

Review Article

Glucagon-Like Peptide-1 Receptor Agonists in Primary Care: Beyond Glycemic Control

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Abstract

Type 2 diabetes (T2D) is no longer considered solely a glucose-centric condition, but rather a chronic cardiometabolic disease that is linked to premature cardiovascular and renal complications and early death. Whereas previously, the level of glycemic control drove management decisions regarding treatment intensification, healthcare providers now have newer classes of agents that not only effectively lower glucose levels but also reduce the long-term risk of cardiovascular and renal complications. Glucagon-like peptide-1 receptor agonists (GLP-1RAs) address several of the progressive multiorgan dysfunctions associated with T2D and a number of GLP-1RAs have been shown to reduce the risk of major adverse cardiovascular events in people with established cardiovascular disease or in those at high cardiovascular risk; GLP-1RAs (or a cardioprotective sodium-glucose cotransporter-2 inhibitor) should be considered in these high-risk patients regardless of their glycated hemoglobin goal attainment status. GLP-1RAs also facilitate substantial weight loss and there is some evidence that they may help to restore β -cell function and slow the decline of kidney function, although further studies are needed to confirm this.

Keywords: β -cell Preservation; Cardiovascular Disease Risk; Glucagon-Like Peptide-1 Receptor Agonist (GLP-1RA); Renal Function/Dysfunction; Type 2 Diabetes (T2D); Weight Control/Management

Abbreviations: CI: Confidence Interval; CV: Cardiovascular; DPP4i: Dipeptidyl Peptidase-4 Inhibitor; eGFR: estimated Glomerular Filtration Rate; ER: Extended-Release; GLP-1: Glucagon-Like Peptide-1; GLP-1RA: Glucagon-Like Peptide-1 Receptor Agonist; HR: Hazard Ratio; LV: Left Ventricular; MACE: Major Cardiovascular Adverse Events; s.c.: subcutaneous; SGLT2i: Sodium-Glucose Cotransporter-2 Inhibitor; SU: Sulfonylurea; T2D: Type 2 Diabetes; TZD: Thiazolidinedione

Introduction

Historically, the focus for patients with type 2 diabetes (T2D) has been the prevention of chronic hyperglycemia using lifestyle and dietary changes, plus glucose-lowering medications [1]. However, these patients are at risk of long-term complications owing to the effects of dysfunctions covering multiple organs and systems [2-6].

The concept of T2D as a multiorgan disease is summarized by the “ominous octet” of eight main dysfunctions (Figure 1) [2], which typically manifest as an interrelated association between glucose dysregulation, weight gain, dyslipidemia, and blood pressure abnormalities, with progressively increasing cardiovascular risk and renal impairment. Newer glucose-lowering therapies, including glucagon-like peptide-1 (GLP-1) receptor agonists (GLP-1RAs), can influence a multitude of these dysfunctions.

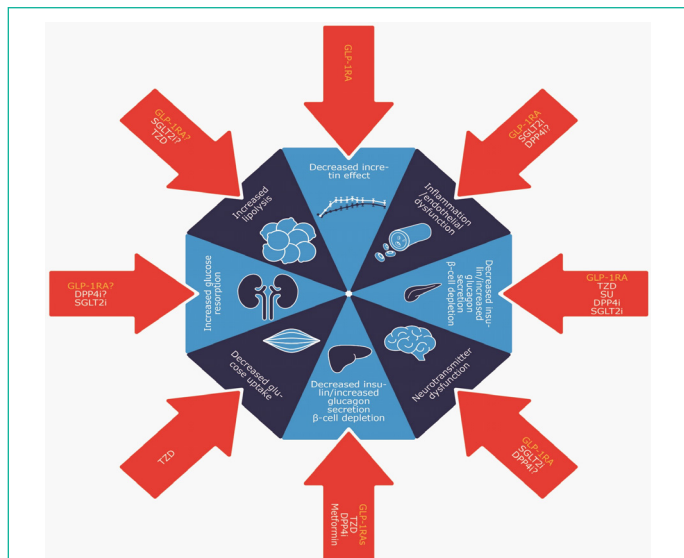


Figure 1: The ominous octet of type 2 diabetes, and glucose-lowering drugs that have a direct or indirect positive effect on each aspect [2,7-9]. DPP4i: dipeptidyl peptidase-4 inhibitor; GLP-1RA: glucagon-like peptide-1 receptor agonist; SGLT2i: sodium-glucose cotransporter-2 inhibitor; SU: sulfonylurea; TZD: thiazolidinedione.

This manuscript reviews recent evidence for the benefits of GLP-1RAs beyond blood glucose regulation, focusing on key aspects of concern to primary care providers caring for patients with T2D.

Literature Search Method

The PubMed database was searched non-systematically for randomized controlled trials of GLP-1RAs in humans with T2D, published in English in the previous 5 years, using the generic names of approved GLP-1RAs (semaglutide, liraglutide, albiglutide, dulaglutide, exenatide, lixisenatide, taspoglutide, and efglenatide) in separate searches with the following terms: (cardiovascular OR cardiorenal OR renal OR kidney) OR (ASCVD or atherosclerotic); (beta cell preservation OR protection) OR (glycemic durability); and (weight loss OR reduction). Titles and abstracts of the 230 retrieved articles were scrutinized to remove irrelevant and duplicate results. The bibliographies of the remaining articles were checked to capture additional relevant references. Further references were added based on supplementary searches and the authors’ own subject knowledge.

