Treatment with GLP-1 Receptor Agonists 20

Sten Madsbad and Jens J. Holst

Contents

S. Madsbad (✉)
Department of Endocrinology, Hvidovre Hospital, University of Copenhagen, Copenhagen, Denmark

The NNF Center for Basic Metabolic Research and the Department of Medical Sciences, Panum Instituttet, University of Copenhagen, Copenhagen, Denmark
e-mail: sten.madsbad@regionh.dk

J. J. Holst
The NNF Center for Basic Metabolic Research and the Department of Medical Sciences, Panum Instituttet, University of Copenhagen, Copenhagen, Denmark
e-mail: jjholst@sund.ku.dk

E. Bonora, R. A. DeFronzo (eds.), *Diabetes Epidemiology, Genetics, Pathogenesis, Diagnosis, Prevention, and Treatment*, Endocrinology,
https://doi.org/10.1007/978-3-319-45015-5_20

Abstract

The GLP-1 RAs have become popular because of their efficacy and durability in relation to glycemic control and their low risk of hypoglycemia in combination with weight loss in most patients. GLP-1 RAs mimic the effects of native GLP-1, which increases insulin secretion, inhibits glucagon secretion, increases satiety, and slows gastric emptying. Notably, the insulinotropic and glucagonostatic effects are glucose dependent, and therefore the risk of hypoglycemia is very low during treatment with a GLP-1 RA. The effect on gastric emptying is primarily observed with the short-acting GLP-1 RAs, since significant tachyphylaxis for this effect develops after few days' treatment with the long-acting GLP-1 RAs. The postprandial glucose control mediated by the short-acting GLP-1 RA seems to be primarily explained through the delaying effect on gastric emptying rather than the effect on insulin and glucagon secretion. In addition, GLP-1 RAs reduce blood pressure during chronic treatment, increase pulse rate, and reduce postprandial triglyceride concentrations. Studies have suggested that GLP-1 receptor agonists might have neuroprotective effects.

The most common adverse events are nausea and other gastrointestinal discomfort. The drawbacks of the GLP-1 RAs include the subcutaneous administration, the gastrointestinal side effects, and the cost.

Several GLP-1 RAs are now licensed for the treatment of type 2 diabetes. However, the intra-class difference raises challenges in relation to individual treatment. In the present chapter, the individual GLP-1 RAs will be presented followed by a head-to-head comparison of GLP-1 RAs. Thereafter, the adverse events and the cardiovascular effects of GLP-1 RAs including the cardiovascular endpoint trials with GLP-1 RAs will be discussed. The efficacy and safety of fixed combination of basal insulin and a GLP-1 RA will be reviewed. The use of GLP-1 RAs in the treatment of patients with type 1 diabetes or in treatment of obesity will also be examined.

Keywords
GLP-1RA · Type 2 diabetes · Type 1 diabetes · Obesity, fixed combination · Head-to-head comparison · Adverse events · Cardiovascular effects

The use of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) has expanded the treatment options for type 2 diabetes (T2DM) over the last decade (Garber et al. 2016; Inzucchi et al. 2015). The GLP-1 RAs have become popular because of their efficacy and durability in relation to glycemic control and their low risk of hypoglycemia in combination with weight loss in most patients (Ostergaard et al. 2016; Meier 2012). GLP-1 RAs mimic the effects of native GLP-1, which increases insulin secretion, inhibits glucagon secretion, increases satiety, and slows gastric emptying (Ostergaard et al. 2016; Meier 2012). Notably, the insulinotropic and glucagonostatic effects are glucose dependent, and therefore the risk of hypoglycemia is very low during treatment with a GLP-1 RA, unless it is combined with sulfonylurea or insulin (Ostergaard et al. 2016; Meier 2012; Nauck et al. 1993). The effect on gastric emptying is primarily observed with the short-acting GLP-1 RAs, since significant tachyphylaxis for this effect develops after few days' treatment with the long-acting GLP-1 RAs (Jelsing et al. 2012; Meier et al. 2003). The postprandial glucose control mediated by the short-acting GLP-1 RA seems to be primarily explained through the delaying effect on gastric emptying rather than the effect on insulin and glucagon secretion (Meier et al. 2003). In addition, GLP-1 RAs reduce blood pressure during chronic treatment, increase pulse rate, and reduce postprandial triglyceride concentrations (Drucker 2016; Hermansen et al. 2013; Kumarathurai et al. 2017a). The potential effect of GLP-1 on cardiovascular function is an area of major interest and will be discussed in detail later in this chapter. Whether treatment with a GLP-1 RA may protect the beta-cell mass through beta-cell regeneration and inhibition of apoptosis and thereby reduce or halt the progression of type 2 diabetes has been debated (Kielgast et al. 2009). In one study, beta-cell function was evaluated after 3 years of treatment with a short-acting GLP-1 RA (exenatide), and during this period there was no deterioration, but the same was true in the control group subjected to intensive insulin therapy (Bunck et al. 2011). In the LEADER study of the cardiovascular safety of liraglutide, hemoglobin A1c levels remained almost unchanged over a period of 5 years, perhaps reflecting some protective action on the beta cells (Marso et al. 2016a). Studies in rodent models of Parkinson's and Alzheimer's diseases and mouse models of ischemic stroke have suggested that GLP-1 receptor agonist might have neuroprotective effects and prevent memory impairment (McClean et al. 2011; Harkavyi et al. 2008; Teramoto et al. 2011). However, studies in humans have not supported the use of GLP-1 RA in cerebral diseases (Calsolaro and Edison 2015), except for one clinical trial of 48 weeks, which suggested that exenatide once weekly had positive effects in Parkinson's disease, which was sustained beyond the period of exposure (Athauda et al. 2017). Whether exenatide affects the underlying disease pathophysiology or the result simply is secondary to long-lasting metabolic improvement effects is uncertain.

The most common adverse events are nausea and other gastrointestinal discomfort (Ostergaard et al. 2016; Meier 2012). The drawbacks of the GLP-1 RAs include the subcutaneous administration, the gastrointestinal side effects, and the cost (Ostergaard et al. 2016).

As a drug class, the GLP-1 RAs have proven efficacy for lowering HbA1c and decreasing weight in T2D, with a reduced risk of hypoglycemia compared with insulin or sulfonylureas (Garber et al. 2016; Inzucchi et al. 2015; Ostergaard et al. 2016). These characteristics underlie the inclusion of GLP-1 RAs in various clinical practice guidelines. Their use as dual therapy with metformin after first-line metformin and as triple therapy (in combination with metformin and a sulfonylurea/thiazolidinedione/insulin) is part of the European Association for the Study of Diabetes/American Diabetes Association recommendations (Inzucchi et al. 2015). Glucagon-like peptide-1 receptor agonists are recommended as monotherapy, dual therapy, and triple therapy by the American Association of Clinical Endocrinologists/American College of Endocrinology guidelines (Garber et al. 2016).

In the present chapter, the individual GLP-1 RAs will be presented followed by a head-to-head comparison of GLP-1 RAs. Thereafter, the adverse events and the cardiovascular effects of GLP-1 RAs including the cardiovascular endpoint trials with GLP-1 RAs will be discussed. The efficacy and safety of fixed combination of basal insulin and a GLP-1 RA will be reviewed. The use of GLP-1 RAs in the treatment of patients with type 1 diabetes or in treatment of obesity will also be examined. Lastly, some future aspects of GLP-1-based therapy will be presented. A thorough review of all trials with GLP-1 RAs in type 2 and type 1 diabetes up to 2016 can be found in Ostergaard et al. (2016), Dejgaard et al. (2016a), and Frandsen et al. (2016).

Characteristics of GLP-1 Receptor Agonists

For therapeutic purposes, continuous subcutaneous administration of native GLP-1 is necessitated because of its extremely short plasma half-life (1–2 min) but has limited therapeutic value (Zander et al. 2002). Therefore, several GLP-1 RAs have been developed with an extended duration of action achieved by various changes of the molecular structure compared with the native peptide (Ostergaard et al. 2016; Madsbad et al. 2011; Madsbad 2016).

Six GLP-1 RAs are currently (2017) approved in Europe and the USA. GLP-1 RAs differ substantially in their molecular structures and sizes, chemical and physiological properties, and duration of action (Table 1; Madsbad 2016). Exenatide (Byetta®), administered twice daily (BID), and lixisenatide (Lyxumia®), administered once daily (QD), are short-acting agents based on the structure of the lizard peptide exendin-4. Liraglutide (Victoza®) is based on the GLP-1 structure, classified as long-acting, and is administered QD, while the very long-acting agents, including exenatide long-acting release (LAR) (Bydureon®), albiglutide (Eperzan® and Tanzeum®), and dulaglutide (Trulicity®), are administered once weekly (QW) (Madsbad 2016). A number of important studies have been reported using another

Table 1 Comparative characteristics of the GLP-1 RAs

	Exenatide BID	Exenatide QW	Liraglutide	Lixisenatide	Albiglutide	Dulaglutide	Taspoglutide
Percentage amino acid sequence similarity to native GLP-1	53%	53% [	97%	≈50%*	95%	90%	93%
Properties of the drug	Resistant to DPP-4 cleavage, largely due to the substitution of alanine in position 2 by glycine	Encapsulated in biodegradable polymer microspheres	C-16 fatty acid confers albumin binding and heptamer formation	Based on exenatide but is modified by the deletion of one proline residue and addition of six lysine residues at the C-terminal	GLP-1 dimer fused to albumin	The GLP-1 portion of the molecule is fused to an IgG4 molecule, limiting renal clearance and prolonging activity	Modifications designed to hinder cleavage by DPP-4 and by serine proteases and also allows greater receptor binding
Half-life	2.4 h	Half-life is unpublished but steady-state concentrations at 6–7 weeks	11–15 h	2.7–4.3 h	6–8 days	≈5 days	165 h
T_{max}	2.1 h	2.1–5.1 h during the first 48 h	≈9–12 h	1.25–2.25 h	72–96 h	24–72 h	4, 6, and 8 h at 1, 8, and 30 mg doses, respectively
Clearance	9.1 l/h	Unpublished	1.2 l/h	21.2–28.5 l/h	67 ml/h	0.75 mg and 1.5 mg at steady state was 0.073 and 0.107 l/h, respectively	Unpublished

(*continued*)

Table 1 (continued)

	Exenatide BID	Exenatide QW	Liraglutide	Lixisenatide	Albiglutide	Dulaglutide	Taspoglutide
Antibody formation	In head-to-head studies, antibodies were more common, and titers were higher with exenatide OW compared with exenatide BID Antibodies did not correlate with rates of reported AEs		From six phase 3 studies, 8.7 and 8.3% of participants had low-titer antibodies to liraglutide 1.2 and 1.8 mg, respectively, after 26 weeks	Antibodies developed in: 56–60% of participants treated with 20 μg OD 43% of participants treated with 10 μg OD and 71% treated with 20 μg BID	Antibodies developed in 3.7% of participants treated with albiglutide	Dulaglutide anti-drug antibodies in 1% of participants and dulaglutide neutralizing anti-drug antibodies in 1% of patients	Detected in 49% of participants

AE adverse event, *BID* twice daily, *DPP-4* dipeptidyl peptidase-4, *GLP-1* glucagon-like peptide-1, *GLP-1 RA* GLP-1 receptor agonist, *IgG4* immunoglobulin 4, *OD* once daily, *OW* once weekly, T_{max} time to maximum plasma concentration

agonist for weekly use, namely, semaglutide, which is structurally related to liraglutide (Lau et al. 2015; Nauck et al. 2016a).

One method to extend the half-life of GLP-1 has been to make it resistant to degradation by DPP-4 by changing the penultimate N-terminal amino acid (Gallwitz et al. 2000). However, the intact hormone is still subject to renal elimination, which alone results in a half-life of 4–5 min (Deacon et al. 1998; Meier et al. 2004). Therefore, other approaches to prolong half-life have been based on reversible or irreversible binding to albumin (liraglutide, semaglutide, and albiglutide), whereby renal filtration is prevented (Meier 2012). Dulaglutide is conjugated with the Fc fragment of IgG to extend the duration of action (Meier 2012). The GLP-1 RA can also be coupled to biodegradable polymer microspheres resulting in a protracted release of the peptide from a subcutaneous depot as in exenatide-LAR (Bydureon) (Meier 2012).

Taspoglutide once weekly was halted in development due to serious hypersensitivity reactions and GI adverse events (AEs) during clinical trials (due to an inexpedient prolongation technique, resulting in an unsuitable plasma profile). Semaglutide once weekly is not yet approved for the treatment of people with type 2 diabetes but is expected in 2017. Therefore, the available data for these two compounds are included here to give a full picture of the GLP-1 RA family.

The different durations of action largely explain the variations among GLP-1 RAs with respect to their impact on fasting plasma glucose (FPG), 24-h glucose profiles, and postprandial plasma glucose (PPG) levels (Kapitza et al. 2013; Meier et al. 2015). Delayed gastric emptying, for example, is more strongly associated with short-acting than longer-acting GLP-1 RAs (Figs. 1 and 2), and this probably explains the greater effects on PPG observed with short-acting GLP-1 RAs. Conversely, the greater half-lives of the longer-acting compounds allow for enhanced effects on the average 24-h glucose level, including FPG (Kapitza et al. 2013; Meier et al. 2015). Longer-acting GLP-1 RAs affect gastric motility to a limited extent. Instead, longer-acting GLP-1 RAs exert more of their effect via the pancreas, increasing insulin secretion and inhibiting glucagon secretion (Kapitza et al. 2013; Meier et al. 2015).

The chemical and pharmacokinetic differences between GLP-1 RAs are also reflected in their varying efficacy with regard to HbA1c reduction and weight loss, their differing tolerability profiles, and potential for immunogenicity (Ostergaard et al. 2016; Meier 2012; Madsbad et al. 2011; Madsbad 2016; Kapitza et al. 2013; Meier et al. 2015). It is important to understand these specific characteristics to make the appropriate choice of GLP-1 RA for the individual patient. Head-to-head clinical trials are the best way to evaluate the differences in efficacy and tolerability, and a number of such studies have been conducted with GLP-1 RAs in T2D, but first the eight GLP-1 RAs will be discussed. The GLP-1 RA family is presented in Fig. 1, and the differences in molecular structure, chemical and physiological properties, and durations of action are summarized in Table 1.

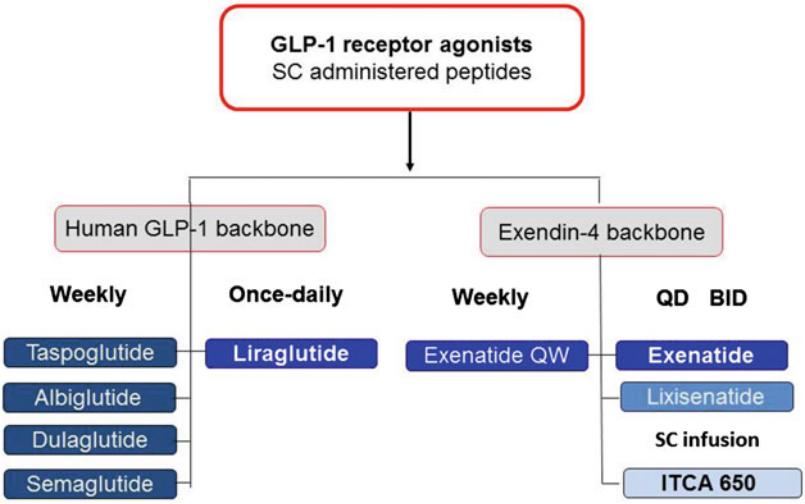

Fig. 1 Shows the glucagon-like peptide-1 receptor agonists, which have already been approved, except for taspoglutide, which was halt in phase 3 development and ITCA 650, which is in phase 3 development. The agonists are subdivided in relation to whether the backbone of the compound is human GLP-1 or exenatide and in relation to the frequency of administration (once weekly, or once daily or twice daily). ITCA is a mini-pump, which infused exenatide for 3–12 months per pump (Fig. 2)

Exenatide Twice Daily

Exenatide (Byetta®), which is a 39-amino-acid peptide, was the first GLP-1 RA introduced to the market (2005). Exenatide BID is derived from the saliva of the Gila monster and is 53% homologous to native GLP-1 with respect to the first 30 amino acids (the sequence of the remaining 9 has no human homologies) (Kolterman et al. 2005). Exenatide BID is indicated as adjunct to diet and exercise in patients with type 2 diabetes. It can be used in monotherapy or in combination with oral antidiabetic agents including basal insulin. After injection, the duration of action is about 8–10 h, and peak levels are achieved 2–3 h after injection (Kolterman et al. 2005). Injection should be administered 20–60 min prior to two main meals at least 6 h apart. The delayed gastric emptying after breakfast and dinner is the main mechanism by which exenatide improves postprandial glucose excursions. Exenatide has only minor effect on lunch glucose excursions. The increase in insulin secretion and reduction in glucagon secretion, which result in a decreased hepatic glucose production, also contributes to the improved glucose metabolism (Cervera et al. 2008), but the effect on fasting plasma glucose is less than that of the long-acting GLP-1 RAs (Buse et al. 2009). Initial dose is 5 μg, increasing to 10 μg BID. Exenatide is not recommended in patients with severe renal impairment (eGFR<30 ml/min). The phase 3 studies are discussed in details in Inzucchi et al. (2015). Exenatide BID has demonstrated similar efficacy as glimepiride or pioglitazone with a reduction of

