TRIUMPH-1/-4 [11, 12]	Retatrutide 12 mg vs pbo	Obesity (±knee OA)	80 wk / 68 wk	Weight -28.3% (-25.0% alt. estimand) / -28.7%; topline only	L3
REDEFINE 1 [13]	CagriSema vs pbo	Obesity, no T2D	3,417; 68 wk	Weight -20.4% vs -3.0%	L1
SURMOUNT-4 [14]	Continue vs withdraw tirzepatide	Obesity, after 36-wk lead-in	670; wk 36–88	-5.5% vs +14.0% from wk 36	L1
SELECT [15]	Semaglutide 2.4 mg vs pbo	CVD + overweight, no T2D	17,604; 39.8 mo	MACE HR 0.80 (0.72–0.90)	L1
FLOW [16]	Semaglutide 1.0 mg vs pbo	T2D + CKD	3,533; 3.4 y	Kidney composite HR 0.76 (0.66–0.88)	L1
SURPASS-CVOT [17]	Tirzepatide vs dulaglutide	T2D + ASCVD	13,165; 4 y	MACE HR 0.92 (95.3% CI 0.83–1.01); non-inferior	L1
SURMOUNT-OSA [18]	Tirzepatide vs pbo	OSA + obesity	469; 52 wk	AHI -25 to -29 vs -5 to -6 events/h	L1
STEP-HFpEF [19]	Semaglutide 2.4 mg vs pbo	HFpEF + obesity	529; 52 wk	Improved symptoms and function (KCCQ-CSS)	L1
SUMMIT [20]	Tirzepatide vs pbo	HFpEF + obesity	731; median 104 wk	CV death/worsening HF HR 0.62 (0.41– 0.95)	L1
ESSENCE part 1 [21]	Semaglutide 2.4 mg vs pbo	MASH, F2–F3	800; 72 wk	Resolution 62.9% vs 34.3%; fibrosis 36.8% vs 22.4%	L1
EVOKE/EVOKE+ [22]	Oral semaglutide 14 mg vs pbo	Early Alzheimer's disease	3,808; ≤156 wk	No slowing of progression (negative)	L1
Henney et al. [23]	Tirzepatide vs semaglutide / liraglutide	OSA + T2D (RW)	7,394 per arm (vs sema)	Broad MACE HR 0.86 / 0.58	L4
Rodriguez et al. [24]	GLP-1 RA users	Overweight/obesity (RW)	125,474	1-y discontinuation 46.5% (T2D) / 64.8% (no T2D)	L4

Note: Weight-change outcomes are reported using the treatment-policy (treatment-regimen) estimand unless otherwise specified. HR, hazard ratio; pbo, placebo; wk, weeks; y, years; T2D, type 2 diabetes; CKD, chronic kidney disease; ASCVD, atherosclerotic cardiovascular disease; HFpEF, heart failure with preserved ejection fraction; OSA, obstructive sleep apnoea; RW, real-world.

hypothalamus, rather than peripheral receptors alone, mediate much of the weight effect, which is why brain-penetrant pharmacology matters as much as receptor affinity. Yet GLP-1 does not act alone: glucose-dependent insulinotropic polypeptide (GIP), glucagon (GCG), amylin, and other enteroendocrine signals jointly govern metabolism through partly complementary pathways.

The defining strategic insight of the field is that engaging these pathways together can be additive or synergistic (Figure 1). A molecule that agonizes both GLP-1 and GIP receptors couples two insulinotropic and appetite-regulating systems; adding glucagon-receptor agonism recruits energy expenditure and hepatic lipid handling. But the molecular detail is subtler than "more receptors, more effect", and two findings illustrate why mechanism, not just target count, governs outcome (Figure 2).

