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Efficacy and Safety of GLP-1 Medicines for Type 2 Diabetes and Obesity

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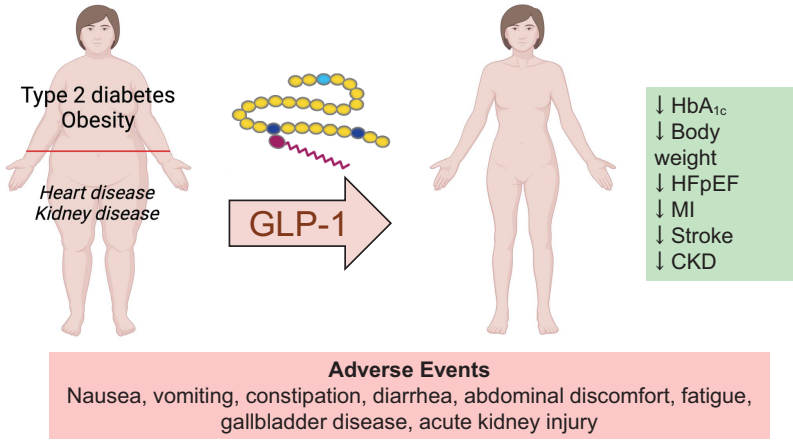

CKD, chronic kidney disease; GLP-1, glucagon-like peptide 1; HFpEF, heart failure with preserved ejection fraction; MI, myocardial infarction.

ARTICLE HIGHLIGHTS

- **Why did we undertake this study?**
  To describe the indications, benefits, and safety issues surrounding use of GLP-1 medicines in a narrative review.
- **What is the specific question(s) we wanted to answer?**
  What are the risks versus benefits of GLP-1 medicines in different populations with type 2 diabetes or obesity?
- **What did we find?**
  GLP-1 medicines exhibit a well-defined safety profile and their use achieves clinically important outcomes in people with type 2 diabetes. There is less evidence to support the overall benefits and long-term safety in people with obesity.
- **What are the implications of our findings?**
  Development of new GLP-1 medicines will require a sizeable investment in studies to scrutinize outcomes and safety for structurally and mechanistically distinct therapies that become approved for people with cardiometabolic disorders.

Efficacy and Safety of GLP-1 Medicines for Type 2 Diabetes and Obesity

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REVIEW

The development of glucagon-like peptide 1 receptor agonists (GLP-1RA) for type 2 diabetes and obesity was followed by data establishing the cardiorenal benefits of GLP-1RA in select patient populations. In ongoing trials investigators are interrogating the efficacy of these agents for new indications, including metabolic liver disease, peripheral artery disease, Parkinson disease, and Alzheimer disease. The success of GLP-1–based medicines has spurred the development of new molecular entities and combinations with unique pharmacokinetic and pharmacodynamic profiles, exemplified by tirzepatide, a GIP-GLP-1 receptor coagonist. Simultaneously, investigational molecules such as maritide block the GIP and activate the GLP-1 receptor, whereas retatrutide and survodutide enable simultaneous activation of the glucagon and GLP-1 receptors. Here I highlight evidence establishing the efficacy of GLP-1–based medicines, while discussing data that inform safety, focusing on muscle strength, bone density and fractures, exercise capacity, gastrointestinal motility, retained gastric contents and anesthesia, pancreatic and biliary tract disorders, and the risk of cancer. Rapid progress in development of highly efficacious GLP-1 medicines, and anticipated differentiation of newer agents in subsets of metabolic disorders, will provide greater opportunities for use of personalized medicine approaches to improve the health of people living with cardiometabolic disorders.

More than 19 years after the introduction of the first glucagon-like peptide 1 receptor (GLP1R) agonist for the treatment of type 2 diabetes and 10 years after the first approval for obesity, two distinct waves of innovation herald new opportunities for broadening the use of new molecules that act primarily through or in combination with medicines that enhance GLP-1 action, hereafter designated GLP-1 medicines, in people with metabolic disorders (Fig. 1). First, multiple new molecular entities, based on GLP-1 action, are in clinical development. These include small-molecule orally administered GLP1R agonists (GLP-1RA), unimolecular glucagon receptor (GCGR)-GLP1R coagonists such as survodutide and pemvidutide, GCGR-GIPR-GLP1R triagonists such as retatrutide, additional GIPR-GLP1R coagonists distinct from tirzepatide, small-molecule oral GIPR-GLP1R coagonists such as orforglipron, higher doses of established agents, and combinations of long-acting amylin receptor (AMLNR) agonists such as cagrilintide together with GLP-1RA (1,2).

A second line of innovation, encompassing new indications potentially ranging from addiction-related behaviors to peripheral vascular disease, type 1 diabetes, metabolic liver disease, and neurodegenerative disorders, is currently under evaluation in clinical trials (3). Collectively, more effective molecules and expanding indications should provide new opportunities for improving the health of a wider range of individuals, beyond currently established indications of type 2 diabetes and obesity (Fig. 1).

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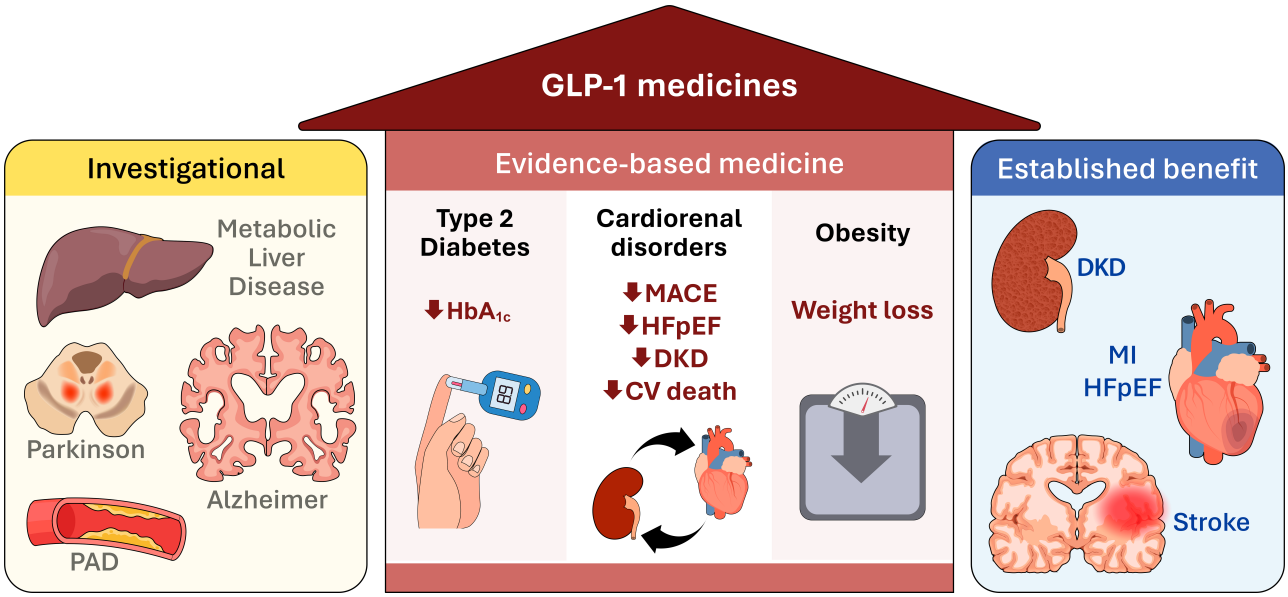

Figure 1—Established and emerging evidence supporting use of GLP-1 medicines. Right panel: Clinical indications where use of GLP-1 medicines is now supported by extensive clinical trial data. Left panel: Potential indications still under study with ongoing phase 3 trials. Center panel: Classical indications encompassing type 2 diabetes, and obesity, as well as cardiorenal indications, where the benefits of GLP-1 medicines are supported by multiple clinical trials. CV, cardiovascular; DKD, diabetic kidney disease; PAD, peripheral artery disease.

Nevertheless, expanding use of these medicines raises the possibility of new safety issues (Fig. 2). In this review, I discuss the current landscape and risk-benefit profile of modern GLP-1 medicines, highlighting existing and emerging indications, as well as controversies surrounding the safety of GLP-1 medicines. The readers are referred to recent reviews for summaries of the investigational GLP-1 medicine pipeline (1,2,4).

OVERVIEW OF MODERN GLP-1–BASED MEDICINES AND TYPE 2 DIABETES

The first clinically approved GLP-1RA, exenatide, was introduced in 2005 as a twice daily injection for the treatment of type 2 diabetes (5). Exenatide twice daily was followed by once daily liraglutide, once weekly exenatide, once daily lixisenatide, once daily oral semaglutide, and several once weekly medicines, including albiglutide, dulaglutide, semaglutide, and tirzepatide, the first GIPR-GLP1R coagonist (1,2). Dulaglutide, semaglutide, and tirzepatide are the three most widely used GLP-1 medicines for type 2 diabetes, supported by extensive data from phase 3 trial programs, including several head-to-head studies. Dulaglutide, at a maximal dose of 1.5 mg weekly, was compared with semaglutide, maximum dose 1 mg weekly, in 1,201 people with type 2 diabetes on metformin therapy over 40 weeks. The hemoglobin A_{1c} (HbA_{1c}) reduction and weight loss were greater with semaglutide relative to therapy with dulaglutide (6). Superior reduction of HbA_{1c} and greater weight loss were seen with tirzepatide than with semaglutide 1 mg once weekly over 40 weeks in people with type 2 diabetes (7). Higher doses of semaglutide (2 mg once weekly) and dulaglutide (up to 4.5 mg once weekly) have subsequently been approved for type 2 diabetes.

