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SUPPLEMENT: INTRODUCING ORAL SEMAGLUTIDE AND THE PIONEER PROGRAM TO PRIMARY CARE

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GLP-1 receptor agonists in the treatment of type 2 diabetes: role and clinical experience to date

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ABSTRACT

Glucagon-like peptide-1 (GLP-1) is a hormone of the incretin system responsible for a variety of glucoregulatory effects, including glucose-dependent secretion of insulin and inhibition of glucagon release, the effects of which are impaired in people with type 2 diabetes (T2D). Targeting this deficiency using GLP-1 receptor agonists (GLP-1RAs) is a well-established approach in T2D, with over a decade of clinical experience now accrued. This article reviews the evidence for subcutaneous GLP-1RAs and their role in T2D treatment, and explores the rationale for an oral GLP-1RA from a primary care perspective.

Clinical trials and real-world studies with subcutaneous GLP-1RAs indicate that these agents have good glycated hemoglobin (HbA_{1c})-lowering efficacy, an inherently low potential for hypoglycemia, and reduce body weight. Cardiovascular outcomes trials have established cardiovascular safety, and three GLP-1RAs have been proven to reduce the risk of major adverse cardiovascular events (MACE) in patients with established cardiovascular disease or at high cardiovascular risk. The most common adverse events associated with GLP-1RAs are gastrointestinal effects, which tend to occur soon after initiation and decline over time.

T2D treatment guidelines recommend GLP-1RAs as a therapeutic option in various settings, including in those patients: i) not achieving HbA_{1c} targets after first-line metformin and lifestyle modifications; ii) at high risk of/with established atherosclerotic cardiovascular disease (regardless of HbA_{1c}; GLP-1RAs of proven benefit); iii) not achieving HbA_{1c} targets on basal insulin if not already receiving a GLP-1RA.

Despite the known benefits of GLP-1RAs, adherence and persistence rates are suboptimal, potentially due in part to injection-related concerns. With some patients having a preference for oral medications, the development of an oral GLP-1RA is a logical approach to improving treatment options for patients with T2D. Co-formulation of semaglutide with an absorption enhancer has enabled the development and recent approval of the first oral GLP-1RA, oral semaglutide, which has the potential to expand use of GLP-1RAs in clinical practice.

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Type 2 diabetes; glucagon-like peptide-1 receptor agonist; primary care; oral semaglutide

Article overview and relevance to your clinical practice

- Glucagon-like peptide-1 (GLP-1) receptor agonists (GLP-1RAs) are an efficacious class of therapeutic agents for type 2 diabetes (T2D), with well-characterized safety and tolerability profiles that can be considered in many clinical scenarios, ranging from patients who are not reaching their glycemic goal with metformin, to those with comorbidities or in whom glycemic control is not achieved despite treatment with several oral antihyperglycemic agents.
- Until recently, these agents were only available in injectable form, but the 2019 US Food and Drug Administration approval of oral semaglutide now provides the option to prescribe a GLP-1RA that is administered as a once-daily tablet.
- The availability of oral semaglutide may create the opportunity for primary care providers to consider GLP-1RAs earlier in the T2D treatment pathway.
- This article will provide a brief overview of the mechanism of action and clinical evidence for currently available GLP-1RAs, and discuss their role in treating people with T2D in the USA.
- We will introduce oral semaglutide and explain how it was possible to develop an oral formulation of a peptide-based drug, before illustrating how the efficacy and safety of this medication has been evaluated in the extensive, global, PIONEER phase 3a clinical trial program.

1. Intensification of type 2 diabetes therapy in primary care

Primary care is central to the management of type 2 diabetes (T2D), and ≥90% of patients in the USA are treated in this setting [1,2]. With several therapeutic classes from which to choose and various comorbidities to address, the management of T2D in primary care is becoming increasingly complex. While diet and

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exercise remain important in managing the disease, pharmacological intervention is usually required. Treatment plans should be tailored to the individual patient and take various factors into consideration, including treatment goals, presence of comorbidities, and patient preference [3].

Despite advancements in the quality of care and number of therapeutic options available, only around 50% of people with T2D in the US are estimated to achieve glycated hemoglobin (HbA_{1c}) levels below 7.0% [4], the target generally recommended by the American Diabetes Association (ADA) [5]. Among the many potential factors that may contribute to this, a key element is the delay in intensifying therapy in order to reach glycemic goals [6], particularly for those requiring initiation of injectable therapies [7].

Since the 2005 approval of the first glucagon-like peptide-1 (GLP-1) receptor agonist (GLP-1RA), exenatide, this class has amassed a wealth of evidence from clinical trials and real-world studies demonstrating efficacy for achieving both glycemic control and weight loss in patients with T2D [8,9,10]. Moreover, some of these agents offer the additional benefit of reducing the risk of major adverse cardiovascular events (MACE) in patients with both T2D and established cardiovascular disease (CVD) [11–13] or multiple cardiovascular risk factors [12].

Within this article, we will explore the background of GLP-1RAs and review the clinical experience with these agents to date, moving on to consider where this therapeutic class fits in the treatment paradigm for T2D and how the approval of the first oral GLP-1RA – oral semaglutide – might impact this.