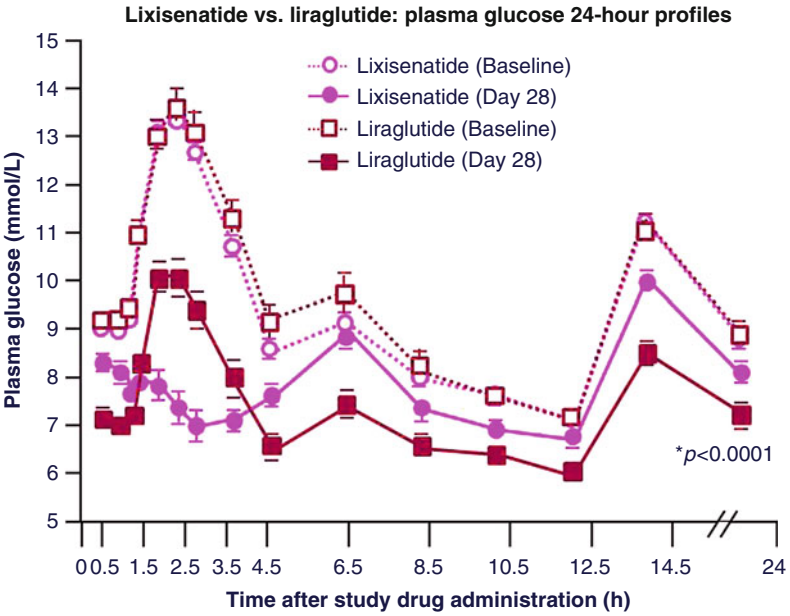

Fig. 2 Mean 24-h postprandial plasma glucose at baseline and after 28 days treatment with the short-acting lixisenatide once daily compared with the longer-acting once-daily liraglutide. With lixisenatide postprandial glucose is lower during breakfast, while during liraglutide treatment plasma glucose is lower from lunch and during the rest of the 24 h

0.8–1.5% in HbA1c and induces a weight loss ranging from 1 to 4 kg (Ostergaard et al. 2016). Compared with basal insulin, the reduction in HbA1c is similar or greater with exenatide BID (Ostergaard et al. 2016). Nausea occurs initially in 30–60% of patients with vomiting in about 15–20% (Ostergaard et al. 2016). The gastrointestinal side effects are often transient. Antibodies against exenatide have been detected in 40–60% of the patients, but in the majority of the patients, their presence does not seem to impair efficacy of exenatide (Buse et al. 2011; Drucker et al. 2008). In patients with very high titers of antibodies, the reduction in HbA1c was smaller compared with patients without antibodies (Buse et al. 2011; Drucker et al. 2008). Apparently, the antigenicity of exenatide has not lead to major clinical complications so far.

Lixisenatide Once Daily

Lixisenatide is identical to exendin-4 but has a proline deletion in position 38 and is extended with six lysine residues at the C-terminus (Ratner et al. 2010). The half-life is 2–3 h, and peak plasma concentrations are achieved 1.5–2.5 h after injection, similar to exenatide, but lixisenatide is nevertheless approved for s.c. administration once daily (Ratner et al. 2010). The dose is 10 μg increasing to 20 μg after 2 weeks.

The efficacy of lixisenatide has been tested in monotherapy and in combination therapy and has been compared with placebo and exenatide BID (Bolli et al. 2014; Fonseca et al. 2012; Rosenstock et al. 2013a, 2014a; Pinget et al. 2013). Compared with exenatide, the mean change in HbA1c was −0.79% for lixisenatide versus −0.96% for exenatide BID (Rosenstock et al. 2013a). Both agents induced weight loss (from 94.5 to 91.7 kg and from 96.7 to 92.9 kg with lixisenatide and exenatide, respectively) (Rosenstock et al. 2013a). Incidence of adverse events (AEs) was similar for lixisenatide and exenatide. Lixisenatide has been added on to insulin in Asian people, and after 24 weeks, the HbA1c changes were −0.77% and +0.11% in the lixisenatide and placebo groups (Seino et al. 2012). A weight loss of 0.4 kg was observed in the lixisenatide group, while a weight gain of 0.1 kg was found in the placebo group. In another 24 weeks study, the reductions in HbA1c were −0.6% and −0.3% and in body weight −1.8 versus −0.5 kg in the lixisenatide and placebo groups, respectively (Riddle et al. 2013). Because of the short action, the effect on fasting plasma glucose is less than with the long-acting GLP-1 RAs (Nauck et al. 2016b). In most of the trials, body weight decreased significantly with lixisenatide compared with placebo. The cardiovascular endpoint trial ELIXA with lixisenatide will be discussed later.

Liraglutide Once Daily

The amino acid sequence of liraglutide shows 97% identity with that of native human GLP-1, and liraglutide has a half-life of approximately 13 h; therefore, it is suitable for subcutaneous administration once daily (Agerso et al. 2002). The peptide differs from GLP-1 owing to a Lys34Arg amino acid substitution and addition of glutamate residue and a 16-carbon free fatty acid to Lys26, modifications that promote non-covalent binding to plasma albumin (Knudsen et al. 2000). Consequently about 99% of the liraglutide molecules are bound to albumin, ensuring a rather constant, high plasma level after once-daily administration (Knudsen et al. 2000).

Dose-finding studies resulted in the doses of 0.6 mg, 1.2 mg, and 1.8 mg being moved forward to the clinical phase 3 development program "Liraglutide Effect and Action in Diabetes" (LEAD™), completed in 2007 (Ostergaard et al. 2016; Madsbad 2009). Treatment is initiated with 0.6 mg for 1 week and then titrated to the standard dose of 1.2 mg, which can be escalated to 1.8 mg once daily (Ostergaard et al. 2016; Madsbad 2009).

In the phase 3 program, the HbA1c reduction was 1.1–1.8% with only minor differences between 1.2 and 1.8 mg, but there was little effect on postprandial glucose excursions during chronic therapy, probably because of the tachyphylaxis with respect to gastric emptying (Ostergaard et al. 2016; Madsbad 2009). The reduction in mean body weight was in the range of 2–3 kg in the LEAD studies (Ostergaard et al. 2016; Madsbad 2009). The effect on body weight seems to be dose dependent, but the greatest mean weight loss of 4.5 kg was observed in subjects with a BMI > 35 kg/m2 and when liraglutide was combined with metformin (Ostergaard et al. 2016; Madsbad 2009). Liraglutide reduced systolic blood pressures by about

2–7 mm HG, and increases in pulse rate of 2–4 beat per minutes were reported (Ostergaard et al. 2016; Madsbad 2009). As discussed later, liraglutide therapy has been associated with reduced risk of cardiovascular events and mortality (Marso et al. 2016a). Nausea was reported by 20–40% of the patients and vomiting in 5–10%, but both were generally transient and could be reduced by slow up-titration (Ostergaard et al. 2016; Madsbad 2009). The number of patients developing antibodies against liraglutide is about 3–10% (Ostergaard et al. 2016; Madsbad 2009).

Liraglutide has been compared with all oral antidiabetic agents and with basal insulin glargine and showed better efficacy with respect to both reduction in HbA1c and weight loss (Ostergaard et al. 2016; Madsbad 2009). As discussed later, liraglutide has also been compared with lixisenatide, exenatide BID, exenatide QW, and dulaglutide QW (Ostergaard et al. 2016; Madsbad 2016, 2009; Nauck et al. 2016b).

Exenatide Once Weekly

Exenatide administered once weekly (QW) (2 mg/dose) was marketed in Europe in 2011 and in the USA in 2012. The drug, in a fixed dose of 2 mg, is encapsulated in biodegradable microspheres (0.06 mm in diameter), allowing the drug to be slowly released through diffusion and microsphere breakdown gradually over 10 weeks (Drucker et al. 2008; Mann and Raskin 2014). The microspheres are reconstituted in a premeasured aqueous solution before injection. The plasma concentration continues to rise for weeks after treatment initiation, and steady-state levels are obtained after 6–7 weeks (Drucker et al. 2008; Mann and Raskin 2014). The gradual release from the formulation eliminates the need for slow up-titration. The main results of the phase 3 DURATION 1–6 trials are discussed in Ostergaard et al. (2016) and Brunton and Davidson (2016). Exenatide QW has been compared with exenatide BID, liraglutide, insulin glargine, and oral antidiabetic agents, and the HbA1c reduction ranges between 1.3% and 1.9% (Ostergaard et al. 2016; Brunton and Davidson 2016). In a head-to-head comparison, the HbA1c reduction was significantly greater (1.9% vs. 1.5%) with exenatide QW compared with exenatide BID, primarily explained by a greater reduction in plasma glucose during nighttime, while postprandial glucose excursions were more reduced with exenatide BID (Drucker et al. 2008). The increase in morning pulse rate was also greater with exenatide QW compared with exenatide BID (Drucker et al. 2008). The reduction in weight did not differ between the short- and long-acting exenatide. More patients developed antibodies against exenatide QW than against exenatide BID (74% vs. 43%), but only in few patients did the antibodies seem to affect efficacy in relation to HbA1c reduction (Drucker et al. 2008). Compared with liraglutide 1.8 mg once daily, the reduction was less (1.48% vs. 1.28%), and patients treated with liraglutide lost more weight than exenatide QW-treated patients (Buse et al. 2013). More patients experienced nausea with liraglutide, while serious adverse events were more often reported with exenatide QW (Buse et al. 2013). Compared with insulin glargine, the reduction in HbA1c was greater with exenatide QW (1.5% vs. 1.3%), and most patients

experienced weight loss in contrast to weight gain during treatment with insulin glargine (Diamant et al. 2014). Hypoglycemia occurred more often with insulin glargine. In a recent trial exenatide once weekly was compared with dapagliflozin (DURATION-8) as add-on to metformin, and after 28 weeks the reduction in HbA1c was 1.6% and 1.4%, respectively, while the reduction was 2.0% in the combined exenatide plus dapagliflozin group (Frias et al. 2016). Weight loss was greater with dapagliflozin compared with exenatide once weekly (2.2 kg vs. 1.5 kg) compared with 3.4 kg in the combined group (Frias et al. 2016).

Because of the consistency of the injection suspension, injections of exenatide previously required a rather large-bore needle (23 gauge, 0.64 mm), and a convenient device was not available. Today, exenatide QW is available in a new, prefilled single-dose pen device, which simplifies reconstitution of the drug. Injection site reactions including erythema, pruritus, and nodules are being reported by about 10–15% of patients (Brunton and Davidson 2016). The most frequent gastrointestinal side effects are the expected: nausea, vomiting, and diarrhea, which, however, occur less frequently than with exenatide BID (Drucker et al. 2008). No cases of pancreatic cancer were reported in the DURATION trials, and exenatide QW was not associated with an increased risk of pancreatitis (Brunton and Davidson 2016). The cardiovascular safety of exenatide QW will be discussed later in relation to the EXSCEL trial.

Albiglutide Once Weekly

Albiglutide is composed of two DPP-4-resistant GLP-1 molecules arranged in tandem and fused to human albumin, which consequently leads to a plasma half-life of 5–8 days, allowing QW dosing. Maximal concentration is observed 3–5 days after s.c. injection (Young et al. 2014). An amino acid substitution (alanine to glycine at residue no 2 from the N-terminus) in the GLP-1 dimer makes it resistant to DPP-4 degradation (Young et al. 2014). Otherwise the two GLP-1 moieties are 97% homologous to native GLP-1 (Young et al. 2014). Albiglutide is a large molecule and is thus relatively inaccessible to the central nervous system; this quality may have implications for gastrointestinal tolerability of the drug and for weight loss. The European Medicines Agency (EMA) and US Food and Drug Administration (FDA) approved albiglutide in 2014. Studies comparing different dosing regimens have suggested that a dose of 30 mg once weekly might be optimal. For patients unable to reach glycemic goal, escalating to 50 mg weekly is appropriate and results in further improvement in glycemic control. The efficacy and safety of albiglutide were tested in the phase 3 HARMONY 1–8 program, and the main results are presented in Ostergaard et al. (2016), Madsbad et al. (2011), Madsbad (2016), and Blair and Keating (2015). The reduction in HbA1c and weight has been less, and rates of gastrointestinal side effects are also reduced compared to other GLP-1 RAs (Ostergaard et al. 2016; Madsbad et al. 2011; Madsbad 2016; Blair and Keating 2015). In the HARMONY 4 study, albiglutide was compared with insulin glargine and gave a reduction of HbA1c of 0.66 versus 0.81 for albiglutide and insulin

glargine, respectively, with an additional small weight loss in the albiglutide group (Ostergaard et al. 2016; Weissman et al. 2014). Compared with liraglutide in the HARMONY 7 trial, the reduction in HbA1c was 0.78% for albiglutide and 0.99% for liraglutide, and liraglutide was also associated with a greater weight loss (Pratley et al. 2014). More gastrointestinal side effects were reported with liraglutide (Pratley et al. 2014). In the HARMONY 6 trial, including patients taking basal insulin, albiglutide add-on was tested versus thrice-daily prandial insulin lispro (Rosenstock et al. 2014b). After 26 weeks, the reduction in HbA1c was 0.82% with albiglutide and 0.66% with lispro, and the weight changes were −0.73 kg and +0.81 kg, respectively (Rosenstock et al. 2014b).

Albiglutide has been associated with up to a 20% incidence of injection site reaction, and antibodies against albiglutide developed in up to 5.5% of patients but had no obvious effect on the efficacy of albiglutide (Blair and Keating 2015). On July 26, 2017, GlaxoSmithKline (GSK) in a press release announced that they plan to discontinue the manufacturing and sale of albiglutide by July 2018.

Dulaglutide Once Weekly

Dulaglutide is a GLP-1 RA constructed by two GLP-1 analogues linked to a human IgG4-Fc heavy chain (Barrington et al. 2011). The association with the IgG4-Fc heavy chain prevents renal clearance (Barrington et al. 2011; Glaesner et al. 2010), and the molecule is resistant to DPP-4 degradation because of amino acid substitutions at position 2 of the GLP-1 parts; additional substitutions are present at positions 8 and 22 (Barrington et al. 2011; Glaesner et al. 2010). The half-life is approximately 5 days, making it suitable for QW administration (Barrington et al. 2011; Glaesner et al. 2010). Dulaglutide was approved in the USA and in Europe in 2014. Dulaglutide is administered as 0.75 mg once weekly, which can be escalated to 1.5 mg once weekly (Barrington et al. 2011). Steady-state concentration is obtained after 2–4 weeks (Barrington et al. 2011; Jendle et al. 2016). Dulaglutide is available as a prefilled pen syringe ready for injection. Across the clinical studies, about 1.6% of dulaglutide-treated patients developed antibodies, which did not reduce the glucose-lowering effect (Jendle et al. 2016). Injection site reactions (rash and erythema) were reported in 0.5% of the patients (Jendle et al. 2016). Dulaglutide's efficacy and safety has been tested in a variety of phase 3 trials known as the AWARD-studies, and the findings are reviewed in Jendle et al. (2016). Dulaglutide has been found to reduce HbA1c more than sitagliptin, metformin, and exenatide BID, while weight reduction and gastrointestinal side effects did not differ between dulaglutide and exenatide (Jendle et al. 2016). Dulaglutide 1.5 mg reduced HbA1c (−0.9% vs. −0.62%) more than insulin glargine (Jendle et al. 2016). In the AWARD-6 trial comparing dulaglutide with liraglutide, the HbA1c reduction was 1.42% with dulaglutide and 1.36 for liraglutide, while patients treated with liraglutide experienced a significantly greater weight loss (3.61 vs. 2.90 kg). The incidence of adverse events did not differ between the two groups (Jendle et al. 2016; Dungan et al. 2014). In AWARD-10 dulaglutide 1.5 mg and 0.75 mg or placebo were add-on to SGLT-2 inhibitor with or without metformin for 24 weeks. The reduction in HbA1c was

for 1.5 mg −1.34 % (−14.7 mmol/mol) and for 0.75 mg −1.21% (−13.2 mmol/mol) compared with −0.54% (−5.9 mmol/mol) for placebo (Ludvig B et al. Lancet Diabetes Endocrinol 2018, Febr 23 epub ahead of print). Head- to head comparison between dulaglutide and semaglutide is discussed below under semaglutide.

Taspoglutide Once Weekly

The GLP-1 receptor agonist, taspoglutide, has 93% homology with the native hormone and contains two α-aminoisobutyric acid substitutions replacing Ala^8 and Gly^{35} of hGLP-1 (7–36)NH_2 (Dong et al. 2011). Taspoglutide is fully resistant to DPP-4 degradation, while protraction is provided by a sustained release formulation (Dong et al. 2011). Its biological actions have been shown to be similar to those of native GLP-1, but after a single dose, a glucose-lowering effect was found for up to 2 weeks.

Taspoglutide was evaluated in seven clinical trials in the T-emerge program using 10 and 20 mg once weekly (Madsbad et al. 2011). Both doses of taspoglutide reduced HbA1c more than exenatide BID (difference 0.33% for 20 mg) with comparable weight loss but with unacceptable levels of nausea/vomiting, injection site reactions, and systemic allergic reactions (Madsbad et al. 2011). Vomiting occurred in most cases on the day of injection in the taspoglutide groups and in the majority already after the first injection. In other trials, taspoglutide reduced HbA1c more than sitagliptin but had similar effects as pioglitazone and insulin glargine (Madsbad et al. 2011). In September 2010 the T-emerge program was halted because a potential association between hypersensitivity reactions and anti-drug antibodies was suggested, and taspoglutide is not expected to come to the market (Madsbad et al. 2011).

