

REVIEW

GLP-1 receptor agonists in the treatment of Type 2 diabetes



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Practice Points

- Incretin therapy is based on the actions of GLP-1.
- GLP-1 receptor agonists are injected subcutaneously twice daily, once daily or once weekly.
- GLP-1 receptor agonists reduce fasting and postprandial glucose, which reduces HbA1c, and reduce bodyweight.
- Clinically important differentiation relates to injection intervals (twice daily, once daily and once weekly) and the relative effect on postprandial versus fasting glucose.
- GLP-1 receptor agonists are associated with nausea and vomiting in the beginning of therapy.
- With regards to risk of pancreatitis and pancreatic cancer, there is no evidence of increased risk with GLP-1 receptor agonists, but continuous follow-up of patients is important.
- With regards to cardiovascular safety, there is no evidence of increased cardiovascular risk with GLP-1 receptor agonists; several cardiovascular safety studies are ongoing.
- GLP-1 receptors are mainly used in combination with metformin and in combination with basal insulin in patients with Type 2 diabetes who are insufficiently controlled on metformin or insulin alone.

SUMMARY Incretin therapy is based on the antidiabetic actions of the incretin hormone GLP-1. The treatment both stimulates insulin secretion and inhibits glucagon secretion, which results in lowering of both fasting and postprandial glycemia. Incretin therapy is used either with GLP-1 receptor agonists or with inhibitors of DPP-4, which is the enzyme that inactivates endogenously released GLP-1. The GLP-1 receptor agonists are injected subcutaneously once or twice daily, or once weekly, and they reduce HbA1c and bodyweight. The GLP-1 receptor agonists are highly tolerable and, apart from nausea and vomiting during the early phases of the treatment, there is a low risk of adverse events. Studies on long-term cardiovascular safety are ongoing. Added advantages are very low risks of hypoglycemia and reduction in bodyweight. GLP-1 receptor agonists are efficacious in combination with oral antihyperglycemic agents and with insulin. Their main use is as an add-on to metformin in patients who are insufficiently controlled on metformin alone, and an important indication is also in combination with insulin therapy.

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Treatment with GLP-1 receptor agonists is based on the actions of the incretin hormone GLP-1 [1]. The hormone, which was discovered as a product of the proglucagon gene in 1983 [2], is released from endocrine cells in the gut during and after meal ingestion [3]. GLP-1 contributes to the incretin effect, which is the high level of insulin secretion after meal ingestion [1]. The function of GLP-1 as a physiological incretin was initially demonstrated in 1987 by Kreyman and collaborators [4]. The effect on the β cells is achieved through activating specific β -cell G-protein-coupled receptors; the formation of cAMP is a main intracellular signaling mechanism [5]. GLP-1 also inhibits glucagon secretion [6]. GLP-1, therefore, has the ability to target the two main pathophysiological defects in Type 2 diabetes, the α - and β -cell dysfunction, which occur very early during the development of the disease [7]. GLP-1 also delays gastric emptying [8] and induces satiety through a central effect in the hypothalamus [9]. In rodent studies, GLP-1 also increases β -cell mass mainly through inhibition of apoptosis [10], although this has not been shown in humans. All these effects were identified during the 1980s as of potential value in the treatment of Type 2 diabetes, which initiated the development of GLP-1-based therapies [11].

Our first study showing that GLP-1 had the potential as an antidiabetogenic agent was presented at the European Association for the Study of Diabetes (EASD) meeting in 1990 and published in 1992, and showed that the hormone reduced the insulin requirement after ingestion of a meal in Type 2 diabetics [12]. An accompanying editorial to the published article stated that “if these interesting findings can be replicated ... GLIP [GLP-1] analogs may become useful in the treatment of patients with noninsulin-dependent diabetes mellitus” [13], and outlined the potential of GLP-1.

The antidiabetic action of GLP-1 in Type 2 diabetes was later confirmed in several other studies, including a 6-week study using continuous subcutaneous infusion of GLP-1 in subjects with Type 2 diabetes showing improved glycaemia and reduced bodyweight caused by the hormone [14]. A challenge in the early therapeutic development of GLP-1 was that the hormone is rapidly inactivated by the enzyme DPP-4 [15]. This enzyme is produced in the endothelial cells and rapidly inactivates GLP-1, making the circulating half-life of the native hormone only 1–2 min. To overcome this challenge, two

strategies for incretin therapy were developed: DPP-4-resistant GLP-1 receptor agonists and DPP-4 inhibitors [16].

