MANAGEMENT OF ENDOCRINE DISEASE

Are all GLP-1 agonists equal in the treatment of type 2 diabetes?

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Abstract

GLP-1, a peptide hormone secreted from the gut, stimulating insulin and suppressing glucagon secretion was identified as a parent compound for novel treatments of diabetes, but was degraded (dipeptidyl peptidase-4) and eliminated (mainly by kidneys) too fast (half-life 1–2 min) to be useful as a therapeutic agent. GLP-1 receptor agonist has been used to treat patients with type 2 diabetes since 2007, when exenatide (twice daily) was approved in 2007. Compounds with longer duration of action (once daily, once weekly) and with increasingly better efficacy with respect to glycaemic control and body weight reduction have been developed, and in a recent ADA/EASD consensus statement, were recommended as the first injectable diabetes therapy after failure of oral glucose-lowering medications. Most GLP-1 receptor agonists (lixisenatide q.d., liraglutide q.d., exenatide q.w., dulaglutide q.w., albiglutide q.w., semaglutide q.w., all for s.c. injection, and the first oral preparation, oral semaglutide) have been examined in cardiovascular outcomes studies. Beyond proving their safety in vulnerable patients, most of whom had pre-existing heart disease, liraglutide, semaglutide, albiglutide, and dulaglutide reduced the time to first major adverse cardiovascular events (non-fatal myocardial infarction and stroke, cardiovascular death). Liraglutide, in addition, reduced cardiovascular and all-cause mortality. It is the purpose of the present review to describe clinically important differences, regarding pharmacokinetic behaviour, glucose-lowering potency, effectiveness of reducing body weight and controlling other cardiovascular risk factors, and of the influence of GLP-1 receptor agonist treatment on cardiovascular outcomes in patients either presenting with or without pre-existing cardiovascular disease (atherosclerotic, ischemic or congestive heart failure).

European Journal of Endocrinology
(2019) **181**, R211–R234

European Journal of Endocrinology

Invited Author profile

Prof. Michael Nauck MD is Head of Clinical Research at the Diabetes Division of St. Josef-Hospital (Ruhr-University Bochum) in Bochum, Germany. He teaches at Georg-August University,Göttingen, and Ruhr-University, Bochum, Germany. Professor Nauck has a particular research interest in the role of gastrointestinal peptide hormones (incretins: glucose-dependent insulinotropic polypeptide, GIP, and glucagon-like peptide-1, GLP-1) in the physiological regulation of metabolism and in the pathophysiology of type 2 diabetes. He has contributed pivotal studies proving a therapeutic potential of GLP-1 in type 2 diabetes. He has contributed to the development of incretin-based glucose-lowering medications such as GLP-1 receptor agonists and inhibitors of dipeptidyl peptidase-4. Additional areas of interest include spontaneous hypoglycaemia (insulinomas), pancreas transplantation, cardiovascular complications of type 2 diabetes, and the modification of cardiovascular risk in type 2-diabetic patients with glucose-lowering pharmacotherapy. His scientific contributions have been honoured with several awards, including the Ferdinand-Bertram Award (1993), the Werner-Creutzfeldt Award (2007) and the Paul Langerhans Medal (2012) of the German Diabetes Association.

https://eje.bioscientifica.com
https://doi.org/10.1530/EJE-19-0566

Published by Bioscientifica Ltd.

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

GLP-1 in human subjects was detected in 1983 as one of two 'glucagon-like' stretches of the proglucagon sequence (i.e., at the mRNA level) (1), which left uncertainty about details of post-translational processing and the resulting peptide structure. GLP-1 (7-36amide) (amidated GLP-1) and - to a lesser extent, GLP-1 (7-37) (glycine-extended GLP-1) - were identified as the peptides produced in intestinal L-cells in 1987 (2, 3). GLP-1 turned out to be a potent insulinotropic agent, stimulating insulin secretion whenever plasma glucose was higher than at fasting concentrations, and suppressing glucagon secretion at normo- and hyperglycaemia, but allowing its counter-regulatory activity in the case of hypoglycaemia (4, 5). On these premises it qualified as an incretin hormone. Unlike the other incretin hormone, glucose-dependent insulinotropic polypeptide (GIP, formerly called gastric inhibitory polypeptide), GLP-1 turned out to be active in patients with type 2 diabetes (4, 6). It was able to reduce hyperglycaemia in fasting type 2-diabetic patients into the normal fasting plasma glucose range, and abolished post-meal glycaemic rises after mixed meals in proof-of-principle studies employing exogenous synthetic GLP-1 administered intravenously (5, 7). Pre-clinical and clinical research also indicated a potential for reducing appetite, food intake, and body weight (8, 9). Studies employing i.v. or s.c. administration of GLP-1 (10) also indicated that GLP-1 is rapidly degraded and inactivated by a ubiquitous protease, dipeptidyl peptiase-4 (DPP-4) and also eliminated from the circulation quickly, resulting in a half-life of 1–2 min only. Consequently, s.c. administration gave rise to short-lived peaks lasting for a maximum of 90 min, even when applying large doses that caused side effects (5, 7). Thus, it became evident that the original GLP-1 peptide needed to be modified to result in peptides resistant to DPP-4 and with slower elimination kinetics, in order to be clinically useful glucose-lowering agents. Molecular structures of GLP-1 receptor agonists and the parent compound, GLP-1, are shown in Fig. 1.

The first GLP-1 receptor agonist to be approved for the treatment of type 2 diabetes was exenatide, which was synthetic exendin-4, a peptide from the saliva of a

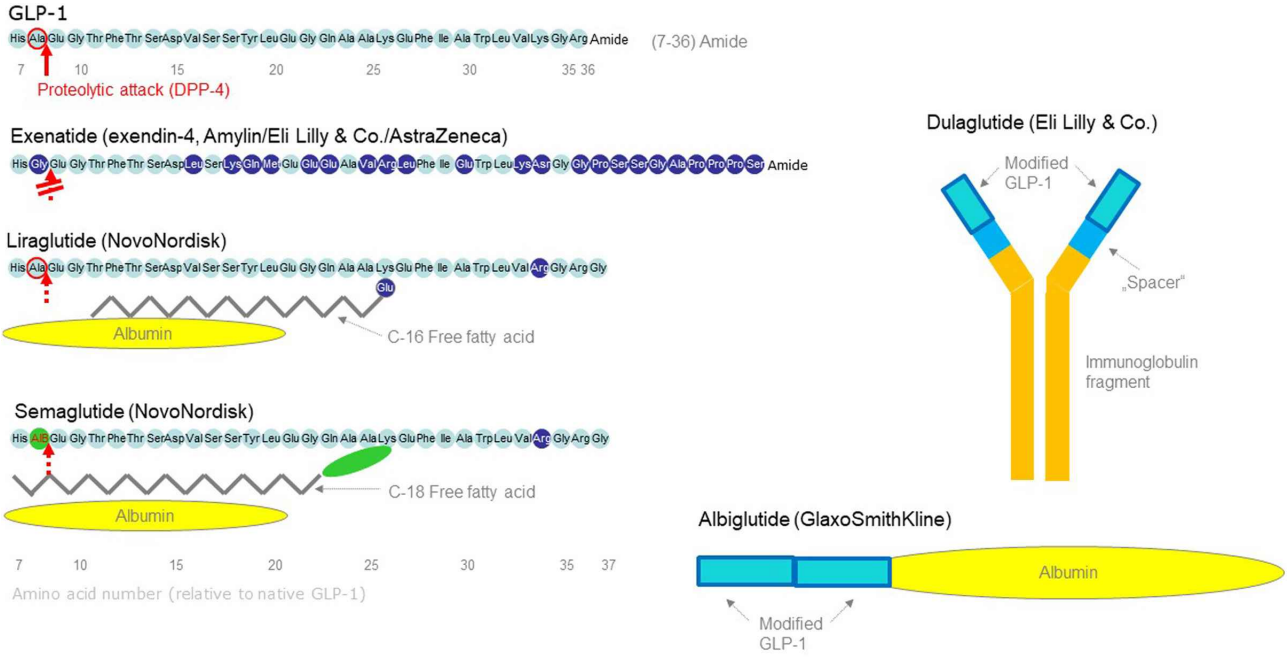


Figure 1

Molecular structures of GLP-1 receptor agonists used for the treatment of type 2 diabetes. For small-molecular-weight compounds, the amino acid sequence is shown (left hand panels). Amino acids identical with mammalian (human) GLP-1 are shown in light green, amino acids differing from the parent compound are shown in dark blue. Large-molecular weight compounds (right hand panels) are shown schematically indicating the large protein component, spacer peptides, and modified GLP-1 peptides. These modifications concern amino acid exchanges prohibiting proteolytic attack by dipeptidyl peptidase-4 (DPP-4).

lizard from Arizona, *Heloderma suspectum*, which was purified without any intention to be in search of a diabetes medication (11). The similarity of the peptide structure to GLP-1 was noticed (Fig. 1), and it was found to stimulate GLP-1 receptors with an affinity like (or even slightly better than) GLP-1 (12). Exenatide happened to be DPP-4-resistant and eliminated more slowly, with a half-life of approximately 2–3 h (7, 12). Regimens with two or three times daily administrations were tested, and a regimen for injecting exenatide subcutaneously before breakfast and before dinner (twice daily) was approved. Exenatide had a 53% sequence homology compared to mammalian GLP-1 and, thus, was dissimilar enough to provoke some immunogenicity leading to antibody formation in the majority of patients, however, without obvious consequences for its therapeutic efficacy (13, 14).

The next agent to be developed was liraglutide, the peptide backbone of which was preserved 97% compared to the original GLP-1 peptide (Fig. 1). Prolonged action was achieved by attaching a free fatty acid side chain through a linker molecule, which promotes binding to albumin in extracellular fluid and plasma (15). Only approximately 1–2% of liraglutide are thought to circulate in a non-albumin-bound state, while the majority represents a reservoir from which liraglutide can dissociate to reach tissues and cells expressing GLP-1 receptors. The approximate half-life is 13 h (16), and liraglutide was approved for once daily s.c. injections in 2009.