Semaglutide Once Weekly

Semaglutide was developed from liraglutide by increasing the albumin affinity and securing full stability against metabolic degradation. The fatty acid moiety and its linking to GLP-1 were the key features securing high albumin affinity and GLP-1 receptor (GLP-1R) potency and also resulted in a prolonged exposure and action of the GLP-1 analogue (Lau et al. 2015). Like liraglutide, semaglutide has an amino acid substitution at position 34 (Lys-Arg) and is derivatized at lysine 26 (Lau et al. 2015). An additional substitution at position 8 (Ala- > Aib) secures DPP-4 resistance. The GLP-1R affinity of semaglutide is similar to that of liraglutide, while the albumin affinity is improved (Lau et al. 2015). The plasma half-life is reported to be 165 h in human (Kapitza et al. 2015). Semaglutide is currently in late phase 3 clinical testing, and the first six trials have been presented in public. In a 12 weeks phase 2 study, semaglutide reduced HbA1c by impressive 1.7% from a baseline of 8.1% and body weight up to 4.8 kg, which was greater than with liraglutide 1.8 mg QD (Nauck et al. 2016a). Semaglutide doses of 0.5 mg and 1.0 mg with a 4-week dose escalation were selected for the SUSTAIN phase 3 program (Nauck et al. 2016a). In SUSTAIN-1, semaglutide

0.5 mg and 1.0 mg in patients with type 2 diabetes reduced HbA1c from a baseline of 8.1% by 1.4% and 1.5% compared with placebo after 30 weeks, and about 73% reached a HbA1c below 7.0% and 60% below 6.5% (Sorli et al. 2017). Weight loss was 2.8 and 3.6 kg greater than with placebo, respectively (Sorli et al. 2017). In the 56 weeks SUSTAIN-2 trial, semaglutide 0.5 mg and 1.0 mg reduced HbA1c by 1.3% and 1.6% versus 0.5% with sitagliptin (baseline, 8.1%). Weight losses were 4.3 kg, 6.1 kg, and 1.9 kg, respectively (Ahren et al. 2017). In the SUSTAIN-3, trial semaglutide was compared with exenatide QW (Ahmann Aj et al. Diabetes Care 2018; 41: 258–66). After 56 weeks, semaglutide 1.0 mg reduced HbA1c by 1.5% from a baseline HbA1c of 8.3%, compared with 0.9% with exenatide QW, and 67% versus 40% reached a HbA1c $<$ 7.0%, respectively. Weight losses were 5.6 kg and 1.9 kg, respectively. Gastrointestinal adverse events occurred in 42% and 33%, and injection site reactions were reported by 1.2% and 22%, respectively. In SUSTAIN-4, semaglutide was compared with insulin glargine in insulin-naïve patients. After 30 weeks, the reduction in HbA1c was 1.2%, 1.6%, and 0.8% from a baseline of 8.2% with 0.5 mg and 1.0 mg of semaglutide and insulin glargine, respectively (Aroda et al. 2017). Weight loss was 3.5 kg and 5.2 kg versus a weight gain of 1.2 kg with insulin glargine (Aroda et al. 2017). Risk of hypoglycemia was also reduced with semaglutide. Efficacy and safety of semaglutide versus placebo as add-on to basal insulin was investigated in SUSTAIN-5. After 30 weeks (baseline HbA1c 8.4%) 61% and 79% versus 11% with 0.5 mg, 1.0 mg, or placebo had achieved a HbA1c below 7.0%. Weight losses were 3.7 kg, 6.4 kg, and 1.4 kg, respectively. The cardiovascular endpoint study SUSTAIN-6 will be discussed later in this chapter (Marso et al. 2016b). The SUSTAIN-7 trial is a head-to-head comparison between semaglutide and dulaglutide as add-on to metformin during 40 weeks (Pratley RE et al. Lancet Diabetes Endocrinol 2018 Jan 31, Epub ahead of print). Patients in the 0.5 mg semaglutide group had a reduction in HbA1c of 1.5% against a 1.1% reduction in the 0.75 mg dulaglutide group. Additionally, 1.0 mg of semaglutide reduced HbA1c by 1.8% compared with a decrease by 1.4% among patients treated with 1.5 mg dulaglutide. Those on 0.5 mg semaglutide lost on average 4.6 kg of body weight compared to 2.3 kg with 0.75 mg dulaglutide. The higher doses led to losses of 6.5 kg and 3.0 kg, respectively. The side effects including changes in retinopathy did not differ between the two GLP-1 RAs.

Semaglutide has not yet been approved for treatment of type 2 diabetes. Overall, semaglutide seems at least as effective and possibly more potent than the other GLP-1 RAs. Safety profile of semaglutide did not differ from those reported with other GLP-1 RAs (Marso et al. 2016b; Sorli et al. 2017). In the SUSTAIN 6 trial semaglutide was associated with a significant increase in the risk of diabetic retinopathy (Marso et al. 2016b). In a post-hoc analyses of the SUSTAIN 6 data the increase in diabetic retinopathy was attributed to the magnitude and rapidly of HbA1c reduction during the first 16 weeks of treatment in patients who had pre-existing diabetic retinopathy and poor glycemic control at baseline, and who were treated with insulin (Vilsbøll T et al. Diabet Obes Metab 2018, 20: 889–97). In the SUSTAIN 1-5 trials there were no imbalance in diabetic retinopathy with semaglutide versus placebo (Vilsbøll T et al. Diabet Obes Metab 2018; 20: 889–97). Semaglutide is also in development as an obesity drug.

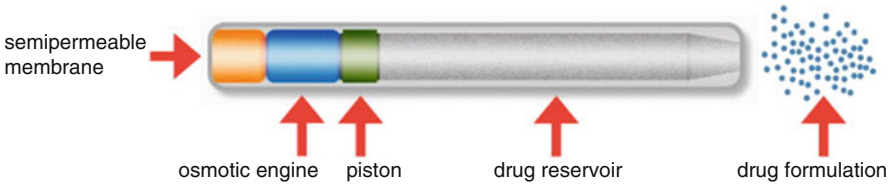

Fig. 3 ITCA 650 utilizes a novel drug delivery technology to provide continuous and controlled subcutaneous delivery of exenatide for as long as 1 year of treatment at a precise and predetermined rate. Initiating treatment with ITCA 650 involves the subcutaneous placement of a matchstick-sized osmotic mini-pump done during a short office procedure that can be performed by a physician, physician's assistant, or other licensed practitioner. ITCA 650 consists of a cylindrical titanium alloy reservoir with external dimensions of 4 mm in diameter by 44 mm in length. The reservoir is capped at one end by a controlled-rate, semipermeable membrane and capped at the other end by a diffusion moderator through which drug formulation is released from the drug reservoir. The drug formulation, piston, and osmotic engine are contained inside the cylinder. ITCA 650 releases drug at a predetermined rate based on the principle of osmosis. Water from the extracellular space enters through the semipermeable membrane directly into the osmotic engine that expands to drive the piston at a slow and consistent rate of travel

Intarcia (ITCA) 650

A new interesting concept is ITCA 650, which provides a constant and continuous subcutaneous delivery of exenatide via an osmotic mini-pump (the size of a matchstick, see Fig. 3) for treatment of patients with type 2 diabetes (Henry et al. 2013a, b, 2014). In the phase 3 FREEDOM program, which also includes a cardiovascular endpoint study, more than 5000 patients with type 2 diabetes are enrolled (Henry et al. 2013a, b, 2014). In the trials, the mini-pumps first delivered for 3 months a 20 mcg/day introductory dose, followed by a 60 mcg/day 6-month maintenance dose. A 12-month mini-pump with a 60 mcg/day delivery is in development with the goal to deliver exenatide with yearly renewal of the pump. In FREEDOM 2, ITCA 650 (baseline HbA1c about 8.6%) reduced HbA1c 1.5% versus 0.8% with sitagliptin. Weight changes were −4.0 kg and 1.3 kg, respectively. ITCA 650 treatment has also been shown to be superior to exenatide BID (Henry et al. 2013a). The adverse events were gastrointestinal as with other GLP-1 RAs, and placement and removal of ITCA were well-tolerated (Henry et al. 2013a, b, 2014).

Safety and Adverse Events of GLP-1 RAs

Gastrointestinal

As discussed above the most frequently observed AEs with GLP-1 RAs are nausea, vomiting, and diarrhea (Ostergaard et al. 2016; Frandsen et al. 2016; Madsbad et al. 2011; Madsbad 2016, 2009; Bettge et al. 2017). They are usually described as gastrointestinal, although they are more likely to be due to interaction with receptors in the central nervous system. Importantly, they can be reduced by slow up-titration

of the dose. In most patients these adverse events are transient, and less than 5% of the patients discontinued treatment in clinical trials (except for taspoglutide), although higher rates may be seen in clinical practice (Ostergaard et al. 2016; Madsbad et al. 2011; Madsbad 2016; Bettge et al. 2017; Cefalu et al. 2014).

Concerns have been raised with respect to potential pancreatic side effects associated with GLP-1 RAs (Egan et al. 2014), but in the four cardiovascular endpoint studies so far available, there was no increased risk of pancreatitis or pancreas cancer (Marso et al. 2016a, b; Pfeffer et al. 2015; Holman et al. 2017). In 2014, FDA and European Medicines Agency (EMA) reviewed studies with over 28.000 patients and concluded that no evidence existed suggesting a causal association between use of GLP-1 RAs and pancreatitis or pancreas cancer (Egan et al. 2014). There are limited published data on the effects of GLP-1 RAs on pancreatic enzymes. In a 26-week study, serum amylase and lipase levels increased with lixisenatide and liraglutide, more so with liraglutide (Nauck et al. 2016b). Notably, the increased enzyme levels are not associated with or predict subsequent development of acute pancreatitis (which occurs with increased frequency in patients with T2DM).

Thyroid

In rodent models, GLP-1 RAs stimulate the release of calcitonin and during long-term exposure may lead to hyperplasia and adenoma formation and with high doses cancer (Bjerre et al. 2010). In humans the C-cells express a very low number of GLP-1 receptors compared to rodents, and the GLP-1 RAs do not stimulate release of calcitonin (Bjerre et al. 2010; Hegedus et al. 2011). In addition, there is no evidence of a causal relationship between GLP-1 RAs and thyroid tumors in humans (Hegedus et al. 2011). In the phase 3 trials and the cardiovascular endpoint trials, there were no cases of medullary thyroid carcinoma in the exposed patients (Hegedus et al. 2011). In a resent post-hoc anlayses of the LEADER trial There was no evidence of a difference in calcitonin concentrations between the liraglutide and placebo groups, and no C-cell malignancies occurred in the liraglutide group (Hegedus L et al. Diabetes Care 2018; 41: 620–22). Nevertheless, GLP-1 RAs should not be used in patients with a personal or familiar history of medullary thyroid carcinoma.

Injection Site Reactions

It is difficult to compare injection site reactions across all studies because of differences in methods of reporting outcomes. Overall, once-weekly GLP-1 RAs appear to be associated with higher incidences of injection site reaction than exenatide twice daily (Ostergaard et al. 2016; Madsbad et al. 2011; Madsbad 2016, 2009) or liraglutide once daily (Ostergaard et al. 2016; Madsbad et al. 2011; Madsbad 2016, 2009).

The exception appears to be dulaglutide once weekly, which in AWARD-6 was associated with low rates (<1%) of injection site reactions, comparable to those observed with liraglutide (Dungan et al. 2014). In SUSTAIN 7 injection site reaction did not differ between semaglutide and dulaglutide (Pratley RE et al. Lancet Diabetes Endocrinol 2018, Jan 31, Epub ahead of print).

Immunogenicity

As GLP-1 RAs are peptides, antibody formation could potentially occur, which might result in injection site reactions, loss of efficacy, and anaphylaxis. Antibody formation has been reported in several head-to-head trials, as discussed in relation to the individual GLP-1 RAs (Ostergaard et al. 2016; Madsbad et al. 2011; Madsbad 2016), but has not resulted in major immune reactions.

Cardiovascular Effects and Endpoint Studies with GLP-1 RAs

Endothelial Function

Multiple studies have demonstrated a role for GLP-1 to regulate endothelial function, but it remains unclear whether direct or indirect activation of GLP-1 receptors in blood vessels is involved in the regulation of blood flow (Drucker 2016; Pujadas and Drucker 2016). It also remains uncertain whether endothelial cells within blood vessels express the GLP-1 receptor.

Blood Pressure and Heart Rate

Improvements in both systolic blood pressure (SBP) and diastolic blood pressure (DBP) preceding weight loss have been reported in clinical trials of GLP-1 RAs (Gallwitz et al. 2010). Indeed, a meta-analysis of trials involving exenatide OW, exenatide BID, or liraglutide found that these treatments all significantly decreased SBP by −1.79 and −2.39 mmHg compared with placebo and active controls, respectively (Robinson et al. 2013). There was also a trend toward decreased DBP with GLP-1 RAs, but the reductions did not reach statistical significance. In the clinical studies, office blood pressure measurements have been used. However, in four studies using 24 h ambulatory blood glucose monitoring in subjects with type 2 diabetes and in one study in type 1 diabetic patients, treatment with liraglutide did not show any significant blood pressure-lowering effect (Dejgaard et al. 2017; Kumarathurai et al. 2017b). The mechanisms linking GLP-1 RA treatment to reduction in blood pressure are poorly understood, but potential mechanisms include vasodilation and natriuresis or unknown neurohormonal mechanisms.

Increases in resting heart rate and cardiac output have been reported with GLP-1 RAs (Drucker 2016; Pujadas and Drucker 2016). Although the underlying

physiological mechanisms have not yet been defined, activation of the GLP-1 receptors in the sinoatrial node and changes in the activity of the autonomic nervous system by enhancing sympathetic and reducing parasympathetic nervous system activity have been proposed to be responsible for the changes (Pyke et al. 2014; Smits et al. 2016). Another potential explanation for the increased heart rate could include a reflex mechanism compensating for vasodilation and lowering of BP (Asmar et al. 2015). A meta-analysis of studies involving exenatide OW, exenatide BID, or liraglutide found that these treatments increased heart rate by 1.86 beats/min (bpm) versus placebo and by 1.90 bpm versus active comparators (Robinson et al. 2013). However, in studies involving 24-h heart rate registration much greater increases may be seen (Kumarathurai et al. 2017a). The acute effect of GLP-1 on BP is an increase, consistent with the increase in heart rate and a consequent increase in cardiac output (Asmar et al. 2015). Postmarketing reports have not demonstrated any prolongation of QT interval during treatment with a GLP-1 RA, but the GLP-1 RA liraglutide has been shown to reduce heart rate variability in conjunction with a decrease in parasympathetic activity suggesting that liraglutide may affect sympatho-vagal balance (Kumarathurai et al. 2017a).

Lipids and Cardiovascular Risk Markers

Effects on lipids have in most trials, including the large outcome trial with liraglutide, been minimal (Marso et al. 2016a, b; Pfeffer et al. 2015; Holman et al. 2017; Pujadas and Drucker 2016), but an interesting study with liraglutide 1.8 mg suggested that liraglutide treatment in patients with T2DM significantly and markedly reduces postprandial excursions of triglyceride and apolipoprotein B48 after a fat-rich meal, independently of gastric emptying (Hermansen et al. 2013). Cardiovascular risk markers as PAI-1, B-type natriuretic peptide, ICAM-1, monocyte chemoattractant protein-1 (MCP-1), and CRP levels were reduced during treatment with GLP-1 RAs (Pujadas and Drucker 2016). Whether GLP-1 RAs exert clinically relevant effects on platelets and coagulation is not yet known (Drucker 2016; Pujadas and Drucker 2016).

Cardioprotection

Animal studies have demonstrated cardioprotection in experimental models of myocardial infarction, reviewed in Drucker (2016) and Pujadas and Drucker (2016). Administration of a GLP-1 RA reduced infarct size, improved survival, and preserved left ventricular function in mice (Drucker 2016; Pujadas and Drucker 2016). However, the precise mechanisms explaining the results remain unclear, especially since it has been a challenge to find GLP-1 receptors on the myocytes and endothelial cells in the heart (Drucker 2016; Pujadas and Drucker 2016). Studies in mice suggested that the primary metabolite of GLP-1 ($9\text{-}36NH_2$) may mediate some of the effects via hypothetical non-GLP-1 receptor-mediated cardioprotective

actions (Ban et al. 2008). Support for a similar mechanism to operate in humans is lacking. In a pilot study, 72 h infusion of native GLP-1 in human with acute myocardial infarction and impaired ejection fraction (< 40%) improved ventricular function (Nikolaidis et al. 2004). In an acute study, intravenous infusions of exenatide were demonstrated to be cardioprotective as an adjunct to primary percutaneous coronary intervention in patients with ST-segment-elevation myocardial infarction (STEMI) (Lonborg et al. 2012). The infusion was commenced 15 min before intervention and maintained for 6 h after the procedure. The exenatide treatment was associated with a 30% decrease in final infarct size, if treatment could be instituted within 130 min after the attack, whereas there was no cardioprotective effect in patients with longer system delay (Lonborg et al. 2012). In another study in patients with STEMI, liraglutide administered 30 min before PCI and continued for 7 days lowered level of troponin T and improved ventricular function (Chen et al. 2015).