GLP-1 receptor agonists

GLP-1 receptor agonists were developed in order to activate the GLP-1 receptors and to be resistant or semi-resistant to inactivation by DPP-4. Today, several GLP-1 receptor agonists exist [17]. They are structurally related to exendin-4 or GLP-1; **Figure 1** shows the structure of the approved GLP-1 receptor agonists and **Table 1** shows the main characteristics of them. **Figure 2** shows the molecular size of the GLP-1 receptor agonists. The first approved GLP-1 receptor agonist was exenatide, which is the synthetic recombinant form of the peptide exendin-4, having approximately 50% structural similarity to GLP-1 [18]. The original exenatide formulation is injected subcutaneously twice daily (b.i.d.; Byetta®; Amylin Pharmaceuticals, CA, USA). A longer acting formulation of exenatide is exenatide once weekly (exenatide QW; Bydureon®; Amylin Pharmaceuticals), in which exenatide is incorporated into microspheres consisting of biodegradable polymers [19]. These microspheres are slowly degraded after subcutaneous injection, allowing exenatide to be slowly released, resulting in a more stable concentration of exenatide over a longer period of time, allowing for weekly administrations [19]. Recently, another exendin-4-based GLP-1 receptor agonist was introduced in the therapy, lixisenatide, which is given once daily [20]. This consists of exendin-4 elongated with a residue of 6 lysines attached to the C-terminal end.

The first GLP-1 analog to be developed was liraglutide (Victoza®; Novo Nordisk A/S, Bagsvaerd, Denmark) in which a fatty acid is bound to a slightly modified GLP-1 molecule [21]. This results in delayed absorption from the subcutaneous space and high albumin binding, resulting in a prolonged half-life, allowing once-daily injection.

Several other GLP-1 receptor agonists are in late clinical development. Albiglutide is a GLP-1 receptor agonist in which two GLP-1 molecules have been coupled and fused to recombinant human albumin [22]. Other novel GLP-1 receptor agonists are dulaglutide, in which two GLP-1 molecules through two linker peptides have been fused to the Fc fragment of immunoglobulin G4 [23]. Semaglutide, the second amino acid of liraglutide has been changed and the coupled

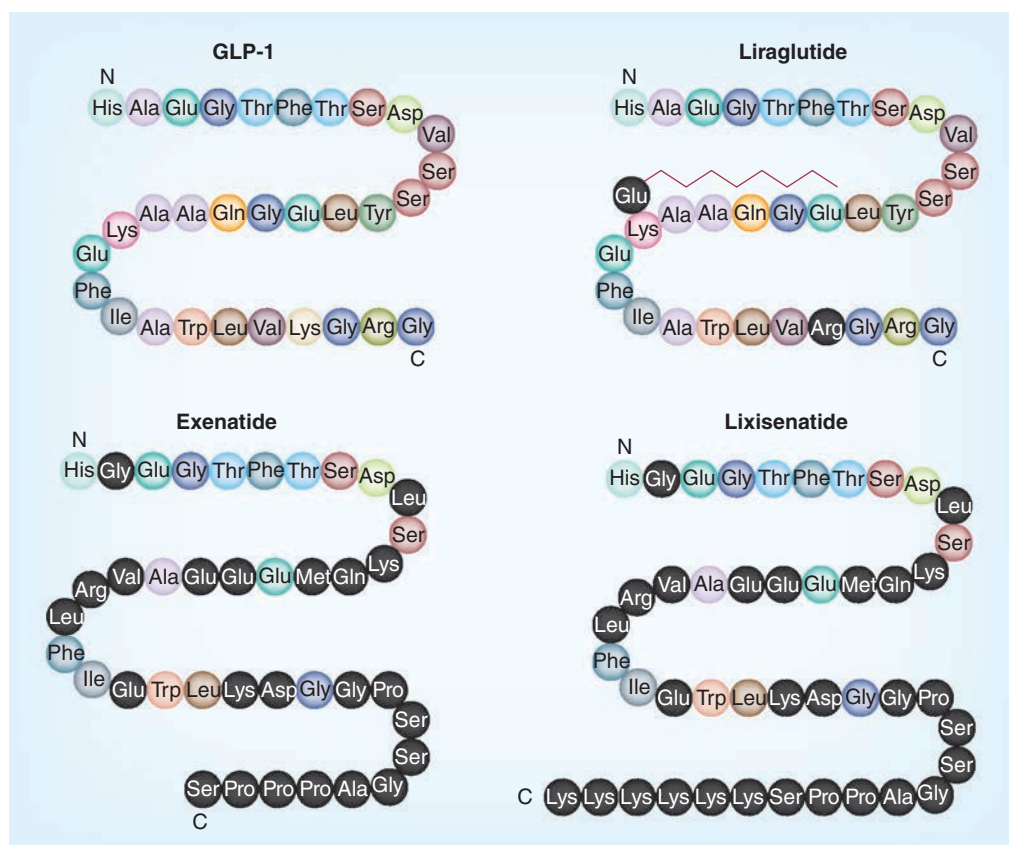


Figure 1. Structure of native GLP-1 and the approved GLP-1 receptor agonists. Amino acids are shown in circles, fatty acids as lines. Amino acids in black are different from those in native GLP-1.

fatty acid is slightly longer than in liraglutide [24]. Albiglutide, dulaglutide and semaglutide are all developed for once-weekly administration.