Beyond achievement of effective glucose control and weight loss, GLP-1RA deliver additional benefits in people with type 2 diabetes through reduction of rates of major adverse cardiovascular events (MACE), heart failure, kidney disease, and cardiovascular death (3,8,9) (Fig. 1). GLP-1RA reduce blood pressure, postprandial lipemia, and inflammation, actions likely contributing to their cardiovascular benefits (9). Some studies have demonstrated that native GLP-1 and GLP-1RA reduce platelet aggregation, although the underlying mechanisms and clinical relevance of these observations remain uncertain (10,11). GLP-1RA also reduce albumin excretion, and the rate of decline in estimated glomerular filtration rate, in people with type 2 diabetes (8), and semaglutide 1 mg once weekly produced a 24% reduction in the primary composite outcome of renal and cardiovascular end points in the FLOW trial in people with type 2 diabetes (12).

The safety of multiple GLP-1 medicines in type 2 diabetes was studied in eight cardiovascular outcome trials, revealing a reduction in rates of nonfatal myocardial infarction (MI), nonfatal stroke, and cardiovascular death with long-acting GLP-1RA (13). Importantly, the reduction in rates of MACE with GLP-1RA in type 2 diabetes is accompanied by an ∼12% reduction in all-cause mortality and an 11% reduction in hospitalization for heart failure, even with concomitant background use of antiplatelet agents and medicines for reduction of blood pressure and cholesterol (8,13). Clinical trial and real-world data suggest that GLP-1RA exert an additive cardiovascular benefit when used concomitantly with sodium–glucose cotransporter 2 inhibitors (SGLT2i) to treat people with type 2 diabetes (14–17).

The safety of tirzepatide is being assessed for people with type 2 diabetes and established cardiovascular disease in A Study of Tirzepatide (LY3298176) Compared With Dulaglutide on Major Cardiovascular Events in Participants With Type 2 Diabetes (SURPASS-CVOT) with a study design randomizing participants with established atherosclerotic cardiovascular disease (CVD) to dulaglutide (1.5 mg once weekly) or tirzepatide (up to 15 mg weekly) (18). Baseline characteristics at trial enrollment include mean age 64.1 years,

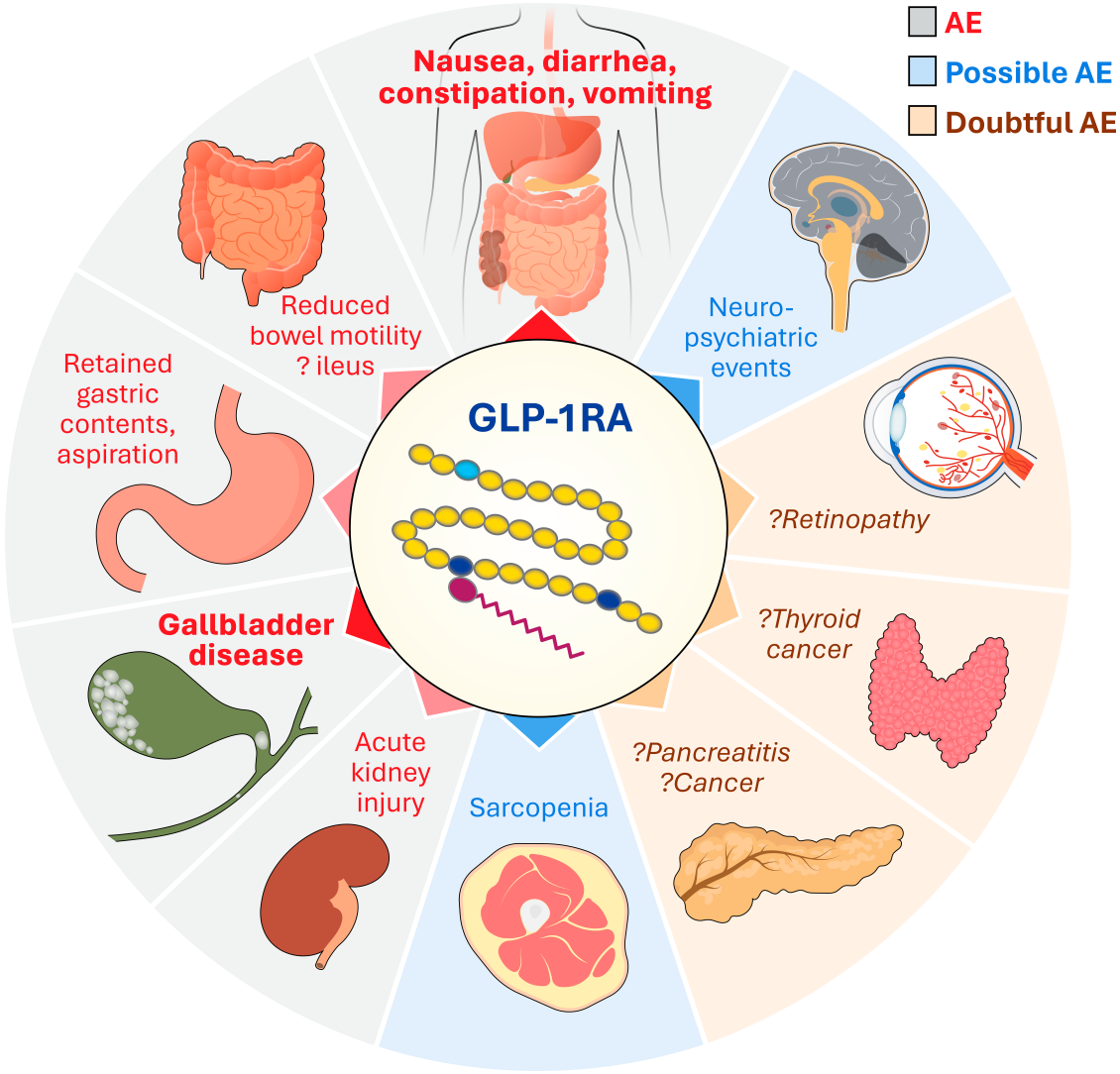

Figure 2—Established and putative AEs associated with GLP-1 medicines. AEs in gray background described with red boldface text are established and common, with gastrointestinal AEs observed in 40%–65% of subjects, whereas gallbladder AEs are reported in up to 3% of exposed subjects, acute kidney injury is reported in <1% of subjects, and AEs such as retained gastric contents and aspiration associated with pneumonia as well as ileus are very rare, generally not reported in outcome trials but reported in the community in case reports or series. Neuropsychiatric events and sarcopenia are rare, and the incidence is uncertain and under investigation. AEs shown in italics with the symbol? are listed as possible side effects but have not been conclusively proven to be associated with use of GLP-1 medicines.

diabetes duration 14.7 years, HbA_{1c} 8.4%, and BMI 32.6 kg/m^2. Trial subjects had a previous history of MI (47.3%), stroke (19.1%), and peripheral artery disease (25.3%) (18). Tirzepatide therapy was not associated with an increase in cardiovascular events in the phase 3 SURPASS program in individuals with type 2 diabetes; however, the total number of individuals with CVD events across the phase 3 program was too small to make clear conclusions about potential cardiovascular benefit (19).

GLP-1 MEDICINES AND THE TREATMENT OF OBESITY

The observations of modest (2%–5%) weight loss in people with type 2 diabetes treated with GLP-1RA spurred the investigation of whether higher doses might generate greater weight loss in people with obesity (20). Liraglutide 3 mg once daily was the first GLP-1RA approved (in 2014) for weight loss in people with overweight and comorbidities or people with BMI >30 kg/m^2 (20–22). Subsequently, semaglutide 2.4 mg once weekly was approved for weight management and the treatment of people with overweight and a related comorbidity or obesity in 2021, followed by the approval of tirzepatide for similar indications in 2023 (20,23). The efficacy of semaglutide 2.4 mg once weekly was demonstrated in the Semaglutide Treatment Effect in People with Obesity (STEP) program trials across a range of populations, with achievement of placebo-subtracted weight loss of ~12%–15% in individuals without type 2 diabetes (20). Consistent with results from other weight loss interventions (8), individuals with overweight or obesity and coexisting type 2 diabetes exhibit attenuated weight loss. In the STEP 2 trial, mean placebo-subtracted weight loss of 6.2% was achieved by participants on semaglutide after 68 weeks (24), substantially less than the magnitude of weight loss observed in the STEP trial in the absence of type 2 diabetes (8).

