GLP-1 receptor agonists and next-generation incretin-based medications: metabolic, cardiovascular, and renal benefits

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See Online for appendix

GLP-1 receptor agonists were initially developed to treat type 2 diabetes and have had a transformative effect on its therapy, and are highly effective for glycaemic control, with the added benefit of bodyweight reduction and a low risk of causing hypoglycaemia. GLP-1 receptor agonists reduce risks for major adverse cardiovascular events (eg, non-fatal myocardial infarction, stroke, and cardiovascular death), and the risk of admission to or treatment within hospital for heart failure. These drugs reduce albuminuria and slow the decline in estimated glomerular filtration rate over time, therefore delaying or preventing kidney failure. Furthermore, GLP-1 receptor agonists (eg, liraglutide and semaglutide) and the dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptor co-agonist tirzepatide have been approved for treatment of obesity, with clinical trials establishing benefits for various obesity-related conditions: prevention of type 2 diabetes; risk for major adverse cardiovascular events; heart failure, especially with preserved ejection fraction; regression of steatosis and prevention of fibrosis in steatotic liver disease; and symptomatic improvements in obstructive sleep apnoea and knee osteoarthritis. Current developments include the exploration of novel indications (eg, neurodegenerative diseases and substance use disorders) with suggestive evidence of efficacy, and the development of small-molecule GLP-1 receptor agonists for oral treatment to improve convenience. Dual (ie, GLP-1–glucagon and GLP-1–amylin) and triple (ie, GIP–GLP-1–glucagon) receptor agonists activating multiple receptors promise greater efficacy than mono-agonists, especially for weight loss. However, some clinical development programmes have a high burden of adverse gastrointestinal events, and dose-escalation regimens should be optimised to reach acceptable tolerability.

Introduction

Incretin-based medications, developed based on the therapeutic potential of GLP-1, have evolved to become highly effective and widely recommended medications to treat type 2 diabetes and obesity complicated by comorbidities. This Review highlights the history of their development, the establishment of robust clinical benefits and safety in well defined patient populations in clinical trials, and the elucidation of their mechanisms of action. We provide a forecast for potential novel indications, with respect to current and future drug developments aiming at improved efficacy and safety. Although incretin hormones have a role in the action of inhibitors of dipeptidyl peptidase-4 (DPP-4), we use the term incretin-based medications exclusively for agonists acting selectively on GLP-1 receptors (ie, mono-agonists) or on GLP-1 and other receptors (ie, dual or triple agonists).

Search strategy and selection criteria

Literature for this Review was gathered by searching PubMed (for papers published in English, German, and French, from database inception to Oct 13, 2025) to identify clinical trials with titles that included the drugs exenatide, efpeglenatide, ecnoglutide, lixisenatide, liraglutide, dulaglutide, albiglutide, semaglutide (for subcutaneous and oral use), tirzepatide, orforglipron, danuglipron, survodutide, mazdutide, cagrilintide, CagriSema, or retatrutide; dual and triple agonists; therapeutic effects on glycaemic control (ie, through glycated haemoglobin or plasma glucose), bodyweight reduction, cardiovascular (ie, atherosclerotic cardiovascular disease or heart failure) outcomes, and renal outcomes; adverse events in individuals with type 2 diabetes; prevention of progression from prediabetes to type 2 diabetes; treatment of heart failure with preserved ejection fraction, metabolic dysfunction-associated steatotic liver disease, obstructive sleep apnoea syndrome, or osteoarthritis; and adverse events in people with overweight or obesity. All authors had collected relevant literature on these and similar topics since 1987, independent from a formal literature search.

Discovering the therapeutic potential of GLP-1

GLP-1 is one of two gut-derived incretin hormones. GLP-1 and its primary amino acid sequence were predicted based on the gene sequence of animal and human proglucagon.[1] In 1987, the GLP-1 peptide structure was identified in gut extracts, and insulinotropic actions were shown,[2,3] indicating an incretin role.[4] Additional milestones in incretin research, eventually leading to the development of incretin-based medications, are shown in figure 1 (further literature is available in appendix p 3). A meta-analysis of head-to-head trials comparing effects of GLP-1 receptor agonists and the dual glucose-dependent insulinotropic polypeptide (GIP)–GLP-1 receptor agonist tirzepatide to basal insulin treatment in type 2 diabetes is shown in the appendix (p 4). The primary endpoint for these trials was a reduction in glycated haemoglobin (HbA_{1c}). These data show superior efficacy for recently developed, incretin-based medications over basal insulin, and a greatly reduced risk for hypoglycaemia, occurring mainly in participants taking sulfonylureas.[5] More details regarding the development of GLP-1 receptor agonists, their glucose-lowering and bodyweight-lowering actions,

and typical adverse events are described in the appendix (pp 2–3).

Rationale for developing dual or triple agonists activating receptors for gastroenteropancreatic hormones

The development of dual and triple agonists was based on technical advances enabling the synthesis of peptides combining amino acid sequences from various peptide hormones, with the resulting hybrid being able to interact with two or more relevant receptors. The rationale to address glucagon receptor activity was anchored in studies of obese rodents, which showed that long-acting glucagon agonists decrease bodyweight and improve glucose control via mechanisms that include suppression of energy intake, elevation of energy expenditure, stimulation of lipolysis, and lipid use.[6,7] GLP-1–glucagon receptor co-agonists were the first dual agonists explored in animals.[8] Other prominent examples include GIP–GLP-1 receptor co-agonists, which yielded stronger suppression of energy intake and, consequently, greater weight loss compared with selective GLP-1 receptor agonists.[9] The additional reduction in bodyweight versus that seen with selective GLP-1 receptor agonists was independent of GLP-1 receptors,[10] and mediated by GIP receptor signalling in GABAergic neurons of the CNS.[11] Tirzepatide was developed successfully based on this dual mechanism of action. The concept of unimolecular, incretin-based polyagonism was expanded in 2015 with the introduction of the first GIP–GLP-1–glucagon receptor triple agonist.[12] This development was based on the assumption that any risk of hyperglycaemia through stimulation of glucagon receptors would be counteracted by the glucose-lowering effect of the incretin co-agonist. Consistent with this assumption, the triple receptor agonist outperformed GIP–GLP-1 receptor co-agonists to yield greater weight loss and further improvements in glucose control in animal experiments, with documented contributions of agonism at each receptor, as verified in mice with individual genetic or pharmacological receptor inhibition and deletion.[12] Receptors for gastroenteropancreatic peptide hormones with therapeutic potential, and their possible mechanisms of action leading to weight reduction and improvements in glycaemic control, are listed in the appendix (p 6).

Trizepatide, a first dual receptor agonist

Tirzepatide is currently the only dual agonist specifically targeting GIP and GLP-1 receptors that has been approved to treat type 2 diabetes and obesity.[13] When compared with the most effective selective GLP-1 receptor agonist (ie, subcutaneous semaglutide), tirzepatide provides greater improvements in glycaemic control in type 2 diabetes.[14] Tirzepatide also leads to greater weight loss than semaglutide for people with type 2 diabetes[14] and than liraglutide for people with obesity.[15] GLP-1 receptor agonists and tirzepatide are the currently available incretin-based medications for both the treatment of type 2 diabetes or obesity. Open questions regarding the role of GIP receptor agonism in the mechanism of action of tirzepatide for improved glycaemic control and bodyweight reduction are discussed in the appendix (p 6).

Key messages

- Currently available GLP-1 receptor agonists, and a dual glucose-dependent insulinotropic polypeptide–GLP-1 agonist, are highly efficacious and safe therapies for treatment of hyperglycaemia in people with type 2 diabetes.
- Some of these agents also induce substantial weight loss for people with overweight or obesity (with and without type 2 diabetes).
- Cardiovascular outcomes trials have established cardiovascular safety of GLP-1 receptor agonists; some agents within this class (eg, liraglutide, semaglutide, dulaglutide, and tirzepatide) reduce the risk of major adverse cardiovascular events in people with type 2 diabetes, or in those with obesity with atherosclerotic cardiovascular disease (ie, semaglutide).
- A placebo-controlled, dedicated kidney outcomes trial of semaglutide, a GLP-1 receptor agonist, showed reduced risks for loss of kidney function, kidney failure, and cardiovascular death, leading to approval for its treatment of chronic kidney disease in people with type 2 diabetes.
- Obesity-associated conditions, such as progression to type 2 diabetes, metabolic dysfunction-associated steatotic liver disease, heart failure with preserved ejection fraction, obstructive sleep apnoea, and knee osteoarthritis, benefit from treatment with GLP-1-based medications, with symptomatic relief and improved prognoses.
- Novel safety concerns, such as non-arteritic ischaemic optic neuritis and critical reduction in muscle mass accompanying weight loss induced by incretin-based medications, should be addressed but do not seem to affect the overal risk–benefit relationship.
- Incretin-based medications are being studied for novel indications (eg, neurodegenerative diseases and substance use disorders), with prelimary evidence for preventing dementia and improving Parkinson's disease. A role in reducing abuse of alcohol and other substances is less clear.
- Next-generation medications, built on existing incretin-based medications, could provide greater efficay (ie, in glycaemic control and bodyweight reduction) and are being studied in large-scale phase 3 trials to establish their clinical benefit and safety.
- When aiming to achieve greater effectiveness, measures should be taken to reduce adverse events and assure acceptable tolerability (eg, by slowed dose escalation upon treatment initiation).