3.1 Biased and imbalanced agonism

Tirzepatide is not a balanced dual agonist. Detailed signalling studies show it engages the GIP receptor more than the GLP-1 receptor, and at the GLP-1 receptor it is *biased*: it favours cyclic AMP generation over β-arrestin recruitment and drives weaker receptor internalization

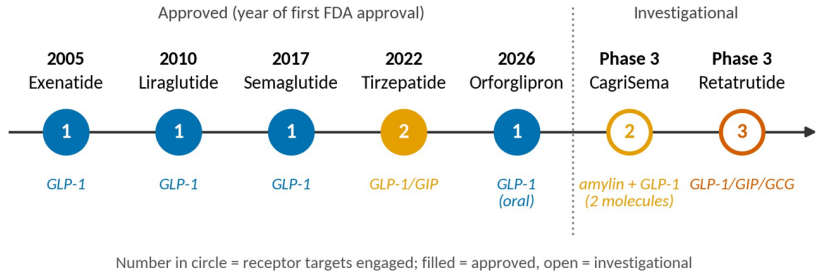

Figure 1 Rational polypharmacology in the incretin class. Approved agents are placed at the year of first FDA approval; investigational agents are in phase 3. The number in each circle is the number of receptor targets engaged. CagriSema is a co-formulation of two molecules (an amylin analogue and semaglutide) rather than a single multi-receptor peptide; orforglipron is an oral small molecule.

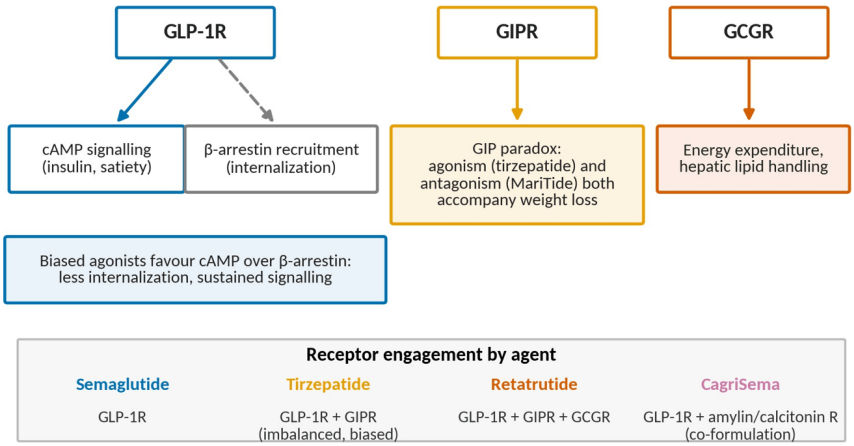

Figure 2 Mechanistic basis of incretin polypharmacology. A single engineered peptide can engage one to three receptors. At the GLP-1 receptor, biased agonists favour cAMP signalling over β-arrestin recruitment, reducing internalization and sustaining signalling. The GIP receptor presents a paradox–both agonism (tirzepatide) and antagonism (MariTide) accompany weight loss–while glucagon-receptor recruitment adds energy expenditure. Evidence is largely mechanistic (L5). GLP-1R, GLP-1 receptor; GIPR, GIP receptor; GCGR, glucagon receptor.

than native GLP-1 [25] (L5). Because β-arrestin 1 limits the insulin response to GLP-1 but not to tirzepatide, this bias may itself enhance insulin secretion—a property later rationalized at atomic resolution by cryo-electron-microscopy structures of the ligand–receptor complexes [26]. The same logic underlies non-peptide agonists such as orforglipron, whose distinct binding mode confers oral bioavailability while retaining favourable signalling [27]. Mechanism, in short, is a design variable, not a by-product.

3.2 The GIP paradox

If receptor engagement operated in a straightforward manner, both agonism and antagonism of the same receptor could not promote weight loss – yet clinical data demonstrate this phenomenon. Tirzepatide is a GIP-receptor *agonist* [7], whereas maridebart cafraglutide (MariTide) couples GLP-1 agonism to GIP-receptor *antagonism*; both are accompanied by substantial weight loss [28]. This GIP paradox–still unresolved–implies that the therapeutic effect depends on tissue-specific receptor context, desensitization kinetics and the balance of central versus peripheral signalling, rather than on simple on/off pharmacology. One proposed reconciliation is that chronic agonism functionally desensitizes the receptor, converging on the same net effect as antagonism; this remains a hypothesis (L5). It is the clearest signal that the next advances will come from understanding incretin biology, not merely from stacking receptors.

