

REVIEW ARTICLE OPEN ACCESS

Incretin-Based Therapies as Cardiometabolic Interventions: Outcome Hierarchy, Receptor-Network Pharmacology and Phenotype-Based Clinical Positioning

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ABSTRACT

Aims: Incretin-based pharmacotherapy was initially developed to improve glucose-dependent insulin secretion and glycaemic control in type 2 diabetes, but its clinical interpretation has expanded substantially with cardiovascular outcome trials, kidney outcome data, obesity studies and next-generation polyagonist development. This narrative clinical review uses structured literature identification and outcome-stratified synthesis to evaluate incretin-based therapies as cardiometabolic interventions across diabetes, obesity, cardiovascular disease and chronic kidney disease.

Materials and Methods: The available evidence was interpreted according to therapeutic class, clinical domain, outcome maturity and safety boundaries, integrating clinical outcome evidence with receptor-network pharmacology.

Results: Selected GLP-1 receptor agonists are supported by hard cardiovascular and renal outcome data, whereas several dual, triple, amylin-linked and oral small-molecule strategies are currently supported mainly by glycaemic, weight-loss, metabolic or early translational endpoints. This distinction is clinically important because treatment positioning should depend on patient phenotype, outcome maturity and safety boundaries rather than mechanistic plausibility alone. In patients with type 2 diabetes and established atherosclerotic cardiovascular disease, GLP-1 receptor agonists with proven cardiovascular outcome benefit should be prioritised when atherosclerotic risk reduction is a major treatment goal. In type 2 diabetes with chronic kidney disease, semaglutide has dedicated kidney outcome evidence. In obesity with cardiometabolic risk, high-magnitude and sustained weight reduction has become a clinically relevant therapeutic target. Receptor-network pharmacology, including GLP-1, GIP, glucagon and amylin receptor signalling, provides a useful explanatory framework for heterogeneous efficacy, tolerability and tissue-level effects.

Conclusions: However, clinical use remains bounded by gastrointestinal tolerability, lean-mass preservation, treatment durability, discontinuation effects and long-term safety. This review therefore proposes phenotype-based clinical positioning rather than a prescriptive treatment algorithm.

Abbreviations: AMYR, amylin receptor; cAMP, cyclic adenosine monophosphate; CKD, chronic kidney disease; GIP, glucose-dependent insulinotropic polypeptide; GIPR, glucose-dependent insulinotropic polypeptide receptor; GLP-1, glucagon-like peptide-1; GLP-1R, glucagon-like peptide-1 receptor; GLP-1RA, glucagon-like peptide-1 receptor agonist; GPCR, G-protein-coupled receptor; HbA1c, glycated haemoglobin; MACE, major adverse cardiovascular events; RAMP, receptor activity-modifying protein; T2D, Type 2 diabetes.

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Highlights

- Incretin-based therapies have outcome-supported clinical relevance in selected cardiovascular, renal and obesity-related cardiometabolic domains.
- Evidence maturity differs across therapeutic classes: established GLP-1 receptor agonists have the strongest cardiovascular and renal outcome support, whereas several newer polyagonist and amylin-linked strategies remain supported mainly by metabolic or weight-loss endpoints.
- Phenotype-based clinical positioning should distinguish Type 2 diabetes with atherosclerotic cardiovascular disease, Type 2 diabetes with chronic kidney disease, obesity with cardiometabolic risk, metabolic liver disease and overlapping multimorbidity.
- Receptor-network pharmacology provides an explanatory framework linking GLP-1, GIP, glucagon and amylin receptor signalling with tissue-level effects, but it should not substitute for outcome evidence.
- Clinical implementation requires attention to gastrointestinal tolerability, body-composition changes, lean-mass preservation, treatment durability and long-term safety.

1 | Introduction and Rationale

Incretins are nutrient-stimulated gut-derived peptide hormones that amplify glucose-dependent insulin secretion and coordinate postprandial metabolic responses. Incretin-based pharmacotherapy was developed to improve glycaemic control in Type 2 diabetes (T2D) with low hypoglycaemia risk, but its clinical interpretation has broadened substantially. Selected GLP-1 receptor agonists (GLP-1RAs) now have established relevance across several cardiometabolic domains, including atherosclerotic cardiovascular disease, chronic kidney disease (CKD) progression, adiposity-related risk and obesity-related multimorbidity [1, 2]. Cardiovascular outcome trials and meta-analyses have shown that selected GLP-1RAs reduce major adverse cardiovascular events (MACE), particularly in patients with T2D and increased cardiovascular risk [3, 4]. Kidney evidence has also progressed from albuminuria-based surrogate signals to dedicated outcome data. In FLOW, semaglutide slowed CKD progression and reduced kidney- or cardiovascular-related outcomes in patients with T2D and established CKD [5].

In parallel, obesity has moved from being viewed mainly as a comorbidity of T2D to a central determinant of cardiometabolic risk, treatment selection and long-term therapeutic strategy. Contemporary standards recognise obesity as a chronic, relapsing disease and emphasise that greater and sustained weight loss is associated with greater metabolic benefit and, in selected patients, a more favourable disease trajectory [6]. The STEP programme demonstrated that semaglutide 2.4 mg produces clinically meaningful and sustained weight loss in individuals with overweight or obesity [7, 8]. This is particularly relevant for incretin therapy, because GLP-1-based agents may influence interconnected domains, including glycaemia, adiposity, vascular inflammation, haemodynamic stress and organ complications.

However, these signals require evidence stratification, since weight-loss, metabolic, inflammatory and organ-level effects do not carry the same degree of outcome validation across therapeutic classes.

1.1 | From Glucose-Centred Therapy to Outcome-Stratified Cardiometabolic Intervention

Cardiovascular outcome trial meta-analyses in T2D have shown that selected GLP-1RAs reduce MACE despite modest differences in glycaemic change and organ-level benefit is reinforced by SELECT, in which semaglutide reduced MACE in individuals with overweight or obesity and established cardiovascular disease but without diabetes, and by FLOW, in which semaglutide slowed CKD progression and reduced kidney-related outcomes in patients with T2D and established CKD [5, 10]. These findings support a clinical interpretation of incretin-based therapy beyond glucose lowering, while recognising that glucose-independent mechanisms remain incompletely defined in humans (Figure 1). They also justify an outcome-stratified approach that separates cardiovascular and kidney outcome evidence from surrogate, exploratory and mechanistic signals.

Next-generation incretin polyagonists add a further layer to this evidence hierarchy. Tirzepatide, a GIP-GLP-1 receptor co-agonist, produces greater HbA1c and body-weight reductions than semaglutide 1 mg in T2D and high-magnitude weight loss in obesity, supporting effects that cannot be explained as stronger GLP-1R agonism alone [11, 12]. GIP receptor engagement may contribute through central and peripheral pathways regulating energy intake, adipose biology and metabolic partitioning, although the relative human contribution of these pathways remains uncertain [2]. In SURPASS-CVOT, tirzepatide was non-inferior to dulaglutide for three-point MACE, but superiority was not shown; placebo-comparative cardiovascular benefit therefore remains indirect [13]. These findings support high metabolic efficacy, while reinforcing the need to separate glycaemic and weight-loss endpoints from hard cardiovascular outcome evidence.

1.2 | Aims and Scope

This narrative clinical review synthesises contemporary clinical, translational and mechanistic evidence on incretin-based therapies within an outcome-stratified cardiometabolic approach. It focuses on GLP-1RAs and next-generation incretin-based therapies, including GIP-GLP-1 and GLP-1-glucagon co-agonists, amylin-linked strategies, triple agonists and oral small-molecule GLP-1RAs. The clinical domains considered are T2D, obesity, atherosclerotic cardiovascular disease, CKD, metabolic liver disease and emerging neural or microvascular areas. The scope is interpretative rather than guideline-based. This review does not provide a prescriptive treatment algorithm, rank individual agents or perform quantitative pooling. Instead, it separates outcome-supported clinical positioning from surrogate, translational and mechanistic evidence. Receptor-network pharmacology is used to explain how GLP-1, GIP, glucagon and amylin receptor (AMYR) pathways may connect molecular