Heart Failure

However, 48 h of native GLP-1 infusion in patients with NYHA class II-III failed to show any benefit (Halbirk et al. 2010). Albiglutide versus placebo over 12 weeks did not improve ventricular function in patients with EF < 40% (Lepore et al. 2016). In a double-blind, placebo-controlled, randomized clinical trial, patients with established heart failure and reduced LVEF (median LVEF of 25%) were randomized to liraglutide 1.8 mg (n = 154) or placebo (n = 146) for 180 days (Margulies et al. 2016). Compared with placebo, liraglutide had no significant effect on the number of deaths or rehospitalizations for heart failure (Margulies et al. 2016). In two other studies, no effect of liraglutide treatment for 12–24 weeks on left ventricular function was reported in patients with or without type 2 diabetes and stable heart failure (Jorsal et al. 2017; Kumarathurai et al. 2016). On the contrary a tendency to an increased frequency of adverse cardiovascular events was reported in Jorsal et al. (2017). These findings do not support the use of liraglutide for the treatment of heart failure. Notably, in the ELIXA, LEADER, SUSTAIN-6, and EXSCEL studies, there was no increased risk of hospitalization because of heart failure in the treated groups (Marso et al. 2016a, b; Pfeffer et al. 2015; Holman et al. 2017).

Cardiovascular Endpoint Studies

In 2008 the FDA recommended that all drugs investigated for diabetes should be evaluated for cardiovascular effects in large and long-term trials. The short-acting GLP-1 RA, lixisenatide, was assessed with respect to cardiovascular outcome versus placebo (the ELIXA trial) in 6068 patients with type 2 diabetes, who had had a recent acute coronary event (Pfeffer et al. 2015). The primary endpoint of cardiovascular death, myocardial infarction, stroke, or hospitalization for unstable angina did not differ between the lixisenatide and placebo groups after a median of 25 months

follow-up (Pfeffer et al. 2015). There was no difference in heart failure or death. Lixisenatide treatment was not associated with a higher risk of hypoglycemia, pancreatitis, or pancreatic neoplasm (Pfeffer et al. 2015).

The safety of liraglutide was evaluated in the LEADER trial, a double-blinded trial, including 9340 type 2 patients with a mean follow-up of 3.8 years (Marso et al. 2016a). Patients included had cardiovascular or kidney disease or were at high risk for developing cardiovascular disease. The primary endpoint: death, nonfatal myocardial infarction, and nonfatal stroke, was reduced by 13% ($p < 0.001$), and mortality from cardiovascular disease was reduced by 22% ($p = 0.007$) and death of any course by 15%, ($p = 0.002$) (Marso et al. 2016a). The incidence of pancreatitis was nonsignificantly *lower* in the liraglutide group. There was a significant reduction in severe hypoglycemic episodes in the liraglutide group. Subgroup analysis showed benefit with liraglutide in patients with eGFR less than 60 ml/min/1.72 m^2 compared with those with higher eGFRs; the benefit also appeared greater in patients with established CVD compared to patients with risk factors for CVD (Marso et al. 2016a). In total, 66 patients had to be treated for 3 years to prevent 1 primary endpoint and 98 patients to prevent 1 death from any cause (Marso et al. 2016a). A secondary analysis shows that liraglutide resulted in lower rates of development and progression of diabetic kidney disease than placebo (Mann et al. 2017). This result was driven primarily by the new onset of persistent macroalbuminuria, which occurred in fewer participants in the liraglutide group than in the placebo group (HR, 0.74).

In SUSTAIN-6, semaglutide for once-weekly administration was evaluated in 2 doses (0.5 mg or 1.0 mg) versus placebo in 3297 type 2 diabetic patients (Marso et al. 2016b). At baseline 83% had established cardiovascular disease, chronic kidney disease, or both. The primary outcome: cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke, was after 104 weeks follow-up reduced by 26% ($p < 0.001$), nonfatal myocardial infarction by 26% ($p = 0.12$), and nonfatal stroke by 39% ($p = 0.04$) (Marso et al. 2016b). Rates of death, including cardiovascular death, were similar in the two groups. In total 45 patients would need to be treated for 2 years to prevent 1 primary endpoint. Revascularization surgery rates were also greatly reduced by semaglutide compared with placebo. Semaglutide is in late phase 3 development and will probably enter the market within the next few years.

In the EXSCEL trial, 14,752 patients (of whom 10,782 (73%) had previous cardiovascular disease) were randomized to treatment with exenatide once weekly or placebo as add-on to usual therapy and followed for a median of 3.2 years (Holman et al. 2017). The primary composite endpoint: death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke, occurred in 839 versus 905 participants in the exenatide and placebo groups (HR, 0.91, $P = 0.06$ for superiority). Once-weekly exenatide did not increase risk of hospitalization for heart failure. Cardiovascular death did not differ between exenatide and placebo groups, but exenatide reduced total mortality by 14%, which was statistically significant (Holman et al. 2017). The incidence of acute pancreatitis, pancreas cancer, and thyroid carcinoma did not differ between the groups.

Taken together, the short-acting lixisenatide had a neutral effect on cardiovascular risk, whereas liraglutide and semaglutide showed a benefit. Liraglutide reduced

cardiovascular and total mortality. Nonfatal stroke was reduced with semaglutide but not with liraglutide. Exenatide OW also reduced cardiovascular risk and total mortality significantly. The GLP-1 receptor agonist had no effect on heart failure in the four endpoint trials.

The mechanism of the cardiovascular benefits is unknown. One suggestion is that GLP-1 RAs have some beneficial effects on the progression of atherosclerosis by reducing the plaque burden or increasing plaque stability. The GLP-1 RAs also have beneficial effects on blood pressure, weight and postprandial lipids, low-grade inflammation, and on the myocardium, but these effects do not readily explain the findings. Therefore, the mechanisms of action of GLP-1 RAs have yet to be elucidated. It is also debated how the four randomized studies with lixisenatide, liraglutide, semaglutide, and exenatide could generate so different results (Marso et al. 2016a, b; Pfeffer et al. 2015; Holman et al. 2017)? First, the patients in ELIXA appeared to be at higher risk for further cardiovascular disease progression than the patients in LEADER, SUSTAIN-6, and EXSCEL, meaning that even a significant beneficial effect of lixisenatide might not be able to influence the very high event rate in this group of patients. In addition, lixisenatide has a short half-life and covers only about 8 h of the day, while liraglutide, semaglutide, and exenatide QW cover all 24 h. In addition, the duration of the trials differ significantly. Moreover, the molecules are quite different and differ in their receptor signalling capacity and biological effects (see Table 1). It is an ongoing discussion, whether the CV benefit of the long-acting human GLP-1 RAs in LEADER and SUSTAIN-6 versus EXSCEL trials can be considered a class effect or might be specific for the liraglutide/semaglutide and exenatide molecules. Additional cardiovascular endpoint studies will be published in the future with FREEDOM-CVO (ITCA 659) and REWIND (dulaglutide). At any rate liraglutide, semaglutide, and exenatide QW have demonstrated beneficial effects on cardiovascular events and mortality in type 2 patients with cardiovascular disease or at high risk for a future cardiovascular events, which is important for the treatment of these patients.

Head-To-Head Comparisons of GLP-1 RAs

Currently, six glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are approved for treating type 2 diabetes (Madsbad 2016), and ten published phase 3 head-to-head trials of 24–30 weeks duration have compared the efficacy and safety of these six GLP-1 RAs and taspoglutide (Buse et al. 2009, 2013; Drucker et al. 2008; Rosenstock et al. 2013a, b; Nauck et al. 2016b; Pratley et al. 2014; Dungan et al. 2014; Blevins et al. 2011; Ji et al. 2013). Exenatide BID and liraglutide were the most common comparators (Figs. 4 and 5).

In general, baseline characteristics were similar across trial populations and between treatment groups (Ostergaard et al. 2016; Madsbad et al. 2011; Madsbad 2016). The mean age of participants ranged from 55 to 61 years across the studies, with mean duration of diabetes ranging from 6 to 9 years (Ostergaard et al. 2016; Madsbad et al. 2011; Madsbad 2016). Mean baseline HbA1c levels were in the range

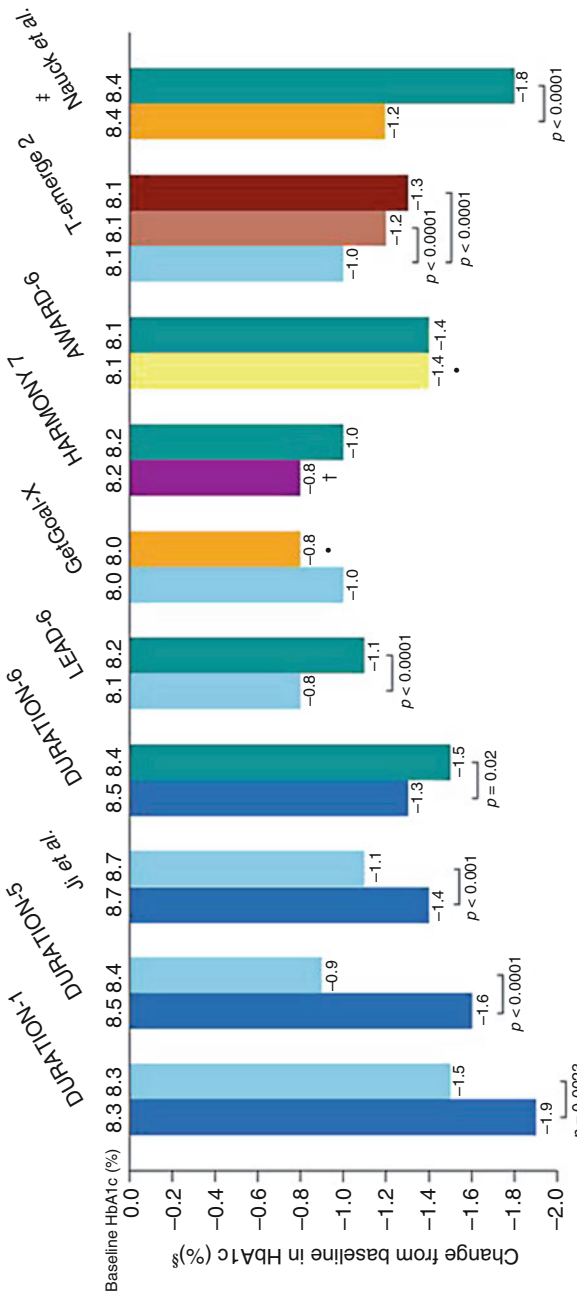

Fig. 4 Reduction in HbA1c in published phase III randomized head-to-head studies of glucagon-like peptide-1 receptor agonists in type 2 diabetes. Duration of studies 24–30 weeks. (Has been modified from reference Lau et al. 2015)

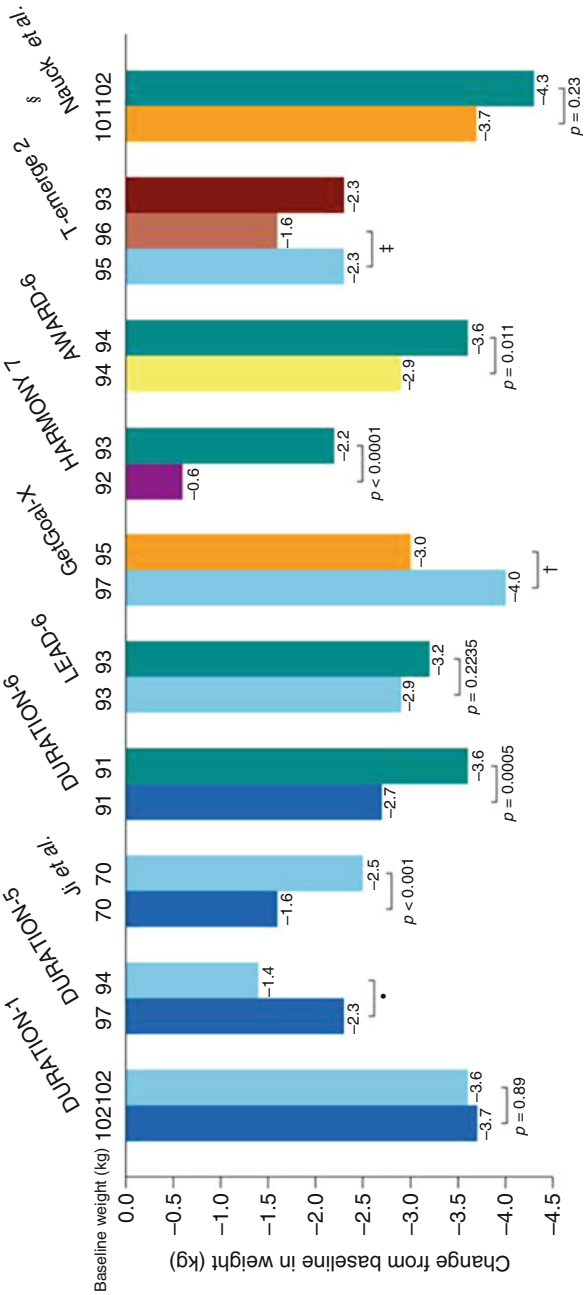

Fig. 5 Reduction in weight in published phase III randomized head-to-head studies of glucagon-like peptide-1 receptor agonists in type 2 diabetes. Duration of studies 24–30 weeks. (Has been modified from reference Lau et al. 2015)

of 8.0 (64 mmol/mol) to 8.7% (72 mmol/mol) across the studies (Ostergaard et al. 2016; Madsbad et al. 2011; Madsbad 2016). Fasting glucose concentrations ranged from 9.1 to 9.9 mmol/l, and mean baseline body weight was consistently in the range 91–102 kg (Ostergaard et al. 2016; Madsbad et al. 2011; Madsbad 2016).

Effect on Glycemic Control

All of the phase 3 trials examined changes in HbA1c as the primary endpoint (Ostergaard et al. 2016; Madsbad et al. 2011; Madsbad 2016). All trials were associated with notable reductions in HbA1c, although liraglutide led to greater decreases than exenatide formulations, lixisenatide, and albiglutide (Fig. 4; Ostergaard et al. 2016; Madsbad 2016). HbA1c reductions did not differ between liraglutide and dulaglutide after 26 weeks (Fig. 4; Dungan et al. 2014). Exenatide once weekly produced more consistent and significantly greater reductions in HbA1c than exenatide twice daily (Drucker et al. 2008; Blevins et al. 2011; Ji et al. 2013). In the T-emerge 2 study, taspoglutide at 10 and 20 mg led to greater reductions in HbA1c than exenatide 10 μg BID (Rosenstock et al. 2013b). In the SUSTAIN-7 trial, semaglutide and dulaglutide as add-on to metformin during 40 weeks were compared (Pratley RE et al. Lancet Diabetes Endocrinol 2018, Jan 31 Epub ahead of print). Patients in the 0.5 mg semaglutide group had a reduction in HbA1c of 1.5% against a 1.1% reduction in the 0.75 mg dulaglutide group. Additionally, 1.0 mg of semaglutide reduced HbA1c with 1.8% compared with a decrease of 1.4% among patients treated with 1.5 mg dulaglutide. The reductions in HbA1c thus ranged from 0.3 to 1.9% (Fig. 4; Buse et al. 2009, 2013; Drucker et al. 2008; Rosenstock et al. 2013a, b; Nauck et al. 2016b; Pratley et al. 2014; Dungan et al. 2014; Blevins et al. 2011; Ji et al. 2013).

The postprandial glucose excursions and fasting plasma glucose were also assessed in many of these trials. As expected, based on the delayed gastric emptying seen with the short-acting GLP-1 RAs, exenatide BID and lixisenatide demonstrated greater effects on postprandial glucose excursions than the longer-acting GLP-1 RAs, but this improvement was seen mainly after the meal following the injection, whereas the longer-acting compounds reduced plasma glucose throughout the 24-h period studied (Fig. 2; Ostergaard et al. 2016; Madsbad 2016; Nauck et al. 2016b). Hence the longer acting resulted in greater improvements in HbA1c compared with the short-acting GLP-1 RAs (Ostergaard et al. 2016; Madsbad 2016; Dungan et al. 2014).