The safety of semaglutide 2.4 mg once weekly was assessed in 17,604 people with BMI $\geq$27 kg/m^2 and a history of atherosclerotic CVD without known type 2 diabetes, mean duration of drug exposure 34 months, with achievement of placebo-subtracted weight loss of 8.51% at 104 weeks. Treatment with semaglutide produced a 20% reduction in nonfatal MI, nonfatal stroke, and cardiovascular death, driven principally by a reduction in MI (25). Prediabetes (HbA$_{1c}$ 5.7%–6.4%) was present in 66% of the trial subjects, with a mean baseline HbA$_{1c}$ of 5.8% at study entry. Intriguingly, the cardiovascular benefits of semaglutide appeared early in individuals with obesity, detectable within months of drug initiation and may not be strictly correlated with the extent of weight loss (25).

The cardiovascular actions of semaglutide 2.4 mg once weekly were also studied over 52 weeks in subjects with obesity and heart failure with preserved ejection fraction (HFpEF), with and without type 2 diabetes. With semaglutide therapy 10.7% placebo-subtracted weight loss was achieved and systemic inflammation reduced and symptoms improved as measured with the Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS) in 529 individuals without diabetes (26). The improvement in symptoms and reduction in biomarkers of inflammation in the STEP-HFpEF trial were directly proportional to the extent of weight loss (27). Similar results were obtained in 616 people with type 2 diabetes and HFpEF randomized to placebo or semaglutide for 52 weeks, with improvements of 7.3 points in the KCCQ-CSS and 6.4% weight loss in semaglutide- versus placebo-treated participants (17).

Tirzepatide was studied in the SURMOUNT trials in individuals with overweight (BMI $>$27 kg/m^2) and one or more complications or obesity (BMI $\geq$30 kg/m^2), with or without type 2 diabetes, with doses of 5–15 mg once weekly. Tirzepatide produced substantial placebo-subtracted weight loss of up to 20% in individuals with obesity without type 2 diabetes, with $\sim$60% of individuals on the 15 mg once weekly dose achieving $\geq$20% weight loss. Consistent with the class of GLP-1RA, gastrointestinal adverse events (AEs) represented the predominant side effects noted with tirzepatide (28). The majority of subjects with obesity and prediabetes reverted to normoglycemia by the end of the 72-week trial. A mean 11.6% placebo-subtracted reduction in body weight was seen over 72 weeks with tirzepatide 15 mg weekly in individuals with obesity and type 2 diabetes (HbA$_{1c}$ eligibility of 7%–10%, BMI $\geq$27 kg/m^2, mean duration of preexisting type 2 diabetes just over 8 years), with mean baseline weight among subjects 100.7 kg, BMI 36.1 kg/m^2, and HbA$_{1c}$ 8.02% (29). Almost 50% of the trial participants achieved HbA$_{1c}$ $<$5.7% after 72 weeks, with a mean end-of-trial HbA$_{1c}$ of 5.9%, and 31% of subjects achieved a mean weight loss of $>$20%. Tirzepatide therapy added after 12 weeks of intensive lifestyle modification to achieve an initial mean weight loss of at least 5% produced additional placebo-subtracted weight loss (estimated treatment difference) of 24.5% after 72 weeks of maximum tolerated (generally 10 or 15 mg once weekly) tirzepatide therapy in the SURMOUNT-3 trial (30). Intriguingly, a substantial proportion (46.2%) of tirzepatide-treated subjects (mean weight loss of 20.9% after active open-label treatment for the first 36 weeks) sustained a mean weight loss of at least 10% 1 year after discontinuation of tirzepatide (31). The rates of gastrointestinal AEs with tirzepatide in the SURMOUNT trials appear slightly lower than rates reported for semaglutide in the STEP trials, despite greater weight loss, perhaps reflecting the actions of GIP to attenuate central GLP-1–induced aversive responses (32).

The safety of tirzepatide, up to a maximum tolerated dose of 15 mg once weekly, in people with overweight or obesity is being studied in A Study of Tirzepatide (LY3298176) on the Reduction on Morbidity and Mortality in Adults With Obesity (SURMOUNT-MMO) (clinical trial reg. no. NCT05556512, ClinicalTrials.gov). The composite primary end point includes all-cause mortality, nonfatal MI, nonfatal stroke, coronary revascularization, and heart failure events that result in urgent medical visits or hospitalization. Individuals eligible for the study are $\geq$40 years old with established CVD or older subjects with a history of multiple cardiovascular risk factors.

INVESTIGATIONAL GLP-1 MEDICINES IN THE CLINIC

Herein we provide a concise summary of late-stage investigational GLP-1 medicines under evaluation for type 2 diabetes and obesity, whereas a broader overview of investigational GLP-1–based medicines is referenced (4). The impressive efficacy of tirzepatide, the first clinically approved GIPR-GLP1R coagonist, has sparked ongoing interest in understanding the directional biology of the GIPR in the control of metabolism. Tirzepatide produces substantial reductions in HbA$_{1c}$ reduction and weight loss in people with type 2 diabetes and obesity, consistent with the effects of GIPR and GLP1R coagonism in preclinical and human studies (33). Dozens of new GLP-1 medicines are being investigated in the clinic, with potential differentiation from semaglutide and tirzepatide on the basis of improvements in tolerability, greater magnitude of weight loss and reduction of HbA$_{1c}$, route and frequency of administration (Fig. 3), cost, and targeting of improved outcomes in people with type 2 diabetes, obesity, and associated comorbidities such as CVD, metabolic liver disease, kidney disease, and neurodegenerative disorders (1,4).

Intriguingly, prior to the compelling success of tirzepatide, two different long-acting GIPR-GLP1R coagonists were evaluated in the clinic over 6–12 weeks in individuals with type 2 diabetes. The reductions in HbA$_{1c}$ and body weight were much less impressive than results reported for tirzepatide (34,35). Furthermore, a combination of a once weekly GIPR agonist together with semaglutide failed to reduce HbA$_{1c}$ and body weight to a greater extent than that observed with semaglutide alone. Nevertheless, additional unimolecular GIPR-GLP1R agonists, such as VK2735, are being evaluated in clinical trials, and preliminary data reveal robust weight loss after 13 weeks of exposure in individuals with obesity (36).

Interestingly, substantial data demonstrate that reducing GIPR signaling, through the use of genetics, peptide antagonists, antibodies, or reduction/immunoneutralization of circulating levels of GIP, also promotes favorable metabolic phenotypes, including resistance to diet-induced obesity, and weight loss (1,37). Human genetics also supports reduction of GIPR signaling, evident from loss-of-function (LOF) *GIPR* mutations (38,39), as a strategy for reduction of body weight and achievement of favorable cardiometabolic outcomes. Preclinical data in rodents and nonhuman primates demonstrate

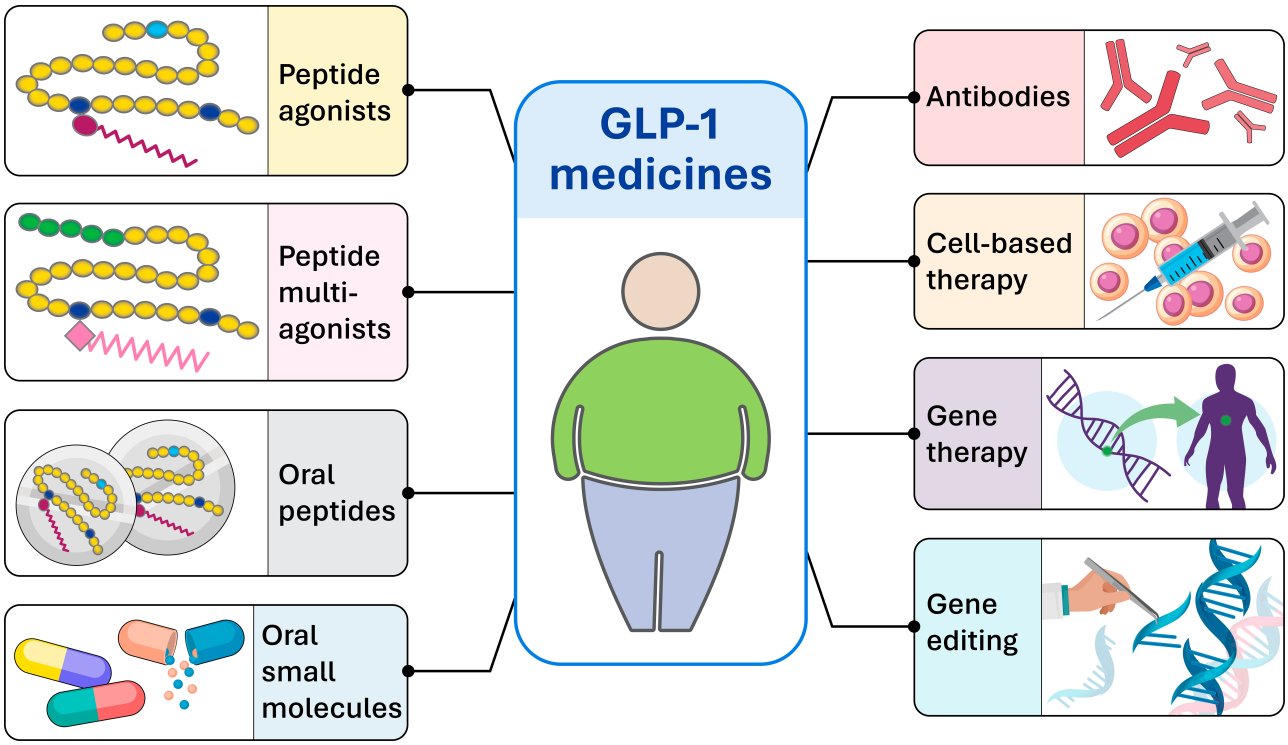

Figure 3—The future of GLP-1 medicines. Left: Established or late-stage investigational methods of delivering GLP-1 medicines. Right: Earlier-stage approaches to delivering GLP-1 medicines that are under active consideration or clinical investigation.

substantial efficacy for glucose reduction and weight loss with use of an antibody that simultaneously blocks the GIP receptor and activates the GLP1R (40,41). The efficacy and tolerability of AMG-133 (maridebart cafraglutide or maritide) was studied in individuals with obesity. Once monthly injections of maritide for a total of three doses produced substantial weight loss (up to 14.6%) (42). Intriguingly, study subjects maintained their reduced body weight even 5 months after the last injection. Maritide is currently being evaluated in phase 2 trials. Collectively, the data for tirzepatide and maritide highlight limitations in ascribing precise mechanisms of action for GLP-1 medicines that also target GIP receptor activity.

