Glucagon-like peptide 1 in health and disease

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Abstract | In healthy individuals, the incretin hormone glucagon-like peptide 1 (GLP1) potentiates insulin release and suppresses glucagon secretion in response to the ingestion of nutrients. GLP1 also delays gastric emptying and increases satiety. In patients with type 2 diabetes mellitus (T2DM), supraphysiological doses of GLP1 normalize the endogenous insulin response during a hyperglycaemic clamp. Owing to the short plasma half-life of native GLP1, several GLP1 receptor agonists (GLP1RAs) with longer half-lives have been developed for the treatment of T2DM. These compounds vary in chemical structure, pharmacokinetics and size, which results in different clinical effects on hyperglycaemia and body weight loss; these variations might also explain the difference in cardiovascular effect observed in large-scale cardiovascular outcome trials, in which certain GLP1RAs were shown to have a positive effect on cardiovascular outcomes. Owing to their metabolic effects, GLP1RAs are also considered for the treatment of several other lifestyle-induced conditions, such as obesity, prediabetes and liver disease. This Review provides insights into the physiology of GLP1 and its involvement in the pathophysiology of T2DM and an overview of the currently available and emerging GLP1RAs. Furthermore, we review the results from the currently available large-scale cardiovascular outcome trials and the use of GLP1RAs for other indications.

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The incretin effect is defined as the augmentation of insulin secretion after oral glucose intake compared with the insulin secretion after an isoglycaemic intravenous glucose infusion when both result in identical plasma glucose values. In healthy individuals, the incretin effect is responsible for up to 70% of insulin secretion after an oral glucose load and is thus essential for postprandial regulation of glucose levels[1]. The incretin effect is mediated by gut-derived peptide hormones, so-called incretins, which are released in response to the oral intake of nutrients. These hormones potentiate insulin secretion at plasma levels of glucose >4 mM (REFS[2,3]). Although several hormones might be involved in postprandial insulin secretion, most of the incretin effect can be explained by increases in gastric inhibitory polypeptide (GIP) and glucagon-like peptide 1 (GLP1)[4]. In healthy individuals, GIP has a key role in mediating the incretin effect and thereby glucose homeostasis, whereas this effect is severely diminished in patients with type 2 diabetes mellitus (T2DM)[5,6]. In contrast to GIP, the insulinotropic properties of GLP1 are partially maintained in patients with T2DM[7]. These properties have been exploited in the development of two antidiabetic drug classes for the treatment of T2DM, namely, the dipeptidyl peptidase 4 (DPP4) inhibitors, which prevent the degradation of endogenously produced GIP and GLP1, and the GLP1 receptor (GLP1R) agonists (GLP1RAs). Over the past few years, the GLP1RAs have attracted increasing interest; in addition to their glucose-lowering properties, they are effective in the management of overweight and obesity and show promising results in reducing cardiovascular risk in high-risk individuals with T2DM.

This Review provides insight into the physiology of GLP1 and its involvement in the pathophysiology of T2DM, and also offers an overview of the currently available and emerging GLP1RAs. Furthermore, we review the results from the latest large-scale cardiovascular outcome trials (CVOTs) in the field and the use of GLP1RAs for other indications that are indicative of future directions for GLP1-based therapy.

GLP1 physiology

GLP1 is produced by post-translational processing of proglucagon by proprotein convertase subtilisin-kexin type 1 (PCSK1) or PCSK3 (also known as furin) and exists in two equally bioactive forms, namely, glycine-extended GLP1 (GLP1 7–37) and amidated GLP1 (GLP1 7–36)[2,3]. GLP1 is secreted from the intestinal L cells that are located with increasing density from the duodenum to the colon[8]. Following the ingestion of nutrients, a rise in the plasma concentration of GLP1 is observed within minutes[9]. However, owing to local

Key points

- The incretin hormone glucagon-like peptide 1 (GLP1) promotes satiety and potentiates insulin release and suppression of glucagon release in response to the ingestion of nutrients.
- Owing to the short plasma half-life of GLP1, several GLP1 receptor agonists (GLP1RAs) were developed with different chemical structures and pharmacokinetic profiles for type 2 diabetes mellitus (T2DM) treatment.
- GLP1RAs can be categorized as short-acting or long-acting according to their time–action profile.
- Both short-acting and long-acting GLP1RAs reduce body weight, whereas short-acting GLP1RAs have a greater effect on postprandial plasma levels of glucose and long-acting GLP1RAs predominantly lower fasting plasma concentrations of glucose.
- Some GLP1RAs (liraglutide and semaglutide) have proved to have positive effects on cardiovascular outcomes in T2DM.
- The effects of GLP1RAs are sought to be exploited in the treatment of several other conditions, including prediabetes, T1DM, obesity and liver disease.

degradation of GLP1 by the enzyme DPP4 and further degradation by DPP4 in the liver, only 10–15% of endogenously released GLP1 reaches the systemic circulation[2]. This rapid degradation of GLP1 by DPP4 is responsible for the short half-life of exogenously administered GLP1, which amounts to ~1–2 minutes. GLP1 exerts its actions through the GLP1R, which is expressed in numerous tissues, including the pancreas, kidney, heart, lung, adipose and smooth muscle, as well as in specific nuclei in the central nervous system. The widespread distribution of the GLP1R suggests that GLP1 has several additional effects other than regulating glucose metabolism (FIG. 1).

In the pancreatic β-cells, stimulation of the GLP1R results in glucose-dependent insulin secretion, meaning that the insulinotropic effects of GLP1 are present only when plasma levels of glucose are above normal fasting plasma levels. Additionally, GLP1 is a strong inhibitor of glucagon secretion (which is also strictly glucose dependent), which is possibly mediated by a direct effect on the pancreatic α-cells. However, this inhibitory effect is more likely to occur via the paracrine effects of increased levels of somatostatin and insulin from neighbouring δ-cells and β-cells, respectively[2,3].

In addition to the effect on the endocrine pancreas, GLP1 has a pronounced effect on gastrointestinal motility. The presence of nutrients in the small intestinal lumen, particularly in the ileum, which is rich in L cells, induces the release of GLP1, which delays gastric emptying and thereby postpones nutrient uptake from the gut to result in reduced postprandial plasma glucose excursions[10,11]. This physiological phenomenon is known as 'the ileal brake'. Importantly, the delay in gastric emptying seems to be dependent on the intermittent activation of the GLP1R, as this effect is lost when GLP1Rs are continuously activated[12]. GLP1 promotes satiety through the activation of GLP1Rs in the hypothalamus and brainstem, which reduces food intake, thus inducing body weight loss[2,3]. A dose-dependent effect of GLP1 on satiety measures and ad libitum food intake has been demonstrated in individuals who are lean or healthy or who have obesity or diabetes mellitus[13].

The GLP1R is also present in the kidney, although its exact anatomical localization remains uncertain. Studies have reported functional GLP1Rs in both renal vasculature and glomerular cells, although the findings are inconsistent[14]. GLP1 at physiological levels increases natriuresis by inhibition of sodium reabsorption (through reduced activity of the sodium–hydrogen exchanger 3) in the proximal tubules, which might explain the small decrease in blood pressure observed in patients treated with GLP1RAs[14,15]. Whether this effect is mediated by a direct activation of the GLP1R in the kidney is unknown. Some studies indicate that modulation of the renin–angiotensin system might be involved, and a neural pathway has also been suggested[14,15]. Studies in rodents have indicated that GLP1 has a renal-protective effect independent of its effects on established risk factors, such as plasma levels of glucose, body weight and blood pressure[15]. Nevertheless, current evidence suggests only a modest improvement in albuminuria during GLP1RA treatment, and uncertainty remains regarding whether this effect is independent of improvement in levels of HbA_{1c} (REF.[14]).