Incretin-based medications and cardiovascular disease

Cardiovascular outcomes trials (CVOTs) have studied the effects of incretin-based medications reported in populations with type 2 diabetes and in people with overweight or obesity with pre-existing atherosclerotic cardiovascular disease (ASCVD; figure 2).[28]

Reduction of major adverse cardiovascular events in people with type 2 diabetes

CVOTs were required by the US Food and Drug Administration between 2008 and 2020 to prove the safety of novel glucose-lowering medications. Most CVOTs (appendix pp 7–8) have shown significant reductions in major adverse cardiovascular events

History of incretin-based therapy for type 2 diabetes and clinical obesity

Year or era	Discoveries, findings, and insights
1964–67	Qualitative description of the incretin effect
1970–73	Discovery of GIP as the first well characterised incretin hormone
1985–87	Loss of insulinotropic activity of GIP in type 2 diabetes, questioning its therapeutic potential
1987	Truncated GLP-1 isolated and functionally characterised as an incretin hormone
1992–93	GLP-1 stimulates insulin secretion and substantially lowers glucose concentrations in type 2 diabetes
1992–98	GLP-1 reduces appetite and ad libitum food (energy) intake
2003–today	Development and approval of GLP-1 receptor agonists for the treatment of type 2 diabetes
2007–today	Development and approval of GLP-1 receptor agonists for the treatment of obesity
2016–today	Cardiovascular outcomes trials report beneficial effects of GLP-1 receptor agonists on cardiovascular and renal outcomes
2013–near future	Development of the concept of dual and triple hormone receptor agonists with increased efficacy for improving glycaemic control and bodyweight reduction
2022–24	Tirzepatide approved as the first dual (GIP–GLP-1) receptor agonist for the treatment of type 2 diabetes and obesity (mechanism of action still only partially understood)
2022–27 (projected)	Development and approval of small-molecule (orally absorbed) GLP-1 receptor agonists
2024–30 (projected)	Development (and approval) of: Glucagon–GLP-1 dual receptor agonists Amylin–GLP-1 dual receptor agonists or combinations GIP–GLP-1–glucagon triple receptor agonists GLP-1 receptor agonist–GIP receptor antagonistic antibody

Figure 1: **Milestones in research related to the pathophysiology of the incretin hormones GIP and GLP-1 as parent compounds for incretin-based medications for treatment of type 2 diabetes and clinical obesity**
Relevant literature is available in the appendix (p 3). Predictions regarding approvals of drugs currently under development are subject to uncertainty. GIP=glucose-dependent insulinotropic polypeptide.

(MACE; comprising non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death) in people with type 2 diabetes, with hazard ratios (HRs) ranging from 0·88 (95% CI 0·79–0·99; REWIND; dulaglutide[22]) to 0·73 (0·58–0·92; AMPLITUDE-O; efpeglenatide[24]), indicating a relative risk reduction of between 12% and 27% (figure 2A). The ELIXA,[17] EXSCEL (ie, exenatide 2 mg per week subcutaneously),[20] PIONEER 6 (oral semaglutide),[23] and FREEDOM CVOT[25] trials did not show significant reductions in MACE, probably because of insufficient exposure over a 24 h period[29] (for the ELIXA trial), a high proportion of participants discontinuing treatment in the EXSCEL trial,[20] and low numbers of MACE events accrued in the PIONEER 6 and FREEDOM CVOT trials.[23,25] Systematic reviews and meta-analyses of CVOTs with GLP-1 receptor agonists in people with type 2 diabetes showed reductions in the risk for MACE by 13–14%, myocardial infarction by 10–14%, stroke by 13–17%, cardiovascular death by 13–14%, all-cause death by 12%, and hospitalisation for heart failure by 11–14%.[16,30,31] Findings from the most recent and comprehensive meta-analysis are displayed in figure 2B.[16] Relative risk reductions were similar in subgroups based on gender, and with or without ASCVD at baseline. Some of these findings have been confirmed in real-world studies (appendix p 8). Tirzepatide, as well as showing some preliminary evidence of cardiovascular safety,[32] was found to be non-inferior to dulaglutide in reducing MACE, which implies superiority over putative placebo.[33] In addition, semaglutide was recently shown to increase the pain-free walking distance in people with type 2 diabetes and peripheral artery disease.[34]

Reduction of MACE in people with overweight or obesity and ASCVD

The SELECT trial recruited people with BMIs of at least 27 kg m² who had established cardiovascular disease, but not type 2 diabetes (HbA_{1c} <6·5% [48 mmol/mol]). The primary endpoint—MACE—was reduced, with a HR of 0·80 (95% CI 0·72–0·90),[28] indicating a separation between the cardiovascular benefits and glucose-lowering effects provided by semaglutide. Furthermore, reductions in hospitalisation or urgent medical visits for heart failure (18%), all-cause mortality (19%), coronary revascularisation (23%), and a kidney composite endpoint (22%; appendix p 9) had upper bounds of 95% CIs of below 1·0, but cannot be considered significant according to the hierarchical statistical testing used.

Mechanisms of ASCVD benefits with GLP-1 receptor agonists

GLP-1 and GLP-1 receptor agonists improve fasting plasma glucose and HbA_{1c}, but also systolic blood pressure, atherogenic lipoproteins (ie, LDL cholesterol, VLDL cholesterol, triglycerides, and chylomicrons), inflammation (eg, high-sensitivity C-reactive protein and interleukin-6) and bodyweight.[35–37] Exploratory mediation analysis based on the LEADER and REWIND trials suggested a role for reductions in HbA_{1c} and albuminuria as potential mediators of cardiovascular benefits.[38,39] In addition, GLP-1 and GLP-1 receptor agonists cause a multitude of effects within blood vessels, including on endothelial cells and nitrous oxide production (ie, vasodilation); on monocytes, macrophages, and foam cells (reducing their secretion of inflammatory cytokines); on smooth muscle cells (reducing their proliferation); and by reducing the activity of matrix metalloproteinases (and thus potentially preventing the digestion of the fibrous caps that seal atherosclerotic plaques),[35–37,40] which could explain the prevention of ischaemic cardiovascular events.

Incretin-based medications and chronic kidney disease

Kidney outcomes in people with type 2 diabetes (with or without chronic kidney disease at baseline)

Clinical trials with incretin-based medications have reported meaningful improvements in kidney outcomes. In people with type 2 diabetes with or without chronic kidney disease (CKD), GLP-1 receptor agonists (eg, liraglutide, semaglutide, dulaglutide, and efpeglenatide) and the GIP–GLP-1 receptor agonist tirzepatide reduced albuminuria and slowed declines in estimated glomerular filtration rates (eGFR; appendix p 10). Major kidney outcomes consisting of eGFR decline, kidney failure, and death from kidney-related causes (sometimes including progression to macroalbuminuria; appendix