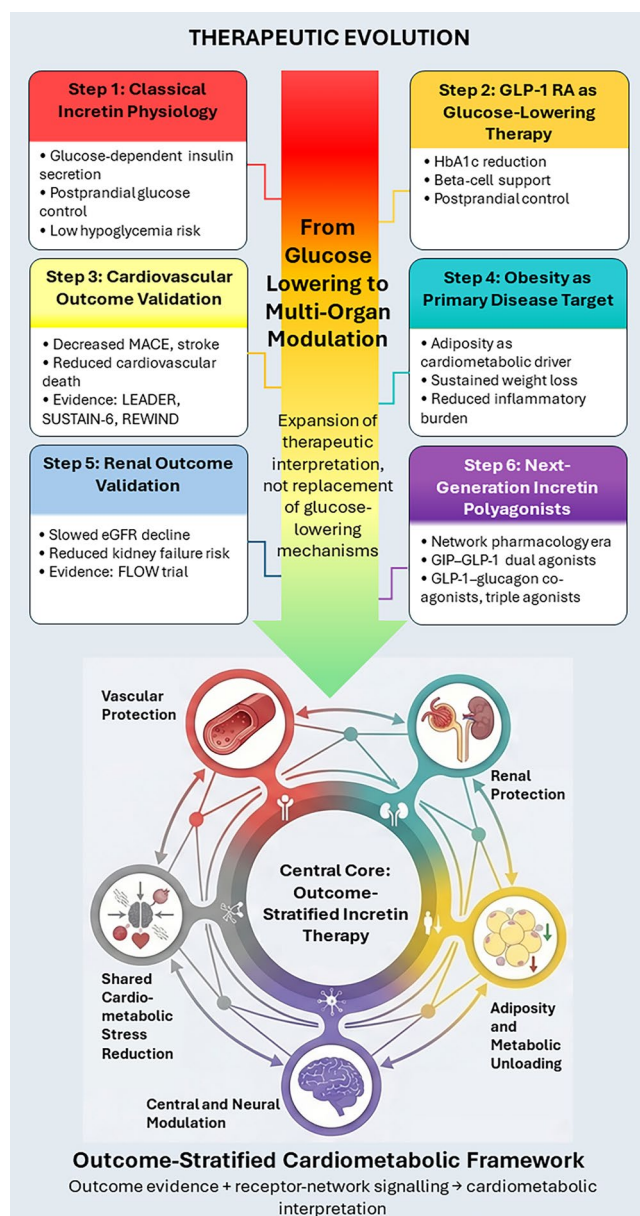


FIGURE 1 | Conceptual evolution of incretin-based therapy from glucose-centred pharmacology towards outcome-stratified cardiometabolic intervention. The figure illustrates the progressive expansion of incretin-based therapy from classical incretin physiology and glucose-dependent insulin secretion towards cardiovascular, renal, obesity-related, and multi-organ cardiometabolic interpretation. Early therapeutic use focused on glycaemic control in Type 2 diabetes. Subsequent cardiovascular outcome trials, obesity studies and dedicated kidney outcome data broadened the clinical relevance of GLP-1 receptor agonists and related incretin-based therapies. The contemporary interpretation requires outcome stratification: Cardiovascular and renal effects are strongest where supported by dedicated outcome trials or large meta-analyses, whereas neural, microvascular, mitochondrial and receptor-topology mechanisms should be interpreted as emerging or hypothesis-generating. Receptor-network signalling provides a biological explanation for multi-domain effects, but clinical positioning remains anchored to evidence maturity, patient phenotype, safety boundaries and treatment durability. CKD, chronic kidney disease; GLP-1, glucagon-like peptide-1; GLP-1RA, GLP-1 receptor agonist; MACE, major adverse cardiovascular events; T2D, Type 2 diabetes.

signalling with tissue-level and clinical patterns. Mechanistic plausibility is treated as supportive rather than sufficient for clinical positioning, which remains anchored to evidence maturity, patient phenotype, safety boundaries, body-composition effects and expected durability.

1.3 | Literature Search and Review Methodology

This article was designed as a narrative clinical review with structured literature identification and outcome-stratified synthesis. Its aim was to integrate clinical outcome evidence, translational mechanistic data and receptor-pharmacology concepts relevant to incretin-based cardiometabolic therapy, rather than to perform a formal systematic review or quantitative meta-analysis. Targeted searches were conducted in PubMed/MEDLINE, Scopus and Web of Science for publications available up to July 2026. Search terms combined incretin-related terms, including GLP-1 receptor agonist, incretin therapy, GIP receptor, glucagon receptor, AMYR, tirzepatide and incretin polyagonist, with clinical-domain terms including cardiovascular outcomes, CKD, obesity, metabolic liver disease, body composition, safety and treatment durability.

Priority was given to large randomised trials, cardiovascular and kidney outcome trials, obesity trials, major meta-analyses, pooled analyses, mechanistic and translational studies and recent integrative reviews in endocrinology, metabolism, obesity medicine, nephrology and cardiovascular medicine. Emphasis was placed on cardiovascular outcomes, CKD progression, high-magnitude weight reduction, metabolic liver disease, receptor signalling, polyagonist pharmacology, body composition, treatment durability and safety.

Given the narrative design, study selection was guided by clinical relevance, conceptual importance and translational applicability rather than predefined systematic-review criteria. No original patient-level data were analysed, and no de novo statistical testing, confounder adjustment, quantitative pooling, formal risk-of-bias assessment or GRADE-based evidence rating was performed. Clinical trials and meta-analyses were interpreted according to their published results and endpoint maturity.

1.4 | Evidence Hierarchy Used in This Review

To avoid overextension of mechanistic interpretation, this review applies a qualitative evidence hierarchy. The highest level is assigned to hard clinical endpoints from dedicated outcome trials or large randomised-trial meta-analyses, including MACE, cardiovascular death, kidney failure, sustained estimated glomerular filtration rate decline and kidney- or cardiovascular-related death.

A second level includes validated surrogate or intermediate endpoints, such as HbA1c, body weight, blood pressure, lipid variables, albuminuria, estimated glomerular filtration rate slope and histological endpoints in metabolic dysfunction-associated steatohepatitis. A third level includes exploratory or translational signals, including inflammatory markers, endothelial function, body-composition measures, food-cue reactivity and

early neural or microvascular endpoints. A fourth level includes mechanistic hypotheses derived from receptor biology, structural pharmacology, receptor trafficking, biased agonism, receptor co-expression and preclinical models.

This hierarchy distinguishes outcome-supported clinical positioning from biological plausibility. Surrogate, translational and mechanistic findings may inform interpretation and identify future therapeutic domains, but they should not be treated as equivalent to hard cardiovascular, kidney or mortality outcomes. Table 1 translates this hierarchy into a phenotype-based clinical positioning framework, whereas Table S2 provides a complementary overview of evidence maturity and remaining evidence gaps across therapeutic classes.

2 | Outcome-Supported Clinical Domains

The evidence hierarchy outlined above places outcome-supported domains before mechanistic interpretation. Cardiovascular, kidney and obesity-related evidence currently provides the strongest clinical basis for interpreting incretin-based therapies as cardiometabolic interventions, whereas hepatic, neural, microvascular and receptor-topology findings require more cautious interpretation according to endpoint maturity [1, 4]. The following sections therefore summarise the principal clinical domains before returning to receptor-network pharmacology as an explanatory approach.

2.1 | Cardiovascular Outcomes and ASCVD Phenotype

Cardiovascular outcome evidence is central to the clinical positioning of incretin-based therapy. Cardiovascular outcome trials and meta-analyses have shown that selected GLP-1RAs reduce MACE, with pooled analyses suggesting particularly consistent effects on stroke risk [3, 9]. In patients with T2D and established atherosclerotic cardiovascular disease, GLP-1RAs with proven cardiovascular outcome benefit should therefore be prioritised when atherosclerotic risk reduction is a major therapeutic goal.

Mechanistically, GLP-1 and GLP-1RAs may influence vascular biology through effects on endothelial function, inflammatory signalling, macrophage activation and foam-cell formation. These mechanisms are consistent with vascular homeostasis and plaque stabilisation, but direct attribution of cardiovascular outcome benefit to any single pathway remains uncertain. Cardiovascular protection is therefore best interpreted as an integrated clinical and biological effect rather than as an isolated anti-atherosclerotic mechanism [16].

2.2 | Kidney Outcomes and CKD Phenotype

Kidney outcomes provide one of the clearest examples of outcome-supported multi-organ benefit with incretin-based therapy. GLP-1RA therapy is associated with albuminuria reduction and slower decline in estimated glomerular filtration rate across trials and pooled analyses [4]. In FLOW, semaglutide reduced a composite kidney endpoint including major estimated

glomerular filtration rate decline, kidney failure and kidney- or cardiovascular-related death in patients with T2D and established CKD [5].

These findings support phenotype-based positioning of semaglutide in T2D with CKD, particularly when kidney disease progression and cardiometabolic risk coexist. Potential mechanisms include systemic and intraglomerular haemodynamic effects, reduced inflammatory and oxidative stress signalling, lower body weight and blood pressure and reduced metabolic load [17]. However, albuminuria reduction, estimated glomerular filtration rate slope and mechanistic renal signals should be distinguished from dedicated kidney outcome evidence when interpreting drug-class positioning.

2.3 | Obesity, Weight Reduction and Cardiometabolic Risk

Obesity and increased adiposity define a major cardiometabolic phenotype in which incretin-based therapy may address hyperglycaemia, excess adiposity, inflammatory burden and vascular risk in parallel. In T2D with obesity, weight reduction and improved glycaemic control support the use of incretin-based therapies within combination treatment strategies, particularly when adiposity, metabolic risk and vascular risk coexist [4]. In individuals with overweight or obesity and established cardiovascular disease but without diabetes, semaglutide 2.4 mg provides outcome-supported evidence for cardiovascular risk reduction, while obesity trials support high-magnitude weight loss as a clinically relevant therapeutic target [10, 12].

Next-generation incretin therapies differ substantially in evidence maturity. GIP-GLP-1 co-agonists have strong glycaemic and weight-loss evidence, whereas GLP-1-glucagon co-agonists, triple agonists, amylin-linked strategies and oral small-molecule GLP-1RAs remain supported mainly by metabolic, weight-loss, tolerability or early translational endpoints [18, 19]. Weight-loss efficacy should therefore be distinguished from established cardiovascular, kidney or liver outcome benefit.

2.4 | Metabolic Liver Disease

Metabolic liver disease represents an increasingly relevant but less mature outcome domain for incretin-based therapy than cardiovascular or kidney disease. In patients with metabolic dysfunction-associated steatotic liver disease, particularly when obesity or T2D coexists, incretin-based therapies may improve hepatic metabolic burden through weight reduction, improved insulin sensitivity and reduced lipotoxic substrate flux. Clinical trials with semaglutide and tirzepatide have reported favourable histological effects on steatohepatitis and fibrosis-related endpoints [14, 15].

These findings strengthen the clinical relevance of incretin-based therapy in metabolic liver disease, but the maturity of evidence remains distinct from that of cardiovascular and kidney outcome trials. Histological improvement, including resolution of steatohepatitis or improvement in fibrosis-related endpoints, represents clinically important intermediate evidence but should not be

TABLE 1 | Outcome hierarchy and phenotype-based clinical positioning of incretin-based therapies.