2. Pathophysiology of T2D and the role of GLP-1RAs

T2D is a complex and multifactorial disease, with fundamental defects in at least eight tissues and organ systems known to contribute to the development and progression of hyperglycemia – the so-called 'ominous octet' [14,15]. Although impaired insulin secretion by pancreatic β-cells and insulin resistance in the liver and muscle are well-recognized as the core defects involved in the etiology of T2D, the ominous octet also comprises increased glucagon secretion, neurotransmitter dysfunction in the brain, enhanced glucose reabsorption in the kidneys, a decreased incretin effect, and increased lipolysis [14,15]. Targeting these pathophysiological defects is therefore fundamental to delaying the progression of the disease and should be a primary goal of T2D management [14,15].

A variety of glucoregulatory effects, including secretion of insulin, inhibition of glucagon release, and promotion of satiety, are mediated by peptide hormones of the incretin system, including GLP-1 [16,17]. In healthy individuals, GLP-1 is secreted by L-cells in the small intestine in response to the presence of food in the gastrointestinal tract [18,19]. In people with T2D, however, the effects of GLP-1 are significantly impaired, thereby greatly reducing the capacity for insulin release in response to food intake [20].

The use of native GLP-1 as a therapeutic option for people with T2D has been explored, but is limited by its very short half-life and rapid degradation by the enzyme dipeptidyl peptidase-4 (DPP-4); for this reason, synthetic GLP-1RAs with enhanced protein binding and slower degradation have been developed [18,21]. By mimicking the effects of native GLP-1 through stimulation of the GLP-1 receptor, GLP-1RAs directly or indirectly target at least six

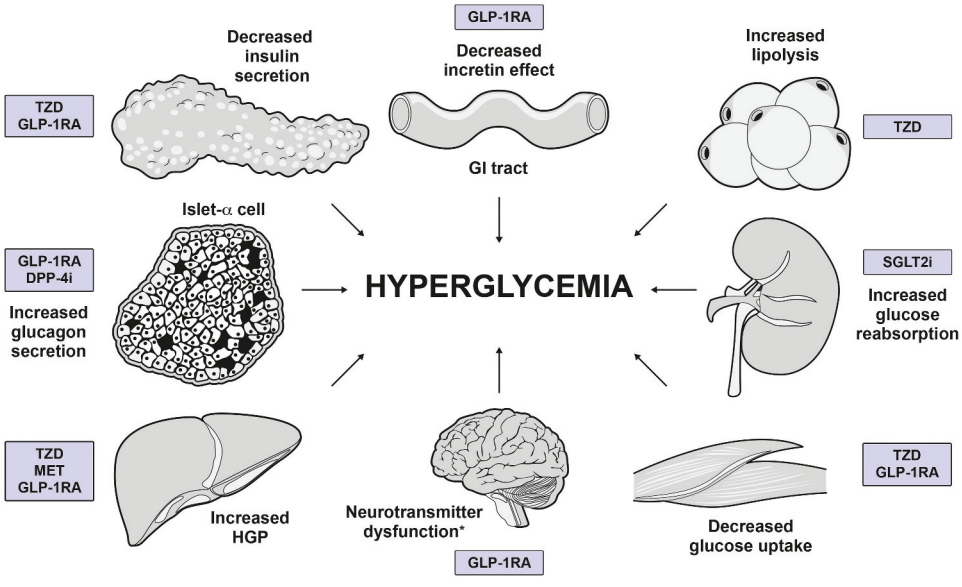

Figure 1. Impact of various classes of antihyperglycemic medications on the 'ominous octet' of pathophysiological defects contributing to hyperglycemia in patients with T2D [14].

*Reduced satiety and appetite suppression.

DPP-4i, dipeptidyl peptidase-4 inhibitor; GI, gastrointestinal; GLP-1RA, glucagon-like peptide-1 receptor agonist; HGP, hepatic glucose production; MET, metformin; SGLT2i, sodium-glucose co-transporter 2 inhibitor; T2D, type 2 diabetes; TZD, thiazolidinedione.

of the eight core defects implicated in the pathogenesis of T2D (excluding increased lipolysis and increased glucose reabsorption in the kidney), more than any other class of antihyperglycemic medication, and ultimately promote insulin secretion and inhibit glucagon secretion [14,15,22] (**Figure 1**). Given that the effects of GLP-1 on insulin secretion are glucose-dependent, GLP-1RAs have an inherently low risk of hypoglycemia [23]. The benefits of GLP-1RAs extend beyond their well-established effects on glycemic control. Indeed, these agents have demonstrated a variety of nonglycemic clinical effects, including weight loss and decreased systolic blood pressure [21,24–26].

Until the approval of oral semaglutide in September 2019, only subcutaneous GLP-1RAs were available for treating people with T2D in the USA, either alone (dulaglutide [12], exenatide [27], exenatide extended-release [28,29], liraglutide [13], lixisenatide [30], and subcutaneous semaglutide [11]) or in combination with insulin (liraglutide + insulin degludec [31] and lixisenatide + insulin glargine [32]); oral semaglutide is the first in this class to be administered in tablet form [33]. While these agents share a common mechanism of action, there are a number of key differences between them, which can include duration of action, dosing frequency and regimen, and administration device (**Table 1**), allowing for individualization of treatment for patients. In terms of the duration of action on the GLP-1 receptor, agents in this class can be categorized as either short-acting (exenatide and lixisenatide) or long-acting (dulaglutide, exenatide extended-release, liraglutide, and semaglutide) [23,25,34]. Short-acting agents primarily reduce postprandial glucose by delaying gastric emptying, whereas long-acting agents have a greater effect than short-acting agents on fasting glucose, and offer the advantages of smaller fluctuations in plasma drug concentrations, improved gastrointestinal tolerability, and more convenient dosing regimens [23,34].