Beyond Glucose Lowering with GLP-1RAs in T2D

GLP-1RAs target at least six of the eight dysfunctions that make up the ominous octet (Figure 1) [2,7,8]. One underlying dysfunction is the reduced sensitivity to the effect of incretin hormones, including GLP-1 [9]. GLP-1 exerts postprandial effects that lead to a reduction in appetite and increased feelings of fullness [10,11]; in addition, GLP-1 also stimulates glucose-dependent insulin secretion and suppresses glucagon secretion. GLP-1 is also thought to increase excretion of sodium via the kidneys and promote glycogen synthesis and glucose oxidation in the muscles [10,12]. Preclinical data suggest that GLP-1 is associated with enhanced β-cell proliferation, as well as uptake of glucose in cells [10,13,14]. GLP-1 also exerts various cardio protective effects [15,16].

Exogenously administered GLP-1RAs circulate at considerably higher concentrations than can be achieved by endogenous GLP-1 to overcome GLP-1 resistance. This explains why their glucose lowering and other effects are greater than those seen with dipeptidyl peptidase-4 inhibitors (DPP4is), which in-

hibit the enzyme responsible for deactivating GLP-1 but cannot increase GLP-1 levels much beyond that which is physiologically available [17].

GLP-1RAs Reduce Cardiovascular Risk

Atherosclerotic cardiovascular disease (coronary heart disease, cerebrovascular disease, and peripheral artery disease caused by atherosclerosis) is the leading cause of morbidity and mortality in people with diabetes, and studies have shown that controlling individual cardiovascular risk factors prevents or delays development of cardiovascular disease [18]. GLP-1RAs are potentially disease-modifying in the setting of T2D and cardiovascular disease [19-26]; dulaglutide is approved in the US for both primary and secondary cardiovascular risk reduction in people with T2D [27], while liraglutide and subcutaneous semaglutide are indicated for cardiovascular risk reduction in adults with T2D and known heart disease [28,29].

All GLP-1RAs have been evaluated in large cardiovascular outcomes trials in patients with T2D who either had established cardiovascular disease or were at elevated risk for a first cardiovascular event [19-26] (Figure 2). Once-daily liraglutide, once-weekly dulaglutide, and once-weekly subcutaneous semaglutide showed a significant reduction in major adverse cardiovascular events when added to standard care, as well as benefits regarding markers of kidney function [20,21,23]. Albiglutide (no longer marketed) [24] and efglenatide (not yet approved) [26] also reduced cardiovascular risk. Lixisenatide, exenatide, and ITCA 650 (continuous subcutaneous infusion of exenatide) were non-inferior to placebo for the risk of cardiovascular events [19,22,30]. A pooled analysis of subcutaneous and oral semaglutide data suggested a cardiovascular benefit regardless of administration route [32]. A long-term, larger, post-approval cardiovascular outcomes study for oral semaglutide (SOUL; NCT03914326) is underway to confirm these findings.

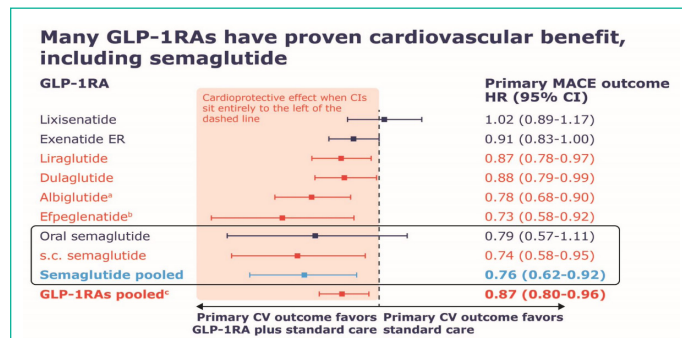


Figure 2: Summary of primary outcomes of cardiovascular outcomes trials of GLP-1RAs and combined meta-analyses [19-26,31,32].

^aAlbiglutide is no longer marketed in the US.

^bEfglenatide is not currently approved for use in the US.

^cAnalysis did not include efglenatide.

Note: Red bars that fall entirely within the shaded area left of the dotted line indicate that a significant reduction in MACE (a composite of first events of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) was demonstrated with GLP-1RA therapy. The light blue bar represents the primary outcome of a *post-hoc* pooled analysis of the prospective oral semaglutide and s.c.semaglutide trials.

CI: confidence interval; CV: cardiovascular; ER: extended-release; GLP-1RA: glucagon-like peptide-1 receptor agonist; HR: hazard ratio; MACE: major cardiovascular adverse event; s.c.: subcutaneous.