Clinical phenotype or domain	Best-supported therapeutic orientation	Mature outcome evidence	Surrogate or emerging evidence	Positioning boundary
T2D with established ASCVD or high atherosclerotic risk	GLP-1RAs with proven cardiovascular outcome benefit	Cardiovascular outcome trials and meta-analyses support MACE reduction for selected GLP-1RAs in T2D with increased cardiovascular risk [3, 9].	HbA1c, body weight, blood pressure, lipid variables and inflammatory markers may improve.	GLP-1RAs with proven cardiovascular benefit should be prioritised when atherosclerotic risk reduction is a major goal. Cardiovascular benefit should be interpreted as agent- and population-dependent rather than automatically class-wide.
T2D with CKD	Semaglutide; GLP-1RAs with renal outcome or renal signal evidence	FLOW provides dedicated kidney outcome evidence for semaglutide in T2D with CKD; meta-analyses support broader kidney benefit signals for GLP-1RAs [4, 5].	Albuminuria reduction, slower eGFR decline, weight reduction and blood pressure improvement.	Semaglutide has the strongest dedicated kidney outcome evidence among incretin-based therapies. Positioning should complement established nephroprotective strategies and account for tolerability, hydration status and renal function.
Overweight or obesity with established cardiovascular disease but without diabetes	Semaglutide 2.4 mg	SELECT supports MACE reduction with semaglutide in individuals with overweight or obesity and established cardiovascular disease but without diabetes [10].	Weight loss, waist reduction, blood pressure reduction, inflammatory marker changes and broader cardiometabolic risk-factor improvement.	Semaglutide 2.4 mg provides outcome-supported cardiometabolic risk reduction beyond glycaemic control. Durability after discontinuation, access, body-composition effects and generalisability to broader obesity phenotypes remain important considerations.
T2D with obesity or high adiposity burden	GLP-1RAs; GIP-GLP-1 co-agonists; selected high-efficacy weight-loss strategies according to dominant clinical need	Hard cardiovascular and kidney outcome evidence depends on agent and trial population. Tirzepatide has active-comparator cardiovascular outcome evidence, but placebo-comparative cardiovascular benefit remains indirect [13].	Large reductions in HbA1c and body weight are supported by diabetes and obesity trials, including tirzepatide studies [11, 12].	Treatment choice should reflect the dominant therapeutic goal: ASCVD risk reduction, kidney protection, glycaemic control, magnitude of weight loss or multimorbidity burden. Weight-loss magnitude should not be interpreted as proportional hard-outcome benefit across all classes.

(Continues)

TABLE 1 | (Continued)

Clinical phenotype or domain	Best-supported therapeutic orientation	Mature outcome evidence	Surrogate or emerging evidence	Positioning boundary
MASLD or MASH phenotype	GLP-1RAs; GIP-GLP-1 co-agonists; selected emerging polyagonists according to indication and evidence maturity	Long-term liver-related hard outcomes remain limited.	Histological MASH endpoints, liver fat reduction, aminotransferases, weight loss and metabolic-inflammatory markers have shown favourable signals with semaglutide and tirzepatide-based strategies [14, 15].	Incretin-based therapy may be clinically relevant when metabolic liver disease coexists with obesity, T2D or cardiometabolic risk. Positioning should remain linked to approved indications, histological evidence, metabolic phenotype and long-term outcome uncertainty.
Overlapping multimorbidity: T2D, obesity, CKD and ASCVD	Outcome-proven GLP-1RAs; selected next-generation incretin therapies according to dominant phenotype	Evidence is strongest when individual domains are supported by outcome trials, particularly ASCVD and CKD domains [3, 5].	Combined improvements may occur in HbA1c, body weight, blood pressure, albuminuria, inflammatory burden and metabolic risk factors.	Multimorbidity supports phenotype-based positioning rather than glucose-centred or molecule-centred selection. Treatment should account for dominant clinical priority, outcome maturity, tolerability, frailty, body composition, adherence, access and treatment durability.

Note: This table is intended as an evidence-orientation and clinical-positioning framework rather than a formal treatment algorithm or guideline recommendation. Hard outcome evidence refers to dedicated cardiovascular, kidney or obesity-related outcome trials and large randomised-trial meta-analyses. Surrogate or translational evidence includes glycaemic, weight, haemodynamic, body-composition, histological, inflammatory, neural, endothelial or mechanistic endpoints. Clinical positioning should remain consistent with approved indications, local guidelines, patient phenotype, tolerability, access and long-term treatment goals. Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CVOT, cardiovascular outcome trial; eGFR, estimated glomerular filtration rate; GIP, glucose-dependent insulinotropic polypeptide; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated haemoglobin; MACE, major adverse cardiovascular events; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; SGLT2, sodium-glucose cotransporter-2; T2D, Type 2 diabetes.

equated with reduction in cirrhosis, hepatic decompensation, liver transplantation or liver-related mortality. Longer-term studies are therefore needed to determine whether improvements in hepatic histology translate into durable liver-related clinical benefit.

2.5 | Multimorbidity and Phenotype-Based Positioning

In clinical practice, T2D, obesity, CKD and atherosclerotic cardiovascular disease frequently coexist, making single-phenotype or molecule-centred treatment selection increasingly artificial. In such patients, therapeutic priorities should first be defined by the clinical domain with the strongest outcome-supported need. When atherosclerotic cardiovascular risk predominates, GLP-1RAs with proven cardiovascular benefit should be prioritised; when CKD progression is the major concern, semaglutide has dedicated kidney outcome evidence in T2D with CKD [5, 10]. When severe obesity or adiposity-related metabolic burden is the dominant unresolved problem, the magnitude and durability of weight reduction become increasingly relevant, but should not be assumed to confer proportional cardiovascular, kidney or liver outcome benefit across therapeutic classes.

In complex multimorbidity, these priorities should be integrated rather than considered independently. Outcome-proven organ protection should generally take precedence when cardiovascular or kidney risk is clinically dominant, while glycaemic and weight-loss efficacy may further guide selection when competing therapies provide comparable organ-specific evidence. Tolerability, frailty, body composition, treatment persistence, access and expected durability then modify the final choice. This framework is intended as a clinical prioritisation logic rather than a prescriptive treatment algorithm.

3 | Receptor-Network Pharmacology as Mechanistic Explanation

Receptor-level pharmacology provides a biological framework for interpreting the heterogeneous effects of incretin-based therapies, but should remain subordinate to clinical evidence maturity. GLP-1R signalling is influenced by ligand structure, receptor conformation, tissue context, signalling duration and pharmacokinetic exposure, while multi-receptor therapies extend this framework across GIP, glucagon and amylin pathways [1, 2]. Incretin polyagonism can therefore be viewed as coordinated modulation of partially overlapping physiological systems rather than amplification of a single receptor pathway. Detailed receptor topology, structural pharmacology, trafficking and tetrad-signalling considerations are provided in Supporting Information Text S2 and Figure S1.

3.1 | GLP-1 Receptor Signalling Bias and Tissue Context

GLP-1R is a class B G-protein-coupled receptor that predominantly signals through Gs-mediated adenylyl cyclase activation and cyclic adenosine monophosphate (cAMP) production.

Different GLP-1RAs may stabilise distinct receptor conformations and engage downstream pathways to different degrees, a phenomenon described as biased agonism [20, 21]. Such signalling diversity, together with tissue-specific receptor expression, may contribute to differences in glycaemic efficacy, appetite regulation and gastrointestinal tolerability (Figure 2). However, direct validation in human tissues remains limited, and receptor bias has not been established as an independent determinant of clinical outcome [2].

Receptor exposure and trafficking may further influence signalling duration. GLP-1R internalisation and intracellular trafficking differ across experimental agonist systems, but sustained endosomal signalling has not been demonstrated as a determinant of human cardiovascular, kidney or weight-related outcomes [2, 22]. These mechanisms should therefore be regarded as explanatory rather than positioning-grade evidence.

3.2 | GIP-GLP-1 Co-Agonism and Neural-Metabolic Integration

GIP receptor signalling illustrates how incretin co-agonism may extend metabolic effects beyond pancreatic insulin secretion. Although classical GIP-mediated insulinotropic responsiveness is reduced in T2D, dual GIP-GLP-1 receptor agonism has renewed interest in extra-pancreatic and neural-metabolic actions of GIP [2]. Tirzepatide provides clinical proof of concept, with greater HbA1c and body-weight reductions than semaglutide 1 mg in T2D and substantial weight loss in obesity [11, 12]. These findings support biologically relevant receptor co-agonism, but the contribution of specific GIP-mediated pathways in humans remains incompletely defined and should not be inferred directly from clinical efficacy.

3.3 | GLP-1-Glucagon Co-Agonism and Energy-Expenditure Coupling

Glucagon receptor signalling adds a metabolic axis centred on substrate mobilisation, hepatic lipid handling and energy expenditure. In GLP-1-glucagon co-agonist constructs, GLP-1 receptor activation may support satiety and glycaemic stability, while glucagon receptor engagement may increase metabolic flux [1, 23]. Early clinical and translational data support weight-loss and metabolic effects, but receptor-dose balance, gastrointestinal tolerability and long-term safety remain important constraints [18, 24]. The independent contribution of glucagon-mediated energy expenditure to human clinical benefit remains uncertain.