3. GLP-1RAs in the T2D treatment paradigm

Individualized treatment plans for T2D are based on the requirements of each patient, including glycemic control and weight loss considerations, as well as the impact of comorbidities (e.g., atherosclerotic CVD, and chronic kidney disease

Table 1. Overview of the key characteristics of GLP-1RAs currently available for treating adults with T2D in the USA [11–13,23,25,27–30,33,34,35].

Agent	FDA approval	Dosing frequency	Recommended dosage	Timing of administration	Administration method
Short-acting agents*					
Exenatide	2005	Twice daily	• 5 µg s.c. twice daily • After 1 month, may increase to 10 µg s.c. twice daily based on clinical response	Take within 60 minutes before morning and evening meals (or before the two main meals of the day, approximately 6 hours or more apart)	Multi-use pens (each containing 60 doses of either 5 µg or 10 µg)
Lixisenatide†	2016	Once daily	• 10 µg s.c. once daily for the first 14 days • On day 15, increase to 20 µg once daily	Take within 1 hour before the first meal of the day	Multi-use pens (each containing 14 doses of either 10 µg or 20 µg)
Long-acting agents*					
Liraglutide‡	2010	Once daily	• 0.6 mg s.c. once daily for 1 week, then increase to 1.2 mg once daily • If glycemic control is unacceptable after a further week, can increase dose to 1.8 mg s.c. once daily	Take at any time of day	Multi-use pen (6 mg/mL pen that delivers doses of 0.6 mg, 1.2 mg or 1.8 mg)
Exenatide extended-release	2012	Once weekly	• 2 mg s.c. once weekly	Take at any time of day	Single-use pen (2 mg), single-dose vial (2 mg), or single-use autoinjector (2 mg)
Dulaglutide	2014	Once weekly	• 0.75 mg s.c. once weekly • May increase to 1.5 mg s.c. once weekly for inadequate glycemic control	Take at any time of day	Single-use pen (0.75 mg or 1.5 mg)
Subcutaneous semaglutide	2017	Once weekly	• 0.25 mg s.c. once weekly for 4 weeks, then increase to 0.5 mg s.c. once weekly • If glycemic control is unacceptable after a further 4 weeks, can increase dose to 1 mg s.c. once weekly	Take at any time of day	Multi-use pens (one delivering doses of 0.25 mg or 0.5 mg, and the other 1 mg)
Oral semaglutide	2019	Once daily	• 3 mg orally once daily for 30 days, then increase to 7 mg orally once daily • If glycemic control is unacceptable after a further 30 days, increase to 14 mg orally once daily	Take at least 30 minutes before first food, drink or other medication of the day	Oral tablet (3 mg, 7 mg, or 14 mg)

*Short acting: drug concentrations decline to low levels a few hours after administration; long-acting: drug concentrations are sustained at effective concentrations for the dosing period [25]; †also available as a fixed-dose combination with insulin glargine 100 U [32]; ‡also available as a fixed-dose combination with insulin degludec 100 U [31].

FDA, US Food and Drug Administration; GLP-1RA, glucagon-like peptide-1 receptor agonist; s.c., subcutaneous; T2D, type 2 diabetes.