Advances in resolution of the structure and functional properties of the GLP1R and preference in some populations for oral medicines have fostered renewed interest in small-molecule oral GLP-1RA. The most advanced oral GLP-1RA, orforglipron, is biased toward G-protein activation versus recruitment of β-arrestin (43) and exhibited up to 2.1% HbA_{1c} reduction from a baseline of 8.1%, and up to 7.8% placebo-subtracted weight loss, over 26 weeks in individuals with type 2 diabetes (44).

Evaluation of orforglipron in people with obesity revealed up to 12.4% placebo-subtracted weight loss (mean baseline BMI 37.9 kg/m^2) over 36 weeks, with a tolerability profile reflecting mild-to-moderate gastrointestinal AEs (45). Assuming these agents avoid unanticipated off-target AEs in larger phase 3 trials, multiple once daily oral GLP-1RA will broaden choice, while offering lower cost of goods and more scalable alternatives to peptide-based GLP-1 medicines, without need for concomitant manufacture of pens or the requirement for cold storage.

The most advanced investigational once weekly unimolecular GLP-1–based multiagonist, retatrutide, also activates the GIPR and GCGR and exhibited unprecedented placebo-subtracted weight loss of >20% at the two highest doses over 48 weeks in individuals with overweight and one weight-related comorbidity, or obesity, mean baseline BMI ∼37 kg/m^2, in a phase 2 trial (46). Retatrutide was also studied over 24 weeks in individuals with type 2 diabetes (mean baseline HbA_{1c} 8.3%, duration of type 2 diabetes 8.3 years, BMI 35 kg/m^2), with 72% of subjects on background metformin therapy (47). Retatrutide reduced HbA_{1c} by 2.16% over 36 weeks at the highest dose (12 mg weekly) tested, with substantial reduction in weight (∼13.5% placebo-subtracted weight loss) and reductions in blood pressure, plasma cholesterol, and triglycerides. Retatrutide is being evaluated in phase 3 trials for people with type 2 diabetes and coexisting overweight or obesity as well as for weight loss in people with obesity. A cardiovascular safety study in 1,800 participants is ongoing, with an estimated duration of 113 weeks (clinical trial reg. no. NCT05882045, ClinicalTrials.gov), in individuals with obesity, BMI ≥35 kg/m^2, and a history of established atherosclerotic CVD.

Beyond molecules activating GIPR, and GCGR, several additional receptors are being targeted, together GLP-RA to improve outcomes (Fig. 4). A long-acting amylin analog, cagrilintide, administered once weekly over 26 weeks, produced placebo-subtracted weight loss of 7.6% at the highest dose tested (4.5 mg weekly), from a mean baseline BMI of 37.8 kg/m^2 (48). Cagrilintide is being studied in combination with semaglutide delivered together in a single pen; the combination seems likely to achieve >20% weight loss and effective glycemic control (49,50). Cagrilintide/semaglutide

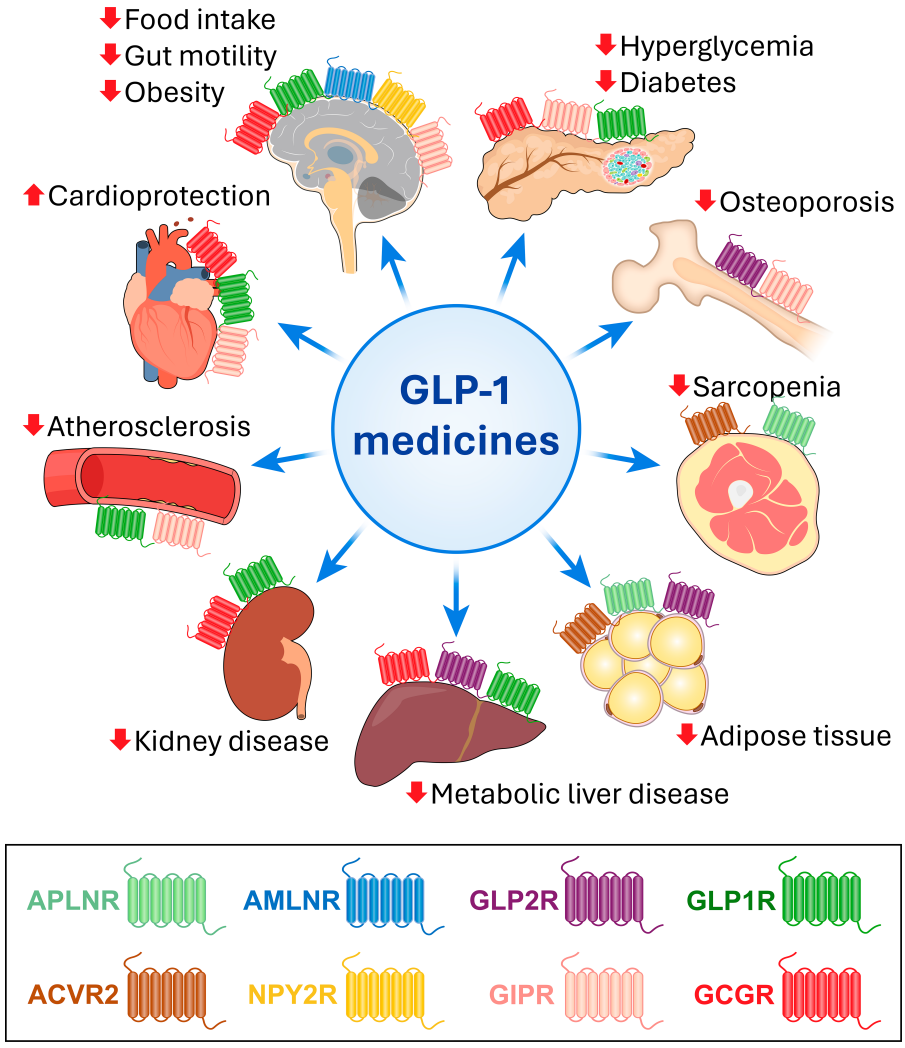

Figure 4—The future of GLP-1 medicines encompasses a multiagonist approach. Among the various receptors and pathways targeted by new emerging medicines (in combination with GLP-1RAs that target the GLP1R) are ACVR2 (activin receptor type 2A), the apelin receptor (APLNR), the amylin receptor (AMLNR), the glucagon receptor (GCGR), the glucose-dependent insulinotropic polypeptide receptor (GIPR), the glucagon-like peptide 2 receptor (GLP2R), and the neuropeptide Y2 receptor (NPY2R). The envisioned directional benefits of targeting these additional receptors for end organ pathophysiology are summarized in pictorial manner.

(CagriSema) is currently being investigated in phase 3 trials for type 2 diabetes and obesity, including a head-to-head trial versus tirzepatide.

Higher doses of oral semaglutide, ranging from 25 to 50 mg once daily, delivered via a new formulation, provided superior glycemic control and weight loss relative to the currently approved highest dose of 14 mg once daily (51,52). However, limitations in scaling peptide manufacturing may limit the short-term feasibility of this option. Higher doses of once weekly injectable semaglutide, up to 7.2 mg weekly, are also being investigated (4). For new molecules simultaneously targeting GLP1R and GLP1R-independent pathways (Fig. 4), evaluation of safety will be paramount to understanding their benefit-risk profile versus current GLP-1 medicines already supported by positive results from outcome trials (13,25).

METABOLIC LIVER DISEASE

Analysis of real-world registry data in Sweden, Denmark, and Norway from 2007–2020 compared the incidence of acute liver events, principally cirrhosis and hepatocellular carcinoma, in individuals with type 2 diabetes initiating therapy with either dipeptidyl peptidase 4 (DPP-4) inhibitors (244,004) or GLP-1RA (n = 91,479). The hazard ratio (HR) was 0.85 for the incident of acute liver events favoring new users of GLP-1RA, principally driven by reduced rates of compensated and decompensated cirrhosis (53).