A meta-analysis of GLP-1RA cardiovascular outcomes trials (not including epeglenatide) found a 13% reduction in major adverse cardiovascular events compared with standard care [33]. GLP-1RAs also reduced the risk of all-cause death by 11% [33]. These outcomes were supported by a more recent analysis [34]. Another meta-analysis found similar results when data were stratified by baseline factors, such as body mass index, glycated hemoglobin, and age [35]. Of note, cardioprotective effects of GLP-1RAs appear to become evident over a period of ~12-24 months, similar to statins [20,21,36]. Notably, there were differences between these trials in terms of design and populations, although patients all had T2D and were at elevated cardiovascular risk [37]. All trials tested cardiovascular safety, and all GLP-1RAs were shown not to increase cardiovascular risk. Two trials are currently recruiting patients to assess the effect of once-weekly subcutaneous semaglutide 2.4 mg in patients with obesity and heart failure with preserved ejection fraction, with and without T2D (NCT04788511 and NCT04916470).

The action of GLP-1 on the heart and blood vessels may be direct or indirect, and involves protective effects, including reducing inflammation, increasing blood flow, and improving endothelial function (Figure 3) [16]. GLP-1-mediated reductions in pro-inflammatory markers and oxidative stress appear likely to be involved [38]. Among the other newer classes of glucose-lowering medications, sodium-glucose cotransporter-2 inhibitors (SGLT2is) also have a positive impact on the cardiovascular system (Figure 3) [8] and have been shown to improve cardiovascular and renal outcomes in people with T2D [39-43].

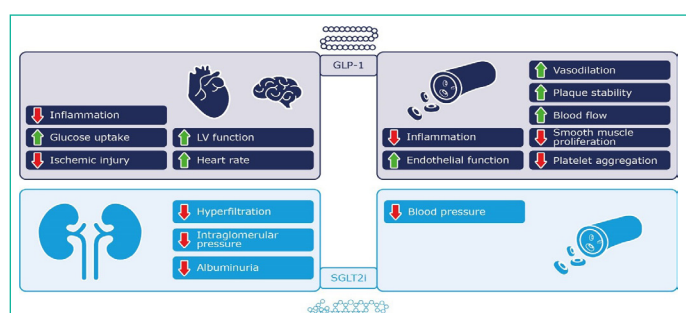


Figure 3: Proposed cardioprotective mechanisms of GLP-1RAs and SGLT2is [8,16].

GLP-1: glucagon-like peptide-1; GLP-1RA: glucagon-like peptide-1 receptor agonist; LV: left ventricular; SGLT2i: sodium-glucose cotransporter-2 inhibitor.

Signals for Renal Protection with GLP-1RAs

Diabetic kidney disease is a common and serious comorbidity in patients with T2D [44], and renal dysfunction often coincides with cardiovascular risk. GLP-1RAs are generally well tolerated in patients with renal impairment without the need for dose adjustment (except for exenatide and lixisenatide), and subgroup analyses of cardiovascular outcomes trials – albeit mostly exploratory – suggest that some GLP-1RAs may have a positive effect on renal function [21,45-50]. A large randomized, placebo-controlled study (FLOW, NCT03819153) is underway to further characterize the profile of once-weekly subcutaneous semaglutide in people with T2D and chronic kidney disease. The primary composite outcome measure is time to any one of the following events: decline in kidney function of $\geq 50\%$ reaching end-stage renal disease, death from kidney disease, or death from cardiovascular disease, with results expected in August 2024. Similarly, the ongoing SOUL trial (NCT03914326) includes

the confirmatory secondary endpoint of time to first occurrence of a composite chronic kidney disease endpoint, including the following events: cardiovascular death, renal death, onset of persistent $\geq 50\%$ reduction in estimated glomerular filtration rate (eGFR) compared with baseline, onset of persistent eGFR < 15 mL/min/1.73 m², or initiation of chronic renal replacement therapy (defined as dialysis or kidney transplant). The results of this trial are expected in July 2024.

GLP-1RAs Mediate Weight Loss

Obesity is intrinsically linked to T2D, cardiovascular disease, and adverse outcomes [18]. Primary care physicians often address weight loss in their patients with diet and lifestyle modification. However, combining behavioral intervention with appropriate pharmacotherapy improves outcomes [51]. As a general principle, the most severe disease often requires pharmacotherapies of different classes and mechanisms of action to work together to achieve optimal outcomes. However, incretin-based treatment offers the potential of a single drug class that works via multiple mechanisms to address obesity.

GLP-1 acts centrally via anorexigenic and orexigenic pathways and slows gastric emptying, thus modifying the physiological and behavioral responses to hunger and satiety and reducing calorie consumption (Figure 4) [52]. In Phase III randomized clinical trials in people with T2D treated with GLP-1RA therapy plus metformin, patients lost an average of 3-5 kg while on treatment for up to 1 year, varying by drug and trial (Table 1). Patients continued to lose weight whilst on therapy, whereas weight loss was found to plateau with some other glucose-lowering medications, such as the SGLT2i empagliflozin. Weight loss was approximately 4 kg with empagliflozin after both 26 and 52 weeks' treatment but improved with oral semaglutide from ~4 kg at 26 weeks to approaching 5 kg after 52 weeks' continuous treatment [62]. Achieving a reduction equivalent to 5% of baseline body weight is considered clinically meaningful [63], and more patients with T2D receiving GLP-1RAs in clinical studies achieved this target than with other classes of comparator glucose-lowering medications [54,56,60,63].