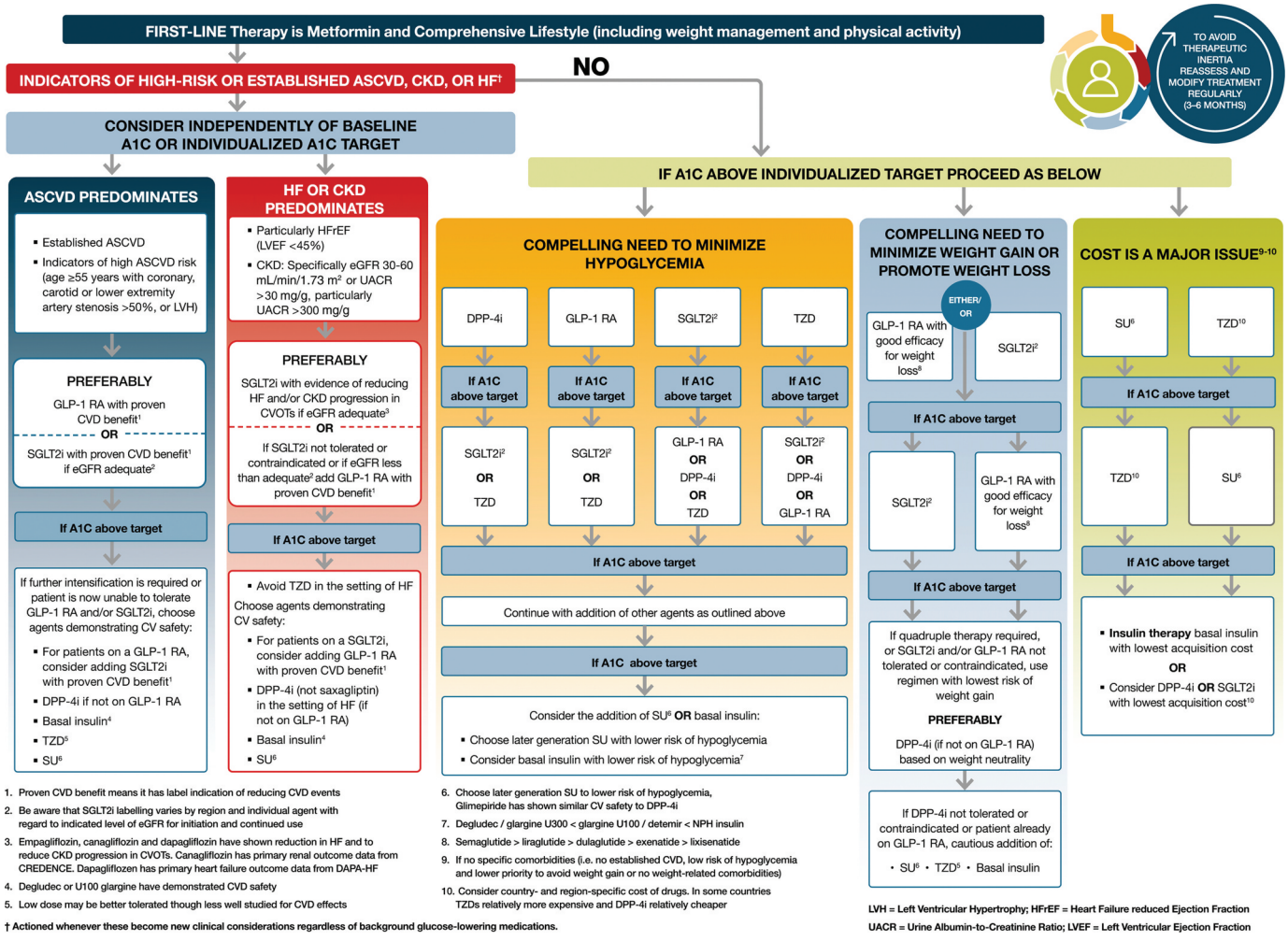

Figure 2. Current ADA recommendations for pharmacological treatment of adults with T2D [3].

American Diabetes Association [*9. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes–2020*, American Diabetes Association, 2020]. Copyright and all rights reserved. Material from this publication has been used with the permission of American Diabetes Association.

A1C, glycated hemoglobin; ADA, American Diabetes Association; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; CVOT, cardiovascular outcomes trial; DPP-4i, dipeptidyl peptidase-4 inhibitor; eGFR, estimated glomerular filtration rate; GLP-1RA, glucagon-like peptide-1 receptor agonist; HF, heart failure; HFrEF, heart failure reduced ejection fraction; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; SGLT2i, sodium-glucose co-transporter 2 inhibitor; SU, sulfonylurea; T2D, type 2 diabetes; TZD, thiazolidinedione; UACR, urine albumin-to-creatinine ratio.

[CKD]) and risk of hypoglycemia [3]. GLP-1RAs are recommended by the ADA as a second-line therapy option after metformin and lifestyle management in patients across the treatment continuum, including those at high risk of or with established atherosclerotic CVD, CKD, or heart failure, and in patients without these comorbidities who have a compelling need to reduce the risk of hypoglycemia, minimize weight gain, or promote weight loss (**Figure 2**) [3].

Irrespective of baseline HbA_{1c} or individual HbA_{1c} targets, a GLP-1RA or sodium-glucose co-transporter-2 (SGLT2) inhibitor with a proven CVD benefit is recommended as a component of the therapeutic regimen for patients in whom atherosclerotic CVD predominates [3]. There are currently three GLP-1RAs indicated for reducing the risk of MACE in patients with T2D and established CVD: dulaglutide, liraglutide, and subcutaneous semaglutide [11–13]; dulaglutide is also indicated for reducing this risk in patients with T2D and multiple cardiovascular risk factors [12]. For those in whom CKD or heart failure predominate, GLP-1RAs are recommended if SGLT2 inhibitors are contraindicated or not tolerated, or if estimated glomerular filtration rate is less than adequate [3] (**Figure 2**).

Further along the treatment pathway, GLP-1RAs can also be considered for treatment intensification in patients with HbA_{1c} above target despite dual or triple therapy with other antihyperglycemic agents, and the ADA recommends that GLP-1RAs should be initiated in most patients prior to insulin [3]. For patients above HbA_{1c} target despite therapy with basal insulin, the addition of a GLP-1RA can be considered [3] (**Figure 2**).

Key clinical take-home pointsparadigm

- Individualized treatment plans are recommended for patients with T2D, based on several factors, including comorbidities, hypoglycemia risk, and impact on weight, as well as patient preference.

Table 2. Overview of key clinical outcomes with GLP-1RAs [11–13,25,27,28,30].