As previously mentioned, GLP1Rs are also expressed in the heart, and administration of GLP1 before cardiac ischaemia reduces infarction size in rats[16]. Additionally, some studies indicate that GLP1 infusion at supraphysiological levels improves left ventricular function in patients with acute myocardial infarction treated with angioplasty and reduces plasma levels of triglycerides and free fatty acids in healthy participants[17,18]. Physiological levels of GLP1 have also been demonstrated to improve endothelial function in individuals with normal glucose tolerance and patients with T2DM[19]. Whereas intermittent administration of GLP1 increases both blood pressure and heart rate, sustained activation of the GLP1R with GLP1RAs results in a modest increase in heart rate but a reduction in blood pressure[19]. Logically, the potential beneficial effect of GLP1 on the heart has attracted a lot of attention.

GLP1 in type 2 diabetes mellitus

The observation that the incretin effect is almost abolished in patients with T2DM indicates that altered function and/or secretion of incretin hormones have a key role in the pathophysiology of T2DM[20]. Whether this defect is primary or secondary to the development of T2DM remains controversial. Studies have demonstrated that GLP1 secretion was normal in first-degree relatives of patients with T2DM, and similar findings were made in a study of identical twins[21,22]. Additionally, patients with chronic pancreatitis and secondary diabetes mellitus exhibit a markedly reduced incretin effect, whereas the incretin effect is preserved in patients with chronic pancreatitis without diabetes mellitus[23]. Likewise, in women with gestational diabetes mellitus and markedly increased risk of future diabetes mellitus, the reduction in the incretin effect was fully reversible, as normal glucose homeostasis was restored postpartum[24]. A cross-sectional study published in 2015 (REF.[25]) including almost 1,500 patients indicated a 25% reduction in GLP1 response after oral glucose tolerance testing in female patients with T2DM or prediabetes compared

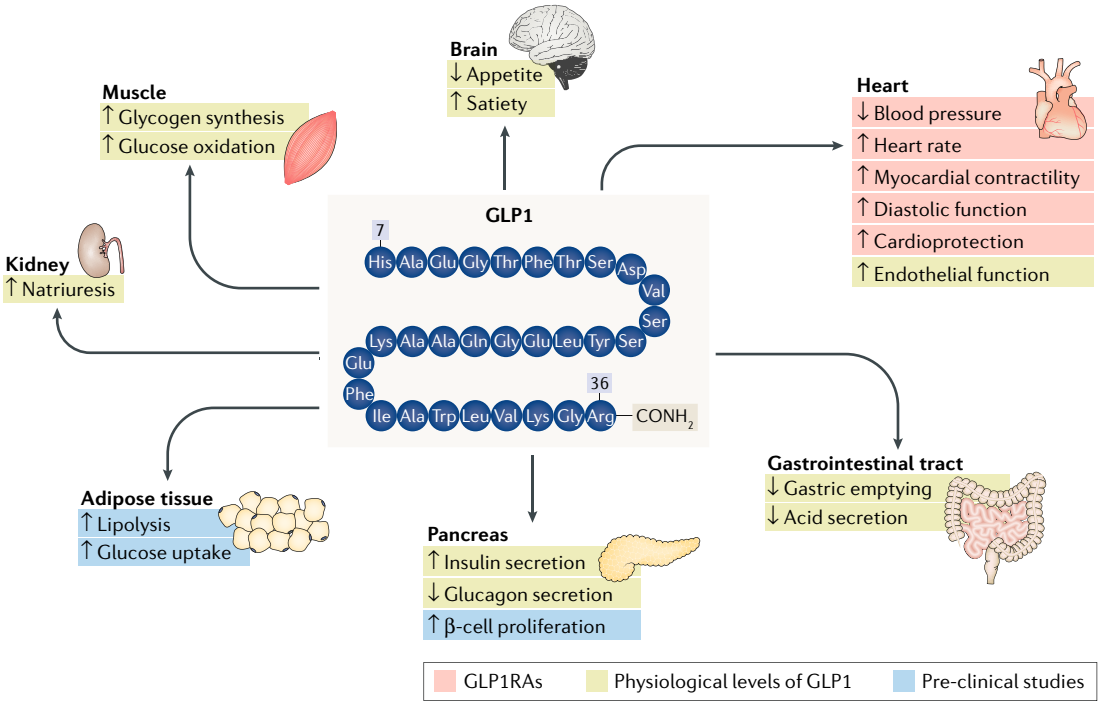

Fig. 1 | **Effects of GLP1 and GLP1RAs on various tissues.** The applied colour code indicates whether the effect on the target tissue has been observed in preclinical studies (blue boxes), at physiological levels of glucagon-like peptide 1 (GLP1) in clinical studies (yellow boxes) or after treatment with GLP1 receptor agonists (GLP1RAs; red boxes). The figure depicts amidated GLP1 (GLP1 7–36)[2,3,11,13,14,126–128].

with individuals with normal glucose tolerance[25]; by contrast, a meta-analysis suggested that GLP1 secretion was not altered in patients with T2DM[26].

Whereas the role of an altered GLP1 secretion in T2DM remains somewhat debated, it is well established that GLP1 maintains robust insulinotropic properties in these patients, although this occurs with a reduced potency compared with that seen in healthy individuals[6,7]. As elimination of GLP1 is unchanged, the reason for the reduced incretin effect in T2DM is likely to be explained by reduced β-cell sensitivity to GLP1 (REF.[27]). Indeed, it has been demonstrated that high doses of GLP1 during a 15 mM hyperglycaemic clamp in patients with T2DM resulted in late-phase insulin responses equal to those of healthy controls undergoing a similar hyperglycaemic clamp (without GLP1)[28]. In line with the strong potentiation of glucose-stimulated insulin secretion by GLP1 and its glucose-dependent inhibition of glucagon secretion, exogenously administered GLP1 completely normalizes plasma levels of glucose in patients with T2DM[29,30]; the foundation for GLP1-based treatment of T2DM was therefore established.

GLP1RAs in type 2 diabetes mellitus

The first challenge to pharmacologically utilizing the antidiabetic actions of native GLP1 was the short plasma half-life of circulating GLP1, which is caused by rapid degradation by DPP4 (REF.[27]) Two different strategies have been applied to overcome this problem. One strategy exploits the naturally occurring peptide exendin 4, which was originally isolated from the saliva of the lizard *Heloderma suspectum*. Exendin 4 shares only 53% structural homology with native GLP1 but activates the GLP1R with the same potency as native GLP1 and it is resistant to degradation by DPP4 owing to a glycine instead of an alanine at position two (the cleavage site of DPP4)[31]. Another strategy is to alter the amino acid sequence of native GLP1 to avoid degradation by DPP4. Currently, seven different GLP1RAs have been approved for the treatment of T2DM, and several more are being developed (TABLE 1). Additionally, fixed-ratio combinations of long-acting insulin and GLP1RAs (insulin degludec:liraglutide and insulin glargine:lixisenatide) have been developed for the treatment of T2DM[32,33], and GLP1–glucagon receptor co-agonists are currently emerging[34].

GLP1RAs can be categorized as short-acting and long-acting compounds according to their pharmacokinetic profile, providing intermittent and continuous exposure, respectively (TABLE 1). The short-acting GLP1RAs (exenatide twice daily and lixisenatide once daily) are resistant to degradation by DPP4; however, their plasma half-life is still only 2–3 hours, as they are still subject to renal elimination. They are administered once daily or twice daily, which results in fairly large fluctuations in plasma concentrations during the day, with intermittent activation of the GLP1R.

