Incretin-based therapies in 2024

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Expanding applications of therapies based on GLP1

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The evidence base in support of the use of medicines based on glucagon-like peptide 1 beyond glucose control and weight loss was substantially bolstered in 2024, as clinical trial data report benefits of these medicines in people with a range of disorders.

Several new trials provide compelling evidence for the efficacy and safety of medicines based on glucagon-like peptide 1 (GLP1) across a wide range of metabolic disorders and comorbidities (Fig. 1). The SELECT trial studied the safety of 2.4 mg of semaglutide once weekly in 17,604 people; participants did not have a history of type 2 diabetes mellitus (T2DM) and either had overweight and one or more weight-related comorbidity or had obesity. The mean follow-up period was 39.8 months. The study participants (mean age 61.6 years, 72% male and mean BMI 33.3 kg/m^2) all had a history of atherosclerotic cardiovascular disease, most commonly myocardial infarction, and ~25% had chronic heart failure[1]. Semaglutide therapy reduced the development of the primary composite outcome (non-fatal myocardial infarction, non-fatal stroke and death from cardiovascular causes) by 20%. Hazard ratios for the heart failure composite outcome and all-cause mortality were 0.82 and 0.81, respectively, favouring semaglutide over placebo. The mean change in body weight after 104 weeks was −9.39% with semaglutide and −0.88% with placebo. The reduction in the primary endpoint was similar across several prespecified subgroups, such as by age, BMI, region, race and ethnicity. Similar reductions in the primary endpoint were observed in male and female study participants[1]. Intriguingly, the benefits of semaglutide were detected within a few months, which is early relative to the longer time period of 12–18 months required for detectable benefit in GLP1 outcome trials in people with T2DM[2]. Study drug discontinuation was observed in 26.7% and 23.6% of individuals randomized to semaglutide versus placebo, respectively. Adverse events, mostly gastrointestinal complaints, that led to permanent discontinuation of the study drug were observed in 16.5% and 8.2% of people receiving semaglutide and placebo, respectively.

The FLOW trial studied the safety and efficacy of 1.0 mg of semaglutide or placebo once weekly in 3,533 patients with T2DM and chronic kidney disease, who were on a stable maximally tolerated dose of renin–angiotensin system inhibitors, with an estimated glomerular filtration rate (eGFR) of 50–75 ml/min/1.73 m^2 and a urinary albumin (measured in mg) to creatinine (measured in grams) ratio of >300 and <5,000, or an eGFR of 25–50 ml/min/1.73 m^2 and a urinary albumin to creatinine ratio of >100 and <5,000 (ref. 3). The primary composite outcome was a reduction in kidney events, or death from kidney or cardiovascular causes[3]. After a median follow-up period of 3.4 years, early trial cessation was recommended by the steering committee after a prespecified interim analysis. Semaglutide reduced the risk of the primary outcome by 24%, and similar efficacy was noted for reduction of kidney events or death from cardiovascular causes; fewer serious adverse events were reported in participants randomized to semaglutide than in those who received placebo. Body weight and HbA_{1c} were reduced by 4.1 kg and 0.81%, respectively, after 24 months of semaglutide versus placebo[3]. All-cause mortality was reduced by 20% with semaglutide. In contrast to previous results in T2DM outcome trials with GLP1 medicines, rates of stroke were not reduced with semaglutide therapy in the FLOW trial. Enrolment was stratified according to baseline use of sodium–glucose co-transporter 2 inhibitors (SGLT2i), and the benefits of semaglutide were apparent in the presence or absence of concomitant SGLT2i use; however, the number of individuals on these agents (550) was insufficient for statistically meaningful scrutiny of individual outcomes by the presence or absence of concomitant SGLT2i therapy[4].

The dual gastric inhibitory polypeptide receptor–GLP1 receptor (GLP1R) co-agonist tirzepatide is approved for the treatment of T2DM as well as for weight loss in people with overweight and one or more comorbidities, or in those with obesity. The efficacy of tirzepatide, at 10 mg or 15 mg weekly as tolerated, was studied in 469 patients with moderate to severe obstructive sleep apnoea and obesity in two phase III trials over 52 weeks; participants either had never received positive airway pressure treatment or had received this treatment for at least 3 months[5]. All participants received lifestyle counselling and were expected to exercise for 30 min at least three times a week and to adhere to dietary and lifestyle recommendations, including a 500 kilocalorie per day deficit and at least 150 min per week of physical activity. In both trials, tirzepatide reduced the number of apnoea or hypopnoea episodes per hour as the primary endpoint, as well as decreasing the hypoxic burden. Significant reductions in body weight (16.1–17.4% placebo-subtracted weight loss), systolic blood pressure (−7.7 to −9.5 mm Hg) and high sensitivity C-reactive protein were observed in participants treated with tirzepatide. The most common adverse events reported were mild to moderate gastrointestinal complaints.

Key advances

- Semaglutide reduces cardiovascular morbidity and all-cause mortality in people with obesity[1].
- Tirzepatide improves outcomes in people with sleep apnoea[5].
- Survodutide reduces fibrosis and inflammation in people with metabolic liver disease[9].
- Semaglutide reduces need for urgent care and hospitalization in individuals with heart failure with preserved ejection fraction[6].
- Semaglutide improves cardiovascular and renal outcomes in people with type 2 diabetes mellitus and chronic kidney disease[3].

