Review

MOLECULAR
METABOLISM

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

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ABSTRACT

Background: GLP-1 receptor agonists (GLP-1 RAs) with exenatide b.i.d. first approved to treat type 2 diabetes in 2005 have been further developed to yield effective compounds/preparations that have overcome the original problem of rapid elimination (short half-life), initially necessitating short intervals between injections (twice daily for exenatide b.i.d.).

Scope of review: To summarize current knowledge about GLP-1 receptor agonist.

Major conclusions: At present, GLP-1 RAs are injected twice daily (exenatide b.i.d.), once daily (lixisenatide and liraglutide), or once weekly (exenatide once weekly, dulaglutide, albiglutide, and semaglutide). A daily oral preparation of semaglutide, which has demonstrated clinical effectiveness close to the once-weekly subcutaneous preparation, was recently approved. All GLP-1 RAs share common mechanisms of action: augmentation of hyperglycemia-induced insulin secretion, suppression of glucagon secretion at hyper- or euglycemia, deceleration of gastric emptying preventing large post-meal glycemic increments, and a reduction in calorie intake and body weight. Short-acting agents (exenatide b.i.d., lixisenatide) have reduced effectiveness on overnight and fasting plasma glucose, but maintain their effect on gastric emptying during long-term treatment. Long-acting GLP-1 RAs (liraglutide, once-weekly exenatide, dulaglutide, albiglutide, and semaglutide) have more profound effects on overnight and fasting plasma glucose and HbA_{1c}, both on a background of oral glucose-lowering agents and in combination with basal insulin. Effects on gastric emptying decrease over time (tachyphylaxis). Given a similar, if not superior, effectiveness for HbA_{1c} reduction with additional weight reduction and no intrinsic risk of hypoglycemic episodes, GLP-1RAs are recommended as the preferred first injectable glucose-lowering therapy for type 2 diabetes, even before insulin treatment. However, GLP-1 RAs can be combined with (basal) insulin in either free- or fixed-dose preparations. More recently developed agents, in particular semaglutide, are characterized by greater efficacy with respect to lowering plasma glucose as well as body weight. Since 2016, several cardiovascular (CV) outcome studies have shown that GLP-1 RAs can effectively prevent CV events such as acute myocardial infarction or stroke and associated mortality. Therefore, guidelines particularly recommend treatment with GLP-1 RAs in patients with pre-existing atherosclerotic vascular disease (for example, previous CV events). The evidence of similar effects in lower-risk subjects is not quite as strong. Since sodium/glucose cotransporter-2 (SGLT-2) inhibitor treatment reduces CV events as well (with the effect mainly driven by a reduction in heart failure complications), the individual risk of ischemic or heart failure complications should guide the choice of treatment. GLP-1 RAs may also help prevent renal complications of type 2 diabetes. Other active research areas in the field of GLP-1 RAs are the definition of subgroups within the type 2 diabetes population who particularly benefit from treatment with GLP-1 RAs. These include pharmacogenomic approaches and the characterization of non-responders. Novel indications for GLP-1 RAs outside type 2 diabetes, such as type 1 diabetes, neurodegenerative diseases, and psoriasis, are being explored. Thus, within 15 years of their initial introduction, GLP-1 RAs have become a well-established class of glucose-lowering agents that has the potential for further development and growing impact for treating type 2 diabetes and potentially other diseases.

Keywords Glucagon-like peptide-1 receptor agonists; Exenatide; Lixisenatide; Liraglutide; Dulaglutide; Albiglutide; Semaglutide; Type 2 diabetes; Cardiovascular disease; Body weight

1. DEVELOPMENT OF GLP-1 RAS

The identification of gut-derived glucagon-like peptide-1 (GLP-1), putatively belonging to the family of incretin hormones (i.e. gastrointestinal hormones released after nutrient intake with the ability to glucose-dependently augment insulin secretory responses during periods characterized by hyperglycemia) triggered the development of GLP-1 receptor agonists (GLP-1 RAs). The groups around Jens Holst (Copenhagen, Denmark) [1] and Joel Habener (Boston, MA, USA) [2] were the first to correctly identify “truncated” GLP-1 (GLP-1 [7–36 amide], the amidated form [1], or GLP-1 [7–37], the glycine-extended form [2]), as the product(s) of proglucagon translational processing in mammalian gut mucosa (L cells) as published in 1987. Based on the proglucagon nucleotide sequence, prior assumptions regarding processing enzymes led to an erroneous GLP-1 sequence longer by 6 N-terminal amino acid residues [3]. However, “truncated” GLP-1 was

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clearly insulinotropic at much lower (picomolar) concentrations compared to the extended GLP-1 sequence [1,2]. Initial studies with rodent models indicated that GLP-1 is highly effective as an insulinotropic agent in non-diabetic, metabolically healthy animals, but shared substantially reduced biological activity in diabetic animals with the previously identified incretin glucose-dependent insulinotropic polypeptide (GIP) [4]. Nevertheless, studies in human subjects with type 2 diabetes surprisingly showed well-preserved insulinotropic activity of both GLP-1 [7—36 amide] [5] and GLP-1 [7—36] that was accompanied by a short-term reduction in plasma glucose in the normal fasting range in patients previously characterized by persistent hyperglycemia [6,7]. However, GLP-1 was found to be proteolytically degraded and inactivated by the ubiquitous protease dipeptidyl peptidase-4 (DPP-4) [8] and both the intact GLP-1 molecule and DPP-4-generated metabolites (GLP-1 [9—36 amide] or [9—36]) were subject to rapid elimination from the circulation, with an elimination half-life of approximately 2 min [9]. Therefore, GLP-1 allowed the “proof-of-principle” that GLP-1 receptor stimulation is a suitable method of reducing plasma glucose in subjects with type 2 diabetes. It also helped clarify the three main mechanisms leading to reductions in plasma glucose concentrations: (a) glucose-dependent insulinotropic actions [5], (b) suppression of glucagon hypersecretion [7] except during episodes characterized by hypoglycemia [10], and (c) a deceleration of gastric emptying, which was found to be associated with marked effects on post-meal glycemic excursions [11]. Relatively early acute changes in appetite, satiety, and prospective food consumption by pharmacological doses of GLP-1 were described, resulting in a corresponding reduction in caloric intake [12], thus increasing the motivation to develop compounds mimicking the physiology of GLP-1 resistant to the proteolytic inactivation by DPP-4 and with slower elimination kinetics to allow for reasonable administration frequencies. As a product of serendipity, the peptide exendin-4 from the saliva of a venomous lizard (*Heloderma suspectum*, the Gila monster) was found to be homologous to mammalian GLP-1 and able to bind and activate GLP-1 receptors [13,14]. Synthetic exendin-4 was named exenatide and, without further modification, was the first GLP-1 receptor agonist approved to treat type 2 diabetes. The detailed background of the (patho)physiology of the incretin system and the history of the development of incretin-based glucose-lowering medications have recently been reviewed [15,16].

2. GLP-1 RAS AVAILABLE IN 2020 AND THEIR PHARMACOKINETIC PROPERTIES (TABLE 1)

Following the approval of exenatide to treat type 2 diabetes (USA: 2005; Europe: 2006), several pharmaceutical companies started diverse developments aiming at GLP-1 receptor stimulation with greater effectiveness and longer duration of action. Exenatide needs to be injected at least twice daily, which mainly provides active circulating concentrations covering two major meals every day, with low levels between the two injections. Liraglutide, approved in 2009, was designed to provide a nearly unchanged amino acid sequence compared to mammalian GLP-1. A free fatty acid side chain was coupled to the peptide, which promotes binding to albumin in plasma and interstitial fluid. Only a minor proportion (estimated 1—2%) of liraglutide circulates in a free (non-albumin-bound) form, ready to diffuse into tissues and bind receptors. The albumin-bound bulk forms a reservoir promoting prolonged action. Overall, the elimination half-life is approximately 13 h, making it a suitable preparation for once-daily injection. The next step was aiming at once-weekly injections of GLP-1 RAs. Exenatide was developed as a novel preparation with the active ingredient slowly released after subcutaneous injection from a matrix dissolving over time. Thus, the onset of action was very much delayed, and a steady state was not reached until 8—10 weeks of treatment [17,18]. Other approaches followed the strategy to couple (modified) GLP-1 to large proteins such as an immunoglobulin Fc fragment (dulaglutide or efpeglenatide) or albumin (albiglutide). These compounds appear to slowly degrade, with half-lives of approximately one week. After subcutaneous injection, they reach effective circulating concentrations relatively early, thus beginning to lower plasma glucose soon after initiating such treatment. Semaglutide is another compound with a structure generally similar to liraglutide (GLP-1 with a free fatty acid side chain) but with a much longer half-life, apparently mediated by even tighter coupling to albumin. Semaglutide is presently available for once-weekly subcutaneous injection. More recently, semaglutide was co-formulated with sodium N-(8-(2-hydroxybenzoyl) amino) caprylate (SNAC) for oral treatment. To account for the relatively low bioavailability of semaglutide when absorbed through the gastrointestinal tract, oral semaglutide needs to be administered daily. This is the first GLP-1 RA approved for oral administration. At equivalent doses, subcutaneous and oral semaglutide seem to have similar effects on HbA_{1c}, body weight, and adverse events [19]. Details regarding the molecular structures of various GLP-1 RAs and additional pharmacokinetic information were summarized by Nauck and Meier in 2019 [20].The time between subcutaneous (or oral) administration and the occurrence of peak concentrations is displayed in Figure 1.

2.1. Recommendations for initial up-titration (Figure 2)

All GLP-1 RAs developed to date have been designed for standardized dosage recommendations applicable to most if not all patients. Nausea and vomiting were noticed as common side effects, mainly occurring after the initiation of injection treatment or after increasing the dose. Peak plasma concentrations may determine the time when these symptoms most likely occur. In the early stages, a strategy of starting exenatide with a lower than maintenance dose, slowly increasing to the desired steady state, was found to reduce problems with gastrointestinal adverse events. Since then, recommendations have been developed for such an up-titration (dose escalation) approach to induce tolerance before patients are exposed to higher doses of GLP-1 RAs (Figure 2). Whether or not initial up-titration has to be recommended for a given compound/preparation depends on these agents' pharmacokinetic properties. This is not necessary for preparations such as once-weekly exenatide because the protracted action is the result of slow absorption, while the elimination of circulating exenatide follows the same kinetics as known for un-retarded (b.i.d.) exenatide (Table 1). Among those agents that have a long duration of action mainly through their slow elimination (long elimination half-life, see Table 1), those with a relatively rapid time to peak concentration ($T_{max} < 24$ h; applies to short-acting GLP-1 RAs, liraglutide, and semaglutide [20]) are those with recommended dose escalation schedules, while those with slower absorption (dulaglutide and albiglutide; $T_{max} \geq 48$ h) (Figure 1) can be initiated at their final dose. This could be explained by the fact that the GLP-1 RAs characterized by a free fatty acid side chain are injected as “free” (non-albumin-bound) compounds and that it takes some time to reach a steady—state equilibrium for binding to albumin. Only after reaching this equilibrium, most of the compound is bound to albumin, and, as such, is unable to diffuse into tissues and elicit effects (including adverse events).

Choosing the appropriate initial dose escalation schedule can have consequences for dose selection in phase 2 of clinical development programs, since doses carried on into phase 3 and suggested for

Table 1 — Characteristics of GLP-1 RAs that have been approved to treat type 2 diabetes as of 2020.

GLP-1 RA	First approved (date)	Molecular weight (Da)[c]	Reference amino acid sequence	Other important components	Elimination half-life	Administration schedule	Pharmaceutical company	Reference
For subcutaneous injection								
Short-acting compounds								
Exenatide b.i.d.	2005 (USA); 2006 (Europe); Byetta	4186.6	Exendin-4	None	3.3–4.0 h	Twice daily	AstraZeneca[i]	[21]
Lixisenatide	2013 (Europe); Lyxumia; 2016 (USA); Adlyxin	4858.5	Exendin-4	Poly-lysine tail	2.6 h	Once daily	Sanofi	[22]
Long-acting compounds/preparations								
Liraglutide	2009 (Europe); 2010 (USA); Victoza	3751.2	Mammalian GLP-1	Free fatty acid[e]	12.6–14.3 h	Once daily	Novo Nordisk	[23]
Once-weekly exenatide	2012; BYDUREON[a]	4186.6	Exendin-4	Active ingredient encapsulated in microspheres of poly-(D,L-lactide-co-glycolide)	3.3–4.0 h[f]	Once weekly	AstraZeneca[i]	[21]
Dulaglutide	2014; Trulicity	59670.6	Mammalian GLP-1	Immunoglobulin Fc fragment	4.7–5.5 d	Once weekly	Eli Lilly and Company	[24]
Albiglutide	2014 (Europe); Eperzan Tanzeum (USA)[b]	72971.3	Mammalian GLP-1	Albumin	5.7–6.8 d	Once weekly	GlaxoSmithKline	[25]
Semaglutide	2017 (USA); 2019 (Europe); Ozempic	4113.6	Mammalian GLP-1	Free fatty acid[e]	5.7–6.7 d	Once weekly	Novo Nordisk	[26]
For oral administration								
Semaglutide (long-acting)	2020; Rybelsus	4113.6	Mammalian GLP-1	Free fatty acid[e]	5.7–6.7 d	Once daily	Novo Nordisk	[27]
Fixed-dose combinations								
With basal insulin (for subcutaneous injection)								
Liraglutide/ insulin degludec (iDegLira)	2014 (Europe); 2016 (USA); Xultophy	3751.2[d]	Mammalian GLP-1	Basal insulin	12.6–14.3 h	Once daily (anytime[g])	Novo Nordisk	[28]
Lixisenatide/ insulin glargine (iGlarLixi)	2016 (USA); Soliqua 100/33; 2017 (Europe); Suliqua	4858.5[d]	Exendin-4	Basal Insulin	2.6 h	Once daily[h]	Sanofi	[29]

[a] Improved once-weekly auto-injector BYDUREON BCise was approved in 2018.
[b] Marketing was discontinued in 2018.
[c] Mammalian GLP-1: 3297.7.
[d] For the GLP-1 RA component only.
[e] Promoting binding to albumin.
[f] Identical to the short-acting preparation.
[g] Approximately the same time every day.
[h] Before meals with the highest expected glycemic excursion.
[i] Previously Amylin Pharmaceuticals, Eli Lilly and Company, and Bristol Myers Squibb.