The long-acting GLP1RAs have been modified by different techniques to avoid renal elimination and to induce a protracted release, which results in continuous activation of the GLP1R throughout the day (FIG. 2). These modifications include incorporation of the therapeutic molecules in an injectable microsphere (exenatide once weekly), attachment of a fatty acid chain that

Table 1 | **Pharmacokinetic properties of available and emerging GLP1RAs**

Compound	Approval year		Structure based on exendin 4 or GLP1	Administration	Dose	Half-life	Elimination[14,129]	Antibody development (% of patients)
	FDA	EMA						
Short-acting GLP1RAs								
Exenatide twice daily	2005	2006	Exendin 4	Twice daily	5–10 µg	2.4 hours	Mainly renal	35 (REF.[51])
Lixisenatide	2016	2013	Exendin 4	Once daily	10–20 µg	3 hours	Mainly renal	56–70 (REFS[49,50])
Long-acting GLP1RAs								
Liraglutide	2010	2009	GLP1	Once daily	0.6–1.8 mg	13 hours	Peptidases, renal (6%) and faecal (5%)	8.6 (REF.[68])
Exenatide once weekly	2012	2011	Exendin 4	Once weekly	2 mg	NA	Mainly renal	57 (REF.[51])
Albiglutide	2014	2014	GLP1	Once weekly	30–50 mg	5 days	Peptidases and renal	5.5 (REF.[66])
Dulaglutide	2014	2014	GLP1	Once weekly	0.75–1.5 mg	4.7 days	Peptidases and renal	1.6 (REF.[69])
Emerging GLP1RAs								
Semaglutide	2017[a]	2017[a]	GLP1	Once weekly	0.5–1.0 mg	165 hours	Peptidases and renal	0.01–3.50 (REFS[85,130,131])
Efpeglenatide	Phase III initiated Oct 2017	Phase III initiated Oct 2017	Exendin 4	Once monthly	NA	NA	Mainly renal	20–31 (REF.[132])
ITCA 650 (Subdermal release of exenatide)	Awaiting approval	Awaiting approval	Exendin 4	Up to 12 months after implantation	20–60 µg daily	NA	Mainly renal	NA

EMA, European Medicines Agency; GLP1, glucagon-like peptide 1; GLP1RA, GLP1 receptor agonist; NA, not available. [a]Currently not marketed.

enables reversible binding to albumin (liraglutide and semaglutide) and covalent binding to larger carrier molecules such as albumin (albiglutide) or antibody crystallizable fragment (Fc) domains of immunoglobulin G (IgG; dulaglutide and efpeglenatide). Additionally, continuous release of exenatide from an implantable subdermal device is under development (ITCA 650)[35,36]. Finally, GLP1RAs could also be subdivided according to their size, as the molecular modifications greatly affect the size of the compounds; these size differences in turn might affect penetration into the brain, where the drugs could impact control of satiety. The following discussion of available and emerging GLP1RAs will highlight that the differences in structure, pharmacokinetics and size have important implications for the efficacy and safety of the different compounds.

Short-acting GLP1RAs. Exenatide twice daily and lixisenatide once daily are the short-acting GLP1RAs currently available. Both compounds are based on an exendin 4 structure (FIG. 2). Whereas exenatide is an identical synthetic version of exendin 4, the structure of lixisenatide has a deletion of proline and an addition of six lysine amino acids at the carboxyl terminus in order to stabilize the peptide in circulation. The resulting half-lives for exenatide and lixisenatide are 2.4 and 3.0 hours, and they are administered twice daily or once daily, respectively, in relation to a meal[31,37] (TABLE 1). Owing to the fairly short plasma half-life of the short-acting compounds, activation of the GLP1R is limited to a few hours after administration. The pharmacodynamic properties of short-acting GLP1RAs are affected by this intermittent stimulation of the GLP1R, and in line with the physiology of native GLP1, short-acting GLP1RAs preserve their ability to delay gastric emptying[38–42]. This delay results in a marked effect on postprandial glucose excursion following the meals where the short-acting compounds are administered, which usually occurs after breakfast (lixisenatide and exenatide twice daily) and dinner (only exenatide twice daily), compared with those for which long-acting compounds were used[41,43,44]. The short-acting compounds also exert their effect through the potentiation of insulin release from β-cells in response to elevated plasma levels of glucose and suppression of inappropriately elevated glucagon levels[45,46]. However, their effect on fasting plasma levels of glucose and HbA_{1c} is inferior to that of the long-acting compounds[47] (FIG. 3).

The efficacy and safety of the two available short-acting GLP1RAs have been compared in the head-to-head trial GETGOAL-X, in which lixisenatide reached the noninferiority criteria in reduction of HbA_{1c} compared with exenatide twice daily. Patients treated with lixisenatide had fewer gastrointestinal adverse effects (43% versus 51%) (FIG. 4) and experienced fewer episodes of symptomatic hypoglycaemia (3% versus 8%). However, lixisenatide was inferior with regard to body weight loss[48] (FIG. 5). Antibody formation against the compounds is frequent after treatment, with exenatide twice daily being more antigenic than lixisenatide. In the LEAD-6 trial, high levels of