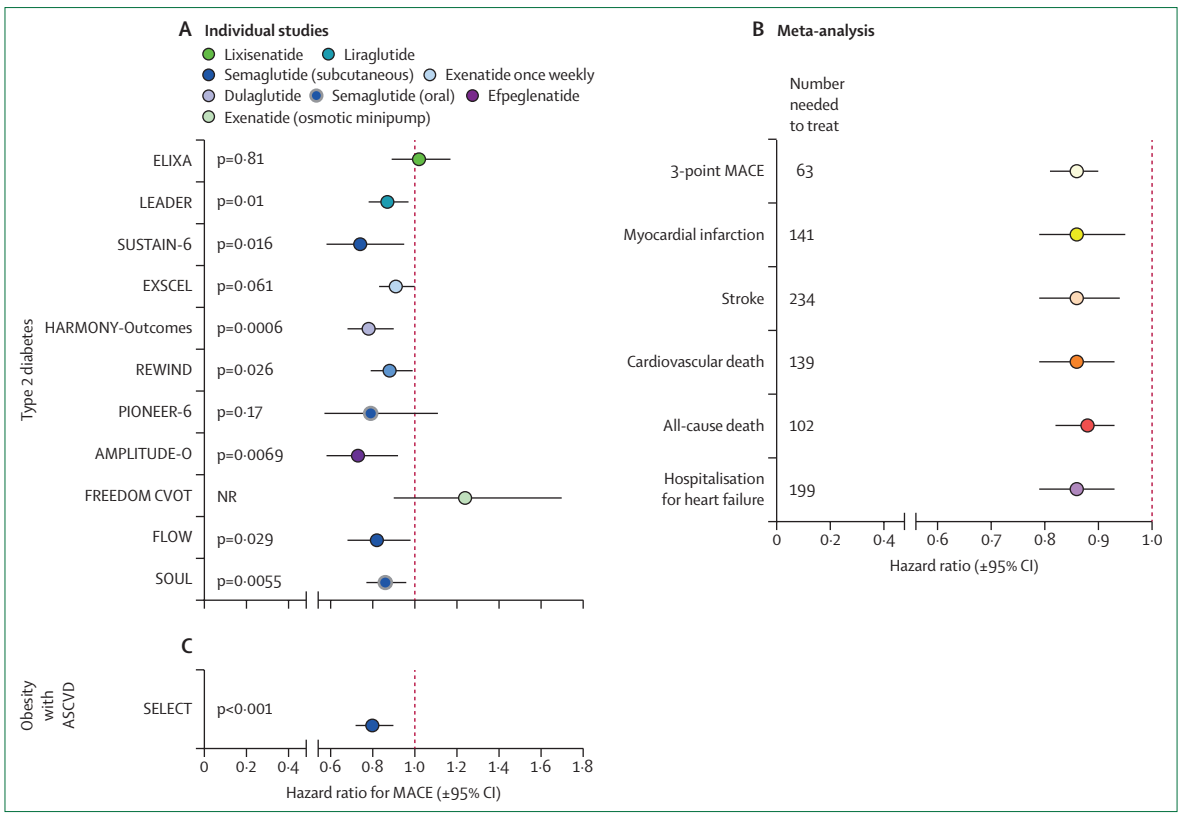

Figure 2: **Results for reductions in MACE from individual cardiovascular outcomes studies (A and C) and for various outcomes from a meta-analysis of cardiovascular outcomes studies (B) in populations with type 2 diabetes and overweight or obesity with ASCVD**

The hazard ratios (for active treatment *vs* placebo, with 95% CIs) are shown. Results of a recent meta-analysis[16] summarising all cardiovascular outcomes trials in populations with type 2 diabetes are shown for the primary endpoint (MACE), the components of MACE (ie, fatal and non-fatal myocardial infarction or stroke and cardiovascular death), all-cause mortality, and hospitalisation for heart failure. Original results were taken from the primary publications: ELIXA,[17] LEADER,[18] SUSTAIN-6,[19] EXSCEL,[20] HARMONY-Outcomes,[21] REWIND,[22] PIONEER-6,[23] AMPLITUDE-O,[24] FREEDOM CVOT,[25] FLOW,[26] SOUL,[27] and SELECT.[28] In the LEADER, SUSTAIN-6, and PIONEER-6 trials, CKD with an estimated glomerular filtration rate of less than 60 mL/min per 1·73 m² body surface was taken as an equivalent of established cardiovascular disease. The meta-analysis[16] disregarded ELIXA's results because of the absence of any effects of lixisenatide. ASCVD=atherosclerotic cardiovascular disease. MACE=major adverse cardiovascular event. NR=not reported.

p 10) were reduced (figure 3).[24,41–46] In the SUSTAIN-6 trial, participants with type 2 diabetes were also more likely to remit to a lower risk category in the Kidney Disease: Improving Global Outcomes (KDIGO) risk classification (HR 1·69, 95% CI 1·32–2·16) and less likely to progress to a higher KDIGO risk category (HR 0·71, 0·59–0·86) with semaglutide treatment compared with placebo.[47] In post-hoc analyses of clinical trials in people with type 2 diabetes, tirzepatide consistently lowered albuminuria and stabilised eGFR compared with active comparators or insulin for glycaemic control, or with placebo.[48,49] The FLOW trial was a dedicated kidney outcome trial conducted in participants with type 2 diabetes and established CKD.[26] Treatment with injectable semaglutide 1 mg once weekly reduced the relative risk for the composite primary outcome (ie, ≥50% eGFR decline, eGFR <15 mL/min per 1·73 m², dialysis or transplant, or death due to kidney disease or cardiovascular disease) by 24% compared with placebo (HR 0·76, 0·66–0·88).[26] Furthermore, semaglutide also significantly reduced the rate of eGFR decline (annual slope difference 1·16 mL/min per 1·73 m², 0·86–1·47), MACE (HR 0·82, 0·68–0·98), and all-cause mortality (HR 0·80, 0·67–0·95) in hierarchical testing of confirmatory secondary outcomes compared with placebo.[26] Benefits regarding composite renal endpoints (appendix p 9) have been confirmed in systematic analyses and meta-analyses, including the aforementioned clinical studies.[16,31]

Kidney outcomes in people with overweight or obesity

The SELECT trial, a CVOT of subcutaneous semaglutide (2·4 mg once weekly) versus placebo in people with overweight or obesity with an established diagnosis of ASCVD, found a 22% lower relative risk (HR 0·78, 95% CI 0·63–0·96) for a composite kidney outcome (ie, onset of macroalbuminuria, ≥50% eGFR decline, eGFR <15 mL/min per 1·73m², dialysis or transplant, or death due to kidney disease).[28,50] As only 21% of participants in the SELECT trial had an eGFR of less than 60 mL/min per 1·73m² or a urinary albumin-to-creatinine ratio of at least 30 mg/g at baseline, these data suggest that CKD

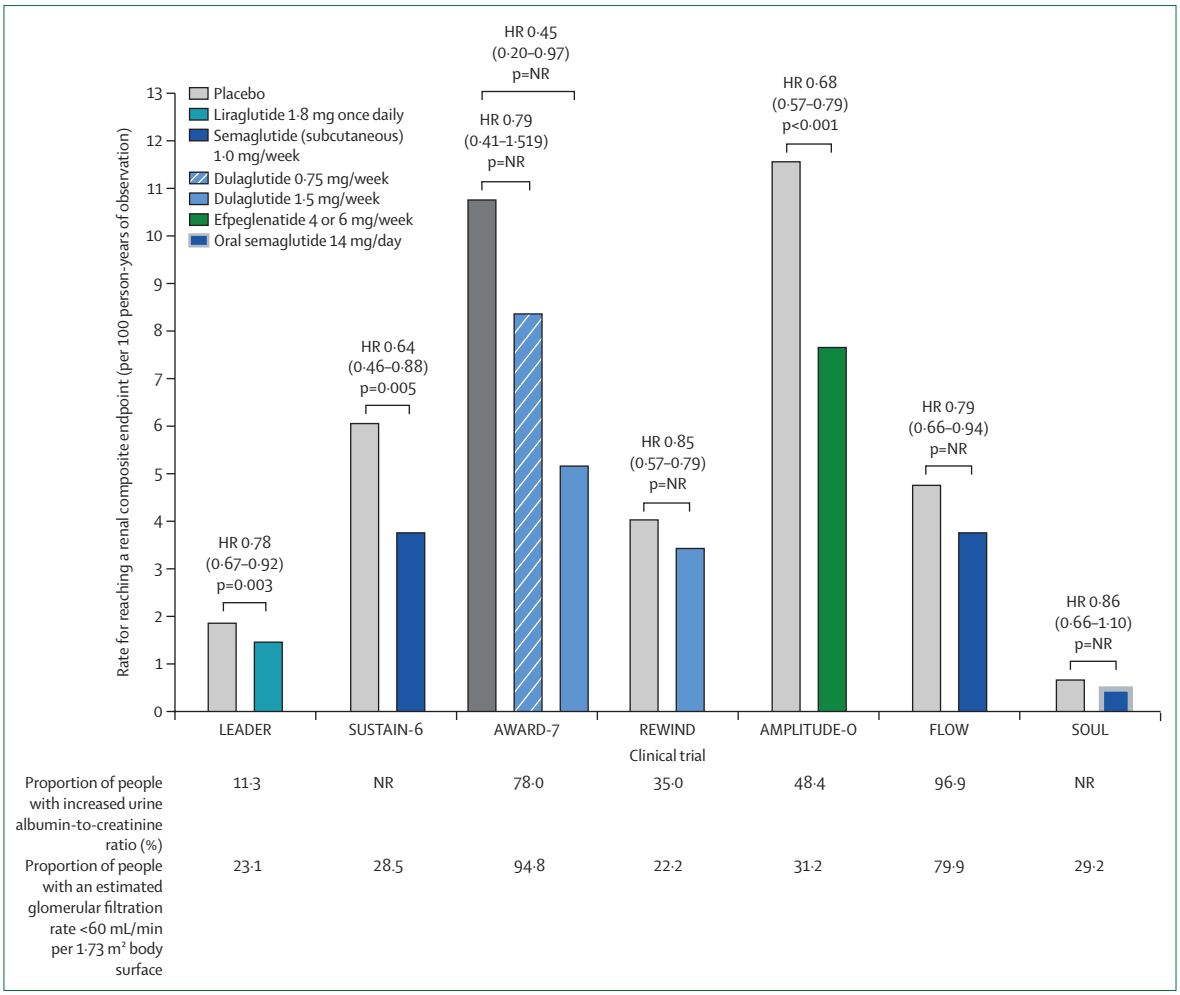

Figure 3: **Effect of GLP-1 receptor agonists on composite kidney outcomes in cardiovascular and kidney outcomes trials in populations with type 2 diabetes**
HRs (*vs* placebo) are shown with 95% CIs and p values indicating the significance of the difference to placebo treatment. Original results were taken from the primary publications: LEADER,[20,41] SUSTAIN-6,[19] AWARD-7,[42,43] REWIND,[622,44] AMPLITUDE-O,[24] and FLOW.[26] Results from the FLOW trial regarding a composite of kidney-specific components of the primary outcome (excluding cardiovascular death) are depicted for better comparability with other studies. This was not the primary outcome of that study. In the LEADER, SUSTAIN-6, and SOUL trials, chronic kidney disease with an estimated glomerular filtration rate of less than 60 mL/min per 1·73 m² body surface was taken as an equivalent of established cardiovascular disease. The ELIXA,[17] EXSCEL,[20] HARMONY-Outcomes,[21] PIONEER-6,[23] and SELECT[28] trials (for people with obesity with established atherosclerotic cardiovascular disease at baseline) did not report these outcomes. Details of the components of composite kidney outcomes in the individual trials are available in the appendix (p 9). In most trials, the primary outcome included cardiovascular death; in this figure, only kidney-specific composite outcomes are depicted. HR=hazard ratio. NR=not reported.