The first compound designed for once-weekly injections was exentide once weekly, which is exenatide 'encaged' in a polymer which slowly dissolves after injections into subcutaneous adipose tissue (17, 18). The compound that is thus slowly released into the circulation is exenatide (identical to the un-retarded compound injected twice daily); however, the slow absorption of the so-called exenatide mircrospheres guarantees steady plasma concentrations slowly rising to a steady state within approximately 10 weeks with once weekly injections (14, 18). This means that after discontinuing this treatment, it will take weeks before all exenatide is absorbed and eliminated.

A novel approach was taken in the case of dulaglutide and albiglutide: Bigger proteins (an immunoglobulin fragment in the case of dulaglutide (19), albumin in the case of albiglutide (20)) were linked to two modified (DPP-4-resistant) GLP-1 molecules, incorporated into the linear sequence of albumin in the case of albiglutide, peripherally attached with the help of linker molecules in the case of dulaglutide (Fig. 1). The big 'carrier' proteins are typically slowly degraded/eliminated from the circulation. Thus, these compounds have half lives in the order of magnitude of 1 week (21, 22, 23) and can be injected once weekly. Since the protracted action of dulaglutide and albiglutide is mainly supported by their slow elimination, relatively rapid absorption leads to an earlier onset of clinically noticeable action as compared to exenatide once weekly (24, 25).

Semaglutide has a molecular structure very much like liraglutide (Fig. 1). However, the alanine in amino acid position 2, which is recognized and 'attacked' by DPP-4, has been exchanged for α-amino butyric acid to make the molecule entirely DPP-4-resistant (26). The binding of the fatty acid side chain seems to be tighter, such that elimination is even slower (27), and supports once-weekly dosing.

Recently, an oral preparation of semaglutide has been developed, which contains semaglutide (identical to the compound used for s.c. injection) and an absorption enhancer, Sodium N-(8-(2-hydroxybenzoyl) Amino) Caprylat (SNAC), which locally raises pH, prevents degradation of semaglutide, and facilitates absorption, most likely through gastric mucosa (28). Note that the bioavailability is still low, and much more peptide needs to be ingested to achieve similar plasma concentrations and efficacy (up to 14 mg per day as compared to 1 mg per week in the case of semaglutide for s.c. injection, i.e. a 98-fold difference). To compensate for low and variable absorption, this oral preparation of semaglutide is recommended to be taken once daily. Predictable absorption and exposure to the drug requires it to be taken after an overnight fast with a small volume of water. A 30-min interval between the ingestion of the drug and the subsequent meal is required, before more fluid, food or other medications can be taken (28). Nevertheless, the development of an oral drug is a remarkable achievement and innovation.

Pharmacokinetic differences between GLP-1 receptor agonist compounds

Important pharmacokinetic characteristics for the individual GLP-1 receptor agonists are summarized in Table 1. Basically, these data support the different intervals between subsequent injections suggested, tested and approved for various compounds belonging to the GLP-1 receptor agonist class.

Exenatide, as a product of serendipity rather than developed by rational drug design, had a relatively short half-life, but was able to reduce glycated haemoglobin

Table 1 Molecular details, pharmacokinetic features and dosing of various GLP-1 receptor agonists approved for the treatment of type 2 diabetes.

	General features					Pharmacokinetics (single dose administration)	
Compound	Structure (Fig. 1)	Molecular weight (g/mol)*	Approved doses (µg or mg)	Interval between injections (h or days)	Initial up-titration recommended?	Time to peak (h/days)	Elimination half-life (h/days)
Exenatide b.i.d. (unretarded)	Natural peptide (exendin-4) from the saliva of the lizard *Heloderma suspectum* (53% homology)	4186.6	• 5 µg • 10 µg	Before breakfast and dinner (twice daily) (30)	Yes	2.1–2.2 h (33)	3.3–4.0 h (33)
Lixisenatide q.d.	Exenatide plus poly-lysine tail	4858.6	• 10 µg • 20 µg	Before breakfast or before the most carbohydrate-rich meal (once daily)	Yes	≈ 2 h (34)	2.6 h (34)
Liraglutide q.d.	Slightly modified GLP-1 (97% homology) with free fatty acid side chain attached	3751.3	• 0.6 mg • 1.2 mg • 1.8 mg	Once daily (approximately the same time every day)	Yes	11.0–13.8 h (35)	12.6–14.3 h (35)
Exenatide once weekly q.w.	See exenatide	4186.6	• 2 mg	Once weekly	No†	Slow‡	See exenatide
Dulaglutide q.w.	Two modified GLP-1 molecules attached to an immunoglobulin (Fc) fragment	59669.8	• 0.75 mg • 1.50 mg	Once weekly	No	48 h (23)	4.7-5.5 day (23)
Albiglutide q.w.	Two modified GLP-1 molecules amino-terminally attached to the linear structure of albumin	72,970.4	• 30 mg • 50 mg	Once weekly	Yes	3–5 day (36)	5.7–6.8 day (36)
Semaglutide (for s.c. injection) q.w.	Slightly modified GLP-1 (94% homology) with free fatty acid side chain attached	4113.6	• 0.5 mg • 1.0 mg	Once weekly	Yes	24 h (27)	7.6 day (27)
Semaglutide (for oral administration) q.d.		4113.6	• 3 mg§ • 7 mg§ • 14 mg§	30 min before breakfast‖ (once daily)	Yes	Early appearance (within 1–4 h) (28)	See semaglutide for s.c. injection

*For comparison, the molecular weight of glucagon-like peptide-1is 3297.7 g/mol; ‖total concentrations (including albumin-bound GLP-1 receptor agonist). Free (non-albumin-bound) concentrations probably represent 1–2% of total concentrations; ***this was a study in healthy subjects; †due to slow absorption from s.c. depots, exenatide concentrations only rise to a steady-state within 8–10 weeks; ‡not formally assessed, since a single injection does not lead to measurable concentrations; the onset of glucose-lowering actions are seen after 4 weeks of treatment and onward; §all doses of oral semaglutide formulated with sodium *N*-(8-[2-hydroxybenzoyl] amino) caprylate (SNAC).

and body weight with twice daily injections to a meaningful extent, but clearly is a short-acting agent that only transiently leads to pharmacologically active drug exposure after each injection (for approximately 6–8 h) (29). However, injecting exenatide three times per day did not result in convincingly better efficacy (30). This means that with exenatide injected twice a day, much of a 24-h period, exenatide plasma concentrations will be too low to fully exploit the potential of GLP-1 receptor agonists for lowering glucose actions.

While lixisenatide is a somewhat optimized derivative of exenatide (with a poly-lysine tail added at the C-terminus), it still has a rather short half-life (31). It is meant to be injected once a day, either before breakfast or before the meal with the largest carbohydrate content (32). With the once-daily injection, plasma concentrations will reach an effective exposure for estimated 8 h, leaving 2/3 of the day with relatively low drug exposure (31).

Liraglutide is the only long-acting GLP-1 receptor agonist to be injected once daily, but still leading to steadily elevated liraglutide concentrations over a full 24-h period (16). The minor decay after reaching a small peak after each s.c. injection of liraglutide leads to fluctuations by approximately 30% during each day (16, 37). Approximately 1–2% of circulating liraglutide is not albumin-bound and is able to freely diffuse into tissues and exert biological effects (38).

Little is known about potential fluctuations in drug exposure during a 24-h period or the week between two injections in the case of once-weekly injected compounds. Extending the interval between two injections of albiglutide to 2 weeks led to fluctuations in fasting plasma glucose reflecting lower drug exposure during the second week, indicating that the interval needs to reflect the elimination kinetics of a given compound (39).

Use of GLP-1 receptor agonists in special populations

Pharmacokinetic properties may depend on renal and hepatic function, depending on the routes of elimination. Table 2 compiles data generated with respect to pharmacokinetics, safety and tolerability of GLP-1 receptor agonists in subjects with impaired renal function. Recommendations regarding their use in patients with hepatic functional impairment are also shown.

As a rule, exenatide and related compounds like lixisenatide are renally eliminated and should not be used in patients with advanced stages of renal functional impairment. Albumin-bound GLP-1 receptor agonists (liraglutide and semaglutide) or large proteins with GLP-1 components attached (dulaglutide, albiglutide) are eliminated independent from renal function. Generally, in mild or moderate chronic renal disease, no dose reduction with lower eGFR is recommended. However, because of limited experience, a general recommendation is to use all GLP-1 receptor agonists with caution in patients with chronic kidney disease and low eGFRs, and not at all below eGFRs of 15 or 30 mL/min (1.73 m^2)$^{-1}$, depending on the compound.

Finding the optimum dose for GLP-1 receptor agonists in phase 2 studies

All new drugs need to be tested in phase 2 clinical studies, which aim at identifying dose regimens that lead to optimized effects on target parameters (e.g. HbA_{1c}, body weight), while being tolerable for patients. Thus, the balance between (wanted) effectiveness and (unwanted) side effects is the main criterion for selecting doses for phase 3 trials and, later, for approval. In the case of GLP-1 receptor agonists, this process can be complicated by the fact that tolerability, in part, depends on the velocity of a rise in exposure to the drug when starting treatment (55). Starting with too high a dose or increasing the dose too quickly and by major steps may provoke nausea, vomiting, or diarrhoea (commonly called 'gastrointestinal' side effects, although they probably are caused by a direct interaction with the brain stem) (56). Careful selection of a dose range, including ineffective and not-so-well tolerable doses, and the choice of an initial up-titration regimen leading to slowly rising drug levels may be crucial for identifying optimum doses for any given GLP-1 receptor agonist.