Clinical effects of approved GLP-1 receptor agonists

The GLP-1 receptor agonists were developed in large clinical programs in which their clinical effects, tolerability and safety were evaluated in 26–30-week studies in several different conditions, such as in monotherapy, in combination with oral antidiabetic agents and in combination with insulin. These programs showed that the GLP-1 receptor agonists reduce fasting and prandial glucose, and bodyweight. In most studies, HbA1c was reduced by ≈ 0.8 – 1.5% (8–15 mmol/mol) from baseline values of 7.5–8.5% (58–68 mmol/mol) [17]. Furthermore, bodyweight was reduced by approximately 1–5 kg. The developmental programs also showed that the GLP-1 receptor agonists are safe and highly tolerable with a notable low risk for hypoglycemia. The only consistent adverse events were nausea and vomiting, which were

most common in the early weeks after start of therapy and subsided thereafter.

Exenatide b.i.d. was developed in the AMIGO program. This consisted of three studies in which exenatide was added to metformin [25], sulfonylureas [26] or metformin plus sulfonylureas [27]. In these studies, baseline HbA1c was 8.2–8.6% (64–68 mmol/mol) and at a dose of 10 μg b.i.d., exenatide reduced HbA1c by 0.8–0.9% (8–9 mmol/mol). Bodyweight was reduced by 1.6–2.8 kg from the baseline bodyweight of 97–99 kg. Exenatide was found to be tolerable, with nausea being the most common adverse event occurring in 45–51% of patients during the early stages of treatment. Hypoglycemia was rare when exenatide was combined with metformin (5%), but higher when exenatide was combined with sulfonylurea (28–36%) [25–27].

The long-acting once-weekly form of exenatide (exenatide QW) was developed in the DURATION program, consisting of six studies evaluating exenatide QW in either monotherapy [28] or in combination with oral antihyperglycemic agents [29–33]. Baseline HbA1c in these

Table 1. Main characteristics of therapy with GLP-1 receptor agonists in Type 2 diabetes.

Parameter	Characterization
Mode of administration	Subcutaneous injection
Degree of GLP-1 stimulation	Pharmacological
Insulin secretion	Stimulation
Glucagon secretion	Inhibition
Gastric emptying	Delay
Fasting and prandial glucose	Reduction
HbA1c	Lowered by ~0.8–1.5% (8–15 mmol/mol) [†]
Bodyweight	Lowered by ~1–5 kg
Risk of hypoglycemia	Low
Adverse events	Nausea or vomiting at the beginning of therapy

[†]Effect on HbA1c is dependent on the baseline HbA1c.

studies was 8.3–8.6% (65–68 mmol/mol) and it was reduced by 1.5–1.9% (15–19 mmol/mol) by exenatide QW. Bodyweight was reduced by 2.0–3.7 kg from 86–102 kg, and nausea was observed in 11–35% of patients, mainly at the beginning of therapy. Injection site reactions, mainly erythema, were reported in 16% of patients and hypoglycemia was observed in 1–8% of the patients.

Liraglutide was developed in the LEAD program, which was a program consisting of six studies in which liraglutide was used either as a monotherapy [34] or as an add-on to metformin [35], sulfonylurea [36] or combinations of metformin with sulfonylureas and/or thiazolidinediones [37–39]. Baseline HbA1c was 8.1–8.6% (64–69 mmol/mol) and was reduced by 1.0–1.5% (10–15 mmol/mol) by liraglutide at 1.8 mg once daily. Bodyweight was reduced by 0.2–3.2 kg from a baseline bodyweight of 83–93 kg. Liraglutide was well tolerated and nausea in the early weeks of therapy, which

occurred in 7–40% of the patients in the different studies, was the only consistent adverse event. Hypoglycemia was observed in 3–10% of patients on a metformin background and in 24–27% of patients on liraglutide at 1.8 mg in combination with sulfonylurea.

Lixisenatide has been developed in the Get-Goal program. In this program, lixisenatide was examined as either a monotherapy [40] or as an add-on to metformin [41,42], pioglitazone [43] or insulin [44,45]. In the studies when lixisenatide was added to oral agents, baseline HbA1c was 8.0–8.1% (62–63 mmol/mol) and was reduced by 0.8–0.9% (8–9 mmol/mol) by lixisenatide. Bodyweight was reduced by 0.2–3 kg from a baseline of 86–94 kg. As with the other GLP-1 receptor agonists, lixisenatide was as safe, with nausea being the only consistent adverse event (16–35% in the different studies, mainly at the beginning of therapy), and hypoglycemia was rare (2.4–5.6% of the patients on lixisenatide reported symptomatic hypoglycemia) [40–43]. In two studies, lixisenatide was evaluated as an add-on to basal insulin. In one of those studies, basal insulin was used at a fixed daily dose of 55 U as a mean [44], whereas in the other study, basal insulin was initially titrated from a daily baseline dose of 44 U as a mean, and then lixisenatide was added [45]. When adding lixisenatide to basal insulin in these two studies, HbA1c was reduced by 0.6 (6 mmol/mol) [44] or 0.7% (7 mmol/mol) [45]. Patients reported that symptomatic hypoglycemia was more common in the lixisenatide groups than with the placebo groups: 28% with lixisenatide versus 22% with placebo [44] and 22% with lixisenatide versus 14% with placebo [45]; although it should be emphasized that the patients on lixisenatide and basal insulin had lower HbA1c than patients on placebo and basal insulin.