could be prevented by a GLP-1 receptor agonist. Moreover, in people with obesity and heart failure without type 2 diabetes, tirzepatide treatment versus placebo was associated with a slight increase in eGFR, with a concomitant reduction in albuminuria over 52 weeks.[51]

Mechanisms of GLP-1 receptor agonists in CKD

In a mediation analysis for kidney outcomes (ie, macroalbuminuria, doubling of serum creatinine, eGFR <45 mL/min per 1·73 m², or kidney failure) from CVOTs of liraglutide and semaglutide in type 2 diabetes, lower levels of glycaemia or blood pressure only moderately mediated 10–25% of these benefits, indicating direct action on the kidney by these GLP-1 receptor agonists.[52] Additionally, no relationship between changes in bodyweight and eGFR was observed in clinical trials of dulaglutide and semaglutide (selective GLP-1 receptor agonists) or tirzepatide (dual GIP–GLP-1 receptor agonist) in study populations with type 2 diabetes or obesity with and without CKD.[53–55] Direct protective effects on the kidney by GLP-1 receptor agonists acting through other mechanisms are therefore probable. GLP-1 receptors are expressed in the kidney,[56] primarily in endothelial cells and vascular smooth muscle cells of the juxtaglomerular apparatus.[57] Non-intrinsic kidney cells could also contribute to CKD progression. Macrophages and T lymphocytes are important drivers of inflammation and fibrosis within the kidney.[37,58,59]

Activation of GLP-1 receptors on these immune cells converts them to less-inflammatory or anti-inflammatory phenotypes.[58] Mouse and rat models show that GLP-1 receptor agonists suppress signals through pro-inflammatory pathways (eg, the receptor for advanced glycation end products and Toll-like receptors), possibly involving GLP-1 actions in the CNS and resulting in immunomodulation via parasympathetic and opioid efferent activity.[60–61] Accordingly, GLP-1 receptor agonists reduce kidney inflammation and fibrosis in mouse and rat models of CKD with or without diabetes.[60–61] In humans with type 2 diabetes and CKD, dulaglutide reduced pro-fibrotic biomarkers in blood and urine.[63] In a mouse model of sepsis, liraglutide decreased lung injury and reduced the death rate,[62] suggesting that resistance to severe illness could be another potential mechanistic link to improved overall survival, as observed in the FLOW trial.[26]

Incretin-based medications for bodyweight reduction in obesity

Based on the experience of participants with type 2 diabetes in clinical trials, GLP-1 receptor agonists liraglutide and semaglutide (subcutaneous) and the dual agonist tirzepatide have been studied in people with overweight (BMI 25·0–29·9 kg/m²) and obesity (BMI ≥30·0 kg/m²). Higher doses of selective GLP-1 receptor agonists are used for treatment of overweight or obesity than those for treatment of type 2 diabetes (eg, 3 mg/day instead of 1·8 mg/day for liraglutide and 2·4 mg/week instead of 1·0 mg/week for semaglutide). Tirzepatide 5, 10, and 15 mg/week are approved doses for treatment of type 2 diabetes, overweight, or obesity. If treatment with incretin-based medications is discontinued, bodyweight will increase at approximately the velocity as it had been lost with treatment.[64–66] The extent of bodyweight reduction is highly variable between individuals,[64,67–69] and some participants gained weight even with the highest dose of tirzepatide.[69] Clinical trials have yielded consistent results regarding their effect sizes for bodyweight reduction for each agent studied (see appendix p 11). In the STEP-8 trial,[70] semaglutide 2·4 mg/week led to greater weight loss (a 15·8% reduction) compared with liraglutide 3·0 mg once daily (a 6·4% reduction); in the SURMOUNT-5 trial,[15] tirzepatide 15 mg caused significantly higher weight reduction (20·2%) compared with semaglutide 2·4 mg (13·7%). Weight loss is generally more pronounced in people with overweight or obesity without type 2 diabetes, perhaps due to reduced glucosuria and fewer calories being lost.[71] Similar differences in effectiveness are found when looking at reductions in waist circumference, systolic blood pressure, and serum triglycerides, with differences in effect sizes reflecting the differences in weight loss in response to liraglutide, semaglutide, and tirzepatide treatment.[15,70]

Disease or condition	Proven clinical benefits of GLP-1 receptor agonists	Tirzepatide
Type 2 diabetes	• **HbA_{1c}↓, FPG ↓, bodyweight↓, waist circumference↓**	√
ASCVD	• Risk for MACE* ↓ • ASCVD at baseline: robust evidence, substantial absolute risk reduction • No ASCVD at baseline: Less robust evidence, smaller absolute risk reduction	√
CKD	• Albuminuria and eGFR decline over time ↓ • Composite kidney outcomes representing kidney function loss of 40% or 50%, kidney failure ↓	?
HFpEF or HFrEF (NYHA class 2–4)	• Heart failure-related endpoints ↓ (eg, hospital admission or urgent treatment for heart failure, cardiovascular death)	?
Symptomatic PVD	• Maximum walking distance↑ • Pain-free walking distance↑	?
Obesity	• **Bodyweight↓, waist circumference↓, blood pressure↓, triglycerides↓**	√
Prediabetes	• Progression to manifest diabetes mellitus ↓	√
ASCVD	• Risk for MACE↓	?
HFpEF	• KCCQ clinical summary score ↑ (heart failure-related symptoms↓) • 6-min walking distance↑ • Heart failure-related hospital admission (urgent treatment) ↓	√ √ √
MASLD	• Resolution of MASLD↑ • Progression of liver fibrosis↓	√ ?
OSAS	• Apnoea–hypopnoea index↓	√
Knee osteoarthritis	• Pain, stiffness, and physical function (WOMAC) index↓	?

Figure 4: **Proven clinical benefits related to GLP-1 receptor agonists and the GIP–GLP-1 receptor co-agonist tirzepatide in people with type 2 diabetes or obesity**
Details of clinical trials supporting the conclusions presented in this figure are in the appendix (p 12). ASCVD=atherosclerotic cardiovascular disease. CKD=chronic kidney disease. eGFR=estimated glomerular filtration rate. FPG=fasting plasma glucose. GIP=glucose-dependent insulinotropic polypeptide. HbA_{1c}=glycated haemoglobin. HFpEF=heart failure with preserved ejection fraction. HFrEF=heart failure with reduced ejection fraction. KCCQ=Kansas City Cardiomyopathy Questionnaire. MACE=major adverse cardiovascular events. MASLD=metabolic dysfunction-associated steatotic liver disease. NYHA=New York Heart Association. OSAS=obstructive sleep apnoea syndrome. PVD=peripheral vascular disease. WOMAC Index=Western Ontario and McMaster Universities Osteoarthritis Index. *Composite endpoint comprised of non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death.

Incretin-based medications and benefits for obesity-associated conditions

Clinical obesity has been defined as "a systemic illness directly and specifically caused by excess adiposity", "causing illness by altering the function of various organs, not only those involved in metabolic regulations".[72] Excess body fat—including the pathophysiologically important visceral adipose tissue—could therefore lead to prediabetes and progression to type 2 diabetes, metabolic dysfunction-associated steatotic liver disease (MASLD) with fibrosis, CKD, ASCVD, obesity-associated heart failure with preserved ejection fraction, obstructive sleep apnoea syndrome (OSAS), and symptomatic knee osteoarthritis.[73] Symptomatic improvements can be achieved with bodyweight reductions of 5–15% for most of these conditions.[74] Therapeutic effects of incretin-based medications in such conditions are presented in figure 4 and the appendix (pp 12–13).

Progression to type 2 diabetes

Liraglutide, semaglutide (subcutaneous), and tirzepatide have shown the potential to slow the progression from prediabetes to type 2 diabetes by 66–93% compared with

placebo.[65,75,76] After wash-out periods (of 12–28 weeks), the effects were at least partly maintained.