Clinical trials have examined the therapeutic utility of GLP-1RA in people with metabolic liver disease. Liraglutide 1.8 mg daily for 48 weeks reduced rates of steatohepatitis and attenuated progression of fibrosis in 26 subjects with metabolic dysfunction–associated steatohepatitis (MASH). For subjects with end-of-treatment liver biopsies, histological resolution of inflammation was evident in 9 of 23 cases (54). A 72-week trial in 320 patients with MASH and stage 1–3 fibrosis demonstrated resolution of steatohepatitis without progression or improvement of fibrosis in 40%–59% of subjects treated with 0.1–0.4 mg s.c. semaglutide once daily (55). In contrast, semaglutide 2.4 mg once weekly for 48 weeks failed to improve histological outcomes, including fibrosis, in 71

subjects (47 people randomized to semaglutide) with biopsy-proven MASH and cirrhosis and BMI of at least 27 kg/m^2 (mean BMI 34.9 kg/m^2), 75% with type 2 diabetes. Semaglutide 2.4 mg once weekly is currently being studied in a phase 3 trial of ∼1,200 individuals with MASH without cirrhosis (clinical trial reg. no. NCT04822181, ClinicalTrials.gov), fibrosis stage 2 or 3, estimated study duration, for efficacy and safety end points, of ∼5 years, with a prespecified look at efficacy after repeat biopsy at 72 weeks. Tirzepatide is also being evaluated in individuals with MASH, as are several GCGR-GLP1R medicines such as survodutide, efinopegdutide, pemvidutide, and retatrutide (56). Given the direct actions of glucagon on hepatocytes to promote fat oxidation and reduce lipid synthesis (57,58), GLP-1 medicines enabling simultaneous GCGR agonism will be particularly effective for the treatment of metabolic liver disease.

SPECIAL CONSIDERATIONS: CHILDREN AND ADOLESCENTS

Several GLP-1RA are approved for treatment of children and adolescents with type 2 diabetes, including once daily liraglutide, approved for children ages ≥10 years in 2019. Liraglutide was studied in teens with type 2 diabetes ages 10–18 years, at doses up to 1.8 mg daily for 26 weeks, on background metformin therapy (59). Liraglutide (n = 66) produced a mean reduction in HbA_{1c} of 0.64%, whereas HbA_{1c} rose by 0.42% in placebo-treated subjects (n = 68). A placebo-subtracted difference in HbA_{1c} of 1.3% was observed at 52 weeks. Weight loss of 2.3 kg was observed with liraglutide at 26 weeks and partially maintained (−1.9 kg) out to week 52 (59). Absolute reduction in HbA_{1c} with exenatide 2 mg once weekly (n = 59) was 0.36% and placebo-subtracted HbA_{1c} 0.85% (n = 23) over 24 weeks in subjects ages 10–18 years (60). Once weekly dulaglutide was studied at doses of 0.75 or 1.5 mg in youth with type 2 diabetes, ages 10–18 years. Absolute HbA_{1c} reductions of 0.6% and 0.9%, respectively, were noted after 26 weeks, whereas HbA_{1c} levels increased in placebo-treated individuals by 0.6%, with no between-group differences in BMI (61), supporting U.S. Food and Drug Administration (FDA) approval in this population in 2022.

In the Satiety and Clinical Adipose Liraglutide Evidence (SCALE) Teens trial investigators studied the efficacy of liraglutide 3 mg (n = 125) or placebo (n = 126) once daily plus lifestyle management for weight loss in individuals ages 12–18 years, BMI ≥30 kg/m^2, with or without type 2 diabetes, with a result of 5% placebo-subtracted weight loss over 56 weeks (62). Baseline characteristics, including age, BMI, pubertal or glycemic status, race, sex, ethnicity, and variability of weight fluctuation, did not predict the weight loss response to liraglutide in the SCALE Teens trial (63). Following discontinuation of liraglutide, substantial weight regain was observed from weeks 56 to 82.

Semaglutide 2.4 mg once weekly was studied in 229 individuals ages 13–18 years living with overweight and comorbidities or BMI ≥30 kg/m^2, in the 68-week STEP TEENS trial (64). Weight loss >5% was observed in 73% of semaglutide- vs. 18% of placebo-administered trial participants, whereas weight loss >10% was observed in 62% vs. 8% of semaglutide- versus placebo-treated subjects, respectively. The AE profile was consistent with that commonly observed with GLP-1RA, principally gastrointestinal complaints, including acute gallbladder disease (64).

Tirzepatide is being studied in 99 children and adolescents with type 2 diabetes ages 10–18 years, on a background regimen of diet and exercise and metformin and/or basal insulin, in the SURPASS-PEDS trial (clinical trial reg. no. NCT05260021, ClinicalTrials.gov). Study criteria include an entry HbA_{1c} >6.5% to ≤11% at screening and BMI >85th percentile based on an age- and sex-matched control population. Tirzepatide is also being studied over 90 weeks in ∼150 children and adolescents ages 12–17 years with obesity or overweight and at least one weight-related comorbidity. Eligibility is also open to individuals with type 2 diabetes, treated with diet and exercise and/or metformin, and HbA_{1c} <9%.

AES LINKED TO GLP-1 MEDICINES

The most common side effects described with use of GLP-1RA are gastrointestinal, principally nausea, diarrhea, constipation, and vomiting (Fig. 2). The majority of these AEs are noted at the time of dose initiation and escalation, often in 50%–60% of subjects, and generally wane over the ensuing weeks (Fig. 2). The frequency of AEs is generally dose dependent, somewhat less common with long-acting GLP-1 medicines (65), and thought to reflect engagement of GLP1R+ regions in the brain linked to aversive responses, as well as brain centers controlling gut motility and reduction of gastric emptying (66). Gastrointestinal AEs if severe and persistent may limit fluid intake and potentially lead to dehydration and acute kidney injury (67) (Fig. 2).

GLP-1RA acutely attenuate cholecystokinin-stimulated gallbladder emptying (68,69), and may produce rapid weight loss, a known risk factor for gallbladder disease. Increased numbers of gallbladder AEs, including cholecystitis, cholelithiasis, and biliary obstruction, sometimes requiring cholecystectomy, have been observed in people with type 2 diabetes and/or obesity following treatment with GLP-1 medicines (70–72). An imbalance of retinopathy events was detected in one cardiovascular outcomes trial with semaglutide, attributed to rapid glucose lowering in trial participants with active retinopathy (73). A dedicated retinopathy study (clinical trial reg. no. NCT03811561, ClinicalTrials.gov) is underway to examine the safety of semaglutide in 1,500 subjects with early evidence of diabetic retinopathy.

ARE GLP-1–BASED MEDICINES LINKED TO PANCREATITIS AND CANCER?

GLP-1RA directly increase pancreatic enzyme secretion through the GLP1R expressed on pancreatic acinar cells (74), and circulating levels of pancreatic enzymes are elevated in some people treated with GLP-1RA (75). Furthermore, levels of amylase and lipase may be elevated in subjects with type 2 diabetes in the absence of pancreatitis. Collectively, these observations complicate the diagnosis of acute pancreatitis in individuals presenting with abdominal distress and mild elevations of pancreatic enzymes. Initial concerns surrounding a possible link between use of GLP-1RA and development of pancreatitis or pancreatic cancer have not been supported by results from randomized controlled trials (76,77) or real-world data (78–80).

Analysis of incident pancreatic cancer over 9 years as documented in the Clalit health care database, covering 3,290,439 person-years for 543,595 adults with type 2 diabetes, revealed an HR of 0.5 for development of pancreatic cancer in users of

GLP-1RA versus insulin, without an increase in pancreatitis in users of GLP-1RA (81). A nationwide cohort study was conducted to examine the incidence of colorectal cancer (CRC) in 1,221,218 drug-naive individuals with type 2 diabetes started on a new glucose-lowering agent from 2005–2019. The primary outcome was the first diagnosis of CRC within 15 years of starting GLP-1RA versus non–GLP-1RA glucose-lowering agents. Fewer CRC diagnoses were recorded for GLP-1RA relative to insulin (HR 0.56) and metformin (HR 0.75) in both men and women (82).

Sustained administration of GLP-1RA produces thyroid C-cell hyperplasia and medullary thyroid carcinoma in rats and mice, via direct activation of GLP1R signaling on thyroid C cells (83). Nevertheless, normal monkey and human thyroid C cells do not express the canonical GLP1R, and in monitoring of tens of thousands of calcitonin measurements in clinical trials evidence has not been detected for a functional GLP1R-calcitonin axis in people with type 2 diabetes (84,85) or obesity (25,86). Real-world assessment of the incidence of thyroid cancer in people with type 2 diabetes on different glucose-lowering agents has yielded inconsistent data with some studies reporting no imbalance (87), yet others reporting an increased incidence of well-differentiated thyroid cancer and medullary thyroid cancer after only 1–3 years of GLP-1RA treatment (88). These studies do not control for detection bias and fail to report the number of ultrasounds performed in different populations (89). A registry was established in the U.S. in 2010 with 28 state cancer registries invited to contribute data for cases of medullary thyroid cancer associated with the use of long-acting GLP-1RA (90).