Agent	Relative efficacy (based on authors' clinical judgment and data from RCTs)*		Composite MACE outcome†
	HbA_{1c} reduction*	Body weight reduction (kg)*	
Exenatide twice daily	+	+(+)	No CVOT performed
Lixisenatide once daily	+	+	Noninferior to placebo when added to standard of care
Liraglutide once daily	++	++	Superior to placebo when added to standard of care‡
Exenatide once weekly	+	+	Noninferior to placebo when added to standard of care
Dulaglutide once weekly	++	++	Superior to placebo when added to standard of care#
Subcutaneous semaglutide once weekly	+++	+++	Superior to placebo when added to standard of care‡
Oral semaglutide once daily	++(+)	++(+)	Noninferior to placebo when added to standard of care§

*These estimates are based on clinical judgment and data from RCTs evaluating GLP-1RAs as monotherapy or as a single addition to oral antihyperglycemic agents reported in the prescribing information; †based on results from CVOTs with a primary outcome of MACE (first events of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) – a prospective CVOT for exenatide twice daily has not been performed; ‡FDA-approved for reducing risk of MACE in adults with T2D who have established CVD; #FDA-approved for reducing risk of MACE events in adults with T2D who have established CVD or multiple cardiovascular risk factors; §a phase 3 clinical study (SOUL; NCT03914326) is ongoing to determine whether oral semaglutide is superior to placebo for reducing the risk of MACE in patients with T2D [37].

CVD, cardiovascular disease; CVOT, cardiovascular outcomes trial; FDA, US Food and Drug Administration; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, glycated hemoglobin; MACE, major adverse cardiovascular events; RCT, randomized controlled trial; T2D, type 2 diabetes.

- If patients are not at goal with metformin, or if metformin is contraindicated, GLP-1RAs can be used throughout the T2D treatment pathway, including in patients with:
  - a need to minimize hypoglycemia;
  - a need to minimize weight gain or promote weight loss;
  - high risk or established atherosclerotic CVD, CKD, or heart failure (agents with proven CVD or renal benefit should be used).

4. Clinical experience with subcutaneous GLP-1RAs

Based on a wealth of data from both clinical trials and real-world studies gathered through more than 10 years of clinical use, subcutaneous GLP-1RAs are well established in the treatment of T2D [8–10,23,36]. The potential direct and indirect effects of GLP-1RAs on glycemic control, body weight, and the composite MACE outcome are summarized in **Table 2**.

Pivotal clinical studies have explored the efficacy and safety of GLP-1RAs as monotherapy versus placebo and – in the majority of studies – as add-on to other therapies, with comparators including placebo, insulin, other GLP-1RAs, SGLT-2 inhibitors, DPP-4 inhibitors, sulfonylureas, and thiazolidinediones [10,36,38]. Real-world data from studies with a variety of GLP-1RAs suggest that the results seen in clinical practice, including in the primary care setting, are consistent with those seen in the clinical trial programs [39,40,41,42,43,44,45]. However, it should be noted that differences between clinical outcomes in these settings may be obscured due to a limited number of studies and potential problems of confounding and selection bias in observational studies [39]. There is also some evidence that the efficacy of GLP-1RAs is maintained through long-term use, with a recently published study reporting sustained improvements in glycemic control and body weight with the use of exenatide once weekly for up to 7 years [46].

4.1. Effects of GLP-1RAs on glycemic control and body weight

4.1.1. Monotherapy or add-on compared with placebo

As monotherapy or add-on therapy, GLP-1RAs have demonstrated greater reductions in HbA_{1c} compared with placebo, with more patients achieving their glycemic targets with GLP-1RAs [36]. Beyond glycemic control, one of the main potential benefits of GLP-1RAs for patients with T2D is their effect on body weight, with weight loss versus placebo commonly reported with GLP-1RAs in studies of monotherapy or add-on therapy [36].

4.1.2. Add-on therapy compared with other oral antihyperglycemic agents or insulin

A 2016 meta-analysis of 57 studies evaluating the comparative efficacy of GLP-1RAs and other agents (metformin, thiazolidinediones, sulfonylureas, DPP-4 inhibitors, and insulin products) concluded that GLP-1RAs: a) provide reductions in HbA_{1c} at least equivalent to those seen with insulin; b) provide greater reductions in body weight compared with most other oral antihyperglycemic agents and insulin; and c) have lower risk of hypoglycemia than insulin or sulfonylureas [10]. In addition, a more recent meta-analysis has indicated that GLP-1RAs provide greater reductions in HbA_{1c} and body weight compared with DPP-4 inhibitors, without an increase in the risk of hypoglycemia [47]. Data from head-to-head clinical trials comparing GLP-1RAs with SGLT2 inhibitors are scarce; however, subcutaneous semaglutide has demonstrated superior HbA_{1c} and body weight reductions to canagliflozin in patients with T2D uncontrolled on metformin in the SUSTAIN 8 study [38]. These results are consistent with a network meta-analysis of clinical trials with GLP-1RAs and/or SGLT2 inhibitors, which suggested that long-acting GLP-1RAs are superior in reducing HbA_{1c} and body weight to SGLT2 inhibitors [48]. Combining GLP-1RAs with SGLT2 inhibitors has been

reported to provide additional reductions in HbA_{1c} and body weight [49,50].

Another meta-analysis concluded slightly greater glycemic control with the addition of GLP-1RAs to oral therapies compared with the addition of insulin, together with weight reductions and lower risk of hypoglycemia [51], although a separate meta-analysis suggested a greater effect on HbA_{1c} compared with insulin was evident with once-weekly but not once-/twice-daily injectable GLP-1RAs [52]. When it is necessary to intensify therapy for patients not achieving their glycemic goal with oral antihyperglycemic agents, the ADA recommends initiating a GLP-1RA prior to insulin in most cases [3] (**Figure 2**).