Obesity-associated heart failure

Heart failure with preserved ejection fraction (ie, impaired diastolic ventricular filling) is closely associated with obesity. Until recently, no specific treatment was available. Clinical trials have been conducted for semaglutide (in people with obesity with[77] or without[78] type 2 diabetes) and tirzepatide (in non-diabetic people[79]). Co-primary endpoints in the semaglutide trials were a change in the Kansas City Cardiomyopathy Questionnaire Clinical Summary Score (KCCQ-CSS; an assessment of physical functioning related to heart failure) and reductions in bodyweight. The SUMMIT trial (for tirzepatide) used time to cardiovascular death or worsening heart failure events over 104 weeks and a change in KCCQ-CSS from baseline to 52 weeks.[79] Additional outcomes were changes in the 6-min walking test and bodyweight. Improvements in the KCCQ-CSS were described (appendix pp 12–13) and bodyweight was reduced (appendix p 11). The 6-min walking distance improved more with either drug than with placebo treatment. More importantly, a prespecified pooled analysis of the two semaglutide trials showed a reduction in time to first heart failure event (ie, an event requiring hospitalisation or an urgent medical visit; HR 0·27, 95% CI 0·12–0·56).[80] Likewise, the SUMMIT trial (for tirzepatide) showed a reduction in events regarding time to cardiovascular death or worsening heart failure over 104 weeks (HR 0·62, 0·41–0·95),[79] indicating improvements in various clinically relevant parameters. The same parameters in clinical trials of semaglutide, tirzepatide, and SGLT2 inhibitors in heart failure with preserved ejection fraction are indirectly compared in the appendix (p 14).

Metabolic dysfunction-associated steatotic liver disease

MASLD is a common complication of obesity that can progress to liver fibrosis, cirrhosis, and hepatocellular carcinoma. Studies have been published for liraglutide (1·8 mg/day),[81] daily injections of semaglutide (0·1–0·4 mg/day; subcutaneous),[82] and tirzepatide (5–15 mg/week).[83] A particular focus of these studies was on the prevention of progression, and potential regression of fibrosis (appendix pp 12–13). The primary outcome for all three studies was resolution of fatty liver disease without worsening of fibrosis, and significant improvements were noted. In addition, liraglutide led to fewer participants with a worsening fibrosis stage,[81] semaglutide showed a trend for improvements in fibrosis stage,[82] and tirzepatide led to an increased proportion of participants reaching an improvement in fibrosis by at least one stage.[83] A recent study reported significant effects on the resolution of MASLD without worsening of fibrosis, but also significant improvements in fibrosis without worsening of MASLD after 72 weeks of treatment with semaglutide.[84] Semaglutide has been approved for the treatment of MASLD based on these results.[85] Similarly, approval for tirzepatide to treat MASLD has been announced to be applied for.[86] Therefore, incretin-based medications for the treatment of MASLD could be made available, supplementing resmetirom as the only approved medication in the USA and Europe.[87]

Obstructive sleep apnoea

The risk for OSAS rises with increasing adiposity, and its successful treatment requires substantial reductions in bodyweight. Liraglutide (3 mg/day) reduced hypopnoea and/or apnoea events over 32 weeks of treatment.[88] Tirzepatide reduced hypopnoea and/or apnoea events significantly in populations either using or not using positive airway pressure therapy (PAPT); in 50·2% of people using PAPT, and in 42·2% of those not using PAPT, the apnoea–hypopnoea index was reduced to the range where PAPT would no longer appear necessary for treatment of OSAS. The US Food and Drug Administration has approved OSAS as a new indication for tirzepatide.

Knee osteoarthritis

Semaglutide (2·4 mg/week) has been shown to cause symptomatic improvement related to moderate knee osteoarthritis as well as bodyweight reduction.[89]

Safety and tolerability issues of current concerns

Optic nerve and retinal disorders have been found to be associated with the use of potent GLP-1 receptor agonists (ie, semaglutide) and the dual agonist tirzepatide, such as non-arteritic ischaemic optic neuropathy, papilloedema, macular oedema, retinal detachment, retinal haemorrhage, retinal tear, vitreous detachment, and vitreous haemorrhage.[90,91] Although such an association has not been confirmed by other studies,[92,93] a small proportion of people with type 2 diabetes treated with potent incretin-based medications could be affected (~0·05% over 2 years).[90] Whether or not this association is related to the potent glucose-lowering ability of semaglutide or tirzepatide, potentially leading to a reduced glucose uptake into neural or retinal tissues after adapting to hyperglycaemia, requires further research.

Because GLP-1 receptor agonists and the dual agonist tirzepatide support major bodyweight reduction, including a reduction in lean body mass (of which ~50% is muscle mass), there is concern that this could also lead to a critical reduction in muscle mass and, consequently, to related functional impairments.[94] Older people with sarcopenia before starting such treatment could be at particular risk.[95] Concerns are mainly based on inferences from the numerical reduction in muscle mass observed with incretin-based weight-loss medications. We are not aware of any systematic assessment of functional impairments (eg, inability to rise from a sitting to a

standing position) arising from use of incretin-based medications. Furthermore, whether a somewhat reduced muscle mass is functionally appropriate after major weight loss (eg, 15% bodyweight reduction), is unclear. In addition, although incretin-based medications numerically reduce muscle mass, they could also improve muscle quality by reducing intramuscular fat infiltration, as shown with tirzepatide.[96] Further research is needed before the importance of this risk can be estimated,[94] and pharmacological treatments are being developed to address the preservation of muscle mass during treatment with GLP-1 receptor agonists.[97]

Other safety and tolerability issues associated with established incretin-based medications are presented in the appendix (pp 18–19). Putative reasons for underusing incretin-based medications and for poor adherence to and persistence with treatment, which are potentially related to safety concerns, are also available (appendix p 19).

New indications for established GLP-1 receptor agonists

Neurodegenerative diseases and substance use disorders

Novel fields of use appear possible for GLP-1 receptor agonists and tirzepatide based on recent exploratory research. GLP-1 is involved in cognitive brain function and learning,[98] and the GLP-1 receptor agonist liraglutide interferes with cognitive decline in individuals with type 2 diabetes.[99] Therefore, therapeutic actions in neurodegenerative diseases, such as Alzheimer's dementia and Parkinson's disease, have been explored both in animal models and in clinical trials (appendix pp 16–17). A recent meta-analysis reported significant reductions in the incidence of all-cause dementia with GLP-1 receptor agonists, but not with SGLT2 inhibitors, with no significant differences for Alzheimer's or vascular forms of dementia.[100] A dedicated prospective study (ie, the EVOKE study, NCT04777396), however, found no significant differences in disease progression between treatment with semaglutide or placebo.[1101]

Three clinical trials consistently describe a slowed decline in motor function when using the short-acting GLP-1 receptor agonists exenatide and lixisenatide in people with Parkinson's disease;[102–104] however, this decline was not confirmed in a study using exenatide once weekly[105] or in another recent trial of NLY01, a brain-penetrant, pegylated exenatide.[106] Less definite information is available regarding other neurodegenerative diseases (eg, Huntington's disease[107]). Because GLP-1 interacts with neurons in brain areas involved in the homeostatic and hedonic regulation of food intake, the role of GLP-1 synthesised in the CNS, and of GLP-1 receptor agonists administered peripherally, in interference with substance use disorders has been a focus of research in recent years.[108] Varying results have been reported for the role of GLP-1 and GLP-1 receptor agonists in inducing or maintaining abstinence from nicotine use (appendix pp 16–17), but the GLP-1 receptor agonist exenatide (given once weekly) increased abstinence by 70%.[109] Results regarding alcohol use also range from no significant overall effect on heavy drinking days—except for a subgroup with BMIs greater than 30 kg/m² with exenatide once weekly[110]—to a 29% reduction in alcohol consumption with dulaglutide[111] and a reduced rate of alcohol intoxication with diverse GLP-1 receptor agonists.[112] A recent clinical trial with once-weekly semaglutide (1 mg/week) reported reduced alcohol self-administration and lower peak breath alcohol concentrations compared with placebo, but no change in average drinks per day, the number of drinking days, or weekly alcohol cravings.[113]

For opioid dependence, exenatide reduced oxycodone intake,[114] but not morphine intake,[115] and liraglutide reduced heroin intake[116] in rodents, indicating some heterogeneity regarding the type of opioid drug. In an observational study based on a database of electronic health records, the risk of opioid overdose was reduced by 42–68% with semaglutide versus other glucose-lowering medication classes.[117] Although animal studies suggest an interference of GLP-1 receptor agonists with cocaine self-administration,[118] this was not confirmed in a clinical trial with short-term exenatide administration.[119] Various clinical trials in the area of neurodegenerative diseases and substance abuse disorders are underway to potentially support the use of GLP-1 receptor agonists for such conditions (appendix pp 16–17).

Next-generation incretin-based medications for easier use or increased efficacy

Over the past 10–15 years, the armamentarium of incretin-based medications has greatly increased. One focus of research was the development of small molecules, readily absorbed from the gastrointestinal tract, which can offer oral therapy to activate GLP-1 and other receptors. Another focus was the development of peptides that can specifically interact with more than one receptor. Tirzepatide is currently the only approved agent of this type.