The beneficial effect of slowly up-titrating GLP-1 receptor agonists was first described in the case of exenatide b.i.d. (55), but later the dose-finding studies were performed with a relatively narrow range of doses (57, 58).

The development of liraglutide was delayed because a first wave of phase 2 studies did not sufficiently identify the upper range of effective, but tolerable doses (59, 60). A second approach was taken, using initial up-titration to prevent excessive side effects, thus arriving at a substantially higher, but still tolerable dose range (61). The doses identified and up-titration regimens were further optimized for phase 3 studies.

Dose finding for exenatide once weekly only relied on a small study testing 0.8 and 2.0 mg per week, with

Table 2 Potential restrictions in the use of GLP-1 receptor agonists in patients with impaired renal and hepatic function and potential renal benefits demonstrated in clinical trials with various GLP-1 receptor agonists.

Compound	**Exenatide** (b.i.d.)	**Lixisenatide** (q.d.)	**Liraglutide** (q.d.)	**Exenatide** (q.w. = once weekly)	**Dulaglutide** (q.w.)	**Albiglutide** (q.d.)	**Semaglutide** (q.w.)
Route of administration	s.c.	s.c.	s.c.	s.c.	s.c.	s.c.	s.c.
Renal elimination and safety in patients with impaired renal function							
Evidence for elimination through the kidneys (yes/no, reference)	Yes (40)	Yes (41)	No (42)	Yes (40)	No	Yes (minor) (43)	Yes (minor, in patients with end-stage renal failure) (27)
Safety/tolerability issues in patients with severely impaired renal function? (yes/no, commentary)	Yes (40)	Yes (41)	Yes (44)	Yes (40)	Not reported	Yes (45)	No (27)
Dose reduction recommended for mild/moderate reductions in renal function? (yes/no)	No (40)	No (41)	No (44)	No (40)	No	No	No
Approved lower limit of eGFR [ml/min 1.73 m^2]	30	30	Approved except for terminal renal failure	30	≥15	30	Approved except for terminal renal failure
Potential renal benefits							
Evidence for reduction in albuminuria?	No (46)	Yes (in patients with macro-albuminuria) (47)	Yes (48)	No (49)	Yes (50, 51)	Not reported	Yes (52)
Slowed reduction in eGFR over time [yes/no]	No (46)	No (47)	Yes (48)	Not reported	Yes (50, 53)	Not clear (54)	Not reported (52)
Evidence for beneficial influence on clinical renal endpoints? (yes/no, reference)	No	No	Yes (48)	No (49)	Yes (50)	Not reported	Yes (52)
Use in patients with impaired hepatic function							
Dose reduction recommended in patients with hepatic dysfunction? (yes/no)	No (limited experience)	No (limited experience)	No (limited experience); use in patients with severe hepatic dysfunction not recommended	No	No	No (limited experience)	No (limited experience)

Information in the present table has mainly been compiled from official package inserts for the medications listed. Recommendations for oral semaglutide have not been issued, since approval is pending. They are likely to be similar to those regarding s.c. semaglutide, since the active ingredient is identical.

the higher dose being significantly more effective (17). No further attempts were made to define the optimum dose range, and 2 mg per week have been used throughout the clinical development and in all trials.

Dulaglutide dose finding was the result of a novel approach, starting with many different doses/up-titration regimens, selecting doses with a beneficial effectivity–tolerability relationship, and continuing those doses for a duration of treatment typical for phase 3 trials (an adaptive, dose-finding, seamless phase 2/3 study) (62, 63). Initially, both doses lower and higher than those identified as the optimized dose range were tested and discontinued for lack of effectiveness or intolerance.

In the case of albiglutide, the phase 2 study did not only include once-weekly, but also bi-weekly and monthly injections of albiglutide (39). Thus, a limited range of doses used once-weekly was tested and carried into phase 3.

Semaglutide doses for phase 3 were selected based on a wide range of candidate doses, both for the s.c. (64) and the oral (28, 65) preparations. Up-titration was optimized for phase 3, to further reduce the risk for adverse events.

Overall, the care applied in selecting optimum doses was highly variable from programme to programme, and may be reflected in the efficacy and tolerability observed in definite clinical trials (*vide infra*). Whether or not the optimum dose(s) have been identified for a given compound will be crucial for determining results of head-to-head comparisons between different GLP-1 receptor agonists. Generally speaking, greater clinical effectiveness seems to be a consequence, among other determinants, of carefully identifying the full dose range from non-effective to non-tolerable doses, which allows the selection of doses with an unequivocally positive benefit–risk relationship.

The experience made with fixed-dose GLP-1/insulin combinations, such as liraglutide/insulin degludec (66, 67) or lixisenatide/insulin glargine (68, 69) has demonstrated that implementing even more and smaller dose up-titration steps may further mitigate the occurrence of GI side effects.

Injection devices, ease of administration and adherence to GLP-1 receptor agonist treatment

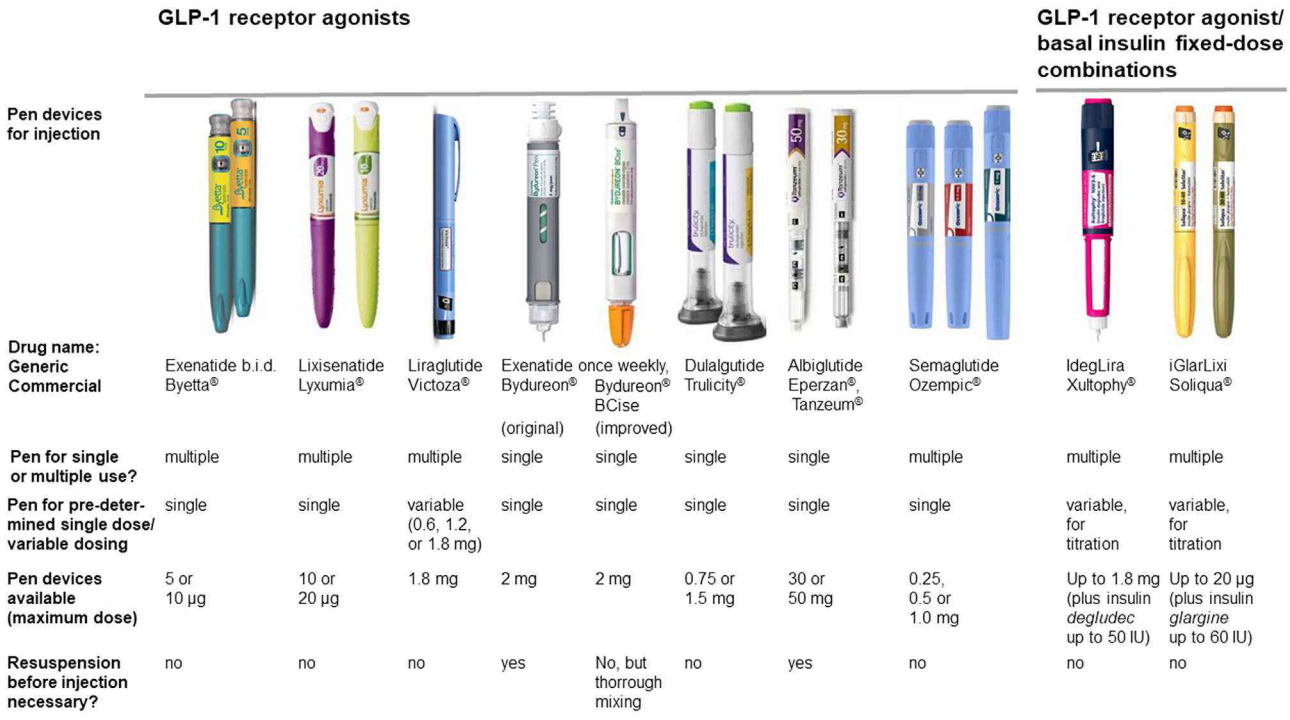
Injection devices coming with a prescription of individual GLP-1 receptor agonists vary considerably, both regarding their optical appearance and concerning essential technical details (Fig. 2). Exenatide once weekly is a suspension of polymer-'encaged' exenatide that originally needed to be resuspended using a dual-chamber pen device containing the active ingredient as a powder and a liquid solvent. Later, a single-chamber pen device became available, containing both constituents, however, requiring thorough shaking to reach an even suspension. Albiglutide is soluble in an aqueous solution, but needed to be dissolved, again using a dual-chamber pen device. This process required approximately 15 min to guarantee a clear solution. All other compounds are injected from pre-filled pen devices. Some can only deliver one pre-determined dose, the liraglutide pen allows to dial step of 0.6, 1.2 and 1.8 mg per dose (and even in between), which make slow and individual up-titration possible, which may be viewed as a major benefit of this device, potentially reducing the number of patients stopping treatment because of side events.

For exenatide b.i.d., lixisenatide, albiglutide, and semaglutide, the pen device has to be changed during the initial up-titration period, when the next dose increase is to be implemented (Fig. 2). It is often assumed that the ease of use of pen-injection devices is an important determinate of preferring one compound over another, and that it contributes to adherence to treatment (keeping the number of missed doses low) and to persistence (not discontinuing treatment altogether). One important factor seems to be the interval between two injections, two injections per day resulting in the worst, and one injection per week predicting the best indices for adherence (70, 71, 72).

Clinical trials have been performed with an osmotic minipump continuously delivering exenatide to subcutaneous adipose tissue for a period of 3 or 6 months after implantation. This ITCA 650 device (73, 74) has not been approved so far, but has been designed to specifically address the problem of non-adherence.