Effect on Weight

Liraglutide was associated with weight reductions similar to those with exenatide BID (3.2 and 2.9 kg, respectively) but greater than those with exenatide OW, albiglutide, and dulaglutide (Fig. 5; Buse et al. 2009, 2013; Drucker et al. 2008; Rosenstock et al. 2013a, b; Nauck et al. 2016b; Pratley et al. 2014; Dungan et al. 2014; Blevins et al. 2011; Ji et al. 2013). Compared to lixisenatide, the weight loss

tended to be greater with liraglutide (4.3 kg vs. 3.7 kg) (Nauck et al. 2016b). Weight loss was not significantly different between the two exenatide formulations. In the T-emerge 2 study, exenatide BID showed a greater (nonsignificant) reduction in weight than taspoglutide 10 mg OW but showed no difference in weight loss compared with taspoglutide 20 mg OW (Rosenstock et al. 2013b). Exenatide BID was associated with greater (nonsignificant) weight loss than lixisenatide. In SUSTAIN-7 those on 0.5 mg semaglutide lost on average 4.6 kg of body weight compared to 2.3 kg with 0.75 mg dulaglutide. The higher doses led to losses of 6.5 kg and 3.0 kg, respectively (Pratley RE et al. Lancet Diabetes Endocrinol 2018, Jan 31 Epub ahead of print). Taken together, all GLP-1 receptor agonists have weight-reduction effect (Fig. 5), and the head-to-head studies revealed significantly greater reduction in weight with liraglutide than the once-weekly GLP-1 RAs (except for semaglutide). The explanation for the different magnitude of weight loss is a matter of contention. It is unclear whether the large molecules albiglutide and dulaglutide hinder transport across the blood-brain barrier or through fenestrated capillaries around hypothalamus (Secher et al. 2014). Alternatively, suboptimal dosing of the once-weekly GLP-1 RAs may play a role; this may also explain the differences in reduction in HbA1c level of the GLP-1 RAs.

Effect on Blood Pressure

Head-to-head trials have not revealed significant differences in effects on blood pressure (BP) among different GLP-1 RAs (Madsbad 2016). However, in the extension phases of DURATION-1 and LEAD-6, which continued to 52 weeks, participants switching from exenatide BID to either exenatide OW or liraglutide experienced further reductions in SBP (–3.8 mmHg in both studies) (Ostergaard et al. 2016; Buse et al. 2010a, b). In a 26-week study, changes in blood pressure did not differ between lixisenatide and liraglutide (Nauck et al. 2016b). Effect on blood pressure did not differ between semaglutide and dulaglutide in SUSTAIN 7 trial (Pratley RE et al. Lancet Diabetes Endocrinol 2018, Jan 31 Epub ahead of print).

Heart Rate

Head-to-head trials have suggested that heart rate increases may be smaller with exenatide twice daily than exenatide once weekly or liraglutide (Buse et al. 2009; Drucker et al. 2008). Dulaglutide is also associated with an increase in heart rate, of similar magnitude, to that with liraglutide (Dungan et al. 2014). Albiglutide did not appear to be associated with clinically relevant increases in heart rate (Pratley et al. 2014).

Since heart rate was mostly estimated during daytime, 24-h monitoring was needed to understand the different effects of the short- and long-acting GLP-1 RAs on heart rate. In a 8-week study, liraglutide doses increased the mean ± SE 24-h heart rate from baseline by 9 ± 1 bpm versus 3 ± 1 bpm with lixisenatide

($P < 0.001$) (Meier et al. 2015). Greater heart rate increases at week 8 with liraglutide were observed at nighttime, while heart rate increases with lixisenatide were greatest during the day (Meier et al. 2015). In another comparison between lixisenatide and liraglutide, the increase in pulse was 2.5 bpm with liraglutide, while a decrease by 1.1 bpm was reported with lixisenatide after 26 weeks (Seino et al. 2012). Note that heart rate primarily has been estimated during daytime in an ambulatory consultation; 24 h monitoring is needed to understand the different effects of short- and long-acting GLP-1 receptor agonists on heart rate. In one study, liraglutide increased 24-h heart rate from baseline by 9 bpm versus 3 bpm with lixisenatide (Meier et al. 2015). Greater heart rate increases with liraglutide were observed at nighttime (Meier et al. 2015). Increase in heart rate was greater with semaglutide 1.0 mg compared with dulaglutide 1.5 mg (4.0 vs 2.4 bpm), while the increase did not differ with the lowest doses (Pratley RE et al. Lancet Diabetes Endocrinol 2018, Jan 31 Epub ahead of print).

Gastrointestinal Adverse Effects

The most frequently observed AEs with GLP-1 RAs were gastrointestinal disorders, particularly nausea, vomiting, and diarrhea; nausea, however, occurred less frequently with exenatide OW and albiglutide than exenatide BID and liraglutide (Buse et al. 2009, 2013; Drucker et al. 2008; Rosenstock et al. 2013a, b; Nauck et al. 2016b; Pratley et al. 2014; Dungan et al. 2014; Blevins et al. 2011; Ji et al. 2013). However, by far the highest rates of nausea were observed with taspoglutide: 53% and 59% with 10 and 20 mg OW, respectively, compared with 35% among participants treated with exenatide BID (Rosenstock et al. 2013b). In a meta-analysis of 32 phase 3 clinical trials with GLP-1 RAs, it was concluded that presence of a background treatment with metformin was associated with more nausea and vomiting (Bettge et al. 2017). Compared to exenatide BID, there was less nausea and diarrhea with lixisenatide (Bettge et al. 2017). Compared to liraglutide, there was a similar risk associated with dulaglutide and less with exenatide QW and albiglutide (Bettge et al. 2017). Long-acting GLP-1 RAs were associated with less nausea and vomiting but with more diarrhea than short-acting agents (Bettge et al. 2017). More premature discontinuation, mostly due to gastrointestinal adverse events was observed with semaglutide compared with dulaglutide in SUSTAIN 7 (Pratley RE et al. Lancet Diabetes Endocrinol 2018, Jan 31 Epub ahead of print).

Injection Site Reactions

Both exenatide formulations and albiglutide may be associated with higher incidences of injection site reactions than liraglutide and dulaglutide (Buse et al. 2009, 2013; Drucker et al. 2008; Rosenstock et al. 2013a, b; Nauck et al. 2016b; Pratley et al. 2014; Dungan et al. 2014; Blevins et al. 2011; Ji et al. 2013), but the once-weekly GLP-1 RAs appear to be associated with higher incidences of injection site reaction

than exenatide BID or liraglutide OD. The exception appears to be dulaglutide OW, in AWARD-6, which was associated with low rates (<1%) of injection site reactions, comparable to those observed with liraglutide (Dungan et al. 2014). Injection site reaction did not differ between semaglutide and dulaglutide in SUSTAIN 7 (Pratley RE et al. Lancet Diabetes Endocrinol 2018, Jan 31 Epub ahead of print).

Antibodies

In head-to-head studies, anti-exenatide antibodies were more common – and titers were higher – with exenatide OW than with exenatide BID (Drucker et al. 2008; Blevins et al. 2011; Ji et al. 2013). However, reductions in HbA1c were still significant in participants with or without antibodies, and the presence of antibodies did not correlate with reported rates of AEs (Drucker et al. 2008; Blevins et al. 2011; Ji et al. 2013).

Antibody formation has also been reported in liraglutide clinical trials, although a meta-analysis of the LEAD studies found lower immunogenicity with liraglutide than with exenatide BID and no effect of antibodies on glycemic efficacy with liraglutide (Buse et al. 2011). Development of antibodies was reported in 56–60% of participants (undergoing different treatment regimens) treated with 20 μg lixisenatide OD (Rosenstock et al. 2013a; Nauck et al. 2016b). In another study, antibodies were found in 43% and 71% of participants treated with 10 μg lixisenatide once daily and 20 μg twice daily, respectively (Ratner et al. 2010; Fonseca et al. 2012). No notable differences were reported in terms of safety and efficacy between antibody-positive and negative participants (Ratner et al. 2010; Fonseca et al. 2012).

Antibody formation occurred relatively rarely in phase 3 trials of dulaglutide and albiglutide, but no comparison could be made with liraglutide in these studies, as anti-liraglutide antibodies were not assessed (Pratley et al. 2014; Dungan et al. 2014).

Finally, in the T-emerge 2 study, anti-taspoglutide antibodies were detected in 49% of participants. In this trial, levels of systemic allergic reactions were also considered to be unacceptably high (6% of participants in each of the taspoglutide groups) (Rosenstock et al. 2013b).

The immunogenicity reported in the trials of exenatide, lixisenatide, and liraglutide appeared to have little impact on the efficacy and safety of these GLP-1 RAs.

Fixed-Ratio Combination Therapy with a GLP-1 Receptor Agonist and Basal Insulin

The complex pathophysiology of type 2 diabetes (T2D) is associated with insulin resistance, obesity, and declining beta-cell function (DeFronzo 2009). It also includes defects in glucagon secretion and a severely impaired incretin effect of glucagon-like peptide-1 (GLP-1) and glucose-independent polypeptide (GIP) in response to a meal (Holst et al. 2011). Consequently, combination therapies,

addressing several of the underlying abnormalities and effectively reducing glycated hemoglobin A1c (HbA1c), mitigating weight gain or inducing weight loss, combined with an impact on the comorbidities associated with T2D are of high interest (Balena et al. 2013; Eng et al. 2014). On this background, in the real world, combination therapy with basal insulin and a GLP-1 RA has turned out to be very popular, and a recent meta-analysis suggests that basal insulin in combination with a GLP-1 RA results in superior glycemic control with no increase in hypoglycemic episodes or weight gain, as compared with basal insulin alone (Eng et al. 2014).

IDegLira

A fixed-ratio combination of the basal insulin degludec and the GLP-1 RA, liraglutide (IDegLira, 50 units degludec/1.8 mg liraglutide), has been approved under the brand name Xultophy 100/3.6 as a once-daily injection for the treatment of type 2 diabetes (T2D). Insulin degludec is an ultra-long-acting basal insulin analogue with a half-life of approximately 25 h and a duration of action of about 41 h compared with about 12 h for insulin glargine (Haahr and Heise 2014). Steady state is obtained within 2–3 days of treatment (Haahr and Heise 2014). Insulin degludec has demonstrated lower intraindividual glycemic variability and lower risk of hypoglycemia as compared to the shorter-acting insulin glargine (Haahr and Heise 2014; Vora et al. 2014). IDegLira has been approved by FDA to improve glycemic control in patients inadequately controlled on basal insulin in doses of up to 50 units/day or a GLP-1 RA. IDegLira has also been approved for use in Europe for the treatment of type 2 diabetes in combination with oral glucose-lowering agents alone or combined with basal insulin.

IDegLira is available in prefilled pen injectors which contain 3 ml, equivalent to 300 units of insulin degludec and 10.8 mg of liraglutide. Each dose step is 1 unit of insulin degludec and 0.036 mg of liraglutide. Administration is by once-daily injection, independent of meal intake or time of day (although it should ideally be injected at the same time each day). The maximal dose is 50 steps corresponding to 50 units of insulin degludec and 1.8 mg of liraglutide. The recommended starting dose in patients treated with OADs alone is 10 dose steps (10 units/0.36 mg), whereas the starting dose is 16 dose steps (16 units/0.6 mg) in patients that were already treated with a GLP-1 RA or insulin.

IDegLira has been investigated in eight 26-week randomized trials (the DUAL™ program) (Buse et al. 2014; Gough et al. 2014; Lingvay et al. 2016; Linjawi et al. 2017; Rodbard et al. 2017). IDegLira reduces HbA1c more than monotherapy with a GLP-1 RA (liraglutide) or insulin (degludec or glargine) despite the fact that IDegLira and insulin degludec or insulin glargine were titrated to similar FPG levels, indicating that the further improvement also includes better PPG control effected by the liraglutide component of the combination therapy (Buse et al. 2014; Gough et al. 2014, 2015; Lingvay et al. 2016; Linjawi et al. 2017; Rodbard et al. 2017). Furthermore, combination therapy leads to weight loss, or a stable body weight, with no increase in hypoglycemia despite the lower HbA1c in the IDegLira group

(Buse et al. 2014; Gough et al. 2014, 2015; Lingvay et al. 2016; Linjawi et al. 2017; Rodbard et al. 2017). These results were found in both insulin-naïve and insulin-treated patients with T2D, independent of diabetes duration and baseline HbA1c (Buse et al. 2014; Gough et al. 2014, 2015; Lingvay et al. 2016; Linjawi et al. 2017; Rodbard et al. 2017). In DUAL VII, IDegLira was compared with basal-bolus insulin therapy (glargine plus insulin aspart up to four times daily) in patients uncontrolled on metformin and insulin glargine. After 26 weeks the HbA1c did not differ between groups (6.7%), but body weight decreased with IDegLira (−0.9 kg) and increased with basal-bolus therapy (+2.6 kg); the rate of hypoglycemia was eightfold lower with IDegLira (Billings LK et al. Diabetes Care 2018; Feb, Epub ahead of print). Daily dose of insulin was 40 units in the IDegLira group compared with 84 units (basal 52 units and bolus 32 units) in the patients treated with basal-bolus. Notably, these results were obtained by one injection and one fasting blood glucose measurement in the IDegLira group compared with multiple injections and multiple blood glucose measurements in the basal-bolus group.

In the DUAL studies, rates of adverse events did not differ between treatment groups; however, gastrointestinal side effects were fewer with IDegLira compared with liraglutide treatment alone, which was titrated using the recommended dose escalation of 0.6 mg per week until a dose of 1.8 mg (Gough et al. 2014, 2015) (although, because of insulin titration, only a maximum dose of 1.4 mg was actually achieved in the large DUAL 1 study). IDegLira may be of more limited value in patient populations that are challenging to manage, e.g., patients with HbA1c values >10%, BMI >40 kg/m^2, or patients receiving insulin doses in excess of 50 U/day. This has to be taken into consideration when switching people treated with large doses of insulin; potentially this may lead to a transient worsening of glycemic control.

iGlarLixi

The combination of once-daily insulin glargine and the short-acting GLP-1 RA lixisenatide (iGlarLixi, formerly known as LixiLan) is recommended to be injected about 1 h before the largest meal (Aroda et al. 2016; Rosenstock et al. 2016a, b). iGlarLixi has been approved by FDA to improve glycemic control in patients inadequately controlled on basal insulin up to 60 units/day or a GLP-1 RA alone. iGlarLixi has also been approved for use in Europe for the treatment of type 2 diabetes in combination with oral glucose-lowering agents alone or combined with basal insulin. iGlarLixi will be available as prefilled pens for dosing of 10–40 units of glargine with 5–20 mcg of lixisenatide or 30–60 units of glargine with 10–20 mcg of lixisenatide. Each dose step contains 1 unit of glargine and 0.33 mcg of lixisenatide.

In the phase 3 program, iGlarLixi demonstrated better HbA1c reduction versus insulin glargine in patients treated with metformin and reduced weight by approximately 1 kg versus an increase of 0.5 kg for those who received glargine (Rosenstock et al. 2016a). Final dose of insulin was 36 versus 39 units and risk of

hypoglycemia did not differ between groups. In the second trial including patients inadequately controlled on basal insulin and with up to 2 oral glucose-lowering agents, iGlarLixi compared to glargine demonstrated better reduction in HbA1c over 30 weeks and a greater proportion of patients (55% vs. 30%) achieving target of <7%. Body weight was reduced with 0.7 kg versus + 0.7 kg, respectively, while final dose of insulin (47 units) and risk of hypoglycemia did not differ between groups (Aroda et al. 2016). In a third study including patients on metformin with or without a second oral glucose-lowering agents, iGlarLixi reduced HbA1c significantly more than with either glargine or lixisenatide alone (−1.6%, −1.3%, and −0.9%, respectively) without increased risk of hypoglycemia with iGlarLixi compared with glargine alone (Rosenstock et al. 2016b). Insulin dose was 39.8 units in the iGlarLixi group and 40.3 units in the glargine group. Changes in body weight were −0.3 kg, +1.1 kg, and −2.3 kg, respectively.

Lixisenatide has a more pronounced effect on PPG excursions in relation to the meal following the injection when compared with liraglutide. Thus, addition of a short-acting GLP-1 RA may be a more convenient intensification strategy compared to adding mealtime rapid-acting insulin, because the fixed dosing does not require adjustments for meal size and carbohydrate content. A limitation with iGlarLixi may be the short duration of lixisenatide and the once-daily administration given 30–60 min before one of the main meals, while IDegLira can be taken independent of meals. A head-to-head comparison with LixiLan and IDegLira will be of interest.

A possible drawback of the combination therapies is the fixed-dose principle, which reduces the flexibility to adjust insulin and GLP-1 RA treatment in an individualized manner. In patients where weight loss is a major aim, a more optimal treatment may be to titrate liraglutide to the maximal dose of 1.8 mg and then add basal insulin (Balena et al. 2013). Thereby less insulin is probably also needed. Nevertheless, the fixed-ratio combinations have been shown to be very effective at lowering glycemia while being associated with lower rate of hypoglycemia and weight gain compared to basal insulin alone and lower gastrointestinal side effects than liraglutide and lixisenatide alone.

GLP-1 RA: Place in Therapy of Type 2 Diabetes

Metformin is considered the first-line therapy in the treatment of type 2 diabetes, but ADA, EASD, and AACE recommend GLP-1 receptor agonists as potential add-on therapy for patients with uncontrolled type 2 diabetes (Garber et al. 2016; Inzucchi et al. 2015). They also may be considered as monotherapy for patients with metformin intolerance. GLP-1 RAs are becoming increasingly popular for the treatment of T2DM because of their excellent HbA1c lowering, positive effects on weight loss, low risk of hypoglycemia, and influence on cardiovascular risk factors (Ostergaard et al. 2016). Their superiority to OADs has been demonstrated in most studies, with greater reductions in both HbA1c and weight (Ostergaard et al. 2016). The fear of injections will, in some patients, remain a barrier for the use of GLP-1 RAs, but this problem can be reduced by using the long-acting agonists for once-weekly injection

or ITCA 650 infusion pump. Compared with insulin, GLP-1 RAs are much easier to initiate, with less need for dose titration and blood glucose monitoring (Ostergaard et al. 2016). Furthermore, in patients in whom weight loss is advisable, GLP-1 RA treatment could be an option instead of insulin, which for many patients is associated with weight gain (Inzucchi et al. 2015). The addition of a GLP-1 RA to insulin treatment has been demonstrated to improve glycemic control, help patients lose weight, and lower the need for insulin (Eng et al. 2014). The results from the degludec/liraglutide and the glargine/lixisenatide fixed combination studies support the concept that initiation of insulin therapy is best carried out as an insulin/GLP-1 combination rather than insulin alone. None of the GLP-1 RAs are marketed for use with basal-bolus regimens.