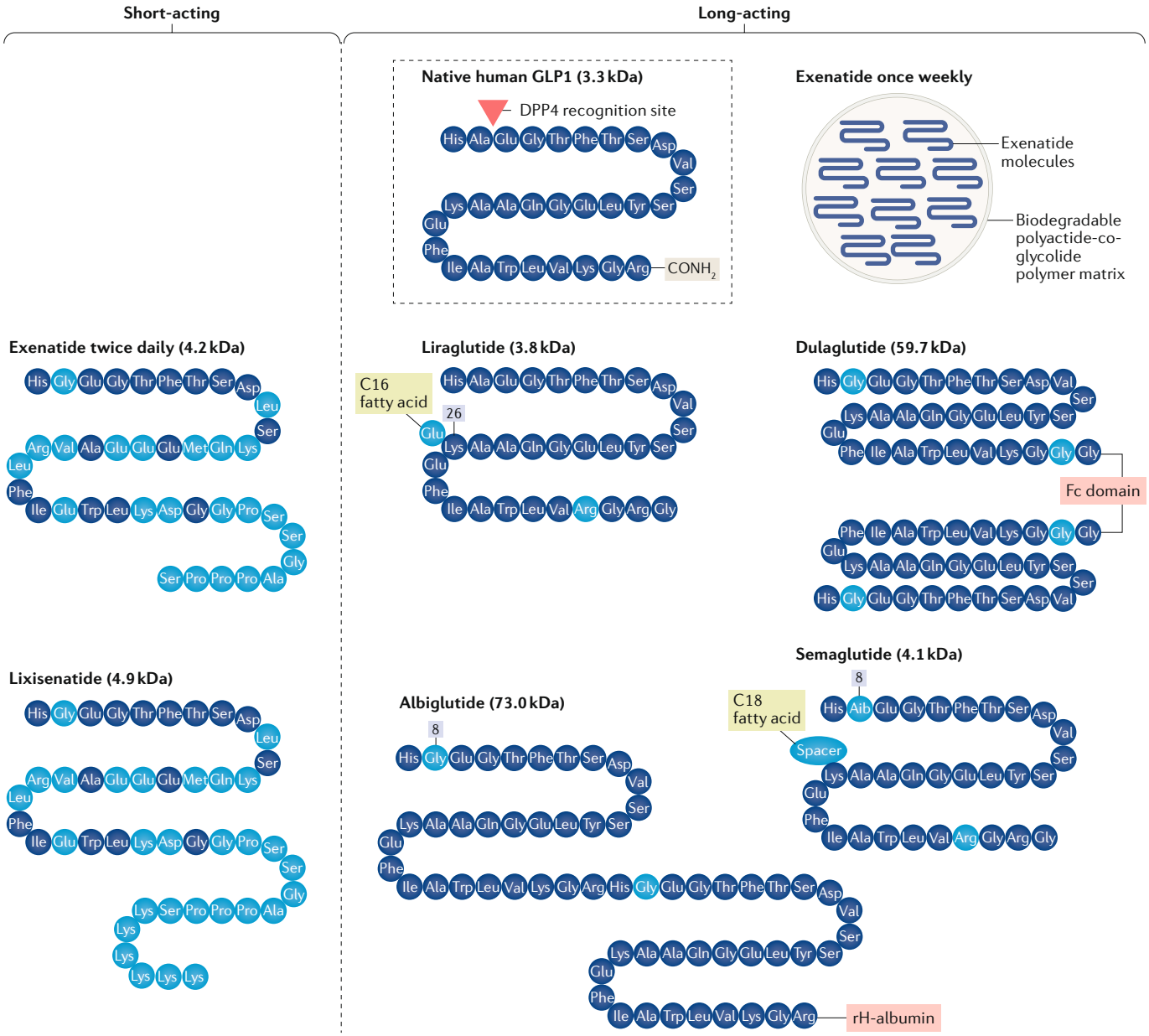

Fig. 2 | **Structure and molecular mass of native GLP1 in comparison with approved and emerging GLP1RAs.** Exenatide twice daily and lixisenatide are short-acting glucagon-like peptide 1 (GLP1) receptor agonists (GLP1RAs) that are based on an exendin 4 structure. Exenatide once weekly is the only approved long-acting GLP1RA that is based on an exendin 4 structure, whereas the remaining long-acting GLP1RAs (liraglutide, dulaglutide, albiglutide and semaglutide) are all based on a GLP1 structure. Liraglutide and semaglutide have fatty acid chain (C16 and C18, respectively) attachments for reversible binding to albumin (yellow boxes). Albiglutide and dulaglutide are covalently bound to larger carrier proteins (red boxes), such as recombinant human serum albumin (rH-albumin) and an immunoglobulin G4 crystallizable fragment (IgG4 Fc) fragment. The dark blue colour indicates homology with native GLP1, while the light blue colour indicates non-homology. Aib, α-aminoisobutyric acid; DPP4, dipeptidyl peptidase 4.

anti-exenatide antibodies were significantly correlated with smaller reductions in HbA_{1c}, whereas several other studies have demonstrated no clinically relevant effect of antibody formation[49–52].

Long-acting GLP1RAs. Currently, four long-acting GLP1RAs are available for the treatment of T2DM. Liraglutide, dulaglutide and albiglutide are all based on a modified synthetic version of native GLP1, whereas exenatide once weekly is structurally similar to exenatide twice daily, but it is dispersed in injectable microspheres for extended release. Liraglutide has a C16 fatty acid chain attached at Lys26, and the hydrophobic properties result in the formation of heptamers, delaying absorption from the subcutis after injection and enabling noncovalent albumin binding, which prevents degradation by DDP4 and renal elimination. Dulaglutide and albiglutide both utilize the substitution of Ala8 to avoid degradation by DDP4, while protein binding to a modified IgG4 Fc domain and albumin, respectively, prevents renal elimination (FIG. 2). The half-lives of these compounds vary between 13 hours (liraglutide) and 5 days

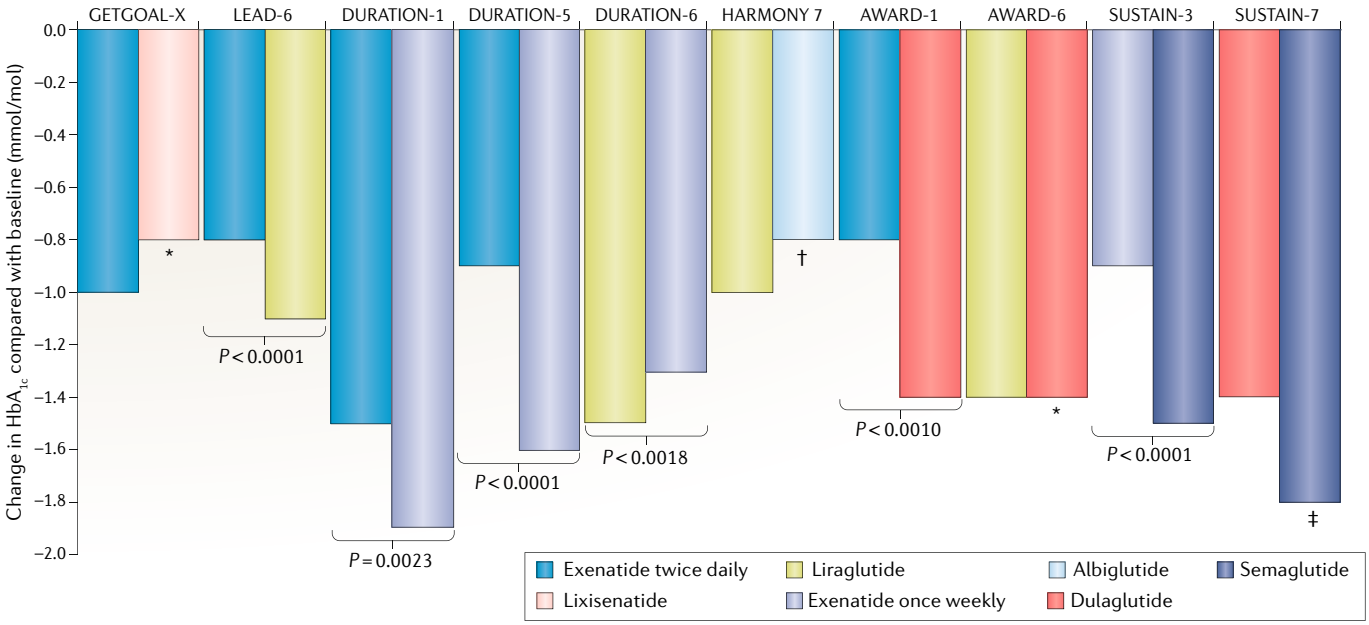

Fig. 3 | **HbA_{1c} reductions in phase III head-to-head trials comparing GLP1RAs in type 2 diabetes mellitus.** The results from the following trials are displayed: GETGOAL-X[48], LEAD-6 (REF.[44]), DURATION-1 (REF.[43]), DURATION-5 (REF.[54]), DURATION-6 (REF.[57]), HARMONY 7 (REF.[58]), AWARD-1 (REF.[55]), AWARD-6 (REF.[59]), SUSTAIN-3 (REF.[71]) and SUSTAIN-7 (REF.[72]). *P* values are reported where appropriate. GLP1RAs, glucagon-like peptide 1 receptor agonists. *Noninferiority criteria met. †Noninferiority criteria not met. ‡Superiority criteria met.

(albiglutide and dulaglutide), and they are administered either once daily (liraglutide) or once weekly (exenatide once weekly, albiglutide and dulaglutide).

In clinical phase III studies, long-acting GLP1RAs have generally proved superior to exenatide twice daily in terms of reducing HbA_{1c} levels and fasting plasma levels of glucose, while lixisenatide has not yet been compared directly with a long-acting GLP1RA in a phase III clinical trial[44,53–55] (FIG. 3). However, in a 28-day head-to-head trial, liraglutide was superior to lixisenatide in terms of reductions in levels of HbA_{1c} and fasting plasma levels of glucose[41]. Whereas the relative effect on HbA_{1c}, fasting plasma glucose and postprandial glucose excursions of short-acting and long-acting GLP1RAs seems to be consistent, no between-class difference in body weight reduction exists. Accordingly, exenatide twice daily has demonstrated similar body weight reductions to exenatide once weekly, liraglutide and dulaglutide[44,53–55]. These findings indicate that the effect of GLP1RAs on body weight is independent of plasma half-life and thereby gastric emptying. Nevertheless, in a 2017 study that used radiolabelled meals to assess gastric emptying, liraglutide 3.0 mg once daily demonstrated a sustained effect on gastric emptying after 16 weeks. Furthermore, body weight loss after 16 weeks was associated with a delay in gastric emptying after 5 weeks[56].