Definition of short- vs long-acting GLP-1 receptor agonists and consequences for fasting plasma glucose, gastric emptying and post-meal glycaemic control

Exenatide (b.i.d.) and lixisenatide (q.d.) are short-acting GLP-1 receptor agonists, because on the recommended injection regimen, drug concentrations rise sharply after each injection, and, after reaching a peak, decay towards very low levels after a few hours (29, 75). The time–drug concentration curve, thus, is characterized by peaks and troughs near zero concentrations, that is, intermittent



Drug name: Generic Commercial	Exenatide b.i.d. Byetta®	Lixisenatide Lyxumia®	Liraglutide Victoza®	Exenatide once weekly, Bydureon® (original)	Bydureon® BCise (improved)	Dulalgutide Trulicity®	Albiglutide Eperzan®, Tanzeum®	Semaglutide Ozempic®	IdegLira Xultophy®	iGlarLixi Soliqua®
Pen for single or multiple use?	multiple	multiple	multiple	single	single	single	single	multiple	multiple	multiple
Pen for pre-determined single dose/ variable dosing	single	single	variable (0.6, 1.2, or 1.8 mg)	single	single	single	single	single	variable, for titration	variable, for titration
Pen devices available (maximum dose)	5 or 10 µg	10 or 20 µg	1.8 mg	2 mg	2 mg	0.75 or 1.5 mg	30 or 50 mg	0.25, 0.5 or 1.0 mg	Up to 1.8 mg (plus insulin *degludec* up to 50 IU)	Up to 20 µg (plus insulin *glargine* up to 60 IU)
Resuspension before injection necessary?	no	no	no	yes	No, but thorrough mixing	no	yes	no	no	no

Figure 2

Pen injection devices for GLP-1 receptor agonists and fixed-dose combinations of GLP-1 receptor agonists with basal insulin preparations. The optical appearance of each pen injection device is shown as well as some essential technical characteristics (single or multiple use, variable or pre-determined fixed dosing, availability of pens delivering different (maximal) doses, necessity for re-suspension (mixing dry material with a solvent for reaching a clear solution (e.g., albiglutide) or a homogeneous suspension (e.g., exenatide once weekly))).

exposure is typical for short-acting GLP-1 receptor agonists. Long-acting GLP-1 receptor agonists (liraglutide, exenatide once weekly, dulaglutide, albiglutide, semaglutide) lead to a more constant drug exposure, with effective GLP-1 receptor agonist concentrations maintained over a whole 24-h period, and/or over a week's period, even if the interval between injections is 1 day or 1 week. The consequences are that tachyphylaxis develops for effects on gastric emptying, which initially is decelerated with GLP-1 and all GLP-1 receptor agonists (76, 77, 78). Gastric emptying is a major determinant of post-meal glycaemic rises (79), and retarded gastric emptying flattens and reduces the rise in glucose concentrations following a carbohydrate-containing meal (78, 80). Tachyphylaxis is observed within hours or days and is complete after a few weeks, when plasma glucose profiles in patients treated with long-acting GLP-1 receptor agonists display more prominent post-meal rises in plasma glucose concentrations than patients treated with short-acting GLP-1 receptor agonists (14, 81). With short-acting GLP-1 receptor agonists, no prominent tachyphylaxis has been observed (82). On the other hand, retardation of gastric emptying almost only occurs after meals before which the short-acting GLP-1 receptor agonist has been administered (one meal per day in the case of lixisenatide, two meals per day in the case of exenatide b.i.d.). It should be noted that there usually are residual effects on gastric emptying after sustained GLP-1 receptor stimulation even after tachyphylaxis has occurred (76, 77). In studies addressing tachyphylaxis regarding the velocity of gastric emptying with long-acting GLP-1 receptor agonists (81), less reliable methods than scintigraphy were used. GLP-1 receptor stimulation also leads to effects on small intestinal motility, which may contribute to overall effects on the temporal pattern of glucose absorption with such therapeutic agents (83).

This is not to say that long-acting GLP-1 receptor agonists do not have the ability to control post-meal rises in glycaemia, but the mechanism is not related to effects on gastric emptying, but rather to the stimulation of insulin and suppression of glucagon secretion (82). However, quantitatively, short-acting GLP-1 receptor agonists have the more prominent effect limiting

post-meal glycaemic rises after meals covered by an injection of the agent (78, 81, 84).

On the other hand, long-acting GLP-1 receptor agonists have more profound effects lowering overnight and fasting plasma glucose concentrations (Fig. 2). This is the result of higher drug concentrations maintained during the overnight fasting period.

Differences in adverse effects elicited by different GLP-1 receptor agonists

The most common adverse events with GLP-1 receptor agonists are nausea, vomiting and diarrhoea, which may occur in up to 30, 15 and 15% of patients, respectively, and may lead to discontinuation of drug treatment (56). Usually, this occurs upon initial exposure to a GLP-1 receptor agonist, or when the dose is increased as part of an up-titration regimen, and symptoms decay thereafter in most patients. Perhaps, this decay is more prominent with long-acting GLP-1 receptor agonists (85). As a rule, such adverse events are dose dependent (for agents with more than one approved dose) and are more prominent on a background of metformin treatment (metformin itself can elicit such side effects) or insulin treatment (perhaps indicating more advanced stages of diabetes) (56). Generally speaking, short-acting GLP-1 receptor agonists are associated with more nausea and vomiting (and drug discontinuations associated with such adverse events), while long-acting GLP-1 receptor agonists are associated with more diarrhoea (56). The exact reasons for these differences are not known. One should be aware that the capture of these side effects in clinical trials usually is by self-reporting rather than by a structured, validated questionnaire, which makes results from different studies less comparable (86).

Comparative effectiveness of various GLP-1 receptor agonists on glycaemic control (on a background of oral glucose-lowering medications)

Numerous head-to-head comparisons among GLP-1 receptor agonists have been performed in patients treated with oral glucose-lowering medications. Results regarding glycaemic control and body weight reduction are summarized in Fig. 3. Important adverse events (nausea representing 'gastrointestinal' adverse events and hypoglycaemia) are shown from the same studies in Fig. 4.

There are some obvious methodological limitations of comparative trials addressing glycaemic control, gastrointestinal adverse effects, or body weight: The majority of these have been 'open-label', with the inherent possibility of bias. The choice of patients examined, their background glucose-lowering medication, of comparators and drug doses often have been guided by commercial interests. Therefore, results from such studies should inform, but not define, clinical practice. With such reservations in mind, several general conclusions can be drawn from such head-to-head comparisons:

On a background of oral glucose-lowering medications, within the short-acting GLP-1 receptor agonists (exenatide b.i.d. vs lixisenatide q.d.) there do not appear to be major differences in glycaemic efficacy (Fig. 3A and D), while body weight is reduced more by exenatide, perhaps related to the greater temporal exposure with two rather than 1 injection per day.

When, again on a background of oral glucose-lowering agents, any short-acting with any long-acting GLP-1 receptor agonist were compared, there were greater effects on glycated haemoglobin with the long-acting agent (Fig. 3B and E), mainly driven by a more substantial lowering in fasting glucose (14, 85, 87, 88). However, there were no clinically significant differences in body weight reduction (14, 85, 87, 88). Thus, continuous exposure does not seem to be a prerequisite for clinically meaningful body weight reductions.

Given the differences in addressing fasting/preprandial vs postprandial plasma glucose between short- and long-acting GLP-1 receptor agonists triggered by differential tachyphylaxis regarding a retardation of gastric emptying (82), their effectiveness on reducing HbA_{1c} may depend on baseline fasting plasma glucose, since the relative impact of postprandial glucose increments on HbA_{1c} is greater at lower fasting glucose concentrations (89). This has not been specifically addressed in clinical studies, but could offer a way to optimize drug choices based on readily available patient factors.

Within the sub-class of long-acting GLP-1 receptor agonists, liraglutide q.d. compared favourably to exenatide q.w. (90) and albiglutide q.w. (91). When these results were the only ones available, one could have thought that going from once-daily to once-weekly injections implied some weakening of the effectiveness (e.g., due to potential fluctuations in drug exposure over a 7-day period). However, dulaglutide q.w. turned out