For the **dedicated prospective study** see https://clinicaltrials.gov/study/NCT04777396

Oral small-molecule GLP-1 receptor agonists

Small-molecule, orally bioavailable, synthetic non-peptide GLP-1 receptor agonists can provide an effective pharmacotherapy as an alternative to peptide-based GLP-1 receptor agonists, without a need for injection.[120,121] Orforglipron is such a molecule (table). The efficacy and safety of orforglipron have been investigated in phase 3 clinical trials in people with overweight or obesity[130,141] and early type 2 diabetes.[122]

In adults with overweight or obesity, plus at least one weight-related coexisting condition, but without type 2 diabetes, the maximum reduction in weight at week 72 was 11·2% with orforglipron 36 mg/day versus 2·1 % with placebo.[130] Orforglipron is further under investigation as a potential treatment for obesity in the phase 3 ATTAIN programme. The ATTAIN-2 study reported a placebo-subtracted bodyweight reduction by

up to 7·1% (95% CI 6·1–8·2).[142] In people with type 2 diabetes, the maximum reduction in HbA_{1c} with orforglipron was 1·1% (0·8–1·3) or 12 (9–14) mmol/mol for 36 mg per day (placebo-corrected), along with a bodyweight reduction of up to 5·9% (4·4–7·4) versus baseline.[122] Gastrointestinal tolerability has been improved since a previous phase 2 trial[143] by prolonging the dose-escalation period (up to 20 weeks), but remained

	Compound or preparation	Dose range and duration	Reduction in bodyweight, percentage of baseline value (95% CI; placebo-subtracted)	Reduction in HbA_{1c}, percentage points *vs* baseline value (95% CI; placebo-subtracted)	Other prominent findings	Reference	Ongoing clinical trials (ClinicalTrials.gov)
Type 2 diabetes							
Small-molecule, oral GLP-1 receptor agonist	Orforglipron	3–36 mg once daily *vs* placebo over 40 weeks	Up to 5·9% (4·4–7·4) with 36 mg/day	Up to 1·07% (0·81–1·33) with highest dose	Low drug discontinuation due to adverse events (<5·7%); weight plateau not reached	Rosenstock et al (2025)[122] (ACHIEVE-1)	NCT06045221 (*vs* semaglutide)
Biased GLP-1 receptor agonist (reduced β-arrestin recruitment)	Ecnoglutide	0·4–1·2 mg/week over 20 weeks	Up to 2·8% (–3·6 to 1·9)	Up to 1·8% (1·4–2·3; highest dose)	Low burden of nausea and vomiting or drug discontinuation	Zhu et al (2024)[123]	NCT05680155 (*vs* placebo)
Biased GLP-1 receptor agonist (reduced β-arrestin recruitment)	Ecnoglutide	0·6 or 1·2 mg/week over 52 weeks	Up to 5·7 ± 0·3% (SEM); change *vs* dulaglutide 1·5 mg/week –3·0% (– 3·7 to –2·2)	Up to 1·8 ± 0·05% (SEM); change *vs* dulaglutide 1·5 mg/week 0·25% (–0·40 to –0·11)	Low drug discontinuation due to adverse events (up to 4%)	He et al (2025)[124]	NA
Dual glucagon–GLP-1 receptor agonist	Survodutide	0·3–2·7 mg/week; 1·2–1·8 mg once every 2 weeks over 16 weeks	Up to 7·5% (95% CI not reported)	Up to 1·7 % (1·5–1·9) *vs* placebo (0·2%)	High drug discontinuation due to adverse events (up to 30%); weight plateau not reached	Blüher et al (2023)[125]	NCT06066528 (focus on weight reduction)
Dual glucagon–GLP-1 receptor agonist	Mazdutide	3–6 mg/week over 20 weeks	Up to 5·7% (3·9–7·6) with 6 mg/week	Up to 1·7% (1·3–2·1) with 3 mg/week	No treatment discontinuation due to adverse events	Zhang et al (2024)[126]	NA
Amylin–GLP-1 receptor agonist combination	Cagrilintide–semaglutide	Cagrilintide 2·4 mg/week; semaglutide 2·4 mg/week for 68 weeks	10·4% (9·5–11·2)	1·4% (1·2–1·6)	Improved physical function (according to IWQOL-Lite-CT and SF-36v2 scores); drug discontinuation due to adverse events 8·4%; weight plateau reached	Davies et al (2025)[127] (REDEFINE-2)	NCT06323161 (*vs* once-daily insulin); NCT 06323174 (*vs* diet and exercise)
Triple GIP–GLP-1–glucagon receptor co-agonist	Retatrutide	0·5–12 mg/week over 36 weeks	Up to 13·9% (10·7–17·1) with highest dose	Up to 1·9% (1·3–2·4) with highest dose; efficacy estimand	High drug discontinuation due to adverse events (up to 17%); weight plateau not reached	Rosenstock et al (2023)[128]	NCT06260722 (*vs* semaglutide); NCT06354660 (not controlled on diet and exercise)
GLP-1 receptor agonist–GIP receptor antagonistic antibody	Maridebart cafraglutide	140–420 mg every 4 weeks for 52 weeks	Up to 12·3% (9·2–15·3)	Up to 1·5% (1·0–1·9)	Nausea in up to 59%, vomiting in up to 75%, drug discontinuation due to adverse events up to 19%; bodyweight plateau not reached	Jastreboff et al (2025)[129]	NCT06660173 (adults); NCT06858878 (with obesity or overweight)
Obesity and overweight							
Small-molecule, oral GLP-1 receptor agonist	Orforglipron	6–36 mg once daily *vs* placebo over 72 weeks	Up to 9·1% (8·1–10·1)	Up to 0·3% (several doses; SEM 0·0%)	High drug discontinuation rate (up to 24%), up to 7% due to gastrointestinal adverse events; weight plateau reached after ~52 weeks	Wharton et al (2025)[130]	NCT05869903 (obesity with weight-related comorbidities); NCT06649045 (obstructive sleep apnoea syndrome)
Biased GLP-1 receptor agonist (reduced β-arrestin recruitment)	Ecnoglutide	1·2–2·4 mg/week over 40 weeks	Up to 13·3% (11·3–15·3)	Up to 0·4% (0·3–0·4)	Low drug discontinuation due to adverse events (up to 3%); weight plateau not reached	Ji et al (2025)[131]	NCT07143227 (in adolescents)
Glucagon–GLP-1 receptor co-agonist	Survodutide	0·6–4·8 mg once weekly over 46 weeks	Up to 12·1% (9·2–15·0) with highest dose	Up to 0·25% (95% CI not reported) with highest dose	High drug discontinuation due to adverse events (up to 29%); weight plateau not reached	Le Roux et al (2024)[132]	NCT06066515 (focus on weight loss); NCT06077864 (SYNCHRONIZE; cardiovascular outcomes trial)

(Table continues on next page)