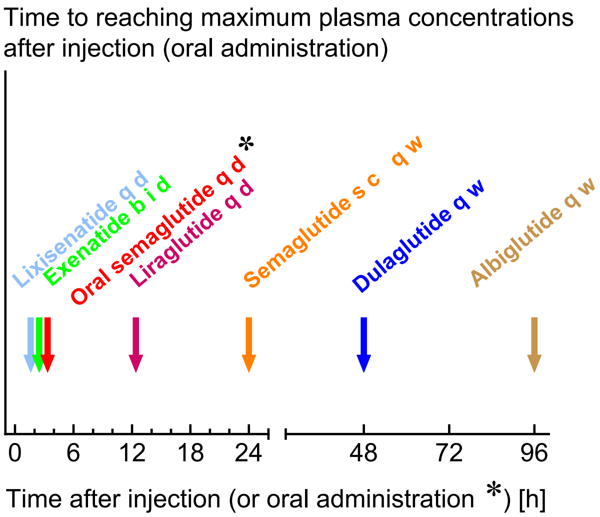


Figure 1: Arrows indicate the time from injection (or oral administration in the case of oral semaglutide) to peak plasma concentrations (C_{max}) for GLP-1 RAs (T_{max}). For references, please see [20]. Peak plasma concentrations may determine the time when nausea and vomiting are observed with GLP-1 RA treatment. The extremely slow absorption of once-weekly exenatide does not allow identification of a peak.

approval have to be effective as well as tolerable and safe. Less than optimal up-titration regimens may lead to (avoidable) side effects and will most likely limit the upper dose range that is considered to have a beneficial efficacy-side effect relationship.

Another question related to initial up-titration is whether it is needed when switching from one agent to another (e.g., for increasing efficacy or avoiding side effects). This is an issue that is not normally clarified by dedicated clinical trials. Therefore, recommendations mainly based on pharmacokinetic modeling are available [30].

2.2. Injection devices (Figure 3)

All GLP-1 RAs are delivered from pre-filled, dedicated pen injection devices developed for each particular product. However, details are considerably different for various products. They vary with respect to one time (mainly once-weekly GLP-1 RAs) vs multiple usage and in their ability to deliver one predetermined dose or whether it can be used to choose between several dose settings. For once-weekly exenatide, the microspheres containing the active drug need to be resuspended in buffer. Originally, this meant reconstitution of the active ingredient in vehicle solutions, which are stored in different vessels. An improved dual-chamber device has simplified this procedure. The dulaglutide pen injection device has received attention

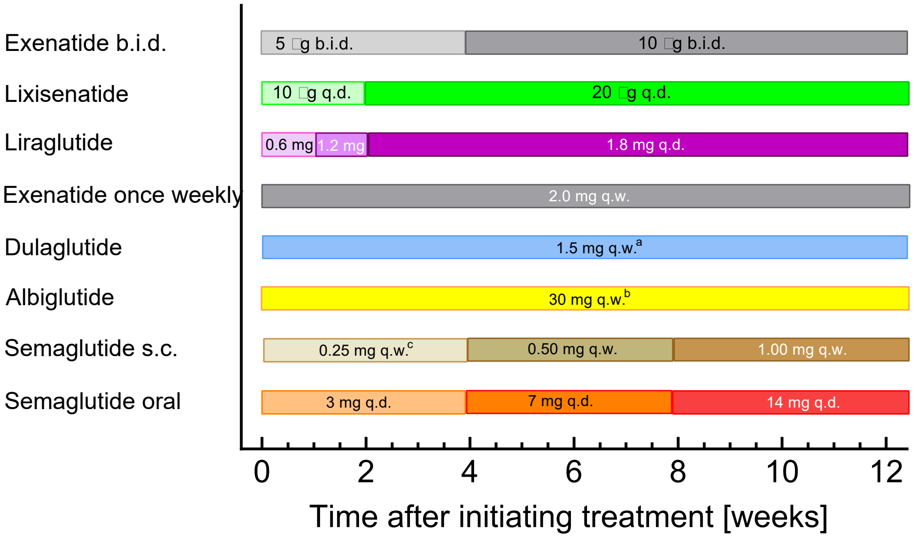
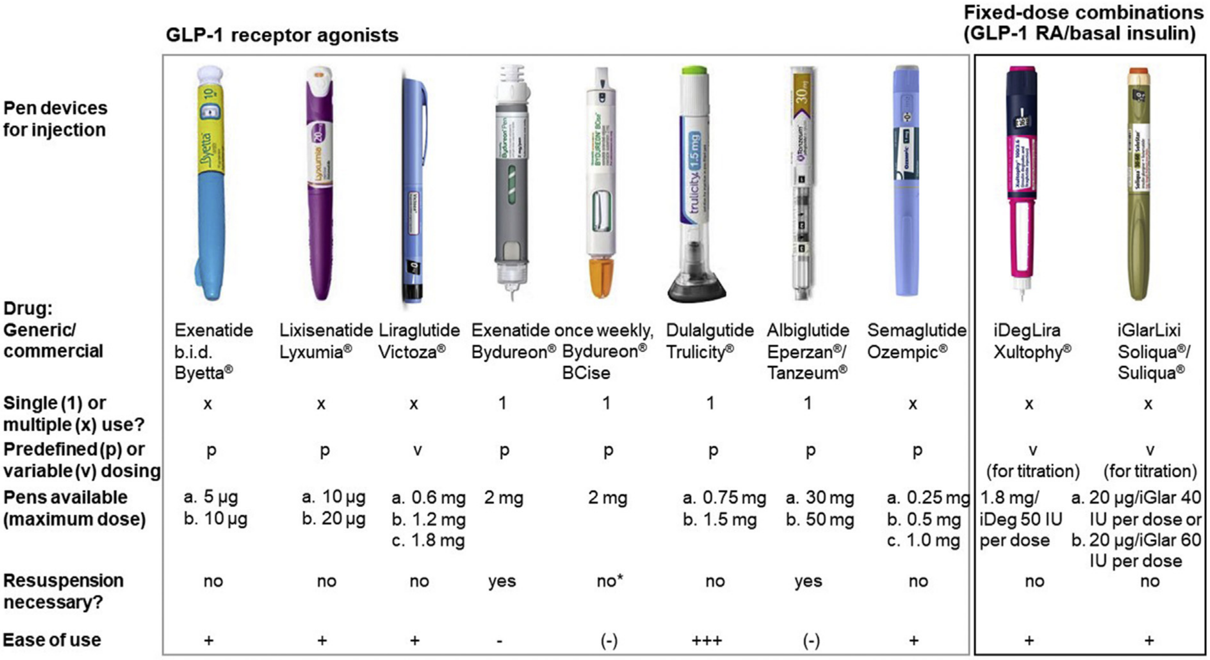


Figure 2: Recommendations issued in official package inserts regarding the necessity for slow up-titration of approved GLP-1 receptor agonists.



	GLP-1 receptor agonists								Fixed-dose combinations (GLP-1 RA/basal insulin)	
Drug: Generic/ commercial	Exenatide b.i.d. Byetta®	Lixisenatide Lyxumia®	Liraglutide Victoza®	Exenatide once weekly, Bydureon®	Bydureon® BCise	Dulalgutide Trulicity®	Albiglutide Eperzan®/ Tanzeum®	Semaglutide Ozempic®	iDegLira Xultophy®	iGlarLixi Soliqua®/ Suliqua®
Single (1) or multiple (x) use?	x	x	x	1	1	1	1	x	x	x
Predefined (p) or variable (v) dosing	p	p	v	p	p	p	p	p	v (for titration)	v (for titration)
Pens available (maximum dose)	a. 5 μg b. 10 μg	a. 10 μg b. 20 μg	a. 0.6 mg b. 1.2 mg c. 1.8 mg	2 mg	2 mg	a. 0.75 mg b. 1.5 mg	a. 30 mg b. 50 mg	a. 0.25 mg b. 0.5 mg c. 1.0 mg	1.8 mg/ iDeg 50 IU per dose	a. 20 μg/iGlar 40 IU per dose or b. 20 μg/iGlar 60 IU per dose
Resuspension necessary?	no	no	no	yes	no*	no	yes	no	no	no
Ease of use	+	+	+	-	(-)	+++	(-)	+	+	+

Figure 3: Optical appearance and properties of pen injection devices for approved GLP-1 receptor agonists (as mono substances or fixed-dose combinations with basal insulin). Modified from Nauck and Meier 2019 [20]. *Thorough shaking was necessary to evenly resuspend the active ingredient. The ease of use was estimated semi-quantitatively based on informal feedback from patients using these pen injection devices.

because of its single-use design and the needle, which is never visible throughout the injection procedure. Figure 3 depicts the visual appearance and some essential properties as well as the authors' evaluation of their ease of use of all available pen injection devices for GLP-1 RAs (free and fixed-dose combinations).

2.3. Classification as short- and long-acting GLP-1 RAs

Since the parent compound of GLP-1 RAs, GLP-1, has a very short elimination half-life that precluded its clinical use outside settings characterized by continuous administration, compounds/preparations with longer intervals between injections have been developed over time (Table 1). While this at first was thought to be mainly relevant with respect to the injection frequency, thus representing a convenience issue, essential pharmacological differences were later identified that suggested that both short- and long-acting GLP-1 RAs may have specific advantages and indications [31]. By definition, short-acting GLP-1 RAs (exenatide b.i.d. and lixisenatide) are characterized by short-lived peaks in plasma drug concentrations following each injection, with intermittent periods of near-zero concentrations. Thus, the time—action profile changes between periods (lasting a few hours) during which patients are exposed to effective circulating drug concentrations, and "resting" periods, during which GLP-1 receptors are not activated. In contrast, long-acting GLP-1 RAs, once at a steady state, are characterized by constantly elevated drug concentrations in a range leading to substantial GLP-1 receptor stimulation and only minor fluctuations between injections (e.g., a 24-h period for liraglutide and a week-long period for semaglutide). Of note, this definition does not rest on the injection frequency alone but on the pharmacological kinetics. Consequently, once-daily lixisenatide is a short-acting compound, whereas once-daily liraglutide is a long-acting GLP-1 RA (Table 1).

One obvious consequence of the different temporal patterns of short- and long-acting GLP-1 RAs with reduced exposure during the night in short-acting compounds is the ability of long-acting GLP-1 RAs to more profoundly lower fasting plasma glucose than short-acting GLP-1 RAs. This was best exemplified by a study comparing un-retarded (b.i.d.) and long-acting release (once-weekly) exenatide [18], although the differences were valid for the comparison of any short- and long-acting GLP-1 RA (Figure 4).

Another peculiarity relates to the effectiveness of GLP-1 RAs to slow gastric emptying in light of tachyphylaxis: while intermittent stimulation of GLP-1 receptors (short-acting GLP-1 RAs) is associated with preserved effects on gastric motility, even long-term continuous stimulation leads to desensitization, which probably begins early (within 4—24 h) and reaches its full expression after several weeks or months [32]. Since the velocity of gastric emptying is tightly coupled to the absorption of nutrient carbohydrates, slowed gastric emptying means reduced and/or delayed glycemic increases after meals. For short-acting GLP-1 RAs, delayed gastric emptying is the main mechanism for post-meal reductions in plasma glucose rises [33]. It has been claimed that short-acting GLP-1 RAs act preferentially on post-meal glycemic rises through their effect on gastric emptying, which are preserved over time [18,33,34], while there is substantial tachyphylaxis for long-acting compounds [18,34]. First, long-acting GLP-1 RAs reduce post-prandial glucose as well, mainly through increasing insulin and suppressing glucagon [31]. The effect on gastric emptying relates only to meals, before which the short-acting GLP-1 RA has been administered (once daily with lixisenatide and twice daily with exenatide b.i.d.), with minor effects at most for other meals [33]. Whether this translates into a net advantage is far from clear. In a recent meta-analysis comparing short- and long-acting GLP-1 RAs on a basal insulin background, post-prandial glucose increases were not significantly different [35]. Conditions under which a reduction in post-