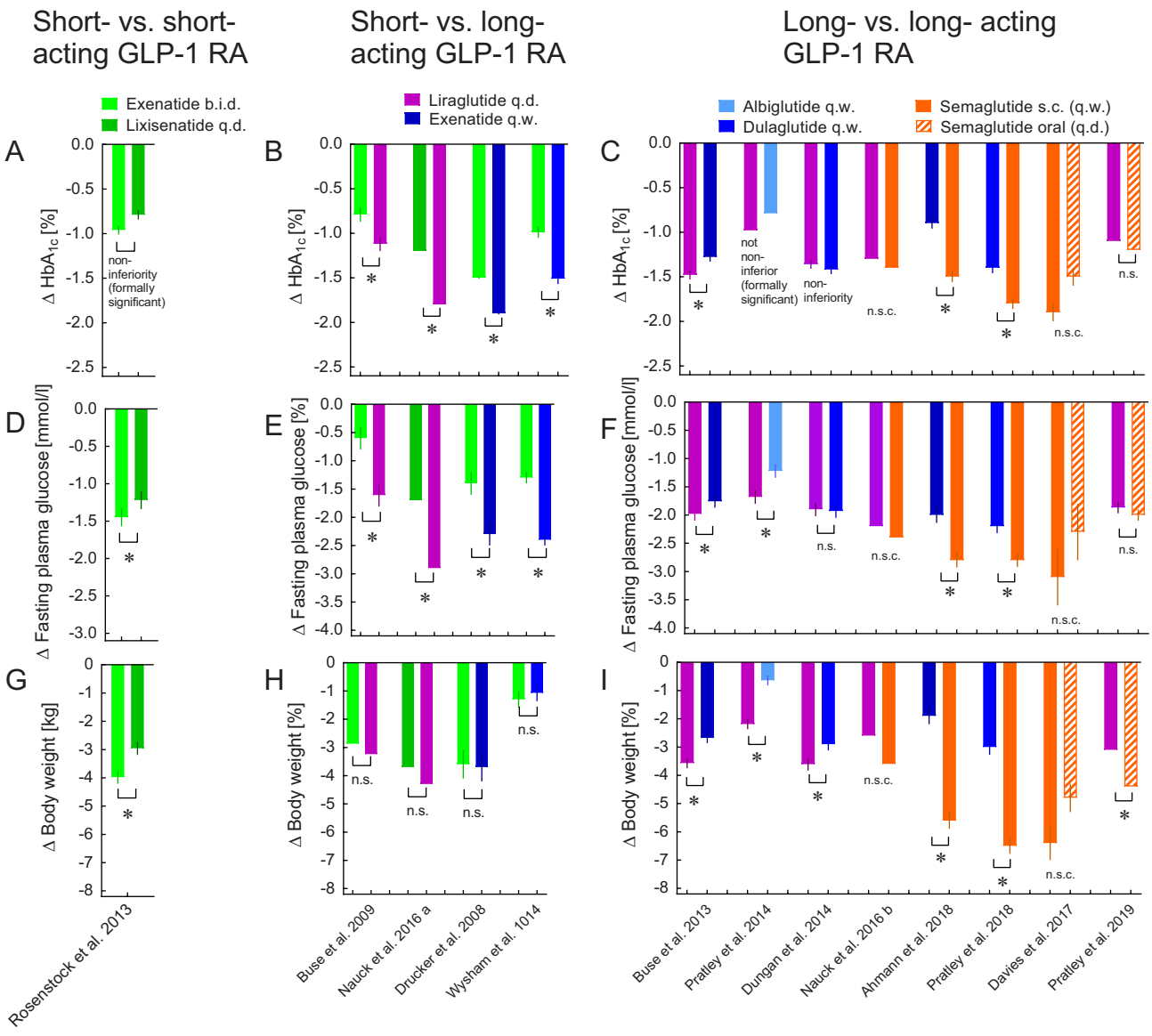


Figure 3

Clinical efficacy results from clinical trials comparing different GLP-1 receptor agonists head-to-head. Reductions in HbA_{1c} (upper row of panels), fasting plasma glucose (middle row of panels) and body weight (lower row of panels) are shown for trials comparing different short-acting GLP-1 receptor agonists (left hand panels), for trials comparing a short- to a long-acting GLP-1 receptor agonist (middle panels) and different long-acting GLP-1 receptor agonists (right hand panels). Each colour represents a specific GLP-1 receptor agonist compound (see legend). The only oral GLP-1 receptor agonist preparation studied (oral semaglutide) is shown in the same colour (orange) as the same compound injected subcutaneously, however, not as homogenously filled bars, but with a striped pattern. Asterisks indicate a significant difference ($P < 0.05$) for the individual head-to-head comparison as reported in the original publication. Non-significant differences are marked n.s. (for not significant). Other conclusions (non-inferiority, non-inferiority not met) are indicated as text. If no formal statistical comparison has been reported, this is indicated as n.s.c. (for no statistical comparison). If an original publication has reported results from several doses for any agent, only results with the highest dose are depicted. GLP-1 receptor agonist doses from phase 2 trials (Nauck *et al*. (87) comparing subcutaneous semaglutide with liraglutide and Davies *et al*. (65) comparing oral and subcutaneous semaglutide) were not identical to those selected for phase 3 trials and approval. In these cases, doses coming close to those selected for phase 3 and approval have been used.

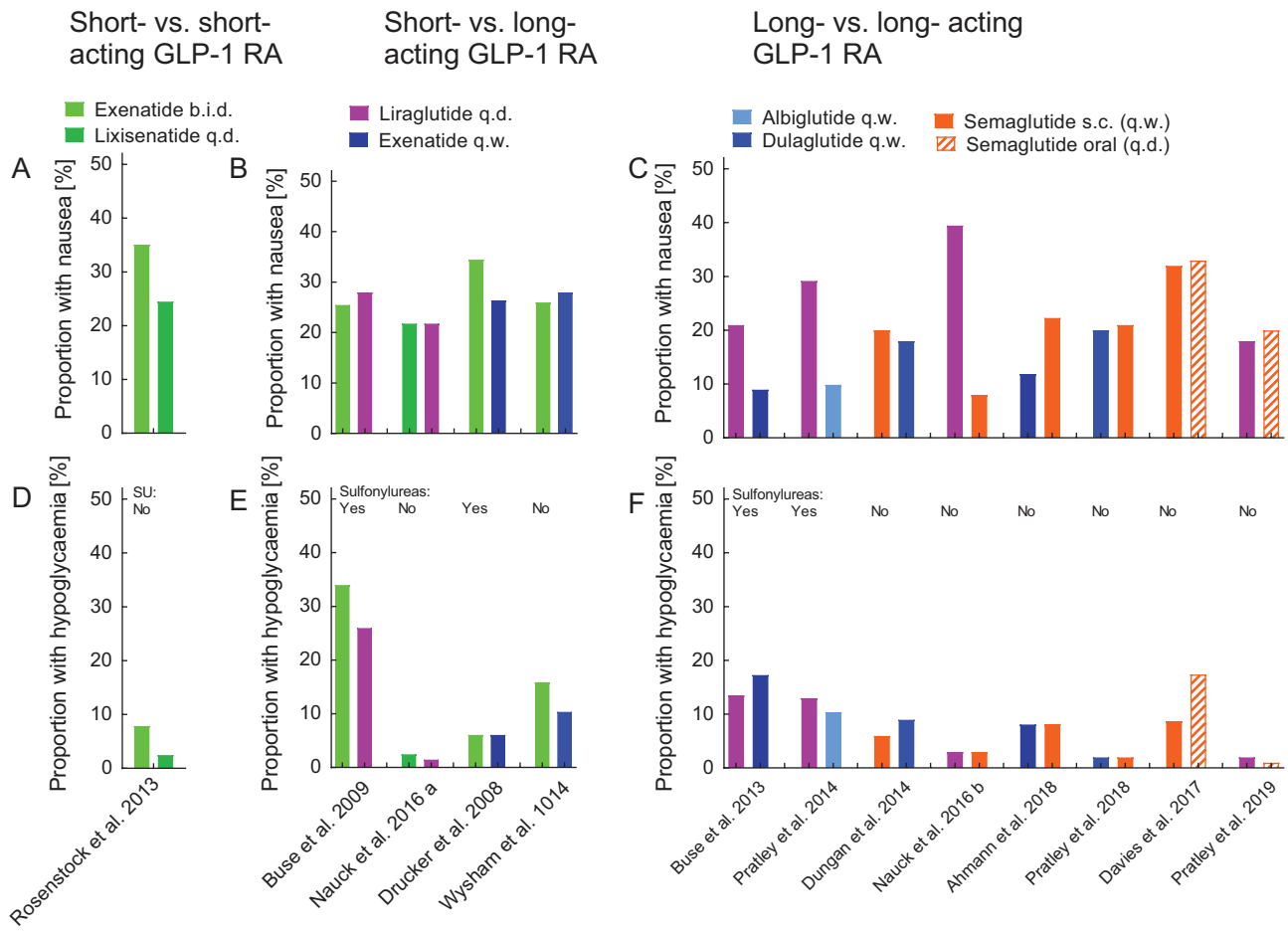


Figure 4

Safety and tolerability results from clinical trials comparing different GLP-1 receptor agonists head-to-head. Proportion of patients reporting nausea (upper row of panels) and proportion of patients reporting any hypoglycaemic episode (lower row of panels) are shown for trials comparing different short-acting GLP-1 receptor agonists (left hand panels), for trials comparing a short- to a long-acting GLP-1 receptor agonist (middle panels) and different long-acting GLP-1 receptor agonists (right hand panels). Each colour represents a specific GLP-1 receptor agonist compound (see legend). The only oral GLP-1 receptor agonist preparation studied (oral semaglutide) is shown in the same colour (orange) as the same compound injected subcutaneously, however, not as homogenously filled bars, but with a striped pattern. Since the original studies usually did not report significance of differences, there are no symbols indicating significant differences. If an original publication has reported results from several doses for any agent, only results with the highest dose are depicted. GLP-1 receptor agonist doses from phase 2 trials (Nauck *et al*. (87) comparing subcutaneous semaglutide with liraglutide and Davies *et al*. (65) comparing oral and subcutaneous semaglutide) were not identical to those selected for phase 3 trials and approval. In these cases, doses coming close to those selected for phase 3 and approval have been used.

to be equally effective compared to liraglutide q.d. (92) with respect to the reduction in HbA_{1c}, but displayed a significantly reduced effect on body weight. In a phase 2 study of various doses of semaglutide (for once weekly s.c. injections) compared to approved doses of liraglutide, high doses of semaglutide suggested a higher effectiveness, both in terms of glycaemic control and body weight reduction (64). Subcutaneous semaglutide has proven superior versus exenatide once weekly (93) and versus dulaglutide (94). Differences were particularly remarkable with respect to body weight reduction. Oral semaglutide was compared to s.c. semaglutide in a phase 2 trial: In principle, higher doses of oral semaglutide had effects very much comparable to those of s.c. semaglutide. However, the doses nearest (10 mg/day) to those selected for phase 3 (up to 14 mg/day) resulted in somewhat lesser

reductions in HbA_{1c}, fasting plasma glucose, and body weight (no formal statistical comparison was performed) (65). Oral semaglutide compared to liraglutide (s.c., q.d.) had similar effects on HbA_{1c} and fasting plasma glucose, but more profoundly lowered body weight after 26 weeks (primary endpoint). After 52 weeks, the effect on HbA_{1c} was superior for oral semaglutide.

Thus, the sub-class of long-acting GLP-1 receptor agonists have not only proven to be more effective than short-acting GLP-1 receptor agonists, but over the period between 2007 and today have evolved to gain greater effectiveness with the most recently introduced compounds, even including a novel oral preparation of semaglutide, which turned out to be almost equally effective compared to the subcutaneous preparation of the same peptide agent, semaglutide.