Recently the ADA and some other national guidelines have suggested that in patients with type 2 diabetes and established CVD treatment should begin with lifestyle management and metformin and subsequently in patients not achieving glycemic goal an agent proven to reduce major cardiovascular events and cardiovascular mortality (liraglutide and empagliflozin) is recommended (ADA Position Statement. Diabetes Care 2018; 41 (Suppl 1): S73–S85).

GLP-1 RA use in clinical practice should be customized for individual patients, based on the clinical profile and patient preferences. Survey data on patient preferences have revealed that efficacy (lowering of HbA1c) is the most important attribute influencing patient preference, followed by absence of nausea and hypoglycemia and simplicity of dosing schedule (Polster et al. 2010). In a survey more patients were likely to prefer once-weekly injection because of greater convenience (Polonsky et al. 2011).

The GLP-1 RAs are generally well-tolerated. The main side effects are gastrointestinal, i.e., nausea and vomiting, which often are transient and can be partly avoided by slowly up-titrating the dose (Ostergaard et al. 2016; Gough et al. 2015). The GLP-1 RAs are not recommended for people with impaired kidney function (estimated glomerular filtration rate (eGFR) <30 ml/min) or for elderly people with reduced appetite and food intake. At present, no clear evidence of a causal relationship between GLP-1 RAs and pancreatitis and pancreatic cancer exists (Ostergaard et al. 2016; Marso et al. 2016a, b; Pfeffer et al. 2015).

The major drawback of GLP-1 RAs is the higher cost compared with that of other antidiabetic agents.

Treatment of Type 1 Diabetic Patients with GLP-1 Receptor Agonists

Type 1 diabetes (T1D) is characterized by severely impaired or absent or minimal insulin secretion (Madsbad 1983). Even the most rapid-acting insulin analogues peak too late when given with meals to match the postprandial glucose absorption resulting in large postprandial glucose excursions. Intensive insulin treatment is associated with weight gain, and about 50% of persons with T1D are overweight in economically developed countries (Conway et al. 2010). In theory, treatment

regimens in T1D may be improved by combining a GLP-1 RA with insulin. Accordingly, acute infusions of native GLP-1 in C-peptide-negative patients with type 1 diabetes resulted in inhibition of gastric emptying, as well as reduction of glucagon levels, which seems to explain the glucose-regulating effect of GLP-1 during a meal, whereas in patients with residual beta-cell function, enhancement of the endogenous insulin secretion is probably also of importance (Kielgast et al. 2011).

Results from open-label short and small clinical trials indicate that GLP-1 RA treatment induces weight loss and reduces insulin requirements, with either improved or unaltered glycemic control, reviewed in Frandsen et al. (2016). In most of the trials, liraglutide has been used (Dejgaard et al. 2016a).

In the first placebo-controlled trial in normal weight type 1 patients with liraglutide 1.2 mg once daily, there was no effect on HbA1c or glycemic variation compared with placebo (Frandsen et al. 2015). Changes in body weight were −3.13 and +1.12 kg with liraglutide and placebo, respectively. The bolus insulin dose decreased in liraglutide-treated patients and did not change with placebo treatment (−4.0 ± 1.3 vs. 0.0 ± 1.0 IU), and systolic blood pressure decreased compared with placebo (between-group difference 3.21 mmHg) (Frandsen et al. 2015). The incidence of hypoglycemia did not differ between groups. Liraglutide does not compromise glycemic recovery, gastric emptying rate, or counterregulatory hormone responses in T1D during hypoglycemia (Frandsen et al. 2017).

In the second trial with obese type 1 patients, HbA1c and glycemic variability did not differ between liraglutide 1.8 mg and placebo after 24 weeks of treatment, but the number of hypoglycemic events was reduced with liraglutide (Dejgaard et al. 2016b). Both bolus insulin (difference −5·8 IU) and body weight (difference −6·8 kg) decreased with liraglutide treatment compared with placebo. Heart rate increased with liraglutide, with a difference between groups of 7·5 bpm (Dejgaard et al. 2016b). Daytime heart rate increased by 3.7 and nighttime heart rate by 7.5 pbm (Dejgaard et al. 2017).

In the randomized, double-blind, placebo-controlled trial ADJUNCT ONE™, liraglutide 0·6 mg, 1·2 mg, 1·8 mg, and placebo as adjunct to insulin treatment were investigated in 1,398 persons with T1D for 52 weeks (Mathieu et al. 2016). From a mean baseline HbA1c of around 8·2%, those treated with 1·2 mg and 1·8 mg showed a numerically greater improvement in HbA1c of around 0·5% compared with 0·3% for placebo (Mathieu et al. 2016). From a baseline body weight of 86 kg, persons treated with 1·2 mg and 1·8 mg achieved a statistically significantly greater weight loss between 3 kg and 4 kg, whereas the placebo groups experienced a weight gain of around 1 kg (Mathieu et al. 2016). The rates of severe hypoglycemia appeared numerically, but not statistically, lower for all doses of liraglutide compared with placebo. A statistically higher rate of confirmed symptomatic hypoglycemia was observed among persons treated with liraglutide 1·2 mg and 1·8 mg compared with those treated with placebo (Mathieu et al. 2016).

In the ADJUNCT TWO™ trial, 835 participants were enrolled in a 26-week, double-blind, placebo-controlled trial and assigned to liraglutide 0·6 mg, 1·2 mg, 1·8 mg, and placebo (Ahren et al. 2016). Maximum insulin dose was fixed for all

treatment arms. From a baseline HbA1c of about 8·1%, the groups treated with liraglutide showed statistically significantly improvements of HbA1c by 0·2% and 0·3% compared with unaltered glycemic control in the placebo-treated group (Ahren et al. 2016). Additionally, the total insulin dose was reduced with liraglutide compared with placebo after 26 weeks. From a baseline body weight of 84 kg, the weight loss in the liraglutide groups was 1–5 kg, whereas the weight was stable in placebo-treated patients (Ahren et al. 2016). A higher rate of symptomatic hypoglycemia was observed among persons treated with liraglutide 1·2 mg (but not with the higher dose) compared with placebo treatment. The incidence of severe hypoglycemia and nocturnal hypoglycemia did not differ between groups (Ahren et al. 2016). Notable, in C-peptide positive patients, liraglutide reduced HbA1c by 0.77% and 0.69% for the 1.8 mg and 1.2 mg doses, respectively (Ahren et al. 2016).

Lastly, efficacy of liraglutide 1.8 mg has also been evaluated in inadequately controlled (HbA1c 8.2%) insulin pump-treated type 1 patients (ADA 2017 abstract OR 71). After 26 weeks the reduction in HbA1c was −0.6% in the liraglutide group, while an increase of 0.2% was observed in the placebo group (between groups, $p < 0.001$), without increased risk of hypoglycemia. Doses of insulin were unchanged in both groups. Body weight was reduced with −7.3 kg in the groups treated with liraglutide and −0.6 kg in the placebo group.

Thus GLP-1 RAs (at least liraglutide) reduce body weight and insulin dose with improved or unaltered glycemic control, without increased risk of hypoglycemia (Frandsen et al. 2016). The effects on HbA1c are conflicting with small, uncontrolled studies showing the most positive findings (Frandsen et al. 2016). In the randomized, placebo-controlled studies, no effect on HbA1c and glucose variability was reported compared with placebo treatment (Frandsen et al. 2016). One area of interest is treatment with a GLP-1 RA from time of diagnosis with the aim to improve and prolong the remission phase, the first years after diagnosis. From animal and in vitro human models, there is evidence that GLP-1 RAs preserve beta cells from destruction as reviewed in Kielgast et al. (2009), which has initiated ongoing trials in new-onset T1D. Whether treatment with a GLP-1 RA has a future in C-peptide-negative T1D is questionable if the primary indication is to improve glycemic control, especially when taking cost into account.

GLP-1 RAs a New Option for Treatment of Obesity

The exact mechanism by which GLP-1 exerts its anorectic effects is a matter of controversy, but both peripheral and brain GLP-1 receptors seem to be involved (Secher et al. 2014; Madsbad 2014). Since albumin-conjugated GLP-1 which presumably does not cross the blood-brain barrier still reduces food intake, one would assume that a peripheral action on vagal afferent neurons could be involved (Madsbad 2016). On the other hand, it is possible that the reduced weight loss obtained with the large molecules, albiglutide and dulaglutide, compared with liraglutide, can be explained by less direct activation of the GLP-1 receptors in the hypothalamic areas and brain stem. Indeed, compared with liraglutide, the larger

molecular sizes of albiglutide and dulaglutide may hinder transport across the blood-brain barrier or through fenestrated capillaries at the area of hypothalamus (Secher et al. 2014; Madsbad 2014). Liraglutide has been reported to directly stimulate pro-opiomelanocortin (POMC) neurons and inhibit neuropeptide-Y and Agouti-related peptide neurons in the hypothalamus resulting in appetite suppression (Secher et al. 2014). The weight-reducing effect may also be explained by attenuation of the decrease in the levels of the anorexigenic hormone, leptin, which accompanies weight loss (Iepsen et al. 2015). GLP-1 RAs do not influence energy expenditure in humans (Harder et al. 2004). Alternatively, however, it is possible that the once-weekly GLP-1 RAs have been suboptimally dosed (with respect to weight loss); in fact, this may also explain the differences with respect to reduction of HbA1c (Madsbad et al. 2011; Madsbad 2016).

Obesity is known as a risk factor for several common diseases including cardiovascular disease, type 2 diabetes, cancers, and osteoarthritis, and obesity is associated with reduced quality of life (Guh et al. 2009). Obesity guidelines mention the use of pharmacological therapy as a possible adjunctive therapy to diet, exercise, and behavior modification in certain patients (Jensen et al. 2014). Weight loss medications can be consider in adults, who have a BMI of 30 kg/m2 or higher or in patients with a BMI of 27 kg/m2 and having at least one overweight-related comorbid condition, e.g., hypertension, dyslipidemia, and type 2 diabetes (Jensen et al. 2014). The response should be evaluated after 3 months treatment, and if weight loss is less than 5%, the treatment should be stopped.

Liraglutide 3.0 mg has been developed for treatment of obesity and was approved in the USA in 2014 and in Europe in 2015. In a dose-finding study of 1.2, 1.8, 2.4, and 3.0 mg doses, it became clear that 3.0 mg was the most effective dose for inducing weight loss (4.8, 5.5, 6.3, and 7.2 kg, respectively) (Astrup et al. 2009).

In the SCALE-Obesity and Prediabetes study with a duration of 56 weeks, 3731 subjects were included, 2285 of whom had prediabetes, a baseline weight of about 106 kg, and BMI about 38 kg/m2 (Pi-Sunyer et al. 2015). The prediabetes group was followed for 160 weeks to assess the ability of liraglutide to delay the onset of progression to type 2 diabetes. After 56 weeks the weight loss was 8 kg in the liraglutide group compared with 2.6 kg in the placebo group. In total 63.2% versus 27.1% and 33.1% versus 10.6% lost more than 5% or 10% of body weight in the liraglutide and placebo group, respectively (Pi-Sunyer et al. 2015). In total 9.9% and 3.8% withdrew due to adverse events in the liraglutide and placebo groups (Pi-Sunyer et al. 2015). Liraglutide was associated with a reduced progression to prediabetes (7.2% vs. 20.7%) and increased reversal of prediabetes (69.2% vs. 32.7%).

In a follow-up after 160 weeks, 2254 participants with prediabetes 1128 had completed the study (Roux et al. 2017). At week 160 2% in the liraglutide group compared with 6% in the placebo group were diagnosed with diabetes while on treatment. The time to onset of diabetes was 2.7 times longer with liraglutide than with placebo, corresponding to a hazard ratio of 0.21 (Roux et al. 2017). Weight loss was greater with liraglutide (−6.1% vs. −1.9%) than with placebo. In a post hoc analysis for individuals who lose >5% body weight after 16 weeks of treatment, the

weight loss was 12% after 1 year and 8.6% at week 160, where 37% and 19% have a weight loss of 10% and 15%, respectively. Thus, early responders achieved greater long-term weight loss than non-responders, and fewer early responders developed type 2 diabetes, and more regressed to normoglycemia while on treatment.

In the SCALE-Diabetes study, 846 patients with type 2 diabetes and a BMI of 37 kg/m2 (106 kg) were followed for 56 weeks and randomized to liraglutide 3.0 mg, 1.8 mg, or placebo (Davies et al. 2015). The weight loss was 6.4 kg, 5.0 kg, and 2.0 kg, corresponding to 54.3%, 40.4%, and 21.4% obtaining a weight loss of at least 5% and 25.2%, 15.9%, and 6.7% obtaining a weight loss of more than 10%. The reduction in HbA1c was −1.3%, −1.1%, and −0.3%, respectively (Davies et al. 2015).

In the SCALE Maintenance trial, overweight subjects (BMI 38 kg/m2, 106 kg) undertook a 1200–1400 kcal/day diet (Wadden et al. 2015) and entered into the trial if they managed to lose >5% in body weight after 12 weeks. The mean weight loss at randomization was 6%. After 1 year, 6.2% more weight loss was obtained with liraglutide than those on placebo (−0.2%). An extra weight loss of >10% was obtained by 26.1% versus 6.3%, respectively (Wadden et al. 2015).

In a randomized study, liraglutide induced a significant reduction in obstructive sleep apnea compared with placebo (Blackman et al. 2016). Recently a 5-week trial that assesses safety and tolerability of 3.0 mg liraglutide in obese adolescents aged 12–17 years concluded that dosing regimen for adults may be appropriate for use in adolescents (Danne et al. 2017).

In the SCALE studies, small reductions in LDL, VLDL, triglycerides, and systolic and diastolic blood pressure were reported.

The adverse events to liraglutide 3.0 mg were the usual gastrointestinal events including nausea, diarrhea, constipation, and vomiting but also gallbladder disease. Nausea peaked after 4 weeks of treatment and subsided thereafter. Liraglutide was associated with a small increase in heart rate, between 2 and 4 beats/min. Gallbladder-related complications including cholelithiasis and cholecystitis were more common in the liraglutide arms. No incidence of medullary thyroid cancer was reported. Hypoglycemia was not a problem during the studies (Pi-Sunyer et al. 2015; Roux et al. 2017; Davies et al. 2015).

Liraglutide 3.0 mg has demonstrated superior weight loss compared with orlistat, but has not been compared with other weight loss medications (Astrup et al. 2012). Tolerability may be problematic for some patients, although it partly can be avoided by a slower up-titration than 0.6 mg per week. Liraglutide 3.0 mg is expensive, and it is currently priced much higher than other pharmacological agents for the treatment of obesity. Patients who may particularly benefit from liraglutide 3.0 mg are those who have prediabetes due to its glucose-lowering effect and potential to delay the progression from prediabetes to diabetes (Pi-Sunyer et al. 2015; Roux et al. 2017). The appropriate duration of treatment is not established, but obesity is a chronic disease, and the weight loss effects are only sustained as long as liraglutide is taken.

In a phase 2 study obese patients treated with semaglutide 0.4 mg daily lost up to 13.8% of body weight after 52 weeks compared with 2.3% in the placebo group. In the semaglutide group 65% lost more than 10% of their body weight (O'Neil PM et

al. Presented at ENDO March 2018 (OR12)). Semaglutide is at present in phase 3 development as an obesity drug.

Future Perspective of GLP-1 RAs

In light of the relatively narrow therapeutic window defined by the balance between efficacy and gastrointestinal side effects, future subcutaneously administered long-acting GLP-1 RAs will probably not provide much better efficacy than observed with, for instance, semaglutide. In the future, the oral administration of GLP-1 or GLP-1 enhancers may be of interest to increase the treatment compliance (Meier and Nauck 2015). Oral GLP-1 for once-daily administration is in phase 3 development, and in a dose-finding study, 40 mg of oral semaglutide reduced HbA1c with 1.9% from a baseline of 7.9%. Reduction in weight was 6.9 kg (Davies M et al. JAMA 2017; 318: 1460–70).

In rodents, co-agonism at the GLP-1 and glucagon receptors has been investigated to achieve weight loss. Rats treated with co-agonism achieved superior weight loss without induction of hyperglycemia compared to rats treated with GLP-1 receptor-selective agonists (Day et al. 2012).

Peptide YY (PYY) is secreted from intestinal L cells and reduces appetite; co-agonism stimulating both the GLP-1 and PYY receptor pathways reduced food intake in humans in experimental studies (De et al. 2011; Tan et al. 2014). Similarly co-agonism with several hormones may open up new treatments for T2DM and obesity. Recently, the first 12 weeks clinical study in patients with type 2 diabetes was published showing sustained effects of a dual GIP/GLP-1 receptor agonist (Frias et al. 2017). The agonist significantly improved glycemic control and reduced body weight, total cholesterol, and leptin compared with placebo.