Figure 3 summarizes the reduction in HbA1c in the developmental studies when exenatide b.i.d., exenatide QW, liraglutide or lixisenatide were examined in monotherapy or as an add-on to oral antihyperglycemic agents. It is seen that HbA1c in these studies was reduced by 0.8–1.9% (8–19 mmol/mol) from a baseline HbA1c of 8.0–8.6% (62–68 mmol/mol). Mean HbA1c reduction (\pm standard deviation) was $-1.2 \pm 0.3\%$ (-12 ± 3 mmol/mol) from a mean of $8.4 \pm 0.2\%$ (66 ± 2 mmol/mol). There was a significant correlation between baseline HbA1c and change in HbA1c ($r = -0.46$; $p = 0.049$), showing that the main explanation

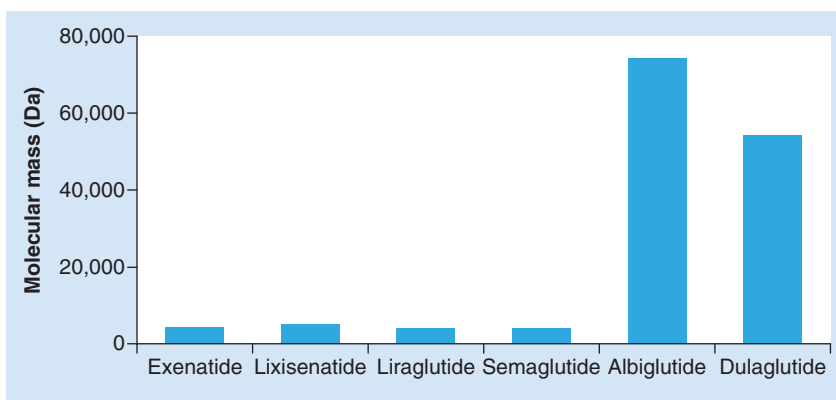


Figure 2. Molecular size of approved GLP-1 receptor agonists and GLP-1 receptor agonists in late clinical development.

for differences between different studies is that the baseline HbA1c was different.

Differentiation of the GLP-1 receptor agonists

The GLP-1 receptor agonists differ in molecular structure, molecular size and pharmacokinetics, which may form the bases for differentiation between them.

■ Molecular structure

The GLP-1 receptor agonists differ in structure based on whether they are developed from the exendin-4 molecule (exenatide and lixisenatide) or from native GLP-1 (liraglutide, albiglutide, dulaglutide and semaglutide). Comparisons of the clinical effects of exendin-4-based versus GLP-1-based GLP-1 receptor agonists have been undertaken in four studies (Table 2). With regards to HbA1c changes, a slightly higher reduction was observed for GLP-1-based receptor agonists compared with exendin-4-based receptor agonists (liraglutide vs exenatide QW: -1.5%; 15 mmol/mol; vs -1.2%; -12 mmol/mol [33]; liraglutide vs exenatide b.i.d.: -1.1%; -11 mmol/mol; vs -0.8%; 8 mmol/mol [39]; albiglutide vs exenatide b.i.d.: -0.9%; 9 mmol/mol; vs -0.5%; 5 mmol/mol [46]; and liraglutide vs lixisenatide: -0.5%; 5 mmol/mol; vs -0.3%; 3 mmol/mol [47]). By contrast, there does not seem to be any consistent difference with regards to reduction in bodyweight, or frequency of nausea or hypoglycemia between the receptor agonists in these studies. A consistent finding, however, is that antibodies developed more frequently during treatment with exendin-4-based GLP-1 receptor agonists than with GLP-1-based GLP-1 receptor agonists. This is explained by the more extensive difference in molecular structure of exendin-4 in comparison with native GLP-1. For example, antibodies were seen in 8% of patients treated with liraglutide versus 43% of patients treated with exenatide b.i.d. in a head-to-head study between these two agents [39]. It should be emphasized that it is difficult to compare the frequency of antibody formation in different studies, due to different techniques of measuring antibodies. In any case, these antibodies do not seem to affect the glucose-lowering ability of the compounds, since the HbA1c reduction is the same in patients who developed antibodies versus those who did not, as evident from two different analyses [48,49]. However, both these analyses also showed that the few subjects with

very high antibody titer had a lower reduction in HbA1c, suggesting that at high titers, some influence on the glucose-lowering ability of the GLP-1 receptor agonists may evolve [48,49].

■ Molecular size

The GLP-1 receptor agonists also differ in size (Figure 2). Most of them have a molecular size in the same range as native GLP-1; this relates to exenatide, lixisenatide, liraglutide and semaglutide. By contrast, albiglutide and dulaglutide are large proteins, with a molecular weight more than 20-times higher than the small GLP-1 receptor agonists. This difference in size may have a potential impact on the tissue penetration of the molecules, although this has not been studied in detail and, hence, the potential clinical consequence, if any, has not been established.