4 The efficacy ladder: from single to triple agonism

Once-weekly semaglutide 2.4 mg established the modern benchmark: in STEP 1 (n = 1,961; 68 weeks) mean weight change was -14.9% versus -2.4% with placebo [6], and weight and glycaemic benefit extended to type 2 diabetes in STEP 2 [29]. Its daily predecessor,

liraglutide 3.0 mg, had produced -8.0% versus -2.6% in SCALE [5]. Tirzepatide raised the ceiling: in SURMOUNT-1 (n = 2,539; 72 weeks) the 15-mg dose produced -20.9% versus -3.1% (treatment-regimen estimand; -22.5% under the efficacy estimand) [7], and in the open-label, head-to-head SURMOUNT-5 (n = 751; 72 weeks) it was superior to semaglutide for weight (-20.2% vs -13.7%) and waist circumference [8]. In type 2 diabetes, SURPASS-2 (n = 1,879; 40 weeks) showed greater glycated-haemoglobin and weight reductions with tirzepatide than with semaglutide 1 mg [9].

Triple agonism extends the ladder further. Retatrutide 12 mg, a GLP-1/GIP/glucagon receptor triagonist, produced -24.2% versus -2.1% at 48 weeks in a phase 2 trial (n = 338) [10]. Sponsor-reported phase 3 topline results, -28.7% at 68 weeks in TRIUMPH-4 (obesity with knee osteoarthritis) and -28.3% at 80 weeks in TRIUMPH-1 (-25.0% under the alternative estimand also reported)—place it, for the first time, in territory previously reserved for bariatric surgery [11, 12]. Because these data had not been peer-reviewed at the time of writing, they are graded L3 and should be read as provisional. The amylin-analogue combination cagrilintide/semaglutide (CagriSema)—a fixed co-formulation of two molecules rather than a single multi-receptor peptide—produced -20.4% versus -3.0% at 68 weeks in REDEFINE 1 (n = 3,417) [13], broadening the mechanistic repertoire beyond the incretin receptors themselves (Figure 3). These cross-trial values are descriptive: populations, durations and estimands differ, and only SURMOUNT-5 and SURPASS-2 provide direct randomized comparisons.

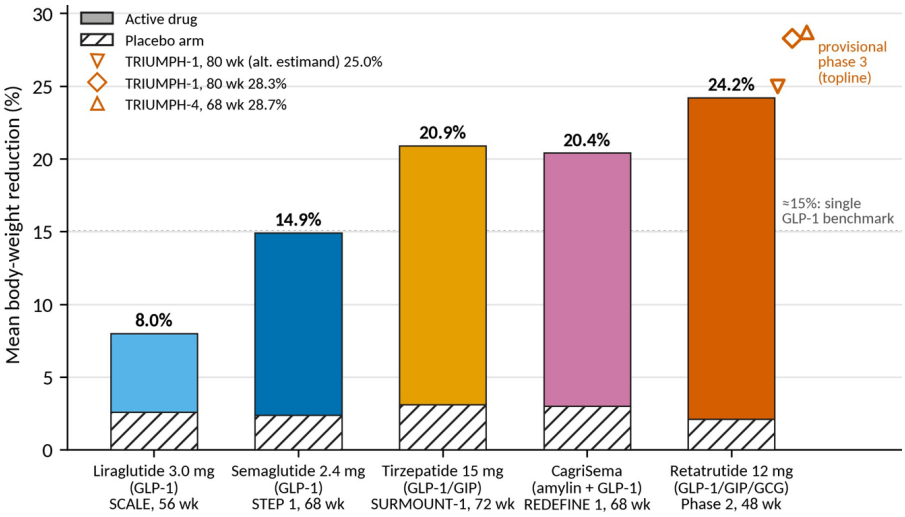

Figure 3 The efficacy ladder. Mean body-weight reduction in the pivotal placebo-controlled trial of each agent (treatment-policy/treatment-regimen estimand; retatrutide phase 2 value as reported). Hatched segments show the placebo arm. Open markers are sponsor-reported phase 3 topline results for retatrutide (L3; not peer-reviewed). Trials differ in population, duration, and estimand; comparisons across bars are therefore descriptive and not inferential.

5 Beyond glycaemic control: cardiovascular, renal, respiratory and hepatic outcomes

While the efficacy ladder explains the class's commercial success, its medical significance rests on outcome trials in which incretin-based therapies reduced hard clinical endpoints in organs far from the pancreas (Figure 4). In SELECT (n = 17,604; mean follow-up 39.8 months), semaglutide 2.4 mg reduced major adverse cardiovascular events (MACE; cardiovascular death, non-fatal myocardial infarction or non-fatal stroke) by 20% (hazard ratio (HR) 0.80, 95% confidence interval (CI) 0.72–0.90) in people with overweight or obesity and established cardiovascular disease but *without* diabetes—decoupling cardiovascular benefit from glucose lowering [15]. In absolute terms, event rates fell from 8.0% to 6.5%, corresponding to a number-needed-to-treat (NNT) of approximately 67 over roughly 3.3 years.