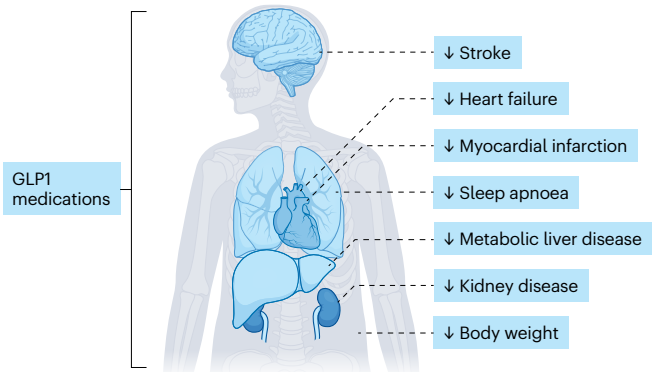

Fig. 1 | The effects of therapies based on GLP1. Glucagon-like peptide 1 (GLP1) medicines reduce the rates of the complications associated with type 2 diabetes mellitus and obesity.

Two trials, STEP HFpEF and STEP HFpEF DM, reported symptomatic improvement with semaglutide therapy in individuals with heart failure with preserved ejection fraction (HFpEF) with or without T2DM. However, the effect of semaglutide on additional meaningful outcomes in individuals with heart failure, including emergency room visits and hospitalization, remained uncertain. Kosiborod et al. reported a post hoc analysis of trial participants with mildly reduced or preserved heart failure pooled from the SELECT, FLOW, STEP-HFpEF and STEP-HFpEF DM trials[6]. The primary outcome was a composite endpoint of time to cardiovascular death or first worsening of heart failure event, the time to first worsening heart failure event and time to cardiovascular death. Semaglutide reduced the risk of the primary endpoint among the 16.8% of the 22,282 trial participants with HFpEF, including a significant reduction (HR of 0.59) of worsening heart failure events, defined as hospitalization or urgent hospital visits. Fewer serious adverse events were reported in participants who received semaglutide than in those who received placebo. The number needed to treat to prevent one worsening heart failure event was 95 over 1 year and 30 over 3 years. No significant reduction in cardiovascular death alone was observed[6]. The results were consistent across most subgroups, including individuals with or without baseline use of SGLT2i or selective mineralocorticoid antagonists, or individuals with mild HFrEF versus HFpEF. These results extend the benefits of semaglutide in heart failure beyond symptomatic improvement to encompass more clinically meaningful endpoints related to the requirement for additional care and risk of cardiovascular death.

Several GLP1 medicines are being studied in people with metabolic liver disease at risk of developing multiple complications and liver failure[7]. The first phase III trial scheduled to report, the ESSENCE trial, is studying the efficacy of 2.4 mg of semaglutide once weekly in individuals with metabolic dysfunction-associated steatohepatitis (MASH; also known as non-alcoholic steatohepatitis)[8]. The actions of GLP1R agonists to improve liver health are thought to reflect the importance of weight loss in reducing inflammation, with possible secondary contributions from GLP1 action in cells other than hepatocytes that indirectly attenuate liver injury. Among the newer classes of GLP1 medicines under development, glucagon receptor (GCGR)–GLP1R co-agonists exhibit considerable potential for the treatment of metabolic liver disease, owing to actions of glucagon to reduce hepatic lipogenesis and augment hepatic lipid oxidation[7]. Sanyal and colleagues reported phase II clinical trial data on the therapeutic efficacy of the GCGR–GLP1R co-agonist survodutide using three doses (2.4, 4.8 or 6.0 mg, once weekly) in participants with biopsy-confirmed MASH and fibrosis stages F1–F3, over 48 weeks[9]. Improvement of MASH without worsening of fibrosis was observed in up to 62% of 293 survodutide-treated trial participants, with improvement in at least one fibrosis stage reported in up to 36% of survodutide-treated participants, versus 22% for those who received placebo. A reduction in hepatic adipose content of at least 30% was observed in up to 67% of people treated with survodutide. Weight loss of 10–13% was achieved in survodutide-treated individuals. Adverse events, predominantly mild to moderate gastrointestinal complaints, were more common with all three doses of survodutide relative to placebo[9].

Although these trials are not designed to reveal mechanisms that underlie the benefits of GLP1 medicines in a wide range of disorders, it seems likely that a subset of benefits might reflect a reduction of inflammation, partly independent of the degree of weight loss achieved[10], which raises important questions about thresholds and goals currently associated with use and reimbursement of GLP1 medicines. Importantly, these trials expand the benefits of GLP1 medicines without revealing new safety concerns[1], which further refines the risk:benefit discussion for long term use of treatments based on GLP1 in populations at risk of serious complications of cardiometabolic disorders.

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Competing interests

D.J.D. has served as a consultant or speaker within the past 12 months to Altimmune, Amgen, Arrowhead, AstraZeneca, Boehringer Ingelheim, Kallyope, Merck Research Laboratories, Novo Nordisk Inc., Pfizer Inc and Zealand Pharma. Neither D.J.D. nor his family members hold issued stock directly or indirectly in any of these companies. D.J.D. holds non-exercised options in Kallyope.