BODY COMPOSITION, MUSCLE STRENGTH, AND FRACTURES

GLP-1 Action on Bone

Loss of lean mass and reduction in bone mineral density is common after weight loss, whether induced by medicines, diet, or bariatric surgery. The GLP-1 receptor is not known to be expressed or functional in the major cell types comprising human bone (91). GLP1Rs indirectly regulate bone turnover through GLP1Rs on calcitonin-secreting C cells in mice and rats; however, this biology is not conserved in humans (83,92). A combination of randomized controlled trial and real-world data analyses does not link use of GLP-1RA to an increased risk of fracture in people with type 2 diabetes (93). Analysis of new users of glucose-lowering agents in Korea from 2013–2020 revealed no differences in fracture rates for postmenopausal subjects with type 2 diabetes treated with GLP-1RA versus SGLT2i (mean age 61 years) (94). Consistent with these findings, in comparisons of 70,694 propensity-matched new users of SGLT2i versus GLP-1RA from 1 April 2013 to 1 September 2020 in the Veterans Health Administration type 2 diabetes administrative database, no differences were detected in fracture rates between groups (95). Similarly, propensity-matched analysis of users of DPP-4 inhibitors versus GLP-1RA from 2007–2018 in the national Danish health care system registry (n = 32,266) did not reveal significant different fracture rates (96). Insufficient data from long-term clinical trials or real-world data are available on fracture rates in people with obesity treated with GLP-1RA.

GIP reduces biomarkers of bone resorption in the postprandial state in healthy humans, in postmenopausal women and in people with type 2 diabetes. Intriguingly, these antiresorptive actions are attenuated after only 6 days of continuous exposure to GIP infusion in healthy male subjects with T1D (97). Initial studies of putative LOF *GIPR* variants in 1,686 perimenopausal Danish women demonstrated lower bone mineral density at the hip and a higher risk of nonvertebral fractures in women homozygous for the variant C allele rs1800437 (Glu354Gln) (98). Subsequent scrutiny of a much larger population did not support the hypothesis that LOF *GIPR* variants are associated with increased risk of fractures. Analysis of up to 1.2 million participants from cohorts with available data from Iceland, the U.K., Denmark, and the U.S. identified individuals with the *GIPR* variant rs1800437 (Glu354Gln) and two rare *GIPR* variants, rs139215588 (Arg190Gln) and rs143430880 (Glu288Gly), as well as additional predicted LOF GIPR variants (99). Notably, these LOF variants were associated with reduction of BMI as previously described (100–102) but were not associated with decreased bone mineral density or differential rates of fracture (99). These findings may inform the long-term safety of GLP-1–based medicines incorporating GIPR blockade within a single molecule, exemplified by maritide (42).

Body Composition, Lean Mass, and Muscle Strength and Function

Individuals with sarcopenic obesity are at increased risk for adverse health outcomes and may constitute a greater proportion of older individuals with obesity and advanced liver, cardiovascular, or kidney disease (103,104). Analysis of human genetics and associated phenotypes from 200,000 subjects in the UK Biobank reveals that LOF variants in the *GLP1R* associate with defective insulin secretion, increased HbA_{1c}, and increased adiposity (105). Body composition analyses in people with type 2 diabetes treated with GLP-1RA have not revealed consistent evidence for disproportionate loss of lean mass or impaired muscle strength. Treatment of 32 male and female subjects (mean age 66.3 years) with type 2 diabetes and overweight or obesity with oral semaglutide for 6 months resulted in ~4 kg weight loss after 6 months (from a starting baseline weight of 76 kg). Assessment of body composition with segmental multifrequency bioelectrical impedance analysis showed a reduction in fat mass but no change in skeletal muscle mass (106).

In the Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes (SUSTAIN) trials assessing the efficacy of once weekly subcutaneous semaglutide in people with type 2 diabetes, weight loss of 3.8–6.5 kg was observed (107). In a substudy of SUSTAIN 8, with comparison of canagliflozin 300 mg daily versus semaglutide 1 mg once weekly, investigators assessed changes in body composition over 52 weeks. A reduction in total fat and lean mass was observed with both treatment arms, yet the final proportion of total lean mass was greater with both canagliflozin and semaglutide after 52 weeks (107). Moreover, quality of life, assessed with the 36-Item Short Form Health Survey (SF-36), was not different (108). Analysis of body composition in semaglutide-treated subjects with overweight or obesity assessed with DEXA revealed substantial reductions in lean body mass with semaglutide 2.4 mg weekly, yet, overall, the proportion of adipose tissue mass loss was greater, and the proportion of lean mass, relative to total body mass, was increased, after 68 weeks (109). Notwithstanding the reductions in lean mass, self-reported exercise capacity and quality of life scores were higher for semaglutide-treated trial participants.

In a small mechanism-of-action study in individuals with type 2 diabetes, tirzepatide (n = 45, 15 mg once weekly) produced greater reductions in body weight versus semaglutide (n = 44, 1 mg once weekly) over 28 weeks, yet both tirzepatide and semaglutide predominantly reduced fat mass rather than fat-free mass (110). Similarly, body composition analysis after 72 weeks of tirzepatide in people with overweight or obesity in the SURMOUNT-1 trial revealed predominant reductions in adipose tissue mass (33.9%) versus lean mass (10.9%) (28). Physical activity, assessed with the SF-36, was increased in tirzepatide-treated subjects with obesity in the SURMOUNT-1 trial.

Despite consistent reductions in lean mass after bariatric surgery, there is little evidence to date for impairment of muscle function, generally assessed through analysis of physical function, exercise capacity, or handgrip strength (111). Similarly, lean mass is reduced after short-term (10 day) fasting with a low-calorie supplement, or more prolonged reduction in calorie intake, yet muscle function, assessed according to physical activity, biomechanical testing, exercise tolerance, or handgrip strength, may not correlate with loss of lean mass (112,113).

As greater loss of body weight and lean mass is anticipated with newer GLP-1 medicines under development for the treatment of obesity, there is substantial interest in developing complementary therapies that preferentially reduce adipose tissue, while sparing lean mass (Fig. 4). Blockade of activin receptor II with the monoclonal antibody bimagrumab (administered by intravenous infusion every 4 weeks for 48 weeks), together with a calorie-restricted diet, resulted in 6.5% weight loss with preferential loss of fat mass and modest augmentation of lean mass assessed with DEXA in subjects with type 2 diabetes and BMI 28–40 kg/m^2 (114). However, there was no change in grip strength after bimagrumab administration. While administration of bimagrumab for 24 weeks preserved or increased lean mass after hip surgery in individuals ages $\geq$60 years, there was no evidence for functional improvement, assessed according to gait speed or analysis of physical performance (115). Similarly, bimagrumab administered once monthly for 60 months to male and female individuals with sarcopenia increased lean mass, without improving parameters of physical function (116). Bimagrumab is currently being studied, alone or together with semaglutide, in individuals with overweight and obesity ages 18–80 years, over 24 weeks, with a 24-week extension, with a primary outcome of change in body weight (clinical trial reg. no. NCT05616013, ClinicalTrials.gov). Secondary outcomes include change in body composition and assessments of quality of life and physical functioning scores. Moreover, a range of interventions, targeting myostatin, activin, and apelin, are under investigation in people with obesity (Fig. 4), with a focus on preservation or augmentation of lean mass and muscle strength. The extent to which loss of functional muscle strength with GLP-1 medicines will become a common clinical problem requiring pharmacological intervention on top of standard of care, which may involve resistance training and exercise, will require further study. Interestingly, analysis of individuals initially randomized to liraglutide alone, or liraglutide plus a structured exercise regimen, after initial induction of diet-induced weight loss, demonstrated greater preservation of weight loss and reduction of body fat content in the group initially assigned structured exercise. The benefit of initial exercise was evident 1 year after discontinuation of the liraglutide, relative to individuals initially randomized to liraglutide alone (117). Hence, further study of diet and exercise regimens to optimize a healthy lifestyle may enable prevention of clinically important sarcopenia that might arise in some individuals after therapy with GLP-1 medicines.

NEUROPSYCHIATRIC ACTIONS OF GLP-1RA

Preclinical studies reveal that physiological and pharmacological GLP1R signaling is coupled to neuroprotection (118). Clinical trial and real-world data on the safety of dulaglutide or semaglutide in people with type 2 diabetes indicate fewer diagnoses of cognitive impairment in trial subjects treated with GLP-1RA (119,120). Exenatide was studied in three clinical trials in people with Parkinson disease. Among 46 individuals with moderate Parkinson disease, those randomized to twice daily exenatide for 12 months in an open-label study exhibited modest improvement in motor and cognitive function assessed with Parkinson disease activity scores, with clinical improvement persisting 2 months following discontinuation of therapy (121). Subsequent follow-up 12 months later revealed persistent improvements in motor activity and dementia rating scales in the exenatide-treated cohort (122). In a larger double-blinded placebo-controlled trial, investigators assessed the effects of exenatide 2 mg once weekly over 48 weeks in 62 subjects. Individuals randomized to exenatide exhibited improved disease activity when assessed 12 weeks following completion of therapy (123), accompanied by a reduced rate of decline in dopamine transporter availability detected with positron emission tomography scans. Mechanistically, evidence for enhanced insulin action in neuronally derived exosomes, assessed according to tyrosine phosphorylation of insulin receptor substrate, levels of total AKT, and phosphorylated mTOR, was correlated with improved Parkinson disease activity in the subjects treated with exenatide once weekly (124). In contrast, a 36-week trial was conducted to study the effect over 36 weeks of NLY01, a pegylated version of exenatide, dosed at 2.5 or 5.0 mg once weekly, in 255 subjects with Parkinson disease and failed to show improvement in motor or nonmotor components of Parkinson disease activity scores in participants randomized to exenatide (125). In a trial with 156 people, ages 40–75 years, with early Parkinson disease investigators examined the effect of lixisenatide 20 mg once daily or placebo over 52 weeks. Significantly less deterioration in functional activity, including motor activity scores, was observed in lixisenatide-treated subjects (126).