■ Pharmacokinetic characteristics

The GLP-1 receptor agonists have different pharmacokinetic characteristics due to differences in circulating half-life. They may be divided into short-acting treatments – that is, administered once or b.i.d. (exenatide b.i.d., lixisenatide and liraglutide) – or long-acting treatments – that is, administered once weekly (exenatide QW, albiglutide, dulaglutide and semaglutide). However,

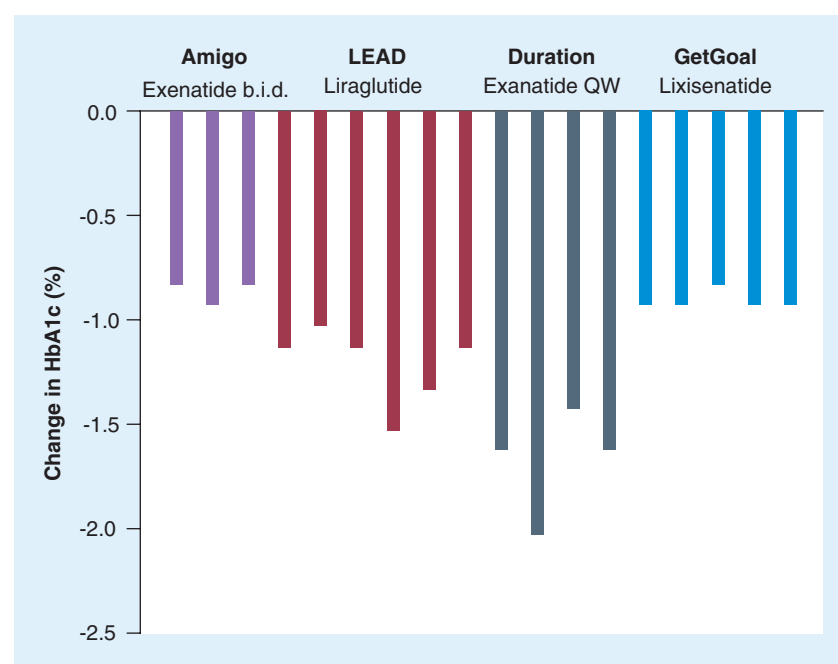


Figure 3. Changes in HbA1c levels and bodyweight in the developmental programs of approved GLP-1 receptor agonists. Each bar represents one specific study. Baseline HbA1c was different in the different studies [25–32,34–44]. b.i.d.: Twice a day; QW: Once weekly.

Table 2. Head-to-head studies comparing different GLP-1 receptor agonists.

Comparison	Molecular structure	Molecular size	Pharmacokinetics	Ref.
Exenatide b.i.d. vs exenatide QW			X	[29,32]
Exenatide b.i.d. vs liraglutide	X		X	[39]
Exenatide QW vs liraglutide	X			[33]
Liraglutide vs lixisenatide	X		X	[52]
Exenatide b.i.d. vs albiglutide	X	X	X	[49]
Liraglutide vs albiglutide		X		[47]
Liraglutide vs semaglutide		X		[51]

X demonstrates whether the studied GLP-1 receptor agonists in each study differed in molecular structure (being derived from exenadin-4 vs GLP-1), molecular size (being of size similar to GLP-1 or manifold larger) and/or pharmacokinetics (being intermittent receptor activators or continuous receptor activators). For further discussion on these different studies see the text. b.i.d.: Twice a day; QW: Once weekly.

a more rational differentiation is to relate pharmacokinetics to exposure time for GLP-1 receptor activation. The GLP-1 receptor agonists may then be divided into those with intermittent receptor activation (acting in less than 24 h) and those with continuous receptor activation (acting continuously throughout the 24 h period). With this division, exenatide b.i.d. and lixisenatide are intermittent activators and the others are continuous activators. This may have a consequence for their relative influence to reduce fasting versus postprandial glycemia. Thus, it has been shown that a reduction in fasting glucose is better with continuous rather than with intermittent GLP-1 receptor activators, as was already demonstrated in a 2001 study infusing GLP-1 for different time periods [50]. By contrast, the effect to delay gastric emptying, which contributes to the reduction in postprandial glycemia, might be better with intermittent GLP-1 receptor activators than with continuous GLP-1 receptor activators, since continuous GLP-1 receptor activation might lead to tachyphylaxis of the delay in gastric emptying [51]. The rationale for division of intermittent versus continuous activators has been verified in head-to-head studies, showing that reduction in fasting glucose was more pronounced with continuous receptor activators whereas the reduction in postprandial glucose was more pronounced with the intermittent activators [29,39,47].

GLP-1 receptor agonists compared with other glucose-lowering therapy

■ **Metformin**

Metformin is the most commonly described glucose-lowering therapy and its main mechanism to lower glucose is to increase insulin sensitivity and reduce hepatic glucose release; although its detailed molecular mechanism is still not established [52]. Metformin is usually the first pharmacological

agent that is given to patients in whom lifestyle changes are not sufficient for achieving glycemic control. Metformin reduces HbA1c by approximately 0.5–1.5% (5–15 mmol/mol) under these conditions and it has a low risk of hypoglycemia, as is evident from the UKPDS study [53]. One study compared metformin with exenatide QW as a monotherapy and showed similar HbA1c reduction (by 1.5%; 15 mmol/mol with exenatide QW; and 1.4%; 14 mmol/mol with metformin; from the baseline of 8.5%; 67 mmol/mol), and also a similar reduction in bodyweight and with very few reports of hypoglycemia [28]. Other studies on GLP-1 receptor agonists in monotherapy have shown a HbA1c reduction with liraglutide of 1.1% (11 mmol/mol) [34] and with lixisenatide of 0.7% (7 mmol/mol) [40], but with no head-to-head comparison with metformin. It should be emphasized that monotherapy is not an approved indication for GLP-1 receptor agonists and, therefore, it is of greater clinical value to compare GLP-1 receptor agonists with other glucose-lowering therapy as an add-on to metformin.