3.4 | Amylin-Linked Strategies and Satiety Layering

AMYR signalling provides a satiety-regulating pathway that is complementary to GLP-1 receptor activation. Endogenous amylin acts predominantly through hindbrain circuits involved in meal termination, gastric emptying and postprandial glucagon regulation [25, 26]. Combined GLP-1-amylin strategies may therefore reinforce appetite suppression through partially

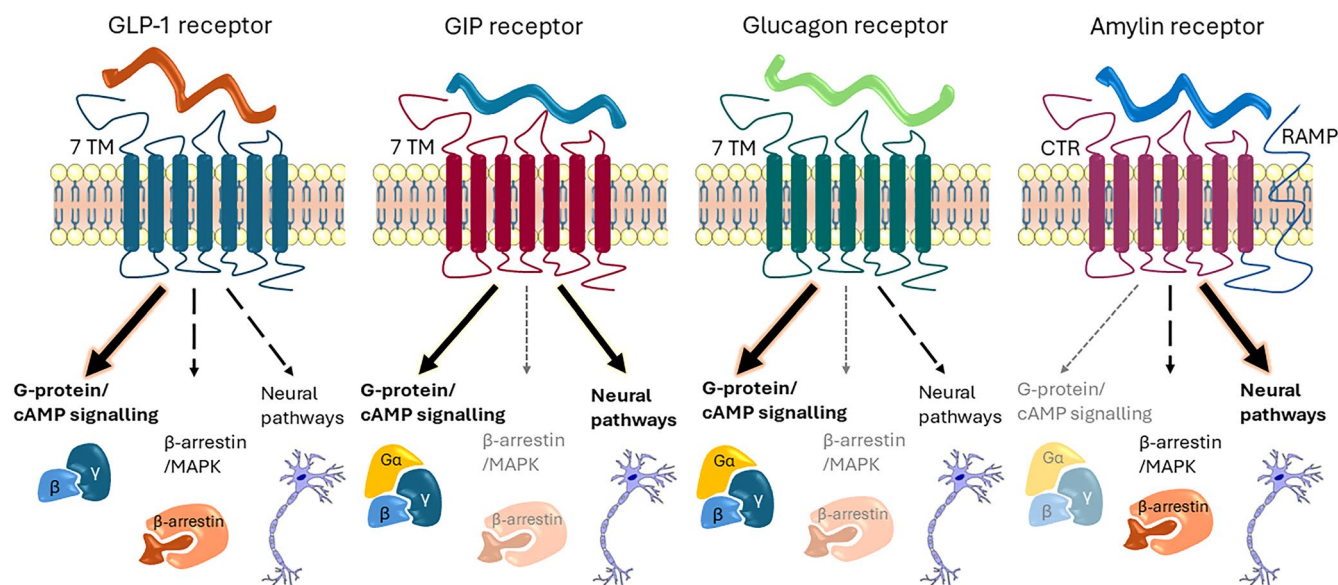


FIGURE 2 | Receptor-network signalling as a mechanistic basis for heterogeneous incretin effects. The figure provides a schematic representation of signalling diversity across GLP-1, GIP, glucagon and AMYR systems. GLP-1, GIP and glucagon receptors are class B G-protein-coupled receptors with seven-transmembrane architecture, whereas AMYR (=CTR-RAMP complex) signalling is mediated through calcitonin receptor complexes modified by RAMP. Differences in ligand structure, receptor conformation, tissue distribution and signalling duration may influence the relative engagement of G-protein/cAMP, β -arrestin/MAPK and neural pathways. These signalling patterns may contribute to differences in glycaemic efficacy, appetite regulation, gastrointestinal tolerability, energy handling and tissue-level cardiometabolic effects. The arrow weights and pathway emphasis are intended as qualitative schematic features rather than quantitative comparisons of pathway strength or clinical effect size. cAMP, cyclic adenosine monophosphate; CTR, calcitonin receptor; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; MAPK, mitogen-activated protein kinase; RAMP, receptor activity-modifying protein; TM, transmembrane.

overlapping but non-identical neural pathways. Clinical studies of cagrilintide–semaglutide and early amycetin data support the therapeutic relevance of this approach for weight reduction [19, 27], although additive and synergistic effects cannot yet be clearly distinguished in humans.

3.5 | Triple Agonism and Biological Limits

Triple receptor agonists targeting GLP-1, GIP and glucagon receptors represent the most explicit form of incretin receptor-network pharmacology. Their rationale is to coordinate pathways regulating energy intake, metabolic signalling, substrate mobilisation and energy expenditure. Structural studies of retatrutide support designed receptor balance across the three receptor systems [28, 29], while Phase 2 trials demonstrate substantial body-weight reduction and clinically relevant glycaemic and metabolic effects [12, 30].

Greater receptor complexity may also introduce biological constraints, including gastrointestinal adverse effects, dose-balance limitations, adaptive metabolic responses and body-composition concerns. High-magnitude weight loss should therefore be interpreted alongside fat-mass reduction, lean-mass preservation and functional metabolic quality [31]. Triple agonism illustrates both the potential and the limits of receptor-network pharmacology: high metabolic efficacy does not by itself establish long-term organ protection. Detailed

receptor-topology considerations are provided in Supporting Information Text S2, while Figure 3 summarises the clinical interpretation of the receptor network.

4 | Translational Tissue-Level Mechanisms

Translational mechanisms provide biological context for the clinical domains described above. Incretin-based therapies may influence neural, adipose, vascular, kidney and hepatic pathways through changes in energy intake, adiposity, substrate flux, inflammatory signalling and haemodynamic load [32, 33]. These mechanisms may help explain multi-organ effects, but should not be interpreted as independent evidence of clinical benefit.

4.1 | Central Nervous System, Appetite and Reward

GLP-1R activation reduces energy intake through homeostatic satiety pathways and may also influence reward-related eating, craving and food-cue responses [34, 35]. GIP receptor signalling may contribute to central intake regulation, whereas AMYR activation promotes meal termination through partly distinct hindbrain circuits [2, 25]. These overlapping neural pathways provide a mechanistic basis for layered appetite regulation, but neural and behavioural endpoints remain translational rather than positioning-grade evidence.

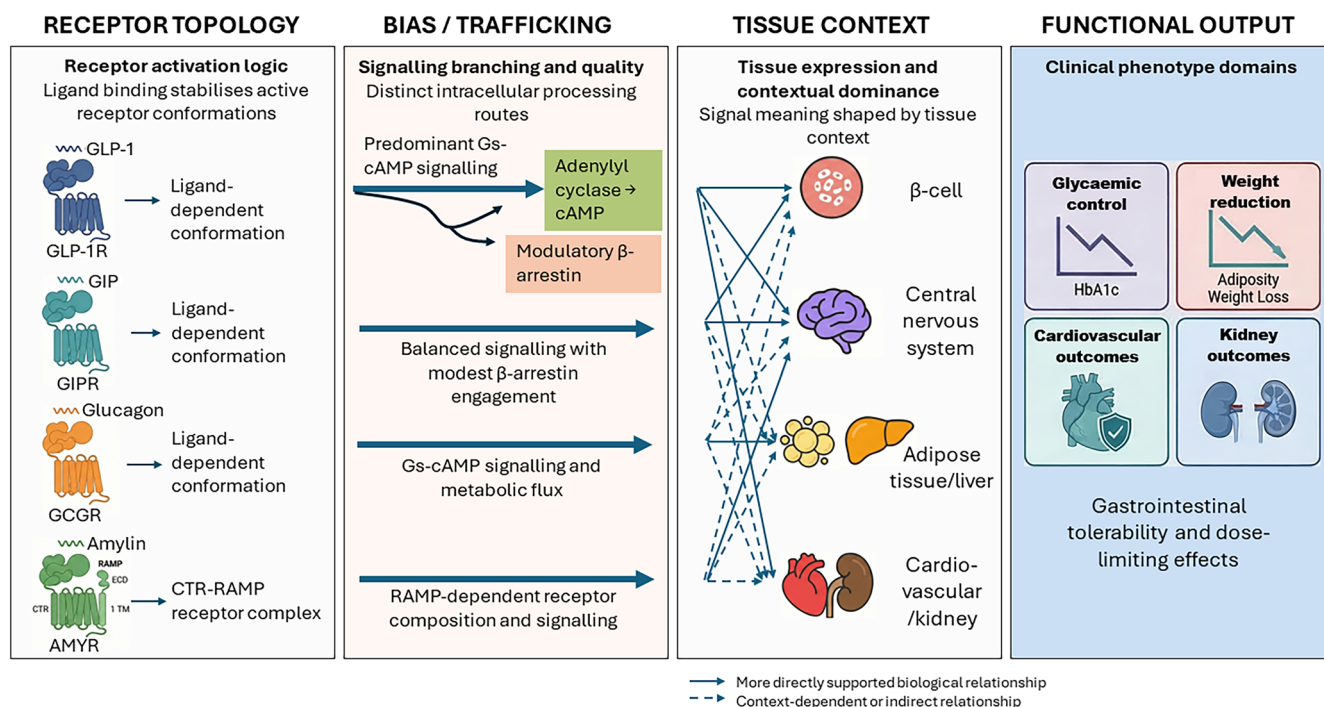


FIGURE 3 | Simplified receptor-network framework linking incretin pharmacology with clinical phenotype domains. The figure provides a simplified overview of how GLP-1, GIP, glucagon and AMYR pathways may contribute to partially overlapping physiological domains relevant to incretin-based therapy. GLP-1R signalling is primarily associated with satiety and glycaemic regulation, GIPR with neural-metabolic modulation, GCGR with substrate mobilisation and energy expenditure and AMYR with meal termination and satiety reinforcement. These pathways may converge on clinical domains including glycaemic control, weight reduction, cardiovascular and kidney protection and metabolic liver effects. The relationships shown are conceptual rather than quantitative and do not imply that receptor-level mechanisms independently establish clinical outcome benefit. Clinical positioning remains determined by outcome maturity, patient phenotype, tolerability and durability. AMYR, amylin receptor; cAMP, cyclic adenosine monophosphate; CNS, central nervous system; GCGR, glucagon receptor; GIP, glucose-dependent insulinotropic polypeptide; GIPR, GIP receptor; GLP-1, glucagon-like peptide-1; GLP-1R, GLP-1 receptor; MAPK, mitogen-activated protein kinase; RAMP, receptor activity-modifying protein.