All long-acting GLP1RAs have demonstrated robust reductions in HbA_{1c}. Nevertheless, liraglutide at a maximum dosage of 1.8 mg has demonstrated a statistically significantly greater effect on HbA_{1c} than both exenatide once weekly and albiglutide, while no difference was found for glycaemic control compared with that seen for dulaglutide. Additionally, liraglutide 1.8 mg has also proved superior to exenatide once weekly, dulaglutide and albiglutide in reducing body weight[57–59]. The limited effect of albiglutide on body weight compared with liraglutide in the HARMONY 7 trial stands out, as patients treated with albiglutide had a body weight reduction of 0.6 kg compared with a 2.2 kg reduction with liraglutide after 32 weeks of treatment[58]. A limited effect on body weight was also observed in the remaining phase III trials, in which albiglutide proved superior to insulin, pioglitazone and sulfonylureas with regard to a change in body weight but was not superior to placebo[60–65]. It has been speculated that the large molecular size of albiglutide might limit penetration of the compound into the brain and, thus, restrict the activation of central GLP1Rs that are of importance for inducing satiety[66]. In July 2017, the manufacturer of albiglutide, GlaxoSmithKline, announced that production of albiglutide would be discontinued owing to limited prescription[67].

Gastrointestinal adverse effects are common in patients treated with GLP1RAs, with nausea being the most frequently reported adverse effect. Dulaglutide treatment seems to be associated with similar rates of nausea as liraglutide treatment, whereas a lower incidence of nausea has been demonstrated with both exenatide once weekly and albiglutide[57–59] (FIG. 4). Exenatide once weekly is the only available long-acting GLP1RA that is structurally based on exendin 4, with markedly higher antibody development than liraglutide, albiglutide and dulaglutide[51,66,68,69]. During phase III trials, anti-exenatide antibodies developed in 57% of patients treated with exenatide once weekly, and 12% of patients exhibited high levels of antibodies, which was associated with reduced efficacy[51].

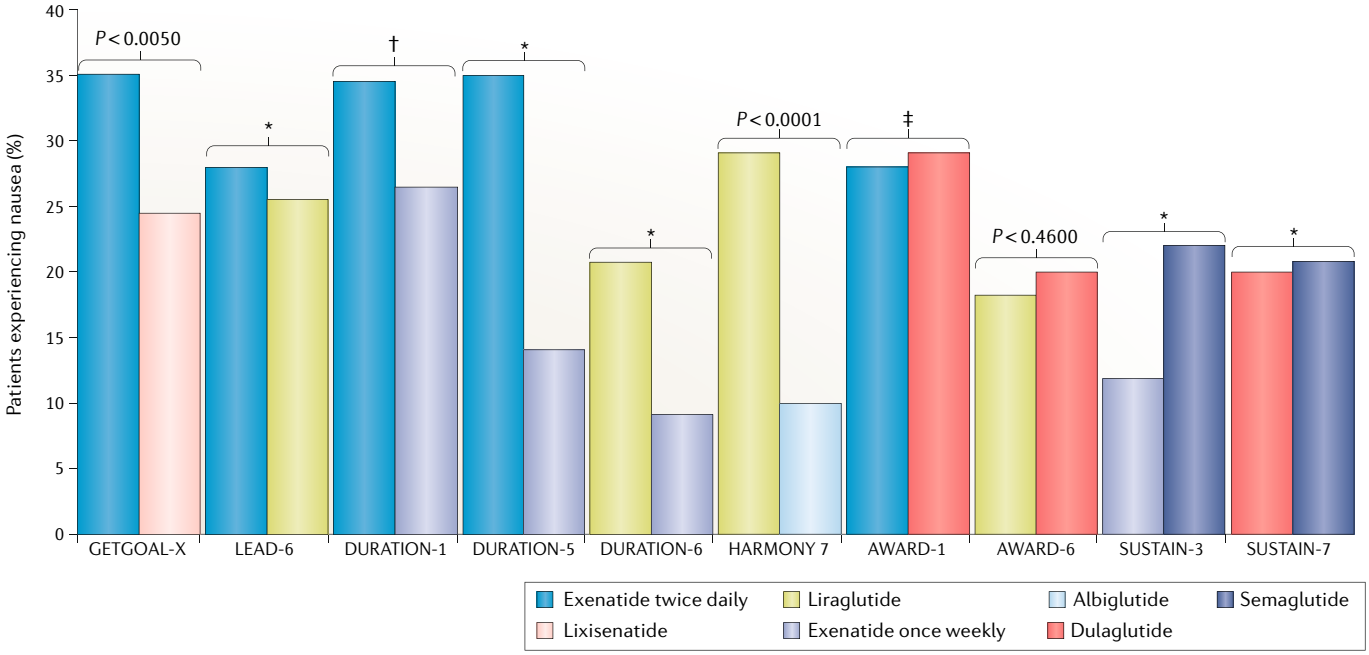

Fig. 4 | **Percentage of patients experiencing nausea in phase III head-to-head trials comparing GLP1RAs in type 2 diabetes mellitus.** The results from the following trials are displayed: GETGOAL-X[48], LEAD-6 (REF.[44]), DURATION-1 (REF.[43]), DURATION-5 (REF.[54]), DURATION-6 (REF.[57]), HARMONY 7 (REF.[58]), AWARD-1 (REF.[55]), AWARD-6 (REF.[59]), SUSTAIN-3 (REF.[71]) and SUSTAIN-7 (REF.[72]). *P* values are reported where appropriate. GLP1RAs, glucagon-like peptide 1 receptor agonists. *Significance not stated. †Significant difference. ‡No significant difference.

Emerging GLP1RAs. Treatment with long-acting GLP1RAs results in dose-dependent reductions in HbA_{1c} and body weight; however, the potential clinical effect is, to some extent, limited by dose-dependent gastrointestinal adverse effects. Therefore, the development of new compounds has focused on extending the plasma half-life, reducing the number of injections and developing an oral formulation to improve convenience for patients.

Semaglutide is a once weekly, subcutaneously administered GLP1RA that is structurally closely related to liraglutide but has the attachment of a C18 fatty acid chain (instead of the C16 fatty acid chain that is in liraglutide) for improved albumin binding; Ala8 is substituted for α-aminoisobutyric acid, which decreases degradation by DDP4 (REF.[70]) (FIG. 2). In the phase III trial SUSTAIN-3, semaglutide proved superior to exenatide once weekly in reducing HbA_{1c} levels, fasting plasma levels of glucose and body weight (FIGS. 3,5). However, gastrointestinal adverse effects were more common in patients treated with semaglutide than in those who received exenatide (42% versus 33%)[71]. Semaglutide has also proved superior to dulaglutide in HbA_{1c} reduction and body weight loss in the SUSTAIN-7 trial[72]. The prevalence of gastrointestinal adverse events was similar in the two groups receiving full doses of semaglutide and dulaglutide.

An oral formulation of semaglutide is under clinical development, and it is currently being investigated in the phase III trial programme PIONEER[73]. In a phase II trial, once daily oral semaglutide at a dose of 40 mg demonstrated reductions in levels of HbA_{1c}, fasting plasma levels of glucose and body weight similar to those seen with once weekly subcutaneous semaglutide[74]. In the PIONEER studies, oral semaglutide is investigated in once-daily doses of 3 mg, 7 mg and 14 mg.

Another approach to simplify administration of GLP1RAs is ITCA 650, an implantable, subdermal, osmotic titanium mini-pump designed to provide continuous release of exenatide for up to 12 months[75]. The phase III trial programme FREEDOM has been completed, and the FDA accepted the new drug application in February 2017 (REF.[76]). Currently, no head-to-head studies comparing ITCA 650 with an available GLP1 agonist have been published.