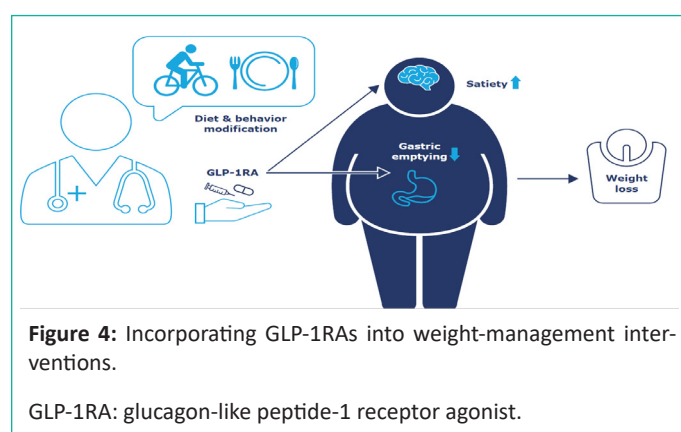


Figure 4: Incorporating GLP-1RAs into weight-management interventions.

GLP-1RA: glucagon-like peptide-1 receptor agonist.

In Phase III trials, semaglutide- and dulaglutide-induced weight loss was consistently greater than for comparators, regardless of baseline body mass index [65,66]. When compared head-to-head in patients with T2D receiving background metformin, once-weekly subcutaneous semaglutide 0.5 mg and 1.0 mg led to significantly greater weight loss (and glycated hemoglobin reduction) than once-weekly dulaglutide 0.75 mg and 1.5 mg after 40 weeks of treatment [67]. Importantly, in patients without overweight/obesity treated with exenatide, there was no excess weight loss [68].

Liraglutide became the first GLP-1RA indicated at a dose of 3.0 mg once daily (higher than the 1.8 mg diabetes dose) for weight loss in patients with overweight/obesity, regardless of their diabetes status [69]. Studies indicate that liraglutide reduces body weight in people with body mass index 27–30 kg/m² (overweight) and ≥30 kg/m² (obesity) and may decrease the long-term risk of developing T2D in people with pre-diabetes [70,71]. Gradual body weight reductions in patients with obesity treated with liraglutide 3.0 mg were not associated with changes in serum creatinine [72]. Subcutaneous semaglutide 2.4 mg has also recently been approved for chronic weight management in the US [73] after demonstrating efficacy for weight loss in patients with overweight/obesity in the STEP 1-4 trials, which included patients with and without T2D [74,77]. In STEP 2, in which patients had diabetes and a body mass index ≥27 kg/m², once-weekly injections of semaglutide 2.4 mg plus behavioral intervention resulted in over two-thirds of patients experiencing at least 5% weight loss from baseline and more than one in eight patients losing over 20% of their pre-treatment weight [75]. Patients with overweight/obesity but without diabetes lost more weight on semaglutide than those with both conditions; 80% of patients in STEP 1, 3, and 4 lost at least 5% of their baseline weight [74,76,77]. Subcutaneous semaglutide 2.4 mg is now being tested to determine its effects on cardiovascular outcomes in patients with overweight/obesity in the SELECT trial, the first such study in this population (NCT03574597).

GLP-1RAs May Help to Preserve β -cell Function

β cells in the pancreas secrete insulin to manage blood glucose levels following the ingestion of nutrients [9]. In people with normal β -cell function, orally administered glucose prompts a greater insulin response than when glucose is infused intravenously, a phenomenon referred to as the incretin effect because of the potentiating effect of incretin hormones on the release of insulin [78]. However, in people with T2D, β cells become stressed and their insulin-secreting ability progressively declines. Glucose-lowering medications are then needed, and eventually exogenous insulin [1], as β -cell function is progressively lost. However, if the incretin response can be stabilized before critical and irreversible loss of β cells, the use of replacement insulin can be delayed.

Recent analyses have provided indirect evidence that GLP-1RAs may preserve β -cell function. Exenatide and dulaglutide have both shown anti-inflammatory and antioxidant effects that are potentially protective of β cells [79,80]. Among the GLP-1RAs, both liraglutide and semaglutide have demonstrated the ability to restore β -cell function in people with T2D (Figure 5) [81,82]. Logically, the earlier GLP-1RAs are started, the greater the amount of residual β -cell function may be protected. Although β -cell function would be still expected to decline over time, a duration of response of at least 2 years with GLP-1RAs has been demonstrated in clinical studies [83,84]. Although early use of GLP-1RAs is preferred, there is still a benefit to adding them later in the disease course (improving glycemic control, reducing cardiovascular risk, etc.), including in patients already receiving insulin, those with advanced age (≥65 years), and people with longer duration of disease (≥10 years) [85].