Comparative effectiveness of various GLP-1 receptor agonists on glycaemic control (on a background of basal insulin therapy)

GLP-1 receptor agonists have been used in addition to basal insulin. Additive effects are expected due to complementary mechanisms of action (95). Both short- (96, 97, 98) and long-acting GLP-1 receptor agonists (99, 100, 101, 102) have been used in conjunction with basal insulin as a free combination, allowing individual dosing for both components.

The short-acting compound lixisenatide is also available as a fixed-dose combination with insulin glargine (called iGlarLixi or, formerly, LixiLan) (68, 69, 103), like the long-acting compound liraglutide, which is available as a fixed-dose combination with insulin degludec (abbreviated IdegLira) (66, 67). These combinations are injected from the same device, with doses of both components being proportional ('fixed ratio') to each other. They have to be titrated slowly, like it is customary for basal insulin. Compared to free combinations of the same agents with insulin, this slow titration results in considerably lower proportions of patients reporting nausea, vomiting and diarrhoea (66, 67, 68, 69, 103), underscoring the concept of a slow rise in exposure to prevent such side effects. In studies comparing these fixed-dose combinations with the insulin component only, IdegLira seems to produce greater differences in HbA_{1c} (66, 67) than IglarLixi (68, 69), compatible with the differences in glycaemic efficacy displayed by the two GLP-1 receptor agonists on a background of oral glucose-lowering agents (87). According to a meta-analysis, IdegLira is more potent in controlling glycaemia and body weight than iGlarLixi (104).

When used in conjunction with (basal) insulin, short-acting GLP-1 receptor agonists have been shown to provide superior additional post-prandial effects on top of fasting plasma glucose being controlled by intermediate- or long-acting insulin preparations (96, 97, 98, 105, 106). However, the post-prandial lowering of glycaemic excursions occurs mainly after those meals, when exenatide or lixisenatide have been injected before. Head-to-head comparisons to long-acting GLP-1 receptor agonists are lacking. A recent indirect comparison performed by a meta-analysis suggests that long-acting GLP-1 receptor agonists provide a greater reduction in HbA1c, fasting plasma glucose, and body weight compared to short-acting ones, mainly driven by their more pronounced effect on fasting plasma glucose (Huthmacher J, Meier J J, Nauck M A, unpublished observations).

Comparative effectiveness of various GLP-1 receptor agonists on body weight reduction

All approved GLP-1 receptor agonists have the potential to induce weight loss by decreasing appetite and increasing satiety, that is, mainly through an interaction with GLP-1 receptors in brain areas involved in the homeostasis of energy (food) intake, energy expenditure, and energy balance (7). However, the quantitative impact is markedly different for various GLP-1 receptor agonists (Fig. 3D, E and F). Furthermore, there is substantially more inter-individual variability regarding weight loss than there is for glycaemic control, with some subjects treated with GLP-1 receptor agonists not losing any weight (or even gaining weight), while others lose up to 25 kg over a period of half a year (14, 107, 108). Typically, a new steady-state plateau of body weight is reached after 3–6 months of treatment. Most of this initial weight loss will be maintained as long as the treatment is adhered to. This is the expected consequence of lowering caloric intake (like with an energy-restricted diet), apparently the main mechanism how GLP-1 receptor agonists lower body weight. If GLP-1 receptor treatment is discontinued, the amount of weight lost with treatment will be re-gained.

In contrast to the glucose-lowering effect, head-to-head comparisons between short- and long-acting GLP-1 receptor agonists do not systematically show superiority of long-acting agents with respect to weight loss (Fig. 3E) (14). This can be taken as indirect evidence that deceleration of gastric emptying (which remains an effect of short-acting

GLP-1 receptor agonists even during long-term treatment, while it is lost due to tachyphylaxis with long-acting GLP-1 receptor agonists) (82) does not trigger a major loss in appetite due to incomplete gastric emptying. Likewise, nausea and vomiting induced in some patients does not provide the main reason for weight loss, since it occurs to almost the same degree in patients never complaining of such 'gastro-intestinal' adverse event (14, 107).

Average weight loss with exenatide b.i.d., lixisenatide q.d., liraglutide q.d., and dulaglutide q.w. is 2–4 kg, with considerable inter-individual variation, while it appears to be less with albiglutide (54, 91) (treatment with which is associated with less nausea/vomiting as well), and more with semaglutide, both concerning the once weekly subcutaneous preparation (65, 93, 94) and the once-daily oral preparation (co-formulated with an absorption enhancer) (109, 110, 111, 112). Differences in uptake across the blood–brain barrier (or in brain access through subfornical organs) have been postulated as an explanation. However, convincing direct evidence is lacking. Effects of GLP-1 receptor agonists on body weights are depicted in Fig. 3 D, E and F.

Comparative effects on antibody formation

Exenatide (both the b.i.d. and the once-weekly preparation) has prompted antibody formation, even in the majority of patients (14, 113), probably due to the low sequence homology to mammalian GLP-1 (Fig. 1). However, this was of uncertain functional consequences, since even high titres were not obviously associated with a reduced effectiveness (14, 113). With liraglutide (114), dulaglutide (115), albiglutide (116) and semaglutide (94), antibody formation is only rarely observed.

Comparative effectiveness of various GLP-1 receptor agonists on other cardiovascular risk factors (blood pressure, lipoproteins, heart rate)

All GLP-1 receptor agonists lower systolic blood pressure by 2–5 mmHg, with less consistent effects on diastolic blood pressure (117). At the same time, an average increase in pulse rate of 2–5 beats per min has been noted in patients treated with GLP-1 receptor agonists (117), the duration of which within a 24-h period matching the exposure to effective GLP-1 receptor stimulation with the various agents (i.e. continuous with long-acting agents, intermittent with short-acting agents) (81). 24-h electrocardiographic monitoring detects more acceleration of heart rate than occasional pulse rate measurements (81). In addition to body weight reduction, and lowering in systolic blood pressure, all GLP-1 receptor agonists slightly, but favourably modify lipoprotein concentrations (lowering of LDL cholesterol and triglycerides) (117). The acceleration in pulse rate does not seem to prevent cardio-vascular benefits of GLP-1 receptor agonists, even in patients in whom a prominent heart rate response was observed.

Cardiovascular outcomes studies with different GLP-1 receptor agonists: technical aspects

Since the first positive report on the LEADER trial examining liraglutide effects on cardiovascular outcomes in high-risk type 2-diabetic patients (118), a body of evidence has accumulated on the potential cardio-vascular benefits elicited by GLP-1 receptor agonists (49, 52, 54, 109, 119, 120). Originally, such trials had become mandatory for all new diabetes drugs after 2008 to prove their cardiovascular safety. Thus, the original aim was to show that outcomes were not worse ('non-inferior') with the active drug as compared to placebo. Typically, populations with pre-existing definite cardio-vascular damage (e.g., previous cardio-vascular events) were studied, (a) because such patients were considered to be a highly most vulnerable population, and (b) because high cardio-vascular event rates could be expected, leading to smaller sample sizes and shorter study durations while still achieving numbers of events providing the necessary power to achieve the study objectives. After several studies had shown positive effects in such populations with pre-existing atherosclerotic cardio-vascular disease, supporting the idea of secondary prevention of cardio-vascular events with GLP-1 receptor agonists, the question arose, whether similar benefits could be demonstrated in lower-risk patients without definite pre-existing cardio-vascular damage. Thus, the proportion of patients with either previous cardio-vascular events or definite cardio-vascular ischemia is a major important variable differing between studies. Other parameters with potential impact on outcomes are the proportion of patients with chronic kidney disease (significant albuminuria and/or reduced glomerular filtration rate), patient and event numbers, duration, and variables indicating adherence to treatment (or discontinuation of the study drug, respectively).

Table 3 Cardio-vascular outcomes trials with GLP-1 receptor agonists: study and patient characteristics.

Compound	Lixisenatide	Liraglutide	Semaglutide	Exenatide	Albiglutide	Dulaglutide	Semaglutide
Details of treatment							
Route of administration	s.c.	s.c.	s.c.	s.c.	s.c.	s.c.	Oral
Interval between administrations	Once daily	Once daily	Once weekly	Once weekly	Once weekly	Once weekly	Once daily
Dose/interval	20 µg/day	1.8 mg/day	0.5/1.0 mg/week	2 mg/week	50 mg/week	1.5 mg/week	14 mg/day
Study acronym, reference	ELIXA (120)	LEADER (118)	SUSTAIN-6 (52)	EXSCEL (49)	HARMONY Outcomes (54)	REWIND (119)	PIONEER-6 (109)
Study characteristics							
Patient number	6068	9340	3297	14 752	9463	9901	3183
Study duration*	2.1	3.8	2.1	3.2	1.6	5.5	1.3
MACE‡ endpoints	805	1302	254	1744	766	1257	137
Premature discontinuation (%)	27.5	n.r.	19.9/22.6	43.0	24.5	26.8	15.3
Exposition to drug (%)‡	90.5	84.0	86.5	76.0	87.0	82.2	n.r.§
Vital state known (%)	98.8	99.7	99.6	98.8	99.4	99.7	99.7
Baseline patient characteristics							
Age (years)	60	64	65	62	64	66	66
Sex: % female	30	36	39	38	30	46	32
Diabetes duration (years)	9	13	14	12	14	10	15
HbA_{1c} (%)	7.7	8.7	8.7	8.0	8.8	7.3	8.2
BMI (kg/m^2)	30.1	32.5	n.r.*	31.8	32.3	32.3	32.3
Pre-existing cardio-vascular disease (%)	100	98.2	72.2	73.3	100	31.4	84.6
Pre-existing heart failure (%)	22.5	17.9	23.1	15.8	20.0	8.6	n.r.
eGFR <60 mL/min (%)	n.r. (mean: 77 mL/min)	±23.9	30.2/26.7	21.3	n.r. (mean: 79 mL/min)	±22.0	27.0

If the original publication did not report details for all patients (treated with active drug or placebo), data on patients treated with the study drug are reported in this table.
*Median; †Mean body weight 92.3 kg; ‡Expressed as individual percentage of the duration of observation with full adherence to randomized drug; §75% of the patients took study drug for >1 year.
n.r., not reported.