Reference

Agerso H, Jensen LB, Elbrond B, Rolan P, Zdravkovic M. The pharmacokinetics, pharmacodynamics, safety and tolerability of NN2211, a new long-acting GLP-1 derivative, in healthy men. Diabetologia. 2002;45:195–202.

Ahren B, Hirsch IB, Pieber TR, et al. Efficacy and safety of Liraglutide added to capped insulin treatment in subjects with type 1 diabetes: the ADJUNCT TWO randomized trial. Diabetes Care. 2016;39:1693–701.

Ahren B, Masmiquel L, Kumar H, et al. Efficacy and safety of once-weekly semaglutide versus once-daily sitagliptin as an add-on to metformin, thiazolidinediones, or both, in patients with type 2 diabetes (SUSTAIN 2): a 56-week, double-blind, phase 3a, randomised trial. Lancet Diabetes Endocrinol. 2017;5:341–54.

Aroda VR, Rosenstock J, Wysham C, et al. Efficacy and safety of LixiLan, a titratable fixed-ratio combination of insulin glargine plus Lixisenatide in type 2 diabetes inadequately controlled on basal insulin and metformin: the LixiLan-L randomized trial. Diabetes Care. 2016;39:1972–80.

Aroda VR, Bain SC, Cariou B, et al. Efficacy and safety of once-weekly semaglutide versus once-daily insulin glargine as add-on to metformin (with or without sulfonylureas) in insulin-naive

patients with type 2 diabetes (SUSTAIN 4): a randomised, open-label, parallel-group, multicentre, multinational, phase 3a trial. Lancet Diabetes Endocrinol. 2017;5:355–66.
Asmar A, Simonsen L, Asmar M, et al. Renal extraction and acute effects of glucagon-like peptide-1 on central and renal hemodynamics in healthy men. Am J Physiol Endocrinol Metab. 2015;308:E641–9.
Astrup A, Rossner S, Van GL, et al. Effects of liraglutide in the treatment of obesity: a randomised, double-blind, placebo-controlled study. Lancet. 2009;374:1606–16.
Astrup A, Carraro R, Finer N, et al. Safety, tolerability and sustained weight loss over 2 years with the once-daily human GLP-1 analog, liraglutide. Int J Obes (Lond). 2012;36:843–54.
Athauda D, Maclagan K, Skene SS, et al. Exenatide once weekly versus placebo in Parkinson's disease: a randomised, double-blind, placebo-controlled trial. Lancet. 2017;390:1664.
Balena R, Hensley IE, Miller S, Barnett AH. Combination therapy with GLP-1 receptor agonists and basal insulin: a systematic review of the literature. Diabetes Obes Metab. 2013;15:485–502.
Ban K, Noyan-Ashraf MH, Hoefer J, Bolz SS, Drucker DJ, Husain M. Cardioprotective and vasodilatory actions of glucagon-like peptide 1 receptor are mediated through both glucagon-like peptide 1 receptor-dependent and -independent pathways. Circulation. 2008;117:2340–50.
Barrington P, Chien JY, Showalter HD, et al. A 5-week study of the pharmacokinetics and pharmacodynamics of LY2189265, a novel, long-acting glucagon-like peptide-1 analogue, in patients with type 2 diabetes. Diabetes Obes Metab. 2011;13:426–33.
Bettge K, Kahle M, Abd El Aziz MS, Meier JJ, Nauck MA. Occurrence of nausea, vomiting and diarrhoea reported as adverse events in clinical trials studying glucagon-like peptide-1 receptor agonists: a systematic analysis of published clinical trials. Diabetes Obes Metab. 2017;19:336–47.
Bjerre KL, Madsen LW, Andersen S, et al. Glucagon-like Peptide-1 receptor agonists activate rodent thyroid C-cells causing calcitonin release and C-cell proliferation. Endocrinology. 2010;151:1473–86.
Blackman A, Foster GD, Zammit G, et al. Effect of liraglutide 3.0 mg in individuals with obesity and moderate or severe obstructive sleep apnea: the SCALE Sleep Apnea randomized clinical trial. Int J Obes (Lond). 2016;40:1310–9.
Blair HA, Keating GM. Albiglutide: a review of its use in patients with type 2 diabetes mellitus. Drugs. 2015;75:651–63.
Blevins T, Pullman J, Malloy J, et al. DURATION-5: exenatide once weekly resulted in greater improvements in glycemic control compared with exenatide twice daily in patients with type 2 diabetes. J Clin Endocrinol Metab. 2011;96:1301–10.
Bolli GB, Munteanu M, Dotsenko S, et al. Efficacy and safety of lixisenatide once daily vs. placebo in people with type 2 diabetes insufficiently controlled on metformin (GetGoal-F1). Diabet Med. 2014;31:176–84.
Brunton S, Davidson JA. Exenatide once weekly: a review of pharmacology and treatment considerations in type 2 diabetes. Clin Ther. 2016;38:582–94.
Bunck MC, Corner A, Eliasson B, et al. Effects of exenatide on measures of beta-cell function after 3 years in metformin-treated patients with type 2 diabetes. Diabetes Care. 2011;34:2041–7.
Buse JB, Rosenstock J, Sesti G, et al. Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6). Lancet. 2009;374:39–47.
Buse JB, Drucker DJ, Taylor KL, et al. DURATION-1: exenatide once weekly produces sustained glycemic control and weight loss over 52 weeks. Diabetes Care. 2010a;33:1255–61.
Buse JB, Sesti G, Schmidt WE, et al. Switching to once-daily liraglutide from twice-daily exenatide further improves glycemic control in patients with type 2 diabetes using oral agents. Diabetes Care. 2010b;33:1300–3.
Buse JB, Garber A, Rosenstock J, et al. Liraglutide treatment is associated with a low frequency and magnitude of antibody formation with no apparent impact on glycemic response or increased frequency of adverse events: results from the Liraglutide Effect and Action in Diabetes (LEAD) trials. J Clin Endocrinol Metab. 2011;96:1695–702.

Buse JB, Nauck M, Forst T, et al. Exenatide once weekly versus liraglutide once daily in patients with type 2 diabetes (DURATION-6): a randomised, open-label study. Lancet. 2013;381:117–24.

Buse JB, Vilsboll T, Thurman J, et al. Contribution of liraglutide in the fixed-ratio combination of insulin degludec and liraglutide (IDegLira). Diabetes Care. 2014;37:2926–33.

Calsolaro V, Edison P. Novel GLP-1 (Glucagon-like Peptide-1) analogues and insulin in the treatment for Alzheimer's disease and other neurodegenerative diseases. CNS Drugs. 2015;29:1023–39.

Cefalu WT, Buse JB, Del PS, et al. Beyond metformin: safety considerations in the decision-making process for selecting a second medication for type 2 diabetes management: reflections from a diabetes care editors' expert forum. Diabetes Care. 2014;37:2647–59.

Cervera A, Wajcberg E, Sriwijitkamol A, et al. Mechanism of action of exenatide to reduce postprandial hyperglycemia in type 2 diabetes. Am J Physiol Endocrinol Metab. 2008;294: E846–52.

Chen WR, Hu SY, Chen YD, et al. Effects of liraglutide on left ventricular function in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention. Am Heart J. 2015;170:845–54.

Conway B, Miller RG, Costacou T, et al. Temporal patterns in overweight and obesity in type 1 diabetes. Diabet Med. 2010;27:398–404.

Danne T, Biester T, Kapitzke K, et al. Liraglutide in an adolescent population with obesity: a randomized, double-blind, placebo-controlled 5-week trial to assess safety, tolerability, and pharmacokinetics of Liraglutide in adolescents aged 12–17 years. J Pediatr. 2017;181:146–53.

Davies MJ, Bergenstal R, Bode B, et al. Efficacy of Liraglutide for weight loss among patients with type 2 diabetes: the SCALE diabetes randomized clinical trial. JAMA. 2015;314:687–99.

Day JW, Gelfanov V, Smiley D, et al. Optimization of co-agonism at GLP-1 and glucagon receptors to safely maximize weight reduction in DIO-rodents. Biopolymers. 2012;98:443–50.

De SA, Salem V, Long CJ, et al. The gut hormones PYY 3-36 and GLP-1 7-36 amide reduce food intake and modulate brain activity in appetite centers in humans. Cell Metab. 2011;14:700–6.

Deacon CF, Knudsen LB, Madsen K, Wiberg FC, Jacobsen O, Holst JJ. Dipeptidyl peptidase IV resistant analogues of glucagon-like peptide-1 which have extended metabolic stability and improved biological activity. Diabetologia. 1998;41:271–8.

DeFronzo RA. Banting lecture. From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. Diabetes. 2009;58:773–95.

Dejgaard TF, Frandsen CS, Holst JJ, Madsbad S. Liraglutide for treating type 1 diabetes. Expert Opin Biol Ther. 2016a;16:579–90.

Dejgaard TF, Frandsen CS, Hansen TS, et al. Efficacy and safety of liraglutide for overweight adult patients with type 1 diabetes and insufficient glycaemic control (Lira-1): a randomised, double-blind, placebo-controlled trial. Lancet Diabetes Endocrinol. 2016b;4:221–32.

Dejgaard TF, Johansen NB, Frandsen CS, et al. Effects of liraglutide on cardiovascular risk factors in patients with type 1 diabetes. Diabetes Obes Metab. 2017;19:734–8.

Diamant M, Van GL, Guerci B, et al. Exenatide once weekly versus insulin glargine for type 2 diabetes (DURATION-3): 3-year results of an open-label randomised trial. Lancet Diabetes Endocrinol. 2014;2:464–73.

Dong JZ, Shen Y, Zhang J, Tsomaia N, Mierke DF, Taylor JE. Discovery and characterization of taspoglutide, a novel analogue of human glucagon-like peptide-1, engineered for sustained therapeutic activity in type 2 diabetes. Diabetes Obes Metab. 2011;13:19–25.

Drucker DJ. The cardiovascular biology of glucagon-like Peptide-1. Cell Metab. 2016;24:15–30.

Drucker DJ, Buse JB, Taylor K, et al. Exenatide once weekly versus twice daily for the treatment of type 2 diabetes: a randomised, open-label, non-inferiority study. Lancet. 2008;372: 1240–50.

Dungan KM, Povedano ST, Forst T, et al. Once-weekly dulaglutide versus once-daily liraglutide in metformin-treated patients with type 2 diabetes (AWARD-6): a randomised, open-label, phase 3, non-inferiority trial. Lancet. 2014;384:1349–57.

Egan AG, Blind E, Dunder K, et al. Pancreatic safety of incretin-based drugs – FDA and EMA assessment. N Engl J Med. 2014;370:794–7.

Eng C, Kramer CK, Zinman B, Retnakaran R. Glucagon-like peptide-1 receptor agonist and basal insulin combination treatment for the management of type 2 diabetes: a systematic review and meta-analysis. Lancet. 2014;384:2228–34.

Fonseca VA, Alvarado-Ruiz R, Raccah D, Boka G, Miossec P, Gerich JE. Efficacy and safety of the once-daily GLP-1 receptor agonist lixisenatide in monotherapy: a randomized, double-blind, placebo-controlled trial in patients with type 2 diabetes (GetGoal-Mono). Diabetes Care. 2012;35:1225–31.

Frandsen CS, Dejgaard TF, Holst JJ, Andersen HU, Thorsteinsson B, Madsbad S. Twelve-week treatment with Liraglutide as add-on to insulin in normal-weight patients with poorly controlled type 1 diabetes: a randomized, placebo-controlled, double-blind parallel study. Diabetes Care. 2015;38:2250–7.

Frandsen CS, Dejgaard TF, Madsbad S. Non-insulin drugs to treat hyperglycaemia in type 1 diabetes mellitus. Lancet Diabetes Endocrinol. 2016;4:766–80.

Frandsen CS, Dejgaard TF, Andersen HU, et al. Liraglutide as adjunct to insulin treatment in type 1 diabetes does not interfere with glycaemic recovery or gastric emptying rate during hypoglycaemia: a randomized, placebo-controlled, double-blind, parallel-group study. Diabetes Obes Metab. 2017;19:773–82.

Frias JP, Guja C, Hardy E, et al. Exenatide once weekly plus dapagliflozin once daily versus exenatide or dapagliflozin alone in patients with type 2 diabetes inadequately controlled with metformin monotherapy (DURATION-8): a 28 week, multicentre, double-blind, phase 3, randomised controlled trial. Lancet Diabetes Endocrinol. 2016;4:1004–16.

Frias JP, Bastyr EJ III, Vignati L, et al. The sustained effects of a dual GIP/GLP-1 receptor agonist, NNC0090-2746, in patients with type 2 diabetes. Cell Metab. 2017;26:343–52.

Gallwitz B, Ropeter T, Morys-Wortmann C, Mentlein R, Siegel EG, Schmidt WE. GLP-1-analogues resistant to degradation by dipeptidyl-peptidase IV in vitro. Regul Pept. 2000;86:103–11.

Gallwitz B, Vaag A, Falahati A, Madsbad S. Adding liraglutide to oral antidiabetic drug therapy: onset of treatment effects over time. Int J Clin Pract. 2010;64:267–76.

Garber AJ, Abrahamson MJ, Barzilay JI, et al. Consensus statement by the american association of clinical endocrinologists and american college of endocrinology on the comprehensive type 2 diabetes management algorithm – 2016 executive summary. Endocr Pract. 2016;22:84–113.

Glaesner W, Vick AM, Millican R, et al. Engineering and characterization of the long-acting glucagon-like peptide-1 analogue LY2189265, an Fc fusion protein. Diabetes Metab Res Rev. 2010;26:287–96.

Gough SC, Bode B, Woo V, et al. Efficacy and safety of a fixed-ratio combination of insulin degludec and liraglutide (IDegLira) compared with its components given alone: results of a phase 3, open-label, randomised, 26-week, treat-to-target trial in insulin-naive patients with type 2 diabetes. Lancet Diabetes Endocrinol. 2014;2:885–93.

Gough SC, Bode BW, Woo VC, et al. One-year efficacy and safety of a fixed combination of insulin degludec and liraglutide in patients with type 2 diabetes: results of a 26-week extension to a 26-week main trial. Diabetes Obes Metab. 2015;17:965–73.

Guh DP, Zhang W, Bansback N, Amarsi Z, Birmingham CL, Anis AH. The incidence of co-morbidities related to obesity and overweight: a systematic review and meta-analysis. BMC Public Health. 2009;9:88.

Haahr H, Heise T. A review of the pharmacological properties of insulin degludec and their clinical relevance. Clin Pharmacokinet. 2014;53:787–800.

Halbirk M, Norrelund H, Moller N, et al. Cardiovascular and metabolic effects of 48-h glucagon-like peptide-1 infusion in compensated chronic patients with heart failure. Am J Physiol Heart Circ Physiol. 2010;298:H1096–102.

Harder H, Nielsen L, Tu DT, Astrup A. The effect of liraglutide, a long-acting glucagon-like peptide 1 derivative, on glycemic control, body composition, and 24-h energy expenditure in patients with type 2 diabetes. Diabetes Care. 2004;27:1915–21.

Harkavyi A, Abuirmeileh A, Lever R, Kingsbury AE, Biggs CS, Whitton PS. Glucagon-like peptide 1 receptor stimulation reverses key deficits in distinct rodent models of Parkinson's disease. J Neuroinflammation. 2008;5:19.

Hegedus L, Moses AC, Zdravkovic M, Le TT, Daniels GH. GLP-1 and calcitonin concentration in humans: lack of evidence of calcitonin release from sequential screening in over 5000 subjects with type 2 diabetes or nondiabetic obese subjects treated with the human GLP-1 analog, liraglutide. J Clin Endocrinol Metab. 2011;96:853–60.

Henry RR, Rosenstock J, Logan DK, Alessi TR, Luskey K, Baron MA. Randomized trial of continuous subcutaneous delivery of exenatide by ITCA 650 versus twice-daily exenatide injections in metformin-treated type 2 diabetes. Diabetes Care. 2013a;36:2559–65.

Henry RR, Logan D, Alessi T, Baron MA. A randomized, open-label, multicenter, 4-week study to evaluate the tolerability and pharmacokinetics of ITCA 650 in patients with type 2 diabetes. Clin Ther. 2013b;35:634–45.

Henry RR, Rosenstock J, Logan D, Alessi T, Luskey K, Baron MA. Continuous subcutaneous delivery of exenatide via ITCA 650 leads to sustained glycemic control and weight loss for 48 weeks in metformin-treated subjects with type 2 diabetes. J Diabetes Complicat. 2014;28:393–8.

Hermansen K, Baekdal TA, During M, et al. Liraglutide suppresses postprandial triglyceride and apolipoprotein B48 elevations after a fat-rich meal in patients with type 2 diabetes: a randomized, double-blind, placebo-controlled, cross-over trial. Diabetes Obes Metab. 2013;15:1040–8.

Holman RR, Bethel MA, Mentz RJ, et al. Effects of once-weekly Exenatide on cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2017;377:1228–39.

Holst JJ, Knop FK, Vilsboll T, Krarup T, Madsbad S. Loss of incretin effect is a specific, important, and early characteristic of type 2 diabetes. Diabetes Care. 2011;34(Suppl 2):S251–7.