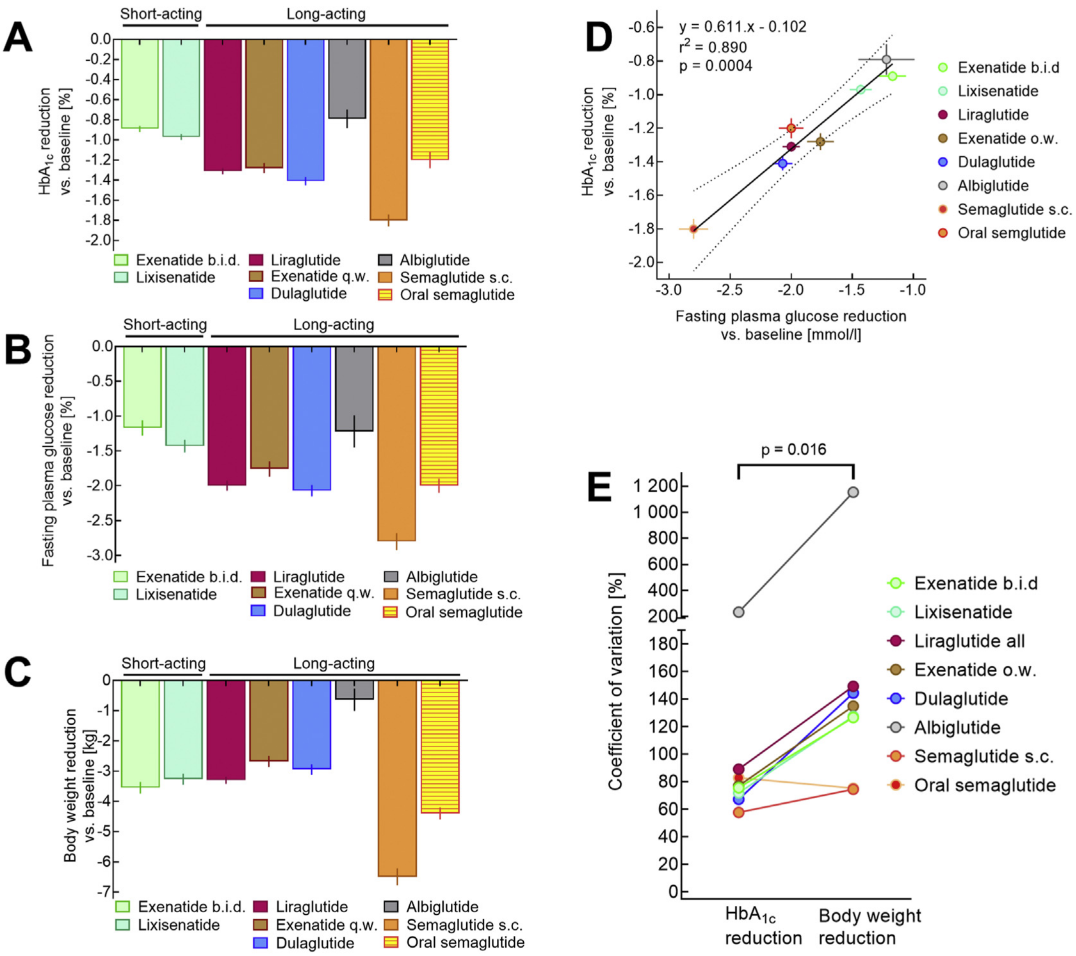


Figure 4: Comparison of approved GLP-1 RAs with respect to their effectiveness in reducing HbA_{1C} (A), fasting plasma glucose (B), and body weight (C). A linear regression analysis relating reductions in fasting plasma glucose to reductions in HbA_{1c} is shown in panel D. A comparison of the reported coefficients of variation for reducing HbA_{1c} and body weight is displayed in panel E. All data are from clinical trials reporting head-to-head comparisons between various GLP-1 RAs (exenatide b.i.d. vs lixisenatide [36], exenatide b.i.d. vs liraglutide [37], lixisenatide vs liraglutide [38], exenatide once-weekly vs liraglutide [39], albiglutide vs liraglutide [40], dulaglutide vs liraglutide [41], subcutaneous semaglutide vs dulaglutide [42], and oral semaglutide vs liraglutide [43]) on a background of oral glucose-lowering agents. Data concerning the same GLP-1 RA were pooled using conventional equations to calculate common means and their standard deviations.

meal glycemic excursions through a lasting deceleration of gastric emptying cause an obvious advantage of short-over long-acting GLP-1 RAs still need to be defined.

The effectiveness of short- and long-acting GLP-1 RAs for controlling fasting plasma glucose and HbA_{1c} in patients with type 2 diabetes otherwise treated with oral glucose-lowering agents was compared in relatively large head-to-head comparison trials conducted in patients receiving oral glucose-lowering medications as background therapy. Figure 5 shows representative data from these clinical trials. The reduction in fasting plasma glucose was systematically more pronounced with long-acting compounds. Consequently, HbA_{1c} values were reduced significantly more by long-acting GLP-1 RAs (since the overnight period represented one-third of the 24 h period). Efficacy regarding reductions in fasting plasma glucose and HbA_{1c} were highly correlated (Figure 4D), underscoring the importance of controlling fasting plasma glucose to achieve acceptable overall glycemic control based on commonly recommended target ranges. Similar conclusions were derived from specifically assessing 4 head-to-head clinical trials comparing short- and long-acting GLP-1 RAs (depicted in Nauck and Meier 2019 [20]).

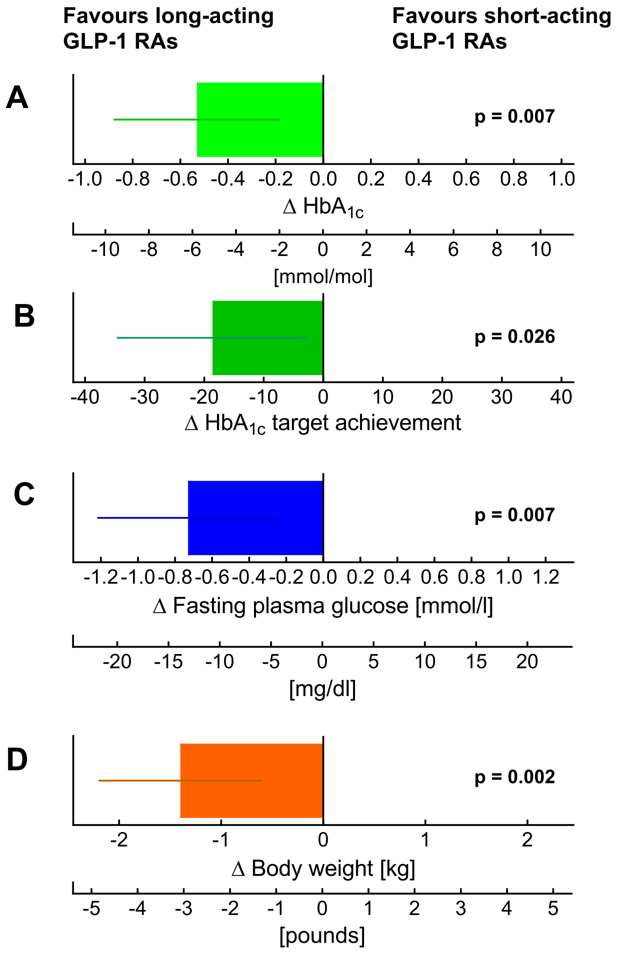


Figure 5: Meta-analysis comparing effects of short- and long-acting GLP-1 receptor agonists added to basal insulin in HbA_{1c} (A), HbA_{1c} target ($\leq$7.0%) achievement (B), fasting plasma glucose (C), and body weight (D). For each variable, the results were significantly better for long-acting compounds (liraglutide, once-weekly exenatide, dulaglutide, and semaglutide based on 6 studies) compared to short-acting compounds (exenatide b.i.d. and lixisenatide based on 8 studies). Both studies with free and fixed-dose combinations were analyzed. Modified from [50].

2.4. Comparison between GLP-1 RA and insulin therapy

According to current recommendations, recently diagnosed type 2 diabetes should be treated with patient education instructing in favor of a healthy lifestyle including nutrition avoiding excess calories and rapidly absorbed carbohydrates and physical exercise. At this early stage or later, single (mostly metformin) or combination therapy with oral glucose-lowering agents is recommended until injectable therapy with more effective drugs (insulin or GLP-1 receptor agonists) becomes necessary. It was surprising that when meta-analyzing studies directly comparing insulin treatment (mainly basal insulin combined with oral agents) with any of the GLP-1 receptor agonists, there was, at most, a minor difference in glycemic effectiveness [44,45]. If anything, GLP-1 receptor agonist had a slightly better effect on reducing HbA_{1c}. In addition, they uniformly led to some weight loss, and were only associated with hypoglycemic episodes when combined with sulfonylureas or insulin. As a factor contributing to more convenience, GLP-1 RAs can be employed using more or less standardized dosing instructions (including initial up-titration), while insulin needs to be individually titrated, with effective doses spread across a wide range. Some features of (basal) insulin and GLP-1 RA therapy in combination with oral glucose-lowering agents are summarized in Table 2. Of note, basal insulin and GLP-1 RAs are similarly effective in patients starting at very high baseline HbA_{1c} values (although patients selected by this criterion often fail to reach conventional target ranges for HbA_{1c}) [46]. Overall, these reasons form the basis of the ADA/EASD recommendation to preferentially use GLP-1 RAs in type 2 diabetes patients failing on oral agents alone [47]. Exceptions are circumstances suggesting type 1 diabetes or latent autoimmune diabetes in adults (LADA) with severe insulin deficiency.

2.5. Combination with (basal) insulin therapy

Therapy with basal insulin may fail because it may be successful in controlling fasting plasma glucose but does not sufficiently limit post-prandial glycemic excursions. Treatment intensification can mean adding one to three prandial insulin injections per day or adding a GLP-1 RA to ongoing insulin treatment. Nevertheless, GLP-1 RA therapy with a background of oral glucose-lowering medications may fail to achieve glycemic targets as well. In this case, combining it with insulin (mainly basal insulin) is a well-documented method of improving fasting, post-prandial, and overall (HbA_{1c}) glycemic control [51—57]. The combination of (basal) insulin with a GLP-1 RA is a highly effective treatment even for advanced stages of type 2 diabetes. It should only be used in patients needing a combination of two injectable treatments, especially considering the costs of such a combination.

When a GLP-1 RA is added to (basal) insulin, the combination is as effective as an intensified (basal bolus) insulin regime in terms of HbA_{1c} control, but with a much lower risk of hypoglycemia and weight gain [58].

When insulin is added to a GLP-1 RA, it helps control fasting plasma glucose. In combination with post-prandial effects of GLP-1 RAs (through decelerating gastric emptying, stimulating insulin, or suppressing glucagon secretion [31]), this provides excellent chances to achieve the target ranges for fasting, post-prandial, and overall (HbA_{1c}) glycemic control. In studies comparing basal insulin and GLP-1 RAs alone and in combination with each other, the combination achieved the lowest HbA_{1c} or highest HbA_{1c} reduction and a body weight transformation in between GLP-1 RA alone (lowest) and insulin alone (highest) [59]. There is a risk of hypoglycemic episodes with this combination, which is higher than treating with GLP-1 RAs alone, but lower compared to insulin treatment alone [59].

Table 2 — Comparison of injectable treatments for type 2 diabetes with basal insulin or GLP-1 receptor agonists (based on meta-analyses of head-to-head comparisons [44,45]).

Criterion	Treatment with		Commentary
	Basal insulin	GLP-1 receptor agonists	
Glycemic control			
Fasting plasma glucose (FPG)	After meticulous titration, FPG concentrations in the target range (for example, 80—110 mg/dl) can often be reached	Substantial reduction can be achieved. Overall, slightly less effective than insulin	An exception is semaglutide for once-weekly injection, which lowered FPG more than insulin glargine [48]
Prandial glycemic excursions	Can be reduced with appropriately dosed basal insulin	Reduced through deceleration of gastric emptying (short-acting GLP-1 RAs) and the influence on insulin and/or glucagon secretion [31]	Short-acting GLP-1 RAs maintain their effect on gastric emptying with continued administration, while there is tachyphylaxis over days/weeks with long-acting GLP-1 RAs [18]
HbA_{1c}	Substantial reduction, often into the target range	Substantial reduction, often into the target range	A slightly better reduction was shown with GLP-1 RAs, which might have been caused by insufficient titration of basal insulin; long-acting GLP-1 RAs achieve lower HbA_{1c} concentrations [44]
Dosing	By titration, often starting with approximately 10 IU/d. Effective doses are somewhere between 15 and 200 IU/d and cannot be precisely predicted based on clinical characteristics (for example, BMI)[a]	Standard dosage recommendations are available for individual GLP-1 RAs (often including some slow up-titration during the initial period)	Hypoglycemia may be dose-limiting for insulin, while nausea and vomiting may suggest using lower doses than generally recommended for GLP-1 RAs
Frequency	Usually once daily ("bedtime" insulin)	Between twice daily (exenatide b.i.d.) and once weekly	Variable for GLP-1 RAs because of their differing elimination kinetics
Changes in body weight	Increases by 1—2.5 kg on average	Decreases by 2—6 kg on average	Within the range typical for each GLP-1 RA, individual weight loss is highly variable
Risk of hypoglycemic episodes	Hypoglycemic episodes are reported in approximately 43% of patients, in part depending on the proportion receiving sulfonylurea treatment [44]	Hypoglycemic episodes are reported in approximately 23% of patients, very much depending on the proportion receiving sulfonylurea treatment [44]	Clinically meaningful hypoglycemia with GLP-1 RAs heavily depends on a co-medication with sulfonylureas [44]
Nausea and vomiting as adverse events	Rare	Nausea (up to 20%) and vomiting (up to 10%) mainly occur after initiating treatment or associated with increases in dosage	Gastrointestinal side effects lead to medication withdrawal in approximately 5—10% [49]

[a] Algorithms are available that aid the titration process.

The fact that a combination of a GLP-1 RA with basal insulin is a highly efficacious glucose-lowering treatment regime for advanced stages of type 2 diabetes has led to the development of fixed-dose combinations. GLP-1 RAs that are usually injected once daily (liraglutide or lixisenatide) were combined with basal insulin designed for once-daily injection (insulin degludec or insulin glargine), resulting in the fixed-dose combinations iDegLira [28,59] and iGlarLixi [60,61]. Since insulin must be titrated slowly as part of the dose-finding process, the GLP-1 RA component of these fixed-dose combinations is titrated slowly as well. This approach for introducing GLP-1 RA therapy has resulted in fewer problems with nausea, vomiting, or diarrhea. Apparently smaller steps of increasing GLP-1 RA exposure better support an adaptation process increasing patients' tolerance to such adverse reactions.