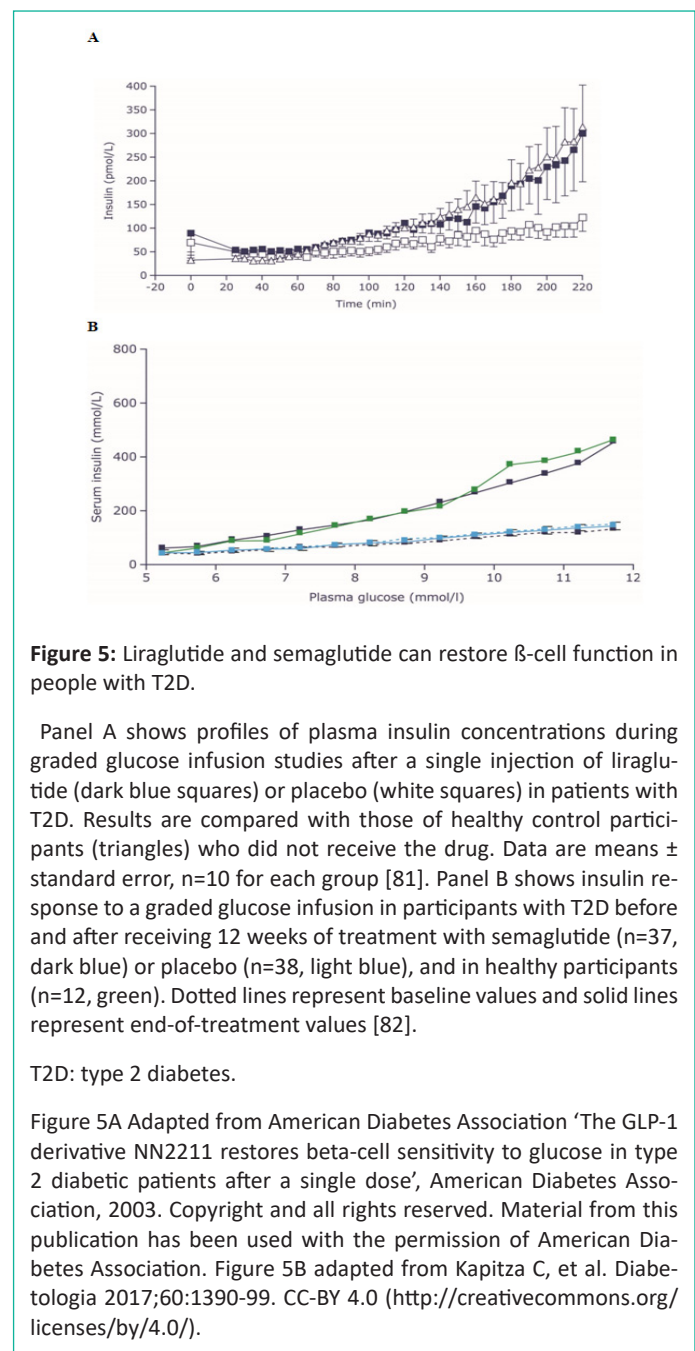


Figure 5: Liraglutide and semaglutide can restore β -cell function in people with T2D.

Panel A shows profiles of plasma insulin concentrations during graded glucose infusion studies after a single injection of liraglutide (dark blue squares) or placebo (white squares) in patients with T2D. Results are compared with those of healthy control participants (triangles) who did not receive the drug. Data are means \pm standard error, $n=10$ for each group [81]. Panel B shows insulin response to a graded glucose infusion in participants with T2D before and after receiving 12 weeks of treatment with semaglutide ($n=37$, dark blue) or placebo ($n=38$, light blue), and in healthy participants ($n=12$, green). Dotted lines represent baseline values and solid lines represent end-of-treatment values [82].

T2D: type 2 diabetes.

Figure 5A Adapted from American Diabetes Association 'The GLP-1 derivative NN2211 restores beta-cell sensitivity to glucose in type 2 diabetic patients after a single dose', American Diabetes Association, 2003. Copyright and all rights reserved. Material from this publication has been used with the permission of American Diabetes Association. Figure 5B adapted from Kapitza C, et al. *Diabetologia* 2017;60:1390-99. CC-BY 4.0 (<http://creativecommons.org/licenses/by/4.0/>).

Other Potential Benefits of GLP-1RA Therapy

An important aspect of any therapy is the effect on the patient's health-related quality of life. When added to metformin with or without sulfonylurea, once-weekly subcutaneous semaglutide improved overall treatment satisfaction compared with daily basal insulin – possibly partly because of less frequent injections [60]. Generally, patients noticed differences in outcomes when they were receiving once-daily oral semaglutide rather than placebo [86]. However, there were also significant improvements in craving control, as well as some positive effects on general health and social functioning, with oral semaglutide over the daily oral SGLT2i empagliflozin [63,86]. Exploratory analyses and other studies of GLP-1RAs have hinted at further beneficial physiological effects on peripheral artery disease, cognitive impairment, and memory function [87-89]. The placebo-controlled STRIDE trial (NCT04560998) is currently investigating the use of semaglutide in people with T2D and peripheral artery disease, with results expected in 2023. In addition, the EVOKE (NCT04777396) and EVOKE Plus trials (NCT04777409) are investigating the potential use of oral semaglutide in people with early Alzheimer's disease.