■ **DPP-4 inhibition**

DPP-4 inhibitors act by inhibiting DPP-4 and, therefore, raise endogenous GLP-1 levels, which is the main mechanism for their glucose-lowering ability. Therefore, there are similarities between the GLP-1 receptor agonists and DPP-4 inhibitors, for example, both target the islet dysfunction in Type 2 diabetes by stimulating insulin secretion and inhibiting glucagon secretion, as well as efficiently reducing HbA1c with a very low risk of hypoglycemia [54]. There are, however, also differences between the two strategies. A main difference is that GLP-1 receptor agonists are given by injection whereas DPP-4 inhibitors are oral tablets. Other differences are that whereas it

is not uncommon for nausea to be experienced at the beginning of therapy with GLP-1 receptor agonists, this, and other adverse events, are not seen during treatment with DPP-4 inhibitors, and whereas GLP-1 receptor agonists result in weight reduction, weight neutrality is seen during treatment with DPP-4 inhibitors. With regards to efficacy, head-to-head-studies have shown that GLP-1 receptor agonists reduce HbA1c slightly more efficiently than DPP-4 inhibitors, as shown for exenatide QW when compared with sitagliptin (-1.5%; -15 mmol/mol; vs -1.2%; -12 mmol/mol [28]; and -1.5%; -15 mmol/mol; vs -0.9%; -9 mmol/mol [30]) and for liraglutide when compared with sitagliptin (-1.5%; 15 mmol/mol; vs -0.9%; -9 mmol/mol [55]). The fact that the continuous GLP-1 receptor agonists are slightly more efficacious than DPP-4 inhibitors was also verified in a meta-analysis of all studies in which incretin therapy was added to metformin in patients with insufficient glycemic control with metformin alone [56].

■ Sulfonylurea

Sulfonylureas stimulate insulin secretion in a glucose-independent manner and, although they are efficacious in reducing HbA1c, are associated with an increased risk for hypoglycemia and weight gain. A direct head-to-head study comparing liraglutide with glimepiride has verified the differences between the two strategies [35]. Thus, whereas the HbA1c reduction was similar for liraglutide and glimepiride (both -1.0%; 10 mmol/mol), liraglutide was associated with weight loss (-2.8 kg at the highest dose), whereas glimepiride was associated with weight gain (1.0 kg). Furthermore, only 3% of patients on liraglutide experienced hypoglycemia compared with 17% of patients on glimepiride.

■ Insulin

GLP-1 receptor agonists have also been compared with insulin glargine as an add-on to oral agents in two studies. In both studies (with exenatide QW [31] and liraglutide [38]), the GLP-1 receptor agonists reduced HbA1c slightly more than insulin glargine (difference between both studies: -0.2% or 2 mmol/mol) without any increase in hypoglycemic events, and no weight gain was seen with insulin glargine.

Hypoglycemia

A main advantage of using GLP-1 receptor agonists is the low risk for hypoglycemia. This is

important because hypoglycemia is common during treatment with other glucose-lowering therapies, mainly insulin and sulfonylureas, and is associated with a negative impact and high cost [57]. The negative impact includes acute symptoms, such as cognitive dysfunction and coma, as well as negative implication for social interactions, sport, and other leisure activities and traffic accidents. Hypoglycemia is also associated with fear of repeated hypoglycemia, which may result in reduced adherence to therapy, in turn, resulting in deteriorated glycemic control. Hypoglycemia is also a mechanism for weight gain due to defensive eating [57,58]. All these negative impacts result in increased costs, both for the patient, the healthcare system and society [58]. Of great importance is that, besides the short-term negative impact of hypoglycemia, there is also a long-term negative impact on cardiovascular diseases [59,60]. Therefore, there are several important aspects of hypoglycemia, both in the short and long term, and the conclusion is that it is very important to develop strategies to avoid hypoglycemia in Type 2 diabetes [57]. Such strategies may include both awareness of the symptoms, and education of patients, relatives and healthcare providers. In addition, it is important to use glucose-lowering agents with a low risk of hypoglycemia. GLP-1 receptor agonists are such agents.

An important mechanism underlying the low incidence rate of hypoglycemia during treatment with GLP-1 receptor agonists is that the islet effects of GLP-1 are glucose dependent, which means that when glucose levels are reduced to normal baseline levels the islet effects of GLP-1 are reduced [1]. It has also been shown that exenatide [61] sustains glucagon counter-regulation to hypoglycemia, which is important in preventing hypoglycemia.