Table 3 displays patient and study characteristics in cardio-vascular outcomes trials with GLP-1 receptor agonists.

Cardiovascular outcomes studies with different GLP-1 receptor agonists: cardiovascular outcomes

Key findings of cardiovascular outcomes trials comparing treatment with a GLP-1 receptor agonist to placebo on a background of standard of care are shown in Fig. 5: (red symbols). For comparison, results of similar studies employing SGLT-2 (sodium-glucose transporter-2) inhibitors (blue symbols) (121, 122, 123) and DPP-4 (dipeptidyl peptidase-4) inhibitors (green symbols) (44, 124, 125, 126) are shown as well. Changes in time to major adverse cardiovascular events ('MACE': first non-fatal acute myocardial infarction, non-fatal stroke, or cardiovascular death), all-and cause mortality, or hospitalization for congestive heart failure are shown.

None of the DPP-4 inhibitors significantly changed the number of major adverse cardiovascular (MACE) events or all-cause mortality (44, 124, 125, 126). Heterogeneous results were reported with respect to the time to first hospitalization for heart failure: As significantly increased risk was reported for saxagliptin, a similar trend with alogliptin, no change with sitagliptin, and a beneficial trend with linagliptin (44, 124, 125, 126).

SGLT-2 inhibitors uniformly showed a major reduction in hospitalization for congestive heart failure (121, 122, 123), had smaller, heterogeneous effects on MACE, and differed widely with respect to all-cause mortality (substantial and highly significant for empagliflozin, trends without significance in the case of canagliflozin and dapagliflozin) (121, 122, 123).

The first trial in type 2-diabetic patients reporting results with a GLP-1 receptor agonist, lixisenatide (ELIXA trial), did not describe any noticeable effect on MACE, all-cause mortality, or hospitalization for heart failure (120). It has to be noted that lixisenatide is a rather short-acting GLP-1 receptor agonists and its recommended use is once daily (31). This will certainly not lead to drug levels sufficient to stimulate GLP-1 receptors for a whole 24-h period (Table 1). One other

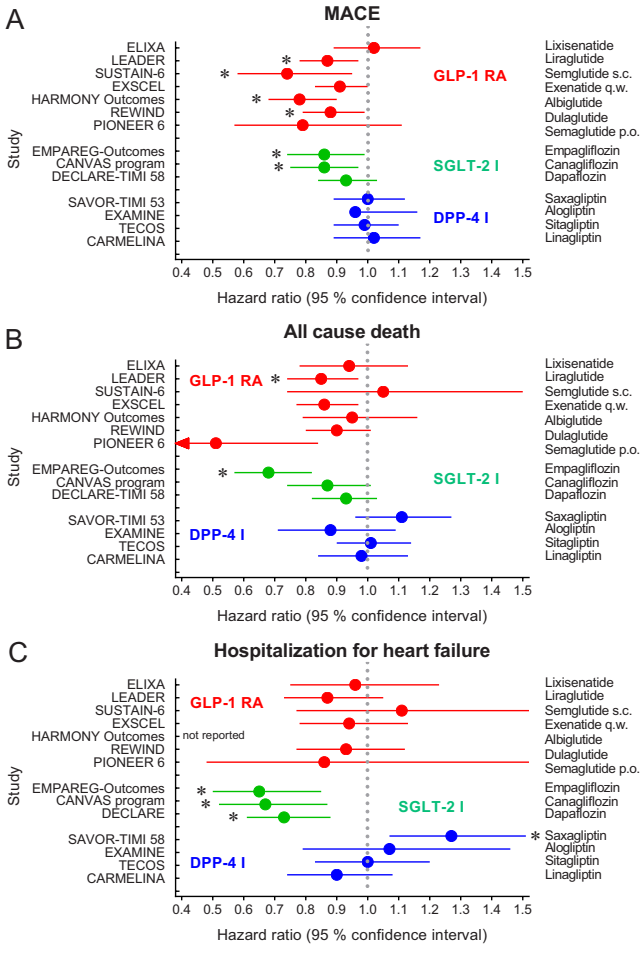


Figure 5

Results of cardiovascular outcomes trials comparing GLP-1 receptor agonists and placebo on a background of standard of care. Effects on 'major adverse cardio-vascular events' (MACE; A), all-cause mortality (B) and hospitalization for heart failure (C) are shown as hazard ratios and their 95% confidence intervals. For comparison, results from equivalent studies with DPP-4 inhibitors (DPP-4 I) and SGLT-2 inhibitors (SGLT-2 I) are also shown. Asterisks indicate significant differences ($P < 0.05$) to placebo treatment (on a background of standard of care). †The dagger marks an apparently significant influence of exenatide once weekly on all-cause mortality (because the confidence interval does not cross the line of unity), however, significance could not be concluded based on a hierarchical testing procedure with an earlier comparison in that hierarchy not showing significant differences.

particular aspect of this ELIXA trial is the recruitment of patients shortly after an acute coronary syndrome. Biological processes dominating clinical complications after such an event and following revascularization (intra-coronary procedures or bypass surgery) may be different from those characterizing the natural history of atherosclerosis, and may be less amenable to modification through GLP-1 receptor agonist treatment as well.

All other cardiovascular outcomes trials testing GLP-1 receptor agonists showed a somewhat consistent pattern with respect to effects on major adverse cardiovascular events: Either a significant reduction (by 12–26%) or at least a trend towards a reduction in MACE events was observed (49, 52, 54, 109, 118, 119, 120) (notable exception: Lixisenatide in the ELIXA trial; Fig. 5A). All GLP-1 receptor agonists except lixisenatide tested are characterized as long-acting compounds (*vide supra* for definition), which provide substantial GLP-1 receptor stimulation throughout a 24-h period.

Most of these trials included a high proportion of patients with pre-existing atherosclerotic cardiovascular disease (based on previous events, necessity for revascularization, or definite results of functional testing or imaging), and a smaller proportion of patients with risk factors only. In LEADER (liraglutide), SUSTAIN-6 (subcutaneous semaglutide), and PIONEER-6 (oral semaglutide), chronic kidney disease with an eGFR <60 mL/min (1.73 m^2)$^{-1}$ was taken as a risk equivalent to proven cardiovascular damage. Thus, their results clearly support the idea of secondary prevention of cardiovascular events in those with pre-existing cardiovascular damage. The proportions of patients without previous evidence of cardiovascular disease, as a rule, were too small to allow definite conclusions for these subgroups. REWIND (dulaglutide) has been the first trial to recruit a majority of patients without proven cardiovascular disease at baseline. MACE was reduced by 12% in the overall population. This percentage reduction of events was not different between subgroups with and without pre-existing cardiovascular disease (non-significant interaction, $P=0.97$, for a difference between hazard ratios for these sub-populations) (119). This result may be interpreted as demonstrating effects in those without cardiovascular damage at baseline, and, thus, a chance for primary prevention of cardiovascular events in type 2-diabetic patients, independent from previous damage to the cardiovascular system. However, when analysed separately, both subgroups did not show significant reductions in MACE ($P>0.10$ for both sub-populations). Therefore, the conclusion that the REWIND study has demonstrated cardioprotection with dulaglutide in primary prevention can be debated.

It is also important to note that the study objectives have been quite different between the trials: Some trials were designed to support preliminary cardiovascular safety of novel glucose-lowering drugs before approval (SUSTAIN-6, PIONEER-6). This could be concluded if the upper bound of the 95% CI of the hazard ratio ends below 1.8 (ruling out an 80% elevation in risk with an error margin of 5%). In those cases, the duration of the trials was shorter, and the number of MACE events accrued during the trials was considerably lower (Table 3), as the main emphasis was on safety, not on proving benefits. Other trials aimed at definitely proving safety (upper bound of the 95% CI of the hazard ratio ends below 1.3, ruling out a 30% elevation in risk with an error margin of 5%), with a secondary analysis for superiority (hazard ratio: point estimate and its 95% CI below 1.0). Sufficient power requires much larger event numbers, which in turn calls for more patients followed for a longer period of time (Table 3). This approach applies to the LEADER, EXSCEL, HARMONY outcomes, and REWIND trials.

A controversial question is whether there is something like a 'class effect' for cardiovascular benefits applying to all GLP-1 receptor agonists. This question can be raised in various ways. One definition could be that the results of all trials examining effects of GLP-1 receptor agonists on cardiovascular events show a comparable pattern, thereby suggesting that the results attest of a common biological mechanism (stimulation of GLP-1 receptors) responsible for the results. Some heterogeneity, especially in quantitative terms, may apply due to differences in pharmacokinetic properties, selection of doses, patient populations and chance. This applies to the reduction in major adverse cardiovascular events ('MACE') with all GLP-1 receptor agonists (Fig. 5), with the notable exception of the ELIXA trial with lixisenatide. The reason most likely is caused by the short-lived increments in lixisenatide concentrations following a single injection every day, which will not guarantee exposure to significant concentrations of the drug for a full 24-h period (Table 1). The second 'outlier' seems to be exenatide once weekly (49). Information provided earlier (vide supra) attests of a missed chance to carefully select optimum dosages for this compound for optimizing clinical effects (17): A dose of 2 mg per week may not be equipotent to those selected for other GLP-1 receptor agonists. Furthermore, exenatide once-weekly may produce subcutaneous nodules as a local reaction to injecting an agent that resides in the subcutaneous adipose tissue for weeks (127, 128). This may be a major determinant of a relatively low adherence to this therapy (129), as shown by a rather high rate of patients discontinuing this drug treatment in this 'pragmatic' trial (Table 3). Thus, it appears possible to explain why cardiovascular outcomes (as well as glycaemic control; Fig. 3) with lixisenatide and exenatide once weekly fall short of what has been corroborated with other GLP-1 receptor agonists.