Table 1: Key features of currently available glucagon-like peptide-1 receptor agonists.

Generic name	Administration route and frequency	Dose and dosing conditions (adults only unless stated)	Representative effect on glycated hemoglobin (% reduction from baseline) and body weight (absolute reduction from baseline) when added to metformin ^a	Most common adverse events (% of patients with at least one event)
Exenatide	Subcutaneous injection twice daily [53]	<ul style="list-style-type: none"> • Start at 5.0 µg • Increase to 10.0 µg after 1 month based on clinical response • Dose ≤1 hour before morning and evening meals (or the two main meals of the day, ≥6 hours apart) [53] 	Glycated hemoglobin (week 24) [54]: <ul style="list-style-type: none"> • -1.0% (10.0 µg) Body weight (week 24) [54]: <ul style="list-style-type: none"> • -3.8 kg (10.0 µg) 	10.0 µg [54]: <ul style="list-style-type: none"> • Nausea: 35% • Vomiting: 13% • Diarrhea: 13%
Exenatide extended-release	Subcutaneous injection once weekly [55]	<ul style="list-style-type: none"> • Start/continue at 2.0 mg • Dose at any time of day, with or without food [55] 	Glycated hemoglobin (week 26) [56]: <ul style="list-style-type: none"> • -1.5% (2.0 mg) Body weight (week 26) [56]: <ul style="list-style-type: none"> • -2.3 kg (2.0 mg) 	2.0 mg [56]: <ul style="list-style-type: none"> • Nausea: 24% • Diarrhea: 18% • Vomiting: 11%
Lixisenatide	Subcutaneous injection once daily [57]	<ul style="list-style-type: none"> • Start at 10.0 µg for the first 14 days • Increase to 20.0 µg • Dose at same time each day, ≤1 hour before the first meal of the day [57] 	Glycated hemoglobin (week 24) [54]: <ul style="list-style-type: none"> • -0.8% (20.0 µg) Body weight (week 24) [54]: <ul style="list-style-type: none"> • -3.0 kg (20.0 µg) 	20.0 µg [54]: <ul style="list-style-type: none"> • Nausea: 25% • Vomiting: 10% • Diarrhea: 10%
Liraglutide	Subcutaneous injection once daily [29]	Adults [29]: <ul style="list-style-type: none"> • Start at 0.6 mg for 1 week • Increase to 1.2 mg. If additional glycemic control is required, increase the dose to 1.8 mg after 1 further week • Dose at any time of day, independent of meals Children ≥10 years [29]: <ul style="list-style-type: none"> • Start at 0.6 mg for ≥1 week • Only increase to 1.2 or 1.8 mg if required • Dose at any time of day, independent of meals 	Glycated hemoglobin (week 26) [58]: <ul style="list-style-type: none"> • -1.0% (1.2 mg) • -1.0% (1.8 mg) Body weight (week 26) [58]: <ul style="list-style-type: none"> • -2.6 kg (1.2 mg) • -2.8 kg (1.8 mg) 	1.2 mg/1.8 mg [58]: <ul style="list-style-type: none"> • Nausea: 16/19% • Diarrhea: 8/15% • Vomiting: 5-7% across the groups
Dulaglutide	Subcutaneous injection once weekly [27]	<ul style="list-style-type: none"> • Start at 0.75 mg • Increase to 1.5 mg, and subsequently up to 3.0 mg or 4.5 mg, after at least 4 weeks on each dose, if needed • Dose at any time of day with or without food [27] 	Glycated hemoglobin (week 36) [60]: <ul style="list-style-type: none"> • -1.5% (1.5 mg) • -1.6% (3.0 mg) • -1.8% (4.5 mg) Body weight (week 36) [59]: <ul style="list-style-type: none"> • -3.0 kg (1.5 mg) • -3.8 kg (3.0 mg) • -4.6 kg (4.5 mg) 	1.5/3.0/4.5 mg [59]: <ul style="list-style-type: none"> • Nausea: 14/16/17% • Vomiting: 6/9/10% • Diarrhea: 8/12/12%
Semaglutide	Subcutaneous injection once weekly [28]	<ul style="list-style-type: none"> • Start at 0.25 mg • Increase to 0.5 mg after 4 weeks. If after at least 4 weeks additional glycemic control is needed, increase to 1.0 mg. If additional glycemic control is needed after at least 4 weeks on the 1.0 mg dose, increase to 2.0 mg. • Dose at any time of day, with or without food [28] 	Glycated hemoglobin (week 30) [60]: <ul style="list-style-type: none"> • -1.2% (0.5 mg) • -1.6% (1.0 mg) (week 40) [61]: <ul style="list-style-type: none"> • -2.2% (2.0 mg) Body weight (week 30) [60]: <ul style="list-style-type: none"> • -3.5 kg (0.5 mg) • -5.2 kg (1.0 mg) (week 40) [61]: <ul style="list-style-type: none"> • -6.9 kg (2.0 mg) 	0.5/1.0 [60]/2.0 mg [61]: <ul style="list-style-type: none"> • Nausea: 21/22/14% • Vomiting: 7/10/8% • Diarrhea: 16/19/9%
Oral semaglutide	Oral tablet once daily [62]	<ul style="list-style-type: none"> • Start at 3.0 mg • Increase to 7.0 mg after 30 days. Dose may be increased to 14.0 mg if additional glycemic control is needed after at least 30 days on 7.0 mg • Dose tablet on an empty stomach with ≤4 fl oz (120 mL) of plain water >30 minutes before any further liquid and the first food and/or other oral medication of the day [62] 	Glycated hemoglobin (week 26) [63]: <ul style="list-style-type: none"> • -1.3% (14.0 mg) Body weight (week 26) [62]: <ul style="list-style-type: none"> • -3.8 kg (14.0 mg) 	14.0 mg [63]: <ul style="list-style-type: none"> • Nausea: 20% • Diarrhea: 9% • Vomiting: 7%