FLOW (n = 3,533; median follow-up 3.4 years), in type 2 diabetes with chronic kidney disease, was stopped early for efficacy. Semaglutide 1.0 mg reduced the primary kidney composite—kidney failure, a sustained $\geq$ 50% fall in estimated glomerular filtration rate, or kidney or cardiovascular death—by 24% (HR 0.76, 0.66–0.88; 18.7% vs 23.2%), MACE by 18% and all-cause death by 20% [16], in a population in which few therapies have ever shown mortality benefit.

The only randomized cardiovascular outcome trial of tirzepatide, SURPASS-CVOT (n = 13,165 analysed; median 4 years), used an *active* comparator, dulaglutide, in type 2 diabetes with atherosclerotic cardiovascular disease. MACE occurred in 12.2% versus 13.1% (HR 0.92, 95.3% CI 0.83–1.01): non-inferiority was met, superiority was not [17]. because dulaglutide itself reduced MACE versus placebo in REWIND [30], this provides evidence of cardiovascular benefit, but it is not a head-to-head comparison against semaglutide; no such RCT has been reported to date. Large propensity-matched real-world analyses suggest lower event rates with tirzepatide than with semaglutide or liraglutide [23], but these are graded L4: they used a broader MACE definition (acute coronary syndrome, heart failure, stroke and sudden cardiac death), and residual confounding cannot be excluded.

Tirzepatide became the first pharmacological agent approved for obstructive sleep apnoea after SURMOUNT-OSA (two trials, n = 469, 52 weeks) reduced the apnoea–hypopnoea index by about 25–29 events per hour versus 5–6 with placebo, with improvements in hypoxic burden, blood pressure and inflammatory markers [18]. In heart failure with preserved ejection fraction and obesity, semaglutide improved symptoms and physical limitation (STEP-HFpEF, n = 529) [19], and tirzepatide reduced the composite of cardiovascular death or worsening heart failure (SUMMIT, n = 731; HR 0.62, 0.41–0.95) [20]. In metabolic dysfunction-associated steatohepatitis (MASH, formerly NASH), phase 2 histological signals [31] were confirmed in part 1 of ESSENCE (n = 800; 72 weeks), in which semaglutide 2.4 mg produced steatohepatitis resolution in 62.9% versus 34.3% and fibrosis improvement in 36.8% versus 22.4% [21]; this supported FDA accelerated approval in August 2025, with liver-outcome data from part 2 still pending. The emerging picture is of a class acting on shared drivers of cardiometabolic, renal, respiratory and hepatic disease rather than on any single organ.

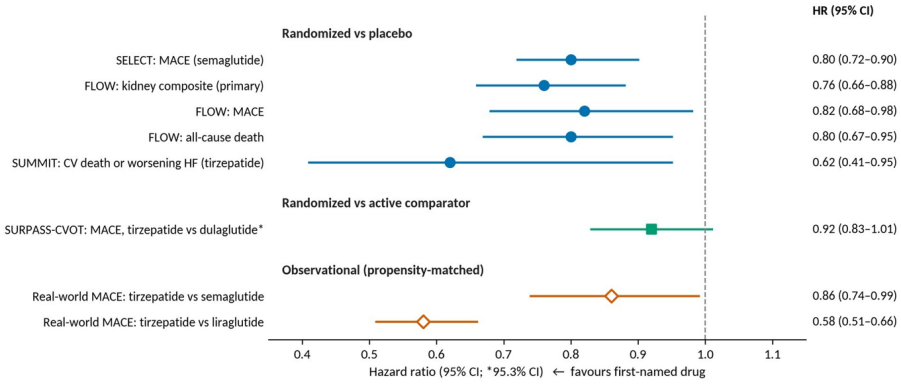

Figure 4 Cardiometabolic outcomes beyond weight and glycaemia. Hazard ratios with 95% CIs (*95.3% CI for SURPASS-CVOT). Filled circles, placebo-controlled RCTs; filled square, active-comparator RCT (non-inferiority met, superiority not); open diamonds, propensity-matched real-world analyses in obstructive sleep apnoea with type 2 diabetes, which used a broader MACE definition and are shown only to indicate direction. No head-to-head cardiovascular RCT of tirzepatide versus semaglutide has reported.