Tolerability & safety

An important value of GLP-1 receptor agonists is their safety and tolerability. Apart from the gastrointestinal adverse events, which occur mainly during the initial phase of treatment, adverse events are rare. Local injection site reactions sometimes occur, although rarely, and are characterized by transient nodules and erythemas around the injection area. Antibodies may be formed to the GLP-1 receptor agonists and are more commonly formed with exendin-4-based agonists (exenatide and lixisenatide) than other GLP-1-based agonists (see the 'Molecular structure' section).

For some years, there has been a discussion of whether there is an increased risk of acute pancreatitis as a result of treatment with GLP-1 receptor agonists. However, the occurrence of acute pancreatitis is, by itself, increased in Type 2 diabetes and may, therefore, occur in all types of therapy, including incretin therapy, and collected patient data do not suggest any association between incretin therapy and pancreatitis. For example, a large claims-based study comparing the risk of acute pancreatitis with exenatide b.i.d. versus metformin or the sulfonylurea glyburide (glibenclamide) showed no higher risk for acute pancreatitis with exenatide b.i.d. [62]. By contrast, a recent study of patients who were hospitalized for acute pancreatitis showed that these patients had a higher rate of incretin therapy than a control group [63]. Whether the acute pancreatitis in those patients was caused by the incretin therapy is, however, not known. Therefore, today there is no evidence of any association between treatment with GLP-1 receptor agonists and pancreatitis. Nevertheless, it is important to follow patients on GLP-1 receptor agonists with regards to this potential complication, although it should be clear that at present there is no such indication.

Since acute pancreatitis may be associated with pancreatic cancer, incretin therapy has also been discussed in this context. However, carefully performed long-term studies in animals, including monkeys, have not shown any sign of malignancy [64] and meta-analyses do not show an increased risk for pancreas cancer [65]. By contrast, it was suggested in a recent study that incretin therapy may be associated with a dysplasia of the pancreatic ducts, which may be associated with development of pancreatic cancer [66]. This study was, however, although highly quoted in the general media, poorly controlled and has been criticized by the scientific community [67]. In fact, today there is no indication of an association between incretin therapy and pancreatic cancer.

At a workshop organized by NIH in June 2013 on the potential association between incretin therapy and pancreatic diseases it was shown that, similarly as discussed above, there is an association between diabetes, acute pancreatitis and pancreatic carcinoma. During the workshop, the US FDA presented a detailed analysis of all preclinical pathologies that had been collected from submissions of incretin therapies. No concerns for pancreatic disease were evident [101].

At the workshop, the human autopsy study was discussed, and, as stated above, the workshop identified significant study limitations and suggested alternative explanations for the findings reported by the investigators. After the workshop, a joint recommendation by the American Diabetes Association, EASD and International Diabetes Federation was issued, concluding that there is insufficient information to modify current treatment recommendations [102]. Today, therefore, the status of this discussion is that there is no indication of an association but that continuous collection of patient information is important as are more experimental studies, which need to be performed with sound scientific technology. The clinical recommendation is that incretin therapy should be avoided in patients who have a history of acute pancreatitis and if acute pancreatitis develops in a patient who is treated with incretin therapy, the therapy should be stopped.

Previous rodent data have also suggested that GLP-1 receptor agonists may be associated with medullary thyroid carcinoma [68]. However, this has not been observed in other animal species or humans. This may be explained by these species' (including human) C cells having a much lower expression of GLP-1 receptors than rodent C cells [69]. Therefore, also for medullary thyroid carcinoma, there is no indication of any association with GLP-1 receptor agonists, but due to the indication of an association in rodents, for safety reasons, patients with a genetic predisposition to medullary thyroid carcinoma should not be prescribed GLP-1 receptor agonists.

Cardiovascular effects

It is well known that hyperglycemia is associated with cardiovascular diseases and it may, therefore, be expected that a reduction in glycemia by GLP-1 receptor agonists will improve cardiovascular complications in Type 2 diabetics. GLP-1 receptor agonists may also have other effects, which may add to the potential beneficial cardiovascular effects of the reduction in glycemia. Thus, they slightly reduce blood pressure, blood lipids and also reduce bodyweight. Furthermore, GLP-1 has been shown to have beneficial effects on the heart and endothelial cells [70]. Therefore, there is a potential for GLP-1 receptor agonists to have beneficial effects on cardiovascular outcomes beyond what would be expected from the reduction in glycemia. At present, meta-analyses have shown that there is

no detrimental effect of GLP-1 receptor agonists [71], and further studies are required for analyses of any potential beneficial effect. Several cardiovascular outcome trials with GLP-1 receptor agonists are ongoing (Table 3). These studies have different lengths, different sizes, and different designs and protocols, but altogether enroll almost 40,000 patients and will give valuable information on the cardiovascular and other long-term effects of treatment with GLP-1 receptor agonists in patients with Type 2 diabetes.

Clinical positioning

An important positioning of GLP-1 receptor agonists is as an add-on to metformin in patients with insufficient glycemic control when treated with metformin alone, in association with lifestyle changes, particularly in patients with obesity. As an add-on to metformin, GLP-1 receptor agonists have advantages over sulfonylureas by avoiding weight gain and having the very low risk of hypoglycemia.