Finally, phase III studies investigating the efficacy and safety of efpeglenatide, a once monthly subcutaneously administered GLP1RA, were initiated in December 2017 (REF.[77]). Efpeglenatide is based on exendin 4, with a single amino acid modification conjugated via a non-peptidyl linker to a non-glycosylated human IgG4 Fc domain. In vitro studies have indicated that efpeglenatide might result in less internalization of GLP1Rs than other long-acting GLP1RAs and that this might lead to an improved effect on levels of HbA_{1c} and body weight reduction[78]. A single phase II study has demonstrated similar effects on HbA_{1c} and body weight with efpeglenatide 4 mg once weekly as with liraglutide 1.8 mg, with no difference in safety profile[79]. Nevertheless, as data regarding efpeglenatide are limited to presentations at scientific meetings and peer-reviewed abstracts, they should be interpreted with caution.

Cardiovascular outcome trials. In 2008, CVOTs became an FDA requirement for approval of new treatments for T2DM, and a similar requirement was subsequently put forward by the European Medicines Agency (EMA)[80,81]. The need for improved data on the

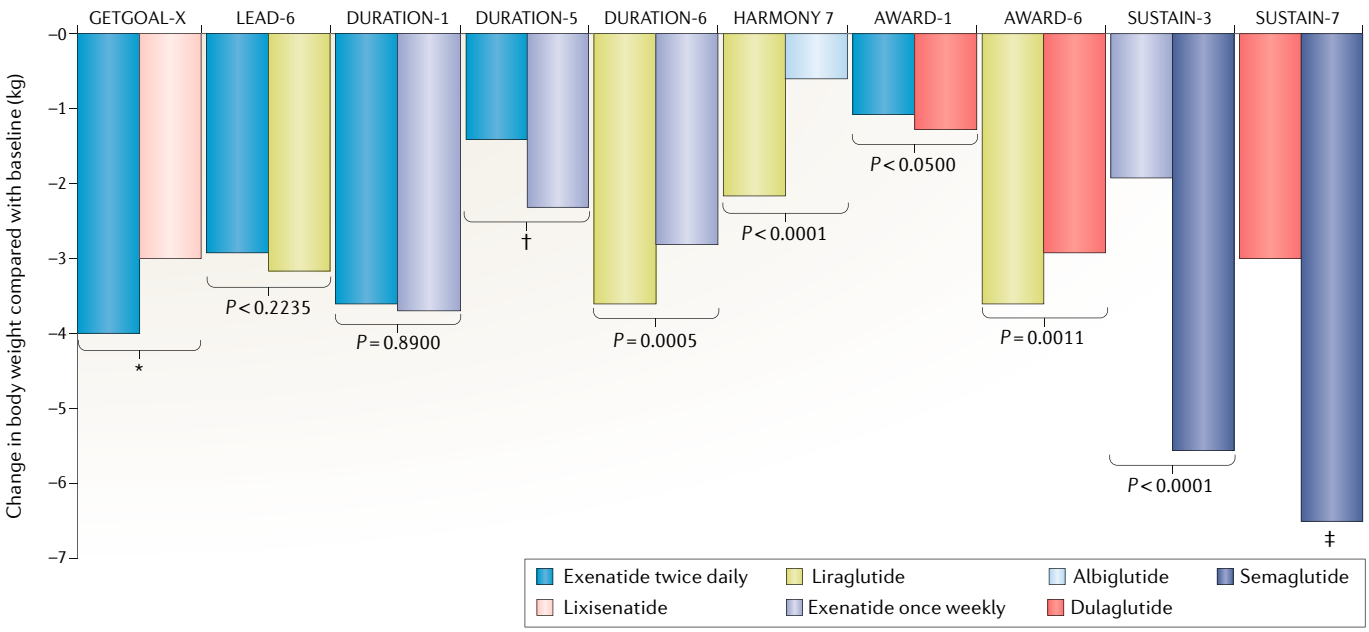

Fig. 5 | **Body weight reductions in phase III head-to-head trials comparing GLP1RAs in type 2 diabetes mellitus.** The results from the following trials are displayed: GETGOAL-X[48], LEAD-6 (REF.[44]), DURATION-1 (REF.[43]), DURATION-5 (REF.[54]), DURATION-6 (REF.[57]), HARMONY 7 (REF.[58]), AWARD-1 (REF.[55]), AWARD-6 (REF.[59]), SUSTAIN-3 (REF.[71]) and SUSTAIN-7 (REF.[72]). *P* values are reported where appropriate. GLP1RAs, glucagon-like peptide 1 receptor agonists. *Significance not stated. †No significant difference. ‡Superiority criteria met.

cardiovascular safety of glucose-lowering therapeutics was highlighted after serious concern was raised about the cardiovascular safety of rosiglitazone owing to a meta-analysis demonstrating a significant increase in the risk of myocardial infarction in patients treated with the compound[82]. Consequently, the cardiovascular effects of all approved and emerging GLP1RAs have been or are being investigated in CVOTs with the exception of exenatide twice daily, which was approved before 2008 (TABLES 2,3).

The first CVOT to present cardiovascular safety data for a GLP1RA was the ELIXA study investigating the cardiovascular effects of lixisenatide[83]. This study included 6,068 patients with T2DM who had acute coronary syndrome or who had undergone hospitalization for unstable angina within the past 180 days. The primary end point was a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke and hospitalization for unstable angina. The trial demonstrated no difference in cardiovascular risk with lixisenatide compared with placebo (HR 1.02; 95% CI 0.89–1.17).

In 2016, data from the LEADER trial (9,340 patients) and the SUSTAIN-6 trial (3,297 patients) — which investigated the cardiovascular effects of liraglutide and semaglutide, respectively, in patients with T2DM and established cardiovascular disease or high cardiovascular risk — were published[84,85]. In the LEADER trial, patients received liraglutide 1.8 mg once daily or the maximum tolerated dose, whereas patients in SUSTAIN-6 were randomly assigned to receive either 0.5 mg or 1.0 mg of semaglutide once weekly. Both studies demonstrated superiority with regard to the primary composite end point, which was defined as first occurrence of death from cardiovascular causes, nonfatal myocardial infarction and nonfatal stroke when compared with placebo (HR 0.87; 95% CI 0.78–0.97 and HR 0.74; 95% CI 0.58–0.95, respectively). In LEADER, the cardiovascular effect was mainly driven by a significant reduction in death from cardiovascular causes (HR 0.78; 95% CI 0.66–0.93), whereas the observed reductions in incidence of nonfatal myocardial infarction or nonfatal stroke were not significant. Following the results of the LEADER trial, the FDA approved liraglutide for a new indication, namely, to reduce the risk of major adverse cardiovascular events in adults with T2DM and established cardiovascular disease[86]. This new indication has also been recognized in the standards of care by the American Diabetes Association and in a summary of product characteristics by the EMA[87,88].

In SUSTAIN-6, the cardiovascular effect was mainly driven by a significant reduction in nonfatal stroke (HR 0.61; 95% CI 0.38–0.99), whereas unlike liraglutide, no reduction in death from cardiovascular causes was found. Nevertheless, the combined findings from LEADER and SUSTAIN-6 indicated a class effect of long-acting GLP1RAs, and results from further CVOTs involving long-acting GLP1RAs were eagerly anticipated. The next CVOT to be completed was the FREEDOM-CVO, which reported noninferiority of ITCA 650 compared with placebo with regards to cardiovascular safety[89]. However, results from this trial have not been published, making interpretation difficult.