It has been postulated that short-acting GLP-1 RAs are particularly suited for combination with basal insulin because the strength of long-acting compounds, a greater effect on fasting plasma glucose, is not needed in this combination since the role of basal insulin would be to control fasting plasma glucose. However, the effect of slowing gastric emptying leading to slower absorption of nutrients (which is preserved over time with short-acting GLP-1 RAs) is a mechanism limiting post-meal glycemic excursion [31]. Notably, with short-acting GLP-1 RAs, this effect only applies to the meal before which the agent has been injected. A recent meta-analysis described the advantages of combining long-acting GLP-1 RAs (compared to short-acting GLP-1 RAs) with basal insulin [50]. This applied to free combinations (dosage determined separately for the GLP-1 RAs and basal insulin) as well as fixed-dose combinations [50]. As depicted in Figure 5, not only HbA_{1c} was lowered significantly more and HbA_{1c} targets were achieved in a higher proportion of patients, but also fasting plasma glucose concentrations and body weight were controlled better with long-acting GLP-1 RAs [50]. In addition, the risk of hypoglycemic episodes and gastrointestinal side effects was slightly, but significantly lower with long-acting GLP-1 RAs [50].

2.6. Weight loss induced by GLP-1 RAs

Intracerebroventricular [62] and peripheral administration of GLP-1 [12] and GLP-1 RAs [20,63] reduces appetite and prospective food consumption, increases satiety and a feeling of abdominal fullness, and limits caloric intake under conditions of ad libitum feeding. All GLP-1 RAs after longer-term treatment lead to weight loss but in varying degrees (Figure 4). Thus, GLP-1 RAs are unique in promoting weight loss while reducing the glycemia level, which in turn limits glucosuria (energy lost through urinary glucose excretion) and therefore should be associated with weight gain. Most other glucose-lowering agents, except for sodium/glucose cotransporter-2 (SGLT-2) inhibitors, usually lead to some weight gain (sulfonylureas, insulin, or thiazolidinediones) or are weight neutral (metformin, DPP-4 inhibitors, or α-glucosidase inhibitors) [47]. Liraglutide (at doses somewhat higher than used to treat diabetes mellitus) is also approved for pharmacological obesity therapy [64,65]. Semaglutide, the GLP-1 RA with the highest efficacy regarding weight loss in clinical trials of type 2 diabetes patients (Figure 4), is also undergoing evaluation as a weight-loss agent in obese subjects without diabetes mellitus [66—68].

The quantitative differences in body weight reduction typically achieved with different GLP-1 RAs critically depend on the respective doses selected in phase 2 studies. Since the primary indication for using GLP-1 RAs is type 2 diabetes, dose selection has mainly addressed glycemic control (HbA_{1c} reduction). Some data suggest that while HbA_{1c} reduction plateaus at relatively lower doses, higher doses may still be more effective for weight loss [69,70]. This is one important reason for testing higher doses, for example, dulaglutide [71], to seek approval for more effective, higher doses of GLP-1 RAs for those who tolerate them.

The fact that some GLP-1 RAs have particularly weak effects with respect to body weight (e.g., albiglutide), whereas other compounds seem to have more pronounced effects (e.g., semaglutide) even if their glucose-lowering effects are similar, has sparked interest in characterizing the mechanism of action. It is obvious that appetite-and weight-reducing effects involve uptake into specific brain regions and interaction with CNS neural circuits involved in the homeostatic or hedonic [77] regulation of energy household and food intake. Table 3 summarizes recent insights gained from comprehensive studies characterizing semaglutide's (and liraglutide) effects on diet-induced obesity in rodents [72,73]. These findings point to a role of the arcuate nucleus within the hypothalamus, area postrema (AP), and nucleus tractus solitarii (NTS) for the influence of systemically administered GLP-1 RAs on appetite, satiety, calorie intake, and body weight as schematically summarized in Figure 6. In this model, GLP-1 RAs seem to be effective at preventing meal initiation by suppressing the activity of NPY/agouti-related peptide (AgRP) producing neurons in the arcuate nucleus and inducing meal termination in the lateral parabrachial nucleus (PB). Signals reaching the PB originate from the arcuate nucleus of the hypothalamus and brain stem (AP and NTS). POMC/CART neurons expressing GLP-1 receptors activate PB neurons and directly or indirectly suppress NPY/AgRP neurons [72,73], leading to disinhibition of suppressive signals to the PB (Figure 6). Recent data indicated subtle differences in how the brain interacts with liraglutide and semaglutide [73], which may help explain why these two GLP-1 RAs differ in their efficacy to reduce body weight (Figure 4). This information may guide the design of GLP-1 RAs or related pharmacological agents with even more pronounced weight loss efficacy. It still remains unclear why albiglutide has a weaker weight-lowering efficacy than other GLP-1 RAs (Figure 4).

Table 3 — Mechanisms involved in GLP-1 RA-associated appetite and weight reduction as reported in a recently published comprehensive study focusing on the effects of semaglutide (compared to liraglutide) on diet-induced obesity in mice (based on Secher et al., 2014 and [72] and Gabery et al., 2020 [73]).

Aspects of the mechanism of GLP-1 RA-induced weight loss	Findings	Explanation/ commentary
Access of peripherally circulating GLP-1 RAs into the central nervous system	• No transport across the blood—brain barrier (BBB) • Uptake of liraglutide and semaglutide into selected brain areas: (a) not protected by the BBB (circumventricular organs); (b) protected by the BBB: for example, nucleus arcuatus (hypothalamus), area postrema, nucleus tractus solitarii, and dorsal motor nucleus of the vagus nerve (brain stem) • A potential role of tanycytes in mediating uptake of semaglutide into some brain areas	• Absence of GLP-1 Rs in brain endothelial cells • Uptake of liraglutide and semaglutide into selected brain areas is similar, but not fully identical (e.g., semaglutide had a distribution extending more laterally and into posterior portions of the nucleus arcuatus)
Access of GLP-1 RAs to GLP-1 receptors in the brain	• Brain areas with a high uptake of semaglutide are equipped with GLP-1 receptors (mainly in the hypothalamus and hindbrain)	• Uptake of fluorescently labeled semaglutide is substantially reduced in GLP-1 R$^{-/-}$ animals
Direct effects of GLP-1 RAs on the hypothalamus (nucleus arcuatus)	• POMC/CART neurons are depolarized (stimulated); NPY/AgRP neurons are hyperpolarized (inhibited)	• As previously shown for liraglutide
Neuronal activation in brain areas accessible for GLP-1 RAs	• C-Fos activation observed in the area postrema and nucleus tractus solitarii (brain stem)	• Immediate consequence of GLP-1 R engagement
Neuronal activation in brain areas not directly accessible for GLP-1 RAs ("secondary activation")	• C-Fos activation in the bed nuclei of the stria terminalis, central amygdala nucleus, midline group of the dorsal thalamus, parasubthalamic nucleus, and parabrachial nucleus (CGRP-expressing neurons)	• These are brain regions that have been identified as part of an appetite-regulation pathway related to meal termination [74]
Food intake and body weight	• Reduced (strong initial effect and some attenuation over time); substantial weight reduction compared to placebo treatment	• Reduced caloric intake is the main mechanism leading to weight loss with GLP-1 RAs
Food preference	• Semaglutide reduced intake of chocolate bars in favor of chow	• These results suggest that GLP-1 RAs may promote healthier food choices
Energy expenditure	• Weight loss induced by caloric restriction leads to a compensatory reduction in energy expenditure • Weight loss induced by semaglutide only transiently did so: energy expenditure returned to baseline levels within a week	• Interferes with an effective compensatory mechanism counteracting weight loss; needs to be confirmed in human studies

BBB: blood—brain barrier, GLP-1 R: glucagon-like peptide-1 receptor, GLP-1 RA: GLP-1 receptor agonist, POMC/CART: proopiomelanocortin/cocaine- and amphetamine-regulated transcript, NPY/AgRP: neuropeptide Y/agouti-related peptide.

Human studies have confirmed the ability of GLP-1 RAs to influence food choices (toward a selection of less energy-dense healthier foods) [66,78]. However, in contrast to some recent findings in rodents [73], studies in human subjects did not observe any interference of semaglutide treatment with a reduction in energy expenditure that usually accompanies weight loss (as one important mechanism for maintaining body weight close to a pre-determined "set point") [66,79]. Twelve weeks may not be sufficient to reach a steady state of weight reduction and possibly compensatory mechanisms. Of interest are the results of questionnaires indicating that obese subjects had fewer food cravings and could better resist food cravings while treated with semaglutide [66]. The answers point to the fact that eating was considered less pleasurable during treatment with semaglutide [66]. This could be in line with functional magnetic resonance imaging showing that GLP-1 R activation decreases anticipatory food reward (the anticipated pleasure of eating certain meals) and increases consummatory food reward (the pleasure offered by eating a meal) [80]. The regulation of energy intake thus is not only subject to homeostatic regulation (nervous system circuits attempting to maintain unchanged body weight), but also interacts with the brain reward system [80—84].

The robust effects of GLP-1 RAs to reduce body weight, usually by 2—7 kg (or % of initial body weight) on average in type 2 diabetes, have led to the exploration of GLP-1 RAs as a novel pharmacological treatment in obese but non-diabetic subjects often with impaired fasting glucose or glucose tolerance ("prediabetes"). Based on the observation that dose—response relationships have shown a plateau for glycemic control at lower doses than for body weight reduction,

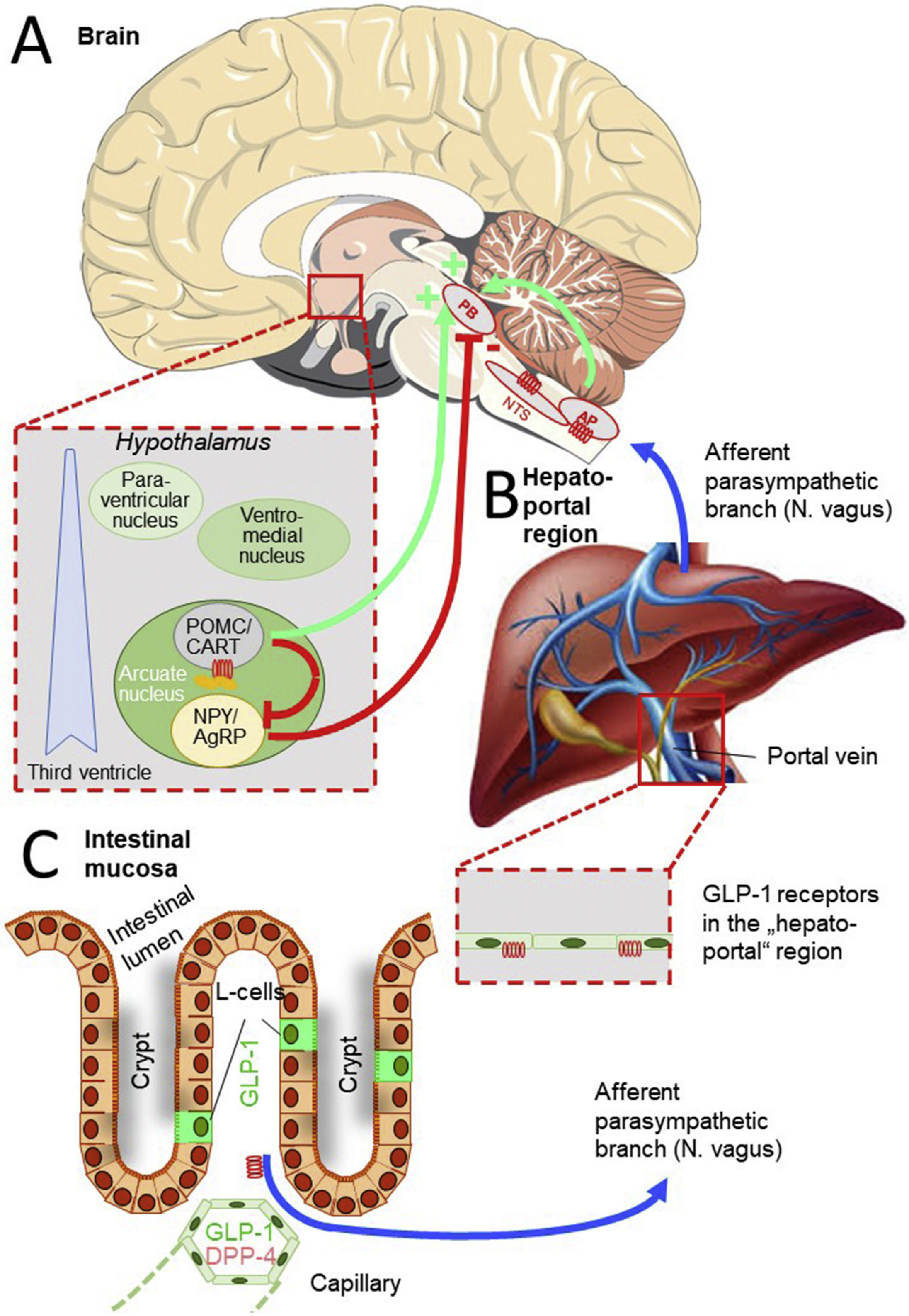


Figure 6: Schematic diagram demonstrating how various methods of GLP-1 or GLP-1 RA administration into the general circulation can reach and influence brain areas involved in the regulation of energy intake and expenditure [72,73]. (A) Evidence also suggests that GLP-1 receptors in the hepatoportal region [75] (B) and on afferent parasympathetic nerve endings in the intestinal mucosa (C) [76] may generate central nervous system signals influencing insulin secretion and metabolism. Stimulatory signals (+) are shown in green, inhibitory (−) signals are depicted in red, and afferent parasympathetic (vagal) signals are denoted in blue. See the text for a more detailed explanation of the mechanisms.

higher doses have been employed to treat obese subjects. Daily doses up to 3.0 mg are approved for liraglutide (1.8 mg is the maximum dose for treating type 2 diabetes) [65], and clinical trials have tested semaglutide at up to 0.4 mg per day (that is, corresponding to 2.8 vs 1.0 mg per week for type 2 diabetes) [68]. Doses of up to 4.5 mg per week (vs a maximum of 1.5 mg for type 2 diabetes) are being explored for dulaglutide [85]. In subjects tolerating these higher doses of GLP-1 RAs, substantially greater reductions in body weight were observed than with “conventional” doses typically employed to treat type 2 diabetes. Impaired glucose tolerance often improves while subjects receive this type of treatment, most likely explained by the glucose-lowering properties of GLP-1 RAs [65,86]. Whether this means a true interference with or a delay in the progression to diabetes needs to be studied in trials assessing the long-term consequences of withdrawing GLP-1 RA treatment. GLP-1 RAs need to be continuously administered after induction of weight loss. After discontinuation of this pharmacological treatment, body weight will revert to baseline values or at least close to baseline values within a few months [87].