Less evidence supports the efficacy of GLP-1 medicines in people with Alzheimer disease. A 14% reduction in diagnoses of cognitive dysfunction was reported in subjects with type 2 diabetes treated with dulaglutide in the Researching cardiovascular Events with a Weekly INcretin in Diabetes (REWIND) cardiovascular outcome trial (119). The use of the GLP-1RA liraglutide and semaglutide was associated with fewer new diagnoses of dementia in cardiovascular outcome trials (HR 0.47) and in a real-world Danish registry of 120,054 patients (120); however, the small number of cases reported limits clear conclusions (120). A pilot study of 27 subjects with early Alzheimer disease treated with exenatide 10 μg twice daily for 18 months did not reveal improvement in disease activity based on assessment of multiple biomarkers, imaging, and clinical and

cognitive assessment in 21 subjects with available data (127). The efficacy of oral semaglutide in people with early Alzheimer disease is being evaluated in two trials, EVOKE (clinical trial reg. no. NCT04777396, ClinicalTrials.gov) and EVOKE Plus (NCT04777409), for up to 173 weeks in individuals age 55–85 years without or with coexisting cerebrovascular disease, respectively (8), with a primary outcome of change in dementia rating scales assessed at 104 weeks.

Rates of several neuropsychiatric disorders (128) are higher among people living with obesity, raising questions as to whether GLP-1 medicines modify rates of anxiety, depression, and suicidal ideation. A retrospective cohort analysis of medical records of >100 million individuals in the TriNetX database prescribed semaglutide included 240,618 patients with overweight or obesity and 1,589,855 subjects with type 2 diabetes. A substantial proportion of the cohort reported preexisting depression, anxiety, or mood disorders. In the population with overweight/obesity, rates of incident and recurrent suicidal ideation were lower with semaglutide use, with HRs of 0.27 and 0.44, respectively with similar findings reported for subjects with type 2 diabetes (129).

Anecdotal reports have described reduction of *1*) smoking, *2*) use of alcohol or addictive substances, and *3*) compulsive behaviors, including shopping, in people treated with GLP-1 medicines. Addition of exenatide 2 mg once weekly to nicotine replacement therapy and smoking cessation counseling in 84 subjects with prediabetes and/or overweight increased rates of smoking abstinence and reduced end-of-treatment cravings, while reducing weight gain (~2.5 kg less) following smoking cessation (130). In a single-center study of 255 participants, investigators assessed the effect of adding dulaglutide 1.5 mg once weekly together with varenicline and behavioral counseling on rates of smoking cessation. Dulaglutide did not modify abstinence rates and had only a transient effect on postcessation weight gain (131). A secondary analysis of the dulaglutide smoking cessation trial revealed 29% less alcohol consumption after 12 weeks of dulaglutide administration.

GLP-1 medicines may reduce rates of alcohol use (132); however, compelling data from randomized trials have not yet been forthcoming. Analysis of new users of GLP-1RA in Denmark (n = 38,454) from 2009–2017 revealed lower rates (HR 0.46) of alcohol-related medical events during the first 3 months of drug use, compared with new users of DPP-4 inhibitors (n = 49,222). Exenatide 2 mg once weekly was studied over 26 weeks in 127 subjects with alcohol use disorder seeking medical therapy. Exenatide did not reduce the number of heavy drinking days yet attenuated functional MRI alcohol cue reactivity in the ventral striatum and septal area and reduced dopamine transporter availability, assessed with single-photon emission computed tomography brain scans (133). Exploratory subgroup analyses suggested a potential effect of exenatide to reduce heavy drinking days and total alcohol intake in subjects with BMI ≥30 kg/m^2. In acute studies, a single dose of exenatide 5 μg s.c. had no impact on the rate of self-administration of, or desire for, cocaine in 13 individuals with cocaine use disorder (134).

RISKS RELATED TO ANESTHESIA, ASPIRATION, AND RETAINED GASTRIC CONTENTS

Short-acting GLP-1RA such as exenatide and lixisenatide robustly inhibit gastric emptying in subjects with type 2 diabetes. However, assessments using paracetamol did not show any delay in gastric emptying in subjects with obesity treated with once weekly semaglutide up to 2.4 mg once weekly for 20 weeks (135). Some delay in gastric emptying is still evident after 4 weeks of once weekly tirzepatide administration (up to 15 mg weekly) in subjects with type 2 diabetes, as assessed according to acetaminophen absorption (136). Nevertheless, the gold standards for assessment of gastric emptying, scintigraphy and the stable isotope breath test, are not regularly used in clinical trials, and estimates based on acetaminophen may not be sufficiently sensitive or accurate to quantify gastric emptying (137).

Reports of retained gastric contents and appreciation of a possible risk for aspiration have increased with more widespread use of GLP-1RA in people with overweight or obesity (Fig. 2). A prospective study of individuals started on semaglutide (19 of 20 without type 2 diabetes, mean BMI 26.9 kg/m^2) and assessed with ultrasound after overnight fasting revealed that 70% of semaglutide-treated subjects vs. 10% of control subjects had retained solid material in the stomach, consistent with digested food, after a minimum of 10 h fasting overnight (138). Similarly, prospective evaluation was conducted to assess residual gastric contents using ultrasound prior to elective surgery in subjects treated with semaglutide, dulaglutide, or tirzepatide, median BMI 33.9 kg/m^2, with the last dose of medication generally within 5 days of assessment, and a period of fasting ranging from 2 to 8 h. A 30.5% higher presence of residual gastric contents was detected in individuals (47% with type 2 diabetes) using GLP-1RA (139). Intriguingly, the prevalence of residual gastric contents in the control group was 19%.

A retrospective analysis of individuals with type 2 diabetes and/or obesity undergoing esophagogastroduodenoscopy revealed a greater proportion of residual gastric contents in semaglutide-treated subjects (6.7% vs. 5.1%, semaglutide-treated vs. control subjects), with symptoms of gastrointestinal distress (nausea/vomiting, dyspepsia, abdominal distension) more common in people with residual gastric contents (140). Analysis of the adequacy of bowel preparation associated with diagnostic colonoscopy in 446 individuals from December 2021–2022 included 265 subjects taking GLP-1RA for type 2 diabetes or obesity. Users of GLP-1RA had slightly higher rates of inadequate colon preparation, reflected by a greater requirement for a second colonoscopy (141).

Analysis of the U.K. Clinical Practice Research Datalink and linked databases demonstrated greater rates of intestinal obstruction in subjects with type 2 diabetes treated with either GLP-1RA (HR 1.69) or DPP-4 inhibitors (HR 2.59) relative to rates among those started on SGLT2i (142). In contrast, analysis of nationwide registry data for a larger population with type 2 diabetes in Denmark, Norway, and Sweden did not detect evidence for greater rates of intestinal obstruction with new users of GLP-1RA (n = 121,254) versus SGLT2i (n = 185,027) (143). A retrospective propensity-matched analysis of people with T2D in the TriNetX database undergoing endoscopy revealed a modestly increased risk of aspiration pneumonia in users of GLP-1RA, notably in those receiving propofol for sedation (144).

Professional societies have issued guidance surrounding the perioperative management of people treated with GLP-1RA. The American Society of Anesthesiologists

issued a consensus guidance communication via press release recommending discontinuing the use of once weekly GLP-1RA at least 1 week prior to surgery, resulting in cancellation of surgery for some individuals unable to comply with this recommendation. In contrast, a rapid clinical practice update from the American Gastroenterological Association highlighted the lack of meaningful data informing guidance in this area and suggested greater attention be paid to individuals with gastrointestinal symptoms and, where possible, switching individuals at risk to a liquid diet prior to endoscopy (145). There are substantial gaps in knowledge surrounding the prevalence of delayed gastric emptying in different populations (type 2 diabetes vs. obesity) on various doses of GLP-1–based medicines for different intervals, and there is even less knowledge of how rates of gastric emptying change in individuals following discontinuation of the various once weekly GLP-1RA. Although case reports have described cases of intestinal obstruction following therapy with GLP-1RA, the available data are limited. Notably, GLP-1RA have been used for the treatment of type 2 diabetes in millions of people for ~19 years, with only a few case reports describing clinically significant perioperative aspiration. Furthermore, measurement of gastric residual volume is not widely standardized, and the correlation between the quantitative detection of gastric residual volume and contents and the risk of clinically significant aspiration has not been clearly established (146,147). Hence, clinical judgment balancing the available data with therapeutic and clinical options in each case should determine guidelines for tapering, stopping, or continuing the use of GLP-1RA prior to elective procedures, as well as the potential utility of point of care ultrasound assessment where clinically indicated in individuals undergoing general anesthesia.