4.2 | Adipose Tissue, Inflammation and Substrate Flux

Weight reduction with incretin-based therapy may be accompanied by adipose remodelling, improved insulin sensitivity and favourable changes in lipid and inflammatory markers, including high-sensitivity C-reactive protein, tumour necrosis factor- α and interleukin-6 [16, 36].

Reduced adiposity may also decrease lipotoxic substrate flux towards the liver, skeletal muscle and vascular tissues. However, the extent to which these tissue-level changes independently mediate cardiovascular or kidney outcomes remains uncertain.

4.3 | Convergent Cardiometabolic Stress Pathways

Across tissues, reduced energy intake, adiposity, inflammatory activity, haemodynamic load and ectopic lipid flux may converge on shared cardiometabolic stress pathways [32, 33]. This convergence supports biological plausibility for multi-organ benefit, but clinical positioning should remain based on validated outcomes: dedicated cardiovascular and kidney outcome

evidence where available, with more cautious interpretation of hepatic, neural, adipose and microvascular signals [4, 5].

5 | Next-Generation Incretin Therapies: Class Characteristics and Evidence Maturity

Incretin-based pharmacotherapy has expanded beyond selective GLP-1 receptor agonism to include GIP-GLP-1 and GLP-1-glucagon co-agonists, amylin-linked strategies, triple receptor agonists, oral small-molecule GLP-1 receptor agonists and early receptor-directed constructs. These classes differ in receptor architecture, dominant clinical axis and evidence maturity. Established GLP-1 receptor agonists have the strongest cardiovascular and kidney outcome support in selected populations, whereas several next-generation strategies remain supported mainly by glycaemic, weight-loss, metabolic, body-composition or early translational endpoints [1, 2].

This distinction is central to clinical positioning. Pharmacological novelty should not be equated with outcome maturity. Class interpretation should remain anchored to patient phenotype, endpoint validation, tolerability, body-composition effects and treatment durability. The major therapeutic classes, dominant

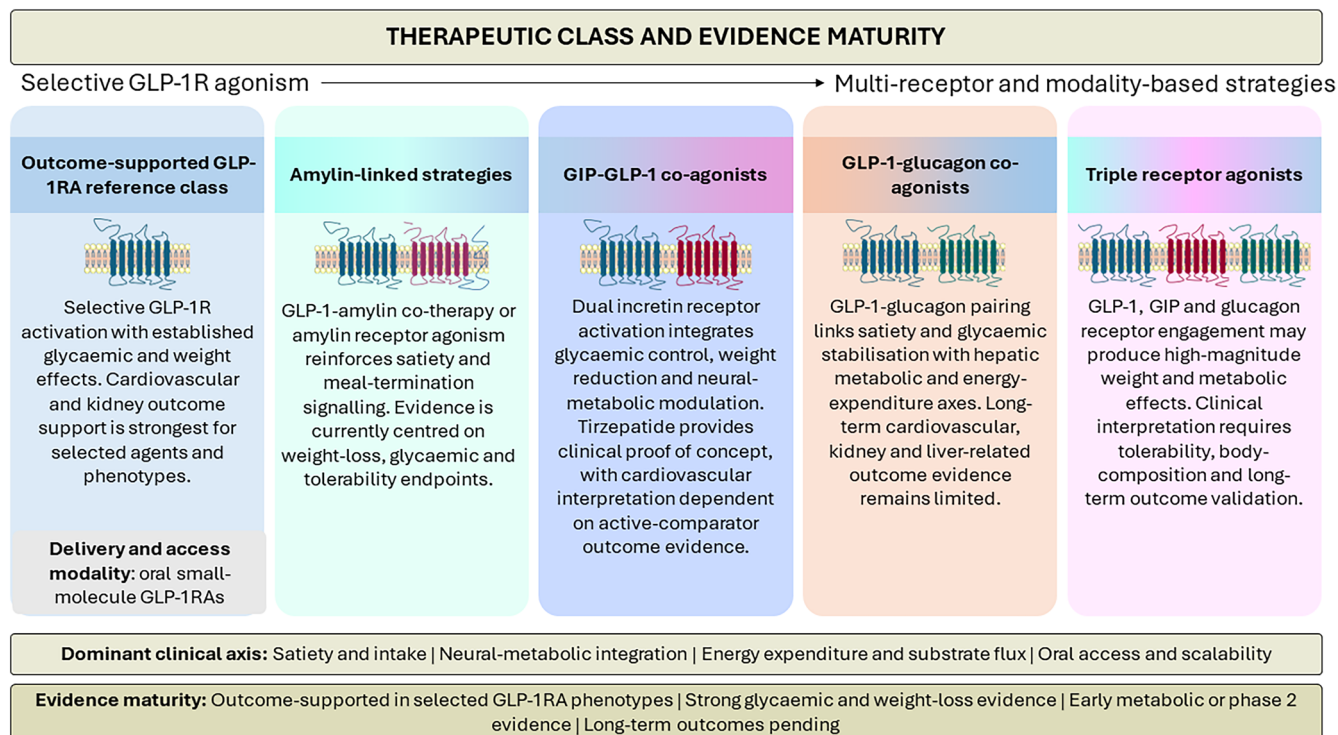


FIGURE 4 | Class characteristics and evidence maturity of next-generation incretin-based therapies. The figure summarises major incretin-based therapeutic classes according to receptor architecture, dominant clinical axis and current evidence maturity. Selective GLP-1 receptor agonism provides the outcome-supported reference class, with cardiovascular and kidney benefit established for selected agents and phenotypes. GIP-GLP-1 receptor co-agonists are supported by strong glycaemic and weight-loss evidence and active-comparator cardiovascular outcome data. GLP-1-glucagon receptor co-agonists link intake reduction with hepatic metabolic and energy-expenditure mechanisms, but long-term outcome evidence remains limited. Amylin-linked and GLP-1-amylin strategies reinforce satiety and meal-termination signalling, with evidence currently centred on weight-loss, glycaemic and tolerability endpoints. Triple receptor agonists show high-magnitude metabolic and weight-loss effects in Phase 2 studies, but require longer-term outcome validation. Oral small-molecule GLP-1 receptor agonists represent a delivery and access-oriented modality rather than receptor-network expansion. Receptor complexity, weight-loss magnitude and mechanistic plausibility should therefore be interpreted alongside endpoint maturity, tolerability, body-composition effects and durability. AMYR, amylin receptor; GCGR, glucagon receptor; GIP, glucose-dependent insulintropic polypeptide; GIPR, GIP receptor; GLP-1, glucagon-like peptide-1; GLP-1R, GLP-1 receptor.

clinical axes and relative evidence maturity are summarised in Figure 4 and Tables S1 and S2.

5.1 | GIP-GLP-1 Receptor Co-Agonists

Dual GIP-GLP-1 receptor agonism is the first clinically established incretin polyagonist class. Tirzepatide produces greater reductions in HbA1c and body weight than semaglutide 1 mg in T2D and substantial, sustained weight loss in obesity [11, 12, 37]. Mechanistically, GIP receptor signalling may contribute to central intake regulation, adipose biology and metabolic partitioning, although the relative contribution of these pathways in humans remains incompletely defined [2, 38].

The clinical interpretation of tirzepatide should distinguish metabolic efficacy from cardiovascular outcome maturity. In SURPASS-CVOT, tirzepatide was non-inferior to dulaglutide for three-point MACE, but superiority was not demonstrated [13]. Thus, active-comparator cardiovascular safety and efficacy data should not be interpreted as equivalent to placebo-controlled

demonstration of cardiovascular risk reduction. Tirzepatide can therefore be positioned strongly when glycaemic control and weight reduction are major therapeutic priorities, whereas established cardiovascular outcome evidence remains an important differentiator when atherosclerotic risk reduction is the dominant treatment goal.

5.2 | GLP-1-Glucagon Receptor Co-Agonists

GLP-1-glucagon receptor co-agonists combine appetite and glycaemic regulation with glucagon-linked effects on substrate mobilisation and hepatic metabolism [23]. Early clinical studies, including survodutide and cotadutide programmes, support weight-loss and metabolic efficacy, but gastrointestinal tolerability, receptor-dose balance and long-term safety remain important constraints [18, 39]. Cardiovascular, kidney and long-term liver-related outcome evidence is not yet sufficiently mature for outcome-based positioning, and the independent clinical contribution of glucagon-mediated energy expenditure remains uncertain [24, 40].

5.3 | Amylin-Linked and GLP-1-Amylin Strategies

Amylin-linked therapies use complementary satiety and meal-termination pathways to enhance weight reduction beyond selective GLP-1 receptor agonism [25, 26]. Cagrilintide–sema-glutide combinations and early amycretin studies support clinically relevant weight-loss efficacy [27, 41]. Current evidence remains centred on body weight, glycaemic measures and tolerability, while dedicated cardiovascular, kidney and long-term organ-outcome data remain unavailable for outcome-based positioning.

5.4 | Triple Receptor Agonists

Triple receptor agonists targeting GLP-1, GIP and glucagon receptors represent high-efficacy multi-receptor pharmacology. Retatrutide has produced substantial weight reduction and clinically relevant glycaemic and metabolic effects in Phase 2 studies [12, 30], while structural data support designed receptor balance across the three receptor systems [28]. However, dedicated cardiovascular, kidney and long-term organ-protective outcome data remain limited. Clinical interpretation should therefore consider durability, gastrointestinal tolerability, dose balance and body composition, particularly lean-mass preservation during high-magnitude weight loss [31].

5.5 | Oral Small-Molecule GLP-1 Receptor Agonists

Oral small-molecule GLP-1 receptor agonists represent a delivery and access-oriented innovation rather than receptor-network expansion. Orforglipron has shown clinically relevant glycaemic and weight-loss effects in obesity and T2D, while danuglipron provides additional proof of concept for non-peptide oral GLP-1 receptor agonism [42–44]. The potential value of this class lies primarily in accessibility, scalability and patient preference, while long-term cardiovascular, kidney and durability data remain necessary for outcome-based positioning.