	Compound or preparation	Dose range and duration	Reduction in bodyweight, percentage of baseline value (95% CI; placebo-subtracted)	Reduction in HbA_{1c}, percentage points *vs* baseline value (95% CI; placebo-subtracted)	Other prominent findings	Reference	Ongoing clinical trials (ClinicalTrials.gov)
(Continued from previous page)							
Glucagon–GLP-1 receptor co-agonist	Mazdutide	3–6 mg/week over 24 weeks; 4 or 6 mg over 48 weeks	Up to 12·3% (10·5–14·1); up to 13·0% (14·3–11·7)	Up to 0·4% (0·33–0·47); values not reported for 4 or 6 mg over 48 weeks	Few participants discontinued treatment due to adverse events (up to 6·6% with 6 mg/week); despite nausea in up to 50·5%, vomiting in up to 43·1%, and diarrhoea in up to 38·6%, only 1·5% (for 4 mg) and 0·5% (for 6 mg) discontinued drug because of adverse events	Ji et al (2023);[133] Ji et al (2025)[134]	NCT06519656 (polycystic ovary syndrome)
Amylin–GLP-1 receptor agonist combination	Cagrilintide–semaglutide	Cagrilintide 2·4 mg/week; semaglutide 2·4 mg/week for 68 weeks	17·3% (16·6–18·1) *vs* placebo; 5·5% (4·3–6·7) *vs* semaglutide alone	0·4% (not more than the effect of semaglutide alone)	Improved physical function (based on IWQOL-Lite-CT and SF-36v2 scores); drug discontinuation due to adverse events 5·9%; weight plateau not reached	Garvey et al (2025)[135] (REDIFINE-1)	NCT06131372 (*vs* semaglutide, cagrilintide, and placebo for chronic kidney disease in people with type 2 diabetes and obesity; NCT06131437 (*vs* tirzepatide)
Amylin–GLP-1 receptor co-agonist	Amycretin (subcutaneous)	Amycretin 1·25–60 mg once weekly	11·7% (6·1–17·3) with 1·25 mg/week; 23·2% (15·6–30·8) with 60 mg/week	0·1% (–0·4 to 0·1) with 1·25 mg/week; 0·5% (–1·0 to 0·0) with 60 mg/week	High risk for nausea (up to 82%), vomiting (up to 60%), and drug discontinuation (up to 35%), also with placebo treatment (nausea up to 94%, vomiting up to 60%)	Dahl et al (2025)[136] (phase 1)	NA
Amylin–GLP-1 receptor co-agonist	Amycretin (oral)	Amycretin two 25 mg tablets, one 50 mg tablet, or two 50 mg tablets daily for 12 weeks	Up to 11·8% (9·0–14·6) with two 50 mg tablets per day	0·3% (SD 0·3) with two 50 mg tablets per day	High risk for nausea (up to 94%), vomiting (up to 56%), but low risk for drug discontinuation (up to 6%), all low with placebo treatment (nausea 8%, vomiting 8%)	Gasiorek et al (2025)[137] (phase 1)	NA
Triple GIP–GLP-1–glucagon receptor co-agonist	Retatrutide	1–12 mg/week over 48 weeks (primary endpoint for bodyweight: 24 weeks)	Up to 22·1% (19·3–24·9) with 12 mg/week	Up to 0·5% (0·3–0·6) with 8 mg (initial dose 2 mg)/week	High drug discontinuation due to adverse events (up to 16% with 12 mg/week); discontinuation for any reason up to 23·5% (with 4 mg/week); weight plateau not reached	Jastreboff et al (2023)[138]	NCT06662383 (*vs* tirzepatide); NCT06383390 (TRIUMPH-Dual primary outcomes: cardiovascular and kidney)
GLP-1 receptor agonist–GIP receptor antagonistic antibody	Maridebart cafraglutide	140–420 mg every 4 weeks for 52 weeks	Up to 16·2% (13·5–18·9)	Up to 0·3%	Nausea in up to 87%, vomiting in up to 87%, drug discontinuation due to adverse events up to 29%; gastrointestinal adverse events and drug discontinuation somewhat improved by slower dose escalation; bodyweight plateau not reached	Jastreboff et al (2025)[129] (phase 2)	NCT06858839 (without type 2 diabetes); NCT07037433 (cardiovascular outcomes); NCT06352892 (Chinese patients); NCT06987695 (Japanese patients)
MASLD (with fibrosis stage F1–F3)							
Dual glucagon–GLP-1 receptor agonists	Survodutide	2·4–6·0 mg/week over 48 weeks	Up to 12·1% (95% CI not reported)	0·7% points (95% CI not reported); 39% of participants with type 2 diabetes	More improvement in MASH with no worsening of fibrosis, reduction in liver fat by ≥30%, numerically more improvement of fibrosis with active treatment	Sanyal et al (2024)[139]	NCT06632457 (LIVERAGE [cirrhosis])
MASLD							
Triple GIP–GLP-1–glucagon receptor co-agonist	Retatrutide	1–12 mg/week over 48 weeks	Up to 25·9% (SEM 2·4)	NA	Reduction in hepatic fat fraction by <86·0%; no histology available to assess fibrosis	Sanyal et al (2024)[140]	NA

Therapeutic approaches of GLP-1 receptor agonists; dual and triple agonists addressing GLP-1, glucagon, amylin, and GIP receptors; a combination of an amylin analogue and a GLP-1 receptor agonist (semaglutide); and a unimolecular GLP-1 receptor agonist–GIP receptor antagonistic antibody in advanced stages of drug development (which is currently unapproved for treatment of type 2 diabetes, overweight or obesity, and MASLD. GIP= glucose-dependent insulinotropic polypeptide. HbA_{1c}=glycated haemoglobin. MASH=metabolic dsyfunction-associated steatohepatits. MASLD=metabolic dysfunction-associated steatotic liver disease. NA=not available.

Table: **Current status of clinical trials exploring advanced GLP-1-based medications for the treatment of type 2 diabetes and obesity, and their complications**

high (nausea in up to 12 % [*vs* up to 28% in phase 2], vomiting in up to 14% [*vs* up to 36%], and drug discontinuation due to adverse events in up to 8% [*vs* up to 19%] of the exposed participants).[122,143] Orforglipron will further be studied as a novel treatment for type 2 diabetes in the ACHIEVE programme. The development of other small-molecular oral GLP-1 receptor agonists (eg, lotiglipron and danuglipron) was halted due to liver toxicity.

Biased GLP-1 receptor agonism: a preferential stimulation of cAMP generation over β-arrestin recruitment

Theoretically, biased agonism should prevent receptor internalisation in response to ligand binding, therefore preserving a greater number of GLP-1 receptors on the cell surface that are available for further stimulation. Overall, this approach aims to initiate greater and prolonged responses, resulting in larger effect sizes compared with non-biased agonists. Clinical results have been reported for ecnoglutide, which has been developed as a biased GLP-1 receptor agonists. These results indicate a slightly greater reduction in HbA_{1c} (0·25% more than dulaglutide, the selective GLP-1 receptor agonist) and bodyweight (3% greater than dulaglutide)[123] in people with type 2 diabetes, and increased weight loss (13·3% greater than placebo treatment) in people with obesity.[131] However, given the established variability in effect sizes between approved GLP-1 receptor agonists,[144] whether ecnoglutide leads to substantially greater effectiveness compared with other so-called unbiased compounds, is unclear.

Dual glucagon–GLP-1 receptor agonists

In human proof-of-concept studies, co-administration of GLP-1 and glucagon revealed benefits over GLP-1 receptor agonists alone, including further reduction in food intake, increased energy expenditure, increased hepatic fatty acid oxidation, reduced hepatic lipid accumulation, and improved mitochondrial function, without compromising glycaemic control.[145]

Survodutide is a dual glucagon–GLP-1 receptor agonist. In a phase 2 trial in people with T2D, after 16 weeks of treatment, doses of survodutide up to 2·7 mg once weekly reduced HbA_{1c} by up to 1·6% (95% CI 1·3–1·8) or 17 mmol/mol (14–20) compared with semaglutide (1 mg once weekly; reduction of 1·5% [16 mmol/mol]; table).[125] Weight loss with survodutide (up to 7·7%) was greater than with semaglutide (5·3%) or placebo (0·9%). The risk of experiencing nausea (up to 46%), vomiting (up to 26%), or drug discontinuation (up to 30%) was greater than with semaglutide (nausea 9%, vomiting 2%, and drug discontinuation due to adverse events 5%) or placebo (nausea 12%, vomiting 4%, and drug discontinuation due to adverse events 4%).[125] A new weight loss plateau was not reached during the study period.[125] Survodutide (3·6 mg and 6 mg once weekly) is currently undergoing phase 3 trials as treatment for obesity (SYNCHRONIZE programme; NCT06066515 and NCT06077864), and a phase 2 study in adults with metabolic dysfunction-associated steatohepatitis and liver fibrosis with and without diabetes has been published.[140]

Mazdutide is another once-weekly dual glucagon–GLP-1 receptor agonist[126,134] that has been mainly studied in Chinese people. In a phase 2 trial in people with type 2 diabetes, after 20 weeks of treatment, mazdutide (up to 6 mg weekly) reduced HbA_{1c} numerically more (by up to 1·7% [19 mmol/mol]) compared with the selective GLP-1 receptor agonist dulaglutide (HbA_{1c} reduction of 1·4% [15 mmol/mol]).[126] Bodyweight was reduced more by all doses of mazdutide (ie, 3–6 mg/week) than by dulaglutide.[126] Similar to a previous phase 2 trial in Chinese adults with overweight or obesity,[133] a recent phase 3 trial (GLORY) described bodyweight reductions after 48 weeks of treatment with 6 mg/week mazdutide of 14·0% (*vs* an increase of 0·3% with placebo).[134] With mazdutide treatment, 51% of participants experienced nausea and 43% experienced vomiting, but drug discontinuation rate due to adverse events was low (2%; table).[126,134] A phase 3 programme (DREAMS) is currently assessing mazdutide (4 mg and 6 mg weekly) as treatment for type 2 diabetes in Chinese populations. Glucagon–GLP-1 receptor co-agonists therefore promise greater weight reduction than with selective GLP-1 receptor agonists, and do not compromise glucose-lowering effects in patients with type 2 diabetes.

Amylin–GLP-1 receptor fixed combinations or unimolecular dual agonists

Amylin is co-secreted with insulin from pancreatic β-cells in response to food intake, delays gastric emptying, inhibits glucagon secretion, improves glycaemia, increases satiety, and reduces food intake without decreasing energy expenditure (appendix p 6),[146–148] with a mode of action that differs from GLP-1.[149] Cagrilintide (once-weekly subcutaneous administration) is an amylin receptor agonist.[150]

Cagrilintide has been studied in a fixed-dose combination with the selective GLP-1 receptor agonist semaglutide (ie, CagriSema) for the treatment of overweight or obesity and in people with type 2 diabetes. In a phase 3 trial in people with type 2 diabetes, cagrilintide–semaglutide (2·4 mg/week of cagrilintide and semaglutide each) reduced HbA_{1c} by 1·4% (95% CI 1·2–1·6) or 15 mmol/mol (13–17), and bodyweight by 10·4% (9·5–11·2; placebo-corrected).[127] In adults with overweight or obesity, cagrilintide–semaglutide reduced bodyweight by 17·3% (16·6–18·1; placebo-subtracted),[135] along with reductions in waist circumference, blood pressure, and improved physical functioning scores.[135] The effects of the drug combination were greater than the effects of either medication alone, but less than the sum of effects for both medications.[135] Gastrointestinal adverse events were slightly more frequent with CagriSema than with semaglutide alone.[135] The REDEFINE-3 trial will assess the

effect of cagrilintide–semaglutide on cardiovascular events in people with overweight or obesity, with and without type 2 diabetes and pre-existing cardiovascular disease.