4.1.3. Add-on therapy compared with other GLP-1RAs

Several head-to-head studies of GLP-1RAs have now been conducted, and indicate variations in clinical efficacy between the agents in this class, as reviewed in detail elsewhere [25,36]. For example, once-weekly subcutaneous semaglutide has been shown to provide greater reductions in HbA_{1c} compared with dulaglutide (add-on to metformin) [53], exenatide extended-release (add-on to one to two oral antihyperglycemic agents) [54], and liraglutide (add-on to one to three oral antihyperglycemic agents) [55], while in turn, exenatide extended-release, administered once weekly, provides significant improvements in HbA_{1c} relative to exenatide twice daily (add-on to diet and exercise or at least one oral antihyperglycemic agent) [56]. A network meta-analysis of studies in patients with inadequate glycemic control on one to two oral antihyperglycemic agents reported similar findings, with subcutaneous semaglutide 1.0 mg found to provide greater reductions in HbA_{1c} and body weight compared with other GLP-1RAs [57].

4.1.4. Add-on to insulin

Several studies have compared the addition of a GLP-1RA to insulin versus intensifying the insulin regimen. Meta-analyses indicate similar or improved glycemic control with the addition of a GLP-1RA, with benefits compared with insulin intensification including reduction in body weight and lower incidence of hypoglycemia [58,59,60].

4.2. Cardiovascular outcomes with GLP-1RAs

The elevated risk of CVD associated with T2D is the leading cause of morbidity and mortality in this patient population, and since 2008 the US Food and Drug Administration (FDA) has required all new antihyperglycemic therapies for T2D to demonstrate an absence of an increased cardiovascular risk [61]. Cardiovascular outcomes trials (CVOTs) have been conducted for all approved subcutaneous GLP-1RAs (except for exenatide twice daily, which was approved prior to the FDA requirement), typically in populations with established CVD or cardiovascular risk factors [27,62,63,64,6566]. These studies have universally shown that subcutaneous GLP-1RAs do not increase the risk of MACE [67]. Moreover, the CVOTs for dulaglutide, liraglutide, and once-weekly subcutaneous semaglutide demonstrated significant reductions in the incidence of such events with these agents relative to placebo [63,65,66]. As a result, dulaglutide, liraglutide, and subcutaneous semaglutide are indicated by the FDA for reducing cardiovascular risk in patients with T2D and established CVD or multiple cardiovascular risk factors (dulaglutide only) [11–13]. These GLP-1RAs with proven CVD benefit are recommended by the ADA as a preferred treatment option, alongside SGLT2 inhibitors with proven CVD benefit, for patients at high risk for or with established atherosclerotic CVD, CKD, or heart failure [3] (**Figure 2** and **Table 2**).

4.3. Safety and tolerability of GLP-1RAs

The most common adverse events with GLP-1RAs are gastrointestinal, primarily nausea, vomiting, and diarrhea [3,23]. These adverse events are generally more likely to occur with GLP-1RAs than with other classes of antihyperglycemic medication, including DPP-4 inhibitors, sulfonylureas, thiazolidinediones, and insulins [10]; however, they are typically most common during the first weeks of treatment, are mild-to-moderate in severity [8,23,36,68], and can be mitigated through approaches such as gradual dose escalation and patient counseling regarding the nature of these effects and how to prevent or relieve them [36,68,69]. Such strategies include advising patients to avoid high-fat foods, stop eating when they feel full, and eat a small portion (perhaps half the usual amount) and wait 20–30 minutes to let satiety occur, before considering consuming any more [68,69].

Although a risk of thyroid C-cell tumors is listed in the prescribing information as a boxed warning for most GLP-1RAs based on observations in rodent studies, clinical studies have failed to establish a risk of thyroid C-cell tumors in patients treated with these agents [8,36,70,71]. In addition, while cases of pancreatitis [8] and pancreatic cancer [8,72,73] have been reported with GLP-1RAs, a causal relationship has not been found [8,36] and recent meta-analyses of clinical trials report a lack of increased risk of such events with GLP-1RAs [70,74]. Cases of acute gallbladder disease, such as cholelithiasis and cholecystitis, have been reported with GLP-1RAs [11–13,28,29,33], and if such events are suspected, gallbladder investigations are required and GLP-1RAs should be discontinued. GLP-1RAs have been associated with serious hypersensitivity reactions, including angioedema and anaphylactic reactions, but these events are uncommon (≥1 event per 1,000 patients treated to <1 event per 100 patients treated) or rare (≥1/10,000 to <1/1,000) [23,75,76,77,78,79,80]. For a more detailed discussion of the clinical relevance of these adverse events, see Brunton et al. [81].

Diabetic retinopathy is a common microvascular complication that occurs as a result of vascular damage in the eye [82]. A recent meta-analysis of trials of all currently available subcutaneous GLP-1RAs concluded no increased risk of diabetic retinopathy (based on Medical Dictionary for Regulatory Activities coding) for any subcutaneous GLP-1RA [83]. An increased incidence of diabetic retinopathy complications

was observed in patients treated with subcutaneous semaglutide compared with placebo (3.0% versus 1.8%) in the large-scale CVOT, SUSTAIN-6 [66]. However, 84% and 83% of these events occurred in patients with diabetic retinopathy at baseline in the semaglutide and placebo groups, respectively [66]. This finding appears to be related to these patients having had large and rapid declines in HbA_{1c} in the first 16 weeks of therapy – a phenomenon that has previously been associated with temporary worsening of diabetic retinopathy during treatment with other antihyperglycemic treatments and in other settings, such as pregnancy [84]. There was no unexpected safety signal for diabetic retinopathy in the other SUSTAIN trials [38,53–55,85,86,87,88,89,90], and a subsequent analysis indicated no increased risk among those without diabetic retinopathy at baseline [84]. Screening for diabetic retinopathy is recommended as part of standard care for all patients with T2D [91] and patients with a history of diabetic retinopathy who are treated with subcutaneous semaglutide should be monitored for progression of this condition [11]. Furthermore, to reduce the risk or slow the progression of diabetic retinopathy, optimization of glycemic control is imperative [91].