It has often been overlooked that the individual weight reduction response of patients with type 2 diabetes treated with GLP-1 RAs is more variable than the reduction in HbA_{1c}. This is obvious when treatment-related weight and HbA_{1c} changes are plotted individually [18,88]. It can also be concluded from a higher coefficient of variation (the standard deviation divided by the mean value expressed as a percentage) depicted in Figure 4E. Why some patients do not reduce their body weight at all when treated with GLP-1 RAs while others respond with weight loss very much exceeding the mean values reported in clinical trials (for example, Figure 4) can only partially be answered with current knowledge. Schlogel et al. [89] examined responders and non-responders (with respect to exenatide’s effect on energy intake) and found hypothalamic effects only in responders. This hints at a biological reason most likely related to the mechanisms summarized in Table 3 and could be the result of genetic polymorphisms, for example, regarding GLP-1 receptors or other components of the signal transduction pathway.

However, the weight-lowering effects of GLP-1 RAs can probably be modulated by lifestyle measures aiming at reduced calorie intake [90], although a systematic examination of the combined efficacy of initiating treatment with GLP-1 RAs and patient education aiming at optimizing the weight-reducing effects of GLP-1 RAs is still lacking (or has failed to provide convincing benefits [91]). Obese patients with type 2 diabetes often tried various dietary approaches to lose weight and failed. One possible explanation for the wide spectrum of weight loss observed with initiating treatment with GLP-1 RAs could be that some patients feel motivated for further attempts to improve their eating behavior and lifestyle because of a realistic chance of success. Other patients may instead believe that the GLP-1 RA will ameliorate their obesity problem without them contributing by willingly restricting caloric intake and engaging in physical activity. This is a hypothesis worth sparking clinical studies, as would be developing a dedicated patient education program aiming at optimizing weight reduction with GLP-1 RAs in type 2 diabetes and in particular when using them in obese, prediabetic subjects to prevent progression to type 2 diabetes [68,86,92].

2.7. Gastrointestinal and other adverse events

Side effects most reported with GLP-1 RAs are nausea, vomiting, and diarrhea, often summarized as gastrointestinal adverse events. They are typically most prominent when initiating treatment with (any) GLP-1 RA or after increasing the dose (e.g., during recommended up-titration regimens). Since these symptoms can occur in fasting subjects, they are probably not related to the effects of GLP-1 RA treatment on gastrointestinal functions (e.g., deceleration of gastric emptying) but instead are caused by direct interactions with CNS GLP-1 receptors (Figure 6) most likely located in the brain stem (area postrema). Nausea is typically reported in up to 25% and vomiting or diarrhea in up to 10% of subjects treated with GLP-1 RAs [20,49]. For most patients, these are short, self-limited episodes that cease spontaneously, even with continued treatment. The time point of occurrence is probably related to the time characterized by maximum drug concentrations typically occurring at T_{max} following several hours to days after each injection (Figure 1). The probability of these side effects varies with sudden incremental exposure to GLP-1 RAs. An often-used recommendation to avoid these adverse events is a standardized, slowly increased exposure through up-titration regimens (Figure 2), which have been shown to mitigate gastrointestinal side effects. Experience with fixed-dose combinations with basal insulin (which must be titrated much more slowly) underscore the effectiveness of this approach.

Summarizing adverse event reporting from clinical trials examining GLP-1 RAs discloses subtle differences in the risk of these side effects depending on the short- (worse) vs long-acting nature (better) background medication (worse in combination with metformin or insulin) that are also related to the individual compound/preparation [49].

In part related to adverse events, patients randomized to GLP-1 RA treatment often discontinue this medication. Table 4 shows reported figures from cardiovascular (CV) outcome trials with GLP-1 RAs, the largest trials available reporting the longest durations of exposure to

Table 4 — Proportions of patients randomized to GLP-1 RA treatment in CV outcome trials discontinuing study drug treatment, proportion of the follow-up period during which patients were exposed to the study drug, and proportions discontinuing due to adverse events.

GLP-1 RA	Proportion of patients permanently discontinuing the study drug [%][a]	Proportion of follow-up period during which the study drug was taken [%]	Proportion of patients discontinuing the study drug because of adverse events [%]	Trial/reference
Lixisenatide	27.5	90.5	11.4	ELIXA [95]
Liraglutide	n.p.	84	9.5	LEADER [96]
Once-weekly exenatide	43.0	76	4.5[c]	EXSCEL [97]
Dulaglutide	26.8	82.2	9.1	REWIND [98]
Albiglutide	24.5	87	8.6	HARMONY Outcomes [99]
Semaglutide s.c.	21.3	86.5	13.2	SUSTAIN-6 [100]
Oral semaglutide	15.3	n.p.[b]	11.6	PIONEER-6 [101]

n.p.: Not presented.

[a] Not counting transient “drug holidays.”

[b] 75% received the study medication for more than 1 year (total follow-up of 15.3 months).

[c] Counting only gastrointestinal adverse events. No CV outcome trial has been reported for exenatide b.i.d. (approved before these studies became mandatory).

GLP-1 RAs. The proportions of patients reporting adverse events were not generally different from shorter clinical trials [49]. This indicates that while the frequency and severity of side effects can be successfully modulated through optimized up-titration regimens, a certain percentage of patients does not tolerate this treatment with the current regimens of initiating GLP-1 RA. Interestingly, in a recent study allowing individual titration of oral semaglutide, most patients discontinuing this treatment did so after exposure to the lowest (initial) dose of 3 mg per day [93]. This may indicate that the sensitivity of patients toward developing gastrointestinal adverse events is considerably heterogeneous, such that some patients fail to tolerate low doses, while for others, higher doses than currently used may offer better effectivity without increasing side effects. Along these lines, higher doses of some GLP-1 RAs are being explored, especially to further reduce body weight [65,67,68,71,86]. The reported nausea, vomiting, and diarrhea rates are generally lower in Japanese than Caucasian populations, suggesting that the cultural background and eating behaviors may also have an impact on the induction of nausea with GLP-1 RAs [94].

When GLP-1 RAs were introduced as novel agents to treat type 2 diabetes, there was uncertainty about several potential adverse effects such as acute pancreatitis, pancreatic cancer, and thyroid cancer [102,103]. The availability of large databases from randomized CV outcome studies that defined pancreatitis, pancreatic cancer, and thyroid cancer as “adverse events of special interest” with protocols carefully adjudicating suspected cases has reduced these concerns since they uniformly reported hazard ratios of these adverse events not significantly different from 1.0 [104]. In retrospect, an elevation in amylase and/or lipase activity commonly observed with GLP-1 RAs [105,106] together with abdominal symptoms typically triggered by GLP-1 RAs may have led to the suspicion of pancreatitis. Since 2 diagnostic criteria are sufficient for this diagnosis, pancreatitis may have been diagnosed even in the absence of imaging results supporting this diagnosis [105]. Nevertheless, thyroid C cells express GLP-1 receptors [107], and subjects at risk of (rare) medullary thyroid cancer (e.g., based on personal or family history or genetic testing) should not be treated with GLP-1 RAs. These subjects were consequently excluded from clinical trials with GLP-1 RAs.

3. CARDIOVASCULAR OUTCOME STUDIES

All GLP-1 RAs were approved for treating type 2 diabetes patients after 2008 (except for exenatide b.i.d., which was approved in 2005). Therefore, all of the compounds/preparations had to provide results of dedicated cardiovascular outcome studies supporting at least the cardiovascular safety of these medications in the target population and compared to placebo both on a background of standard of care (allowing any additional glucose-lowering medication necessary to meet targets recommended by current guidelines). The typical primary endpoint was major adverse cardiovascular events (MACE: time to first event of either CV death or non-fatal myocardial infarction or stroke). According to guidelines by the US Food and Drug Administration, definite proof of CV safety would be a hazard ratio for MACE near or below 1.0 with a confidence interval not exceeding 1.3 (equivalent to a 30% elevation in risk). If a study provides preliminary proof of safety (upper limit of the confidence interval below 1.8), another CV outcome study aiming at definite proof is required. Depending on the ambitions, studies with different patient numbers and durations are needed. This explains the heterogeneity in study designs, sample sizes, and follow-up periods between the trials summarized in Figure 7 [20,108]. Another differentiator is the proportion of patients with pre-existing cardiovascular damage, albeit defined by previous events or supported by functional testing and/or imaging, which ranged from 31% (REWIND [98]) to 100% (ELIXA [95] and HARMONY Outcomes [99]) and obviously had an important impact on the CV event rate observed during the trials.

3.1. Heterogeneity regarding principal results from CV outcome trials comparing GLP-1 RAs with placebo

Figure 7A displays hazard ratios (active treatment vs placebo) for MACE and their 95% confidence intervals for all published CV outcome trials with GLP-1 RAs. With the exception of lixisenatide, all other GLP-1 RAs at least show a trend of a reduced incidence of MACE events, which was significant in four studies and not significant in 2 additional studies. Hence, the results are, from a clinical perspective, quite heterogeneous and suggest that some GLP-1 RAs are more suitable to prevent CV events than others. Assessing heterogeneity mathematically as part of the meta-analysis, however, resulted in I^2 values suggesting at most moderate heterogeneity. Our interpretation is that comparing the various trials indicates a common mechanism of action, but important differences related to pharmacokinetic properties (one injection per day of lixisenatide does not fully cover a 24 h period), optimized dosages as a result of phase 2 dose-finding studies (probably applies to 2 mg per week of once-weekly exenatide), and drug discontinuation rates impact the degree of CV benefit that can be achieved with individual compounds/preparations as suggested by Caruso et al. [109]. Remarkably, the reduction in MACE events with albiglutide is very much comparable if not more pronounced than with other effective GLP-1 RAs (Figure 7A) despite its reduced ability to lower HbA_{1c}, fasting plasma glucose, and body weight in clinical trials (Figure 4) [40]. When choosing a GLP-1 RA to prevent CV events, one of the compounds significantly reducing MACE should be selected. Liraglutide (LEADER trial) was unique in not only significantly reducing MACE events, but also CV and all-cause mortality [96]. Semaglutide (subcutaneous, SUSTAIN-6 [100], and oral, PIONEER-6 [101]) trials showed impressive results, especially considering their small sample sizes and short durations. This was due to their primary ambition to demonstrate safety, the minimum requirement for approval, which requires smaller patient numbers, a shorter trial duration, and fewer events. This preliminary nature makes additional larger trials necessary to fully characterize the potential to prevent CV complications of type 2 diabetes (oral semaglutide: SOUL, ClinicalTrials.gov NCT 03914326) or obesity (once-weekly semaglutide s.c.: SELECT ClinicalTrials.gov NCT03574597).