6 Durability, tolerability and the chronic-disease reality

Enthusiasm must be tempered by three durable limitations. First, the effect is conditional on continued treatment. In SURMOUNT-4, 670 participants who had lost 20.9% of body weight during a 36-week open-label tirzepatide lead-in were randomized to continue or switch to placebo; from week 36 to week 88 those switched to placebo regained 14.0% of body weight, whereas those who continued lost a further 5.5% (net change from baseline -9.9% *vs* -25.3%; Figure 5) [14]. Obesity represents a relapsing-remitting condition; these medications manage but cannot cure the disease.

Second, adherence in practice is far lower than in trials. In a US cohort of 125,474 adults with overweight or obesity, 46.5% of those with type 2 diabetes and 64.8% of those without discontinued GLP-1 receptor agonist therapy within one year [24] (L4). By contrast, discontinuation because of adverse events was 4–7% in the pivotal obesity RCTs [6, 7], which suggests that cost, coverage and supply—not only tolerability—drive real-world attrition.

Third, a substantial fraction of the weight lost is lean mass. In dual-energy X-ray absorptiometry substudies, lean mass accounted for close to two-fifths of weight lost with semaglutide

in STEP 1 [6] and about one quarter with tirzepatide in SURMOUNT-1 [7] (L2). These proportions resemble those seen with caloric restriction, and absorptiometric lean mass is not synonymous with skeletal muscle, but functional outcomes—strength, falls, fractures—have not been measured in adequately powered trials. This motivates resistance-exercise counselling and combination approaches intended to preserve muscle.

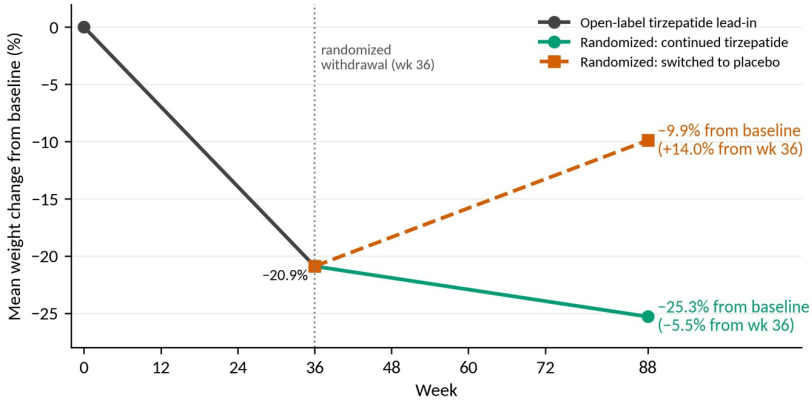

Figure 5 Durability is conditional. SURMOUNT-4 randomized-withdrawal design: after a 36-week open-label tirzepatide lead-in (-20.9%), participants were randomized to continue tirzepatide or switch to placebo until week 88. Points are reported mean values; connecting lines are straight and do not depict the true trajectory. Changes in parentheses are relative to week-36 weight.

7 Safety and the limits of current knowledge

A balanced appraisal must weigh a real, if mostly manageable, safety profile, expressed where possible in absolute terms (Table 2). Gastrointestinal effects–nausea, vomiting, diarrhoea, constipation—are the commonest adverse events and the commonest cause of discontinuation. In STEP 1, gastrointestinal adverse events occurred in 74.2% of participants versus 47.9% under placebo, and discontinuation due to adverse events occurred in 7.0% versus 3.1% (number-needed-to-harm, NNH $\approx$ 26) [6]; over the longer exposure of SELECT, permanent discontinuation because of adverse events was 16.6% versus 8.2% (NNH $\approx$ 12 over about 3.3 years) [15]. Delayed gastric emptying also underlies a newer concern: post-marketing reports of pulmonary aspiration during anaesthesia prompted label updates in November 2024 and revised peri-operative guidance [32].