Amycretin is a novel, unimolecular dual amylin–GLP-1 receptor agonist that can be administered subcutaneously[136] or orally,[137] and has been studied in people with overweight or obesity. In a phase 1b/2a trial over 36 weeks, amycretin (once-weekly subcutaneous administration) dose-dependently reduced bodyweight by up to 23·2% (95% CI 15·6–30·8; 60 mg/week) versus baseline (placebo-subtracted).[136] Oral amycretin (two tablets of 50 mg daily) reduced bodyweight by up to 11·8% (9·0–14·6; placebo-subtracted) after 12 weeks in a phase 1 trial.[137] The proportion of people reporting nausea or vomiting was high, as was the drug discontinuation rate with subcutaneous amycretin,[136] but not with oral amycretin.[137]

Triple GIP–GLP-1–glucagon receptor agonists

Preclinical studies with the triple agonist retatrutide showed greater weight loss and reductions in plasma glucose concentration compared with tirzepatide.[151] Retatrutide is in clinical development for once-weekly administration (table) in people with obesity,[138] type 2 diabetes,[128] and MASLD.[140]

In the retatrutide phase 2 trial for people with overweight or obesity (BMI ≥30 kg/m²), or with a BMI of at least 27 kg/m² with one or more weight-related condition, the mean bodyweight reduction at week 48 in the retatrutide (12 mg once-weekly) groups was up to 24·2% (95% CI 21·8–28·6) compared with 2·1% (0·7–3·5) with placebo.[138] In a retatrutide phase 2 trial for people with type 2 diabetes, 36 weeks of treatment with retatrutide (of doses up to 12 mg/week) resulted in a HbA_{1c} reduction of up to 2·2% (SEM 0·1) or 24 mmol/mol (SEM 1), compared with a 1·4% (SEM 0·1) or 15 mmol/mol (SEM 1) reduction with dulaglutide 1·5 mg and a 0·3% (SEM 0·2) or 3 mmol/mol (SEM 3) reduction with placebo.[128] A dose-dependent reduction in bodyweight of up to 16·9% (SEM 1·3%) was also observed (3% [SEM 1] with placebo and 2% [SEM 1] with dulaglutide 1·5 mg/week).[128] Mild-to-moderate gastrointestinal side-effects were reported in a similar proportion to the selective GLP-1 receptor dulaglutide.[128] However, adverse events leading to treatment discontinuation were experienced by up to 17% of participants given retatrutide, compared with 2% given dulaglutide and 4% given placebo. Currently, the efficacy and safety of retatrutide are being assessed for treatment of obesity in a programme of phase 3 trials (TRIUMPH) in people with overweight or obesity and type 2 diabetes.

GLP-1 receptor agonist–GIP receptor antagonist combination

Although agents such as tirzepatide have been designed to provide stimulation to both GIP and GLP-1 receptors, recent research has shown that combining a GLP-1 agonist with a GIP receptor antagonist will also provide more weight reduction than with a selective GLP-1 receptor agonist alone.[152] Maridebart cafraglutide is an antagonistic GIP receptor antibody coupled with a GLP-1 receptor agonist.[153] In a phase 2 trial of people with obesity (with or without type 2 diabetes) who received maridebart cafraglutide every 4 weeks for 52 weeks, bodyweight was reduced by up to 16·2% (95% CI 13·5–18·9) compared with a 1·7% reduction with placebo. Furthermore, HbA_{1c} was reduced in the cohort with type 2 diabetes by up to 1·5% (1·0–1·9) versus an increase of 0·1% with placebo.[129] The proportion of participants given the study drug who reported nausea (up to 87%) or vomiting (up to 92%) was high but somewhat improved by a slower dose escalation, and up to 29% of participants discontinued drug treatment because of adverse events. Similar effects of GIP receptor agonism and antagonism on bodyweight can be explained by their different target pathways: GIP receptor agonists act on GABAergic neurons, which leads to reduced food (energy) intake,[11] whereas GIP receptor knock-out in GABAergic neurons sensitises people to weight loss induced by GLP-1 receptor agonists.[154]

Taken together, dual and triple agonists addressing receptors for gastroenteropancreatic peptide hormones with therapeutic potential promise greater effects regarding glycaemic control and bodyweight reduction. However, at this stage, these medications carry a higher burden of (mainly gastrointestinal) adverse events compared with selective GLP-1 receptor agonists, indicating a need to optimise dose-escalation regimens and induce tolerance to such side-effects, or, in the choice of appropriate doses, avoid unnecessary nausea and vomiting.

Conclusions

Incretin-based medications have gained an established role in the treatment of type 2 diabetes and obesity. Robust evidence exists for their cardiovascular benefits in people with type 2 diabetes or obesity, and for preservation of kidney function and prevention of kidney failure or cardiovascular death in people with type 2 diabetes and CKD. Within the spectrum of clinical obesity, closely associated conditions—including progression to type 2 diabetes, MASLD, heart failure with preserved ejection fraction, obstructive sleep apnoea, and knee osteoarthritis—benefit in terms of symptomatic relief and improved prognoses. In addition, novel indications could arise, exemplified by several neurodegenerative diseases and substance use disorders currently being studied. Next-generation medications building on existing incretin-based medications could provide even greater metabolic efficacy but require large-scale phase 3 trials to establish clinical benefits, safety, and tolerability. More widespread use, together with the future availability of generic drugs, should reduce treatment costs, which currently restrict availability for many people who could

benefit from the rapidly emerging portfolio of incretin-based therapies.

Contributors

MAN, KRT, MHT, and MB: conceptualisation, literature search, data interpretation, writing, and reviewing and editing. MAN: drafting figures and table. KRT, MHT, and MB: reviewing and editing figures and table. All authors approved the final version before submitting for publication.

Declaration of interests

MAN has been member on advisory boards or has consulted with Boehringer Ingelheim, Eli Lilly & Co, Medtronic, Merck, Sharp & Dohme, NovoNordisk, Pfizer, Regor, Sun Pharma, and Structure Therapeutics (Gasherbrum); has received grant support from Merck and Sharp & Dohme; has served on the speakers bureau of Eli Lilly & Co, Merck, Sharp & Dohme, Medscape, Medical Learning Institute, and NovoNordisk; and is on a Data Monitoring and Safety Board for Inventiva. KRT has received investigator-initiated grant support from Travere, Bayer, Benaroya Research Institute, the Doris Duke Charitable Foundation, and Breakthrough-T1D; reports consultancy fees from Boehringer Ingelheim, Eli Lilly, Novo Nordisk, AstraZeneca, Alnylam, Bayer, and ProKidney; and reports speaker fees from Novo Nordisk, Bayer, and Boehringer Ingelheim. She reports US National Institutes of Health research grants R01MD014712, U2CDK114886, UL1TR002319, U54DK083912, U01DK100846, OT2HL161847, UM1AI109568, OT2OD032581, and US Centers for Disease Control and Prevention project numbers 75D301-21-P-12254 and 75D301-23-C-18264. She reports being chair of Data Safety Monitoring boards for the US National Institutes of Health National Institute of Diabetes and Digestive and Kidney Disease, and the George Clinical Institute, and reports being a member of the Data Safety Monitoring Board for AstraZeneca. She reports leadership roles as chair for the Diabetic Kidney Disease Collaborative for the American Society of Nephrology, chair for Kidney Week 2025 Program Committee, member of the American Heart Association publication committee, and a member of the American Heart Association–American College of Cardiology Cardiovascular Kidney Metabolic Guideline Committee. MHT has delivered scientific lectures for Boehringer Ingelheim (2024), KG (2024), AstraZeneca (2024), Lilly Deutschland (2024), and Novo Nordisk (2024). He is co-founder of the biotech startup Bluewater Biotech (founded in 2024). As CEO and CSO of Helmholtz Munich, he is co-responsible for countless collaborations of the employees with a multitude of companies and institutions, worldwide. In this capacity, he discusses potential projects with and has signed/signs contracts for the centre's institute(s) related to research collaborations worldwide, including but not limited to pharmaceutical corporations such as Boehringer Ingelheim, Novo Nordisk, Roche Diagnostics, Arbormed, Eli Lilly, SCG Cell Therapy, and others. As the CEO of Helmholtz Munich, he was/is further overall responsible for commercial technology transfer activities. He confirms that, to the best of his knowledge, none of the above funding sources or collaborations were involved in or had an influence on the preparation of this manuscript. MB received honoraria as a consultant and speaker from Abbott, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Daiichi–Sankyo, Lilly, MSD, Novo Nordisk, Novartis, Pfizer, and Sanofi; and reports chairing a Clinical Trial Data Safety Monitoring Board for Boehringer Ingelheim.

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