POLYCYSTIC OVARY DISEASE, FERTILITY, AND PREGNANCY

Negative energy balance during pregnancy may be harmful, and it is currently recommended that use of GLP-1RA be discontinued several months in advance of attempts to concieve as well as during pregnancy. Nevertheless, there is ongoing interest in understanding the potential benefit of using GLP-1 medicines to enhance fertility and to reduce pregnancy-associated complications that are more common in women with type 2 diabetes or obesity. The use of liraglutide 3 mg once daily enabled weight loss (5.7%) and reduction of androgen levels over 32 weeks in 55 women with polycystic ovary syndrome (PCOS) and obesity (148). Women with polycystic ovary disease contemplating pregnancy may be treated with GLP-1 medicines to achieve weight loss, and reductions in insulin resistance, which may indirectly lead to resumption of ovulatory cycles and an increased likelihood of pregnancy (149). A small study demonstrated that addition of liraglutide (1.2 mg daily) to metformin for 12 weeks improved pregnancy rates in 28 infertile women with PCOS undergoing in vitro fertilization–assisted conception (150). Observational data support a possible role for liraglutide therapy in men with obesity, severe erectile dysfunction, and hypogonadism. Use of liraglutide (uptitrated to 3 mg daily for ~3 months) improved erectile function and increased sperm concentration and motility in men with insulin resistance and metabolic infertility (151).

The use of noninsulin glucose-lowering medicines in women with type 2 diabetes around the time of pregnancy was evaluated in four Nordic countries, as well as with the documentation in the U.S. MarketScan database and the Israeli Maccabi Healthcare Services databases. The study included >50,000 pregnancies resulting in live births, with exposure defined according to filling a prescription within the span of 90 days before pregnancy to the end of the first trimester (152). The prevalence of PCOS and obesity was highest in the cohort of GLP-1RA users. Compared with use of insulin, exposure to GLP-1RA (n = 938) was not associated with increased reports of major congenital malformations (HR 0.95). The increasing use of GLP-1RA for weight management makes it likely that more women will be inadvertently exposed to GLP-1 medicines early on during pregnancy; hence, education surrounding the importance of monitoring for pregnancy and discontinuation of the medicines should be targeted to appropriate populations.

ALLERGIC AND ANAPHYLACTIC REACTIONS

Antidrug antibodies (ADA) are reported with all injectable GLP-1RAs but do not seem to meaningfully impact drug efficacy. There has been considerable interest in ascertainment of whether exendin-4–based GLP-1RA might be more immunogenic, given the larger divergence in peptide sequence, relative to other GLP-1 medicines. Exenatide once weekly is administered with a formulation including biodegradable poly(D,L-lactide-co-glycolide) microparticles that itself might promote immunogenicity, is more immunogenic than exenatide twice daily, and was associated with >50% of subjects developing ADA in clinical trials, yet the antibodies have minimal effect on therapeutic responses (153). Notably, with delivery of exenatide through the BCise autoinjector delivery system there is a slightly different formulation, with microspheres and a non-aqueous medium-chain triglycerides vehicle. However, the rates of ADA with this formulation may not be meaningfully different versus exenatide once weekly delivered with older formulations (154).

Relative to exenatide twice daily, injection site, hypersensitivity, and allergic reactions were more frequent in individuals with type 2 diabetes randomized to the investigational GLP-1RA taspoglutide in an open-label study conducted over 24 weeks in 1,188 individuals (155). Taspoglutide was subsequently discontinued due to a high rate of gastrointestinal AEs coupled with rare anaphylactic reactions in phase 3 trials (155). Low rates of ADA with semaglutide use, either the oral or injectable formulations, have been described, yet do not diminish the therapeutic response (either reduction of HbA_{1c} or body weight). Among 1,648 subjects with type 2 diabetes and heart disease treated with injectable semaglutide 0.5 mg or 1 mg once weekly for ~2 years in a cardiovascular outcome study, ADA were detected in 30 subjects. In trials assessing semaglutide 2.4 mg once weekly in people with obesity, rates of ADA are low and more frequently reported in regulatory submissions versus peer-reviewed articles, described as 2% in STEP 6 (156).

ADA were reported in 51.1% of tirzepatide-treated subjects with type 2 diabetes studied in the phase 3 program (157). Neutralizing antibodies blocking the activity of tirzepatide at the GIP and GLP-1 receptors were detected in 1.9% and 2.1% of patients, respectively, with <1% of subjects demonstrating antibodies that might block the actions of GIP or GLP-1 (157). Mild-to-moderate hypersensitivity

reactions (most commonly urticaria, eczema, and rash) and injection site reactions were reported in 3.6% of patients in the phase 3 program and were more common in antibody-positive individuals. However, no anaphylactic reactions were reported among the 5,025 tirzepatide-treated patients evaluated for ADA. The presence or absence of tirzepatide ADA had no effect on tirzepatide pharmacokinetics or reduction of HbA_{1c} (157).

Allergic or anaphylactic reactions are rare but have been reported with all injectable GLP-1 medicines. More common are complaints relating to injection site reactions, observed with increased frequency in people treated with exenatide once weekly (155). A pharmacovigilance study carried out from 1 January 2008 to 1 April 2018 with use of VigiBase demonstrated a twofold higher rate of anaphylactic reactions with exendin-based GLP-1RA relative to rates among users of human analog GLP-1RA (158). In assessment of real-world data of rates of anaphylactic reactions in new users of glucose-lowering agents from 2007–2019, investigators observed 36.9–40.7 cases per 100,000 users of GLP-1RA, rates slightly higher than among control groups with type 2 diabetes started on DPP-4 inhibitors or SGLT2i (159). In a cohort study in the U.S. with assessment of rates of anaphylaxis from January 2017 to June 2021 in 696,089 new users of GLP-1RAs, with 456,612 person-years of exposure in individuals with type 2 diabetes, low rates of anaphylaxis were demonstrated: ~4.2 episodes per 10,000 person-years of exposure (160).

Notwithstanding rare cases of hypersensitivity, GLP-1RA exhibit anti-inflammatory actions (66), prompting their assessment in people with type 2 diabetes and a history of asthma. A retrospective review of new users of glucose-lowering agents from January 2000 to March 2018 in the Partners Healthcare Research and Patient Data Repository demonstrated lower rates of asthma exacerbation, defined as requirement for glucocorticoids, and fewer medical encounters for asthma, within 6 months of commencement of GLP-1RA use relative to use of SGLT2i, DPP-4 inhibitors, or insulin (161). Mechanistically, acute liraglutide administration reduces platelet activation ex vivo and decreases release of proinflammatory mediators from platelets of normal subjects and patients with aspirin-exacerbated respiratory disease (162). Whether GLP-1RA meaningfully reduce exacerbations of chronic obstructive pulmonary disease in people with type 2 diabetes is unclear; this depends on the population under study and the comparator group (163). GLP-1RA reduce sepsis-induced lung injury and inflammation in preclinical studies (164,165) and decrease rates of reported respiratory disorders, including bronchitis and pulmonary edema, in randomized controlled trials of people with type 2 diabetes, overweight, or obesity (166). However, there is insufficient evidence to support a definitive role for GLP-1RAs in reducing lung infection in human studies.

SUMMARY AND CONCLUSIONS

More than 19 years after the first approval of twice daily exenatide, new, more effective once weekly GLP-1 medicines, exemplified by semaglutide and tirzepatide, have expanded the interest in the long-term efficacy and safety of GLP-1 medicines. An extensive safety database derived from outcome studies and real-world data provides considerable reassurance for the use of these medicines in people with type 2 diabetes, the majority of whom are also living with overweight or obesity. Moreover, GLP-1 medicines reduce the risk of MACE and cardiovascular death in people with type 2 diabetes or obesity and decrease rates of chronic kidney disease in people with type 2 diabetes. Much less information is available on the long-term safety of semaglutide in people with obesity without CVD, and outcome trials for tirzepatide are ongoing. Given the challenges of preventing weight gain and cardiovascular and kidney disease in people with atypical diabetes or type 1 diabetes, additional randomized trials of GLP-1 medicines are warranted in these populations (167). There is much more limited experience in some populations, including children and adolescents, the hospitalized with severe illness, and the elderly. Dozens of new GLP-1 medicines are in development, from small-molecule GLP-1RA to antibodies to new hybrid molecules that modify additional signaling pathways distinct from the canonical GLP1R (Figs. 3 and 4). These new molecules will require careful scrutiny to ensure they deliver the same or greater benefits, without adding new safety liabilities (Fig. 2). Many of the uncertainties discussed herein will benefit from additional scrutiny and well-conducted trials. The extent to which clinically significant sarcopenia will be revealed, justifying adjuvant anabolic muscle-sparing therapy, is not yet known. Although not discussed here, further progress in precision medicine may help us identify individuals more likely to experience greater benefits or AEs associated with use of GLP-1 medicines, Finally, for the full benefits of these medicines to be realized on a global scale, considerable ongoing investment in and

attention to cost-effective manufacturing and improving the supply chain are required to increase equitable access and lower cost. It would be shameful to conclude, once the final story of GLP-1 medicines is written, that their potential to improve global health remained unfulfilled, due to persistent challenges with equitable pricing and universal affordability.

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