Iepsen EW, Lundgren J, Dirksen C, et al. Treatment with a GLP-1 receptor agonist diminishes the decrease in free plasma leptin during maintenance of weight loss. Int J Obes (Lond). 2015;39:834–41.

Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycaemia in type 2 diabetes, 2015: a patient-centred approach. Update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetologia. 2015;58:429–42.

Jelsing J, Vrang N, Hansen G, Raun K, Tang-Christensen M, Knudsen LB. Liraglutide: short-lived effect on gastric emptying – long lasting effects on body weight. Diabetes Obes Metab. 2012;14:531–8.

Jendle J, Grunberger G, Blevins T, Giorgino F, Hietpas RT, Botros FT. Efficacy and safety of dulaglutide in the treatment of type 2 diabetes: a comprehensive review of the dulaglutide clinical data focusing on the AWARD phase 3 clinical trial program. Diabetes Metab Res Rev. 2016;32:776–90.

Jensen MD, Ryan DH, Apovian CM, et al. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. J Am Coll Cardiol. 2014;63:2985–3023.

Ji L, Onishi Y, Ahn CW, et al. Efficacy and safety of exenatide once-weekly vs exenatide twice-daily in Asian patients with type 2 diabetes mellitus. J Diabetes Investig. 2013;4:53–61.

Jorsal A, Kistorp C, Holmager P, et al. Effect of liraglutide, a glucagon-like peptide-1 analogue, on left ventricular function in stable chronic heart failure patients with and without diabetes (LIVE)-a multicentre, double-blind, randomised, placebo-controlled trial. Eur J Heart Fail. 2017;19:69–77.

Kapitza C, Forst T, Coester HV, Poitiers F, Ruus P, Hincelin-Mery A. Pharmacodynamic characteristics of lixisenatide once daily versus liraglutide once daily in patients with type 2 diabetes insufficiently controlled on metformin. Diabetes Obes Metab. 2013;15:642–9.

Kapitza C, Nosek L, Jensen L, Hartvig H, Jensen CB, Flint A. Semaglutide, a once-weekly human GLP-1 analog, does not reduce the bioavailability of the combined oral contraceptive, ethinylestradiol/levonorgestrel. J Clin Pharmacol. 2015;55:497–504.

Kielgast U, Holst JJ, Madsbad S. Treatment of type 1 diabetic patients with glucagon-like peptide-1 (GLP-1) and GLP-1R agonists. Curr Diabetes Rev. 2009;5:266–75.

Kielgast U, Holst JJ, Madsbad S. Antidiabetic actions of endogenous and exogenous GLP-1 in type 1 diabetic patients with and without residual beta-cell function. Diabetes. 2011;60:1599–607.

Knudsen LB, Nielsen PF, Huusfeldt PO, et al. Potent derivatives of glucagon-like peptide-1 with pharmacokinetic properties suitable for once daily administration. J Med Chem. 2000;43: 1664–9.

Kolterman OG, Kim DD, Shen L, et al. Pharmacokinetics, pharmacodynamics, and safety of exenatide in patients with type 2 diabetes mellitus. Am J Health Syst Pharm. 2005;62:173–81.

Kumarathurai P, Anholm C, Nielsen OW, et al. Effects of the glucagon-like peptide-1 receptor agonist liraglutide on systolic function in patients with coronary artery disease and type 2 diabetes: a randomized double-blind placebo-controlled crossover study. Cardiovasc Diabetol. 2016;15:105.

Kumarathurai P, Anholm C, Larsen BS, et al. Effects of Liraglutide on heart rate and heart rate variability: a randomized, double-blind, placebo-controlled crossover study. Diabetes Care. 2017a;40:117–24.

Kumarathurai P, Anholm C, Fabricius-Bjerre A, et al. Effects of the glucagon-like peptide-1 receptor agonist liraglutide on 24-h ambulatory blood pressure in patients with type 2 diabetes and stable coronary artery disease: a randomized, double-blind, placebo-controlled, crossover study. J Hypertens. 2017b;35:1070–8.

Lau J, Bloch P, Schaffer L, et al. Discovery of the once-weekly glucagon-like Peptide-1 (GLP-1) analogue Semaglutide. J Med Chem. 2015;58:7370–80.

le Roux CW, Astrup A, Fujioka K, et al. 3 years of liraglutide versus placebo for type 2 diabetes risk reduction and weight management in individuals with prediabetes: a randomised, double-blind trial. Lancet. 2017;389:1399–409.

Lepore JJ, Olson E, Demopoulos L, et al. Effects of the novel long-acting GLP-1 agonist, Albiglutide, on cardiac function, cardiac metabolism, and exercise capacity in patients with chronic heart failure and reduced ejection fraction. JACC Heart Fail. 2016;4:559–66.

Lingvay I, Perez MF, Garcia-Hernandez P, et al. Effect of insulin glargine up-titration vs insulin Degludec/Liraglutide on glycated hemoglobin levels in patients with uncontrolled type 2 diabetes: the DUAL V randomized clinical trial. JAMA. 2016;315:898–907.

Linjawi S, Bode BW, Chaykin LB, et al. The efficacy of IDegLira (Insulin Degludec/Liraglutide combination) in adults with type 2 diabetes inadequately controlled with a GLP-1 receptor agonist and oral therapy: DUAL III randomized clinical trial. Diabetes Ther. 2017;8:101–7.

Lonborg J, Kelbaek H, Vejlstrup N, et al. Exenatide reduces final infarct size in patients with ST-segment-elevation myocardial infarction and short-duration of ischemia. Circ Cardiovasc Interv. 2012;5:288–95.

Madsbad S. Prevalence of residual B cell function and its metabolic consequences in type 1 (insulin-dependent) diabetes. Diabetologia. 1983;24:141–7.

Madsbad S. Exenatide and liraglutide: different approaches to develop GLP-1 receptor agonists (incretin mimetics) – preclinical and clinical results. Best Pract Res Clin Endocrinol Metab. 2009;23:463–77.

Madsbad S. The role of glucagon-like peptide-1 impairment in obesity and potential therapeutic implications. Diabetes Obes Metab. 2014;16:9–21.

Madsbad S. Review of head-to-head comparisons of glucagon-like peptide-1 receptor agonists. Diabetes Obes Metab. 2016;18:317–32.

Madsbad S, Kielgast U, Asmar M, Deacon CF, Torekov SS, Holst JJ. An overview of once-weekly glucagon-like peptide-1 receptor agonists – available efficacy and safety data and perspectives for the future. Diabetes Obes Metab. 2011;13:394–407.

Mann KV, Raskin P. Exenatide extended-release: a once weekly treatment for patients with type 2 diabetes. Diabetes Metab Syndr Obes. 2014;7:229–39.

Mann JFE, Orsted DD, Brown-Frandsen K, et al. Liraglutide and renal outcomes in type 2 diabetes. N Engl J Med. 2017;377:839–48.

Margulies KB, Hernandez AF, Redfield MM, et al. Effects of Liraglutide on clinical stability among patients with advanced heart failure and reduced ejection fraction: a randomized clinical trial. JAMA. 2016;316:500–8.
Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2016a;375:311–22.
Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med. 2016b;375:1834.
Mathieu C, Zinman B, Hemmingsson JU, et al. Efficacy and safety of Liraglutide added to insulin treatment in type 1 diabetes: the ADJUNCT ONE treat-to-target randomized trial. Diabetes Care. 2016;39:1702–10.
McClean PL, Parthsarathy V, Faivre E, Holscher C. The diabetes drug liraglutide prevents degenerative processes in a mouse model of Alzheimer's disease. J Neurosci. 2011;31: 6587–94.
Meier JJ. GLP-1 receptor agonists for individualized treatment of type 2 diabetes mellitus. Nat Rev Endocrinol. 2012;8:728–42.
Meier JJ, Nauck MA. Incretin-based therapies: where will we be 50 years from now? Diabetologia. 2015;58:1745–50.
Meier JJ, Gallwitz B, Salmen S, et al. Normalization of glucose concentrations and deceleration of gastric emptying after solid meals during intravenous glucagon-like peptide 1 in patients with type 2 diabetes. J Clin Endocrinol Metab. 2003;88:2719–25.
Meier JJ, Nauck MA, Kranz D, et al. Secretion, degradation, and elimination of glucagon-like peptide 1 and gastric inhibitory polypeptide in patients with chronic renal insufficiency and healthy control subjects. Diabetes. 2004;53:654–62.
Meier JJ, Rosenstock J, Hincelin-Mery A, et al. Contrasting effects of Lixisenatide and Liraglutide on postprandial glycemic control, gastric emptying, and safety parameters in patients with type 2 diabetes on optimized insulin glargine with or without metformin: a randomized, open-label trial. Diabetes Care. 2015;38:1263–73.
Nauck MA, Kleine N, Orskov C, Holst JJ, Willms B, Creutzfeldt W. Normalization of fasting hyperglycaemia by exogenous glucagon-like peptide 1 (7-36 amide) in type 2 (non-insulin-dependent) diabetic patients. Diabetologia. 1993;36:741–4.
Nauck MA, Petrie JR, Sesti G, et al. A phase 2, randomized, dose-finding study of the novel once-weekly human GLP-1 analog, Semaglutide, compared with placebo and open-label Liraglutide in patients with type 2 diabetes. Diabetes Care. 2016a;39:231–41.
Nauck M, Rizzo M, Johnson A, Bosch-Traberg H, Madsen J, Cariou B. Once-daily Liraglutide versus Lixisenatide as add-on to metformin in type 2 diabetes: a 26-week randomized controlled clinical trial. Diabetes Care. 2016b;39:1501–9.
Nikolaidis LA, Mankad S, Sokos GG, et al. Effects of glucagon-like peptide-1 in patients with acute myocardial infarction and left ventricular dysfunction after successful reperfusion. Circulation. 2004;109:962–5.
Ostergaard L, Frandsen CS, Madsbad S. Treatment potential of the GLP-1 receptor agonists in type 2 diabetes mellitus: a review. Expert Rev Clin Pharmacol. 2016;9:241–65.
Pfeffer MA, Claggett B, Diaz R, et al. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. N Engl J Med. 2015;373:2247–57.
Pinget M, Goldenberg R, Niemoeller E, Muehlen-Bartmer I, Guo H, Aronson R. Efficacy and safety of lixisenatide once daily versus placebo in type 2 diabetes insufficiently controlled on pioglitazone (GetGoal-P). Diabetes Obes Metab. 2013;15:1000–7.
Pi-Sunyer X, Astrup A, Fujioka K, et al. A randomized, controlled trial of 3.0 mg of Liraglutide in weight management. N Engl J Med. 2015;373:11–22.
Polonsky WH, Fisher L, Hessler D, Bruhn D, Best JH. Patient perspectives on once-weekly medications for diabetes. Diabetes Obes Metab. 2011;13:144–9.
Polster M, Zanutto E, McDonald S, Conner C, Hammer M. A comparison of preferences for two GLP-1 products – liraglutide and exenatide – for the treatment of type 2 diabetes. J Med Econ. 2010;13:655–61.

Pratley RE, Nauck MA, Barnett AH, et al. Once-weekly albiglutide versus once-daily liraglutide in patients with type 2 diabetes inadequately controlled on oral drugs (HARMONY 7): a randomised, open-label, multicentre, non-inferiority phase 3 study. Lancet Diabetes Endocrinol. 2014;2:289–97.

Pujadas G, Drucker DJ. Vascular biology of glucagon receptor superfamily peptides: mechanistic and clinical relevance. Endocr Rev. 2016;37:554–83.

Pyke C, Heller RS, Kirk RK, et al. GLP-1 receptor localization in monkey and human tissue: novel distribution revealed with extensively validated monoclonal antibody. Endocrinology. 2014;155:1280–90.

Ratner RE, Rosenstock J, Boka G. Dose-dependent effects of the once-daily GLP-1 receptor agonist lixisenatide in patients with Type 2 diabetes inadequately controlled with metformin: a randomized, double-blind, placebo-controlled trial. Diabet Med. 2010;27:1024–32.

Riddle MC, Aronson R, Home P, et al. Adding once-daily lixisenatide for type 2 diabetes inadequately controlled by established basal insulin: a 24-week, randomized, placebo-controlled comparison (GetGoal-L). Diabetes Care. 2013;36:2489–96.

Robinson LE, Holt TA, Rees K, Randeva HS, O'Hare JP. Effects of exenatide and liraglutide on heart rate, blood pressure and body weight: systematic review and meta-analysis. BMJ Open. 2013;3:e001986.

Rodbard HW, Bode BW, Harris SB, et al. Safety and efficacy of insulin degludec/liraglutide (IDegLira) added to sulphonylurea alone or to sulphonylurea and metformin in insulin-naive people with Type 2 diabetes: the DUAL IV trial. Diabet Med. 2017;34:189–96.

Rosenstock J, Raccah D, Koranyi L, et al. Efficacy and safety of lixisenatide once daily versus exenatide twice daily in type 2 diabetes inadequately controlled on metformin: a 24-week, randomized, open-label, active-controlled study (GetGoal-X). Diabetes Care. 2013a;36:2945–51.

Rosenstock J, Balas B, Charbonnel B, et al. The fate of taspoglutide, a weekly GLP-1 receptor agonist, versus twice-daily exenatide for type 2 diabetes: the T-emerge 2 trial. Diabetes Care. 2013b;36:498–504.

Rosenstock J, Hanefeld M, Shamanna P, et al. Beneficial effects of once-daily lixisenatide on overall and postprandial glycemic levels without significant excess of hypoglycemia in type 2 diabetes inadequately controlled on a sulfonylurea with or without metformin (GetGoal-S). J Diabetes Complicat. 2014a;28:386–92.

Rosenstock J, Fonseca VA, Gross JL, et al. Advancing basal insulin replacement in type 2 diabetes inadequately controlled with insulin glargine plus oral agents: a comparison of adding albiglutide, a weekly GLP-1 receptor agonist, versus thrice-daily prandial insulin lispro. Diabetes Care. 2014b;37:2317–25.

Rosenstock J, Diamant M, Aroda VR, et al. Efficacy and safety of LixiLan, a titratable fixed-ratio combination of Lixisenatide and insulin glargine, versus insulin glargine in type 2 diabetes inadequately controlled on metformin monotherapy: the LixiLan proof-of-concept randomized trial. Diabetes Care. 2016a;39:1579–86.

Rosenstock J, Aronson R, Grunberger G, et al. Benefits of LixiLan, a titratable fixed-ratio combination of insulin glargine plus Lixisenatide, versus insulin glargine and Lixisenatide Monocomponents in Type 2 diabetes inadequately controlled on oral agents: the LixiLan-O randomized trial. Diabetes Care. 2016b;39:2026–35.

Secher A, Jelsing J, Baquero AF, et al. The arcuate nucleus mediates GLP-1 receptor agonist liraglutide-dependent weight loss. J Clin Invest. 2014;124:4473–88.

Seino Y, Min KW, Niemoeller E, Takami A. Randomized, double-blind, placebo-controlled trial of the once-daily GLP-1 receptor agonist lixisenatide in Asian patients with type 2 diabetes insufficiently controlled on basal insulin with or without a sulfonylurea (GetGoal-L-Asia). Diabetes Obes Metab. 2012;14:910–7.

Smits MM, Muskiet MH, Tonneijck L, et al. Exenatide acutely increases heart rate in parallel with augmented sympathetic nervous system activation in healthy overweight males. Br J Clin Pharmacol. 2016;81:613–20.

Sorli C, Harashima SI, Tsoukas GM, et al. Efficacy and safety of once-weekly semaglutide monotherapy versus placebo in patients with type 2 diabetes (SUSTAIN 1): a double-blind, randomised, placebo-controlled, parallel-group, multinational, multicentre phase 3a trial. Lancet Diabetes Endocrinol. 2017;5:251–60.

Tan TM, Salem V, Troke RC, et al. Combination of peptide YY3-36 with GLP-1(7-36) amide causes an increase in first-phase insulin secretion after IV glucose. J Clin Endocrinol Metab. 2014;99:E2317–24.

Teramoto S, Miyamoto N, Yatomi K, et al. Exendin-4, a glucagon-like peptide-1 receptor agonist, provides neuroprotection in mice transient focal cerebral ischemia. J Cereb Blood Flow Metab. 2011;31:1696–705.

Vora J, Christensen T, Rana A, Bain SC. Insulin degludec versus insulin glargine in type 1 and type 2 diabetes mellitus: a meta-analysis of endpoints in phase 3a trials. Diabetes Ther. 2014;5:435–46.

Wadden TA, Hollander P, Klein S, et al. Weight maintenance and additional weight loss with liraglutide after low-calorie-diet-induced weight loss: the SCALE Maintenance randomized study. Int J Obes (Lond). 2015;39:187.

Weissman PN, Carr MC, Ye J, et al. HARMONY 4: randomised clinical trial comparing once-weekly albiglutide and insulin glargine in patients with type 2 diabetes inadequately controlled with metformin with or without sulfonylurea. Diabetologia. 2014;57:2475–84.

Young MA, Wald JA, Matthews JE, et al. Clinical pharmacology of albiglutide, a GLP-1 receptor agonist. Postgrad Med. 2014;126:84–97.

Zander M, Madsbad S, Madsen JL, Holst JJ. Effect of 6-week course of glucagon-like peptide 1 on glycaemic control, insulin sensitivity, and beta-cell function in type 2 diabetes: a parallel-group study. Lancet. 2002;359:824–30.