5.6 | Emerging Receptor-Directed and Multi-Domain Constructs

Emerging receptor-directed and multi-domain constructs include GLP-1-based targeting approaches and non-classical combinations designed to modify tissue exposure or pathway-selective pharmacology [45, 46]. Their current relevance is primarily translational, and they should not be positioned alongside outcome-tested GLP-1 receptor agonists or more mature Phase 3 metabolic therapies.

5.7 | Evidence Maturity and Clinical Interpretation

Receptor architecture and evidence maturity should be considered separately when interpreting next-generation incretin therapies. Receptor architecture may help explain differences

in glycaemic efficacy, weight reduction, satiety, energy handling and tolerability, whereas evidence maturity determines how confidently these effects can support clinical positioning [1, 2]. Agents with dedicated cardiovascular or kidney outcome evidence therefore occupy a different evidentiary category from therapies supported mainly by glycaemic, weight-loss, body-composition or early metabolic endpoints [4, 5].

This distinction becomes clinically relevant when therapeutic goals compete. High-efficacy polyagonists may be prioritised when glycaemic control or severe adiposity is the dominant unresolved problem, but greater metabolic efficacy should not be assumed to confer greater cardiovascular or kidney protection. Conversely, when established atherosclerotic cardiovascular disease or CKD defines the principal treatment priority, outcome-proven organ protection should carry greater evidentiary weight. Figure 4 and Tables S1 and S2 summarise these class-level differences and remaining evidence gaps.

6 | Clinical Boundaries, Safety and Durability

The clinical value of incretin-based therapies depends not only on efficacy, but also on tolerability, treatment persistence, body-composition effects and long-term safety [1, 2]. This is increasingly important as incretin pharmacology moves from selective GLP-1 receptor agonism towards higher-efficacy polyagonists, amylin-linked strategies and oral small-molecule GLP-1 receptor agonists. Gastrointestinal tolerability, gallbladder and biliary events, lean-mass preservation, nutritional adequacy and long-term persistence all shape therapeutic positioning rather than functioning as secondary considerations [47, 48].

6.1 | Gastrointestinal Tolerability and Dose-Limiting Effects

Gastrointestinal adverse effects are the most common practical limitation of GLP-1-based therapy and remain relevant across selective GLP-1 receptor agonists and several next-generation incretin strategies. Nausea, vomiting, diarrhoea, constipation and abdominal discomfort may influence dose escalation, adherence and persistence. Gradual titration, patient education, meal-size adjustment and individualised dose escalation may reduce these effects, but symptoms can still become dose-limiting in a clinically meaningful proportion of patients [1, 49].

Gastrointestinal tolerability is particularly important for higher-efficacy polyagonists. Greater receptor engagement may increase weight-loss efficacy, but may also narrow the tolerability window through nausea, vomiting or other gastrointestinal symptoms [18, 50]. Tolerability is therefore not simply an adverse-event category; it determines whether pharmacological efficacy can be maintained long enough to produce durable clinical benefit.

6.2 | Gallbladder and Biliary Considerations

Gallbladder and biliary events require specific attention during incretin-based weight-loss therapy. A systematic review and

meta-analysis of randomised clinical trials reported an increased risk of gallbladder or biliary disease with GLP-1 receptor agonists, particularly at higher doses, with longer treatment duration and in weight-loss indications [47]. This signal should be interpreted in the context of both drug exposure and rapid or substantial weight reduction, because weight loss itself may increase gallstone risk.

Clinical implementation should include counselling on biliary symptoms, especially in patients with previous gallbladder disease, rapid weight loss, persistent abdominal pain or recurrent gastrointestinal complaints. These considerations do not preclude therapy in most patients, but support timely assessment of persistent or severe symptoms. For newer polyagonists and amylin-linked strategies, longer exposure and larger outcome datasets are needed before gallbladder and biliary risk can be interpreted with the same confidence as for established GLP-1 receptor agonists [2, 19].

6.3 | Body Composition, Lean Mass and Nutritional Quality of Weight Loss

High-magnitude weight loss is clinically valuable in obesity and obesity-related cardiometabolic disease, but its interpretation should include the quality of weight loss. Fat-mass reduction is the desired target, whereas excessive lean-mass loss may be clinically relevant in older adults, patients with frailty, sarcopenic obesity, CKD, chronic inflammatory disease or low baseline muscle reserve. Body-weight reduction should therefore be assessed alongside body composition, physical function and nutritional status [31, 48].

Body-composition analyses with retatrutide show substantial fat-mass reduction during high-efficacy incretin polyagonism, while lean-mass changes require careful interpretation during large weight-loss responses [31]. This consideration applies across high-efficacy GLP-1-based, GIP-GLP-1, amylin-linked and other weight-loss pharmacotherapies. Resistance exercise, adequate protein intake and maintenance of functional capacity should be integrated into long-term implementation, particularly in older adults, patients with multimorbidity, established cardiovascular disease, CKD, mobility limitation or previous unintentional weight loss [6, 48]. The therapeutic goal is clinically meaningful adiposity reduction with preservation of muscle mass, strength and nutritional resilience, not maximal weight loss at any cost.

6.4 | Treatment Durability, Persistence and Discontinuation

Durability is central to the clinical interpretation of incretin-based therapy. Obesity is recognised as a chronic, relapsing disease and long-term benefit generally requires long-term treatment strategies rather than short-term pharmacological exposure [6]. Longer-term obesity trials support sustained weight loss during continued treatment with semaglutide and tirzepatide-based strategies, but persistence depends on tolerability, access and behavioural or nutritional support [8, 37].

Discontinuation is therefore a clinical boundary. After semaglutide withdrawal in the STEP 1 trial extension, weight regain and partial reversal of cardiometabolic improvements were observed [51]. This does not indicate pharmacological failure, but reflects regulation of chronic metabolic pathways without necessarily curing the underlying disease biology [1, 6]. Treatment plans should therefore address continuation, dose adjustment, temporary interruption, re-initiation, affordability and patient preference. For high-efficacy therapies, the key question is how much benefit can be maintained safely, acceptably and equitably over time [2, 8].

6.5 | Patient Selection and Implementation Boundaries

Once the dominant clinical priority and evidence maturity have been defined, treatment selection should be modified by factors that determine whether benefit can be delivered safely and sustained over time. In patients with multimorbidity, relevant considerations include gastrointestinal tolerability, frailty, body composition and nutritional status, gallbladder history, hydration and renal function, concomitant nephroprotective therapy, treatment persistence and access [5, 17, 48, 50]. These factors become particularly important during high-magnitude weight loss and in older adults, patients with CKD, low muscle reserve or previous unintentional weight loss.

Implementation should therefore distinguish pharmacological efficacy from practical treatment suitability. A highly effective therapy may be less appropriate when tolerability, nutritional vulnerability, frailty or limited persistence threatens sustained benefit. Conversely, when more than one treatment option is supported for the dominant clinical priority, these implementation factors may guide the final choice. Patient selection should therefore integrate outcome-supported benefit with the feasibility of maintaining treatment safely and durably.

6.6 | Integrative Clinical Interpretation

Clinical implementation should integrate evidence-supported benefit, dominant patient phenotype, safety and durability. When organ protection is the principal treatment goal, dedicated cardiovascular or kidney outcome evidence should carry the greatest evidentiary weight [4, 5], whereas high-efficacy weight-loss strategies should also be judged by tolerability, body composition and treatment persistence [31, 48]. Mechanistic plausibility may support therapeutic interpretation but should not replace endpoint validation [1, 2].

7 | Limitations

This review was designed as a narrative clinical review with structured literature identification rather than a formal systematic review or meta-analysis. Study selection was guided by clinical relevance, conceptual importance and translational applicability. No quantitative pooling, formal risk-of-bias assessment, GRADE-based evidence rating, patient-level reanalysis

or statistical adjustment for confounding was performed. The review should therefore be interpreted as an outcome-stratified synthesis and clinical-positioning framework rather than a formal evidence-grading document or treatment guideline.

The evidence base is heterogeneous across therapeutic classes, clinical domains and endpoint types. Selected GLP-1 receptor agonists are supported by dedicated cardiovascular or kidney outcome trials, whereas several newer incretin-based strategies remain supported mainly by glycaemic, weight-loss, body-composition, histological or early translational endpoints. Direct comparisons across classes are therefore limited, and metabolic efficacy or mechanistic plausibility should not be considered equivalent to validated organ protection.

Several receptor-network interpretations remain hypothesis-generating and are derived partly from structural, cellular, preclinical or translational studies. In addition, trial efficacy may not fully capture real-world factors including gastrointestinal tolerability, gallbladder and biliary risk, nutritional vulnerability, body-composition changes, treatment persistence, discontinuation, cost, access and patient preference. Older adults, frail individuals and patients with advanced multimorbidity or low muscle reserve may also be under-represented in clinical trials.

Finally, the therapeutic landscape is evolving rapidly. Long-term cardiovascular, kidney, hepatic, body-composition, safety and durability data remain incomplete for several next-generation therapies. The clinical positioning proposed here should therefore remain provisional and responsive to emerging outcome evidence.

8 | Conclusions

Incretin-based therapy has evolved from glucose-centred pharmacology towards outcome-stratified cardiometabolic treatment. Selected GLP-1 receptor agonists now have established cardiovascular and kidney outcome relevance in defined phenotypes, while high-magnitude weight reduction has become an important therapeutic target in obesity and obesity-related cardiometabolic disease.