GLP-1RAs are associated with increases in heart rate, typically of 2–3 beats per minute [11–13,24,28,29,33], although the clinical relevance of such effects is uncertain [24]. It has been suggested that increases in heart rate may imply a need for caution in patients with cardiac arrhythmias or heart failure [34]. In a relatively small study of 241 patients with chronic heart failure, left ventricular ejection fraction ≤45% and in New York Heart Association functional class I–III, liraglutide increased heart rate and there were more cardiac adverse events with liraglutide than placebo, including a small number of events relating to tachycardia and atrial fibrillation (in 8 patients in the liraglutide group and 3 with placebo) [92]. However, a subsequent analysis did not identify an association between heart rate changes and cardiac adverse events in this study [93]. Furthermore, a recent meta-analysis of seven CVOTs with GLP-1RAs reported a small reduction in the risk of heart failure hospitalization (9–24% of patients in these studies had heart failure at enrollment) [94]. The ADA standards of care recommend the use of an SGLT2 inhibitor with evidence of reducing heart failure progression (e.g., dapagliflozin) in patients with heart failure, with GLP-1RAs an alternative for those in whom SGLT2 inhibitors are not appropriate [3].

Key clinical take-home points

- GLP-1RAs have demonstrated efficacy for glycemic control and weight loss when studied as a monotherapy and as an adjunctive therapy alongside insulin or oral antihyperglycemic agents.
- Results from CVOTs have universally shown no increased risk of cardiovascular events with GLP-1RAs, with some agents (dulaglutide, liraglutide, and once-weekly subcutaneous semaglutide) specifically indicated for reducing cardiovascular risk in patients with T2D and established CVD.
- GLP-1RAs have a well-characterized safety and tolerability profile following over a decade of clinical use in people with T2D. The most common adverse events with these agents are gastrointestinal, namely nausea, vomiting, and diarrhea, but these events are typically transient and mild-to-moderate in severity.

5. Therapeutic adherence and persistence with injectable GLP-1RAs

Although GLP-1RAs have demonstrated effective glycemic control with a low risk of hypoglycemia and a reduction in body weight [3,8], reported adherence and persistence rates with injectable GLP-1RAs are suboptimal [95–97]. This has been partly addressed by the advent of once-weekly injectable GLP-1RAs, which are typically associated with improved adherence and persistence compared with once- or twice-daily agents [96,98,99,100]. Nevertheless, in a US claims-based analysis, approximately 40% of patients were not fully adherent to the once-weekly GLP-1RA dulaglutide after 6 months [96], and suboptimal adherence therefore remains a concern with these therapies. It is important to note that this issue is not unique to GLP-1RA therapy; poor adherence and persistence are well-established barriers to effective treatment with several chronic disease medications, including other antihyperglycemic agents, antihypertensives, antidepressants, and lipid-lowering drugs [101].

Lack of medication adherence and persistence is a significant concern, given that patients who are more adherent to GLP-1RA treatment achieve greater HbA_{1c} reductions [96,102]. Indeed, adequate diabetes control during the first year after diagnosis has been associated with a lower risk of long-term diabetes complications such as retinopathy and cardiovascular events, and mortality [103,104,105].

Suboptimal adherence and persistence across the GLP-1RA class may be attributed to a variety of factors of importance to both patients and prescribers, including frequency of injections, administration device, needle size, efficacy, gastrointestinal side effects, and safety [106], as well as the more general consideration of affordability [107]. Although the variation across this class does allow for individualization of treatment for people with T2D, prescribers are faced with the challenge of familiarizing themselves with the dosing regimens and devices for several agents, with limited time and resources to educate patients on the correct administration and titration of these medications [68,108]. As oral medications may be preferred by some patients and potentially considered less burdensome by both patients and healthcare providers, the availability of an oral GLP-1RA may, therefore, expand the utilization of this class and lead to earlier use in the treatment continuum [109].