The most recent large-scale CVOT to report results is the EXSCEL trial, including 14,752 patients of whom 73.1% had previous cardiovascular disease, with a median follow-up of 3.2 years and a similar primary end point as in LEADER and SUSTAIN-6 (REF.[90]). Exenatide once weekly demonstrated noninferiority with regard to the primary composite end point (HR 0.91;

Table 2 | **Completed cardiovascular outcome trials for GLP1RAs**

Compound	Trial name	Month and year of completion	*n*	Median follow-up (months)	Exposure to trial drug during follow-up period	Risk factors at baseline			Effect on primary composite cardiovascular end point (HR; 95% CI)]
						Age	HbA_{1c}	CVD (% of patients)	
Lixisenatide	ELIXA[83]	Feb 2015	6,068	25	• Lixisenatide: 690 days • Placebo: 712 days	• Lixisenatide: 59.9 • Placebo: 60.6	7.7	100	1.02; 0.89–1.17
Liraglutide	LEADER[84]	Dec 2015	9,340	46	• Liraglutide: 84% • Placebo: 83%	• Liraglutide: 64.2 • Placebo: 64.4	8.7	81.3	0.89; 0.78–0.97
Semaglutide	SUSTAIN-6[85]	Mar 2016	3,297	25	• Semaglutide 1.0 mg: 88% • Semaglutide 0.5 mg: 85% • Placebo 1.0 mg: 90% • Placebo 0.5 mg: 90%	• Semaglutide 1.0 mg: 64.7 • Semaglutide 0.5 mg: 64.6 • Placebo 1.0 mg: 64.4 • Placebo 0.5 mg: 64.8	8.7	83.0	0.74; 0.58–0.95
ITCA 650	FREEDOM-CVO[89]	May 2016	4,000	NA	NA	NA	NA	NA	Noninferiority compared with placebo
Exenatide once weekly	EXSCEL[90]	May 2017	14,752	38	• Exenatide once weekly: 76% • Placebo: 75%	• Exenatide once weekly: 62.0 • Placebo: 62.0	8.0	73.1	0.91; 0.83–1.00

CVD, cardiovascular disease; GLP1RA, glucagon-like peptide 1 receptor agonist; NA, not available.

95% CI 0.83–1.00) but did not reach superiority ($P = 0.06$) when compared with placebo. Patients in EXSCEL were younger, had lower HbA_{1c} at baseline and had lower prevalence of cardiovascular disease than those in LEADER and SUSTAIN-6 (REFS[84,85,90]). Importantly, the mean percentage of time patients were on active treatment was markedly lower in the EXSCEL trial than in LEADER and SUSTAIN-6 (76% versus 84% and 87%). The differences in baseline characteristics and treatment adherence between EXSCEL, LEADER and SUSTAIN-6 might in part explain the outcome differences in these trials. The question remains as to whether the cardiovascular benefits of liraglutide and semaglutide, which are structurally closely related, are compound specific or a result of a class effect of the long-acting GLP1RAs. Nevertheless, in light of the EXSCEL trial, it seems that some differences in cardiovascular efficacy between the long-acting compounds might exist. Results from the ongoing REWIND (dulaglutide) and HARMONY Outcomes (albiglutide) trials might provide additional information on whether a class effect of the long-acting GLP1RAs does exist[91,92] (TABLE 3). As of early 2018, previously published meta-analyses of the phase III trials have not indicated any increased risk of cardiovascular events in patients treated with dulaglutide or albiglutide, respectively[93,94].

GLP1RAs for other indications

The combination of a glucose-dependent glucose-lowering effect, with minimal risk of hypoglycaemia and body weight reduction (as demonstrated by the GLP1RAs) might be utilized in the treatment of several other conditions. Currently, liraglutide (3.0 mg once daily) is approved for the treatment of obesity, and the potential of GLP1RAs for indications other than T2DM is being investigated. This section includes short descriptions of the most promising potential new indications for GLP1RA treatment.

Type 1 diabetes mellitus. The efficacy and safety of GLP1RAs in treating T2DM has been thoroughly investigated; however, the potential of GLP1RAs for the treatment of T1DM remains partly unexplored. Although the insulinotropic effects of GLP1RAs cannot be exploited in T1DM owing to autoimmune β-cell destruction, mechanistic studies have demonstrated a glucagonostatic effect and delayed gastric emptying in patients with T1DM after administration of GLP1RAs[95,96]. The most thoroughly studied GLP1RA for the treatment of T1DM is liraglutide. In the ADJUNCT ONE and ADJUNCT TWO trials, liraglutide at 0.6 mg, 1.2 mg and 1.8 mg was compared with placebo as an add-on to insulin therapy. The studies were designed to be treat-to-target (ADJUNCT ONE) and with capped insulin dose (ADJUNCT TWO). Liraglutide 1.2 mg and 1.8 mg demonstrated significant placebo-adjusted reductions in HbA_{1c} (0.15–0.35%), body weight (3.6–5.1 kg) and total insulin dose (estimated treatment ratios 0.90–0.95%). However, in both trials, liraglutide significantly increased the rate of symptomatic hypoglycaemia and hyperglycaemia with ketosis[97,98]. Owing to these safety issues, an expansion of the on-label use of liraglutide to include T1DM is currently not being pursued. Currently, no large-scale, placebo-controlled, randomized trials have explored the potential of short-acting GLP1RAs for the treatment of

Table 3 | **Ongoing cardiovascular outcome trials for GLP1RAs**

Compound	Clinicaltrials.gov identifier	Trial name	Data expected	Estimated *n*	Anticipated maximal duration (months)
Dulaglutide	NCT01394952	REWIND[91]	Jul 2018	9,622	78
Semaglutide (oral)	NCT02692716	PIONEER 6 (REF.[133])	Oct 2018	3,176	19
Albiglutide	NCT02465515	HARMONY Outcomes[92]	May 2019	9,400	60

GLP1RA, glucagon-like peptide 1 receptor agonist.

T1DM. However, exenatide twice daily has proved to statistically significantly delay gastric emptying, reduce glucagon secretion and reduce the severity of postprandial glucose excursions in response to a meal in patients with T1DM[96]. Additional studies are needed to determine the role of GLP1RAs (particularly short-acting GLP1RAs) in the treatment of T1DM.

Prediabetes. The potential for treatment of prediabetes with GLP1RAs has primarily been explored for liraglutide. In the SCALE obesity and prediabetes trial, treatment with liraglutide 3.0 mg once daily was compared with placebo as an adjunct to reduced calorie intake and increased physical activity in patients with obesity and prediabetes[99]. After 3 years follow-up, onset of T2DM was recorded in 3% of patients taking liraglutide compared with 11% of patients in the placebo group, and significantly more patients in the liraglutide arm converted to normal glucose tolerance than in the placebo arm (66% versus 36%). The number of patients who converted to normal glucose tolerance was, however, reduced to 50% after a 12-week off-drug period, indicating that liraglutide might improve glycaemic regulation without altering the underlying pathophysiology. In a 24-week placebo-controlled study investigating the effect of exenatide twice daily in combination with lifestyle intervention in patients with obesity and prediabetes, normalization of glucose tolerance was more frequent in the exenatide twice-daily arm than in the placebo arm (77% versus 56%), without any difference in the number of patients developing T2DM[100]. At present, none of the GLP1RAs are indicated for the treatment of individuals with prediabetes.

Obesity. GLP1 has a documented effect on satiety[2,3], and the ability of GLP1RAs to promote weight loss has been established in multiple phase III trials; however, the magnitude of the weight loss varies between compounds. Currently, liraglutide 3.0 mg once daily is the only GLP1RA approved by the FDA and EMA for treatment of obesity. The efficacy and safety of liraglutide for treatment of obesity were investigated in the SCALE trials, which included >5,000 patients with either overweight and comorbidities or obesity (with or without comorbidities)[101–104]. In these trials, liraglutide 3.0 mg once daily in addition to lifestyle modifications including reduced calorie intake and increased physical activity provided an additional weight reduction of 4.0–5.4% of body weight after 56 weeks compared with placebo and lifestyle intervention alone[102–104]. Twelve weeks after treatment cessation, the placebo-adjusted weight reduction was reduced to 2.0–4.4% of body weight, with weight curves demonstrating a tendency to a further reduction in between-group differences with continued treatment cessation, indicating that lifelong treatment might be necessary to maintain weight loss. In a 3-year follow-up of the SCALE trials, early responders to liraglutide 3.0 mg once daily, defined as ≥5% body weight loss after 16 weeks, had a greater body weight loss, greater regression to normoglycaemia and less development of T2DM than non-early responders. This finding indicated that early response might help identify those who might benefit from treatment with liraglutide 3.0 mg once daily[105]. Currently, the potential of semaglutide for the treatment of obesity is being investigated. In a phase II trial including 957 patients randomly assigned to receive semaglutide, liraglutide or placebo for 52 weeks, semaglutide resulted in a placebo-adjusted weight reduction of 11.5%. However, data from this study remain to be published[106,107].