Evidence maturity remains heterogeneous across therapeutic classes. GIP-GLP-1 co-agonists and other next-generation strategies may provide substantial glycaemic and weight-loss efficacy, but metabolic efficacy should not be assumed to confer equivalent cardiovascular, kidney or liver protection without dedicated outcome evidence. Receptor-network pharmacology provides a useful biological explanation for heterogeneous effects, but clinical positioning should remain anchored to validated outcomes, patient phenotype, tolerability, body composition and durability.

Future studies should determine whether the metabolic and mechanistic advantages of newer incretin-based therapies translate into sustained cardiovascular, kidney, hepatic and functional benefit, while defining how these effects can be delivered safely across patients with complex cardiometabolic multimorbidity.

Author Contributions

Ferenc Sztanek conceptualised the review, developed the receptor-network framework and drafted the manuscript. Hajnalka Lőrincz critically revised the manuscript for intellectual content and contributed to the interpretation of metabolic and translational aspects. Mariann Harangi critically revised the manuscript for intellectual content and contributed to the interpretation of cardiometabolic and vascular aspects. Attila Csaba Nagy critically revised the manuscript for intellectual content and contributed to methodological and evidence-synthesis considerations. All authors reviewed and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing is not applicable to this article, as no datasets were generated or analysed during the current narrative review.

Peer Review

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References

1. D. J. Drucker, "GLP-1-Based Therapies for Diabetes, Obesity and Beyond," *Nature Reviews. Drug Discovery* 24, no. 8 (2025): 631–650, <https://doi.org/10.1038/s41573-025-01183-8>.
2. M. A. Nauck, K. R. Tuttle, M. H. Tschöpp, and M. Blüher, "Glucagon-Like Receptor Agonists and Next-Generation Incretin-Based Medications: Metabolic, Cardiovascular, and Renal Benefits," *Lancet* 407, no. 10531 (2026): 892–908, [https://doi.org/10.1016/S0140-6736\(25\)02105-1](https://doi.org/10.1016/S0140-6736(25)02105-1).
3. N. Sattar, M. M. Y. Lee, S. L. Kristensen, et al., "Cardiovascular, Mortality, and Kidney Outcomes With GLP-1 Receptor Agonists in Patients With Type 2 Diabetes: A Systematic Review and Meta-Analysis of Randomised Trials," *Lancet Diabetes and Endocrinology* 9, no. 10 (2021): 653–662, [https://doi.org/10.1016/S2213-8587\(21\)00203-5](https://doi.org/10.1016/S2213-8587(21)00203-5).
4. S. V. Badve, A. Bilal, M. M. Y. Lee, et al., "Effects of GLP-1 Receptor Agonists on Kidney and Cardiovascular Disease Outcomes: A Meta-Analysis of Randomised Controlled Trials," *Lancet Diabetes and Endocrinology* 13, no. 1 (2025): 15–28, [https://doi.org/10.1016/S2213-8587\(24\)00271-7](https://doi.org/10.1016/S2213-8587(24)00271-7).
5. V. Perkovic, K. R. Tuttle, P. Rossing, et al., "Effects of Semaglutide on Chronic Kidney Disease in Patients With Type 2 Diabetes," *New England Journal of Medicine* 391, no. 2 (2024): 109–121, <https://doi.org/10.1056/NEJMoa2403347>.

6. American Diabetes Association Professional Practice Committee for Diabetes, "8. Obesity and Weight Management for the Prevention and Treatment of Diabetes: Standards of Care in Diabetes-2026," *Diabetes Care* 49 (2026): S166–S182, <https://doi.org/10.2337/dc26-S008>.
7. J. P. H. Wilding, R. L. Batterham, S. Calanna, et al., "Once-Weekly Semaglutide in Adults With Overweight or Obesity," *New England Journal of Medicine* 384, no. 11 (2021): 989–1002, <https://doi.org/10.1056/NEJMoa2032183>.
8. W. T. Garvey, R. L. Batterham, M. Bhatta, et al., "Two-Year Effects of Semaglutide in Adults With Overweight or Obesity: The STEP 5 Trial," *Nature Medicine* 28, no. 10 (2022): 2083–2091, <https://doi.org/10.1038/s41591-022-02026-4>.
9. S. L. Kristensen, R. Rørth, P. S. Jhund, et al., "Cardiovascular, Mortality, and Kidney Outcomes With GLP-1 Receptor Agonists in Patients With Type 2 Diabetes: A Systematic Review and Meta-Analysis of Cardiovascular Outcome Trials," *Lancet Diabetes and Endocrinology* 7, no. 10 (2019): 776–785, [https://doi.org/10.1016/S2213-8587\(19\)30249-9](https://doi.org/10.1016/S2213-8587(19)30249-9).
10. A. M. Lincoff, K. Brown-Frandsen, H. M. Colhoun, et al., "Semaglutide and Cardiovascular Outcomes in Obesity Without Diabetes," *New England Journal of Medicine* 389, no. 24 (2023): 2221–2232, <https://doi.org/10.1056/NEJMoa2307563>.
11. J. P. Frias, M. J. Davies, J. Rosenstock, et al., "Tirzepatide Versus Semaglutide Once Weekly in Patients With Type 2 Diabetes," *New England Journal of Medicine* 385, no. 6 (2021): 503–515, <https://doi.org/10.1056/NEJMoa2107519>.
12. A. M. Jastreboff, L. J. Aronne, N. N. Ahmad, et al., "Tirzepatide Once Weekly for the Treatment of Obesity," *New England Journal of Medicine* 387, no. 3 (2022): 205–216, <https://doi.org/10.1056/NEJMoa2206038>.
13. S. J. Nicholls, I. Pavo, D. L. Bhatt, et al., "Cardiovascular Outcomes With Tirzepatide Versus Dulaglutide in Type 2 Diabetes," *New England Journal of Medicine* 393, no. 24 (2025): 2409–2420, <https://doi.org/10.1056/NEJMoa2505928>.
14. A. J. Sanyal, P. N. Newsome, I. Kliers, et al., "Phase 3 Trial of Semaglutide in Metabolic Dysfunction-Associated Steatohepatitis," *New England Journal of Medicine* 392, no. 21 (2025): 2089–2099, <https://doi.org/10.1056/NEJMoa2413258>.
15. R. Loomba, M. L. Hartman, E. J. Lawitz, et al., "Tirzepatide for Metabolic Dysfunction-Associated Steatohepatitis With Liver Fibrosis," *New England Journal of Medicine* 391, no. 4 (2024): 299–310, <https://doi.org/10.1056/NEJMoa2401943>.
16. F. Sztanek, L. I. Tóth, A. Pető, M. Hernyák, Á. Diószegi, and M. Harangi, "New Developments in Pharmacological Treatment of Obesity and Type 2 Diabetes-Beyond and Within GLP-1 Receptor Agonists," *Biomedicine* 12, no. 6 (2024): 1320, <https://doi.org/10.3390/biomedicines12061320>.
17. J. F. E. Mann, P. Rossing, G. Bakris, et al., "Effects of Semaglutide With and Without Concomitant SGLT2 Inhibitor Use in Participants With Type 2 Diabetes and Chronic Kidney Disease in the FLOW Trial," *Nature Medicine* 30, no. 10 (2024): 2849–2856, <https://doi.org/10.1038/s41591-024-03133-0>.
18. C. W. le Roux, O. Steen, K. J. Lucas, E. Startseva, A. Unseld, and A. M. Hennige, "Glucagon and GLP-1 Receptor Dual Agonist Survodutide for Obesity: A Randomised, Double-Blind, Placebo-Controlled, Dose-Finding Phase 2 Trial," *Lancet Diabetes and Endocrinology* 12, no. 3 (2024): 162–173, [https://doi.org/10.1016/S2213-8587\(23\)00356-X](https://doi.org/10.1016/S2213-8587(23)00356-X).
19. W. T. Garvey, M. Blüher, C. K. Osorio Contreras, et al., "Coadministered Cagrilintide and Semaglutide in Adults With Overweight or Obesity," *New England Journal of Medicine* 393, no. 7 (2025): 635–647, <https://doi.org/10.1056/NEJMoa2502081>.
20. M. A. Nauck and T. D. Müller, "Incretin Hormones and Type 2 Diabetes," *Diabetologia* 66, no. 10 (2023): 1780–1795, <https://doi.org/10.1007/s00125-023-05956-x>.
21. J. D. Douros, J. Mokrosinski, and B. Finan, "The GLP-1R as a Model for Understanding and Exploiting Biased Agonism in Next-Generation Medicines," *Journal of Endocrinology* 261, no. 2 (2024): e230226, <https://doi.org/10.1530/JOE-23-0226>.
22. B. Jones, T. Buenaventura, N. Kanda, et al., "Targeting GLP-1 Receptor Trafficking to Improve Agonist Efficacy," *Nature Communications* 9, no. 1 (2018): 1602, <https://doi.org/10.1038/s41467-018-03941-2>.
23. J. B. Winther and J. J. Holst, "Glucagon Agonism in the Treatment of Metabolic Diseases Including Type 2 Diabetes Mellitus and Obesity," *Diabetes, Obesity & Metabolism* 26, no. 9 (2024): 3501–3512, <https://doi.org/10.1111/dom.15693>.
24. R. Golubic, J. Kennet, V. Parker, et al., "Dual Glucagon-Like Peptide-1 and Glucagon Receptor Agonism Reduces Energy Intake in Type 2 Diabetes With Obesity," *Diabetes, Obesity & Metabolism* 26, no. 7 (2024): 2634–2644, <https://doi.org/10.1111/dom.15579>.
25. M. K. Hankir and C. Le Foll, "Central Nervous System Pathways Targeted by Amylin in the Regulation of Food Intake," *Biochimie* 229 (2025): 95–104, <https://doi.org/10.1016/j.biochi.2024.10.012>.
26. M. Rejili, M. S. Hussain, Y. Khan, et al., "Amylin Receptors as Therapeutic Targets in Obesity: Emerging Peptide-Based Strategies," *Vascular Pharmacology* 162 (2026): 107563, <https://doi.org/10.1016/j.vph.2025.107563>.
27. K. Dahl, S. Toubro, S. Dey, et al., "Amycretin, a Novel, Unimolecular GLP-1 and Amylin Receptor Agonist Administered Subcutaneously: Results From a Phase 1b/2a Randomised Controlled Study," *Lancet* 406, no. 10499 (2025): 149–162, [https://doi.org/10.1016/S0140-6736\(25\)01185-7](https://doi.org/10.1016/S0140-6736(25)01185-7).
28. W. Li, Q. Zhou, Z. Cong, et al., "Structural Insights Into the Triple Agonism at GLP-1R, GIPR and GCGR Manifested by Retatrutide," *Cell Discovery* 10, no. 1 (2024): 77, <https://doi.org/10.1038/s41421-024-00700-0>.
29. A. Novikoff and T. D. Müller, "Pharmacological Advances in Incretin-Based Polyagonism: What We Know and What We Don't," *Physiology* 39, no. 3 (2024): 142–156, <https://doi.org/10.1152/physiol.00032.2023>.
30. J. Rosenstock, J. Frias, A. M. Jastreboff, et al., "Retatrutide, a GIP, GLP-1 and Glucagon Receptor Agonist, for People With Type 2 Diabetes: A Randomised, Double-Blind, Placebo and Active-Controlled, Parallel-Group, Phase 2 Trial Conducted in the USA," *Lancet* 402, no. 10401 (2023): 529–544, [https://doi.org/10.1016/S0140-6736\(23\)01053-X](https://doi.org/10.1016/S0140-6736(23)01053-X).
31. T. Coskun, Q. Wu, N. C. Schloot, et al., "Effects of Retatrutide on Body Composition in People With Type 2 Diabetes: A Substudy of a Phase 2, Double-Blind, Parallel-Group, Placebo-Controlled, Randomised Trial," *Lancet Diabetes and Endocrinology* 13, no. 8 (2025): 674–684, [https://doi.org/10.1016/S2213-8587\(25\)00092-0](https://doi.org/10.1016/S2213-8587(25)00092-0).
32. J. P. Psaltis, J. A. Marathe, M. T. Nguyen, et al., "Incretin-Based Therapies for the Management of Cardiometabolic Disease in the Clinic: Past, Present, and Future," *Medicinal Research Reviews* 45, no. 1 (2025): 29–65, <https://doi.org/10.1002/med.22070>.
33. A. Avogaro and G. P. Fadini, "Incretins and the Cardiovascular System: Bridging Digestion With Metabolism," *Lancet Diabetes and Endocrinology* 13, no. 9 (2025): 790–802, [https://doi.org/10.1016/S2213-8587\(25\)00166-4](https://doi.org/10.1016/S2213-8587(25)00166-4).
34. G. Amorim Moreira Alves, M. Teranishi, A. C. Teixeira de Castro Gonçalves Ortega, F. James, and A. S. Perera Molligoda Arachchige, "Mechanisms of GLP-1 in Modulating Craving and Addiction: Neurobiological and Translational Insights," *Medical Science* 13, no. 3 (2025): 136, <https://doi.org/10.3390/medsci13030136>.