Approved labels carry a boxed warning for thyroid C-cell tumours, extrapolated from rodent medullary thyroid carcinoma and C-cell hyperplasia; a causal human risk remains unconfirmed, but the class is contraindicated in personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2 [33, 34]. Gallbladder events increase with rapid, large weight loss, whereas acute pancreatitis was not more frequent than with placebo in SELECT (0.2% vs 0.3%) [15]. Worsening of diabetic retinopathy with rapid glycaemic improvement was first signalled in SUSTAIN-6, in which retinopathy complications occurred in 3.0% versus 1.8% [35]. A widely publicized question of suicidal ideation was investigated by regulators and in large pharmacovigilance analyses and has not, to date, been substantiated as causal [33].

7.1 Special populations

Evidence is thinnest where risk may be greatest. Older adults, particularly those with sarcopenic obesity or frailty, are under-represented in pivotal trials, so the balance between cardiometabolic benefit and loss of lean mass is uncertain for them. The drugs are not recommended in pregnancy; labelling advises stopping semaglutide at least two months before a planned conception, and because tirzepatide reduces exposure to oral contraceptives, a non-oral or additional barrier method is advised for four weeks after initiation and after each dose increase [33, 36]. Data in advanced chronic kidney disease are now reassuring for semaglutide (FLOW) [16], but long-term safety beyond four to five years of exposure, and in adolescents treated for decades, remains unknown.

8 Oral and next-generation incretins

The next inflection point is route of administration. Injectable peptides impose cost, cold-chain and acceptability barriers; orally available agents could greatly expand the treatable

Table 2 Principal safety signals for incretin-based therapies: evidence level, absolute data and practical implication

Signal	Level	Absolute data (where available)	Practical implication
Gastrointestinal events / discontinuation	L1	STEP 1: GI events 74.2% vs 47.9%; stopped for AEs 7.0% vs 3.1% (NNH $\approx$ 26) [6]. SELECT: stopped for AEs 16.6% vs 8.2% (NNH $\approx$ 12 over $\sim$ 3.3 y) [15]	Slow dose titration; dietary counselling; avoid in severe gastroparesis
Thyroid C-cell tumours	L5 / L4	Rodent MTC and C-cell hyperplasia; human causality unconfirmed [33, 34]	Contraindicated with personal/family MTC or MEN-2
Acute pancreatitis	L1	SELECT: 0.2% vs 0.3% (no excess) [15]	Stop if suspected; caution with prior pancreatitis
Gallbladder disease	L1	Increased with rapid, large weight loss [33]	Counsel; evaluate biliary symptoms
Diabetic retinopathy (T2D)	L1	SUSTAIN-6: complications 3.0% vs 1.8% [35]	Retinal monitoring when glycaemia falls rapidly in pre-existing retinopathy
Peri-operative aspiration	L4	Post-marketing reports; labels updated November 2024 [32]	Disclose before anaesthesia; follow current fasting/withholding guidance
Suicidality	L4	Regulatory and pharmacovigilance reviews: not substantiated as causal [33]	Routine clinical vigilance
Lean-mass loss	L2	$\approx$ 25–40% of weight lost (DXA substudies) [6, 7]; functional outcomes unmeasured	Resistance exercise and protein intake; muscle-preserving combinations in trials
Pregnancy and contraception	—	Insufficient human data [33, 36]	Stop semaglutide $\geq$ 2 months before planned conception; with tirzepatide use, non-oral/barrier contraception for 4 wk after start and each dose increase

Note: NNH, number needed to harm (computed from the cited arm-level proportions); MTC, medullary thyroid carcinoma; MEN-2, multiple endocrine neoplasia type 2.

population. Orforglipron, a non-peptide small-molecule GLP-1 receptor agonist taken once daily without food or water restrictions, produced about 12% weight loss at 72 weeks at its highest dose in ATTAIN-1 [37] and was approved by the FDA for chronic weight management on 1 April 2026 [38]; an oral 25-mg formulation of semaglutide for weight management has also reached the market [39]. In parallel, monthly dosing (the GIP-antagonist/GLP-1-agonist maridebart cafraglutide) [28] and amylin and triple-agonist combinations [12, 13] promise both greater convenience and a higher efficacy ceiling. The competitive and scientific frontier is shifting from how much weight a drug removes to how durably, how safely and how accessibly it can be delivered.

Beyond metabolism, the central nervous system has been the most anticipated frontier—and has so far disappointed. In EVOKE and EVOKE+ (n = 3,808), oral semaglutide 14 mg improved Alzheimer's disease-related biomarkers but did not slow clinical progression on the Clinical Dementia Rating–Sum of Boxes or on any functional or cognitive secondary measure in biomarker-confirmed early Alzheimer's disease [22]. The earlier observational signal of lower dementia risk among users therefore did not survive randomization, a cautionary precedent for the addiction indications, where evidence of reduced alcohol and nicotine use remains largely observational (L4) [4]. Those trials are ongoing; until they report, neuropsychiatric benefit should be regarded as a hypothesis.