Another definition of 'class effect' could be that differences between compounds belonging to a class are negligible, such that the choice of agent could be left to cost considerations or even chance. This description does not fit the heterogeneity of results obtained in clinical trials with GLP-1 receptor agonists, both with respect to glycaemic and body weight control (Fig. 3) and concerning documented and published cardiovascular outcomes (Fig. 5).

GLP-1 receptor agonists have not shown any consistent effects on the risk for hospitalization for congestive heart failure (Fig. 5B). Advanced stages of heart failure had been exclusion criteria in most studies. Dedicated clinical trials addressing potential benefits of liraglutide treatment in patients with pre-existing advanced congestive heart failure failed to show such benefits and rather tended to show an increased mortality (not significant (130, 131)). These results probably indicate that liraglutide (and other GLP-1 receptor agonists) should not be used in patients with advanced stages of heart failure because of safety considerations.

Because of the cardiovascular benefits associated with the use of GLP-1 receptor agonists, this class is recommended as a preferred treatment for patients with pre-existing atherosclerotic cardio-vascular disease (Fig. 5 and Table 3) (132). Since similar benefits have been described for SGLT-2 inhibitors (Fig. 5), a decision has to be made whether to prefer GLP-1 receptor agonists or SGLT-2 inhibitors for a given patient (132). While this decision may be difficult in some patients, SGLT-2 inhibitors will be preferred if there is a prominent risk for congestive heart failure complications or the need to prevent progression of chronic kidney failure (132). GLP-1 receptor agonists may be the better class to prevent ischaemic complications of atherosclerotic disease. Potential frequent adverse events (predominantly genital infections in the case of SGLT-2 inhibitors versus gastrointestinal adverse events in the case of GLP-1 RAs) may also be taken into consideration.

Potential mechanisms of action of GLP-1 receptor agonists on cardiovascular endpoints

GLP-1 receptor agonists have beneficial actions on well-characterized cardiovascular risk factors (glycaemic control,

body weight, blood pressure, fasting and postprandial lipoproteins), but also influences a multitude of biological processes in blood vessels and the heart, ranging from improved substrate uptake and ischemia tolerance in the heart to vasodilation, reduced low-grade inflammation, and improved plaque stability (133). These effects have recently been reviewed extensively (117). Most likely, GLP-1 receptor agonists exert anti-atherosclerotic effects that, in part, seem to be independent from the obvious risk factor improvement that accompanies such treatment.

Effects of GLP-1 receptor agonists on microvascular diabetic complications

Only late after the introduction of GLP-1 receptor agonists into clinical practice, beneficial effects on albuminuria and the progressive loss of kidney function (eGFR) have been described (Table 2). The potential to reduce albuminuria to prevent progression to advanced stages of albuminuria (micro- or macro-albuminuria) and to interfere with the natural history characterized by a slow, but relentlessly progressive loss in renal filtration capacity has only been recognized in recent years, following the publication of the LEADER trial (48, 118). While earlier trials may have missed a chance to document such renal benefits, more recent studies have confirmed similar effects for semaglutide (134), dulaglutide (50), and, with a transient effect on eGFR, for albiglutide (54). Composite renal endpoints (as a rule including progression to macro-albuminuria, a measure of a substantial reduction in eGFR, advancement to the state of terminal renal failure requiring dialysis or kidney transplantation, and death for renal causes) have shown significant advantages for patients treated with liraglutide (48, 118), semaglutide (134), and dulaglutide (50), all driven by a major effect on the progression to albuminuria. The other endpoints only rarely occurred, as expected for populations with relatively normal renal function at baseline (Table 3).

Clinical endpoints related to diabetic eye disease (need for photo-coagulation, intra-vitreal injection therapy, or vitrectomy) have been found increased with the use of liraglutide (non-significant trend) (118), semaglutide (significant difference) (52) and dulaglutide (non-significant trend) (50, 119). The majority of these patients had pre-existing advanced retinopathy (requiring specific ophtalmological therapy) (135). One reason may be the rapid drop in plasma glucose and HbA_{1c} induced by initiating GLP-1 receptor therapy, which has previously been associated with so-called 'initial worsening' in type 1-diabetic patients intensifying their glucose-lowering therapy with multiple daily injections or pump therapy (136). Care should be taken that diabetic eye disease is diagnosed and treated before initiating such treatment with the potential to dramatically improve glycaemic control within short periods of time. It will take more studies to decide, whether there is a specific risk for the progression of diabetic eye disease with GLP-1 receptor agonists.

Administration:	subcutaneous						oral
Compound:	**Exenatide**	**Lixisenatide**	**Liraglutide**	**Exenatide**	**Dulaglutide**	**Semaglutide**	**Semaglutide**
Frequency:	b.i.d.	q.w.	q.d.	q.w.	q.w.	q.w.	q.d.
Effects:							
HbA_{1c} reduction:	+	+	++	+	++	+++	++(+)
Post-prandial glucose	++[a]	++[a]	+	+	+	+	+
Body weight reduction:	+(+)	+	++	+	+(+)	+++	++(+)
Injection device:	+	+	++	(+)	+++	++	n.a.
Conveniance/adherence:	(+)	+	++	+	+++	+++	+++?[b]
CV benefit („MACE"):	not known	±	++	(+)	++	++	(+)
Mortality benefit:	not known	±	++	(+)	±	±	±
Renal benefit:	±	(+)	+	±	+	+	+
Nausea/vomiting:	- -	-	- (-)	-	- (-)	- (-)	- (-)
Immunogenicity[c]:	++	++	(+)	++	(+)	(+)	? (not known)

Figure 6
Comparison of beneficial and adverse effects elicited by currently available and soon to be approved GLP-1 receptor agonists. The semi-quantitative estimates are derived from published clinical trials, but represent the authors' opinions and their subjective clinical judgement. Data concerning albiglutide are not considered, since this compound is no longer available. [a]Mainly through persistent effects on gastric emptying (deceleration, absence of tachyphylaxis). [b]Potential judged to be good because this is administered as a tablet; however, as of now, comparative data are lacking. [c]Antibody formation.

The challenge of individual choices

In light of the current or future availability of currently eight different GLP-1 RA preparations (even excluding the fixed-ratio combinations with insulin), the question arises how to determine to optimal choice of a GLP-1 RA for a given patient. Several aspects may be taken into consideration: In terms of the overall glucose-lowering potential, semaglutide appears to provide the greatest efficacy (perhaps with the s.c. version being slightly more efficacious than the oral preparation), followed by liraglutide and dulaglutide. If reduction in postprandial hyperglycaemia is a key therapeutic target, lixisenatide (once daily) or exenatide (twice daily) may be suitable candidates. Weight loss has been most pronounced with s.c. semaglutide, followed by oral semaglutide and liraglutide. The incidence of gastrointestinal adverse events has been found to be lowest with albiglutide and exenatide-once weekly, and highest with exenatide b.i.d.. Heart rate increases appear to be less pronounced with lixisenatide and exenatide, owing to the shorter periods of exposure to effective drug levels. The greatest convenience and ease of use can be attributed to dulaglutide, which is delivered in an easy-to-use single use pen, followed by semaglutide s.c. and liraglutide. Whether oral semaglutide, which has to be administered daily 30 min prior to meal ingestion, will be preferred over the weekly injectable therapies, is yet to be determined. Finally, the most convincing results in terms of reducing the overall numbers of MACE events in secondary prevention have been obtained for liraglutide, whilst some evidence for cardioprotection in primary prevention may be considered for dulaglutide. Taken together, these unequal properties and effects highlight the concept of individualized care even within the broad class of GLP-1 RAs (Fig. 6).

Conclusions

More than 10 years after the introduction of the first GLP-1 receptor agonist, exenatide b.i.d. into clinical practice, this class of incretin-based glucose-lowering medications has evolved to progressively provide improved glycaemic control and body weight reduction. They are now recommended as the first injectable therapy after the failure of oral glucose-lowering agents (as a rule, before starting insulin therapy) (132). Specific benefits associated with this therapy are the prevention of cardiovascular events (addressing macro-vascular diabetic complications) and renal (micro-vascular) endpoints. It is the purpose of the present overview to highlight differences between agents belonging to the GLP-1 receptor agonist class or the evidence for benefits that have been described in clinical trials with such agents. This information is hoped to support the selection of the most appropriate treatment as part of an individualized treatment decision for patients with type 2 diabetes mellitus.

Declaration of interest

M A N has been member on advisory boards or has consulted with AstraZeneca, Boehringer Ingelheim, Eli Lilly & Co., Fractyl, GlaxoSmithKline, Hoffman La Roche, Menarini/Berlin Chemie, Merck, Sharp & Dohme, NovoNordisk, and Versatis. He has received grant support from Eli Lilly & Co., Menarini/Berlin-Chemie, Merck, Sharp & Dohme, and Novartis Pharma. He has also served on the speakers' bureau of AstraZeneca, Boehringer Ingelheim, Eli Lilly & Co., GlaxoSmithKline, Menarini/Berlin Chemie, Merck, Sharp & Dohme, NovoNordisk, and Sun Pharma. J J M has received consulting and speaker honoraria from Astra Zeneca, Eli Lilly& Co., Merck, Sharp & Dohme, Novo Nordisk and Sanofi. He has received research support from Eli Lilly & Co., Boehringer-Ingelheim, Merck, Sharp & Dohme, Novo Nordisk, Novartis and Sanofi.

Funding

J J M has been supported by the Deutsche Forschungsgemeinschaft (DFG), grant ME 2096/8-1.

Author contribution statement

M A N has designed the review, performed the literature review, and wrote the first draft of the present review. J J M has provided input into the figures and tables, and has revised the manuscript for critical intellectual content. Both authors have decided to submit the final version for publication. M A N is the guarantor for the content and vouches for the accuracy of data presented.

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Received 22 July 2019
Revised version received 11 September 2019
Accepted 9 October 2019