35. J. Cao, M. J. Belousoff, R. M. Johnson, et al., "Structural and Dynamic Features of Cagrilintide Binding to Calcitonin and Amylin Receptors," *Nature Communications* 16, no. 1 (2025): 3389, <https://doi.org/10.1038/s41467-025-58680-y>.
36. T. Ábel and É. Csobod Csajbókné, "Semaglutide-Mediated Remodeling of Adipose Tissue in Type 2 Diabetes: Molecular Mechanisms Beyond Glycemic Control," *International Journal of Molecular Sciences* 27, no. 3 (2026): 1186, <https://doi.org/10.3390/ijms27031186>.
37. T. A. Wadden, A. M. Chao, S. Machineni, et al., "Tirzepatide After Intensive Lifestyle Intervention in Adults With Overweight or Obesity: The SURMOUNT-3 Phase 3 Trial," *Nature Medicine* 29, no. 11 (2023): 2909–2918, <https://doi.org/10.1038/s41591-023-02597-w>.
38. J. D. Douros, S. A. Mowery, and P. J. Knerr, "The Premise of the Paradox: Examining the Evidence That Motivated GIPR Agonist and Antagonist Drug Development Programs," *Journal of Clinical Medicine* 14, no. 11 (2025): 3812, <https://doi.org/10.3390/jcm14113812>.
39. V. E. R. Parker, D. Robertson, T. Wang, et al., "Efficacy, Safety, and Mechanistic Insights of Cotadutide, a Dual Receptor Glucagon-Like Peptide-1 and Glucagon Agonist," *Journal of Clinical Endocrinology and Metabolism* 105, no. 3 (2020): dgz047, <https://doi.org/10.1210/clinem/dgz047>.
40. M. P. Valdecantos, L. Ruiz, C. Folgueira, et al., "The Dual GLP-1/Glucagon Receptor Agonist G49 Mimics Bariatric Surgery Effects by Inducing Metabolic Rewiring and Inter-Organ Crosstalk," *Nature Communications* 15, no. 1 (2024): 10342, <https://doi.org/10.1038/s41467-024-54080-w>.
41. J. P. Frias, S. Deenadayalan, L. Erichsen, et al., "Efficacy and Safety of Co-Administered Once-Weekly Cagrilintide 2.4 mg With Once-Weekly Semaglutide 2.4 mg in Type 2 Diabetes: A Multicentre, Randomised, Double-Blind, Active-Controlled, Phase 2 Trial," *Lancet* 402, no. 10403 (2023): 720–730, [https://doi.org/10.1016/S0140-6736\(23\)01163-7](https://doi.org/10.1016/S0140-6736(23)01163-7).
42. S. Wharton, T. Blevins, L. Connery, et al., "Daily Oral GLP-1 Receptor Agonist Orforglipron for Adults With Obesity," *New England Journal of Medicine* 389, no. 10 (2023): 877–888, <https://doi.org/10.1056/NEJMoa2302392>.
43. D. B. Horn, D. H. Ryan, S. G. Kis, et al., "Orforglipron, an Oral Small-Molecule GLP-1 Receptor Agonist, for the Treatment of Obesity in People With Type 2 Diabetes (ATTAIN-2): A Phase 3, Double-Blind, Randomised, Multicentre, Placebo-Controlled Trial," *Lancet* 406, no. 10522 (2026): 2927–2944, [https://doi.org/10.1016/S0140-6736\(25\)02165-8](https://doi.org/10.1016/S0140-6736(25)02165-8).
44. A. R. Saxena, J. P. Frias, L. S. Brown, et al., "Efficacy and Safety of Oral Small Molecule Glucagon-Like Peptide 1 Receptor Agonist Dapaglipron for Glycemic Control Among Patients With Type 2 Diabetes: A Randomized Clinical Trial," *JAMA Network Open* 6, no. 5 (2023): e2314493, <https://doi.org/10.1001/jamanetworkopen.2023.14493>.
45. M. M. Véniant, S. C. Lu, L. Atangan, et al., "A GIPR Antagonist Conjugated to GLP-1 Analogues Promotes Weight Loss With Improved Metabolic Parameters in Preclinical and Phase 1 Settings," *Nature Metabolism* 6, no. 2 (2024): 290–303, <https://doi.org/10.1038/s42255-023-00966-w>.
46. J. Petersen, M. Q. Ludwig, V. Juozaityte, et al., "GLP-1-Directed NMDA Receptor Antagonism for Obesity Treatment," *Nature* 629, no. 8014 (2024): 1133–1141, <https://doi.org/10.1038/s41586-024-07419-8>.
47. L. He, J. Wang, F. Ping, et al., "Association of Glucagon-Like Peptide-1 Receptor Agonist Use With Risk of Gallbladder and Biliary Diseases: A Systematic Review and Meta-Analysis of Randomized Clinical Trials," *JAMA Internal Medicine* 182, no. 5 (2022): 513–519, <https://doi.org/10.1001/jamainternmed.2022.0338>.
48. J. C. Locatelli, J. G. Costa, A. Haynes, et al., "Incretin-Based Weight Loss Pharmacotherapy: Can Resistance Exercise Optimize Changes in

Body Composition?," *Diabetes Care* 47, no. 10 (2024): 1718–1730, <https://doi.org/10.2337/dci23-0100>.

49. V. R. Aroda, U. Erhan, P. Jelnes, et al., "Safety and Tolerability of Semaglutide Across the SUSTAIN and PIONEER Phase IIIa Clinical Trial Programmes," *Diabetes, Obesity & Metabolism* 25, no. 5 (2023): 1385–1397, <https://doi.org/10.1111/dom.14990>.

50. A. M. Jastreboff, L. M. Kaplan, J. P. Frias, et al., "Triple-Hormone-Receptor Agonist Retatrutide for Obesity—A Phase 2 Trial," *New England Journal of Medicine* 389, no. 6 (2023): 514–526, <https://doi.org/10.1056/NEJMoa2301972>.

51. J. P. H. Wilding, R. L. Batterham, M. Davies, et al., "Weight Regain and Cardiometabolic Effects After Withdrawal of Semaglutide: The STEP 1 Trial Extension," *Diabetes, Obesity & Metabolism* 24, no. 8 (2022): 1553–1564, <https://doi.org/10.1111/dom.14725>.

Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Figure S1:** Incretin receptor tetrad and putative physiological-output domains. **Supporting Information: Text S2.** Receptor topology and tetrad signalling framework. **Table S1:** Receptor architecture and dominant clinical axis of incretin-based therapeutic classes. **Table S2:** Evidence maturity across incretin-based therapeutic classes.