Individual CV outcome trials were not powered to assess single CV endpoints, but a composite endpoint such as MACE. However, a meta-analysis pooling results from all individual trials provided some insight that CV events can generally be prevented by GLP-1 RA treatment [108]. As shown in Figure 7B, across all of the trials, significant reductions by 9—16% in the incidence of acute myocardial infarction, stroke, cardiovascular, and even all-cause death could be achieved for the GLP-1 RA class as a whole, while in the individual trials, these effects on individual cardiovascular outcomes were only occasionally significant. However, the number of such events (myocardial infarction, stroke, CV death, etc.) in individual trials was too low to provide the power to detect significant differences. This also applied to a reduction in the hospitalization for heart failure, which was not significant in any of the individual trials, but in the meta-analysis (hazard ratio, 0.91; 95% confidence interval, 0.83—0.99). This figure contrasts with the consistent ≈35% risk reduction for hospitalization for heart failure in all studies employing SGLT-2

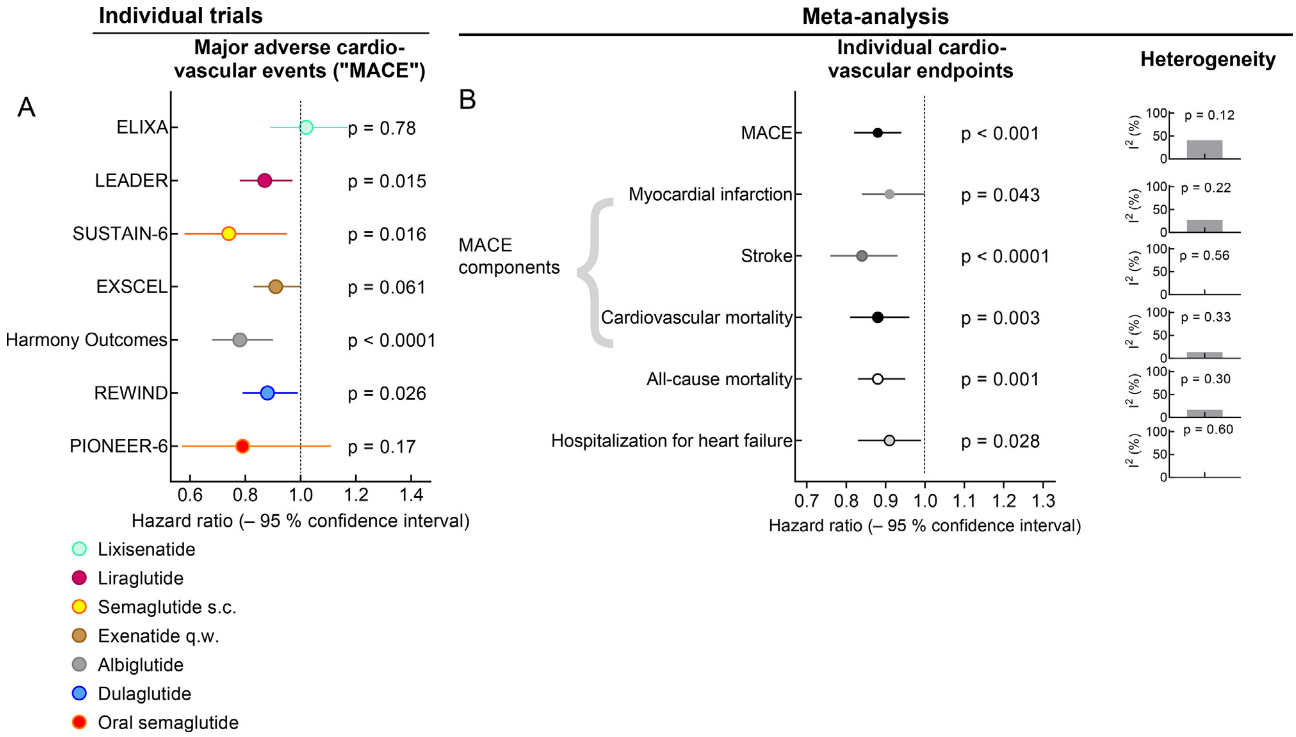


Figure 7: Results of cardiovascular outcome studies comparing GLP-1 RAs with placebo on a background of standard of care. (A) Reduction in major adverse cardiovascular events (MACE: time to first event) in published individual clinical trials. (B) Results of a published meta-analysis [108] analyzing various cardiovascular endpoints across all of the clinical trials shown in panel A. MACE (a combination of either cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) was the primary endpoint in all studies. Meta-analysis results are supplemented with I^2 and related p values indicating the heterogeneity of the analysis of individual endpoints (column of panels to the far right) as reported in [108].

inhibitors [110,111]. Of note, patients with NYHA IV heart failure were excluded from the CVOTs with GLP-1 RAs, such that no firm conclusions could be drawn regarding these patients. In light of the dedicated studies of liraglutide in patients with advanced heart failure, which not only failed to prove benefits, but suggested some potential for harm caused by GLP-1 RAs [112,113], GLP-1 RAs are usually not recommended as first choice if the objective is to prevent heart failure complications. Indeed, the small increase in heart rate observed with GLP-1 RA treatment may represent an unfavorable mechanism in patients with advanced (NYHA III/IV) heart failure [34]. Instead, the pattern of effects observed in CV outcome trials suggests a primary mode of action preventing complications of atherosclerosis such as ischemic events (myocardial infarction and stroke) and associated mortality (vide infra).

Most CV outcome trials with GLP-1 RAs recruited patients with type 2 diabetes characterized by established CV disease (e.g., previous CV events) or indicators of a high risk of CV events. These studies were originally primarily designed as safety trials, and accruing a large number of CV events in high-risk patients was one strategy to limit the sample size and duration of these trials. Therefore, the results of these trials cannot be extrapolated to the general population of type 2 diabetes patients including those with short disease duration and lack of CV comorbidities. The REWIND study (employing dulaglutide as the GLP-1 RA) was exceptional in having recruited a mixed population with 31.5% with and 68.5% without pre-existing atherosclerotic vascular damage [98]. Subgroup analyses of the REWIND trial (dulaglutide vs placebo, both on a background of standard of care) highlighted that dulaglutide was able to induce a significant MACE reduction in the overall study population and quantitatively similar regardless of the patients' history of CV events (p for interaction was 0.97). Those with or without CV co-morbidities at baseline had identical risk reductions (that for both subgroups just missed statistical significance) [98]. These data suggest a potential to prevent CV complications even in lower-risk type 2 diabetes patients, yet fall short of definite proof.

Along the same lines, a subgroup analysis within the meta-analysis by Kristensen et al. [108] identified no statistically significant heterogeneity for the effect of GLP-1 RAs on MACE between primary vs secondary prevention ($p = 0.24$) The more recent meta-analysis by Marsico et al. [114] strengthened this conclusion. However, since the absolute risk reduction was smaller in the primary prevention population, it remains to be ascertained whether this intervention would be cost-effective in lower-risk patients.

3.2. Mediation analyses aiming to define the mechanism(s) leading to beneficial cardiovascular effects of GLP-1 RAs

As previously demonstrated in detail [115], GLP-1 RAs modify a number of risk factors for cardiovascular complications, including body weight reduction, lower systolic blood pressure, reduced plasma LDL cholesterol and triglyceride concentrations, and improved glycemic control (reductions in fasting and post-meal plasma glucose resulting in lower HbA_{1c}; see Figure 4). Thus, a reduction in the incidence of ischemic events could be the consequence of a more beneficial risk profile under treatment with GLP-1 RAs. Mediation analysis is an approach to identify potential mediators that might explain the findings observed in terms of endpoints. While several mathematical approaches have been developed, their common aim is to show that taking into account the changes in a potential mediator reduces the effect size with respect to the endpoint of interest. Potential mediators are variables measured in the trial that are differentially affected by active drugs and placebo. For example, GLP-1 RAs reduce systolic blood pressure by 2—4 mmHg compared to placebo treatment [115]. Considering this reduction in systolic blood pressure, if the difference in MACE outcomes is reduced, it can be concluded that a reduction in systolic blood pressure mediates the prevention of MACE. If the effect is nullified, this mechanism is responsible for 100% of the effect, but partial mediation is also possible.

Using slightly different approaches, mediation analyses have been published on the effects of liraglutide in the LEADER trial [116] and the effects of dulaglutide in the REWIND study [117]. Interestingly, both analyses concluded that HbA_{1c} reduction was a potential mediator, responsible for up to 82% of the total effect. A reduction in urinary albumin excretion was found to be another potential mediator in the LEADER trial (responsible for up to 33% of the total effect). Of note, any potential mechanism that does not leave a measurable trace or has not been assessed in a given trial will never be identified as a potential mediator using this approach. This applies to intravascular changes associated with the progression of atherosclerosis unless they are accompanied by, for example, inflammatory responses, which can be identified by measuring C-reactive protein or inflammatory cytokines (which was not done in any of the CV outcome trials of GLP-1 RAs). Hence, identifying HbA_{1c} reduction as a potential mediator of CV benefits induced by GLP-1 RAs leaves a number of open questions, especially since it has been difficult to establish a relationship of HbA_{1c} reduction with cardiovascular benefits in other glucose-lowering medications [118].

For CV outcome studies of GLP-1 RAs, a relationship that links the magnitude of the HbA_{1c} reduction achieved (versus placebo) to the hazard ratio for major adverse CV events was suggested by Caruso et al. [119]. In particular, they identified a relationship between the mean reduction in HbA_{1c} in individual trials and the corresponding hazard ratio for stroke [119]. Figure 8 presents a similar analysis, however, including CV outcome studies with DPP-4 and SGLT-2 inhibitors. Remarkably, these additional data points were positioned along the same regression lines, and the relationship between the reduction in HbA_{1c} and MACE (Figure 8A) or stroke (Figure 8C) remained significant. Similar trends of non-fatal acute myocardial infarction and CV death were non-significant. A significant reduction in hospitalizations for heart failure was restricted to SGLT-2 inhibitors and independent from reductions in HbA_{1c} (Figure 8F). Such an analysis may not only confirm the relationship initially observed by Caruso et al. [119], but may also explain why DPP-4 inhibitors and SGLT-2 inhibitors did not consistently reduce MACE [110,111,115]. Given that all of the CV outcome trials aimed at glycemic equipoise (similar if not identical glycemic control for active drug and placebo treatment), only trials with potent glucose-lowering medications such as GLP-1 RAs, which failed to achieve glycemic equipoise, underscored the potential for a CV benefit.

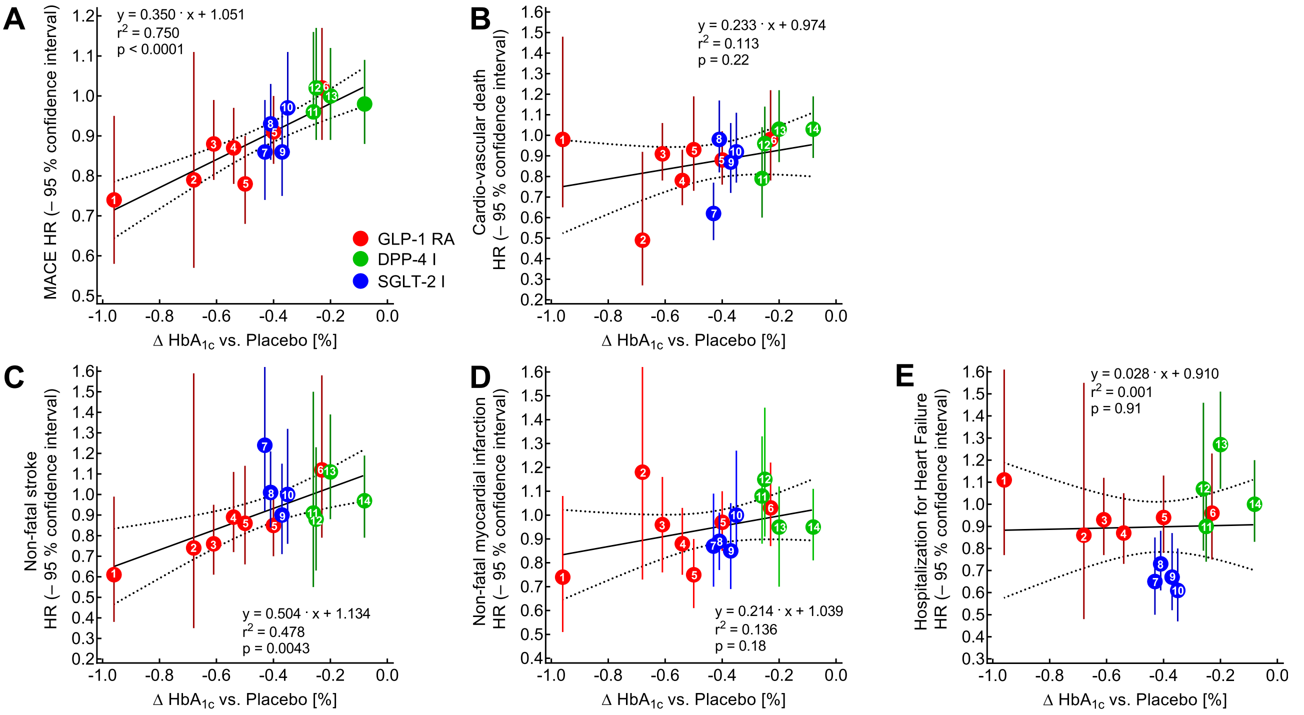


Figure 8: Regression analysis of differences achieved in HbA_{1c} concentrations between patients treated with placebo and active drug vs hazard ratios for major adverse cardiovascular outcomes (MACE; A), cardiovascular death (B), non-fatal stroke (C), non-fatal myocardial infarction (D), and hospitalization for heart failure (E) reported from cardiovascular outcome studies with GLP-1 receptor agonists (red), SGLT-2 inhibitors (blue), and DPP-4 inhibitors (green). Significant associations are shown for MACE (A) and non-fatal stroke (C) with similar slopes of the regression lines, while for cardiovascular death (B) and non-fatal myocardial infarction (D), a less prominent, non-significant correlation resulted from the analysis. Regarding hospitalization for heart failure (E), hazard ratios did not vary with HbA_{1c} reduction. Analyzing GLP-1 receptor agonists only resulted in significant correlations for MACE and stroke as well as previously reported by Caruso et al. [119] but not for the other endpoints. Numbers in symbols identify the clinical trials: 1: SUSTAIN-6 (subcutaneous semaglutide) [100], 2: PIONEER-6 (oral semaglutide) [101], 3: REWIND (dulaglutide) [98], 4: LEADER (liraglutide) [96], 5: EXCSEL (once-weekly exenatide) [97], 6: ELIXA (lixisenatide) [95], 7: EMPA-REG Outcomes (empagliflozin) [120], 8: DECLARE-TIMI-58 (dapagliflozin) [121], 9: CANVAS program (canagliflozin) [122]; 10: VERTIS-CV (ertugliflozin, presented at the 80th scientific session of the American Diabetes Association); 11: EXAMINE (alogliptin) [123], 12 CARMELINA (linagliptin) [124], 13: SAVOR-TIMI-53 (saxagliptin) [125], and 14: TECOS (sitagliptin) [126].