9 Access, equity and the economics of a blockbuster class

The class's scale is without modern precedent. Company-reported 2025 sales of tirzepatide were US$36.5 billion [3]. For 2026, analysts project about US$45.5 billion for tirzepatide (Mounjaro US$25.8 billion and Zepbound US$19.7 billion) and about US$39.5 billion for the semaglutide franchise, of which Ozempic and Wegovy account for US$34.8 billion and the remaining $\approx$ US$4.7 billion is other semaglutide products, principally Rybelsus—a combined $\approx$ US$85 billion (Figure 6) [40]. These are projections, not audited results. In November 2025, 18% of US adults reported having ever used a GLP-1 drug and 12% current use, and more than half of surveyed users reported these therapies to be unaffordable [41].

This commercial success is precisely what makes access the central unsolved problem. List prices place sustained therapy beyond the reach of many of the patients who would benefit most, payers are straining under demand for what may become lifelong prescriptions, and the global distribution of a class that could alter population-level cardiometabolic risk remains deeply

inequitable. For a therapy whose benefits are conditional on continuous use, affordability is not a peripheral concern but a determinant of clinical effect.

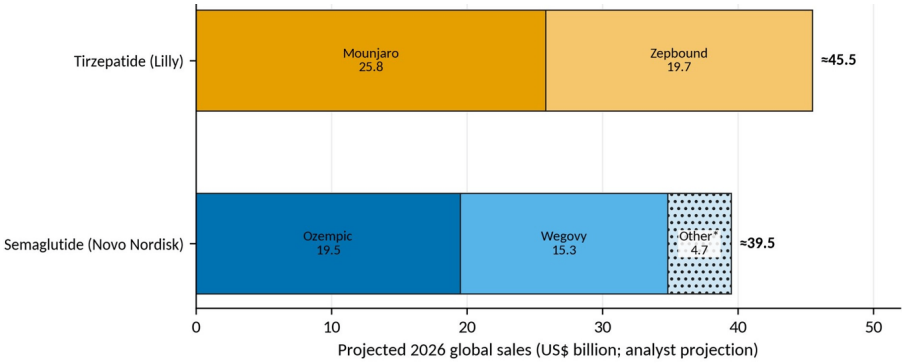

Figure 6 Incretin franchises in pharmaceutical sales. Analyst-projected 2026 global sales (US$ billion). *The 'other semaglutide' segment (≈ US$4.7 billion, mainly Rybelsus) is the difference between the franchise projection (US$39.5 billion) and the Ozempic and Wegovy projections (US$34.8 billion). Brand totals: tirzepatide ≈ US$45.5 billion; semaglutide ≈ US$39.5 billion; combined ≈ US$85 billion (≈ US$80.3 billion for the four named brands alone). Projections, not audited results.

10 Outlook

Incretin polypharmacology has done more than produce effective weight-loss drugs; it has demonstrated that a single, mechanistically rational intervention can simultaneously address obesity, diabetes, and cardiovascular, renal, respiratory and hepatic disease—conditions long treated as separate specialties. The coming decade will test three propositions: that triple agonism and amylin combinations can push efficacy toward surgical magnitudes without prohibitive toxicity; that oral and long-interval formulations can convert efficacy into population-level impact; and that health systems can finance a chronic therapy for a substantial fraction of humanity. The core scientific question – whether we can safely re-engineer human energy balance – appears increasingly answerable in the affirmative. However, results from the EVOKE trials serve as a reminder that not every plausible therapeutic indication will prove successful. The harder questions are now those of durability, lean-mass preservation, long-term safety, equity and cost. On current evidence, incretin-based medicine is not a passing pharmacological fashion but the foundation of a new, integrated cardiometabolic therapeutics—provided the field is as rigorous about its limitations as it has been ingenious about its mechanisms.

Data availability

All data are from the cited public trials, labels and filings. The numerical values plotted in every figure are held in a single machine-readable file, and the figure-generating scripts are available from the author.

Conflicts of interest

The author declares no financial or non-financial competing interests and received no industry funding.

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