Practical Considerations for Managing GLP-1RA Therapy in the Primary Care Setting

Despite having been available for nearly 15 years, GLP-1RAs have often been considered the preserve of the diabetes specialist and primary care providers may have been hesitant to prescribe them. However, this is slowly changing because of increasing evidence for the benefits of earlier initiation of GLP-1RAs in people with T2D [1], and potentially now the availability of an oral GLP-1RA.

Which Patients Could/Should Receive GLP-1RAs?

The latest American Diabetes Association guidelines suggest that GLP-1RAs should be considered before basal insulin as the first injectable medication for patients whose T2D is uncontrolled on metformin with or without other oral glucose-lowering medications [1]. Because of their potential to modify cardiovascular risk, GLP-1RAs with proven cardiovascular benefit are recommended for *all* patients with T2D who have established cardiovascular disease or who are at high risk of cardiovascular events, regardless of their glycated hemoglobin target [1,89]. SGLT2is with proven cardiovascular benefit are preferred to GLP-1RAs in patients with T2D and heart failure and/or chronic kidney disease, but with GLP-1RAs as second choice if a SGLT2i is not appropriate [1,90]. The 2021 American Heart Association/American Stroke Association guidelines note that SGLT2is, unlike some GLP-1RAs, do not show a specific effect on the secondary prevention of stroke [91]. Of note, DPP4is are neutral for cardiovascular outcomes and are not generally recommended to be combined with GLP-1RAs [1,90]. The GRADE trial compared outcomes with a sulfonylurea (glimepiride), DPP4i (sitagliptin), GLP-1RA (liraglutide), and insulin glargine, each given as add-on to metformin. Preliminary results showed that over the 5-year observation period, liraglutide and insulin were the most effective of the four treatments for glycemic control and cardiovascular disease prevention, and liraglutide and sitagliptin provided greatest weight loss [92].

Choosing a GLP-1RA – Mode of Administration and Associated Considerations

Most GLP-1RAs are injected, either daily or weekly. One GLP-1RA – semaglutide – is now available as a daily oral tablet [61], which may facilitate earlier GLP-1RA initiation by helping to overcome barriers in injection-naïve patients. Nevertheless, some patients may prefer a once-weekly injection to a daily tablet and innovations in injectable delivery devices are improving the ease of self-injection. This should be communicated to patients to help them feel more comfortable if an injectable GLP-1RA is under consideration. Dosing instructions for each available GLP-1RA are shown in Table 1.

The once-weekly injectable GLP-1RAs can be dosed at any time of day regardless of mealtimes (Table 1). This is also true of once-daily liraglutide, but time of day and mealtimes must be considered with other once-daily GLP-1RAs. For oral semaglutide, to ensure optimal absorption, it is advised that the patient takes the tablet in the morning on an empty stomach [62].

Choosing a GLP-1RA – Efficacy and Tolerability

When selecting a GLP-1RA, patient preference (daily vs weekly injections or daily oral therapy) and payer coverage are potentially the most important short-term considerations. However, between the longer-acting GLP-1RAs, small differences in glucose control and weight loss, as well as proven

cardiovascular benefit, tend to favor once-weekly subcutaneous semaglutide and dulaglutide, and once-daily liraglutide (Table 1) [54,56,58,59,60,63,93]. When added to metformin in clinical trials, GLP-1RAs at their currently approved doses reduced glycated hemoglobin by 0.8-1.8%, depending on the treatment and dose, baseline glycated hemoglobin, and time point of the primary outcome measurement [54,56,58,59,60,63,93]. Semaglutide appears to be the most effective option for weight loss, with the 1.0 mg subcutaneous dose providing an average 5 kg reduction after 30 weeks [60], but all GLP-1RAs help patients to lose weight (Table 1). Glycated hemoglobin and body weight reductions are generally maintained with ongoing treatment [54,56,58,59,60,63,93]. Semaglutide 2.0 mg was superior to 1.0 mg in reducing glycated hemoglobin, with additional body weight loss and a similar safety profile [61], and dulaglutide 4.5 mg provided superior glycated hemoglobin reductions compared with 1.5 mg, with a similar safety profile [61]. Dulaglutide is now approved at additional doses of 3.0 mg and 4.5 mg if additional glycemic control is needed [27]. Although once-weekly subcutaneous semaglutide 2.4 mg is now indicated for weight loss in people with overweight/obesity, this dose should not be used for management of T2D in patients with body mass index <27 kg/m² [73].