3.3. Mechanisms explaining cardiovascular benefits

Understanding the robust interference of GLP-1 RAs with the progression and complications of atherosclerosis requires detailed knowledge of the pathomechanisms involved and consequences of GLP-1 receptor stimulation. Various steps and mechanisms involved in atherogenesis [127] are displayed in Figure 9A, while the effects of GLP-1 receptor stimulation in arterial vessel walls are shown in complementary Figure 9B.

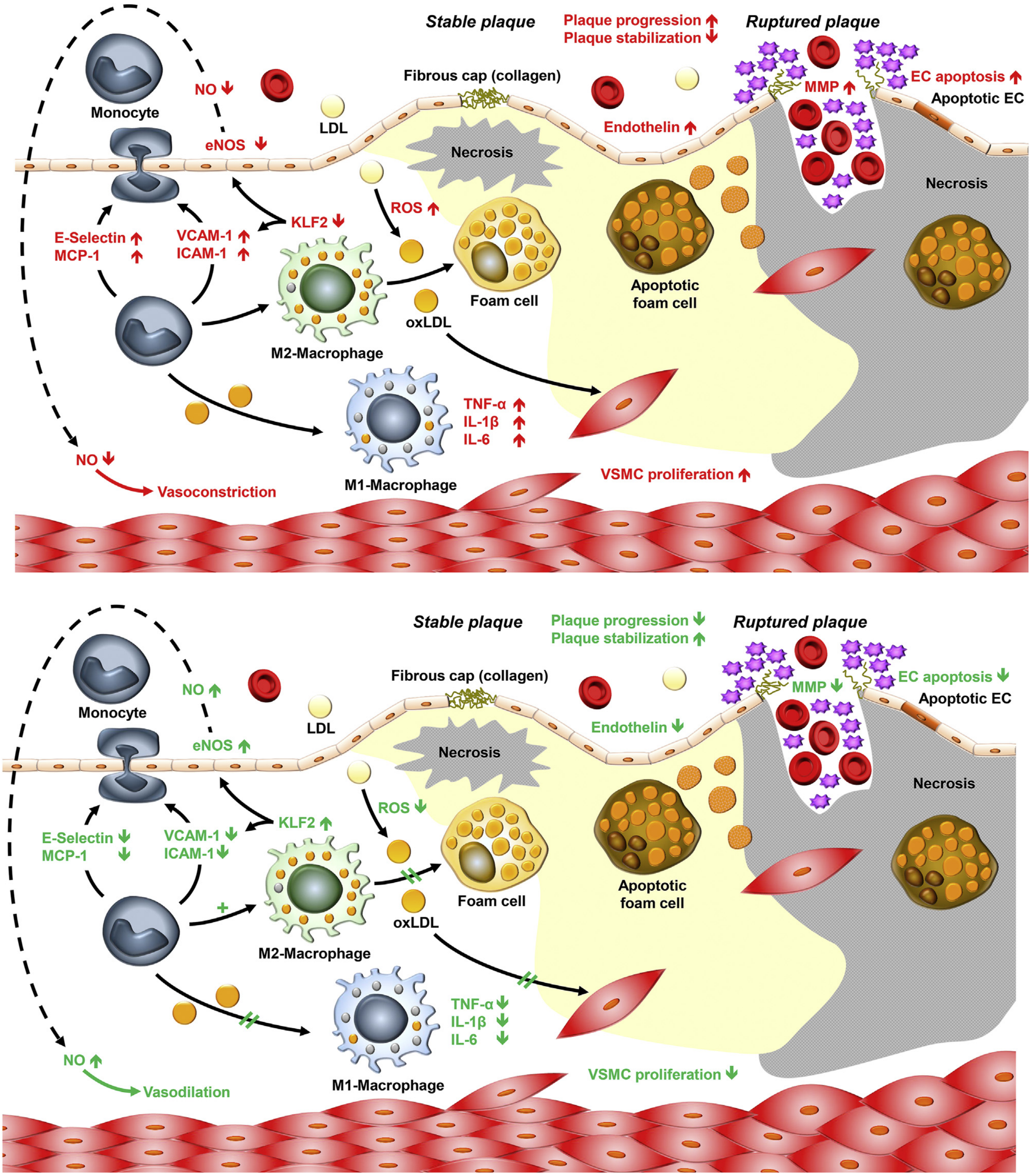


Figure 9: Mechanisms driving the development of atherosclerotic lesions in patients with type 2 diabetes (A) and effects of GLP-1 RAs on the progression of atherogenesis and the development of its complications (B). See the text for further details on the mechanisms involved and references to the supporting literature. EC: endothelial cell, eNOS: endothelial nitrous oxide synthase, ICAM-1: intercellular adhesion molecule-1, IL: interleukin, KLF-2: Krüppel-like factor-2, LDL: low-density lipoprotein, MCP-1: monocyte chemoattractant protein-1, NO: nitrous oxide, oxLDL: oxidized low-density lipoprotein, ROS: reactive oxygen species, TNF-α: tumor necrosis factor, VCAM-1: vascular cell adhesion protein 1, VSMC: vascular smooth muscle cell.

3.4. Atherogenesis in patients with type 2 diabetes (Figure 9A)

LDL cholesterol is transported across the intima layer of arterial blood vessels and in part oxidized to oxidized LDL particles (oxLDL) through reactive oxygen species (ROS). Contact of monocytes and macrophages with oxLDL and ROS promotes further infiltration of monocytes by secreting adhesion molecules such as vascular cell adhesion protein 1 (VCAM-1), monocyte chemoattractant protein 1 (MCP-1), intercellular adhesion molecule 1 (ICAM-1), and E-selectin. Stimulated by oxLDL, monocytes transform into macrophages. M1 macrophages produce pro-inflammatory cytokines such as tumor necrosis factor α (TNF-α), interleukin (IL)-6, and IL-1β. M2 macrophages take up lipid particles through phagocytosis and suppress the formation of Krüppel-like factor 2 (KLF-2), which in turn suppresses endothelial NO synthase (eNOS), leading to lower NO production and preventing vasodilation through NO-mediated vascular smooth muscle relaxation. In an environment dominated by ROS and oxLDL, M2 macrophages transform into foam cells that can undergo apoptosis and release their lipid content into the lipid core of nascent atherosclerotic plaques. Stable plaques are characterized by a dense fibrous cap mainly composed of collagen that helps prevent rupture. However, as atherogenesis progresses, larger necrotic areas form, endothelial cells (EC) undergo apoptosis, and matrix metalloproteinases (MMP) proteolytically destroy the fibrous cap. This results in plaque rupture, thrombus formation, and bleeding into necrotic plaque areas.

3.5. Interference of GLP-1 RAs with the atherogenesis process (Figure 9B)

As demonstrated in animal studies and experiments using human cells, GLP-1 receptors expressed in endothelial cells, monocytes, macrophages, and vascular smooth muscle cells produce numerous effects potentially interfering with the process of atherosclerotic plaque formation or rupture. First, ROS production is reduced by GLP-1 [128—130], exenatide [131], liraglutide [130,132—136], and semaglutide [137]. The oxLDL-mediated activation of monocytes and macrophages and the consecutive activation of adhesion molecules such as VCAM-1, MCP-1, E-selectin, and ICAM-1 is successfully reduced by GLP-1 receptor stimulation (e.g., GLP-1 [138], exenatide [138—140], dulaglutide [141], and liraglutide [142]). This results in a reduction of monocyte accumulation in the vascular wall, as shown for example with exenatide [143]. Endothelial cells express more eNOS, produce more NO, and suppress endothelin formation that overall lead to vascular smooth muscle relaxation and endothelium-derived vasodilation (e.g., GLP-1 [130,144], exenatide [144], and liraglutide [130,133,145]). M2 macrophages instead of M1 macrophages preferentially form from monocytes (e.g., lixisenatide [146] and liraglutide [147]) and the otherwise suppressed KLF-2 formation instead increases (e.g., by lixisenatide [146], liraglutide [147], and dulaglutide [141]). The reduced exposure to ROS after GLP-1 receptor stimulation slows the process of foam cell formation (e.g., GLP-1 [148,149] and liraglutide [150]) and reduces caspase-mediated apoptosis of foam cells (e.g., GLP-1 [151] and semaglutide [152]) and the formation of necrosis in the core of atherosclerotic plaques (e.g., GLP-1 [153] and lixisenatide [154]). Furthermore, GLP-1 receptor stimulation reduces vascular smooth muscle proliferation (e.g., exenatide [155] and liraglutide [156]) and possible migration into plaques (liraglutide [157]). The integrity of endothelial cells was shown to be stabilized by exenatide [158,159]. Plaque hemorrhage was reduced by semaglutide [160]. The reduced expression of MMP preserves intact fibrous caps and prevents plaque rupture (e.g., GLP-1 [153], exenatide [161] and semaglutide) [160]. The overall result is a slowing of plaque progression and plaque stabilization. The formation, extent, and vulnerability of atherosclerotic lesions in animal models characterized by rapidly progressive atherosclerosis was substantially reduced by GLP-1 RA [160]. Studies in humans have partially confirmed anti-inflammatory [162] and anti-atherosclerotic actions of GLP-1 RAs [163].

4. RENAL EFFECTS OF GLP-1 RAS

The discovery of beneficial renal effects using GLP-1 RAs is a recent achievement mainly based on the observations that GLP-1 RAs prevented new-onset macroalbuminuria [99,164,165], reduced urinary albumin excretion [164,165], or slowed the decline in the estimated glomerular filtration rate (eGFR) over time [164—166]. The mechanisms leading to these renal benefits are largely unknown. While significant reductions in achieving renal composite outcomes were reported [99,164,165], they heavily relied on dominating effects preventing new-onset persistent macroalbuminuria. Clinical events indicating progression to end-stage renal disease (doubling in serum creatinine, major reduction by 30—50% in eGFR, achieving eGFR below 15 ml/min per 1.73 m^2, necessary to initiate renal replacement therapy or perform renal transplantation, or death due to renal causes) have rarely been reported in numbers allowing a meaningful analysis. This is due in part to the fact that the populations studied had fairly good renal function at baseline. Studies of selected patients with prominent or advanced renal disease are lacking. A dedicated trial studying the effects of semaglutide on renal outcomes in type 2 diabetic patients with chronic kidney disease is underway to clarify these issues: FLOW (ClinicalTrials.gov NCT03819153). Since most GLP-1 RAs can be used in chronic kidney disease, while SGLT-2 inhibitors lose some of their glucose-lowering efficiency with reduced glomerular filtration rates, further studies appear to be needed, especially since patients with reduced eGFR at baseline seem to benefit most in terms of preventing rapid declines in eGFR [164]. For the time being, more robust effects have been reported for SGLT-2 inhibitors, which are preferred glucose-lowering medications interfering with the progression of diabetic renal disease even in patients with moderately reduced eGFR [110,111,167].

5. ADHERENCE AND PERSISTENCE (OBSERVATIONAL STUDIES)

While initiating GLP-1 RA treatment in clinical practice is already discrepant from current guidelines, suboptimal treatment persistence and adherence are additional important issues [168]. A recent study suggested that HbA$_{1c}$ reductions with GLP-1 RAs observed in real-world studies were $\sim$0.5% below those observed in controlled clinical trials [169]. The authors attributed approximately three-fourths of this gap to poor medication adherence in clinical practice. In a retrospective analysis comparing different GLP-1 RAs, once-weekly injectable dulaglutide demonstrated greater adherence rates than once-weekly exenatide or once-daily injectable liraglutide [170]. Of note, over a six-month treatment period, 26.2% of dulaglutide and 48.4% of once-weekly exenatide patients discontinued treatment, and in a direct comparison of dulaglutide and liraglutide, the respective discontinuation rates were 28.0% and 35.6% [170]. When the proportion of days covered (PDC) was compared between once-weekly exenatide and liraglutide, the proportions of patients with good adherence (PDC $>$ 0.80) after 6 months were 53.4% and 48.1%, respectively [171]. Likewise, an analysis of Medicare recipients in the US reported a PDC $>$80% of 43.2% in patients receiving exenatide

QW, 39.0% in patients receiving exenatide b.i.d., and 35% in patients receiving liraglutide [172]. Hence, no consistent data on differences in adherence between short- and long-acting GLP-1 RAs could be found. A recent real-world retrospective observational study showed that dulaglutide users were less likely to interrupt treatment than semaglutide and exenatide BCise users [173]. In a pairwise meta-analysis comparing treatment adherence and persistence between GLP-1 RAs and long-acting insulin analogues, the odds ratio for non-adherence was 1.95, suggesting better adherence with the insulin analogs [174]. As a general trend from these comparisons, adherence to GLP-1 RAs seems to be better with lower injection frequencies.

However, these studies must be interpreted with caution because of the retrospective study designs and partially incomplete data assessment. Furthermore, observation periods of 6—12 months are still too short to judge the long-term adherence to GLP-1 RAs.