GLP-1 receptor agonists have also been shown to be effective as add-ons to insulin in patients treated with metformin and insulin as well as in those where glycemic control is insufficient [72]. The reason for this is that adding GLP-1 receptor agonists to insulin will further reduce HbA1c but with a lower risk for hypoglycemia than if the insulin dosage is increased in combination with a prevented increase in bodyweight. Several studies have verified that GLP-1 receptor agonists in combination with basal insulin reduce HbA1c further than continuing on basal insulin, and that this is seen without an increased risk for hypoglycemia, prevention of the weight gain induced by insulin, and allows a reduction in the insulin dose. This has been shown for exenatide b.i.d. [73] and lixisenatide [44,45] when added to basal insulin, and, in reverse, by liraglutide when basal insulin was added to liraglutide [74]. When combining with insulin, it may be important

that the continuous GLP-1 receptor activators may be preferable when the target for fasting glucose is not reached with insulin therapy. By contrast, intermittent activating GLP-1 receptor agonists may be preferable when the target for fasting glucose is reached by insulin but still the HbA1c target is not reached, due to a persistent high postprandial glucose [17].

In most clinical guidelines, incretin therapy is placed as an add-on to metformin in patients in whom metformin alone is insufficient for glycemic control, and some guidelines, in addition, include incretin therapy as part of a triple therapy. This was clearly seen in the recent joint American Diabetes Association/EASD position statement on glucose-lowering therapy in Type 2 diabetes, which was published in 2012 [75]. The reason why incretin therapy previously was not introduced earlier in guidelines has been due to the desire to observe the long-term outcome of the therapies as well as the higher price of incretin therapy in comparison with the other therapies (e.g., sulfonylurea). Since now, however, the long-term experience is accumulating; there is currently an increasing interest in introducing incretin therapies at earlier stages than in previous guidelines. Furthermore, with regards to the cost for compounds within the incretin therapy class of drugs, it should be emphasized that health economy studies need to be performed in more detail and not only the cost of the compound should be taken into consideration. Thus, the cost of other aspects of therapy, such as the cost of hospital admissions and hypoglycemia, which may be lower during incretin-based therapy, needs to be accounted for.

It has been discussed whether it is possible to predict the response to GLP-1 receptor agonists – that is, whether it would be possible to identify patients with particularly high or low rates of response. If that were the case, more optimized individualized therapy would be a possibility. Apart from the result that HbA1c

Table 3. Ongoing long-term cardiovascular outcomes trials with GLP-1 receptor agonists.

Study name	GLP-1 receptor agonist	Patients (n)	Start of study (year)	Expected end of study (year)	Ref.
EXSCEL	Exenatide QW	9800	2010	2017	[103]
LEADER	Liraglutide	8750	2010	2016	[104]
ELIXA	Lixisenatide	6000	2010	2014	[105]
REWIND	Dulaglutide	9600	2011	2019	[106]
SUSTAIN™ 6	Semaglutide	3260	2013	2016	[107]

QW: Once weekly.

reduction is better if baseline HbA1c is higher, it has, however, been difficult to identify a prediction factor; age, duration of diabetes and body-weight do not seem to affect the outcome of clinical studies. One interesting recent finding in Japanese patients, however, was that β -cell function may predict the clinical response to liraglutide as evident by analyzing the C-peptide response to intravenous glucagon before initiation of therapy [76], and, similarly, that a low increment in C-peptide during a glucagon stimulation test predicted a poor outcome when switching from insulin therapy to liraglutide [77]. Another interesting observation has been that Asian patients with Type 2 diabetes may respond better to therapy with GLP-1 receptor agonists than patients of other ethnic origins, as suggested from a review of effects of liraglutide in global studies [78]. These aspects of potential individualization need to be confirmed and studied in more detail.

Conclusion & future perspective

GLP-1 receptor agonists have been on the market of glucose-lowering therapies for several years and have been used extensively. There are exciting future prospects for this therapy and these may be important from several viewpoints. One important future aspect of the GLP-1 receptor agonists is a growing experience of the agonists with more long-term follow-up documentation of durability and long-term safety. Another is the development of more long-term GLP-1 receptor agonists, particularly those with long (weekly) duration. A third development is an increased

use of GLP-1 receptor agonists in combination with basal insulin therapy, instead of introducing meal-time insulin. A fourth development is the potential of using incretin therapy beyond its glucose-lowering action in Type 2 diabetes. Thus, it has been suggested that GLP-1 receptor agonists may also be used in complications, including liver steatosis, in Type 2 diabetes with effects beyond the glucose-lowering action [79]. Since GLP-1 is a powerful inhibitor of glucagon secretion and hyperglucagonemia is seen also in Type 1 diabetes, incretin therapy may also be used in Type 1 diabetes [80]. Furthermore, GLP-1 receptor agonists may be used as a therapy for obesity without diabetes [81], heart failure or acutely after myocardial infarction [82], as a therapy for neurodegenerative disorders [83] or psoriasis [84]. Therefore, overall, we may be expecting an exciting future development of incretin therapy [85].

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