Tolerability profiles are generally consistent between the GLP-1RAs; all agents are associated with a low risk of hypoglycemia when used in combination with other anti-diabetes agents besides insulin and/or a sulfonylurea [54,56,58,59,60,63,93]. This is because GLP-1RAs, like endogenous GLP-1, only act on elevated levels of blood glucose. Gastrointestinal side effects, primarily nausea, vomiting, and diarrhea [54,56,58,59,60,63,93], are the most common adverse events, but their nature and intensity can differ between drugs in the class. Generally, the more potent GLP-1RAs are associated with a greater incidence of gastrointestinal side effects, although most events are mild or moderate, occur at the start or intensification of treatment, and resolve with ongoing use [54,56,58,59,60,63,93].

A gradual increase in the intensity of therapy can mitigate gastrointestinal events, and dose-escalation schedules are recommended in the prescribing information for GLP-1RAs (Table 1). Dose flexibility also provides the option to reduce the dose or pause treatment if an adverse event occurs. Patients should be made aware that gastrointestinal side effects are not unexpected. Suggesting dietary modifications, such as reducing portion sizes and avoiding fatty foods, can help patients manage gastrointestinal issues [94]. Patients should report any serious or ongoing side effects to their physician. Renal function should be monitored in patients with renal impairment reporting severe adverse gastrointestinal reactions [27-29,53,55,57,62].

An appreciable proportion of patients may experience fatigue and/or asthenia when starting GLP-1RA treatment [55,69,73]. This may be due to adjustments in caloric intake rather than a direct effect of the medication. As with gastrointestinal events, this phenomenon generally stabilizes within a few weeks, and counseling patients to expect fluctuations in their energy levels could help encourage treatment persistence.

Contraindications, Warnings, and Precautions

Most GLP-1RAs can be used in patients with renal impairment, including end-stage kidney disease [27-29,62] without dose adjustment. However, exenatide is not recommended in patients with creatinine clearance <30 mL/min (twice-daily formulation) [53] or eGFR <45 mL/min/1.73 m² (weekly extended-

release formulation) [55], and lixisenatide is not recommended in patients with end-stage renal disease (creatinine clearance <15 mL/min) [57].

GLP-1RAs have been associated with the development of thyroid C-cell tumors in rodents, but the clinical relevance of this in humans is unknown. There are post-marketing reports of medullary thyroid carcinoma in patients with T2D treated with liraglutide, but in insufficient numbers to establish or exclude a causal association [29]. Nevertheless, a boxed warning in the prescribing information for most GLP-1RAs mandates contraindication in patients with a personal or family history of medullary thyroid carcinoma or in patients with multiple endocrine neoplasia syndrome type 2 [27-29,55,62]. Routine monitoring of serum calcitonin or using thyroid ultrasound is not advocated. Patients should be counseled regarding the potential risk of medullary thyroid carcinoma and symptoms of thyroid tumors [27-29,55,57,62].

The risk of hypoglycemia increases when GLP-1RAs are combined with insulin or sulfonylurea, both of which are associated with increased rates of death in the setting of severe hypoglycemia [94]. Therefore, consideration should be given to lowering the dose of insulin or sulfonylurea if combined therapy is used [27-29,53,55,57,62].

There was a low risk of acute pancreatitis in clinical trials of GLP-1RAs; patients should be counseled on the symptoms of pancreatitis and be advised to discontinue their GLP-1RA if pancreatitis is suspected. If confirmed, the GLP-1RA should not be restarted [27-29,53,55,57,62].

Diabetic retinopathy complications have been reported in a clinical trial with semaglutide [21,28]. Retinopathy status should be assessed in patients receiving GLP-1RAs [96,97], and patients with a history of diabetic retinopathy should be monitored [27,28,62].

Conclusion

GLP-1RAs address multiple aspects of the physiological dysfunction associated with T2D, potentially slowing disease progression and modifying its course, in particular with relation to cardiovascular outcomes. Earlier initiation of GLP-1RAs in the treatment paradigm of T2D should be considered, particularly in patients at increased cardiovascular risk regardless of glycosylated hemoglobin target.

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Conflicting and Competing Interests

JL is an advisor and speaker for Novo Nordisk.

TMB holds stock in TransMedics Group and has previously held stock in Novavax.

KU reports advisory board participation for Esperion and Novo Nordisk and is a consultant/speaker for Amarin, AstraZeneca, Esperion, Medicure, and Novo Nordisk.

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KMP reports, in the previous 12 months, being a member of the speakers' bureau of AstraZeneca, Corcept Therapeutics, Merck, and Novo Nordisk; a consultant for AstraZeneca, Bayer, Corcept Therapeutics, Diasome, Merck, Novo Nordisk, and Sanofi; and receiving research support from Bayer, Merck, Novo Nordisk, and Twin Health.

Contributors

JL, KU, and KMP were responsible for the conceptualization of the manuscript. The original draft was created by the medical writer, under the direction of the authors. All authors reviewed and edited the drafts and approved the final version for submission.

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