6. DISCONTINUATION RATES IN RANDOMIZED CV OUTCOME TRIALS

As presented in Table 4, some patients randomized to GLP-1 RA treatment discontinued the assigned medication. The proportion withdrawing from GLP-1 RA treatment in CV outcome trials ranged from 15% (oral semaglutide) to approximately 25%; an exceptionally high withdrawal rate was observed with once-weekly exenatide (43%), possibly related to the less comfortable pen injection device requiring resuspension of the active ingredient in buffer (Figure 3) or the occurrence of subcutaneous nodules at injection sites [175]. Approximately one-half of the discontinuations were reported to be associated with adverse events (Table 4). In the trials reporting discontinuation because of any adverse events and those specifically due to gastrointestinal side effects, the latter were responsible for approximately one-half of the withdrawals. Another potential reason contributing to withdrawals was a perception of ineffective glycemic and body weight control achieved (including a suspicion to have been randomized to placebo), perhaps as a consequence of the progression of the type 2 diabetes mellitus disease process [176]. Whether or not GLP-1 RA treatment counters this progression (e.g., through β cell-preserving effects [177]) remains an open question. In rodents, these effects are restricted to earlier periods in life [178] when β cells have a propensity to proliferate, which they lose in adult animals [179]. Overall, randomized controlled clinical trials showed that high persistence regarding GLP-1 RA treatment could be maintained for periods up to 5 years, which contrasts with data from observational studies (as previously described). Efforts to encourage persistent use of GLP-1 RA, as successful in clinical trials, may be necessary to achieve better persistence in clinical practice as well.

7. GUIDELINE RECOMMENDATIONS AND CLINICAL REALITY

The current ADA/EASD consensus algorithm suggests that GLP-1 RAs should be preferentially used after metformin failure in (a) patients with established atherosclerotic cardiovascular disease and (b) patients without established cardiovascular disease with high-risk indicators, such as age $\geq$ 55 years, carotid, lower extremity or coronary artery stenosis $>$50%, left ventricular hypertrophy, eGFR $<$ 60 ml/min, or albuminuria [180]. GLP-1 RAs may also be used to prevent hypoglycemia or weight gain. The ESC guidelines have gone even further in recommending GLP-1 RAs (or SGLT-2 inhibitors) as first-line therapy in patients with established atherosclerotic cardiovascular disease or in those at high or very high risk (that is, three or more major risk factors or diabetes duration $\geq$ 10 years without target organ damage, plus any other additional risk factors) [181]. According to these international recommendations, $\sim$30—60% of patients with type 2 diabetes would qualify for a GLP-1 RA. However, in clinical reality, the percentage of patients receiving GLP-1 RA treatment remains low, ranging between 1% and 10% in different countries [182].

The reasons for this apparent gap between guideline recommendations and clinical reality are heterogeneous: first, the cost of treatment with GLP-1 RAs is considerably higher than most oral glucose-lowering drugs, but instead comparable to the cost of an intensified insulin treatment regimen (including glucose-monitoring costs). Although various cost-effectiveness analyses suggested that the overall benefits associated with GLP-1 RA treatment outweigh the direct treatment costs [183], the price of the currently available GLP-1 RAs remains a major barrier in most countries. Second, the need for daily or weekly injections discourages some patients from initiating GLP-1 RAs [184]. Third, contraindications (i.e., history of pancreatitis, diabetic retinopathy, or medullary thyroid cancer) may prevent the use of GLP-1 RAs in affected patients [185]. Finally, gastrointestinal adverse events remain an important limitation of GLP-1 RA treatment [49].

8. OPPORTUNITIES FOR FUTURE DEVELOPMENT OF GLP-1 RAS

Since 2005, when exenatide was first approved, rapid development began that has yielded progress with respect to GLP-1 RAs pharmacokinetics, with the obvious consequence that instead of 2 (or more) injections per day, now once-weekly injections are available. While advances making GLP-1 RA treatment more comfortable are welcome, it should not be overlooked that the effectiveness of GLP-1 RAs has increased in large steps (e.g., going from exenatide to liraglutide, the first long-acting GLP-1 RA, but also advancing to semaglutide, which clearly has superior efficacy than other GLP-1 RAs, especially with respect to body weight reduction as depicted in Figure 4). These significant advances, occurring in substantial leaps, suggest that this development has not yet come to an end.

8.1. Oral administration of GLP-1 RAs

One development worth noting is that, despite the peptide nature of all of the GLP-1 RAs, semaglutide is now available for oral administration. An absorption enhancer molecule (SNAC; see Section 2) must be part of the oral preparation to promote absorption through the gastric mucosa. Low bioavailability after oral administration makes daily administration of a semaglutide tablet necessary to avoid wide fluctuations in drug exposure. It must be taken on an empty stomach, and for 30 min after taking oral semaglutide, no other food, drink, or medication should be administered to allow undisturbed absorption. With these precautions, in principle, quantitatively similar effects can be achieved with respect to glycemic control and lowering body weight [19]. The phase 3 PIONEER program, however, was conducted with somewhat lower doses (maximum, 14 mg/d) than would be necessary to match the effectiveness of subcutaneous semaglutide at 0.5 or 1.0 mg/week [43].

In addition to developing peptide-based GLP-1 RAs for oral administration, some reports described small molecules with GLP-1 receptor agonist properties that should be suitable for oral administration without additives and/or sensitive procedures. To date, the binding affinities of these compounds has been too low to support further development as clinically effective drugs [186—189].

8.2. Use in patients with type 1 diabetes

Effects of GLP-1 or GLP-1 RAs on residual insulin secretion [190], glucagon suppression [190,191], gastric emptying delay [190], and plasma glucose [192,193] in type 1 diabetic subjects were described starting in the early stages of GLP-1 discovery. Clinical trials employing liraglutide or exenatide (un-retarded preparation usually administered b.i.d.) in addition to intensified insulin regimens, however, did not demonstrate convincing benefits (e.g., with respect to optimized glycemic control or the frequency of hypoglycemic episodes) or described potential adverse outcomes such as a higher risk of ketoacidosis. Only body weight and insulin doses were consistently reduced [194—197]. However, these results do not rule out benefits for specific subgroups (e.g., obese patients with type 1 diabetes or subjects at high risk of cardiovascular complications) or with dosage recommendations that may differ from those used to treat type 2 diabetes.

8.3. Individualized use in well-defined type 2 diabetes subtypes

Cluster analysis was applied to define subgroups within the type 2 diabetes population that differ with respect to insulin secretory capacity, insulin sensitivity, age at diagnosis, and the presence of autoimmune markers [198—200]. These subgroups display significant differences in the development of CV and renal complications [198—200]. Thus, given the beneficial actions of GLP-1 RAs on preventing CV events (and on the progression of nephropathy), they may turn out to be particularly effective in those presenting a high a priori risk of these complications. Identifying a central pathophysiological defect (e.g., reduced insulin secretory capacity) may also help select a specific therapy addressing this point (e.g., GLP-1 RAs augmenting insulin secretion triggered by hyperglycemia). While prospective studies comparing various therapies in type 2 diabetes patients belonging to different subgroups are lacking, this sub-classification promises to be a helpful tool assisting in a more individualized approach toward selecting glucose-lowering medications for a given patient.

8.4. Combination treatment with GLP-1 RAs plus SGLT-2 inhibitors

In addition to GLP-1 RAs, SGLT-2 inhibitors are another class of glucose-lowering medications that have proven beneficial CV effects, especially regarding the prevention of heart failure complications (Figure 6 [110,111]). This raises the question of differential indications [201]. Based on the pattern of effects on various CV endpoints, GLP-1 RAs seem to better prevent ischemic events potentially resulting from anti-atherogenic effects (as previously described). The mechanisms of action of SGLT-2 inhibitors differ and aim to prevent heart failure complications (using hospitalization as an indicator) and the progression toward end-stage renal failure [110,111]. Therefore, if a patient seems to be at risk of ischemic events (e.g., because of previous events), GLP-1 RAs appear to be the better option. However, if the risk of congestive heart failure complications is considered the primary problem, SGLT-2 inhibitors are the better choice.

Since the severalfold elevated risk of CV events that type 2 diabetes demonstrates is only partially reduced by both GLP-1 RAs and SGLT-2 inhibitors, it may be necessary to combine medications from both classes to further improve their effectiveness. Combining dapagliflozin with exenatide once weekly lowers plasma glucose and body weight more than any of the single agents alone [202], even for prolonged periods of time [203]. Similar results were observed after adding empagliflozin to liraglutide in Japanese patients [204] and when adding canagliflozin to liraglutide treatment [205]. The weight loss induced by the combination compared to the single agents appeared to be additive, but HbA_{1c} reduction was less than additive. When adding dulaglutide to pre-existing treatment with SGLT-2 inhibitors, HbA_{1c} decreased substantially, while body weight declined by only 1 kg (at a higher dose of 1.5 mg) [206]. Systolic blood pressure was also lowered substantially by this combination [204—208]. The effects of combining GLP-1 RAs with SGLT-2 inhibitors were corroborated in a meta-analysis by Castellana et al. [209], confirming this combination's potential.

This leads to the essential question, will combining GLP-1 RAs and SGLT-2 inhibitors result in even better CV outcomes? No data are available to estimate the effects on CV outcomes using this combination. It is uncertain whether a large enough clinical trial addressing this question will ever be conducted. Real-world studies analyzing existing databases documenting medication use and clinical outcomes may help in this respect, but no such analysis seems to be currently available.

8.5. Unimolecular oligo-hormonal agonists address more than just GLP-1 receptors

One avenue of further increasing the potency of GLP-1 RAs is developing molecules that address not only GLP-1 receptors, but a second (co-agonist) or even a third (tri-agonist) receptor (choosing from glucagon, glucose-dependent insulinotropic polypeptide [GIP], or peptide YY [PYY] receptors). Preliminary findings suggest that highly effective compounds (e.g., tirzepatide [210]) can be developed this way, in particular providing weight loss far exceeding that reported with pure GLP-1 RAs. These developments will be the focus of another manuscript on the present supplement volume (Baggio et al. [211]).

8.6. Pharmacogenomics

Since GLP-1 RAs exert their biological effects by interacting with the GLP-1 receptor, interindividual differences in the expression of these receptors or polymorphisms at the GLP-1 receptor gene may modify biological responses [212—215]. Along these lines, certain polymorphisms regarding the TCF7L2 gene (probably involved in determining β cell mass and the expression of GLP-1 receptors) impair insulin responses to exogenous GLP-1 [216]. One study described a modification of the in vitro effects of GLP-1 RAs for the GLP-1 receptor variant T149M (methionine instead of threonine in position 149) on β cells [217]. However, a preliminary clinical study did not describe differences in pharmacological effects in response to short-term treatment with exenatide [218]. Given the potential of selecting patients with a predicted greater clinical effectiveness [219], the issue of pharmacogenomics regarding GLP-1 RA still appears to be an understudied research area. Furthermore, patients not responding to GLP-1 RAs as expected, either when initially exposed to GLP-1 RAs (primary non-responders) or after a satisfactory response period (secondary non-responders), have often been observed in clinical practice. Systematic studies elucidating the mechanisms of a potential non-response to GLP-1 RA treatment (such as genetics or lifestyle issues) remain lacking.

8.7. Potential novel indications: neurodegenerative diseases and psoriasis

Interest in using GLP-1 RAs to treat neurodegenerative diseases emerged from preclinical studies showing that GLP-1 receptor signaling is involved in cognitive functions [220] and GLP-1 RAs can induce neuronal growth and synaptic plasticity and reduce apoptosis and oxidative stress [221].

In Alzheimer's disease, the most prevalent form of dementia, animal studies have shown the positive effects of GLP-1 RAs on cognitive impairment [222,223]. In a clinical trial of patients with prediabetes and type 2 diabetes, memory function improved after 4 months of liraglutide administration [224]. However, there was no placebo control. In another trial with non-diabetes subjects at increased risk of Alzheimer's disease, administration of liraglutide for 3 months improved brain region connectivity (assessed by functional MRI), but cognitive functions did not improve [225]. Another trial in non-diabetes patients with Alzheimer's disease found that 6 months of liraglutide treatment prevented a further decline in brain glucose uptake (assessed by positron emission tomography), but did not change cognitive function tests [226]. A larger clinical trial is currently ongoing that is investigating the effects of liraglutide on mild Alzheimer's disease using comprehensive neurological and cognitive assessment [227].

Parkinson's disease is another neurodegenerative disease for which GLP-1 RAs are being explored as treatment options [221,228]. In a mouse model of Parkinson's disease, a novel GLP-1 RA protected dopaminergic neurons and ameliorated behavioral deficits, most likely by blocking the formation of a neurotoxic astrocyte variant [229]. In clinical trials, exenatide improved the MDS-UPDRS score (a standardized assessment scale for patients with Parkinson's disease) [230,231]. Nevertheless, a recent systematic Cochrane Database review declared the evidence of improved motor impairment in GLP-1 RA-treated patients with Parkinson's disease as "low certainty" [232]. In an animal model of Huntington's disease, mice treated with exendin-4 for 9 weeks presented with reduced huntingtin protein aggregates in the cortex compared to placebo and had longer life spans [233]. We are not aware of any clinical trials in human patients with Huntington's disease.

Psoriasis is associated with type 2 diabetes [234]. Two case reports generated interest in using GLP-1 RAs as a potentially novel treatment option for psoriasis [235,236]. Two subsequent prospective studies found positive effects on psoriasis severity scores in type 2 diabetes patients treated with GLP-1 RAs [237,238], a finding that could not be confirmed in non-diabetes subjects [239]. This possibly suggests a clinical effectiveness that may differ in diabetes and non-diabetes patients.

9. CONCLUSIONS

Clinical research conducted over the past 30 years has established GLP-1 RAs as a widely recommended class of glucose-lowering agents. The best representatives of this class are capable of lowering plasma glucose comparable to insulin regimens, but with a lower risk of hypoglycemia and the added benefit of weight loss. The ability to prevent CV events in high-risk patients has re-emphasized the particular benefits that GLP-1 RAs may generate in type 2 diabetes therapy. Despite these past achievements, there is a potential for further increasing effectivity, optimizing molecules and dosing regimens, and exploring specific patient groups that will particularly benefit from GLP-1 RAs.

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CONFLICT OF INTEREST

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