6. Development of oral semaglutide

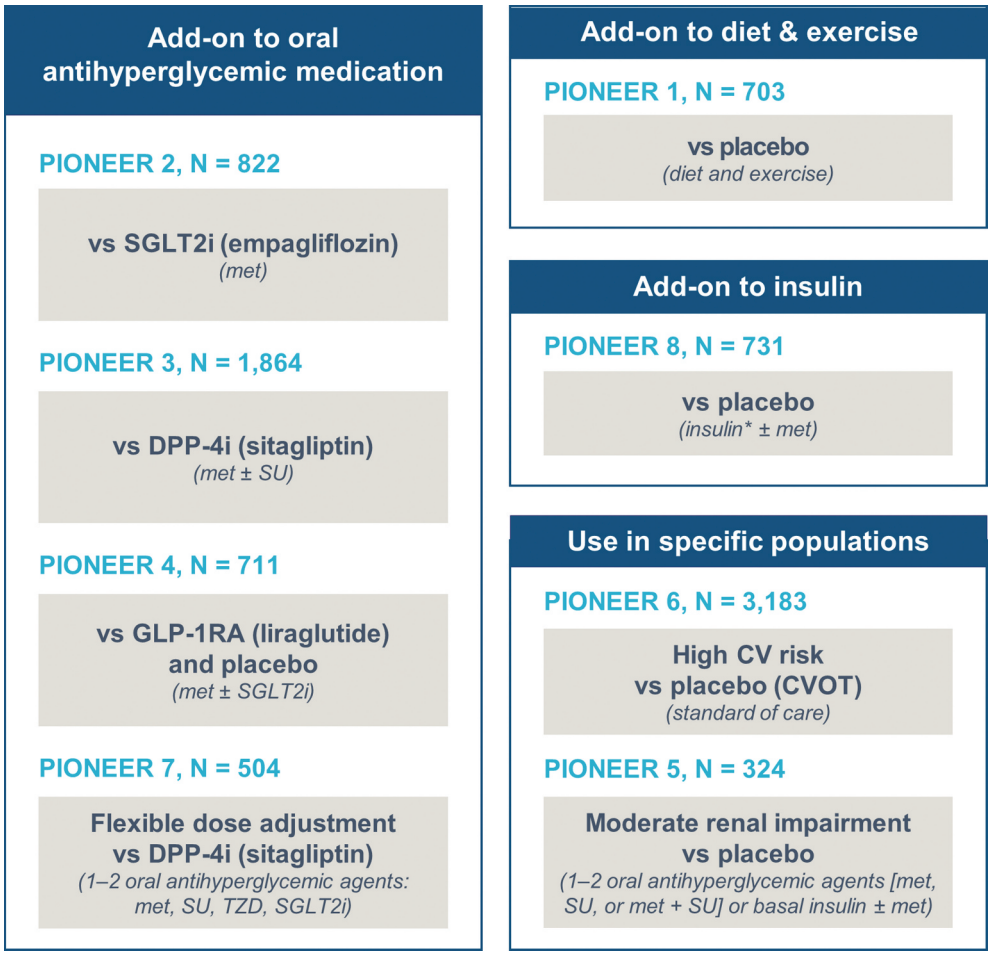

Figure 3. Overview of the global PIONEER clinical trial program for oral semaglutide [117–124].

Text in italics indicates allowed background medications.

*In PIONEER 8, patients could receive basal, basal bolus, or premixed insulin regimens.

CV, cardiovascular; CVOT, cardiovascular outcomes trial; DPP-4i, dipeptidyl peptidase 4 inhibitor; GLP-1RA, glucagon-like peptide-1 receptor agonist; met, metformin; SGLT2i, sodium-glucose co-transporter-2 inhibitor; SU, sulfonylurea; TZD, thiazolidinedione; vs, versus.

As semaglutide is a protein-based drug, oral bioavailability is restricted by degradation in the stomach and limited absorption across the gastrointestinal barrier [110,111]. To overcome this challenge, oral semaglutide was co-formulated with the absorption enhancer sodium N-(8-[2-hydroxybenzoyl] amino) caprylate (SNAC) for administration in tablet form [110,112]. The buffering action of SNAC raises the local pH surrounding the tablet, thereby helping to protect semaglutide from proteolytic degradation, and promoting localized transcellular absorption of semaglutide across the gastric mucosa [110]. Although oral semaglutide has a half-life of around one week, once-daily administration of this medication is required to achieve therapeutic steady state due to low bioavailability [110,112].

Oral semaglutide was approved by the FDA in 2019 as the first oral formulation of a GLP-1RA [35], and is now also approved in Canada, Japan, Europe, Switzerland, and the UK [113,114,115,116]. Approval was based on a suite of phase 3a clinical trials referred to as the Peptide InnOvatioN for Early diabEtes tReatment (PIONEER) program. The PIONEER program included eight multinational studies (PIONEER 1–8) (**Figure 3**) [117,118,119,120,121,122,123,124] and two studies in people from Japan with T2D (PIONEER 9 and 10) [125,126]. Over 9,500 adults with T2D were randomized in these studies to evaluate the effect of oral semaglutide as monotherapy and as add-on to various background therapies, including metformin, sulfonylureas, SGLT2 inhibitors, thiazolidinediones, and insulin. Comparators included placebo, injectable GLP-1RAs, a DPP-4 inhibitor, and an SGLT2 inhibitor. In addition to studies in uncomplicated T2D, the PIONEER program also assessed the effect of oral semaglutide in those with moderate renal impairment (PIONEER 5 [121]) and in those with high cardiovascular risk (PIONEER 6 [122]).

Within the subsequent articles in this supplement, the results of the multinational PIONEER trials are reviewed in detail, closing with a discussion of their significance for clinical

practice in primary care.

Key clinical take-home points

- Specially formulated to facilitate absorption in the stomach, oral semaglutide is the first oral formulation of a GLP-1RA to be approved in T2D.
- Oral semaglutide was evaluated in an extensive phase 3a clinical trial program, PIONEER, in patients from across the spectrum of T2D and against several key comparators.
- By overcoming some of the challenges with subcutaneous formulations, the availability of an oral GLP-1RA creates an opportunity to expand utilization and enable earlier use of this treatment class across a wide spectrum of patients with T2D.

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