Liver disease. As the GLP1RAs can reduce body weight, several studies have investigated the potential for GLP1RAs in the treatment of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH). A meta-analysis published in 2016 that included 136 patients with NAFLD and T2DM treated with either a GLP1RA (exenatide twice daily or liraglutide) or DPP4 inhibitors, concluded that incretin-based treatment was effective in reducing biochemical biomarkers of NAFLD and significantly reduced signs of inflammation, steatosis and fibrosis in biopsy samples and imaging[108]. In the LEAN study, which included 52 patients with NASH, liraglutide 1.8 mg once daily resulted in biopsy-confirmed resolution of NASH in 39% of patients, compared with 9% in the placebo group[109]. Furthermore, in a study comparing 26 weeks of treatment with liraglutide 3.0 mg once daily to lifestyle intervention (the currently recommended treatment), patients in both groups achieved similar reductions in levels of alanine aminotransferase, liver fat fraction, liver stiffness and body weight[110]. Further studies are needed to establish whether GLP1RAs have a role in the treatment of NAFLD and/or NASH.

Neurodegenerative diseases. The development of the neurodegenerative diseases Alzheimer disease and Parkinson disease has been linked to impaired insulin signalling, which was the rationale for investigating the potential for GLP1RAs as a therapeutic for both

conditions. In Parkinson disease, exenatide once weekly was demonstrated to halt disease progression after 48 weeks of treatment and a 12-week wash-out period[111]. However, whether this finding represents an underlying disease modifying effect or merely a long-lasting symptomatic effect is uncertain. Currently, the efficacy and safety of liraglutide is also being investigated in a phase II trial[112]. Liraglutide was investigated for the treatment of Alzheimer disease in a trial, the results of which were published in 2016. Whereas liraglutide prevented a decline in brain glucose metabolism, which might reflect disease progression, the trial demonstrated no effect on amyloid deposition or cognition. However, the results should be interpreted with caution, as the trial might have been underpowered[113].

Safety issues

Since the introduction of GLP1RAs in 2005, a suspected association with an increased risk of pancreatitis and pancreatic cancer has been a concern. In 2011, a study evaluating post-marketing reporting found a marked increase in pancreatitis and pancreatic cancer among patients treated with exenatide twice daily compared with other glucose-lowering drugs[114]. Owing to these concerns, both preclinical and clinical studies regarding the risk of pancreatitis and pancreatic cancer have been extensively evaluated by the FDA and EMA, with the conclusion that the data were inconsistent with a causal association between GLP1RAs and the pancreatic adverse effects[115]. This conclusion is supported by a meta-analysis that was published in 2017, which included data from >9,000 patients treated with GLP1RAs for a minimum of 24 months and found no evidence of an increased risk of pancreatitis (pancreatitis was a predefined and adjudicated adverse event in all trials)[116]. Likewise, no evidence of an increased risk of pancreatic cancer was found in a large retrospective cohort study including almost 1 million patients initiating glucose-lowering drugs[117]. However, owing to the rare incidence of pancreatic cancer, sufficiently powered prospective studies are almost impossible to perform. Consequently, a causal link between GLP1RAs and pancreatic cancer cannot be fully excluded. Owing to an increased incidence in rodents during preclinical studies, GLP1RAs have also been linked to thyroid C cell tumours[118], and GLP1R expression has been demonstrated to be higher in thyroid C cell tumour tissue than in non-neoplastic tissue[119]. However, monitoring of calcitonin levels during clinical trials has not raised concern, and no increased risk of thyroid tumours was observed in any of the published human CVOTs (with a duration >2 years)[83–85,90].

GLP1RAs have also been associated with an increased risk of gallbladder-related adverse events. In the SCALE trials, the incidence of cholelithiasis and cholecystitis was higher in the liraglutide-treated groups than in the groups that received placebo[102,103]. Additionally, in a retrospective cohort study that was published in 2016, treatment with GLP1RAs significantly increased the risk of gallbladder-related adverse effects, including cholelithiasis, cholecystitis and cholangitis[120]. The adverse effect of GLP1RAs on the gallbladder might be explained by altered gallbladder contraction[121], however, further studies are needed to the determine the role of GLP1RAs in gallbladder-related disease and the underlying mechanism.

Conclusion

All marketed GLP1RAs have proved effective in reducing levels of HbA_{1c} and body weight. However, the extent of these reductions varies with pharmacokinetic profile and molecular structure[122]. In general, long-acting GLP1RAs induce greater reductions in HbA_{1c} and fasting plasma levels of glucose than short-acting GLP1RAs, whereas short-acting GLP1RAs induce greater reductions in postprandial plasma levels of glucose. The ability of GLP1RAs to reduce body weight seems to be independent of their plasma half-life. Liraglutide stands out as the only currently available GLP1RA with a positive effect on cardiovascular disease in a CVOT[84]. A reduced incidence of cardiovascular disease has also been demonstrated with subcutaneously administered semaglutide[85]. Recently, semaglutide was approved by both the FDA and EMA and is expected to reach the market in 2018. Interestingly, the effect on the different elements of the composite primary cardiovascular outcome is different for liraglutide and semaglutide, and the mechanisms promoting the beneficial cardiovascular effects are still largely unexplained. Treatment with GLP1RAs improves several cardiovascular risk factors, including body weight, blood pressure and lipid profile, but a small increase in heart rate is also observed[123]. Accordingly, it seems likely that the beneficial effect of liraglutide and semaglutide on cardiovascular risk is achieved through multiple effects on the cardiovascular system, which in combination outweigh the potential deleterious effect of an increased heart rate. However, further studies are ongoing and aim to delineate the mechanisms by which these compounds might affect cardiovascular risk, and results from such studies might provide clinicians with information and understanding of which patients might benefit from treatment with GLP1RAs.

Another class of glucose-lowering drugs that also reduces the incidence of cardiovascular disease in T2DM is the sodium–glucose cotransporter 2 (SGLT2, also known as SLC5A2) inhibitors, namely, empagliflozin and canagliflozin[124,125]. These compounds exert their effect through completely different modes of action than GLP1RAs, and an additive effect of GLP1RAs and SGLT2 inhibitors might exist when used in combination, but this is currently uncertain. Future studies investigating the potential for cardiovascular risk reduction in T2DM by GLP1RA–SGLT2 inhibitor combination therapy should be explored.

For now, CVOTs are focused on patients with established cardiovascular disease or high cardiovascular risk, and results from these trials cannot be extrapolated to the general T2DM population. However, the cardiovascular effects of GLP1RAs in patients with T2DM without established cardiovascular disease or high cardiovascular risk remain uncertain. Such trials should be conducted to evaluate the effect of primary intervention, but these trials would have to be long and include large populations.

However, it seems reasonable to take into account the potential cardiovascular effect when choosing first-line and second-line treatments in patients with T2DM and fairly low cardiovascular risk. Currently, GLP1RAs are indicated for improving glycaemic control and reducing cardiovascular risk in T2DM, as well as for promoting weight loss in obesity. Interestingly, GLP1Rs are found in numerous tissues, and GLP1RAs might exert an effect in multiple tissues. Further research is needed to elucidate their role in prevention of cardiovascular disease in T2DM and to explore the potential of GLP1RAs for other indications.

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